The Anginal Syndrome Associated with Normal Coronary Arteriograms

Report of a Six Year Experience

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Although the occurrence of normal coronary arteriograms in patients with anginal pain is now recognized as a clinical entity, a large-scale study of such patients has not been reported. Accordingly, the historic aspects, laboratory findings and subsequent clinical course of 200 subjects (101 men and 99 women) with this syndrome were analyzed. Their average age was 47 years. No specific feature in the history could be discerned which separated these patients from those with angina due to coronary heart disease. The frequency of noncardiac sources of chest pain was similar in all patients. The electrocardiogram demonstrated abnormalities in the ST-T waves in slightly over 50 per cent of the patients, and the postexercise electrocardiogram was abnormal in another 20 per cent. Objective evidence for myocardial ischemia (myocardial lactate production) was three times more frequent in women than in men. The frequency of carbohydrate and/or lipid abnormalities was approximately half that in patients with coronary heart disease and did not correlate with the presence of myocardial ischemia. Long-term follow-up of these patients indicated that over half showed gradual improvement without specific therapy, whereas only 8 per cent had an increase in chest pain. Six patients died (four of unknown cause) in an average follow-up period of three years. Mortality, however, as determined by the life table method, was no greater than in a sex-age matched cohort derived from actuarial data. Although the etiology of this syndrome has not yet been demonstrated, its prognosis both in terms of persistence of pain and mortality appears to be benign.

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After nearly two centuries of controversy, the classic studies of Blumgart and others [1,2] seemed to establish coronary atherosclerosis as the underlying pathologic condition in patients with angina pectoris. Because angina is a syndrome defined by history, it was inferred that inaccuracy in evaluating the history accounted for any exceptions that occurred. Yet, scrutiny of the data of Blumgart et al. reveals that a small percentage of patients who apparently had classic angina pectoris during life had no significant coronary atherosclerosis, aortic valve disease or evidence of hypertensive vascular disease at postmortem.

The increasingly widespread application of coronary arteriog-

TABLE I Anginal Syndrome with Normal Coronary Arteriograms: Historic Findings

Clinical Features	Group 1		Group 2		Total	
	No.	%	No.	%	No.	%
Pain precipitated by						
Exertion	88	100	34	30	122	61
Cold	44	50	22	20	66	33
Emotion	65	74	39	35	104	52
Night	43	49	22	20	65	33
Eating	29	33	11	10	40	20
Rest	48	54	84	75	132	66
Pain relieved by						
Nitroglycerin less than 5 min	53	60	28	25	81	41
Pain radiation						
Left precordium or arm	66	75	56	50	122	61

NOTE: Group 1 = 88 subjects with pain predominantly related to exertion; group 2 = 112 subjects with pain not predominantly related to exertion.

raphy re-awakened interest in this apparently settled issue because arteriograms did not always confirm the anginal histories. Several centers have reported normal coronary arteriograms in as many as 30 per cent of the patients with chest pain suggestive of ischemic heart disease. Narrowing the issue to patients whose chest pain is predominantly related to exertion, approximately 10 per cent are free of major vessel coronary disease as defined by arteriography [3–6]. Both the etiology and pathophysiology of this type of chest pain remain unknown.

Our purpose here is to review a six year experience with patients who had chest pain but whose coronary arteriograms were normal.

MATERIALS AND METHODS

Two hundred subjects with chest pain suggestive of coronary artery disease, who were subsequently found to have normal coronary arteriograms, were studied at the Peter Bent Brigham Hospital between January 1964 and January 1970. These subjects comprise the study population. The group was made up of 101 men and 99 women ranging in age from 19 to 68 years (average 47 years). Subjects were admitted to the study population consecutively.

