Pathology of Stable and Unstable Angina Pectoris

By Richard B. Guthrie, M.D., Zeev Vlodaver, M.D., Demetre M. Nicoloff, M.D., and Jesse E. Edwards, M.D.

SUMMARY
The clinical and pathological data from 46 patients who died during or shortly after coronary bypass surgery and one patient who died shortly after angiography were studied. Each patient was placed into one of three clinical categories of angina pectoris. Twelve were classified as having unstable angina pectoris, 20 as stable severe angina, and 15 as stable moderate angina. No significant difference was found between the three categories when age, sex, presence of hypertension, lipid abnormalities, diabetes, smoking, family history of myocardial infarction, or history of previous myocardial infarction were examined. Most patients in all classes of angina had extensive atherosclerotic coronary disease: 12 patients had triple vessel plus left main disease; 25, triple vessel disease; nine, double vessel disease; and only one, single vessel disease.

There was no difference in severity or distribution of coronary disease when the three categories of angina were compared. Thirty-six of the 47 patients had evidence of scarring of one or more aspects of the left ventricular wall. There was likewise no significant difference between extent and distribution of myocardial scarring between the three clinical categories. Four of the 12 patients with unstable angina pectoris had pathologic evidence of preoperative myocardial infarction, whereas this was not found in any of the 35 patients with stable angina.

Additional Indexing Words:
Coronary atherosclerosis
Coronary heart disease

IN THE ANGINAL PATIENT, only unusual circumstances allow for a correlation of the pathological changes present at or near the time of clinical evaluation.

In this study, we examined the clinical and pathological features in 47 anginal patients who had been evaluated clinically. Forty-six of these were operated upon soon after examination and died either at the time of or shortly after coronary bypass surgery. With this patient selection, it was felt that any pathological changes occurring subsequent to operation could be identified. Pathological changes not so identified could thus be correlated with clinical studies, usually done within two weeks of operation. Specific pathological profiles corresponding with the various clinical types of angina were sought. Of interest, also, was the question of frequency of clinically unidentified acute myocardial infarction in patients with unstable angina pectoris.

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Materials and Methods

Forty-seven patients with various types of angina were studied. Forty-six died after a coronary bypass procedure and one other patient died shortly after coronary arteriography. From the clinical records, each patient was classified as to the type of angina according to the following definitions.

Angina pectoris was subdivided into major types, stable and unstable. Stable angina was defined as anterior thoracic pain related to effort and relieved by rest. The duration varied from between three and ten minutes. The pattern of occurrence of stable angina does not change but may be of varied severity and may be subdivided into the moderate and severe types. Characteristic of stable angina was prompt relief of discomfort with rest or nitroglycerin.

Unstable angina was characterized as angina of recent onset (less than three weeks prior to clinical evaluation) or as angina characterized by a recent change in pattern (i.e., stable angina which has recently worsened in terms of frequency, severity, intensity and ease of provocation). Nocturnal or angina at rest, as well as episodes of prolonged angina, were often characteristic in these patients. There was no electrocardiographic or enzymatic evidence of recent myocardial infarction.

Most patients with unstable angina had been hospitalized for at least four days prior to operation, and clinical evaluation, including electrocardiographic and enzyme studies, had not shown evidence of acute myocardial infarction.

The clinical records were abstracted for a history of previous myocardial infarction, valvular disease, diabetes and smoking habits, as well as levels of blood pressure, cholesterol and triglycerides. Also, the presence or absence of a family history of myocardial infarction was noted.

At autopsy the hearts of each of the 47 cases were examined and the cardiac weight and thickness of the left ventricular wall were recorded. The coronary arteries were ex-
amined by making multiple cross-sections about 3 mm apart. The results of observations were recorded according to subdivisions of the arteries as follows: the anterior descending artery and left circumflex artery each into proximal and distal halves. The right coronary artery was divided into three segments. These were 1) the anterior (from its origin to its marginal branch), 2) the intermediate (from the marginal branch to the origin of the posterior descending branch), and 3) the posterior descending artery. The main left coronary artery was not subdivided.

The arterial obstruction by atherosclerosis was graded on a basis of 1–4. Grade 1 was from 0–25% obstruction of the lumen; grade 2, 26–49%; grade 2+, 50–74%; grade 3, 75%; grade 3+, 76–99% obstruction; and grade 4, complete occlusion. Grades 3, 3+, or 4 hereinafter will be designated as significant atherosclerosis.

