LATENT CORONARY SPASM DURING ANGINA-FREE PERIODS IN PATIENTS WITH VARIANT ANGINA

— Comparative Study with Nitroglycerin Administration —

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Coronary artery diameters were analyzed in 13 patients with variant angina and in 12 control patients. Sequential coronary arterial angiography was performed during control periods, during attacks and after administration of nitroglycerin, and coronary vasospasm was documented during anginal attacks and accompanied by electrocardiographic changes in all 13 patients with variant angina. In 7 patients (Group I) with variant angina, anginal attacks occurred more than 4 times a week, more than twice during the 3 days prior to coronary angiography and in the morning of coronary angiography. In another 6 patients (Group II) with variant angina, attacks occurred less than once a week and never occurred during the 3 days preceding the coronary angiography. Though the degree of coronary stenosis at the sites of spasm was not significantly different between Group I ($52.9 \pm 23.4\%$) and Group II ($38.3 \pm 27.3\%$) after administration of nitroglycerin, the percent stenosis in the lesions in Group I ($77.9 \pm 14.1\%$) was significantly ($p < 0.01$) higher than that in Group II ($33.3 \pm 28.0\%$) in the control angiography. Therefore, the degree of stenosis observed in the control angiography decreased significantly ($p < 0.01$) after administration of nitroglycerin in Group I (change in %: $-25.0 \pm 19.8\%$), but not in Group II (change in %: $5.0 \pm 10.0\%$). In 12 patients with chest pain syndrome in whom coronary spasm was not demonstrated by infusion of ergonovine maleate, coronary stenosis at control angiography was not changed significantly after nitroglycerin administration. We conclude that coronary spasm appears to be present in the absence of angina even at the time of control angiography and to be closely related to the generation of the anginal attacks in patients with variant angina.

Key Words:

Variant angina
Coronary angiography
Coronary spasm
Coronary stenosis
Nitroglycerin

IT has been established that coronary arterial spasm plays an important role in the genesis of anginal attacks in patients with variant angina.¹⁻⁵ In fact, coronary vasospasm is often demonstrated at a site of pre-existing fixed stenosis.⁶⁻⁸ Several factors are concerned with the generation of coronary arterial spasm,⁹⁻¹⁵

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but the exact mechanism related to the occurrence of coronary arterial spasm remains unknown.

Anginal attacks in patients with variant angina occur frequently during the night or early in the morning but less often in the daytime^{7,13,15,16} Yasue et al¹⁶ reported that there probably was a circadian variation in the coronary arterial tone in these patients. If the coronary arterial tone is high, a slight coronary arterial spasm might easily induce severe obstruction of coronary blood flow and produce myocardial ischemia.

The provocative method of anginal attacks by intravenous infusion of ergonovine maleate appears to be valuable to differentiate patients with variant angina from those with chest pain syndrome.¹⁷⁻¹⁹ However, the frequency of anginal attacks varies extensively among patients with variant angina, and a wide day-to-day variability of symptoms is also observed.²⁰ In some patients anginal attacks are frequent and stable, while in others spontaneous attacks are rare and faint, though ergonovine maleate can provoke anginal attacks.

We attempted to evaluate coronary angiographic findings in the basal state in patients with variant angina. We performed coronary arteriography in the morning when anginal attacks usually occurred, and assessed how much coronary vasoconstriction contributed to coronary stenosis during angina-free periods compared with the stenosis of post-nitroglycerin administration.

MATERIALS AND METHODS

Eleven men and 2 women with variant angina were selected for the study. Age ranged from 37 to 71 years old with an average of 53. Group I included 7 patients with variant angina in whom anginal attacks occurred more than 4 times a week during a medication-free period, and more than twice during the 3 days prior to and on the morning immediately before coronary angiography. Six patients with variant angina in whom attacks occurred less than once a week during medication-free period and never occurred for 3 days preceding coronary angiography were classed as Group II. Twelve patients with atypical chest pain during which no significant electrocardiographic changes were demonstrated and with negative ergonovine provocative tests were selected and classified into control group. Age at this group ranged from 21 to 62 years old with an average of 49. Patients with prior myocardial

infarction, left main coronary obstruction and a fixed coronary stenosis over 90% were excluded. No studies were performed on amenorrheic premenopausal women, or on patients with allergic tendencies to contrast medium or with anginal pain relatively refractory to sublingual nitroglycerin. All patients in Groups I and II had variant angina pectoris, characterized by non-exertional chest pain that occurred at night or early morning and was accompanied by ST-segment elevation on the electrocardiograms. Clinical data of these patients are shown in Tables I and II. The frequency of anginal attacks was observed without any medication for at least one week after hospitalization and all medication, including premedication for coronary angiography, was discontinued during the 3 days prior to angiographic studies except for nitroglycerin. All anginal attacks were confirmed electrocardiographically.