History and Physical. A standardized history was taken independently by at least two staff members of the Cardiovascular Division. This history included general characterization of the pain; precipitation by exertion, emotion and cold weather; occurrence at night and during or after eating; relief by rest or nitroglycerin; and radiation. Each subject had chest pain with some characteristic or combination of characteristics sufficient to suggest the pain of ischemic heart disease. For purposes of this study patients who had smoked at least 1/2 pack of cigarettes for at least one year were classified as smokers. A thorough physical examination was performed. Diastolic blood pressure greater than or equal to 100 mm Hg (or history of such an elevation) was regarded as evidence of hypertension. The subjects in the study were separated into two groups on the basis of the historic information obtained. Those in group 1 (88 subjects) had a history of chest pain predominantly brought on by exertion and relieved by rest. Those in group 2 had a history of chest pain which was not predominantly related to exertion. The historic evaluation of these two groups will be discussed further.

Laboratory Data. An intravenous glucose tolerance test was performed in 114 subjects. In the majority it was accomplished two days after hospitalization while they were on a high carbohydrate diet. After an overnight fast, glucose (0.5 g/kg body weight) was given intravenously, and blood samples were analyzed for glucose content at 10 minute intervals for one hour. A rate constant was determined as $K = 70/t\ 1/2$ in min. K values less than or equal to 1.0 were considered to indicate abnormal glucose tolerance. Fasting blood samples were drawn on the day of admission and analyzed for cholesterol (190 subjects) and triglyceride (155 subjects) content. Cholesterol values in excess of 300 mg/100 ml and triglyceride values in excess of 200 mg/100 ml were considered abnormal. Because lipoprotein electrophoresis was not available in patients studied prior to 1967, this information is not reported herein.

Extracardiac sources of pain were studied in 155 subjects by means of an x-ray series of the upper gastrointestinal tract, a cholecystogram and x-ray examination of the cervicodorsal spine. During the series of x-ray films of the gastrointestinal tract, the subject was specifically examined in the Trendelenberg position for hiatus hernia. Nonvisualized gallbladders were reexamined by administering a double dose of the contrast agent. Films were interpreted by the Radiology Department of the Peter Bent Brigham Hospital and reviewed as well by staff members of the Cardiovascular Division.

Electrocardiography and Exercise Tests. A standard 12 lead electrocardiogram was obtained in all 200 subjects at rest. One hundred and twenty subjects who were not taking digitalis were exercised utilizing Master's double 2-step test. The test was performed in the standard manner, the end point being either chest pain, undue fatigue or dyspnea, or completion of the required number of trips. Full 12 lead electrocardiograms were obtained immediately and at one, three, five and eight minutes after exercise. Segmental R-ST depression of greater than or equal to 0.5 mm occurring in 50 per cent of recorded complexes in any lead was considered a positive response. T wave changes alone were not considered as positive responses. Postexercise S-T segment elevation, conduction defects or sustained arrhythmias were not observed.

Catheterization Data. All subjects underwent right and left heart catheterization with selective coronary cine arteriography and left ventriculography. Hemodynamic parameters were measured in a standard man-

ner using Statham P23DB strain gauges and a Sanborn 530 photographic recorder. To exclude clearly identifiable cardiomyopathy with chest pain, patients whose left ventricular end-diastolic pressure was greater than 15 mm Hg, or who had an abnormally large left ventricle (end-diastolic volume greater than 120 ml/m^2) or a reduced ejection fraction (less than 0.50) were not included.

Arteriography was performed by the Sones technic utilizing either GE or Siemens x-ray image intensification systems (9 to 6 inch dual field) and recording on 16 mm film. Multiple projections of both coronary arteries were obtained. At least two members of the staff reviewed these films and agreed as to the normality of the coronary circulation. Isolated, minor (less than or equal to 10 per cent of lumen) irregularities in the vessel lumen were no cause for exclusion.

A left ventriculogram was obtained in the right anterior oblique projection (30 degrees) in all subjects.

