Coronary Spasm: Clinical Features and Pathogenesis

Hirofumi Yasue and Kiyotaka Kugiyama

Coronary artery spasm (coronary spasm) is an abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia and its incidence is relatively high in Japanese as compared with Caucasians. Coronary spasm occurs most often from midnight to early morning when the patient is at rest and it is usually not induced by exercise in the daytime. Coronary spasm can be induced by acetylcholine, an endothelium-dependent vasodilator which causes vasodilation in the normal coronary artery. Spasm artery is hyperresponsive to the vasodilator effect of nitroglycerin, an nitric oxide (NO) donor and is deficient in NO activity. The major risk factor for coronary spasm is cigarette smoking. Coronary spasm can be a cause of not only variant angina but also ischemic heart disease in general, including unstable angina, acute myocardial infarction and sudden ischemic death.

(Internal Medicine 36: 760-765, 1997)

Key words: acetylcholine, calcium antagonists, endothelium, nitric oxide (NO), variant angina

Introduction

Coronary artery spasm (coronary spasm) plays an important role in the pathogenesis of not only variant angina but also ischemic heart disease in general, including other forms of angina, acute myocardial infarction, and sudden cardiac death (1-6). We define coronary spasm as an abnormal contraction of an epicardial coronary artery resulting in myocardial ischemia (2, 4). The typical syndrome caused by coronary spasm is variant angina, which occurs at rest and is associated with ST segment elevation on the electrocardiogram (ECG) (7).

Circadian Variation of the Attack of Coronary Spasm

Variant angina occurs at rest, particularly from midnight to early morning and is usually not induced by exercise in the daytime (7-9). Figure 1 shows the diurnal distribution of the attack of myocardial ischemia recorded with ambulatory ECG monitoring in 71 patients with variant angina. There is a marked circadian variation in the distribution of the attack with a peak incidence occurring from midnight to early morning in patients with variant angina, and 52% of the attack occurred in 6 hours from 0:AM to 6:00 AM in this series. Also to be noted is the fact that two-thirds or 67% of the attack were asymptomatic or silent myocardial ischemia as shown in the open box in the figure.

Variant angina was said to occur at rest, whereas in the afternoon even vigorous exercise usually does not induce the attack. Thus, there is a circadian variation of exercise capacity in most patients with variant angina (9). However, even in the morning, moderate single stage exercise is more likely to induce an attack than multistage exercise which causes so-called “warm up phenomenon”. The inducibility of the attack depends not only on the time of day, but also on the type of exercise.

We examined the effects of propranolol, a beta blocking agent, calcium antagonists diltiazem and nifedipine, and phenotolamine, an alpha blocking agent, on the attack induced reproducibly by single stage treadmill exercise in the morning in patients with variant angina (2, 5). Propranolol, a beta blocking agent, which reduces myocardial oxygen demand and which is widely used for the treatment of exertional angina did not suppress the attack completely in any of the patients (2, 5, 10, 11). It rather aggravated the attack in about half of the patients. In contrast, both diltiazem and nifedipine, calcium antagonists, suppressed the attack completely in most of the patients, respectively. Phentolamine also suppressed the attack in about half of the patients. These results indicate that the attack is not induced by increased myocardial oxygen demand caused by exercise and suggest strongly that the attack is caused by coronary spasm and alpha-adrenergic receptors are involved in the genesis of the attack.

Indeed, we confirmed that coronary spasm actually occurs during an attack by performing coronary angiography in the early morning because an attack is easily induced by exercise in the early morning (9). In the early morning, the tone of the coronary artery is increased and its lumen is narrow. Under such...
a condition, an attack is easily induced by exercise and coronary angiogram showed that spasm appeared and completely occluded the artery during the attack and disappeared with subsidence of the attack after nitroglycerin administration and the artery was markedly dilated as compared with the control. However, when coronary angiography was done in the afternoon, the coronary arteries are already dilated and its tone is low in the control state. Under such a condition, even vigorous exercise cannot induce the attack and nitroglycerin dilates the artery slightly further. To document quantitatively the difference of the tone of the large coronary artery between early morning and afternoon, we compared the change of the diameter of the large coronary artery to nitroglycerin between early morning and afternoon. The large coronary artery dilates markedly in response to nitroglycerin in the early morning because the basal tone is increased, whereas in the afternoon, the artery dilates less to nitroglycerin because it is already dilated in the control state. Thus, there is a circadian variation of the tone of the large coronary artery in most patients with variant angina, which seems to be related to the circadian variation of the attack in these patients (9).

