Long-Term Observations in Patients with Angina and Normal Coronary Arteriograms

By Carl R. Bemiller, CDR, MC, USN, Carl J. Pepine, LCDR, MC, USN, and Albert K. Rogers, CDR, MC, USN

SUMMARY

Thirty-seven patients (mean age 42.7 years) with angina pectoris (AP), ischemic myocardial abnormalities, and normal coronary arteriograms were followed for 4.1 years (mean). Twenty patients had typical and 17 atypical AP. Ten had abnormal serum lipids, and eight had abnormal glucose tolerance tests. Rest-to-exercise hemodynamics revealed increased left ventricular (LV) end-diastolic pressure (mean $11.2 \pm 2.6$ mm Hg $\rightarrow 19.1 \pm 3.6$, $P < 0.05$), while stroke-work index increased (+29%). LV ischemia was detected by abnormal lactate extraction with atrial pacing in 10 or $\geq 1$ mm S-T segment depression during exercise or pacing in 27 patients.

After a mean follow-up period of 4.1 years, AP decreased in 80% of cases and remained stable in the other 20% of cases. One patient died suddenly, and autopsy revealed normal coronary arteries and myocardium. In the remainder, complications of ischemia, i.e., progression of symptoms, infarction, and heart failure were absent. Seven patients restudied 4.5 years (mean) later had no changes in their previously documented hemodynamic abnormalities and normal coronary arteriograms.

The fate of patients with AP and normal coronaries with ischemic LV abnormalities (ECG, metabolic, or hemodynamic) appears favorable. AP responds to nitrate and propranolol therapy. These long-term clinical observations with angiographic and hemodynamic restudies suggest a nonprogressive disorder.

Additional Indexing Words:
Coronary angiography Angina pectoris Atypical angina pectoris Myocardial ischemia
Propranolol

Ischemic electrocardiographic, hemodynamic, and myocardial metabolic abnormalities accompany significant coronary obstruction in the large majority of angina pectoris patients studied.1-4 Considerable interest, however, has attended recent reports indicating that angina pectoris associated with evidence of myocardial ischemia may be encountered in patients having angiographically normal coronary arteries without other types of cardiovascular disease.5-11 Since angina pectoris in the presence of significant coronary artery disease has been associated with a heightened incidence of morbidity and sudden death, the recognition of this symptom in the absence of obstructive coronary artery disease has raised numerous questions.

Central among these relates to the clinical significance of angina pectoris in this setting as a harbinger of serious morbidity. The purpose of this study is to report our long-term observations in such a group of patients with the anginal syndrome and normal coronary angiography.

Materials and Methods

The study group comprised 37 patients (21 males, 16 females) who underwent diagnostic studies to evaluate an anginal syndrome. All had normal selective coronary angiography reviewed independently by two of us, and objective evidence (electrocardiographic and/or myocardial metabolic studies) of myocardial ischemia. Only patients followed for at least 1 year are included.

Clinical evaluation included complete history and physical examination, cardiac X-ray series, resting and submaximal exercise electrocardiograms, multiple fasting serum cholesterol and triglyceride levels, and lipoprotein electrophoretic pattern. A 4-hour glucose tolerance test and/or fasting and a 2-hour postprandial glucose test was performed in all. All patients in this study had episodic chest discomfort consistent with an anginal syndrome. These complaints were considered typical of angina pectoris when they were felt to

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conform to the broad criteria outlined by Hurst and Logue by at least two physicians. The chest pain syndrome was considered atypical angina pectoris when some inconsistent feature was present with respect to location, duration, or provocation by effort or stress.

**Clinical Findings**

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Total 37
Mean/42.7
**SEM** 9.1%

Abbreviations: Isch = ischemic; LAD = left-axis deviation (≥ -30°); LBBB = left bundle-branch block; R = resting; E = exercise; P = atrial pacing; GTT = glucose tolerance test; T = typical; At = atypical; N = normal; Abn = abnormal.

*Nonspecific ST-T wave changes.
†Pacing-induced angina.

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was performed with a no. 7 Zucker catheter and retrograde left ventricular catheterization with a no. 7 NIH catheter. Pressure and cardiac output measurements were made according to technics previously described from our laboratory.