Sections of the coronary arteries also were studied for the presence or absence of thrombi. The ventricular myocardium was examined by making gross serial sections from the base to the apex, each varying 1 to 1.5 cm in height. Records were made as to the size and location of scars and representative sections for histologic study were obtained from the myocardium. The hearts were also examined for evidence of valvular disease. Any lesions which were considered complications of the surgical procedure were not considered as part of the basic pathologic processes.

Pathologic examination was done without knowledge as to the type of angina which had been present clinically.

Results

Of the 47 cases reviewed, 12 were classified as having unstable angina and 35 as stable. The latter were subdivided into 20 with severe stable angina and 15 with moderate stable angina (table 1).

Of the 46 operated patients, 24 did not survive the operation, 21 of the deaths being cardiac in origin while three resulted from hemorrhage. Eight of the patients who died between the first and the seventh postoperative days had experienced either arrhythmias or low cardiac output and three postoperative hemorrhage. When death occurred between the seventh and thirtieth postoperative days (11 patients), the cause of death was usually noncardiac. The forty-seventh patient had not been operated but died shortly after coronary arteriography. There was no dominance of one type of angina over another among the patients in each of the operative or postoperative groups.

Clinical Features

From the clinical data, there was no difference between the patients with various types of angina as regards factors of age, sex, blood pressure, lipid levels, smoking, diabetes, family history or the patient's own history of antecedent acute myocardial infarction (table 1). In the entire series, the male was the dominant sex, as there were 39 men (83%) and eight women. The average age of the entire group was 54 years.

Hypertension was present in 14 of 45 (31%) in which the blood pressure had been recorded in the hospital records. Abnormalities of serum lipids were present in 47% and diabetes in 28%. Of the 34 patients in whom an adequate history of smoking could be obtained, 65% were smokers. A family history of myocardial infarction was present in 41% of the patients and there was a history of previous myocardial infarction in 60%.

Pathological Features

Among patients with all types of angina, significant coronary atherosclerosis was extensive (table 2), both as to numbers of vessels involved and as to multiplicity of lesions in involved arteries. Characteristically, when significant atherosclerosis was present in a given vessel, there were multiple foci of such involvement. There was no significant difference in distribution of severe coronary atherosclerosis among the three categories of angina studied (fig. 1).

In most of the cases (37) there was coinvolvement of the anterior descending, left circumflex and right coronary arteries by significant atherosclerosis, either with or without similar involvement of the main left coronary artery. In nine other cases, only two coronary arteries were involved with significant obstruction, while in only one case was there single vessel disease (the right coronary artery). When two vessels were involved, the most common pattern of distribution was involvement of the right coronary artery with either the anterior descending or the left circumflex arteries. In only two of the 47 cases was the right coronary artery not affected by significant disease and in three

Table 1

<table>
<thead>
<tr>
<th>Category of angina</th>
<th>Number of patients</th>
<th>Average age (years)</th>
<th>Sex distribution</th>
<th>Lipid abnormalities</th>
<th>Diabetes</th>
<th>Smoking</th>
<th>Family history of myocardial infarction</th>
<th>History of previous myocardial infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable</td>
<td>12</td>
<td>53</td>
<td>4</td>
<td>8</td>
<td>4/12</td>
<td>3/11</td>
<td>1/12</td>
<td>7/9</td>
</tr>
<tr>
<td>Stable severe</td>
<td>20</td>
<td>55</td>
<td>2</td>
<td>18</td>
<td>5/18</td>
<td>12/17</td>
<td>9/19</td>
<td>9/12</td>
</tr>
<tr>
<td>Stable mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/16</td>
<td>10</td>
</tr>
<tr>
<td>to moderate</td>
<td>15</td>
<td>55</td>
<td>2</td>
<td>13</td>
<td>5/15</td>
<td>15/3</td>
<td>3/15</td>
<td>6/13</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>54</td>
<td>8</td>
<td>39</td>
<td>14/45</td>
<td>20/43</td>
<td>13/46</td>
<td>22/34</td>
</tr>
<tr>
<td>Percent of total</td>
<td>100</td>
<td></td>
<td>17</td>
<td>83</td>
<td>31</td>
<td>47</td>
<td>28</td>
<td>65</td>
</tr>
</tbody>
</table>