**Acetylcholine and Coronary Spasm**

The precise mechanism by which coronary spasm occurs remains to be elucidated. However, several precipitating factors are known, one of which is the stimulation of alpha-adrenergic receptors. When alpha adrenergic receptors are stimulated by injection of epinephrine after beta adrenergic blockade with propranolol, coronary spasm can be induced in patients with variant angina (12). However, because injection of phenylephrine, a predominant α1 stimulant, induces coronary spasm only occasionally, α2 receptor may be more important in inducing coronary spasm (13).

The attack of coronary spasm is also induced by intracoronary injection of ACh, the neurotransmitter of the parasympathetic nervous system in more than 90% of patients with variant angina (14–17). This response is suppressed by prior administration of atropine and is thus mediated by way of muscarinic receptors. Furchgott showed that ACh causes vasodilatation by releasing endothelium-derived relaxing factor or EDRF, when vessels are normal, whereas it causes vasoconstriction when the endothelium is removed or damaged (18). Now EDRF has been shown to be identical with nitric oxide (NO) or substances closely related to it (19). In humans, intracoronary infusion of ACh induces coronary vasodilatation in young healthy subjects, whereas it causes vasoconstriction in patients with coronary atherosclerosis (20).

We examined the change of the large coronary artery diameter in response to intracoronary injection of ACh in patients younger than 30 years and in patients older than 30 years with angiographically normal coronary arteries in the 3 major coronary arteries at each segment (20). In the younger subjects, all major coronary arteries dilated in response to ACh at each segment except at the proximal portion of the left anterior descending artery, whereas in the older, all arteries constricted at all segments in response to ACh. On the other hand, nitroglycerin, an endothelium-independent vasodilator, dilated all
coronary arteries at all segments and there was no difference in the response between the younger and the older. Thus, the difference of the response to ACh between the younger and the older subjects is due to the difference of the response in the endothelium and it may be said that most of the subjects older than 30 years have endothelial dysfunction in their coronary arteries even though they may have angiographically normal coronary arteries.

The coronary artery with angiographically apparent organic stenosis constricted in response to ACh not only at stenotic sites but also at angiographically normal sites. To be noted is the fact that angiographically normal coronary arteries in these patients also constricted to ACh. On the other hand, nitroglycerin dilated all the coronary arteries at all segments irrespective of the presence or absence of organic stenosis and there was no difference in the response among these arteries. The coronary arteries in patients with coronary spasm, however, are characterized by marked constriction, resulting in spasm in response to ACh and marked dilatation in response to nitroglycerin as compared with those in the other patient groups (21, 22). The characteristics of hyperresponsiveness to vasoconstrictor effect of ACh and vasodilator response to nitroglycerin are shown not only in the spasm artery but also in the entire coronary tree in patients with coronary spasm (21, 22).

**Coronary Spasm and NO**

Coronary spasm can also be induced by ergonovine, or histamine, which are all endothelium-dependent vasodilators by releasing NO as ACh, in patients with coronary spastic angina (23–25). It has recently been shown that nitroglycerin or a nitrate causes vasodilatation by being converted into NO in vivo, which stimulates soluble guanylate cyclase, resulting in increased cyclic GMP and thus vasodilatation (19). It is thus possible that hyperresponsiveness of spasm arteries to nitroglycerin or a nitrate is due to the deficiency of NO activity in these arteries. NO is synthesized from L-arginine by way of NO synthase (NOS) and NO synthesis is specifically blocked by NG monomethyl-arginine (L-NMMA) (19). We measured the changes of coronary artery diameter in response to intracoronary infusion of L-NMMA to examine whether NO activity is deficient or not in coronary arteries involved in spasm in patients with coronary spastic angina (26). We found that the coronary artery diameter was decreased in response to L-NMMA in the control subjects, whereas it changed little in response to L-NMMA in patients with coronary spasm. These observations are in agreement with previous reports (27, 28) and indicate that NO is released in the basal state and is involved in the regulation of basal vascular tone in normal humans. Our study also showed that NO activity is deficient in the coronary artery in patients with coronary spasm. We also found that NO release in response to ACh is deficient in the coronary artery in patients with coronary spasm. There was 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 hyperresponsiveness to nitroglycerin is related to the deficiency of endogenous NO in the coronary artery in patients with coronary spasm. Coronary spasm is induced by ACh, ergonovine, or histamine in patients with coronary spasm probably because all of these agonists are endothelium-dependent vasodilators and endothelial NO release by these substances is impaired in these patients. NO is also known to suppress the production of endothelin and angiotensin II which are potent vasoconstrictors and proliferators of vascular smooth muscle and deficiency of NO production may enhance the synthesis of these potent vasoconstrictors (29, 30). Endothelial NO is synthesized by e-NOS and recently we found that coronary spasm is significantly associated with a mutation in exon 7 and the promoter region of the e-NOS gene (31, 32). Furthermore, not only coronary arteries but also the brachial arteries are deficient in NO bioactivity, suggesting that NO deficiency may occur not only in the coronary arteries but also in the entire vascular system (33).

