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Temporal variability and correlation with geometric parameters in vasospastic angina: a quantitative angiographic study

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Long-term changes in vasocontractility were examined in 23 coronary segments from 20 patients with variant angina using computer-based quantitative coronary angiography and ergonovine provocation tests repeated at an interval of 42 ± 14 months. Measurements of vasospasticity at the sites of fixed stenoses were compared with values predicted by an elementary geometric theory based on the assumption that the cross-sectional area of a vessel wall is constant regardless of its state of vasoconstriction. While all patients were symptomatic initially, only 11 remained symptomatic at follow-up. At the initial provocation test, the response was correctly predicted in four segments, was lower than expected in one, and was stronger in 18. At follow-up, only one of the four segments in which the response had been initially predicted correctly again showed the predicted response and the remaining three showed a response weaker than expected; the one segment which was initially hypocontractile remained hypocontractile at follow-up; and of the 18 segments which were initially hypercontractile, 12 exhibited hypercontractility again, four had the predicted value and the remaining two showed hypocontractility. In only one of 23 segments did the geometric theory predict the behaviour of vasospasticity at the site of fixed stenosis on both tests. Vasospastic responsiveness is a dynamic process demonstrating temporal variability and is not directly predicted by geometric theory.

Introduction

Coronary vasospasticity plays an integral role in the genesis of variant angina[1–8], but the precise mechanism of spasm at sites of fixed coronary stenosis remains undetermined and proposed theories have included hypersensitivity to either vasoactive agents or parasympathetic tone. It has been proposed that the coronary spasm of variant angina is due to the amplification of normal vasoconstriction at sites of atheromatous luminal encroachments, the degree of vasoconstriction being related to the severity of encroachments (the geometric theory)[9]. The present study was performed to determine the applicability of the geometric theory to the coronary spasm of patients with variant angina and to assess the variability of coronary spasm over time by computer-based quantitative coronary angiography. We assessed vasocontractility in 20 patients with variant angina by measuring the maximal changes in coronary arterial diameter induced by repeated ergonovine provocation tests. Using elementary geometric principles, we calculated the vasospastic changes that might be expected to occur at sites of fixed coronary stenosis on the basis of proportional vasomotion in normal proximal reference segments.

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Methods

PATIENT SELECTION AND VASOMOTOR TONE TESTING

Twenty patients, admitted to Anjo Kosei Hospital (Anjo, Japan) who met the following criteria of variant angina were included in the present study: (1) chest pain at rest; (2) pain relief immediately following the administration of sublingual nitroglycerin; (3) no subsequent evidence of myocardial infarction and (4) coronary spasm associated with chest pain and ischaemic ECG changes provoked by ergonovine during angiography[10–13]. The study was approved by the hospital's committee on human research and fully informed written consent was obtained from each patient prior to each examination. The follow-up angiography and provocation test were performed to estimate progression of atherosclerosis as well as vasospastic activity and to provide information on the necessity to continue on long-term medication[14,15]. Progression of coronary stenosis was defined as progression to luminal narrowing of 30% or more after administration of isosorbide dinitrate (ISDN)[13]. After control angiograms of the

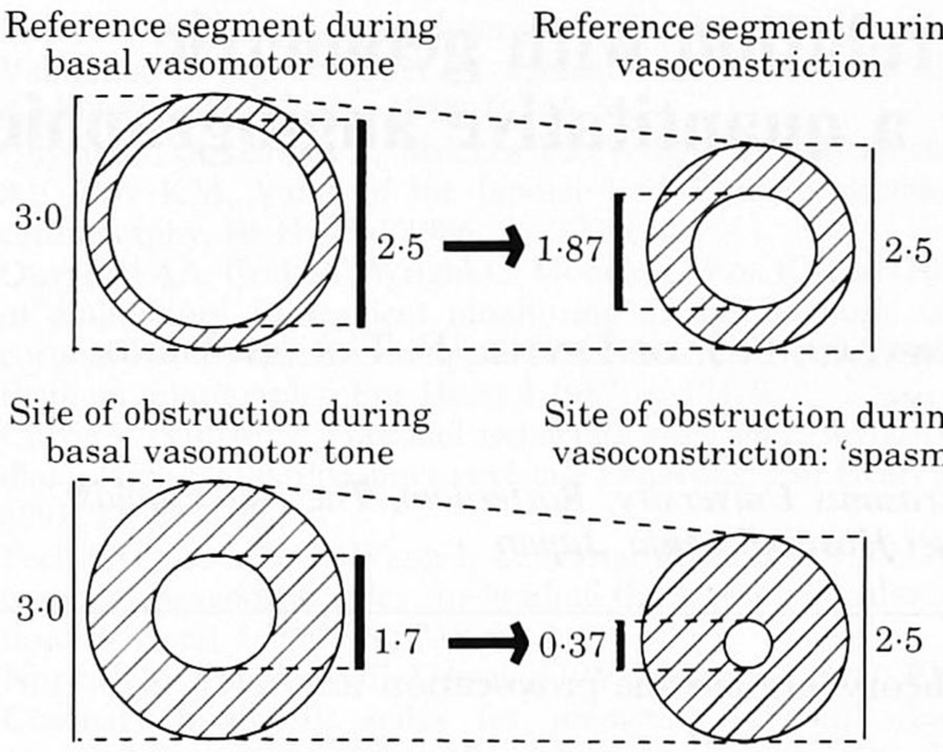

Figure 1 Contribution of vascular wall thickening to luminal narrowing during coronary vasoconstriction. The basic concept of the geometric theory: (1) the transverse cross-sectional area of a vessel wall is constant regardless of its state of constriction; (2) the constriction of the vessel outer diameter at the reference and obstruction segments is identical — thus, when the luminal diameter at the reference segment constricts from 2·5 mm to 1·87 mm, the luminal diameter at the site of obstruction constricts from 1·7 mm to 0·37 mm, producing 'spasm'.

right and left coronary arteries had been obtained, 0·2 mg ergonovine maleate was administrated intravenously by a rapid bolus injection. Heart rate and aortic pressure were monitored continuously, and 12-lead ECGs were recorded at 30 s intervals. Whenever chest pain or significant ST segment changes were observed, selective coronary angiograms were immediately performed. Coronary vasospasm was relieved by the intracoronary administration of 2 mg to 5 mg ISDN. Radiographic projections were identical during the sequential angiographic studies.

