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Increased Basal Tone and Hyperresponsiveness to Acetylcholine and Ergonovine in Spasm Related Coronary Arteries in Patients with Variant Angina

— Basal Coronary Artery Tone in patients with Variant Angina —

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In patients with variant angina, previous data have been inconclusive as to whether basal coronary artery tone is elevated at the spastic and non-spastic sites. Thus, the purpose of this study was to assess the basal coronary artery tone and the responsiveness to acetylcholine(Ach) and ergonovine(Erg) in patients with variant angina. We compared the basal coronary artery tone and the constrictive responses to Ach and Erg between 31 patients(Group 1) with variant angina in whom spasm was provoked by the low doses of Ach(intracoronary 20ug) or Erg(intravenous 50ug) and 35 patients(Group 2) provoked by higher doses of Ach(intracoronary 100ug) or Erg(intravenous cumulative dose of 350ug), and 26 control subjects. Patients with variant angina in whom spasm was provoked by low doses of Ach or Erg, had a higher incidence of mixed disease, multi-vessel spasm and higher disease activity. The basal coronary artery tone at the spastic and nonspastic sites of spasm related artery was significantly more elevated in Group 1 than that in Group 2(44±17 vs 14±11 % and 26±14 vs 16±10 % respectively, $P<0.05$), but not in the nonspasm related artery, The magnitudes of vasoconstrictive responses to Ach and Erg at the nonspastic sites were also greater in Group 1 than those in Group 2 and the control groups(Ach ; 40±20 vs 26±11, 27±12 % : Erg ; 37±18 vs 12±8, 13±10 % respectively, $P<0.05$). However, the basal coronary artery tone was not elevated at the spastic and nonspastic sites in Group 2 compared to the in control subjects. These findings suggest that the basal coronary artery tone is increased in patients with variant angina with higher disease activity at the spastic sites and nonspastic sites of the spasm-related artery, and this may be related to the occurrence of coronary artery spasm.

Key Words : *Variant angina, Coronary artery spasm, Basal tone, Acetylcholine, Ergonovine*

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INTRODUCTION

Coronary artery spasm is usually associated with an atherosclerotic lesion. Vanhoutte et al. speculated that coronary vasospasm induced by ergonovine is significantly enhanced in coronary arteries with endothelial dysfunction(Vanhoutte et al., 1989). Coronary artery tone is regulated by the net effects of various vasoconstrictor and vasodilator stimuli such as the autonomic nervous system, humoral factors and endothelium-derived vasoactive substances. Yasue et al.(1990) suggested that all coronary arteries in patients with variant angina are affected by endothelial injury or atherosclerosis, even though some of these arteries may appear angiographically normal. Thus, this diffuse atherosclerosis and endothelial dysfunction may play a major role in the pathogenesis of coronary spasm. It is easy to speculate that the generalized increase in basal tone may reflect abnormal vasoconstriction with diffuse endothelial injury or dysfunction induced by various intrinsic stimuli. However, previous data have been inconclusive as to whether basal coronary artery tone is elevated at the spastic and non-spastic sites in patients with vasospastic angina(Brown 1981 ; Hill et al., 1982 ; Hackett et al., 1987 ; Hoshio et al., 1989 ; Kaski et al., 1989, 1991). Thus, the present study was designed to assess whether basal coronary artery tone is elevated at the spastic and nonspastic sites, and to evaluate the responsiveness of epicardial coronary arteries to acetylcholine and ergonovine in patients with variant angina.

MATERIALS AND METHODS

Study patients

The study group was comprised of 92 patients ; 66 patients with variant angina, and 26 control subjects with chest pain undergoing diagnostic coronary angiography with provocation test. The 26 control subjects(20 men and 6 women with a mean age of 53 ± 10 years) had atypical chest pain and normal exercise test results but no provocation of coronary spasm by intracoronary acetylcholine(n=11) or intravenous ergonovine(n=15). The 66 patients with variant angina had typical episodes of chest pain at rest with angiographically documented coronary spasm. These patients were divided into 2 groups. Group 1 consisted of the 31 patients(28 men and 3 women with a mean age of 53 ± 11 years)with provoked coronary artery spasm by low dose of acetylcholine(intracoronary 20ug, A_1) or ergonovine(intravenous 50 ug, E_1). Group 2 consisted of the 35 patients(29 men and 6 women with a mean age of 54 ± 8 years) with provoked coronary artery spasm by high doses of acetylcholine(intracoronary 100ug, A_3) or ergonovine(intravenous cumulative dose 350ug, E_3). Patients who had had previous myocardial infarction, valvular heart disease or congestive heart failure were excluded from the study.