Coronary Circulatory Studies. A catheter was placed in the coronary sinus, and paired arterial-coronary sinus blood samples were analyzed for lactate concentration in 100 subjects. In all subjects samples were obtained at rest and during isoproterenol infusion (2 to 6 μg/min, 88 subjects) or during atrial pacing up to rates of 150 beats/min (12 subjects). Lactate concentrations were determined in duplicate by a slight modification of the method of Horn and Bruns previously reported from this laboratory [7]. An extraction coefficient (F) was calculated

$$F = \frac{L_A - L_{CS}}{L_A} \times 100$$

L_A equals arterial lactate concentration and L_{CS} equals coronary sinus lactate concentration in millimoles/liter. A negative F value (production) was interpreted as an ischemic response. Coronary blood flow was measured by the inert radioactive gas technic utilizing either ^{85}Kr or ^{133}Xe [8]. Flows were obtained in 18 subjects at rest and in six subjects during isoproterenol infusion (2 to 6 μg/min). Paired arterial-coronary sinus blood samples obtained simultaneously were analyzed for oxygen content by the manometric technic. Oxygen extraction (F) was calculated

$$F = \frac{O_{2A} - O_{2CS}}{O_{2A}} \times 100$$

Follow-up Data. Subjects who failed to respond to mailed questionnaires were interviewed by telephone. When patients or their immediate families could not be contacted, follow-up data were sought from their referring physicians. In addition, these physicians were contacted to establish causes of death or to verify reports of prolonged hospitalization for chest pain.

RESULTS

History (Table I). A detailed analysis of the history in the 200 subjects is shown in Table I. By definition, all the subjects in group 1 had precipitation of pain by exertion, however nearly 30 per cent of the subjects in group 2 also had occasional but unpredictable precipitation of pain by exertion. A relatively high proportion had a history of pain at rest without known precipitating cause. Two-thirds of the subjects whose pain was predominantly related to exertion (group 1) obtained rapid relief after taking nitroglycerin sublingually. Thirty-nine per cent of the patients were smokers and 22 per cent had hypertension; there were no significant differences between the groups.

TABLE II Anginal Syndrome with Normal Coronary Arteriograms: Carbohydrate and Lipid Studies

Study	Group 1 No.	Group 1 %	Group 2 No.	Group 2 %	Total (no.)
Carbohydrate					
Tested	55	63	59	57	114
Positive	23	42	27	46	50
Lipid					
Tested	86	98	105	94	191
Positive	27	31	29	28	56

Predisposing Metabolic Factors to Coronary Heart Disease (Table II). Carbohydrate intolerance, as defined by an abnormal fasting plasma glucose level or by the intravenous glucose tolerance test, was present in 23 of 55 subjects tested (42 per cent) in group 1 and in 27 of 59 tested (46 per cent) in group 2. Overt diabetes was present in only one subject. Abnormalities of lipid metabolism, either triglyceride or cholesterol, were present in 56 of 191 subjects tested in both groups.

Extracardiac Source of Pain (Table III). Of the 13 subjects with abnormalities of the gallbladder, two had stones and underwent cholecystectomy. Neither experienced significant relief of pain. Cervical laminectomy in one patient with severe disc disease effected no relief of the pain syndrome. Findings in other patients were not considered severe enough to explain the pain or to justify spe-

TABLE III Anginal Syndrome with Normal Coronary Arteriograms: Noncoronary Pain Factors

Roentgenographic Procedures and Result	Group 1	Group 2	Total
Oral cholecystograms	54	58	107
Abnormal	6	7	13
Series of upper gastrointestinal tract	58	75	133
Abnormal	10	18	28
Cervicodorsal spine films	60	68	128
Abnormal	24	30	54
Patients undergoing 1 or more of these procedures	73	82	155
Patients with at least 1 abnormality on x-ray film	33	41	74

TABLE IV Anginal Syndrome with Normal Coronary Arteriograms: Resting Electrocardiogram

Resting Electrocardiogram	Group 1	Group 2	Total
Normal	41	56	97
Arrhythmia	7	5	12
AF	1	2	
VPB	5	3	
APB	1	0	
ST-T wave abnormality	30	39	69
T wave abnormality	7	3	10
QRS abnormality	15	13	28
LBBB	5	3	
RBBB	5	4	
WPW	1	1	
LAD	1	3	
RAD	1	0	
LVH	3	2	
1° A-V block	2	2	4
Acute myocardial infarction	2		
Possible	1	0	
Certain	1	1	
Diaphragmatic myocardial infarction			
Possible	0	1	
Certain	1	1	
Subtotal	3	3	6
Total*	64	65	129

NOTE: AF = atrial fibrillation; VPB = ventricular premature beats; APB = atrial premature beats; LBBB = left bundle branch block; RBBB = right bundle branch block; WPW = Wolf-Parkinson-White syndrome; LAD = left axis deviation; RAD = right axis deviation; LVH = left ventricular hypertrophy.

