Variability in Coronary Hemodynamics in Response to Ergonovine in Patients With Normal Coronary Arteries and Atypical Chest Pain

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Because an increase in coronary vascular resistance in response to ergonovine maleate has been suggested as a possible diagnostic aid for variant angina, changes were evaluated in coronary hemodynamics and serial myocardial thallium-201 perfusion scans in 15 patients without angina and with normal coronary arteries in response to ergonovine (0.05, 0.10 and 0.20 mg intravenously). For the group, heart rate-blood pressure product increased significantly ($p < 0.001$) without any change in coronary sinus flow, coronary vascular resistance, myocardial oxygen extraction, arterial-coronary sinus oxygen difference and lactate extraction. In 7 of 15 patients, however, coronary vascular resistance increased (mean 39%, range 11 to 75%, probability [p] < 0.001), and coronary sinus flow decreased (14%, $p < 0.001$), despite an increase in heart rate-blood pressure product (36%, $p < 0.02$). No electrocardiographic, metabolic or thallium-201 scan abnormalities occurred. Therefore, significant increases in coronary vascular resistance in response to ergonovine may occur in patients with normal coronary arteries and atypical chest pain.

Administration of ergonovine maleate has been used as a provocative test for inducing coronary artery spasm in patients with variant angina (1,2). The test has been found to be highly sensitive and specific by angiographic criteria. Chest pain, electrocardiographic changes indicative of myocardial ischemia, reversible severe focal coronary artery narrowing (1–4) and reduction in coronary sinus flow (5–9) have been observed in patients with spasm, but not in patients without spasm. Reversible thallium scan perfusion defects have been shown reflecting reduction of regional myocardial blood flow (10–12).

Measurement of coronary sinus flow has been reported to be a sensitive test for the detection of coronary artery spasm (5). In patients with spasm, a marked decrease in coronary sinus flow and an increase in coronary vascular resistance (defined as the ratio of mean arterial pressure to coronary sinus flow) are seen. However, when spasm is isolated to the right coronary artery, coronary sinus flow may not be a sensitive test for spasm because the right coronary artery may drain into the coronary sinus near the ostium, or directly into the right atrium (13), and therefore may not contribute measurably to coronary sinus flow. Although a large reduction in flow in relation to demand has been shown in patients with spasm of the left coronary artery, there are few data on the range of hemodynamic and metabolic responses to ergonovine in patients with normal coronary arteries (5–8).

We therefore studied a group of patients with chest pain atypical for angina who had no documented episodes of electrocardiographic changes for ischemia during chest pain and whose coronary arteriogram and left ventricular angiogram were normal. In these patients we determined the variations in coronary sinus flow, coronary vascular resistance, oxygen consumption and lactate metabolism in response to provocative testing with ergonovine maleate.

Methods

Study patients (Table 1). We studied 15 consecutive patients, 5 men (mean age 50.4 years, range 51 to 56) and 10 women (mean age 45 years, range 16 to 64), referred to us for evaluation of atypical chest pain. All but one patient (Case 10) had previously undergone cardiac catheterization (a young girl, age 17, did not have coronary arteriography). Eleven of 14 patients had no luminal

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Table 1. Characteristics of Study Group