Disease activity is difficult to assess because electrocardiographic monitoring covers only brief periods and coronary spasm often causes silent myocardial ischemia. Therefore, we used the frequency of anginal pain relieved by sublingual nitroglycerin administration as an index of disease activity. After acetylcholine or ergonovine provocation, total or near total occlusion occurred at the coronary artery segment with more than 50 % luminal narrowing, it was defined as mixed disease.

Catheterization procedure

Antianginal drugs and smoking were discontinued at least 3 days before procedure, with the exception of sublingual nitrates. Coronary arteriography was performed with use of a femoral approach. An appropriate view that allowed clear visualization of the coronary artery was selected and used throughout the procedure. The distances from the X-ray focus to the patients and from the patients to the image intensifier were kept constant during the study. Heart rate, arterial pressure and a 12-lead ECG were continuously monitored.

1) Acetylcholine provocation

After coronary angiography was performed without premedication as a control, intracoronary acetylcholine was administered as a bolus injection with incremental doses of 20ug and 50ug in the right coronary artery, and 20, 50 and 100ug the in the left coronary artery every 4 minutes. Coronary angiography was performed immediately if typical chest pain or ECG changes indicating myocardial ischemia occurred after acetylcholine administration. Coronary artery spasm was defined as total or near total coronary artery constriction after acetylcholine with typical chest pain or ECG changes suggesting myocardial ischemia. In the absence of these symptoms, coronary arteriography was repeated 2 minutes later after each dose of acetylcholine administration.

2. Ergonovine provocation

After control coronary angiography was performed, intravenous ergonovine was administered as a bolus injection cumulatively with doses of 50, 100 and 200ug upto a total dose of 350ug. Coronary angiography was performed 3 minutes after each dose of ergonovine. When anginal pain or ECG changes occurred, coronary angiography was immediately performed. Coronary artery spasm was defined as ≧75 % coronary artery constriction after ergonovine with typical chest pain or ECG changes suggesting myocardial ischemia. If coronary artery spasm was confirmed, intracoronary nitroglycerin 200ug was administered.

Two minutes after intravenous nitroglycerin, coronary angiograms were again recorded in multiple views to assess atherosclerotic stenosis of the coronary arteries. Both acetylcholine and ergonovine provocation test were not performed in same patients because of different mechanism of action between acetylcholine and ergonovine.

Analysis of coronary angiogram

Serial measurements were taken at end-diastole in the 30' right anterior oblique projection of the left coronary artery and the 60' left anterior oblique projection of the right coronary artery using a computerized videodensitometer(Cardio Trace System). The coronary artery diameter(in millimeters) was calculated with reference to a 7F Judkin's catheter tip(2.3mm). Coronary artery diameter was measured in the proximal, middle and distal segments of the three major coronary artery branches and the left main trunk, as well as in the spastic segments, in which coronary spasm was provoked by ergonovine or acetylcholine. The intraobserver and interobserver correlations for coronary diameter measurement were $r=0.96(p<0.0001)$ and $0.93(p<0.001)$, respectively. The basal coronary artery tone and percent constriction produced by acetylcholine(Ach) or ergonovine(Erg) were calculated as follows;

$$\text{Basal coronary artery tone}(\%) = \frac{\text{Diameter after nitroglycerin} - \text{Baseline diameter}}{\text{Diameter after nitroglycerin}} \times 100$$

$$\text{Percent vasoconstriction by acetylcholine or ergonovine}(\%) = \frac{\text{Diameter after nitroglycerin} - \text{Diameter after Ach or Erg}}{\text{Diameter after nitroglycerin}} \times 100$$

In the control subjects, the basal coronary artery tone and the constrictive reponses to acetylcholine or ergonovine were examined in 10 segments and the mean values were used for analysis. In patients with variant angina, when the spastic segment was at the same site as 1 of the 10 divided nonspastic segments, the segment was excluded from the measurement of the nonspastic segment. Small coronary arteries(diameter < 1 mm after nitroglycerin) or segments overlapped by other branches were not analyzed.

