RELATIONSHIP BETWEEN THE CORONARY DIAMETER AND OCCURRENCE OF VASOSPASTIC ANGINA IN PATIENTS WITH NORMAL CORONARY ARTERIES

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Coronary artery diameters were measured after various interventions in 30 patients without angina pectoris (group 1) and in 15 with angina pectoris (group 2: rest, or rest and effort angina) who had normal coronary arteries. The coronary artery diameters were significantly smaller in many coronary segments in group 2 than in group 1 during a control state, after exercise and ergonovine, but became nearly identical after isosorbide dinitrate in both groups. Patients in group 1 had diffuse narrowing but no focal vasoconstriction after ergonovine and all the segments had a diameter of more than 50% of that after isosorbide dinitrate. The change of coronary artery diameter in group 2 patients who had no vasospasm by ergonovine was the same as that in group 1. Patients in whom vasospastic angina was induced had local vasoconstriction or severe diffuse narrowing (< 45%). These results indicate that angina pectoris patients with normal coronary arteries had an acceleration of coronary arterial basal tone, but vasospastic angina pectoris was not induced just by the general response of the coronary artery to various interventions in addition to the accentuated basal tone. For vasospastic angina to occur, local abnormal response to various interventions must be present.

CORONARY arteriosclerosis¹⁻³ has long been recognized as the cause of ischemic heart disease. However, coronary arterial spasm⁴⁻¹¹ has also attracted attention as another significant cause. Although various neural^{10,12-14} and humoral¹⁵⁻²⁰ mechanisms have been proposed, the genesis of coronary spasm is as yet undefined. Recently, local nonspecific hypersensitivity of the coronary vessels to diverse stimuli^{21,22} was suggested as the mechanism underlying coronary

spasm. The purpose of this study was to clarify 1) the relation between normal coronary tone and coronary spasm and 2) the role of local factors in the occurrence of coronary spasm by examining the change of coronary diameters after various interventions in patients without coronary stenosis.

METHOD

Patient selection: Forty-five patients with chest pain and normal coronary arteries (< 20% organic stenosis) were studied. The patients were divided into two groups based on clinical information: Group 1 comprised 30 patients (20 men and 10 women with mean age of 50.7 ± 9.2

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years) with no evidence of angina pectoris. Group 2 (Table I) comprised 15 patients (13 men and 2 women with mean age of 50.4 ± 9.7 years) who were diagnosed as having rest angina, or rest and effort angina in our hospital by

TABLE I CLINICAL FINDINGS IN GROUP 2

Patient	Age (yr)	Sex	Angina Pectoris	ST Change
1	38	M	R	↓
2	46	M	R	↓
3	49	M	R	↓
4	53	M	R	↓
5	51	M	R + E	↓
6	62	F	R	↓
7	53	M	R	↓
8	37	M	R + E	↓
9	57	M	R + E	↓
10	32	M	R	↑
11	62	M	R	↑
12	54	M	R	↑
13	56	M	R	↑
14	42	F	R	↑
15	64	M	R	↑

R = at rest; E = on effort; ↓ = elevation;
↑ = depression

Holter monitor electrocardiogram, heart corder, exercise test, scintigraphic evaluation or coronary angiography. Twelve patients had rest angina, including 6 variant angina; 3 patients had rest and effort angina. The patients with syndrome X were excluded from this study. All had a right dominant coronary artery.

Procedures: Medical treatment was interrupted 2 days before the coronary arteriographic examination and the study was done in the morning. Control coronary arteriograms of the left coronary artery in the right anterior oblique (30°) projection and of the right coronary artery in the left anterior oblique (60°) projection were performed by the Sones technique. A bicycle exercise test was done in the supine position with a work load of 35 watts for 3 min and second coronary arteriograms were obtained immediately thereafter. After heart rate, blood pressure, electrocardiogram and the cardiac output had returned to the control state, 0.02–0.2 mg of ergonovine maleate was injected into the Valsalva sinus. If neither chest pain nor ST change was induced after 4 min, 0.02–0.2 mg of ergonovine maleate was added (maximum dose; 0.4 mg). Third coronary arteriograms were obtained immediately after chest pain and/or ST change of the electrocardiogram, or 4 min after last injection in patients without those changes. Iso-sorbide dinitrate (5 mg) was injected into the

Fig.1. Schematic diagram of the right and left coronary artery, describing the locations where measurements were made. LCA = left coronary artery; RCA = right coronary artery.