* Do not necessarily add up to number of patients because some patients had multiple abnormalities.

cific therapeutic measures. Medical management was applied to all 11 subjects with small sliding hernias, but none was relieved of pain. Other abnormal findings, such as duodenal scarring, were minor in degree.

Electrocardiogram (Table IV). Some abnormality in the electrocardiogram was noted in slightly over half the subjects, the most frequent being nonspecific changes in the S-T segment and T waves. Patterns considered diagnostic of prior transmural myocardial infarction were present in four subjects, two in each subgroup. These were evenly divided between patterns of anterior and inferior infarction. No clear differentiation in the electrocardiogram could be made between subjects with and without pain predominantly related to exertion. The electrocardiogram was further analyzed on the basis of sex; it was normal at rest in 41 of 99 women and in 56 of 101 men. The frequency of nonspecific S-T segment and T wave abnormalities was significantly higher in women than in men (p less than 0.01).

Postexercise Electrocardiogram (Table V). Thirty-one (20 per cent) of 152 Master double 2-step tests were positive; 10 of 64 in group 1 and 21 of 86 in group 2. The difference between the two groups was not significantly different. Of the total group with normal resting electrocardiograms 14 per cent showed segmental R-ST depression after exercise.

Analysis of these data on the basis of sex revealed that 11 per cent of the men and 34 per cent of the women in both groups had a positive response to exercise. Further, only one man with a normal control electrocardiogram had a positive response to exercise, so that seven of the eight positive responses in men occurred in the presence of an abnormal resting electrocardiogram. This differed from the female patients in whom nearly half of the positive responses (11 of 23) occurred in subjects with normal control tracings.

Myocardial Lactate Metabolism (Table VI). Approximately 20 per cent of the subjects in groups 1 and 2 had metabolic evidence of ischemia during stress, without significant difference between the two groups. Of 51 female patients, 16 (31 per cent) had an abnormal response. Of 49 male patients, only 6 (12 per cent) had an abnormal response.

Coronary Hemodynamics. Coronary blood flow at rest was 101 ± 22 ml/100 g/min. In six subjects receiving isoproterenol infusion, coronary flow was 140 ± 25 ml/100 g/min. Oxygen extraction

TABLE V Anginal Syndrome with Normal Coronary Arteriograms: Results of 2-Step Postexercise Tests

	No. Patients Tested	No. Positive
Group 1 (64 patients)		
Control electrocardiogram		
Normal	38	4
Males	25	1
Females	13	3
Abnormal	26	6
Males	10	1
Females	16	5
Group 2 (86 patients)		
Control electrocardiogram		
Normal	50	8
Males	30	0
Females	20	8
Abnormal	36	13
Males	18	6
Females	18	7
Total	150	31

TABLE VI Anginal Syndrome with Normal Coronary Arteriograms: Lactate Extraction During Stress

	No. Studied	No. Abnormal
Group 1 (53 patients)		
Males	24	2
Females	29	10
Group 2 (47 patients)		
Males	25	4
Females	22	6
Total	100	22

NOTE: Total females tested = 51, abnormal 16, per cent = 31. Total males tested = 49, abnormal 6, per cent = 12.

at rest was 66 ± 8 per cent and fell to 60 ± 5 per cent during isoproterenol infusion in eight subjects. Coronary sinus oxygen content was 5.8 ± 1.6 volumes per cent at rest. This value was 7.0 ± .64 volumes per cent in eight subjects studied during isoproterenol infusion. These data do not differ significantly from those found in normal subjects [9].

Correlative Data. We attempted to correlate predisposing factors to atherosclerosis with metabolic or electrocardiographic evidence for myocardial ischemia. Of 200 subjects 50 showed an abnormality in either the postexercise electrocardiogram or in myocardial lactate metabolism. Eleven of the 47 subjects with an abnormal intravenous glucose tolerance test and 12 of 57 subjects with lipid metabolic abnormalities had evidence of ischemia. Therefore, no specific relationship was seen. Of 50 patients with evidence of ischemia, 7 had a lipid disorder and 11 carbohydrate intolerance. These proportions are the same as the prevalence of the metabolic disorders in the study groups as a whole.