QUANTITATIVE ANGIOGRAPHIC ANALYSIS SYSTEM

Arterial dimensions were measured at specific distances from identifiable branch points in end-diastolic frames during the control state, after the administration of ergonovine and after the administration of ISDN. The cinefilms obtained were analysed off-line with the new version of the Coronary Angiography Analysis System (CAAS), which has recently been validated by in-vitro and in-vivo studies[16].

GEOMETRIC CONSIDERATIONS: DYNAMIC VASCULAR WALL THICKENING

Quantitation of vasomotion observed by angiography is limited to comparing the luminal diameter in two or more states of vasomotion. Because we cannot see the arterial wall itself, we do not always appreciate the changes which produce the variations in luminal dimensions, which we call 'vasomotion'[9,17,18]. The elementary geometric principle used to predict the narrowing expected at a site of fixed stenosis, given the severity of the fixed stenosis and the degree of vasoconstriction at

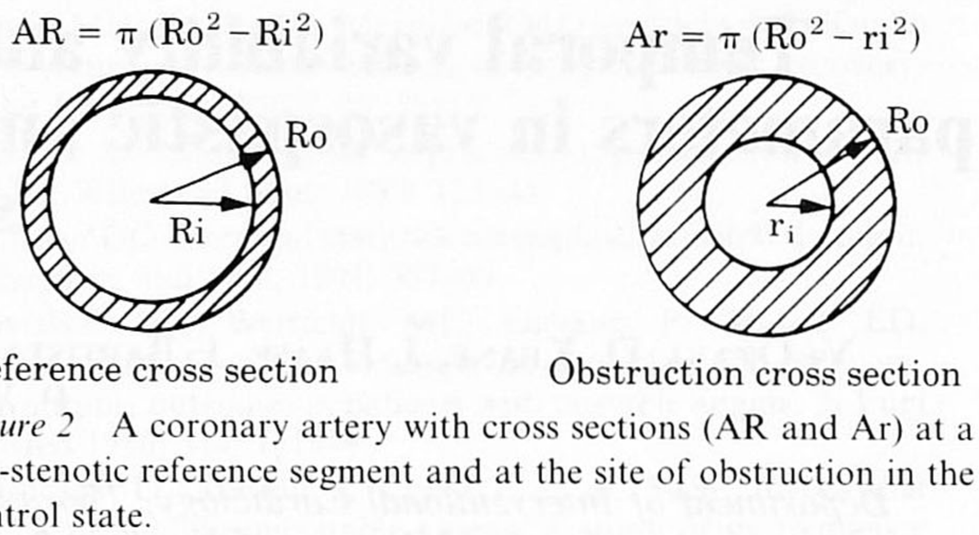

Figure 2 A coronary artery with cross sections (AR and Ar) at a pre-stenotic reference segment and at the site of obstruction in the control state.

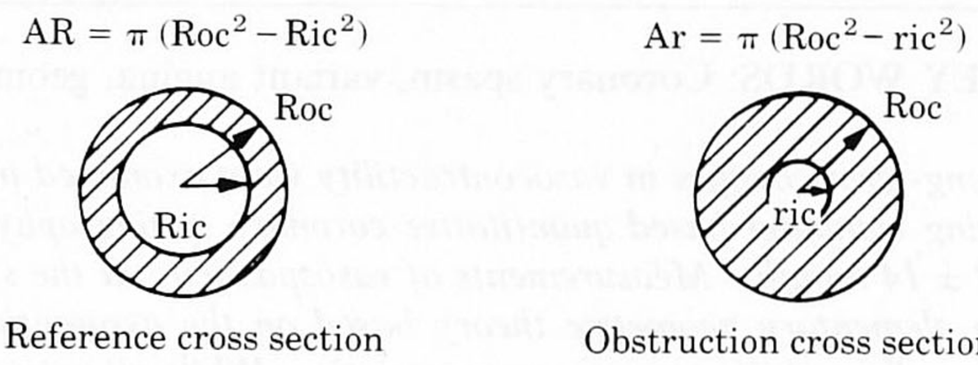

Figure 3 A coronary artery with cross sections (AR and Ar) at a prestenotic reference segment and at the site of obstruction in the vasoconstricted state.

the normal proximal reference segment, is shown in Figs 1 to 3.

For practical purposes, we assume the material of the arterial wall to be plastic (i.e. it can be moulded) but not compressible (of constant volume). If we exclude any change in the length of the artery as a result of varying diameter and any extrusion of tissue from the constricted area into non-constricted adjacent parts of the artery, the cross sectional area of the arterial wall will be constant at any point of the artery regardless of the state of its contraction or dilation. The coronary artery is assumed to be circular in cross-section when distended by a normal blood pressure and its outer diameter is assigned to include the media but exclude the adventitia.