TABLE II HEMODYNAMIC DATA AFTER VARIOUS INTERVENTIONS

	Heart Rate (beat/minute)				
	C	Ex	Ev	ID	
Group 1	72 ± 10	108 ± 14**	80 ± 11**	83 ± 13**	] NS
Group 2	68 ± 12	113 ± 22**	76 ± 18*	75 ± 10*	
	Arterial Mean Pressure (mmHg)				
	C	Ex	Ev	ID	
Group 1	104 ± 15	114 ± 14*	109 ± 17	104 ± 15	] NS
Group 2	109 ± 11	126 ± 17*	116 ± 16	103 ± 19	
	Double Product (mmHg/minute)				
	C	Ex	Ev	ID	
Group 1	10398 ± 2449	17685 ± 3300**	11880 ± 2723*	11365 ± 2843	] NS
Group 2	10307 ± 2037	17794 ± 4943**	10542 ± 2503*	9498 ± 1936	
	Left Ventricular End-diastolic Pressure (mmHg)				
	C	Ex	Ev	ID	
Group 1	12.1 ± 5.0	18.9 ± 7.3**	15.7 ± 6.2*	8.8 ± 4.5**	] NS
Group 2	14.6 ± 3.4	18.3 ± 5.9	17.4 ± 6.0	8.9 ± 7.0*	

* $p < 0.05$; ** $p < 0.01$ (versus control); C = control state; EV = ergonovine; EX = exercise; ID = isosorbide dinitrate; NS = not significant.

Valsalva sinus and fourth arteriograms were performed one minute later. A standard 12-lead electrocardiogram was continuously recorded using a radiolucent carbon electrode. Left ventricular end-diastolic pressure was monitored by a Sones catheter and cardiac output was obtained by a Swan-Ganz catheter. Informed consent was obtained from each patient before the study.

Coronary artery diameter measurement: Cine films were magnified 8 to 10 times and coronary artery diameters were measured in end-diastole using an electronic caliper (Model/EC-1, Standhill) by 3 mutually blinded observers. The measurement of coronary arteries was done in 10 segments (AHA classification), i.e., the middle part of segments 1, 2, 3, 5, 6, 7, and 11 (or 13 in the case where the obtuse marginal branch originated from the extreme proximal portion of the left circumflex artery) and the proximal part of segments 8, 12 and 14 (Fig. 1). If a segment was too small or too short to measure, it was excluded from the measurement. The location of focal vasoconstriction was measured separately. The tip of the Sones catheter positioned within the right and the left coronary artery

ostium was measured and actual coronary diameters were calculated.

Coronary artery diameter compared to those after isosorbide dinitrate: As the size of coronary artery diameter after isosorbide dinitrate was nearly identical in both groups, the diameter after various interventions in relation to the diameter after isosorbide dinitrate was calculated. The percentage of the control state diameter = diameter at control state / diameter after isosorbide dinitrate $\times 100$, the percentage diameter after exercise = diameter after exercise / diameter after isosorbide dinitrate $\times 100$ and the percentage diameter after ergonovine = diameter after ergonovine / diameter after isosorbide dinitrate $\times 100$. The average coronary diameter of segments 1, 2 and 3 (right coronary artery), segments 6, 7 and 8 (left anterior descending artery) and segments 11, 12 and 14 (left circumflex artery) were calculated.

Statistical analysis: The data were expressed as mean $\pm$ standard deviation. Student's t-test and a paired t-test were used to compare the hemodynamics of the two groups. Analysis of the variance of repeated measurements and