Statistics

Values are expressed as mean value ± SD. We used the unpaired *t* test for comparison of basal coronary artery tone between the patient and control groups. For comparison of basal coronary artery tone between the spastic and nonspastic sites, the paired *t* test was used. To compare the dose-response relation with ergonovine or acetylcholine among patients with variant angina and control subjects, we used two-way analysis of variance with Bonferroni's test. For comparison of basal coronary artery tone between more than two groups(group 1, group 2 and control), an analysis of variance(ANOVA) was used. If a significant value was found, Scheffe's test for multiple comparisons was used to identify difference among groups. Values were considered to be statistically different when P was less than 0.05.

RESULTS

Clinical and angiographic characteristics

Disease activity defined by the frequency of anginal pain or the mean frequency per week was significantly higher in patients with provoked coronary artery spasm by low doses of acetylcholine(intracoronary 20ug) or ergonovine(intravenous 50ug)(Group 1) than that in patients with provoked coronary artery spasm by higher doses of acetylcholine or ergonovine(Group 2). The frequency of chest pain greater than 5 times

per week was 23 % in Group 1 and 8.5 % in Group 2($P<0.05$). The clinical patterns of chest pain, risk factors and rate of positive treadmill test were not different between the two groups(Table 1).

In 66 patients with variant angina, a total of 73 spastic segments and 246 nonspastic segments(124 sites in spasm-related artery ; 122 sites in non-spasm related artery) were analyzed. In 26 control subjects, 178 segments were analyzed. Spasm was observed in the right coronary artery in 30 patients, the left anterior descending coronary artery in 29 patients, the left circumflex artery in 13 patients and the left main trunk in 1 patient. In 44 patients with provoked spasm by acetylcholine, 36 patients had spasm in one major coronary artery, 6 had spasm in two, and 2 patients had spasm in three major coronary arteries. The prevalence of combined mixed disease and multivessel spasm, and significant ischemic electrocardiographic changes during the provocation were higher in Group 1 than in Group 2(Table 2).

Table 1. Clinical Profiles of 66 patients with Variant Angina.

	Group 1(n=31)	Group 2(n=35)
Age(years)	53±11	54±8
Sex(M/F)	28/3	29/6
Pain Characteristics		
Resting pain	30(97%)	31(87%)
Effort Pain	11(35)	11(31)
Nocturnal or morning chest pain	23(74)	21(60)
Frequency of pain (≧5 times/week)	7(23%)*	3(8.5%)
Mean frequency/week	2.4±1.9*	1.5±1.7
Risk Factors		
Smoking	23(74%)	21(60%)
Hypertension	8	12
Family history	1	4
Alcohol relation	3	4
Cholesterol(ml/dL)	179±79	192±37
Triglyceride(ml/dL)	187±184	154±93
HDL-cholesterol(ml/dL)	34±21	33±18
Positive Treadmill test	2/24	2/29

Group 1 : patients with provoked coronary spasm by low dose of acetylcholine (intracoronary, 20 μg) or ergonovine(intravenous 50 μg), Group 2 : patients with provoked coronary spasm by higher dose of acetylcholine(intracoronary, 100 μg) or ergonovine(intravenous cumulative dose of 350 μg). The asterisks denote that the frequency of chest pain as an index of disease activity was significantly greater in Group 1 than that in Group 2 ($P<0.05$).

Basal coronary artery tone

Segment diameter after nitroglycerin was similar in the contol and the patients groups(Table 3). Taking the entire group, the basal coronary tone in patients with variant angina was not increased compared to the control group(24 ± 12 vs 19 ± 17 %). However, the basal coronary artery tone at the spastic sites was

Table 2. Data from Catheterization Procedures.