**Coronary Spasm and Autonomic Nervous System**

The precise mechanism(s) by which coronary spasm occurs at rest and is in general not induced by exercise in the daytime is not known. We postulate the following concept regarding the relationship between coronary spasm and the autonomic nervous system. At rest, the activity of the parasympathetic nervous system is enhanced and ACh, its neurotransmitter, stimulates muscarinic receptors, which lead to vasoconstriction or spasm in the presence of endothelial damage or deficiency of NO release. On the other hand, the sympathetic nervous system is activated by exercise, which stimulates both α and β receptors, the former causing vasoconstriction and the latter vasodilatation. When the sympathetic nervous system is suddenly stimulated as in the early morning, alpha activity predominates over β activity, resulting in vasoconstriction, particularly in the presence of endothelial damage and this may lead to spasm. On the other hand, when the sympathetic nervous system is continuously stimulated as in the afternoon, β adrenergic activity predominates, resulting in vasodilatation and no spasm may occur. However, deficiency of endothelial NO activity may not explain the complete mechanism of coronary spasm because all atherosclerotic coronary arteries are not necessarily associated with coronary spasm in spite of the deficiency of NO activity. In addition to deficient endothelial NO activity, hyperreactivity of the coronary smooth muscle seems to play an important role in the pathogenesis of coronary spasm (26, 34–36).

**Smoking and Coronary Spasm**

We compared various clinical characteristics between the patients with coronary spastic angina and those with organic angina using multivariate analysis. Mean age and the incidence of hypercholesterolemia were significantly lower and the incidence of smoking was significantly higher in the patients with
coronary spasm than in those with organic angina. These results
are in agreement with those of previous studies (37, 38) and
indicate that smoking is the most significant risk factor for
coronary spasm. The incidence of smokers was 92% in men and
36% in women in patients with coronary spasm, whereas it was
80% in men and 14% in women in patients with organic angina.
The mechanism(s) by which smoking is related to coronary
spasm is not entirely clear. However, we have shown that
cigarette smoke extract markedly suppressed the ACh induced
endothelium-dependent relaxation and that the suppression
was prevented by antioxidants or SOD in isolated rabbit aorta
(39, 40). Thus, it is quite probable that smoking reduces NO
activity by way of oxygen radicals contained in it.

Coronary Spasm and Hyperventilation or
Magnesium

The attack of coronary spasm can also be induced by
hyperventilation which causes respiratory alkalosis (41–43).
The inducibility of the attack depends on the disease activity
and was higher or 83% in patients with high disease activity,
whereas it was lower or 44% in patients with low disease
activity and the inducibility was 65% as a whole. However, the
attack could not be induced in any of the 153 patients in whom
coronary spasm was not demonstrated. Thus, the sensitivity
of the test is 65% and the specificity is 100%. This means that this
test is specific for coronary spasm and it may safely be said that
coronary spasm really exists when an anginal attack is induced
by hyperventilation (43). Respiratory alkalosis caused by hy-
perventilation probably enhances Na-H exchanger followed by
Na-Ca exchanger, resulting in an increased intracellular Ca
concentration.

Magnesium is said to be an endogenous calcium antagonist
(44), and infusion of magnesium suppresses hyperventilation-
induced attack in patients with coronary spasm (45, 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).