After control measurements of heart rate, left ventricular pressure, and cardiac output were made, 14 patients underwent atrial pacing stress tests. Coronary sinus and arterial blood samples were withdrawn simultaneously for lactate and oxygen determinations (Instrumentation Laboratories model no. 182) at rest and during pacing.

All patients were exercised after the above control measurements or following the atrial pacing and myocardial metabolic studies on a bicycle ergometer (Collins) at a constant work load previously determined to evoke angina, significant S-T segment depression (≧ 1 mm), or 85% maximal heart rate. Hemodynamic measurements were repeated during angina pectoris or at 2 and 4 min if angina did not occur.

Left ventricular stroke-work index (g-m/beat/m²) was calculated as LVSP-LVEDP x 1.36 x SI/100, where LVSP is left ventricular systolic pressure, LVEDP is left ventricular end-diastolic pressure, and SI is stroke index. Results were analyzed by the t test for paired data.

Selective coronary angiography was performed with multiple views of both coronary arteries. Only studies with satisfactory details are included. Left ventricular angiography was performed in the right anterior oblique position.

An age-matched group of 37 patients with coronary artery disease (CAD) studied in an identical manner were used as a comparison group. All patients in this CAD group had significant (> 75%) narrowing of at least one major coronary artery observed during selective coronary angiography.

Follow-up. All patients were followed at periodic intervals (usually monthly) during the study. They were evaluated with regard to frequency, severity, and character of chest pain. Analysis of the following clinical events—sudden death, myocardial infarction, congestive heart failure, and arrhythmias—was performed. Symptomatic deterioration was defined as an increase in severity and/or frequency of chest discomfort or symptoms requiring hospitalization during the observation period. Seven patients in the normal coronary artery group underwent hemodynamic and coronary angiographic restudies during this follow-up period.

**Results**

The clinical findings are summarized in table 1. The mean age of the normal coronary artery (NCA) patients was 42.7 years, and the age-matched CAD group was 43.5 years. There were 16 (43.2%) female patients in the NCA group and only one (2.1%) female patient in the CAD group. Although all patients had an anginal syndrome, 17 of those with NCA had chest discomfort atypical for angina pectoris, compared to seven with atypical angina in the CAD group (fig. 1). The pertinent physical findings are summarized in figure 1. Results of the laboratory risk factors evaluated (fig. 2) revealed that 28.5% of patients with NCA had an abnormal lipoprotein electrophoretic pattern. In patients with CAD 75% were abnormal. An abnormal glucose tolerance test was found in 32.5% of the CAD patients and in 21.6% of the NCA group. Over one half of the patients in each group had abnormal resting electrocardiograms (fig. 2). In the NCA group, 16 had ST-T wave changes, two had left-axis deviation (≧ -30°), and two had left bundle-branch block. Similar changes were noted in the patients with CAD. However, four patients in this group also had Q waves diagnostic of myocardial infarction. Exercise and pacing electrocardiographic stress tests revealed 27
(of 37) patients had an ischemic response to either form of stress. Examples of these responses from the NCA group are seen in figure 3.

*Hemodynamic data* at rest and during exercise in both groups are shown in figure 4. Left ventricular function, evaluated by the relation of stroke-work index to left ventricular end-diastolic pressure, reveals that at rest both groups had abnormal left ventricular function. With exercise the patients with NCA increased their LVEDP from 11.2 ± 2.6 mm Hg (mean ± SEM) to 19.1 ± 3.6 as stroke-work index increased 29%. Thirty NCA patients experienced angina during these hemodynamic studies. In this subgroup, exercise ventricular function (LVEDP 22.2 ± 4.0 mm Hg, SWI 93.8 ± 5.1 g-m/beat/m²) was also significantly different from the CAD patients who all experienced angina during study. In the CAD patients, LVEDP increased from 14.0 ± 2.9 mm Hg to 29.4 ± 5.6 mm Hg, while stroke-work index increased only 12%.

**Figure 3**

Electrocardiographic stress tests characteristic of ischemia were evoked in 73.1% of the patients with normal coronary arteries during atrial pacing (left) of exercise (center). Myocardial lactate metabolism was typical of anaerobiosis in the remaining patients during tachycardia stress (right).