Effect of Antianginal Agents (Table VII). The history of the effect of nitroglycerin administration, which was obtained at the time of admission for cardiac catheterization, has been presented earlier for both groups (Table I). The data obtained by questionnaire at the end of the study period (summer, 1971) was very similar: slightly more than 50 per cent reported prompt diminution in pain after taking nitroglycerin (Table VII).

Of 50 patients who received propranolol and were sampled by questionnaire at the end of the study, 30 (60 per cent) reported some diminution in the frequency and severity of pain. A somewhat greater proportion of patients with exertional pain (group 1) obtained relief as compared to patients with predominantly nonexertional pain (group 2) (Table VII). However, when a subgroup of these patients was subjected to a more rigorous drug-response evaluation using personal physician interviews and double-blind technics, only 6 of the 26 subjects (23 per cent) were adjudged to have obtained prolonged improvement. Methods and results of this trial, and comparison with subjects with coronary artery disease have been reported in detail elsewhere [10].

Follow-up Data (Table VII). Follow-up data were obtained on all 200 patients during a six year period (mean duration three years). About 40 per cent of the total group had mainly exertional chest pain at the time of first evaluation. Of the six deaths, two were due to noncoronary causes and four were from unknown causes. One of these four patients had a history of idiopathic ventricular tachycardia. In another one of the four an autopsy was performed in a small New England community hospital. The heart was normal on both gross and microscopic examination, and the official cause of death was undetermined.

Life table analysis (Figure 1) indicates that longevity in these patients is similar to the population at large [11]. The benign nature of the disease in the surviving patients is also illustrated in Table VII. Less than half the subjects required medication, and very few patients complained of worsening symptoms. There were 19 hospitalizations for chest pain, none of which culminated in a proved

TABLE VII Follow-Up Data on 200 Patients with Chest Pain Syndromes and Normal Coronary Arteriograms

	Total	Group 1	Group 2
Total group	200	88	112
Alive as of 9/1/71	194	86	108
Deceased	6	2	4
Lost to follow-up	0		
Frequency and severity of pain			
Improved	108	46	62
Unchanged	71	28	43
Worse	15	12	3
Response to nitroglycerin			
Adequate trial	81	43	38
Prompt relief	41	24	17
Slow relief	23	11	12
No effect	17	8	9
Response to propranolol			
Adequate trial	50	23	27
Improved	30	18	12
No effect	16	3	13
Worse	4	2	2
Hospitalizations for chest pain	18	7	11
Other medical problems	17	8	9

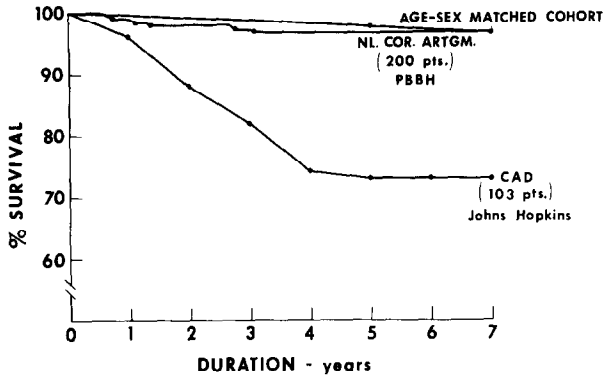

Figure 1. Comparison of mortality between the study population and (upper curve) an age-sex matched cohort taken from U.S. population life tables (Vital Statistics of the United States, Volume II. Mortality, printed by USPHS, 1967) and subjects with arteriographically proved coronary artery disease taken from the study of Friesinger, Page and Ross [11].

myocardial infarction. In one patient congestive heart failure developed and a diagnosis of idiopathic cardiomyopathy was subsequently made.