TABLE III CORONARY DIAMETERS (mm) AFTER VARIOUS INTERVENTIONS

Segment	Group 1				
	n	C	Ex	Ev	ID
1	30	3.01 ± 0.63	3.09 ± 0.56	2.68 ± 0.54	3.50 ± 0.72
2	30	2.74 ± 0.45	2.73 ± 0.40	2.34 ± 0.38	3.21 ± 0.55
3	30	2.53 ± 0.50	2.50 ± 0.38	2.12 ± 0.40	2.87 ± 0.55
5	27	3.61 ± 0.54	3.85 ± 0.63	3.60 ± 0.63	4.09 ± 0.66
6	30	3.09 ± 0.64	3.09 ± 0.51	2.79 ± 0.51	3.49 ± 0.63
7	30	2.36 ± 0.70	2.35 ± 0.58	2.10 ± 0.58	2.75 ± 0.70
8	30	1.79 ± 0.35	1.89 ± 0.34	1.64 ± 0.32	2.14 ± 0.38
11 (13)	30	2.53 ± 0.57	2.64 ± 0.55	2.38 ± 0.54	3.01 ± 0.74
12	16	1.69 ± 0.59	1.75 ± 0.53	1.63 ± 0.51	2.15 ± 0.67
14	29	1.71 ± 0.46	1.80 ± 0.47	1.58 ± 0.36	2.02 ± 0.52

Segment	Group 2				
	n	C	Ex	Ev	ID
1	15	2.54 ± 0.44	2.64 ± 0.55	2.08 ± 0.79	3.29 ± 0.54
2	15	2.29 ± 0.40	2.28 ± 0.43	1.77 ± 0.72	3.10 ± 0.56
3	15	2.17 ± 0.38	2.09 ± 0.52	1.79 ± 0.55	2.82 ± 0.55
5	13	3.44 ± 0.91	3.53 ± 0.97	3.44 ± 1.02	3.81 ± 0.94
6	15	2.43 ± 0.63	2.49 ± 0.68	2.14 ± 0.82	2.90 ± 0.57
7	15	2.07 ± 0.41	1.91 ± 0.44	1.57 ± 0.39	2.41 ± 0.46
8	15	1.60 ± 0.36	1.57 ± 0.31	1.39 ± 0.34	2.07 ± 0.37
11 (13)	12	2.20 ± 0.44	2.27 ± 0.53	1.93 ± 0.64	2.74 ± 0.42
12	11	1.65 ± 0.30	1.72 ± 0.45	1.52 ± 0.38	2.10 ± 0.49
14	13	1.54 ± 0.25	1.68 ± 0.42	1.44 ± 0.42	2.09 ± 0.53

Comparison Among Various Interventions (group 1 and group 2 in common except for segment 8)

Segment	C-Ex	C-Ev	E-ID	Ex-Ev	Ex-ID	Ev-ID
1	NS	**	**	**	**	**
2	NS	**	**	**	**	**
3	NS	**	**	**	**	**
5	*	NS	**	**	**	**
6	NS	**	**	**	**	**
7	NS	**	**	**	**	**
8 [group 1	NS	*	**	**	**	**
group 2	NS	*	**	NS	NS	NS
11 (13)	NS	**	**	**	**	**
14	NS	*	**	**	**	**

Comparison Between Group 1 and 2

Segment	C	Ex	Ev	ID
1	*	*	*	NS
2	**	**	**	NS
3	NS	NS	NS	NS
5	NS	NS	NS	NS
6	**	**	**	NS
7	*	*	*	NS
8	*	*	*	NS
11 (13)	NS	NS	NS	NS
14	NS	NS	NS	NS

The location of focal vasoconstriction in group 2 was excluded from measurement. * $p < 0.05$; ** $p < 0.01$; C = control state; Ev = ergonovine; Ex = exercise; ID = isosorbide dinitrate; NS = not significant.

Fig. 2. Coronary artery diameter compared to those after isosorbide dinitrate. The location of focal vasoconstriction in group 2 was excluded from estimation. $\circ$ = group 1; $\bullet$ = group 2; C = control state; Ev = ergonovine; Ex = exercise; ID = isosorbide dinitrate; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

Bonferroni's multiple comparison were used to compare values after various interventions. A p value < 0.05 was considered significant. Segment 12 was excluded from analysis due to a lack of data.

RESULTS

Hemodynamic data (Table II): There was no significant difference in heart rate, mean arterial pressure, double product or left ventricular end-diastolic pressure between groups 1 and 2 during all interventions.

Coronary artery diameters (Table III): The size of the coronary artery diameter after exercise did not change significantly compared with the control state except for segment 5 in both groups. The coronary artery diameter in segment 5 increased significantly after exercise. The coronary artery diameter after ergonovine was smallest for all segments but segment 5. The coronary artery diameter after isosorbide dinitrate was largest in all segments for both groups except for segment 8 in group 2.

When the coronary artery diameters of the two groups after various interventions were compared, group 2 (except for segments 3, 5, 8 and 14) had significantly smaller coronary artery

diameters than group 1 during the control state, after exercise or after ergonovine. There was no significant difference in the coronary artery diameters after isosorbide dinitrate in the two groups.