Case	Age (yr)/Sex	History	Physical Examination	Chest X-ray Film	ECG	Echo	Exer. Test	Cardiac Catheterization: Cor. Art.	Cardiac Catheterization: LV Angio	Cardiac Catheterization: Ergo.	Cardiac Catheterization: Date	CCU Ergo. Test Date
1	33F	ACP	MVP	NL	NL	—	ECG	NL	MVP	—	2/81	4/81
2	64F	ACP, HTN, PAT	NL	NL	NL	NL	BL	NL	NL	—	9/80	4/81
3	55F	1V-CABG, ACP, pseudo-seizures	NL	NL	Nonspec. abnor., LAHB	—	—	30% LAD, graft open	NL	Neg	8/81	4/81
4	39F	ACP	MVP	NL	NL	—	—	NL	MVP	Neg	2/81	2/81
5	59F	ACP, FBD, LBP	MVP	NL	NL	NL	ECG, 2 mm ST↓; TL, NL	NL	NL	—	10/80	3/81
6	44F	ACP, multiple vasc. surg.	NL	NL	NL	—	—	30% LAD, 30% RCA	NL	—	6/78	9/80
7	46M	DM, ACP	NL	NL	?IMI	NL	NL	NL	NL	—	1/81	2/81
8	53F	ACP, HTN	NL	NL	LVH, IMI	LVH	TL, rever. isch.	40% LAD	NL	—	1/81	3/81
9	46F	ACP, HTN	NL	NL	NL	—	ECG, 2 mm ST↓; TL, NL	NL	NL	—	5/80	7/81
10	17F	ACP, PAT, migraine, cyclic vomiting	MVP	NL	NL	MVP	ECG, NL; TL, NL	—	MVP, ASD (1.5:1)	—	7/80	7/81
11	56M	ACP, HTN	NL	NL	NL	NL	ECG, NL	NL	NL	—	6/81	7/81
12	51M	ACP, PVC	NL	NL	Freq. PVCs	—	ECG, neg. isch., VT with exer.	NL	NL	—	12/77	9/81
13	41F	ACP	MR	NL	NL	NL	ECG St↓; TL-rever. isch.	NL	NL	—	5/79	6/81
14	50M	ACP	NL	Pleural thick.	Nonspec. abnor.	—	—	NL	NL	—	7/81	10/81
15	49M	PUD, ACP	NL	NL	Nonspec. abnor.	—	—	NL	NL	—	7/80	11/81

ACP = atypical chest pain, ASD = atrial septal defect; BL = borderline; 1V-CABG = one vessel coronary artery bypass graft; Cor art = coronary arteriography; CCU = coronary care unit; DM = diabetes mellitus, ECG = electrocardiogram; Echo = echocardiogram; Ergo = ergonovine provocation; Exer. = exercise; F = female; FBD = functional bowel disease; Freq. = frequent; HTN = hypertension, IMI = inferior myocardial infarction; isch = ischemia; LAD = left anterior descending coronary artery, LAHB = left anterior hemiblock, LBP = low back pain, LV Angio. = left ventricular angiogram, LVH = left ventricular hypertrophy; M = male, MVP = mitral valve prolapse, Neg. = negative, Neg Isch = negative for ischemia; NL = normal; Nonspec abnor = nonspecific abnormality; PAT = paroxsymal atrial tachycardia, PUD = peptic ulcer disease; PVCs = premature ventricular complexes, RCA = right coronary artery; rever. = reversible, ST↓ = ST segment depression; Surg = surgery, Thick = thickening, TL = thallium scan; vasc = vascular; VT = ventricular tachycardia, — = not done or not known

irregularities of any of the coronary arteries. Three patients had a single insignificant luminal narrowing (decrease in luminal diameter) in one or two coronary vessels (Case 3, 30% lesion in the left anterior descending coronary artery; Case 8, 40% lesion in the left anterior descending coronary artery and Case 6, 30% lesions in the left anterior descending and right coronary arteries). Patient 10 was included in this group even though she did not undergo prior coronary arteriography because of the absence of symptoms, risk factors, age and a normal exercise thallium test.

No patient had a documented myocardial infarction or ischemic electrocardiographic changes with chest pain. Patient 3, who had one vessel (left anterior descending artery) bypass graft surgery, underwent repeat catheterization 4 months after this study. A patent graft and a 30% left anterior descending coronary artery lesion were found. An ergonovine test was repeated and was negative by angiographic and electrocardiographic criteria.

Coronary hemodynamic studies. After informed consent was obtained, all patients were brought to the coronary care unit where a radial artery cannula, coronary sinus thermodilution catheter (Wilton Webster, Inc., Altadena, California) and peripheral intravenous lines were placed. The coronary sinus catheter was placed in the midcoronary sinus to reduce error due to reflux (14) and its position verified by injection of small amounts of contrast medium visualized by fluoroscopy at the start and termination of the study. The catheter was firmly secured to the skin by suture material at its point of venous entry. Coronary sinus flows were determined by the constant infusion thermodilution technique at 46 ml/min using a Harvard pump and 5% dextrose in water at room temper-

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ature (14). Coronary sinus flow (CSF) was computed from the formula: $CSF = 4.6 \times 1.08 \times \left(\frac{Tb - Ti}{Tb - Tm} - 1\right)$ ml/min, where Tb, Ti and Tm represent, respectively, temperature of the blood, injectate and mixture.