COMMENTS

A syndrome of chest pain in the absence of major coronary arterial obstruction has been observed over a six year period. In contrast to other studies [5], this syndrome occurred with equal frequency in men and women. Coronary heart disease is frequently suspected not only because of the history, but also because of an abnormal resting electrocardiogram. The latter, of course, may be a factor in the preselection of patients for study, since a patient with chest pain and an abnormal resting electrocardiogram is more likely to be referred for catheterization and angiography than is a patient with a normal electrocardiogram. When a Master's double 2-step test was performed, 20 per cent showed an ischemic electrocardiographic response. Metabolic disorders predisposing to atherosclerosis were present, but the prevalence was much lower than in subjects with proved coronary heart disease [12]. Because patients with abnormal hemodynamics were excluded, the symptoms could not be explained on this basis. Coronary physiology, as determined by measurements of coronary blood flow, and myocardial oxygen extraction were normal. On the other hand, lactate utilization by the myocardium was abnormal in approximately 20 per cent of the total group, suggesting that cellular hypoxia may develop during certain stressful states, such as isoproterenol infusion or pacing induced tachycardia. The occurrence of ischemic electrocardiographic responses to exercise and lactate production by the heart during stress strongly support the view that the pain is of cardiac origin, at least in those patients who have such abnormalities. No pathologic correlation is as yet available, however. No specific historic features [13] or evidence concerning sources of noncardiac pain [14] could differentiate these patients from patients with coronary heart disease. Interestingly, objective evidence of myocardial ischemia was found three times more frequently in women than in men. The explanation for this observation is not known. The most accurate diagnostic approach has been a multifactorial one, as reported recently from this laboratory [15].

Management of these patients is difficult. Of 87 patients taking nitroglycerin 41 responded promptly to this drug or to one of the longer acting nitrate compounds, and 30 of 50 patients showed a favorable response to beta adrenergic blocking agents. When an apparent emotional component was present, we encouraged patients to be evaluated with possible long-term psychotherapy in mind. Although hard to analyze objectively, our impression is that beneficial results have only rarely been obtained.

Long-term follow-up with or without specific medical management, however, has been encouraging. About half of the patients obtained relief of pain over several years, and in only 8 per cent did the pain syndrome worsen. No myocardial infarctions have been documented during the follow-up period, although four patients had had a clear cut infarction prior to study.

As noted by others [11,16], and confirmed in the present study, mortality is not increased over that of the population at large when matched for sex and age. Four patients died suddenly; autopsy in one revealed an essentially normal heart.

The question of the underlying etiology of this syndrome requires further consideration. The major hypotheses are as follows:

(1) Psychosomatic etiology. Some investigators believe that normal coronary arteriograms associated with a normal left ventriculogram and left ventricular pressures rule out organic heart disease. They contend that the chest pain in such patients, therefore, is psychosomatic in origin. The occurrence of electrocardiographic abnormalities at rest as well as after exercise, and the metabolic evidence of ischemia cited and reported by others [17], are, however, left unexplained by the psychosomatic theory. At least two reasons make it difficult to assess this hypothesis: (1) the obvious difficulty of scientifically quantifying psychiatric disease and (2) the high incidence

of emotional disorders in patients with chronic chest pain and proved coronary heart disease.

(2) Misinterpretation of the arteriogram. In a recent editorial it was suggested that the majority of these patients have coronary atherosclerosis which has escaped diagnosis by the coronary arteriogram [18]. This possibility has also concerned us because the undetected lesion could easily explain the occurrence of electrocardiographic and metabolic evidence of ischemia. In addition, one can postulate such lesions as "flush" occlusions of secondary branches of the coronary arteries that would defy proper interpretation even by the most skillful arteriographer. The only study directly bearing on the issue of accuracy suggests that when coronary arteriograms are of excellent roentgenographic quality, few, if any, errors are made in interpretation [19]. This may be partly due to the nature of the disease process. "Flush" occlusions of single vessels are rarely found at necropsy without ample evidence of atherosclerosis elsewhere in the coronary circulation or of local collateral vessels filling a distal segment. Furthermore, the finding of a single occluded secondary branch of a coronary artery at postmortem is only rarely associated with antemortem symptoms. Finally, five patients in this study underwent coronary arteriography at widely separated intervals in time. No lesions of the coronary arteries were identified at subsequent study.