Coronary artery diameters compared to those after isosorbide (Fig. 2): The average percentage diameter of 3 coronary vessels was 87 ± 11 , 86 ± 12 and $84 \pm 12\%$ in group 1, and 77 ± 14 , 82 ± 13 and $80 \pm 12\%$ in group 2 (right coronary artery, left anterior descending artery and left circumflex artery, respectively) during the control state. The percentage diameters after various interventions showed similar changes except for segment 5. The minimum value in all segments in group 1 was 51% which was seen after ergonovine and only 9 (3.2%) of 282 segments after ergonovine had values ranging from 51 to 59%.

Detailed data of coronary artery diameter after ergonovine in group 2 (Table I, Table IV): The induction rate of vasospastic angina by ergonovine maleate in group 2 was 66.7%. Patients 1 to 5 had ST depression during angina pectoris but it was not induced by ergonovine during catheterization. Diffuse narrowing over 1 to 3 segments was observed but focal vasoconstriction did not occur in these patients. A minimum value of the segment with diffuse narrowing was

TABLE IV PERCENTAGE DIAMETER OF EACH SEGMENT AFTER THE ADMINISTRATION OF ERGONOVINE MALEATE FOR GROUP 2

Patient	Segment										ST Change after Ergonovine
	1	2	3	5	6	7	8	11 (13)	12	14	
1	70	73	83	87	77	52	63	74	—	78	no change
2	69	57	70	79	77	74	53	58	65	83	no change
3	58	45	55	52	53	61	67	59	—	71	no change
4	81	68	67	—	66	70	70	—	63	49	no change
5	86	61	69	93	98	54	59	99	56	73	no change
6	69 (29)	69	67	113	109	87 (67)	100 (57)	66	101	69	slight ST ↓ V ₅₋₆
7	65	72	72	98	86	65	61	60	—	64	ST ↓ V ₆ , <i>junc</i> ST ↓ V ₄₋₅
8	74 (36)	76	90	45	56	58	67	59	69	—	ST ↓ I, II, III, aV _F , V ₄₋₆
9	69	22 (5)	23	93	81	57 (39)	63	79	71	62	ST ↑ II, III, aV _F
10	75	74	80	98	52	69 (44)	84	70	70	64	ST ↑ V ₁₋₄
11	78 (20)	35 (31)	37 (30)	87	63	62	58	67	71	71	ST ↑ II, III, aV _F
12	25 (0)	?	?	—	92	80	72	—	82	—	ST ↑ II, III, aV _F
13	49	10	63	93	106	86	76	94	78	84	ST ↑ II, III, aV _F
14	63	63	59	91	19	51	59	—	83	89	ST ↑ V ₁₋₃
15	34	(0)	?	99	99	59	55	49	—	(0)	ST ↑ II, III, aV _F

() = focal vasoconstriction; ↑ = elevation; ↓ = depression; ? = not determined; — = not measured; *junc* = junctional.

45% in the right coronary arteries. Three (patients 6 to 8) of the 10 patients with ergonovine-induced vasospastic angina had ST depression and the other 7 patients (patients 9 to 15) had ST elevation. Focal vasoconstriction was observed in 7 patients, including 2 patients with ST depression and 5 patients with ST elevation. Patient 13 and 14 with ST elevation did not have focal vasoconstriction but severe diffuse narrowing (10% and 19%, respectively). Patient 8 had angina pectoris during exercise only in the early morning but neither chest pain nor ST change was induced by exercise during catheterization. In this patient, the coronary artery diameter of segment 5 after exercise was 58% which became 45% after ergonovine when vasospastic angina was induced. Patient 7 had ST depression by ergonovine but we could not find the cause by coronary arteriography.