For each of the control state and vasoconstricted state, a set of values is assigned for the inner (luminal) and outer diameters of the normal proximal (reference) segment and the segment containing the stenosis (obstruction):

Thus, where
AR = arterial wall area at the reference cross section
Ar = arterial wall area at the obstruction
2Ro = outer diameter of artery at baseline
2Ri = inner diameter at the reference segment at baseline
2ri = inner diameter at the obstruction at baseline
2Roc = outer diameter of artery during vasoconstriction
2Ric = inner diameter at the reference segment during vasoconstriction
2ric = inner diameter at the obstruction during vasoconstriction,

the following equation holds;
(i) $AR = \pi(Roc^2 - Ric^2) = \pi(Ro^2 - Ri^2)$
(ii) or $Ro^2 - Roc^2 = Ri^2 - Ric^2$
(iii) and $Ar = \pi(Roc^2 - ric^2) = \pi(Ro^2 - ri^2)$
(iv) or $Ro^2 - Roc^2 = ri^2 - ric^2$

Table 1 Quantitative coronary analysis in three phases of vasomotion in patients with persistent angina at initial and follow-up studies (group A)

Patient number	Vessel and phase	First angiogram			Second angiogram		
		RD (mm)	MLD (mm)	%DS	RD (mm)	MLD (mm)	%DS
1	RCA-control	2·80	2·38	15	2·53	2·22	12
	RCA-erg	2·41	0·83	66	2·16	0·87	60
	RCA-ISDN	3·41	2·72	20	3·67	2·86	22
2	LAD-control	2·33	1·47	37	2·18	1·20	45
	LAD-erg	2·19	0·69	68	2·10	0·67	68
	LAD-ISDN	2·54	1·62	36	2·59	2·17	16
	RCA-control	2·48	1·82	27	2·37	1·87	21
	RCA-erg	2·10	0·80	62	1·56	0	100
	RCA-ISDN	2·96	2·52	15	2·99	2·07	31
3	RCA-control	3·00	1·28	57	2·70	1·01	63
	RCA-erg	2·68	0·71	74	2·13	0	100
	RCA-ISDN	3·51	1·90	46	2·72	1·20	56
4	RCA-control	1·72	0·95	45	2·92	2·51	14
	RCA-erg	1·65	0·50	70	2·62	0	100
	RCA-ISDN	3·40	2·15	37	3·70	3·17	14
5	RCA-control	2·70	1·99	26	2·59	1·30	50
	RCA-erg	2·26	0·88	61	2·52	0·71	72
	RCA-ISDN	3·02	2·55	16	3·03	2·44	19
6	LCX-control	3·21	2·39	26	3·41	2·46	28
	LCX-erg	2·82	1·07	62	2·99	1·03	66
	LCX-ISDN	3·47	2·50	28	3·49	3·11	11
7	LAD-control	2·56	1·10	57	2·61	1·09	58
	LAD-erg	2·31	0·52	77	2·32	0·58	75
	LAD-ISDN	2·84	1·27	55	2·62	1·16	56
	RCA-control	2·82	1·32	53	2·77	1·58	43
	RCA-erg	2·76	1·11	60	2·42	1·08	55
	RCA-ISDN	3·10	1·37	56	3·27	1·81	45
8	RCA-control	2·49	1·78	29	2·33	1·36	42
	RCA-erg	2·32	0·81	65	2·14	0·77	64
	RCA-ISDN	3·18	2·37	25	2·76	1·96	29
9	LCX-control	1·93	1·13	41	1·62	1·26	22
	LCX-erg	2·05	0·34	83	1·23	0	100
	LCX-ISDN	2·58	1·49	42	2·46	1·80	27
10	RCA-control	2·63	1·93	27	2·59	1·77	32
	RCA-erg	1·90	0	100	2·07	0	100
	RCA-ISDN	3·17	2·64	17	3·49	2·83	19
11	LAD-control	2·42	0·96	60	2·55	1·18	54
	LAD-erg	2·23	0	100	2·32	0	100
	LAD-ISDN	3·03	2·51	17	3·07	1·52	50

RCA=right coronary artery; LAD=left anterior descending artery; LCX=left circumflex coronary artery; erg=after administration of ergonovine; ISDN=after administration of isosorbide dinitrate; RD=reference diameter; MLD=minimal luminal diameter; %DS=% diameter stenosis.

Then equation (ii) and (iv) yield:

(v) $ric^2 = ri^2 - Ri^2 + Ric^2$

Therefore, if we know the reference diameter in the control state (2Ri), after vasoconstriction (2Ric) and the obstruction diameter (2ri) in the control state, we can predict the obstruction diameter (2ric) after vasoconstriction from Equation (v). Equations (i) to (v) are equally valid for both vasoconstriction and vasodilatation. Thus, for a given degree of vasoconstriction at any segment of a vessel, it should be possible to predict the decrease in the luminal diameter at any other site in the same vessel from simple geometric principles. On account of the greater arterial wall area due to the atherosclerotic plaque, the percentage reduction in luminal diameter should be greater at the site of fixed stenosis.

STATISTICAL METHODS

Vasoconstriction at the spastic segment was considered to be correctly predicted if the minimal luminal diameter (MLD) measurement was within ± 10% of the value derived by the geometric theory as described above. Changes in MLD and reference diameter (RD) induced by ergonovine and ISDN were compared by the Student's t-test for paired data. Differences between patient group characteristics were compared by the chi-square test or the Student's t-test for unpaired data.