Coronary atherosclerosis is usually progressive relative to morbidity and mortality, and atherosclerosis is cumulative as a function of time [20]. The clinical course of this syndrome therefore virtually excludes the possibility of these patients having unrecognized coronary atherosclerosis. The gradual resolution of the pain syndrome over several years in the majority of patients and the benign prognosis speak strongly against this explanation accounting for anything but a rare patient. Nevertheless, it must be kept constantly in mind, particularly when the arteriograms are not of the highest roentgenographic quality.

(3) Defect of oxyhemoglobin dissociation. In a recent report, Eliot and Bratt [21] showed significant rightward shifts of oxyhemoglobin dissociation curves at rest in 14 of 15 women with findings consistent with myocardial ischemia and normal coronary arteriograms. They suggested that this abnormality may play a causative role in this condition. This type of defect, however, would cause oxygen to be *more* dissociated from hemoglobin at the same saturation and pH, i.e., hemoglobin would have a lower affinity for oxygen, thus releasing it to the tissues more readily. Hemoglobin affinity for oxygen was examined in 19 patients in this series and was found to be normal [22]. In addition, this theory is unappealing because the normal regulatory mechanisms can augment coronary blood flow many fold to provide adequate oxygen in states with reduced arterial oxyhemoglobins such as anemia and arterial hypoxemia [23]. Further, if a defect in hemoglobin oxygen dissociation were the cause of oxygen deprivation, one would expect to find high resting coronary blood flow, low oxygen extraction and high coronary venous oxygen content, whereas our data indicate that these parameters are normal. On balance, abnormalities of oxyhemoglobin dissociation appear to be an unlikely explanation for this syndrome.

(4) Disease of the small vessels of the myocardium. Attention has been directed recently toward disease that can occur in coronary arteries that are between 0.1 and 1.0 mm in diameter [24]. Disease of such small vessels is not readily identified by the technic of coronary cine arteriography. Diffuse obstructive disease at this level could account for regional ischemia and in every way simulate obstruction of the major coronary branches. Because each individual obstructed artery supplies relatively little myocardium, the benign nature of the clinical course might be accounted for. James [24] has pointed out, however, that the clinical course of patients with proved small vessel disease is characterized by a high incidence of conduction disturbances and arrhythmias. Although a few such abnormalities were present in our patients, chest pain and not arrhythmias dominated the clinical picture. In this study two patients had rheumatoid arthritis, and a third had arthritis of unknown etiology. Rheumatoid arthritis may involve the small vessels of the myocardium. Three other patients in our series complained of pain and blanching of the finger tips on exposure to cold, but none had objective evidence of tissue necrosis. No supporting data for scleroderma, lupus erythematosus or polyarteritis could be accrued. Two other instances of systemic disease occurred in our study group: fibromuscular hyperplasia of the external iliac arteries bilaterally and ulcerative colitis.

(5) Spasm of the coronary arteries. Soon after the advent of coronary arteriography, it was appreciated that intense, localized vasoconstriction of the major coronary arteries could be seen either at the catheter tip or a few centimeters distal to it, apparently induced mechanically. Spasm could be completely relieved by nitroglycerin. The angiographic picture is quite striking because the lumen can be almost obliterated. Spasm occurs most frequently in women and after the injection

of the right coronary artery. The patient is characteristically asymptomatic during the period in which the arterial segment is in spasm. Whether spasm ever occurs in the absence of manipulation of the coronary arteries is unknown. Nevertheless, the ability of the coronary arteries to exhibit a "functional" stenosis of profound degree demands our continued interest.

(6) Heterogeneous etiology. The syndrome may be caused by any one of the previously mentioned etiologies. In patients who exhibit objective evidence of myocardial ischemia, the etiology might be masked coronary artery obstruction, vasculitis, coronary spasm, cardiomyopathy or an as yet unidentified defect in myocardial metabolism. In patients without ischemic changes, the cause may be either emotional or due to an as yet unidentified extra cardiac factor.

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