All of the patients were told that they would be given a drug that might produce a marked coronary artery narrowing which might explain the cause of chest pain. Written informed consent was obtained from each patient prior to coronary angiography. Electrocardiograms and blood pressure were continuously monitored during the procedure. Sublingual and intravenous nitroglycerin was made available for possible emergency administration. Ergonovine maleate was given in intravenous bolus injections after initial control angiography. Ergonovine maleate was given with an initial dose of 0.05 mg, followed by 0.05, 0.10 and 0.20 mg successively every 3 min until chest pain or electrocardiographic ischemia appeared. Then, coronary arteriography was performed immediately. After completing coronary arteriography during the attack, sublingual nitroglycerin (0.3 mg) was given and the coronary arteriography was repeated 3 min later.

The diameters of the coronary arteries were measured with calipers on adequately magnified views of 35 mm cineframes. The measurements were made at end-diastole and in the same projections of arteriography at control, during attacks and after nitroglycerin administration. The severity of the coronary artery stenosis where spasm was demonstrated during attacks was estimated as a percent rounded-off to the nearest 5% of the normal luminal diameter. With this technique, the inter- and intra-individual differences of measurement in coronary stenosis were both within 6.2% ($p < 0.05$) in our labora-

TABLE I CLINICAL DATA OF

Case	Age	Sex	ECG at rest	ECG during attacks	Frequency of attacks		
					per week	3 days before C.A.	2 days before C.A.
Group I							
1	67	M	Normal	ST↑ II, III and aVF	9	0	2
2	45	M	T flat V _{5,6}	ST↑ or ↓ V ₁₋₅	5	1	3
3	71	M	Normal	ST↑ or ↓ II, III and aVF	4	0	1
4	42	M	Normal	ST↑ V ₁₋₄	5	0	0
5	62	M	Normal	ST↑ V ₁₋₅	7	0	1
6	56	M	Normal	ST↑ V ₁₋₅	6	3	0
7	60	M	T inversion V ₂₋₅	ST↑ V ₁₋₅	5	1	1
mean ± SD							
Group II							
8	53	M	Normal	ST↑ II, III and aVF	0	0	0
9	56	M	Normal	ST↑ V ₁₋₅	1	0	0
10	46	M	Normal	ST↑ or ↓ V ₄₋₆	0	0	0
11	46	F	Normal	ST↑ V ₁₋₅	1	0	0
12	55	F	Normal	ST↑ V ₁₋₅	1	0	0
13	37	M	Normal	ST↑ V ₁₋₅	0	0	0
mean ± SD							

Abbreviations: ECG = electrocardiogram, C.A. = coronary angiography, NTG = nitroglycerin, EM = ergonovine maleate, ↑ = elevation, ↓ = depression

tory. The change of coronary artery stenosis was determined by the difference of percent stenosis observed on the coronary angiograms taken before and after administration of nitroglycerin. The degree of organic stenosis was determined on the coronary angiogram obtained at the time of thorough coronary dilatation after nitroglycerin administration. Diffuse type of coronary spasm was not included in our cases. All of these procedures were started at 9:00 a.m. and control coronary arteriography was performed within one hour. No untoward event occurred throughout the procedures.

Student's *t*-test was used for statistical analysis, and paired *t*-test was used to examine the statistical significance of the change in coronary stenosis between a control and after administration of nitroglycerin.

RESULTS

Coronary arterial spasm was documented during anginal attacks in all 13 patients in Groups I and II, in all of whom organic stenotic findings were present in the lesions where spasm was recognized. Percent stenosis of the coronary artery in those lesions during control periods was $77.9 \pm 14.1\%$ (mean ± standard deviation) in Group I (*n* = 7) and $33.3 \pm 28.0\%$ in Group II (*n* = 6) (Fig. 1). There was significant difference (*p* < 0.01) between two groups. After administration of nitroglycerin, percent stenosis of the coronary artery in the same lesions was $52.9 \pm 23.4\%$ in Group I and $38.3 \pm 27.3\%$ in Group II. There was no significant difference between two groups. In Group I the percent stenosis in those lesions during control periods ($77.9 \pm 14.1\%$) was

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the day before	Time of the last attack prior to C.A.	Coronary angiograms where spasm occurred		Other findings of coronary angiograms after NTG	Dose of EM required to induce angina (mg)
		Control	NTG		
4	8:06 a.m.	85% RCA	20%	Normal	0.05*
2	6:00 a.m.	50% LAD	20%	Normal	0.2
6	8:00 a.m.	95% LCX	65%	80% RCA	0.05
2	7:00 a.m.	80% LAD	65%	Normal	0.1
1	8:40 a.m.	75% LAD	60%	60% LCX 25% RCA	0.05
1	6:00 a.m.	85% LAD	80%	50% RCA	0.2
1	6:30 a.m.	75% LAD	60%	60% LCX	0.1
		77.9 ± 14.1%	52.9 ± 23.4%		0.11 ± 0.07
0		15% RCA	15%	70% LAD	0.4
0		80% LAD	85%	50% LCX 40% RCA	0.1*
0		35% LCX	25%	30% LAD	0.1
0		15% LAD	35%	Normal	0.1
0		50% LAD	55%	Normal	0.4
0		5% LAD	15%	Normal	0.4
		33.3 ± 28.0%	38.3 ± 27.3%		0.25 ± 0.16

* bedside data obtained within a week from C.A.