Table 2 Quantitative coronary analysis in three phases of vasomotion in patients with resolution of angina at initial study which had resolved at follow-up (group B)

Patient number	Vessel and phase	First angiogram			Second angiogram		
		RD (mm)	MLD (mm)	%DS	RD (mm)	MLD (mm)	%DS
12	RCA-control	2·73	1·71	37	3·46	2·70	22
	RCA-erg	2·28	0	100	2·35	1·48	37
	RCA-ISDN	4·08	2·56	37	3·93	2·68	32
13	LAD-control	1·50	0·85	43	2·51	1·34	47
	LAD-erg	1·46	0·46	68	2·28	1·56	32
	LAD-ISDN	2·32	1·30	44	2·53	2·02	20
14	LCX-control	2·63	1·77	33	2·46	1·82	26
	LCX-erg	2·13	0	100	2·24	1·29	42
	LCX-ISDN	2·70	1·85	31	2·86	2·06	28
15	LAD-control	1·67	1·20	28	1·91	1·25	35
	LAD-erg	1·50	0·61	59	2·02	1·41	30
	LAD-ISDN	2·19	1·68	23	2·03	1·71	16
16	LAD-control	2·38	1·07	55	2·88	1·89	34
	LAD-erg	2·21	0·57	74	2·37	1·67	30
	LAD-ISDN	2·78	1·22	56	2·72	1·76	35
17	RCA-control	2·52	1·05	58	2·83	1·91	33
	RCA-erg	1·95	0	100	2·38	1·60	33
	RCA-ISDN	3·75	2·44	35	3·61	2·55	29
18	RCA-control	2·48	1·37	45	2·43	1·77	27
	RCA-erg	1·97	0	100	2·18	1·30	40
	RCA-ISDN	2·85	2·53	11	2·83	2·02	29
19	LAD-control	2·67	2·01	25	2·56	2·10	18
	LAD-erg	2·57	0·83	68	2·43	1·93	21
	LAD-ISDN	3·00	2·83	6	2·80	2·10	25
20	RCA-control	2·67	1·76	34	3·80	2·09	45
	RCA-erg	2·48	0·99	60	3·72	2·03	45
	RCA-ISDN	3·54	2·35	34	3·94	2·16	45
	LCX-control	2·33	1·31	44	2·63	1·75	33
	LCX-erg	1·99	0	100	2·58	1·74	33
	LCX-ISDN	2·69	1·62	40	2·70	1·85	31

RCA = right coronary artery; LAD = left anterior descending artery; LCX = left circumflex coronary artery; erg = after administration of ergonovine; ISDN = after administration of isosorbide dinitrate; RD = reference diameter; MLD = minimal luminal diameter; %DS = % diameter stenosis.

Results

At the time of the initial study all 20 patients had classical symptoms of variant angina; at follow-up the symptoms persisted in only 11 (group A) and had resolved in nine (group B).There was no significant difference in age (55 ± 8 vs 56 ± 8) or sex (number of female patients; 1 of 11 vs 1 of 9) between the two groups. The follow-up studies in group A were performed 40 ± 14 months after the initial study, while those in group B were done 43 ± 14 months after the initial study. The follow-up period was similar for both groups. All patients were treated with a calcium antagonist (diltiazem), the dose of which immediately after the initial test was 172 ± 36 mg/day in group A and 167 ± 38 mg/day in group B (not significant). In group B who showed negative follow-up test results, diltiazem was gradually reduced or discontinued after the follow-up test.

Twenty-three spastic coronary segments in 23 vessels from the 20 patients were analysed. The mean diameter of the normal proximal segment was used as the reference diameter. The results of quantiative analysis for the control, ergonovine and ISDN phases of the initial and follow-up studies for both groups are given in Tables 1 and 2.

In group A, ergonovine induced a significant reduction in the RD and MLD at spastic segments during both the initial and follow-up studies; ISDN, on the other hand, induced a significant increase in the MLD and RD. The mean values of the initial and follow-up studies for group A are compared in Figs 4 and 5. In group B a significant reduction in both MLD and RD at spastic segments was observed during the initial study, while neither MLD nor RD changed significantly during the follow-up study; both MLD and RD increased following the administration of ISDN during both tests. The mean values of the initial and follow-up studies for group B are compared in Figs 6 and 7.

During the initial study, two out of 11 patients in group A and five out of nine patients in group B developed total transient spastic occlusion in response to ergonovine. At the level of the spastic segment atherosclerosis was seen to have progressed significantly after

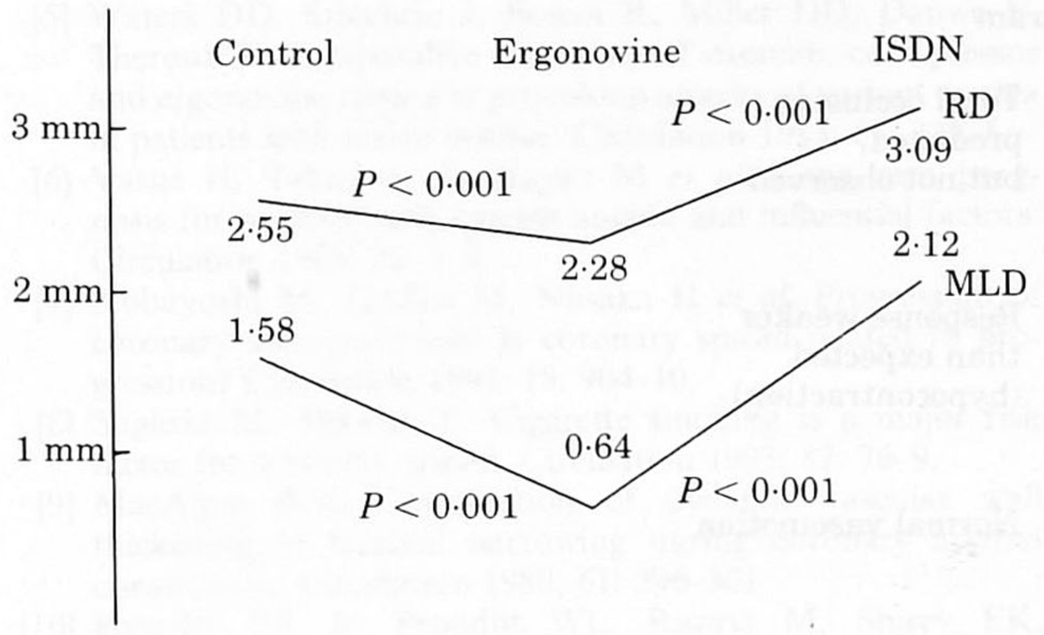

Figure 4 Mean values of reference diameter (RD) and minimal luminal diameter (MLD) during the control state, after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in group A during initial angiography.