Arterial and coronary sinus venous blood oxygen saturation were determined using an OSM2 hemoximeter (Radiometer Co., Copenhagen, Denmark). When comparing the use of this hemoximeter with the Van Slyke method, the standard error of the estimate for oxygen content was found to be 0.65 ml/dl. This measurement was not made in duplicate. The error (mean ± standard deviation) for repeated determinations of oxygen saturation in the same sample was −0.7 ± 3.1%.

Oxygen content was calculated from the formula: oxygen content = oxygen saturation × hemoglobin × 1.34. Lactate (in mg) was determined by an automated enzymatic method (15). No duplicate measurements were made. The derived variables were calculated as follows:

Rate-pressure product = RP (mm Hg/min × 10^3) = heart rate (HR) × systolic pressure (SBP).

Arterial-coronary sinus oxygen content difference ($ACDO_2$) (ml/liter) = arterial-coronary sinus oxygen content.

Myocardial oxygen consumption = $M\dot{V}O_2$ (ml/min) = CSF (ml/min) × $ACDO_2$ × 10^{-3}, where CSF = coronary sinus flow.

Myocardial lactate extraction (% lactate) = (arterial-coronary sinus lactate)/arterial lactate × 100.

Coronary vascular resistance (CVR) (mm Hg-min/ml) = MAP/CSF, where MAP = mean arterial pressure and CSF = coronary sinus blood flow.

Study protocol. Cardiac medications were discontinued 12 to 24 hours before the study. Blood pressure, a single channel electrocardiographic lead (V_5) and coronary sinus flows were recorded continuously on a multichannel strip chart recorder. Two baseline determinations were taken 10 minutes apart, consisting of blood pressure, heart rate, coronary sinus flow, arterial and venous lactate, and oxygen saturation measurements were made. A 12 lead electrocardiogram was recorded. Ergonovine maleate was then given in three doses: 0.05, 0.10 and 0.20 mg intravenously, at 6 minute intervals. After each dose, a sufficient flush ensured administration of the full amount. A 12 lead electrocardiogram was recorded every 2 minutes during the study, and patients were asked for symptoms after the completion of each electrocardiogram. If electrocardiographic changes were noted, defined as more than 1 mm ST deviation from baseline, no larger dose of ergonovine was given. All patients in this study, however, received the full three doses of ergonovine. Three minutes after the 0.2 mg dose of ergonovine, repeat hemodynamic, metabolic and coronary sinus flow measurements were made. Thallium-201 was injected, and imaging was performed 5 to 10 minutes later at the bedside with a portable camera in the anterior, left anterior oblique (30°, 45° and 60°) and lateral projection views. If defects were detected, redistribution images were obtained. The anterior image was acquired to 300,000 counts and subsequent images acquired to isotime. All images were computer-processed according to our standard method (16).

Sublingual and parenteral nitroglycerin were available if needed. The test was performed in the coronary care unit with a physician in attendance at all times. No complications occurred.

Statistical analysis. The mean ± standard deviation was determined for all data during control and peak ergonovine testing. Statistical significance was determined by using the paired *t* test to compare data from baseline periods with peak values. A probability (p) value of less than 0.05 was considered statistically significant. A nonpaired *t* test was used to compare the group of patients whose coronary vascular resistance increased (Group A) with the remaining patients (Group B).

Two baseline measurements were made 10 minutes apart before ergonovine stimulation. These measurements were averaged when less than a 10% difference was observed; otherwise, the second measurement was used as baseline.

Results

Of the 15 patients who received ergonovine, 11 (73%) developed chest pain. No patient had myocardial perfusion defects during thallium-201 scintigraphy or electrocardiographic changes during ergonovine provocation indicative of myocardial ischemia.

Hemodynamic and metabolic data (Tables 2 and 3). Repeated baseline measurements of systemic and coronary hemodynamic and metabolic variables were made 10 minutes apart before ergonovine stimulation. The reproducibility of our measurements of coronary sinus flow was estimated by computing the difference (mean ± standard deviation) of those measurements where the baseline heart rate-systolic blood pressure product varied by no more than 10%. The difference in coronary sinus flows was 0.1 ± 4.02 ml/min; the difference for lactate was −0.4 ± 0.3 mg.