TABLE II CLINICAL DATA OF THE PATIENTS WITH CHEST PAIN SYNDROME
(CONTROL GROUP)

Case	Age	Sex	ECG at rest	Coronary Angiograms	
				Control	NTG
1	54	F	Normal	Normal	Normal
2	62	M	Normal	25% RCA 60% LCX	30% 65%
3	49	M	Normal	Normal	Normal
4	52	F	Normal	30% LAD 65% LCX 50% RCA	40% 65% 55%
5	55	F	Normal	60% LAD	50%
6	43	M	Normal	45% LAD	60%
7	60	M	Normal	65% LAD 50% LCX 30% RCA	60% 65% 40%
8	58	F	Normal	Normal	Normal
9	46	M	Normal	Normal	Normal
10	21	F	Normal	Normal	Normal
11	56	F	Normal	15% LCX	25%
12	36	M	Normal	Normal	Normal

Abbreviations: ECG = electrocardiogram, NTG = nitroglycerin

Fig.1. Coronary artery percent stenosis in the lesions where spasm occurred during attacks, in the control angiography (C) and after administration of nitroglycerin (NTG). In Group I (left), the percent stenosis in the control angiography is significantly ($p < 0.01$) higher than those after administration of nitroglycerin, but not in Group II (right).

significantly larger ($p < 0.01$) than that after nitroglycerin administration ($52.9 \pm 23.4\%$), but there was no significant difference between control periods and after administration of nitroglycerin in Group II (Fig. 1). The change in percent stenosis between the control and after administration of nitroglycerin was $-25.0 \pm 19.8\%$ in Group I and $5.0 \pm 10.0\%$ in Group II, respectively. Total dose of ergonovine maleate required to provoke anginal attacks was 0.11 ± 0.07 mg in Group I and 0.25 ± 0.16 mg in Group II and this difference is statistically significant ($p < 0.05$). In the control group, neither anginal attacks nor coronary arterial spasm was documented. In 7 patients of the group, organic coronary stenotic findings were observed, but percent stenosis at the control angiography ($45.0 \pm 17.5\%$, $n = 11$) did not change significantly after nitroglycerin administration ($50.5 \pm 14.6\%$) (Fig. 2). Typical cases of each group are shown in Figs. 3–7.

Fig.2. Coronary artery percent stenosis in the control angiography (C) is not significantly changed after administration of nitroglycerin in patients in the control group. See Table II for details.

As shown in Figs. 3–5, coronary stenosis was already severe on the control angiogram (A) at the site of spasm which was demonstrated during attacks (B), but was markedly decreased after administration of nitroglycerin (C) in patients in Group I. As shown in Fig. 6, coronary stenosis in the control angiography (A) did not alter so much after nitroglycerin administration (C) in patients in Group II. Coronary stenosis in patients in the control group did not significantly change after nitroglycerin administration as shown in Fig. 7.

Thus, coronary spasm or vasoconstriction was observed both in the control study and during attacks in patients in Group I, and only during attacks in patients in Group II, but never observed significantly in patients in the control group.

DISCUSSION

Coronary arterial spasm can occur in angio-

Fig.3. Right coronary arteriograms in Patient 1 in Group I.

- A) Control. The artery was already severely stenotic at the middle portion.
- B) During the attack. Spasm appeared spontaneously and occluded the coronary artery almost completely at the proximal and the middle portions.
- C) After nitroglycerin administration. Spasm disappeared and the artery appeared to be nearly normal.

Fig.4. Left coronary arteriograms in Patient 2 in Group I.

- A) Control. The middle portion of the left anterior descending coronary artery was already in a vasoconstrictive state.
- B) During the attack. Ergonovine maleate induced coronary spasm and occluded the artery almost completely.
- C) After nitroglycerin administration. The stenotic portion became dilated. The fixed stenotic findings were mild.

Fig.5. Left coronary arteriograms in Patient 3 in Group I.