	Group 1(n=31)	Group 2(n=35)
Provocation by Ach/Erg	21/10	23/12
ECG changes		
ST elevation	15(48%)	13(37%)
ST depression	6(20)	4(11)
Minimal changes	5(16)	3(9
No singnificant changes	5	15
Coronary Angiogram		
Normal	12(39%)	25(71%)
Fixed disease,	19(61%)*	10(29%)
<50%	16	8
>50% and <70%	3	2
Degree of stenosis(%)	32±13	34±17
Multi-vessel spasm	6/21(29%)*	2/23(9%)

*$P<0.05$, Ach : acetylcholine, Erg : ergonovine, ECG : electrocardiographic. The asterisks denote that a combined fixed disease and multivessel spasm were more prevalent in Group 1 than in Group 2 ($P<0.05$).

Table 3. Coronary Artery Diameter after Intracoronary Nitroglycerin Administration(mm).

Location	Control	Patients with Variant Angina
LMCA	4.29±0.11	3.87±0.93
LAD		
Proximal	3.57±0.13	3.60±0.15
Mid	3.22±0.8	2.96±0.63
Distal	2.38±0.17	2.78±0.41
RCA		
Proximal	4.01±0.15	4.20±0.22
Mid	3.68±0.16	3.70±0.13
Distal	3.02±0.15	3.41±0.16
LCX		
Proximal	3.20±0.11	3.32±0.30
Distal	2.58±0.65	2.78±0.71

LMCA : left main coronary artery, LAD : left anterior descending coronary artery, RCA : right coronary artery, LCX : left circumflex artery

Table 4. Basal Coronary Artery Tone and Vasoconstrictive Responses to Acetylcholine or Ergonovine(%).

	Spansm site			Nonspasm site				
	Basal	Response to		Basal	(SRA	Non-SRA)	Response to	
		Ach_1	Erg_1				Ach_1	Erg_1
Group 1	44±17*	99±2**	84±9**	22±14	26±14*	18±13	40±20*	37±18 *
Group 2	14±11	41±14	33±28	17±10	16±10	17±10	26±11	12±8 #
Control				19±17			27±12	13±10#

Ach_1 : intracoronary acetylcholine 20 μ g, Erg_1 : intravenous ergonovine 50 μ g, Basal : basal coronary artery tone, SRA : spasm-related artery, Non-SRA : nonspasm related artery. The asterisks denote that basal coronary artery tone(*P<0.05) and the magnitude of constrictive responses to acetylcholine or ergonovine (**P<0.01) at the spastic sites and nonspastic sites were significantly greater in Group 1 than those in Group 2 and the control subjects. The asterisks (#) denote that the responses to acetylcholine were constrictive responses, on the contrary, the responses to ergonovine were dilator responses(P<0.05).

significantly elevated in Group 1 in whom spasm was provoked by low doses of acetylcholine or ergonovine than that in Group 2(44 ± 17 vs 14 ±11 % respectively, P<0.05)(Fig. 1, Table 4). Similarly, the basal coronary artery tone at the nonspastic sites of spasm-related artery was also greater in Group 1 than that in Group 2(26 ± 14 vs 16 ± 10 % respectively, P < 0.05)(Table 4). However, the basal coronary artery tone of the non-spasm related artery was the same in both groups. In Group 1, the basal coronary artery tone was greater at the spastic than at the nonspastic site, but in Group 2, the basal coronary artery tone was not different at the spastic and nonspastic sites(Table 4). In comparison to the control group, the basal coronary artery tone was increased in Group 1 at the spastic and non-spastic sites, but there was no difference between Group 2 and the control group.

Vasoconstrictive response to acetylcholine and ergonovine

Intracoronary acetylcholine and intravenous ergonovine both produced vasoconstriction at the spastic and nonspastic sites in both Group 1 and Group 2(Table 4, Fig. 1). However, the magnitude of vasoconstrictive responses to acetylcholine at the nonspastic sites was greater in Group 1 than in Group 2(40 ± 20 vs 26 ± 11 %, P<0.05) or in the control group(40 ± 20 vs 27 ± 12 %, P<0.05). Similarly, the magnitude of vasoconstrictive response to intravenous ergonovine at the nonspastic sites was greater in Group 1 than in Group 2(37 ± 18 vs 12 ± 8 %, P< 0.05) or in the control group(37 ± 18 vs 13 ± 10 %, P<0.05)(Fig. 2, Table 4).