In the group as a whole, mean blood pressure increased 14% with the peak dose of ergonovine ($p < 0.001$). Heart rate-systolic blood pressure product increased 25% ($p < 0.001$) and heart rate increased 11% ($p < 0.05$). Coronary sinus flow, coronary vascular resistance, lactate extraction, arterial-coronary sinus oxygen content difference and myocardial oxygen consumption did not change. However, a subgroup of seven patients (Group A) had an increase in coronary vascular resistance (Fig. 1). In the remaining patients (Group B), coronary sinus flow and myocardial oxygen consumption increased by 38 and 40%, respectively ($p < 0.001$), and there was a concomitant slight increase in heart rate-systolic blood pressure product of 16% (although this did not reach statistical significance). In contrast, in Group A patients, despite a 36% ($p < 0.02$) increase in heart rate-systolic blood pressure product, coronary sinus flow decreased by 14% ($p < 0.02$). Coronary vascular resistance increased by 39% (range 11 to 75%, $p < 0.001$). There were no differences in the baseline absolute values for blood pressure, heart rate-blood pressure product, coronary sinus flow, percent lactate, myocardial oxygen consumption and arterial-coronary sinus oxygen content difference for the two groups.

Table 2. Hemodynamic Data

Case	Blood Pressure (mm Hg) C S/D	C M	E S/D	E M	Heart Rate (beats/min) C	E	SBP × HR (mm Hg × 10⁻³) C	E	CSF (ml/min) C	E	CVR (mm Hg/ml per min) C	E	$ACDO_2$ (ml/liter) C	E	% Lactate Extraction C	E	MVO_2 (ml/min) C	E
Group A																		
1	137/75	(95)	142/83	(101)	69	63	9.3	8.9	40.9	34 1	2.30	3.00	122	111	37	35	5.0	3 8
3	90/64	(73)	110/74	(86)	60	60	5.4	6.6	67.6	55.9	1.08	1.54	99	100	47	47	6.7	5.6
4	135/55	(82)	137/72	(94)	75	114	10.1	15.6	46 6	48 1	1 75	1.95	115	128	33	50	5 4	6.1
5	147/70	(95)	190/85	(120)	77	81	11.2	15.4	28.9	24.8	3.33	4 84	111	—	20	—	3.2	—
9	120/70	(89)	165/90	(115)	63	72	8.0	11.9	104.0	87.2	0.86	1 32	137	129	50	25	14.3	11.2
10	102/60	(74)	124/80	(95)	89	118	9.1	14.6	43 7	32.0	1.69	2.96	113	123	—	—	5 0	3.9
14	140/75	(96 7)	150/85	(107)	58	72	8.1	10 8	44 5	40.3	2 20	2 60	132	134	29	44	5 9	5 4
Mean		86.3		103	70	83	8.7	12 0	53.7	46.1	1 89	2 6	118	121	36	40	6 6	6.0
SD		10 2		12.1	11	23.7	1.8	3 5	24.9	20.9	0.83	1 2	13	12.9	11.2	10 2	3.6	2 7
p value: Group A, C vs E			< 0.002		NS		< 0 02		< 0.02		< 0.01		NS		NS		NS	
Group B																		
2	93/50	(64)	101/56	(68)	68	51	4.7	6.1	44.2	57 6	1.45	1 18	138	138	17	33	6 1	7 9
6	125/65	(82)	125/70	(88)	102	96	11.7	12.0	46.3	59 3	1.76	1 49	121	148	32	44	5.6	8.8
7	175/85	(112)	180/87	(118)	84	90	14.6	16.2	37 4	44.3	3 01	2.66	154	159	—	—	5.8	7.1
8	165/60	(90)	225/85	(132)	110	111	18 2	25.0	46 4	76 2	1 94	1 73	94	89	18	18	4 4	6 8
11	164/75	(105)	160/80	(107)	96	99	15.7	15 8	125.0	168.0	0.84	0.64	126	125	21	49	15 7	20 9
12	115/70	(102)	170/70	(103)	87	96	14.4	16.3	35 5	49.7	2 90	2.09	155	160	—	62	5.5	8.0
13	125/64	(84)	137/67	(90)	81	78	10 1	10 7	86.0	118.9	0.98	0.70	109	108	73	41	9.4	14.0
15	143/79	(100)	152/82	(105)	63	69	9.0	10 5	73 8	108.5	1 34	0.97	118	123	38	40	8 7	13 4
Mean		92.4		101.4	84	91	12.3	14.1	61.8	86.6	1.78	1 43	127	131	33	41	7.7	10.9
SD		15.4		17.0	20	13.9	4 3	5.7	31.1	44.3	0.81	.70	21 3	24.9	21 2	13 9	3 7	4.9
p value: Group B, C vs. E			NS		NS		NS		< 0.001		< 0.001		NS		NS		< 0.001	
C, Group A vs. C, Group B			NS		NS		NS		NS		NS		NS		NS		NS	
Group A + B																		
Mean		90		102	78	85	10.4	13.1	58.1	68.1	1 83	1 98	123	125	36	39	7 4	8.8
SD		13		16	17.2	19.7	3.9	4.7	27.7	39.9	0.79	1.10	18	21	16.3	10.1	3.5	4 6
p value: C vs E			< 0.001		< 0.05		< 0.001		NS		NS		NS		NS		NS	