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STABLE AND UNSTABLE ANGINA

Table 2

Number of Vessels Involved by Severe (Grade 3 or Higher) Atherosclerotic Lesions in the Three Categories of Angina

<table>
<thead>
<tr>
<th>Angina Type</th>
<th>Total Cases</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>3+ L.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable</td>
<td>12</td>
<td>0</td>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Stable</td>
<td>20</td>
<td>1†</td>
<td>3</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Stable mild to moderate</td>
<td>15</td>
<td>0</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Total in all 3 categories</td>
<td>47</td>
<td>1</td>
<td>9</td>
<td>25</td>
<td>12</td>
</tr>
</tbody>
</table>

*1 = single vessel; 2 = double vessel; 3 = triple vessel; 3+ L.M. = triple vessel + left main.
†Right coronary artery with multiple lesions.

cases the anterior descending artery was spared. When the distribution of significant lesions in the right coronary artery was examined, it was found that involvement of the anterior and intermediate segments of this artery together was the most common pattern (26 of 45 cases). In the anterior descending artery, the proximal segment was more commonly involved than the distal. In the left circumflex artery, the proximal segment was more commonly obstructed than the distal but the difference was not as striking as in the anterior descending artery. In the entire series of 47 cases, the intermediate segment of the right coronary was the most commonly involved by severe obstructive disease (93%), followed by the proximal left anterior descending (89%), and in turn, by the proximal segment of the left circumflex (77%) and anterior segment of the right coronary (75%) (fig. 2). No correlation was present between the number of vessels involved and the type of angina.

Significant atherosclerosis of the main left coronary artery was observed in 14 of the 47 cases. In all of these cases there were other sites of significant disease. In 12 of the 14 cases with significant disease of the main left coronary artery, each of the remaining three arteries was also severely involved. Main left disease was associated with severe disease of two other arteries in one case and in one case only the anterior descending was additionally involved.

Among the 14 cases with significant involvement of the main left coronary artery, the distribution as to the types of angina was as follows: stable moderate, six cases; stable severe, six cases; and unstable, two cases.

Coronary thrombi were observed in 17 cases; 15 of these also exhibited acute myocardial infarction. Since histologic designation of age of a coronary thrombus is difficult, the associated infarction, when present, was used to determine the age of the injury. We wanted to determine whether the acute process was present or imminent when the clinical study was done, or whether the infarction developed at some time after the clinical study, for example, postoperatively.

Six of the 12 cases with unstable angina exhibited coronary thrombosis and five of these had associated acute myocardial infarction. In four of the latter, the histologic age of at least some of the infarcted tissue clearly antedated the time of operation and thus in each of these the infarct may have been present at the time of or shortly after the basic clinical study. Among 35 subjects with stable angina, either severe or moderate, there were 11 cases with coronary thrombosis, ten of which also exhibited acute myocardial in-

Figure 1

Distribution of grades III or IV atherosclerosis by arteries in the several types of angina (47 cases). R.C. = right coronary; L.A.D. = left anterior descending; Circ. = circumflex; L.C. = left coronary.

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Figure 2

Averages of grades of atherosclerosis (grade 3 or more) by arteries of all three types of angina studied (47 cases). Desc. = descending; see figure 1 for other abbreviations.
faction. However, in contrast to the group with un-
stable angina, each of the infarcts appeared to have
occurred postoperatively and could not be related to
the preoperative state.

For purposes of tabulating scars, the myocardium
was divided into the posterior (inferior), lateral,
anteroseptal, and septal walls. Scars involving one or
more of these regions of the left ventricular wall were
observed in 36 of the 47 patients (67%) (table 3). The
scars were restricted to one aspect in 17 cases and
involved two or more in 19. There was no significant
difference between the presence or absence of scarring
and the extent of scarring among subjects with three
different categories of angina.

Scars were most commonly located in the posterior
(inferior) wall of the left ventricle (ten alone and 13
with another zone, usually the anteroseptal). Less
commonly, the anteroseptal region was involved (16
cases) (three alone and 13 with another zone, usually
the posterior).

Scars of the lateral wall were seen in 11 cases (three
alone, four with scarring of the anteroseptal wall, and
four others with scars of the posterior wall).

Left ventricular hypertrophy, as judged by
thickness of the left ventricular wall exceeding 1.5 cm
and cardiac weight in excess of 350 grams for women
and 450 grams for men, was present in 38 of the 47
patients (81%). There was no significant difference as
to the incidence of left ventricular hypertrophy in one
class of angina as compared with another.