At nonspastic sites, the responses to a low dose of acetylcholine(intracoronary 20ug) were constrictive in Group 2(from 17 ± 10 to 26 ± 11 %, P<0.05) as well as in the control group(from 19 ± 17 to 27 ± 12 %, P<0.05). However, the low dose of intravenous ergonovine 50ug induced minimal insignificant dilation

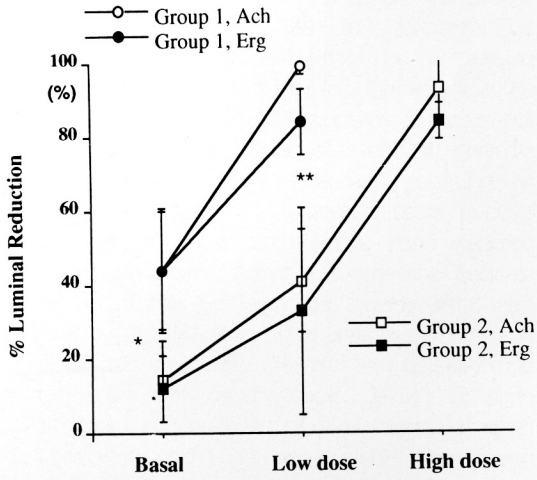

Fig. 1. Dose-response relation at the spastic sites(n=73) in patients with variant angina. Group 1(n=31) : patients with provoked coronary spasm by low dose of acetylcholine(intracoronary, 20ug) or ergonovine(intravenous 50ug), Group 2(n =35) : patients with provoked coronary spasm by higher dose of acetylcholine(intracoronary, 100ug) or ergonovine(intravenous cumulative dose of 350ug), Ach : acetylcholine, Erg : ergonovine, Basal : basal coronary artery tone, Low dose : intracoronary acetylcholine 20ug or intravenous ergonovine 50ug, High dose : intracoronary acetylcholine 100ug or intravenous cumulative dose of ergonovine 350ug. The asterisks denote that basal coronary artery tone(*P<0.05) and the magnitude of constrictive responses to acetylcholine or ergonovine(**P<0.01)were significantly greater in Group 1 than those in Group 2.

of the nonspatic sites in Group 2(from 17 ± 10 to 12 ± 8 %) and in the control group(from 19 ± 17 to 13 ± 10 %)(Table 4, Fig. 2).

DISCUSSION

The results of previous studies have been inconclusive as to whether basal coronary artery tone is elevated at the coronary artery segments where spasm is provoked by ergonovine in patients with variant angina(Brown 1981 ; Hill et al., 1982 ; Hackett et al., 1987 ; Hoshio et al., 1989 ; Kaski et al., 1989, 1991). Hill et al.(1982) first reported that basal coronary artery tone was greater at spastic sites compared to nonspastic sites in patients with variant angina. Hoshio et al.(1989, 1991) reported the same finding and also noted that coronary artery tone at the nonspastic sites was also significantly greater in patients with variant angina than in control subjects. In contrast, some investigators observed that the basal coronary artery tone did not significantly differ at the spastic and nonspastic sites in patients with variant angina(Hackett et al., 1987 ; Kaski et al., 1991).Several possibilities such as the residual effects of antianginal drugs, the diurnal variation of coronary artery tone and the effects of antianginal drugs or discontinuation of smoking, may have accounted for the different results among these previous studies(Yasue et al., 1979). To exclude these nonspecific influences to the basal coronary artery tone, in our study all patient had stopped smoking and taking antianginal drugs at least 3 days before the procedure, with the exception of sublingual nitrates. Kuga et al.(1993) have already demonstrated that smoking withdrawal did not influence the basal coronary artery tone, and higher doses of ergonovine did not blunt the response to nitroglycerin. However, in the previous studies, all patients with variant angina were grouped together, and the data were not analyzed according to the dose of drugs required to provoke spasm or the clinical activity of the disease.