Coronary Spasm and Blood
Coagulation/Fibrinolysis

Coronary thrombosis is now known to be the cause of acute
coronary syndromes including acute myocardial infarction,
unstable angina and ischemic sudden death (48–50). Coronary
spasm may also be involved in the pathogenesis of acute
coronary syndromes (51–53). We have shown that plasma
levels of fibrinopeptide A, a marker of thrombin generation, are
increased after attacks of coronary spasm (54, 55) and that a
circadian variation occurs in parallel with that of the attacks of
coronary spasm (56). Plasma levels of plasminogen activator
inhibitor-1 (PAI-1) also show a circadian variation in parallel
with that of the attacks of coronary spasm (57, 58). These facts
indicate that coronary spasm can be a trigger of coronary
thrombosis and may result in acute coronary syndromes includ-
ing acute myocardial infarction and unstable angina (51–53).

Coronary Angiographic Findings in
Patients with Coronary Spasm

Coronary spasm has been thought to occur at a site of organic
stenosis of a major coronary artery (1). However, our experi-
ence as well as others shows that coronary spasm appears in
angiographically normal arteries as well as in arteries with
organic stenosis (13–17, 59). Furthermore, coronary spasm
occurs not only at one major coronary artery but also at two or
three major coronary arteries in the same patient (16, 17, 21, 42).
Of the 179 patients with coronary spasm at our institution,
126 (70%) had no significant organic stenosis in their coronary
arteries. Thirty-four (19%) of the patients had one vessel
disease and the remaining 19 (11%) of the patients had
multivessel disease. Thus, coronary spasm is more likely to
occur at angiographically normal coronary arteries than coro-
nary arteries with organic stenosis. Coronary spasm at more
than one major coronary artery or multivessel spasm was
demonstrated in 93 (52%) of the patients and there was no
significant organic stenosis in 77 (83%) of the 93 patients with
multivessel spasm. Spasm appeared at the left anterior descen-
ding coronary artery in 23%, at the left circumflex coronary
artery in 5% and at the right coronary artery in 20% of the 179
patients with coronary spasm. Thus, spasm is less likely to
appear at the left circumflex artery than either at the left anterior
descending artery or the right coronary artery.

The patients with multivessel coronary spasm had the fol-
lowing characteristics: 1) most of them had angiographically
normal coronary arteries, 2) they were resistant to treatment and
often required large amounts of Ca antagonists to suppress the
attacks, which often recurred on cessation of intake of Ca
antagonists, 3) they were more likely to have lethal arrhythmias
such as ventricular tachycardia or ventricular fibrillation and
were possibly more likely to suffer from sudden death than
those with single vessel spasm.

Summary and Conclusion

Coronary spasm plays an important role in the pathogenesis
of not only variant angina but also of ischemic heart disease in
general, including acute myocardial infarction and ischemic
sudden death. Intracoronary injection of ACh induces coronary
vasoconstriction in the elderly or patients with coronary ather-
sclerosis, whereas it causes coronary vasodilatation in the
young with normal coronary arteries. This is probably because
ACh releases EDRF/NO from endothelium in the normal vessel
resulting in vasodilatation, whereas it causes vasoconstriction
in the presence of injured endothelium by its direct effect on
vascular smooth muscle. Coronary arteries in patients with
coronary spasm result in spasm in response to intracoronary
injection of ACh and dilate markedly in response to nitroglyc-
erin, an NO donor. Thus, NO activity seems to be deficient in
the coronary arteries in patients with coronary spasm. Indeed,
it has been demonstrated that both basal and ACh-stimulated NO activity is deficient in spasm arteries by intracoronary infusion of L-NMMA, a specific inhibitor of NO synthase. ACh is the neurotransmitter of the parasympathetic nervous system and its activity is elevated at rest and suppressed during exercise in the daytime. This may explain at least partially why coronary spasm occurs most often at rest, particularly from midnight to early morning, and is usually not induced by exercise in the daytime. Cigarette smoking is the most important risk factor for coronary spasm and reduces endothelium-dependent vasodilation probably by way of oxygen radicals. Genetic factors are also important in the genesis of coronary spasm and the association of the mutations in e-NOS gene with coronary spasm has been demonstrated. This may explain the relatively high prevalence of coronary spasm in the Japanese population.

References

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