Angina Pectoris at Rest**

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Anginal attack at rest has been a subject of long-lasting controversy in nomenclature, mechanism and clinical significance. During the past decade tremendous progress has been achieved, and recently increasing interest is focused on coronary vasospasm as the pathophysiology and on efficacy of Ca^{++} antagonists. Many of the Japanese researchers have contributed a great deal to this progress. This report is a summary of the clinical and experimental studies performed in our department.

I. Incidence and clinical course of various types of anginal syndrome

Protocols of consecutive 233 hospitalized patients were analyzed on clinical course in view of trigger of the anginal attack. Eighty-eight percent of 233 cases had anginal attacks triggered by exercise in some period in the clinical course (E), 44% during sleep or early morning in bed, 20% in rest state during daytime (R), and 28% had anginal pain triggered by daily life activity such as meal (especially breakfast), face-washing, urination, defecation or bath (D). Attacks of different types were experienced in the same or in different periods of their clinical course. Forty-four percent of total 233 cases had E or E+D, 10% had R or R+D and 46% had E+R. D was associated with a quarter of both E and R.

As the initial anginal attack, E was seen in 65%, R (including D) in 18% and E+R in 17%. Frequently D appeared or disappeared in association with R. The clinical course from the initial stage until hospitali-

zation was variable in each case in view of the three categories, but about a half of initial effort angina remained in the same category, while most of initial rest angina became symptom-free within one year or turned to category E or E+R after several months or years. About one-third of initial effort angina were hospitalized because of additional rest angina after several years of stable stage.

At the hospitalization, E, R (including D), and E+R were 90 cases (42.5%), 81 cases (38.2%) and 41 cases (19.3%) respectively. Cases with rest angina had younger average age, relative preponderance of female and variant angina, and less multiple coronary lesions than typical effort angina. Combined rest and effort angina was intermediate between rest angina and effort angina with respect to these clinical features.

Careful history-taking with special reference to the presence and duration of effort angina was rewarding for clinical evaluation of rest angina.

II. Pathophysiology of rest angina

A. Clinical observations

1) Temporal relation between onset of ischemia and hemodynamic changes

In our previous report on continuous ECG recording on 12 cases of nocturnal angina, heart rate increased during the attack, but in most instances the beginning of the increase occurred just before or almost simultaneously with the onset of ST deviation. Current studies using more sophisticated monitoring system have confirmed that ECG change precedes onset of an-

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ginal pain, and that hemodynamic changes such as LVEDP, PCWP, abnormality of segmental wall motion occur simultaneously with or slightly earlier than onset of ECG change, while increase of heart rate and blood pressure may take place with onset of anginal pain. Accordingly these temporal relations may be sometimes misleading in the diagnosis of rest or effort angina, and the limitation is more obvious with ischemic episodes following the daily life activity.

2) REM-sleep as a trigger of nocturnal angina

Nowlin et al. observed frequent coincidence of episodes of nocturnal angina and REM sleep stages in four cases, and suggested as provoking factor a role of changes in tone of autonomic nervous system during this sleep stage. We observed that merely 18 out of 87 nocturnal episodes in 10 cases occurred during REM sleep stages, and that the coincidence was frequent in some cases while there was no relation in other cases. However, incidence of the coincidence per unit hour was 2-4 times more frequent than in the other sleep stages. Moreover, when a series of successive episodes were counted as one attack, which might be induced by a single provoking cause, the first episode of the series and other isolated attacks per unit hour were 5-10 times more frequent in REM stage than in the other sleep stages in variant angina. Accordingly, although some researchers have negative opinion, REM sleep seems to play an important role at least in some cases of variant angina. Because increase of heart rate and blood pressure was not observed before ST deviation associated with REM sleep stage, REM sleep did not seem to induce anginal episode through increased myocardial oxygen consumption, but presumably through direct action of tonic effect of sympathetic nerve on coronary artery in specified patients.

Apart from REM sleep stage, diurnal change of sympathetic activity in the morning may explain the well known tendency that anginal attacks of any type can be

easily provoked in this time of the day.