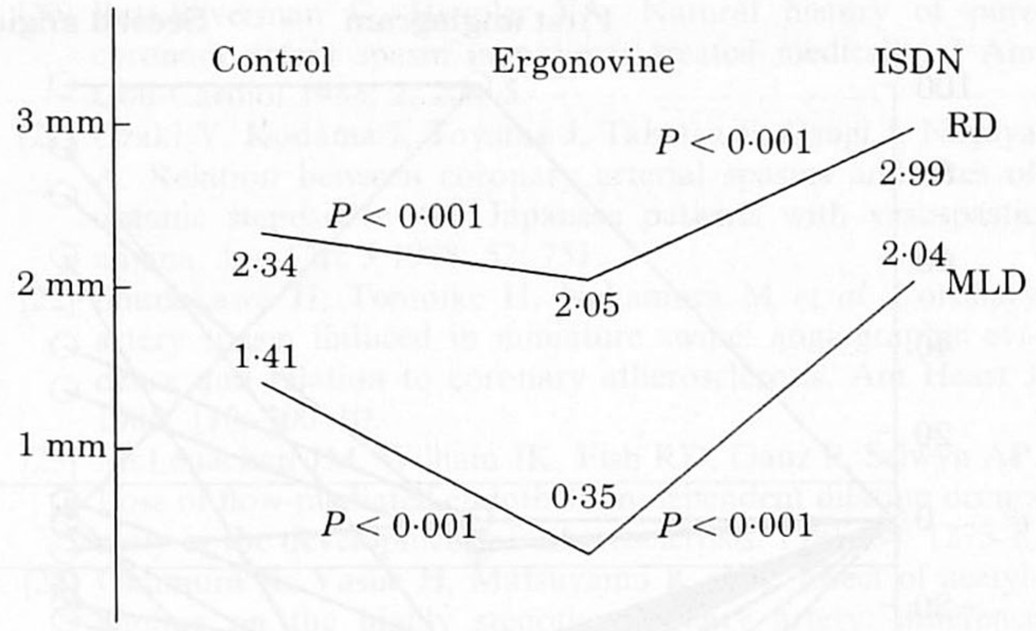

Figure 6 Mean values of reference diameter (RD) and minimal luminal diameter (MLD) during the control state, after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in group B during initial angiography.

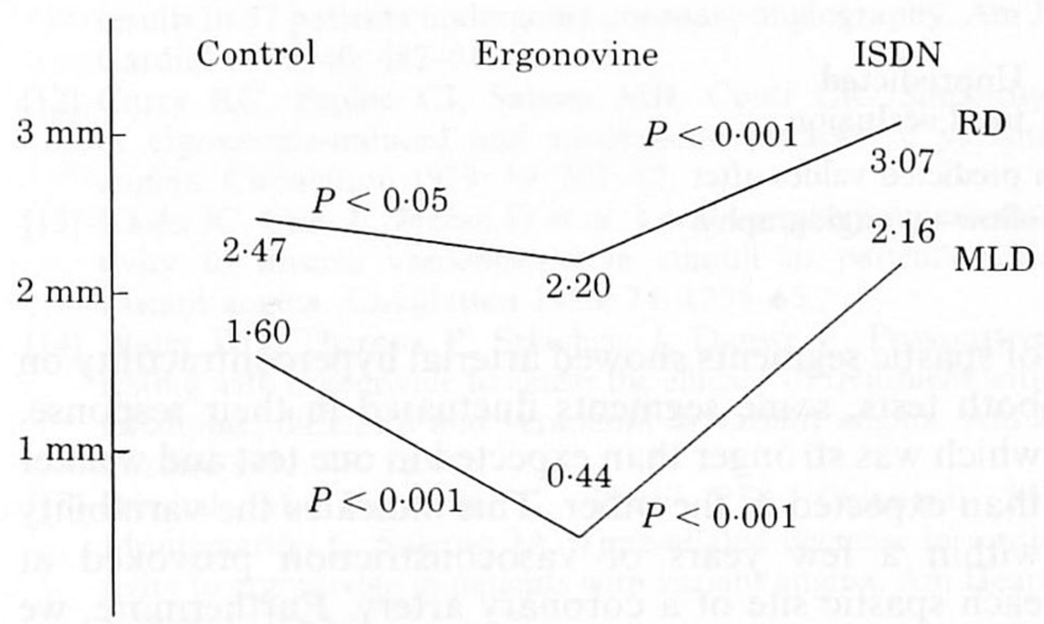

Figure 5 Mean values of reference diameter (RD) and minimal luminal diameter (MLD) during the control state, after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in group A at follow-up.