*Myocardial metabolic studies.* Abnormalities of myocardial lactate extraction (<10%) or during controlled atrial tachycardia (mean 9.1% ± 4.8%) were found in 10 (of 14) patients studied. Thus, 37 patients had “ischemic” electrocardiographic or lactate responses. An example from one of the 10 patients with an anaerobic response is pictured in figure 3.

*Follow-up.* The NCA group follow-up ranged from 7.2 years to 1 year with a mean of 4.1 years. The CAD group was followed for 4.5 years (mean). In the NCA group chest pain decreased in 80% of the cases, remained stable in the remaining 20%, and no case worsened. Therapy, in addition to usual medical management, included nitrates and propranolol (mean dose 200 mg) in 75% of these patients. Angina decreased in 60% of the CAD patients while 23.8% maintained a stable condition. Deterioration occurred in 16.2%, necessitating withdrawal from the study for saphenous vein bypass
procedures. All patients in the CAD group were treated with nitrates and propranolol (mean dose 240 mg) (fig. 5). Analysis of significant clinical events is summarized in figure 5. During the observation period, 43.2% of the CAD patients had myocardial infarctions and/or sudden death.

CLINICAL EVENTS DURING FOLLOW-UP PERIOD

LONG TERM COURSE OF CHEST PAIN

Figure 4

Left ventricular function graphs relating stroke-work index (SWI) and left ventricular end-diastolic pressure (LVEDP) reveal significantly more depressed function in those patients with coronary artery disease compared to those with normal coronary arteries during exercise. Repeat studies in seven patients (right) 4.6 years later demonstrate no further deterioration of ventricular function. The normal ventricular response to exercise is a shift of the SWI and LVEDP relationship upward and to the left.16

Figure 5

(Left) The incidence of new clinical events associated with ischemic heart disease occurring during the follow-up period is illustrated. Acute myocardial infarction or sudden death occurred in over one third of these patients with coronary artery disease (CAD). Symptomatic deterioration requiring hospitalization and congestive heart failure also occurred frequently. Except for one sudden death (asterisk) in the normal coronary (NCA) group, these events were absent. (Right) The long-term course of chest pain decreased or was unchanged in all those with NCA although three quarters of these patients required propranolol in addition to nitrates. In the comparison group with CAD the outcome was not as favorable.
whereas in the NCA group there were no episodes of myocardial infarction and one sudden death. Autopsy revealed that the coronary arteries and heart of this patient were normal. Congestive heart failure, absent in those with NCA, occurred in 13.5% of cases in the CAD group. Two patients in each group had arrhythmias necessitating hospitalization.

**Restudy.** Seven of the NCA patients underwent restudy after a mean interval of 4.5 years. Left ventricular function depicted by the relation of stroke-work index to left ventricular end-diastolic pressure (fig. 4) at rest and during exercise at identical work loads revealed no significant changes between studies. Selective coronary angiography, repeated in these seven patients, again demonstrated normal coronary arteries. Selected cine frames from a case typical of the group are seen in figure 6.

**Discussion**

Until recently the dictum that myocardial ischemia and its attendant clinical manifestations are a sine qua non of significant atherosclerotic coronary artery obstruction has been widely held. Reports, however, now indicate that angina pectoris, electrocardiographic signs of ischemia, and even myocardial infarction may be encountered in patients having angiographically normal coronary arteries, and, in the few postmortem studies available, anatomically patent coronary arteries have been reconfirmed. Although this problem was suggested in 1910 by Osler's description of a patient with years of recurrent angina pectoris who at autopsy had normal coronary arteries, the incidence, pathogenesis, and prognosis of these findings remain obscure.

Some aspects of this enigmatic chest pain syndrome are no doubt distorted by attempts to include patients without objective evidence of myocardial ischemia. While there probably are

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**Figure 6**

Coronary arteriograms. A typical example of the normal coronary arteriograms seen in the seven patients restudied.
patients within the spectrum of this syndrome with ischemia that remain undetected, until this syndrome is further clarified, more rigid criteria should be utilized. Thus, all patients included in this study had objective evidence of myocardial ischemia associated with their chest pain syndrome. This included significant electrocardiographic S-T segment depression (≥ 1 mm) and/or abnormal myocardial lactate utilization (< 10% extraction), and in most, transient left ventricular hemodynamic dysfunction. By closely following the clinical course of this group of patients, we sought to define the prognosis of patients with angina and normal coronary arteries compared to those with coronary artery disease. These observations should also help answer questions relating to whether these patients represent an early stage of coronary artery disease not yet apparent angiographically.