Acetylcholine caused endothelium-dependent relaxation through the activation of endothelial muscarinic cholinergic receptors in various animals and human coronary arteries in vitro(Furchgott 1983 ; Kalsner 1985). In pathologic states such as hypercholesterolemia, hypertension, and atherosclerosis, the vasodilator responses to acetylcholine in a specific dose range is lost and replaced by vasoconstrictive responses(Furchgott 1983 ; Bossaller et al., 1984 ;

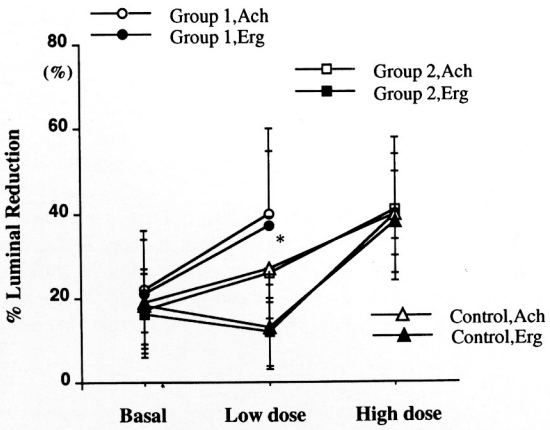

Fig. 2. Dose-response relation at the nonspastic sites(n=73) in patients with variant angina and the control subjects. Control(n=26) : control subjects without provoked coronary spasm, Ach : acetylcholine, Erg : ergonovine, Basal : basal coronary artery tone, Low dose : intracoronary acetylcholine 20ug or intravenous ergonovine 50ug, High dose : intracoronary acetylcholine 100ug or intravenous cumulative dose of ergonovine 350ug. The asterisks denote that the magnitude of constrictive responses to acetylcholine or ergonovine(*$P<0.05$)were significantly greater in Group 1 than those in Group 2 and the control subjects.

Habib et al., 1984 ; Harrison et al., 1987).This paradoxical vasoconstriction induced by acetylcholine appears to be related to endothelial dysfunctions-(Maseri and Chierchia, 1982 ; Ludmer et al., 1986 ; Werns et al., 1989 ; Vita et al., 1990).

The contraction elicited by ergonovine in porcine coronary arteries is mediated by activation of 5-HT(hydroxytryptamine)$_2$ serotonergic receptors with little contribution of α_1-adrenergic receptors(Muller-Schweinitzer 1980 ; Brazenor and Angus, 1981 ; Griffith et al., 1984 ; Shimokawa et al., 1989).Ergonovine also caused the release of endothelium-derived relaxing factor(EDRF ; most likely nitric oxide) through the activation of endothelial 5-HT$_1$ serotonergic receptors with small contributions of α_2-adrenergic receptors on the endothelium in the rabbit aorta and in the porcine coronary arteries(Griffith et al., 1984, Shimokawa et al., 1989). Augmented contractions to ergonovine have been reported in various atherosclerotic animal models(Henry and Yokoyama, 1980 ; Yokoyama et al., 1983 ; Kawachi et al., 1984 ; Shimokawa et al., 1985 ; Egashira et al., 1992). These ergonovine induced augmented vasoconstrictions may also be related to the hyperreactivity of vascular smooth muscle cells by

activation of serotonergic receptors other than the 5-HT_2 serotonergic receptor, as well as endothelial dysfunction(Yokoyama et al., 1983).