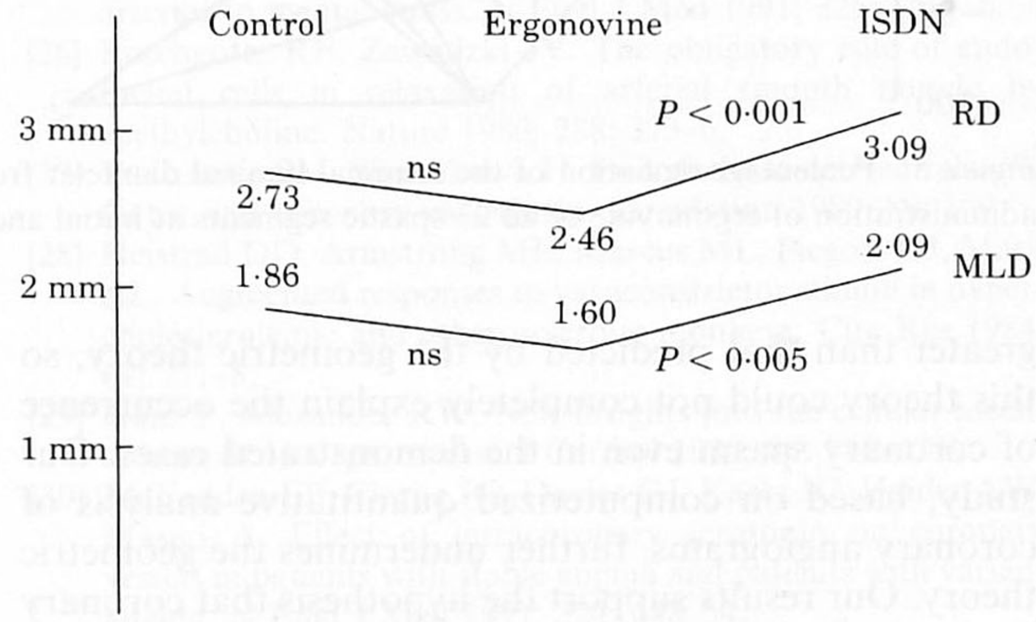

Figure 7 Mean values of reference diameter (RD) and minimal luminal diameter (MLD) during the control state, after administration of ergonovine and after administration of isosorbide dinitrate (ISDN) in group B at follow-up.

ISDN administration in one case from group A but in none from group B.

Using the elementary geometric principles described above, we calculated the changes that would be expected to occur at spastic sites if vasoconstriction was uniform throughout the coronary vessel. Figure 8 shows the behaviour of the 23 spastic segments during both provocation tests.

During the initial study, the decrease in MLD at the spastic site was proportional to the vasoconstriction in the RD in only four segments, i.e.vasospasm at the site of fixed stenosis was correctly predicted in those cases. In one segment, vasoconstriction at the site of the fixed stenosis was less than predicted, whereas in 18 segments clear hypercontractility was exhibited at the sites of fixed stenosis. During the follow-up study, only one of the four segments in which the response was correctly predicted at the initial test, again developed the predicted value in MLD; the other three segments showed hypocontractility. The one segment in which hypocontractility was initially observed, similarly demonstrated hypocontractility at follow-up. Of the 18 segments which showed hypercontractility during the initial test, 12 again exhibited hypercontractility, four developed their pedicted MLD values and the remaining two developed less contraction than predicted (hypocontractility).

Thus, the majority of spastic segments were hypercontractile during both tests while some segments changed from being initially hypercontractile to being hypocontractile at follow-up. In only one vessel could the behaviour of a fixed stenosis be correctly predicted by the geometric theory during both provocation tests.

Discussion

During the past decade, clinical understanding of changes in the vessel wall cross-sectional area during coronary spasm has been influenced by the geometric theory proposed by MacAlpin[9]. This theoretical model suggested that vascular hypersensitivity was due to the amplification of normal vasoconstriction at the sites of atheromatous luminal encroachment, the degree of vasoconstriction being related to the severity of encroachment. In the report by MacAlpin, arterial measurements were performed in three cases to support the geometric theory[9]. However, in at least one of the three cases, vasoconstriction induced by ergotamine was