3) Methods for provocation of variant angina

As early as in 1967, we experienced one case of variant angina, in whom pilocarpine and methacholine could induce ischemic attack with the same character of his spontaneous attacks. After this case report, pilocarpine and methacholine test have been noticed in Japan as methods for induction of variant angina. Now a variety of provocative methods are available such as intravenous catecholamic, ergonovine maleate, hyperventilation with or without Trisbuffer, and cold pressor test and so on. A common mechanism of these methods is suspected as activation of alpha-receptor on large coronary artery, which are induced directly or indirectly through reflex mechanism.

Exercise test is noticed recently as another method for provocation of ischemic attack of variant angina through coronary vasospasm. We observed that cases with variant angina had frequently history of effort angina and showed positive exercise test in at least 40% of the cases. In 26 cases without old myocardial infarction, higher frequency of positive response with ST elevation was seen in the period with frequent spontaneous attacks, while exercise test turned to less frequent positive response with ST depression when performed in quiescent period after treatment. On the other hand, rest angina with ST depression showed high frequency of positive response with ST depression. Abnormally sensitive sympathetic receptor of the large coronary artery during active period of variant angina may be postulated, because a variety of procedures can provoke the ischemic attack. Attacks during daily life activity might be understood by this assumption.

4) Cyclicity of attacks of variant angina

As well documented, attacks of variant angina frequently form a chain of recurrent episodes with interval around 10 minutes. Prinzmetal et al. noticed this phenomenon as an evidence suggesting contractions of

coronary arterial smooth muscle. We studied the mode of appearance of nocturnal ischemic episodes using continuous ECG recording on 15 cases with variant angina (37 nights) in comparison to 15 cases with ST depression during attacks including 4 cases with aortic regurgitation (20 nights). When the cyclicity was defined tentatively as a chain of 3 or more successive episodes with interval within 30 minutes, the following results were obtained. (1) Approximately half of the cases of variant angina showed the cyclicity. In contrast, none of the cases with ST depression showed the cyclicity. (2) Time interval between two successive episodes: 2-25 minutes with most frequent intervals around 10 minutes. (3) Number of episodes in a chain: 3-10 when associated with frank pain, occasionally numerous especially when chest pain was slight. (4) Tendency to cyclicity was variable in length, cycle and regularity even in same patient.

Recognition of the cyclicity of variant angina is not only valuable in diagnosis of variant angina and evaluation of drug effect, but also important in the implication that single provocative factor may be responsible for successive episodes.

B. Experimental studies using partially constricted coronary artery of dog and their clinical implications

1) Effects of electrical stimulation of sympathetic cardiac nerve on pentobarbital-anesthetized and chest-opened dog with various degrees of partial constriction of the large coronary artery.

Myocardial ischemia with ST elevation on the surface electrocardiogram was induced only when the constriction was severe. The myocardial ischemia was associated with decreased coronary blood pressure distal to the constriction, but without appreciable change of heart rate and systemic blood pressure. The coronary pressure reduction was not abolished by propranolol, but was prevented by phentolamine. This experimental preparation may be a model of episode of variant angina with severe

fixed coronary stenosis, which can be provoked by increased sympathetic tone.

On the same experimental preparation, transient drop of systemic blood pressure which was induced by cardiac standstill due to electrical stimulation of vagal nerve, provoked similar myocardial ischemia with the coronary blood pressure reduction. This may represent that the reflex increase of sympathetic nerve tone acted likewise as the direct electrical sympathetic stimulation. Pilocarpine- or methacholine-induced myocardial ischemia in variant angina may be related to this experimental setting.

2) Cyclic reduction of coronary blood flow of the partially constricted coronary artery associated with cyclic appearance of transient myocardial ischemia.

The above experimental preparation, without any further intervention, showed frequently cyclic appearance of transient myocardial ischemia with several minutes duration and with cycle length of 2-25 minutes, which mimicked a chain of ischemic episodes of variant angina. The cyclic myocardial ischemia was accompanied by cyclic reduction of flow of the coronary artery with partial constriction and the coronary blood pressure distal to the constriction. The cyclic phenomenon was abolished by i.v. nitroglycerin, papaverine or PG I₂, and but not by propranolol or phentolamine. As reported by Folts et al., it was also abolished by i.v. aspirin.