Comparison of the chest pain characteristics, physical findings, and rest and stress electrocardiograms in the patients with normal coronary arteries and those with significant coronary atherosclerotic disease revealed only minimal differences between the groups. These findings, in general, were of limited usefulness in the clinical differentiation between CAD and normal coronary arteries in individual angina patients. The female sex comprised approximately one half of our cases with NCA. When compared to other studies, some component of the chest pain syndrome, atypical for angina pectoris, was encountered twice as frequently in patients with normal coronary arteries compared to those with CAD. Analysis of laboratory risk factors revealed a higher incidence of abnormal serum lipoprotein patterns and glucose tolerance (fig. 2). However, the electrocardiographic, hemodynamic, and myocardial metabolic abnormalities seen in the NCA group were similar to those in the CAD group.

The patients were followed at periodic intervals for almost 5 years (fig. 5). In approximately 80% of the cases with NCA, their chest pain decreased in intensity and severity over this period. Three quarters of the patients with normal coronary arteries received propranolol and long-acting nitrates, and in the remainder no specific antianginal agent was utilized. All the patients in the CAD group required propranolol and long-acting nitrate therapy at some time during this observation period. Sixty percent of these cases noted a decrease in severity and frequency of their chest symptoms. However, six patients in this group deteriorated and were withdrawn from the study for saphenous vein bypass procedures. Chest discomfort remained stable in about 20% of patients in both groups during this observation period.

This study illustrates a striking absence of complications in patients with chest pain and normal coronary angiography over almost 5 years. Analysis of the occurrence of significant clinical events revealed that the CAD patients had a 43.2% incidence of myocardial infarction and/or sudden death. In the NCA group there were no episodes of myocardial infarction. One sudden death at autopsy revealed that the coronary arteries and heart were normal. Although sudden death has been reported previously in patients with normal coronary arteries, the incidence is unknown but appears to be very low and may not necessarily relate to this syndrome. Additionally, deterioration with respect to chest discomfort occurred in 16.2% of patients in the CAD group but was absent in the patients with NCA. Congestive heart failure did not occur in the NCA group but evolved in 13.5% of cases with CAD. The incidence of serious arrhythmias necessitating hospitalization in both groups was very low and possibly related to the antiarrhythmic effects of propranolol.

Data from the seven patients in the NCA group who were restudied (fig. 4) further support the benign nature of this syndrome. Analysis of left ventricular function revealed no significant deterioration between the original and later study. Selective coronary angiography again revealed normal coronary arteries. These hemodynamic and angiographic findings suggest a nonprogressive disorder and are strong evidence against this syndrome representing an early stage of coronary atherosclerotic heart disease. The relation of this group of patients to other patients with chest pain and normal coronary arteries, namely IHSS, the “vasoregulatory” syndrome, and abnormal oxygen-hemoglobin dissociation curves, is unknown at this time.

In conclusion, 37 patients with chest pain, normal coronary angiography, and objective evidence of myocardial ischemia were observed for a mean 4.1 years. Reliable clinical differentiation of this group from those with significant coronary atherosclerotic artery disease was not possible with the criteria analyzed. Their symptoms appeared to be improved...
with nitrate and propranolol therapy. Clinical, hemodynamic, and angiographic deterioration was not observed over approximately 5 years. These observations appear to suggest that a nonprogressive disorder, possibly unrelated to coronary artery disease, exists in some patients with angina pectoris and objective evidence of myocardial ischemia.

Addendum
Since the original completion of this paper, the patient follow-up time has been extended to a mean 4.8 years. There has been no clinical deterioration nor deaths observed in the NCA group.

Acknowledgment
We are indebted to Mrs. K. Dennish and J. Sartori, U.S. Navy, for their excellent assistance and cooperation during this study.

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