- A) Control. The left circumflex branch was already stenotic and not visualized in the middle portion.
- B) During the attack. Ergonovine maleate induced coronary spasm and occluded the artery completely.
- C) After nitroglycerin administration. Spasm disappeared and fixed stenotic findings were observed where spasm occurred. However, the degree of the stenosis after nitroglycerin administration was markedly lower than that of the control angiography.

graphically normal arteries.^{13,15,16,20,21} Recent findings indicated that atherosclerotic lesions in cholesterol-fed animals appeared to have high sensitivities to vasospasm.^{23,24} However, it is quite possible that coronary artery vasomotion even in normal degree might completely obstruct coronary blood flow in the presence of critical fixed-stenosis.²⁵ In the present study patients with critical fixed-stenosis were excluded from the analysis.

It is characteristic of variant angina that anginal attacks usually occur during the midnight or early in the morning but rarely in the daytime.^{7,13,15,16} As an explanation for this phenomenon, Yasue et al.^{12,15,16} reported that hydrogen ions which competed with calcium ions for cellular entry decreased when metabolism slowed

Fig.6. Right coronary arteriograms in Patient 8 in Group II.

- A) Control. The artery was not stenotic and appeared to be nearly normal.
- B) During the attack. Spasm occurred by administration of ergonovine maleate and occluded completely at the proximal portion of the artery.
- C) After nitroglycerin administration. Spasm disappeared and the fixed stenotic findings was only mild.

down, resulting in increase of coronary arterial tone at midnight or early morning, and that anginal attacks could be induced easily by coronary arterial spasm. Indeed, coronary vasodilatation after administration of nitroglycerin in the morning was higher in magnitude than that in the afternoon in patients with variant angina.¹⁶

There are numerous reports concerning coronary arterial vasospasm observed in cases of coronary arteriography. "Spasm" generally indicates localized vasoconstriction leading to transient myocardial ischemia, but "spasm" is also present without myocardial ischemia. This condition might be described as increased coronary basal tone by some, but we call this state as "latent spasm".

All of our patients with variant angina demonstrated more or less atherosclerotic lesions angiographically where coronary spasm occurred during the attacks. We assessed the basal vasoconstrictive state in such lesions in these patients. In the patients in Group I who were considered to be prone to anginal attacks and indeed ex-

Fig.7. Left coronary arteriograms in Patients 4 in the control group.

- A) Control. The middle portion of the left anterior descending coronary artery and the distal portion of the left circumflex branch were moderately stenotic. Coronary spasm was not demonstrated by infusion of ergonovine maleate.
- B) After nitroglycerin administration. Stenotic findings in the lesion did not decrease.

perienced attacks on the morning immediately prior to coronary angiography, the stenosis of the coronary arteries was already severe on the control angiography compared to findings after nitroglycerin administration, suggesting the presence of latent coronary arterial spasm. Such phenomenon was not observed in patients in Group II. The degree of the fixed stenosis of the coronary arteries in Group II differed insignificantly from that in Group I. Coronary arterial spasm by intravenous injection of ergonovine maleate was also confirmed invariably during attacks in both Group I and Group II. In the control group neither coronary arterial spasm nor latent spasm was observed.

Stenosis in the coronary artery involves two mechanisms, one organic and the other functional. The functional mechanism is divided into basic coronary arterial tone and transient coronary vasoconstriction. It may be difficult to assume that even a powerful, spontaneous spasm could lead to complete obstruction in nearly normal coronary arteries. However, if coronary arterial vasoconstriction was already present in the basal state, added spasm of even a low degree could easily occlude the coronary arteries and attacks of angina would be triggered.

Though the sensitivity and the specificity in diagnosis of variant angina as provoked by ergonovine maleate are reportedly high,¹⁷⁻¹⁹ there are questions as to whether the spasm induced by ergonovine maleate is actually the same as that seen in cases of spontaneous attacks

in patients with variant angina. Cases refractory to sublingual nitroglycerin have been reported²⁶ in vasospasm induced by ergonovine maleate. Some investigators indicated that coronary spasm induced by infusion of ergonovine maleate might be more potent than that in cases of spontaneous attacks in patients with variant angina, and of the danger of myocardial infarction and death due to irreversible complications.^{18,19,26-28}

In Group I, coronary vasoconstriction was present in the basal state where spasm occurs during attacks, and added spasm would easily lead to a complete obstruction. In Group II, coronary vasoconstriction was not so evident in the basal state and vasoconstriction occurring spontaneously can lead to coronary obstruction less frequently, though a powerful spasm caused by administration of ergonovine maleate can induce acute coronary obstruction.

Thus, the spontaneous generation of anginal attacks in patients with variant angina is considered to be closely related to the coronary arterial vasoconstriction in the basal state.

It may be important to assess latent coronary vasospasm present at the control angiography in patients with variant angina for a decision of prophylactic treatment. In those patients in Group I who have significant vasoconstriction in the basal state, it is probably essential to administer calcium antagonists or long-acting nitrates to alleviate latent vasospasm. However, it will need further investigations whether coronary vasodilators are necessarily to be administered prophylactically to patients in Group II.

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