Coronary angiography performed during the phase of coronary blood pressure fall revealed transient narrowing of the constricted segment and/or distal portion of the coronary artery. The narrowing had a variety of configurations which were diffuse-concentric or rosary-like in many instances, but some of which were localized-eccentric narrowing suggesting thrombus or platelet aggregate.

On the other hand, the same preparations which did not show the cyclic phenomenon spontaneously, turned to show the cyclic phenomenon by i.v. epinephrine, indomethacin or sympathetic nerve stimulation.

It has been reported that segment of bovine or human coronary artery shows phasic and tonic contraction with cyclicity in vitro, suggesting that rhythmic contraction is assumed to be a fundamental property of smooth muscle of large coronary artery.

C. Mechanism of coronary vasospasm in variant angina

Based on our clinical and experimental observations and recent knowledge on physiological property of coronary artery, and also on currently confirmed angiographic findings that spasm occurs mostly at the region with more or less atherosclerotic lesion, mechanism of coronary vasospasm may be summarized as shown in Table 1. Coronary vasospasm may have two extreme situations: increased physiologic tone of coronary artery with severe fixed stenosis

and severe, nonphysiological contraction of widely patent coronary artery with slight atherosclerotic lesion.

D. Differences of two types of rest angina with ST elevation and depression.

Rest angina with ST depression during the attack has not been studied so extensively as variant angina. Many authors believe that the difference of the ECG changes means merely different degrees of myocardial ischemia induced by different amount of coronary spasm. However, there remain several problems to be answered in order for this concept to be accepted. (1) our experiences of continuous ECG recording disclosed extremely rare cases with attacks with both ST elevation and depression confirmed by three orthogonal leads during one night. (2) Spatial direction of ST deviation was too different in the two

Table 1. Background and trigger of coronary artery spasm

Background	Trigger
I. Physiological a. spontaneous contractility of the smooth muscle of the large coronary artery b. intrinsic substances inducing contraction of coronary artery and their receptors catecholamines prostaglandins acetylcholine histamine serotonin c. physiologic change of sympathetic nerve activity early morning coldness II. Pathological a. coronary artery lesion 1. fixed narrowing 2. unstable wall tension distal to fixed stenosis 3. abnormality of I-a and I-b in undefined process during development of atherosclerosis b. constitution	I. Unknown II. Stimulus of cardiac sympathetic nerve (+ parasympathetic ?) a. reflex coldness daily life activity b. change during sleep c. exercise III. Transient formation of thrombosis platelet aggregate

types to assume that the myocardial ischemia existed in same local myocardium perfused by the same coronary artery. This difference was clearly demonstrated by precordial mapping method. (3) Nocturnal angina with the two types was different in the mode of appearance such as frequency of attacks in one night, average duration of attack, peak frequency of attacks in nightly hours and tendency of cyclicity. Moreover, we observed that there was more extensive coronary lesion in average in ST depression type than in variant angina, and that nocturnal angina with ST depression in cases with aortic regurgitation had the same mode of appearance as in cases with atherosclerotic coronary lesions.

III. Prognosis and efficacy of drug therapy of unstable angina

Rest angina has been recognized as an important subcategory among various subsets of unstable angina. Appearance of rest angina after longstanding effort angina or sudden onset of rest angina with or without effort angina is followed not infrequently by myocardial infarction or sudden death.

Anginal attacks associated with daily life activity, which might be recognized as a variant of rest angina, seem to be an important clinical syndrome of unstable angina with severe coronary lesion.

On the in-hospital prognosis of 133 cases diagnosed as unstable angina with the criteria of American Heart Association, incidence of succeeding myocardial infarction was 14.2% and death rate was 6.0%. Among them, recent therapy including Ca^{++} antagonists resulted in 3% of myocardial infarction and 0% of death in 33 cases. This promising results should be confirmed in future in Japan where variant angina with slight coronary lesion is more frequently encountered. Favorable results of Ca^{++} antagonists have been accumulated on rest angina especially on variant angina, but 15% of our cases, most of which were cases with extensive coronary lesion associated with ST depression during the attacks, could not have sufficient drug effect.

REFERENCES

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