The percentage with left ventricular hypertrophy in
each of the classes of angina was as follows: stable
moderate, 53%; stable severe, 70%; and unstable,
50%.

Three patients had aortic valvular disease. Two
were from the stable severe group and one from the
stable moderate group. Nine patients had evidence of
mitral regurgitation associated with scarring of the
posteromedial papillary muscle and posterior left ven-
tricular wall. Three were from the group with un-
stable angina, three from the stable severe and three
from the stable moderate groups.

Table 3
Location of Scars of Healed Myocardial Infarction in
Patients with Three Categories of Angina Pectoris

<table>
<thead>
<tr>
<th>Type</th>
<th>Left ventricular scarring by walls (anterior, septal, posterior, lateral)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angina</td>
</tr>
<tr>
<td>Unstable</td>
<td>12</td>
</tr>
<tr>
<td>Stable severe</td>
<td>20</td>
</tr>
<tr>
<td>Stable mild to moderate</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
</tr>
</tbody>
</table>

Comment
To the best of our knowledge, this is the first study
in which the clinical and pathologic features of
patients with angina pectoris have been examined
within a timeframe that allows correlations to be made
between the pathologic and the clinical findings near
the time that the angina was categorized. Several
other studies\textsuperscript{1,2} have included patients who died from
unrelated causes (carcinoma, heart failure, etc.)
several years following clinical evaluation of angina, a
time span making precise correlation impossible.

In our series, the sex and age distribution cor-
responds with the usual distribution among patients
with clinically evident coronary disease. In contrast to
the study on angina by Zoll and associates,\textsuperscript{3} in which a
high incidence of hypertension was present (60%),
our study revealed a history of hypertension in only 31%.
However, the much higher incidence of left ven-
tricular hypertrophy (58%) than hypertension in our
series suggests that some of the cases classified as nor-
motensive may have been hypertensive for some
period prior to the time of clinical evaluation.

A high proportion of patients (77%) had myocardial
scars. Since only 60% had a previous history of myo-
cardial infarction, 17% of the patients most likely had
suffered silent acute myocardial infarction in the past.

The hearts of our anginal patients generally showed
multifocal severe coronary disease involving all three
vessels. Single vessel disease was present in only one
case and two vessel disease in only nine of 47 cases.
The distribution of lesions in the coronary arteries
among our anginal patients was essentially the same
as that found earlier in a group of patients with signifi-
cant coronary atherosclerosis but unselected as to the
clinical manifestations.\textsuperscript{3} Other studies from this
laboratory have demonstrated that angiography may
underestimate the degree of atherosclerotic narrowing
and may miss significant lesions altogether.\textsuperscript{4}

We acknowledge that since all except one of our
patients died following operation we are dealing with
a selected series. It might be claimed that fatal com-
plications would be more likely in subjects with severe
disease than in those with lesser degrees. Because
many of our patients died of noncardiac causes, we
feel that the group of patients is a valid representa-
tion of the patients undergoing bypass surgery but we
cannot deny that among operated patients who survived
there was less extensive disease than in those included
in this study. However it is important to point out that
the pathological profile including distribution and
severity of coronary disease, left ventricular hyper-
trophy, and antecedent myocardial infarction did not
differ appreciably among the classes of angina.

Differences, however, were noted with regard to
coronary thrombosis and/or acute myocardial infarc-
tion. In four of the 12 cases with unstable angina, these changes appeared to have been coexistent with the unstable angina. In contrast, in none of the subjects with stable angina was coronary thrombosis and/or acute myocardial infarction, when present, considered to have existed preoperatively. This suggests that many cases classified as having unstable angina pectoris may actually be suffering an acute myocardial infarction which is undetected by usual clinical tests.

Two points need to be emphasized with regard to significant atherosclerosis of the main left coronary artery. First, in our series, there were no cases in which significant atherosclerosis was restricted to this artery. Second, among patients in whom significant atherosclerosis was present in the left main artery, there was not a strong tendency toward a particular type of angina. While our figures are too small for further generalization, an important finding was that, in our study, when the left main coronary artery was involved, the most prevalent type of angina was stable, moderate.

References
Pathology of stable and unstable angina pectoris.
R B Guthrie, Z Vlodaver, D M Nicoloff and J E Edwards

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