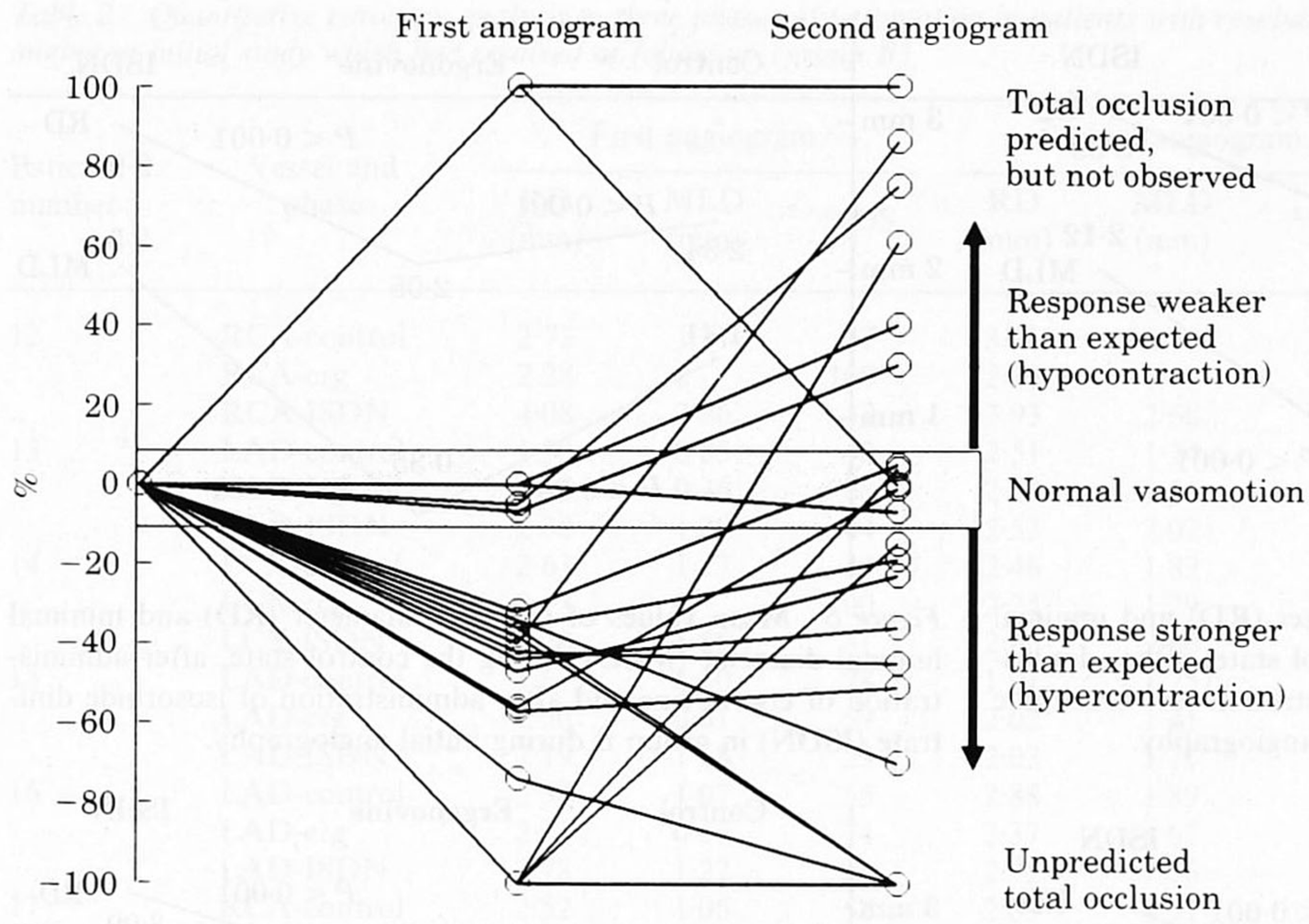

Figure 8 Percentage deviation of the minimal luminal diameter from predicted values after administration of ergonovine of all 23 spastic segments at initial and follow-up angiography.

greater than that predicted by the geometric theory, so this theory could not completely explain the occurrence of coronary spasm even in the demonstrated cases. Our study, based on computerized quantitative analysis of coronary angiograms, further undermines the geometric theory. Our results support the hypothesis that coronary artery spasm results from hypersensitivity to vasoconstrictors at atherosclerotic sites, as previously suggested by other investigators.

Coronary artery spasm in normal coronary arteries has also been reported by several authors[4,19,20]. In a study investigating the severity of fixed stenosis at the site of coronary spasm in 406 patients[21], 12% of the patients had no fixed stenosis in any coronary artery after administration of ISDN and only 30% of patients had severe fixed stenosis. It is clear from these results that the geometric theory alone cannot explain vasospasm in patients with angiographically normal coronary arteries. It is of interest that coronary spasm has been observed in a swine model in angiographically normal coronary arteries; however, subsequent histological studies revealed that early atherosclerotic changes were already present[22]. Both clinical and experimental studies have demonstrated that hypercontractility of coronary arteries, in response to a variety of vasoconstrictive agents, is integrally related to the pathological process of atherosclerosis; specifically, to the disruption of endothelial control of vascular smooth muscle tone[23–28] and to the release of vasoactive products by platelets[29,30]. While such endothelial damage will usually progress it may occasionally heal over the course of several months[31,32]. Other factors unrelated to advanced atherosclerosis, such as mediation of the autonomic nervous system, might play a role in the genesis of coronary spasm[33]. A finding of particular interest in our investigation was that while the majority of spastic segments showed arterial hypercontractility on both tests, some segments fluctuated in their response, which was stronger than expected in one test and weaker than expected in the other. This indicates the variability within a few years of vasoconstriction provoked at each spastic site of a coronary artery. Furthermore, we observed in a recent long-term study[34] that the location of coronary spasm shifts over a period of a few years in some patients with vasospastic angina. This indicates that coronary spasm is not a permanent condition regulated by the severity of atherosclerosis but a dynamic process only partly influenced by geometric factors. The nature of the temporal and spatial variability of vasospastic angina remains to be elucidated.

In conclusion, vasoconstriction at sites of fixed coronary stenoses occurs as a result of hypersensitivity to vasoconstrictor substances rather than as a simple geometrical phenomenon. Coronary vasospastic responsiveness is a dynamic process demonstrating temporal variability.

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References

[1] Prinzmetal M, Kennedy R, Meliss R, Wada T, Bor T. Angina pectoris I. A variant form of angina pectoris. Am J Med 1959; 27: 375–88.

[2] Maseri A, Severi S, De Nes M *et al.* 'Variant' angina; one aspect of a continuous spectrum of vasospastic myocardial ischemia. Am J Cardiol 1978; 42: 1019–35.

[3] Serruys PW, Steward R, Booman F, Michels R, Reiber JHC, Hugenholtz PG. Can unstable angina pectoris be due to increased coronary vasomotor tone? Eur Heart J 1980; 1: 71.

[4] Bertrand ME, Lablanche JM, Tilmant PY *et al.* Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary arteriography. Circulation 1982; 65: 1299–1306.