Patients in whom the spasm was provoked by low doses of acetylcholine or ergonovine

The main findings of our study are that basal coronary artery tone and the magnitude of constrictive responses to acetylcholine or ergonovine are greater at both the spastic and nonspastic sites of the spasm-related artery in patients with variant angina, in whom, the spasm was provoked by low doses of these drugs, but not in the other group, which is, consistent with the results of Kaski et al.(1989). However, the basal coronary artery tone and the magnitude of constrictive responses to these drugs of nonspasm-related artery were not exaggerated even in these patients. These findings suggest that endothelial dysfunctions may be limited to the spasm related coronary arteries in these patients. Moreover, the level of generalized vasoconstrictive stimuli may determine the basal coronary artery tone as well as the sensitivity to acetylcholine or ergonovine at the spastic sites in patients with variant angina(Kuga et al., 1993). According to this hypothesis, the basal coronary artery tone is elevated by enhanced vasoconstrictive stimuli, and the coronary vasospasm may result from locally exaggerated responses to the vasoconstrictive stimuli of the spasm related arteries, in which endothelial dysfunction and superimposed local hyperreactivity of vascular smooth muscles may be present. It was also found that this subgroup of patients with elevated basal coronary artery tone tended to have the clinical characteristics of high disease activity, combined mild fixed diseases and multivessel spasm.

Patients in whom the spasm was provoked by high doses of acetylcholine or ergonovine

The basal coronary artery tone and the magnitude of constrictive responses of nonspasm sites were not elevated compared to the normal controls. In these patients, the generalized vasoconstrictive stimuli may be relatively weak and endothelial function may be preserved in the spasm related artery, requiring a high dose of ergonovine or acetylcholine to induce coronary vasospasm(Egashira et al., 1992). These findings also suggest that localized hyperreactivity of vascular smooth muscles plays a major pathophysiologic role in the occurrence of coronary vasospasm in these patients. Our findings, that basal coronary artery tone and the sensitivity to these two drugs at the spasm site vary among patients with variant angina are consistent with the results of Matsuda et al.(1986). The dose of acetylcholine or ergonovine required for provocation of spasm correlated negatively with basal coronary tone at the spastic site. An unexplained finding of our study was a paradoxical response to low doses of acetylcholine and ergonovine. Specifically, the "low dose" acetylcholine induced coronary constriction whereas the "low dose" ergonovine induced slight vasodilation. In the present study, we used different concentrations of these two drugs by different administration routes for the provocation of clinically relavant coronary spasm. We assumed that intracoronary injection of acetylcholine 20ug may be comparable to the in vivo concentration of 10^{-6}M, and intravenous ergonovine 50ug may be comparable to the concentration of 3×10^{-8}M.

However, it is possible that the real in vivo concentration of "low dose" acetylcholine was much higher than that of ergonovine to induce a similar physiological response. Thus, the paradoxical response to these two drugs may be related to the endothelium dependent relaxing factor's response to the relatively smaller dose of ergonovine(Griffith et al., 1984 ; Shimokawa et al., 1989).

In summary, the basal coronary artery tone of the spasm related artery in the patients with variant angina requiring higher doses of acetylcholine or ergonovine was not increased compared to the control group. However, in the patients with higher disease activity, requiring smaller doses of acetylcholine or ergonovine, the basal coronary tone of the spasm related artery was increased compared to the other group as well as the control group. These findings suggest that increased generalized vasoconstrictive stimuli and enhanced vasoconstrictive responses associated with endothelial dysfunction of the spasm related artery as well as localized hyperreactivity of vascular smooth muscles at the spastic sites may play the major pathophysiologic roles in coronary spasm. However, in the patients with lower clinical activity(requiring larger doses of acetylcholine or ergonovine to induce coronary spasm), there may be weaker vasoconstrictive stimuli and it may not be related to the enhanced constrictive responses at the basal coronary tone of the spasm related artery at both spastic and nonspastic sites were not elevated.

Therefore, in these patients, localized hyperreactivity of vascular smooth muscle at the spastic sites may be the main pathophysiologic mechanism.

Limitations of this study

Acetylcholine or ergonovine provocation tests were performed to document coronary vasospasm for the diagnosis of variant angina. Thus, this study was not designed to evaluate the degree of endothelial dysfunction in patients with variant angina prospectively. Futhermore, these two drugs were administered in different doses, different routes and manners. Thus, the final real concentrations of each drug in vivo could be quite different from the values we intended to achieve. To evaluate the degree of endothelial dysfunction in patients with variant angina, studies using constant infusion of these drugs at varying concentrations would be required.

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