$ACDO_2$ = arterial-coronary sinus oxygen content difference, C = control, CSF = coronary sinus flow, CVR = coronary vascular resistance, D = diastolic, E = ergonovine, M = mean; MVO_2 = myocardial oxygen consumption; NS = not significant; p = probability; S = systolic, SBP × HR = systolic blood pressure times heart rate, SD = standard deviation.

Discussion

Hemodynamic responses to ergonovine administration. Ergonovine maleate is an ergot alkaloid that has been used for provoking coronary artery spasm for the diagnosis of variant angina. Ergot alkaloids, in general, produce vasoconstriction by a direct alpha-adrenergic stimulation of receptors in smooth muscle cells in arteries and veins, resulting in an increase in arterial and venous tone. Ergot alkaloids may also produce alpha-blocking effects in large doses, and blunting of the baroreceptor response, mediated by central nervous system mechanisms. Ergonovine maleate, however, has less peripheral vasoconstriction effect (17). In human subjects, the hemodynamic responses to the usual doses of ergonovine maleate are an increase (5–8) or no change in arterial pressure, no change in heart rate (2,6–8) and an increase in rate-pressure product (7,8). In patients without spasm, mild (15 to 25%) diffuse narrowing of epicardial coronary arteries is seen (5–8) with possibly a greater effect on smaller resistance arteries and arterioles (3–7). This degree of narrowing has been thought to be insignificant and myocardial oxygen extraction remains unchanged; no electrocardiographic evidence of ischemia is observed. In one study (7), an increase in myocardial oxygen extraction

Table 3. Response to Ergonovine

Patient	Chest Pain	ECG Changes	Thallium Scan	Percent Change HR	BP	HR × SBP	CSF	CVR	Lactate Extraction	$ACDO_2$	$M\dot{V}O_2$
Group A											
1	+	–	–	−8.7	+6.3	−4 3	−16.6	+30.4	−5	−9 1	−24
3	+	–	–	0.0	+18.3	+22.2	−17.3	+43.0	−6	+0.9	−16
4	+	–	–	52.0	+14.7	+54.5	+3.2	+11.4	+52	+11.0	+13
5	+	–	–	5.9	+26.3	+37.5	−14.0	+45.3	—	—	—
9	+	–	–	14.3	+29.0	+49.0	−16.0	+53.0	+50	−6.0	+1
10	+	–	–	33.0	+28.0	+61.0	−27.0	+75.0	—	+9.0	−22
14	+	–	–	24	10.3	+33.0	−9 4	+18.0	48	1.0	−8.4
Mean				19	17.2	36.1	−13.9	39.4	7.8	1:2	−13.2
SD				9	20.9	22.2	9.2	21.7	42.6	0.1	14.1
Group B											
2	–	–	–	17.6	6.2	29.8	+30.0	−19.0	+94	0.0	30
6	–	–	–	−5 9	8 1	2.6	23.0	−15.3	+38	22.0	57
7	–	–	–	+6.7	4 8	18.8	18.4	−4.2	—	3.4	22
8	+	–	–	1.0	46.2	37 4	64.2	−10.8	0	−5.3	55
11	+	–	–	3.0	2.0	1.0	34.0	−24.0	133	−1.0	+33
12	+	–	–	10.3	1 5	13.2	40.0	−28.0	—	3.0	45
13	+	–	–	−3.7	7.1	5.9	50.0	−29.6	−44	15.0	28
15	–	–	–	9.5	5 0	17.0	47.0	−28.0	32	4.0	54
Mean				10.1	4 8	15.7	38.3	−19.9	42 1	1.3	40.4
SD				14 7	7.8	12.9	15.1	9.2	63.7	.3	13.9
p value											
Group A vs. B				NS	NS	$p < 0.05$	$p < 0.001$	< 0 001	NS	NS	< 0.001
Group A + Group B											
Mean				10.6	14.3	25.2	14.0	7.8	26.5	3.4	17.4
SD				16.1	12.8	20.2	29.6	34.3	55.4	8.5	30.7
p value, C vs. E				< 0 05	< 0.001	< 0.001	NS	NS	NS	NS	NS