[5] Waters DD, Szlachcic J, Bonan R, Miller DD, Dauwe F, Theroux P. Comparative sensitivity of exercise, cold pressor and ergonovine testing in provoking attacks of variant angina in patients with active disease. Circulation 1983; 67: 310–5.
[6] Yasue H, Takizawa A, Nagao M *et al.* Long-term prognosis for patients with variant angina and influential factors. Circulation 1988; 78: 1–9.
[7] Nobuyoshi M, Tanaka M, Nosaka H *et al.* Progression of coronary atherosclerosis: Is coronary spasm related to progression? Circulation 1991; 18: 904–10.
[8] Suglishi M, Takatsu F. Cigarette smoking is a major risk factor for coronary spasm. Circulation 1993; 87: 76–9.
[9] MacAlpin RN. Contribution of dynamic vascular wall thickening to luminal narrowing during coronary arterial constriction. Circulation 1980; 61: 296–301.
[10] Heupler FA Jr, Proudfit WL, Razavi M, Shirey EK, Greenstreet R, Sheldon WC. Ergonovine maleate provocative test for coronary arterial spasm. Am J Cardiol 1978; 41: 631–40.
[11] Schroeder JS, Bolen JL, Quint RA *et al.* Provocation of coronary spasm with ergonovine maleate. New test with results in 57 patients undergoing coronary angiography. Am J Cardiol 1977; 40: 487–91.
[12] Curry RC, Pepine CJ, Sabom MB, Conti CR. Similarity of ergonovine-induced and spontaneous attacks of variant angina. Circulation 1979; 59: 307–12.
[13] Kaski JC, Crea F, Meran D *et al.* Local coronary supersensitivity to diverse vasoconstrictive stimuli in patients with variant angina. Circulation 1986; 74: 1255–65.
[14] Water DD, Theroux P, Szlachcic J, Dauwe F. Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem and verapamil in variant angina. Am J Cardiol 1981; 48: 123.
[15] Prevital M, Panciroli C, Ponti RD, Chimienti M, Montemartini C, Salerno JA. Time-related decrease in sensitivity to ergonovine in patients with variant angina. Am Heart J 1989; 117: 92–9.
[16] Haase J, Escaned J, van Swijndregt EM *et al.* Experimental validation of geometric and densitometric coronary measurements on the new generation cardiovascular angiography analysis system (CAAS II). Cathet Cardiovasc Diagn 1993; 30: 104–14.
[17] Serruys PW, Lablanche JM, Reiber JHC, Bertrand ME, Hugenholtz PG. Contribution of dynamic vascular wall thickening to luminal narrowing during coronary arterial vasomotion. Z Kardiol 1983; 72: 116–23.
[18] Freedman SB, Richmond DR, Kelly DT. Pathophysiology of coronary artery spasm. Circulation 1982; 66: 705–9.
[19] Vrints CJ, Bult H, Hitter E, Herman AG, Snoeck JP. Impaired endothelium-dependent cholinergic coronary vasodilation in patients with angina and normal coronary arteriograms. J Am Coll Cardiol 1992; 19: 21–31.
[20] Bott-Silverman C, Heupler FA. Natural history of pure coronary artery spasm in patients treated medically. J Am Coll Cardiol 1983; 2: 200–5.
[21] Ozaki Y, Kodama I, Toyama J, Takatsu F, Osugi J, Nagaya A. Relation between coronary arterial spasms and sites of organic stenosis in 406 Japanese patients with vasospastic angina. Jpn Circ J 1988; 52: 751.
[22] Shimokawa H, Tomoike H, Nakamura M *et al.* Coronary artery spasm induced in miniature swine: angiographic evidence and relation to coronary atherosclerosis. Am Heart J 1985; 110: 300–10.
[23] McLenachan JM, William JK, Fish RD, Ganz P, Selwyn AP. Loss of flow-mediated endothelium-dependent dilation occurs early in the development of atherosclerosis. 1991; 84: 1273–8.
[24] Okumura K, Yasue H, Matsuyama K *et al.* Effect of acetylcholine on the highly stenotic coronary artery: difference between the constrictor response of the infarct-related coronary artery and that of the noninfarct-related artery. J Am Coll Cardiol 1992; 19: 752–8.
[25] Yeung AC, Vekshtein VI, Krantz DS *et al.* The effect of atherosclerosis on the vasomotor response of coronary arteries to mental stress. N Engl J Med 1991; 325: 1551–6.
[26] Furchgotte RF, Zawadzki JV. The obligatory role of endothelial cells in relaxation of arterial smooth muscle by acethylcholine. Nature 1980; 288: 373–6.
[27] Vanhoutte PM, Shimokawa H. Endothelium-derived relaxing factor and coronary vasospasm. Circulation 1989; 80: 1–9.
[28] Heistrad DD, Armstrong ML, Marcus ML, Piegors DJ, Mark AL. Augmented responses to vasoconstrictor stimuli in hypercholesterolemic and atherosclerotic monkeys. Circ Res 1984; 61: 711–8.
[29] Ganz P, Alexander RW. New insights into the cellular mechanisms of vasospasm. Am J Cardiol 1985; 56: 11E–15E.
[30] McFadden EP, Clarke JG, Davies GJ, Kaski JC, Haider AW, Maseri A. Effect of intracoronary serotonin on coronary vessels in patients with stable angina and patients with variant angina. N Engl J Med 1991; 324: 648–54.
[31] Schwartz SM, Stemerman MB, Benditt EP. The aortic intima. II. Repair of the aortic lining after mechanical denudation. Am J Pathol 1975; 81: 15–42.
[32] Forrester JS, Litvak F, Grundfest W, Hichey A. A prospective of coronary disease seen through the arteries of living man. Circulation 1987; 75: 505–13.
[33] Yasue H, Horio Y, Nakamura N *et al.* Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. Circulation 1986; 74: 955–63.
[34] Ozaki Y, Takatsu F, Osugi J *et al.* Long-term study of recurrent vasospastic angina using coronary angiograms during ergonovine provocation tests. Am Heart J 1992; 123: 1191–8.