DISCUSSION

In 1979 Yasue et al²³ reported circadian

variation of the large coronary tone in patients with Prinzmetal's variant angina. They observed that the tone of the large coronary artery was high and had a smaller diameter in the early morning, while having low tone with larger diameter in the afternoon. Further, the changes of the coronary diameter with various drugs,²⁴⁻³¹ cold pressor test^{32,33} and exercise³⁴ have been reported. In previous studies,²⁷⁻³⁰ various interventions were given separately to the patients with atypical chest pain or effort angina pectoris. In the present study, various interventions were given to the same patients to observe the intra-individual change in the coronary diameter. Patients without coronary stenosis were selected in order to investigate the pure change of the coronary arterial tone. The coronary artery diameters of many segments in group 2 were significantly smaller than those in group 1 during the control state but the difference disappeared after isosorbide dinitrate. It is unlikely that patients of angina pectoris with normal coronary artery have anatomically small coronary arterial

size. Thus, our results suggest that the basal tone is high in group 2 and had an increased response to nitrates.³⁵

The increase of coronary blood flow during exercise³⁶ results from the dilatation of precapillary resistance vessels mediated by myocardial metabolites. Large coronary vessels are not responsive to the alteration in myocardial metabolisms³⁷ and a previous study³⁴ indicated that coronary artery diameter was not influenced by exercise. In our study, a significant increase of coronary artery diameter was observed in segment 5 after exercise. The reason why the increase of the diameter occurred only in segment 5 is unclear, but this phenomenon fits the purpose of maintaining sufficient coronary flow during exercise.

Although ergonovine decreased coronary artery diameter in most of the segments in group 1, each segment had a different response to ergonovine, which suggests that the response to ergonovine varies with the location. However, focal vasoconstriction did not occur in these patients and the percentage diameter was never below 50%. Therefore, as reported by Feldman,²⁶ it is adequate to determine a boundary between the normal and abnormal response to ergonovine maleate to be 50%.

The degrees of change in coronary artery diameter from the control state to exercise and from exercise to ergonovine in the two groups were nearly identical except for the site of vasoconstriction. The response of the coronary artery in general to various interventions was not specific in group 2 and the smaller coronary artery diameters after exercise and ergonovine in group 2 when compared to group 1, were due to the smaller size of the coronary artery diameter in the control state.

The provocation of spasm by ergonovine may raise a controversy. The most important effects of the ergot alkaloids are actions on the central nervous system and direct stimulation of smooth muscle.³⁸ To observe the change of right and left coronary artery diameter simultaneously under the same condition, we injected ergonovine maleate into the aorta. Therefore, we can not exclude the effect of ergonovine maleate on the central nervous system. However, ergonovine maleate, an amine ergot alkaloid, has no adrenergic blocking activity—unlike other ergot alkaloids.³⁸ The precise mechanism of action with respect to the arterial wall is not completely understood but the study of transplanted heart

by Cipriano²⁹ and ergonovine-induced spasm of a coronary bypass graft by Martin³⁹ indicate that arterial contraction by ergot alkaloid is mediated by a receptor on the arterial wall⁴⁰ which is independent of neural control extrinsic to the heart. We believe that the effect of ergonovine maleate on the central nervous system has no significant effect on the coronary artery system.

The provocation of vasospastic angina by ergonovine is not always reproducible⁴¹ and it is affected by a slight variation of the coronary arterial tone with the time of day,²³ periodicity of the spasticity and the response to various pharmacologic agents.⁴² However, we could determine the condition of the coronary artery when vasospastic angina occurred, by observing the cases with or without vasospastic angina after ergonovine. Patients in group 2 who did not have ST change after ergonovine showed diffuse narrowing of more than 45%, but focal vasoconstriction was never observed. Hackett et al²² reported no significant difference in the reduction of coronary caliber between the non-spastic vessels in patients with variant angina and vessels in patients without variant angina after ergonovine. A similar effect was noted with our patients in group 1 and group 2 without ST change after ergonovine. Change in local factors or the increase of the basal coronary arterial tone may be considered as the mechanisms for the occurrence of rest angina in group 2 patients who had no anginal attack after ergonovine. Most patients with ST change caused by ergonovine had focal vasoconstriction or severe diffuse narrowing of less than 45% in the responsible site of ischemia. These results indicate that a percentage diameter of about a 45% after ergonovine is considered to be a critical point for the genesis of vasospastic angina. Thus, a local factor was responsible for the genesis of vasospastic angina. This result was consistent with the studies by Kaski et al²¹ who suggested that in patients with variant angina, a local nonspecific supersensitivity rather than abnormal specific agonist-receptor interaction plays a major role in the genesis of coronary arterial spasm, and of Hackett et al²² who reported that ergonovine caused coronary spasm by direct local effect, which seems to be caused by localized arterial hyperreactivity rather than supersensitivity.

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