BP = blood pressure; ECG = electrocardiographic; other abbreviations as in Table 2

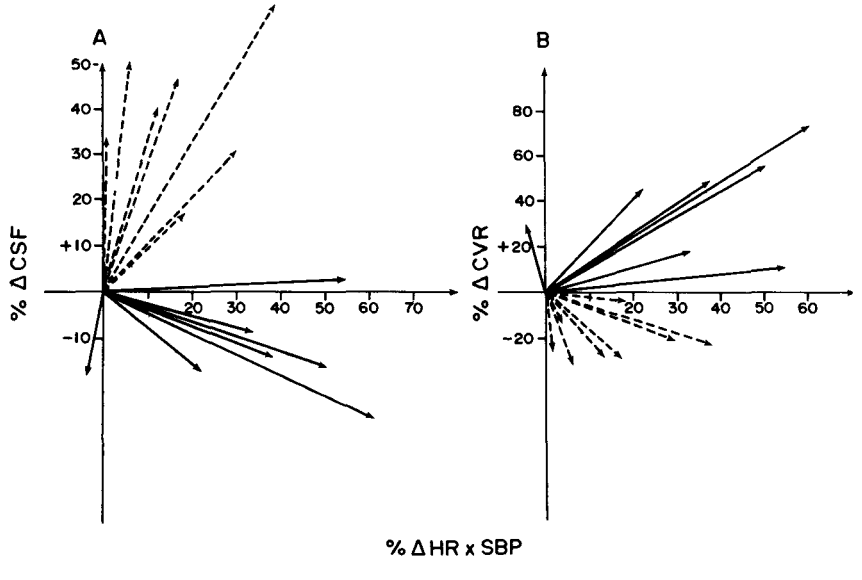

Figure 1. Individual responses of percent change in coronary sinus flow (△ CSF) and percent change in coronary vascular resistance (△ CVR) versus percent change in heart rate-systolic blood pressure (HR × SBP) product 2 minutes after the administration of a total dose of 0.35 mg of ergonovine intravenously. Values in patients whose coronary vascular resistance increased (Group A) are plotted with **solid lines**; patients whose coronary vascular resistance decreased (Group B) are plotted with **dashed lines.**

was reported. Left ventricular end-diastolic pressure and volume (7,8) increase with ergonovine.

In patients with severe obstructive coronary artery disease, ergonovine may precipitate classic angina associated with ischemic electrocardiographic changes, presumably as a result of increases in the determinants of myocardial oxygen demand. In patients with variant angina, ergonovine induces focal coronary artery spasm (85 to 100%) (5,8,10) and reliably reproduces the clinical syndrome.

Coronary hemodynamics in patients with variant angina versus atypical chest pain after ergonovine. Few studies (5,7,8,10) have measured coronary blood flow under conditions of spontaneous or provocable coronary artery spasm. The lack of an increase in myocardial blood flow has been demonstrated in patients with variant angina due to coronary artery spasm. In previous studies, a 30 to 50% decrease in coronary sinus flow was observed in patients with documented variant angina after ergonovine administration (5,8,10). Calculated coronary vascular resistance increased more than 40% (5,8), and in some patients myocardial lactate production (5,6) and increased oxygen extraction (5,10) occurred. In contrast, in patients without variant angina, but with atypical chest pain, no significant change (5,7) or a decrease (8) in coronary vascular resistance was observed and coronary sinus flow increased (5,7,8). There was also no electrocardiographic and metabolic evidence of myocardial ischemia (6) in these patients after ergonovine provocation. These findings suggested that the determination of changes in coronary hemodynamics after administration of ergonovine may be helpful in the diagnosis of variant angina due to focal coronary artery spasm and in differentiating these patients from those who present with atypical chest pain (5).

The results of our present study, however, indicate that the diagnosis of variant angina due to coronary artery spasm cannot be made on the basis of changes in coronary vascular resistance or coronary sinus flow alone after ergonovine stimulation. Our patient population contained no patients with significant coronary artery disease. None of our patients had clinical or electrocardiographic evidence of variant angina. Furthermore, after ergonovine stimulation, no patient developed changes in the electrocardiogram or in myocardial perfusion and there was no change in lactate extraction or arterial-coronary sinus oxygen difference. Although 73% of patients developed their typical chest pain syndrome, the cause does not appear to be cardiac as judged from these metabolic, scintigraphic and electrocardiographic variables. Other causes for chest pain that can be provoked with ergonovine administration such as esophageal spasm (18) are also possible.

The expected systemic hemodynamic effects of ergonovine were seen. An increase in blood pressure and heart rate-blood pressure product occurred in almost all patients. Yet, in 7 of 15 patients, coronary vascular resistance increased and no clinical, electrocardiographic, metabolic or scintigraphic evidence for myocardial ischemia could be detected. This suggests that in response to ergonovine, a transient increase in coronary vascular resistance and decrease in coronary blood flow, despite increased myocardial oxygen demand, can occur in normal subjects without variant angina.

These findings indicate that a wide variability in response to ergonovine occurs in patients with normal coronary arteries and normal left ventricular function. The changes in coronary vascular resistance in normal subjects overlap the range of increases that have been reported for patients with spasm. We did not do simultaneous coronary angiography, but in other studies the observation of hemodynamically minor changes in the large epicardial arteries implies that the increased coronary vascular resistance probably occurs at an arteriolar level, as suggested previously, and no significant metabolic changes were recorded to indicate that these changes in resistance were physiologically important.

Methodologic considerations. Coronary vascular resistance is a function of blood pressure and coronary sinus flow. The measured value of coronary sinus flow, in turn, is the sum of a component due to measurement error and a component due to physiologic alterations in coronary hemodynamics. The component due to measurement error is not insignificant. Unrecognized changes in catheter position may contribute to this error. One way this can happen is by including or excluding branches of the coronary venous drainage as the catheter moves either more distally or more proximally thereby changing the calculated coronary sinus flow. A second way is by reflux of blood from the right atrium into the coronary sinus when the catheter is too proximally located (14). We therefore took care to position our catheter in the midcoronary sinus to prevent this error. In doing so, we undoubtedly missed the contribution of veins that enter the coronary sinus near its ostium, explaining the low flows recorded in some cases. However, because we interpreted our data in terms of relative changes in flow, we believe our conclusions should be valid.

It also needs to be emphasized that coronary sinus flow is an estimate of total left ventricular arterial flow. Regional contributions cannot be distinguished. Furthermore, actual arterial flow is not measured, although coronary sinus flow has been shown to correlate well with total left ventricular arterial flow in the dog (13). Finally, decreases in coronary sinus flow may result from increases in the left ventricular end-diastolic pressure which have been reported with ergonovine (7,8) in the absence of coronary artery spasm. Although some of the decreases in coronary sinus flow were relatively small, so that measurement error may have contributed significantly to the observation of the decrease, our findings are still valid. Even if no significant change in coronary sinus flow had been observed (that is, the decrease in observed coronary sinus flow was totally attributed to measurement error), the response of this group to ergono-

vine would still be striking in the light of the significant increase in heart rate-systolic blood pressure product (36%, $p < 0.02$).

Coronary vascular resistance data must be interpreted cautiously when the aforementioned factors contributing to the measurement error in coronary sinus flow are considered. The reproducibility of repeated measurements in our laboratory, which has a large experience in coronary sinus flow determinations, is similar (5,7,8) to that in other laboratories employing this technique. Our data indicate that substantial increases in coronary vascular resistance (mean 39%, range 11 to 75%) can be seen in a subgroup in whom average coronary sinus flow decreased significantly.

Clinical implications. Our findings indicate a range in the responsiveness of coronary hemodynamics to ergonovine provocation. Most patients without variant angina show an increase in the determinants of oxygen demand in response to ergonovine and an expected increase in coronary sinus flow and decrease in coronary vascular resistance. However, there is a group of patients who have an unexpected response to the drug, resulting in an increase in coronary vascular resistance with an inappropriately small increase or decrease in coronary sinus flow. Therefore, coronary sinus flow and coronary vascular resistance measurements alone may not be diagnostic of variant angina. Associated hemodynamic findings, electrocardiograms, thallium scans and metabolic values must also be considered in the diagnosis of variant angina.

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