Natural History of Unstable Angina with Medical or Surgical Therapy*

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In order to establish the natural evolution of unstable angina under medical treatment and to determine the possible benefits of revascularization surgery, 113 patients were studied; 51 received medical treatment (24 with intermediate syndrome and 27 with progressive angina), and 62 others received surgical treatment (28 with intermediate syndrome and 34 with progressive angina). After a mean follow-up of 32 months, the mortality in the medically treated groups was 46 percent (11/24) with intermediate syndrome and 7 percent (2/27) with progressive angina (P < 0.005), and the incidence of myocardial infarction was 38 percent (9/24) and 7 percent (2/27), respectively (P < 0.01). Moreover, in comparing cases treated medically or surgically, the mortality was as follows: intermediate syndrome treated medically, 46 percent (11/24) vs 11 percent (3/28) in those treated surgically (P < 0.005); and progressive angina treated medically, 7 percent (2/27) vs 9 percent (3/34) in those treated surgically (P = 0.85). The incidence of myocardial infarction was as follows: intermediate syndrome treated medically, 38 percent (9/24) vs 14 percent (4/28) in those treated surgically (P ≤ 0.056); and progressive angina treated medically, 7 percent (2/27) vs 12 percent (4/34) in those treated surgically (P > 0.55).

Stable angina pectoris and acute myocardial infarction are two entities which can be schematically considered as known extremes in a series of different clinical syndromes of ischemic cardiopathy. In the medical literature, there is a lack of full agreement concerning the terminology and definitions for these syndromes. A variety of terms have been used, including impending coronary occlusion,1,2 coronary failure,3 preinfarctional angina,4-6 acute coronary insufficiency,7 preinfarction syndrome,8 unstable angina,9 impending myocardial infarction,10 impending infarction,11 intermediate syndrome,12,13 etc. For this reason, it is difficult not only to compare the results obtained by different groups, but also to validate the usefulness of new therapeutic resources, because to date the natural history of these cases is not completely known.

In 1970, as a result of the aforementioned problems, we developed a classification of ischemic cardiopathy based on angina.14 This report represents a further attempt to substantiate our views. Here we will discuss the results of one of our studies (that related to unstable angina) in order to complete a previous preliminary publication.15 We are also studying groups of patients with angina of recent onset, Prinzmetal's angina, acute myocardial postinfarctional angina, and acute persistent ischemia. The results of these studies will be disclosed in future communications.

Materials and Methods

This study was initiated in 1970; a total of 163 patients were admitted up to April 1973. Within the group with unstable angina, two clinical syndromes were distinguished, the intermediate syndrome and progressive angina.

Four major and two minor criteria had to be fulfilled for a diagnosis of intermediate syndrome. The major criteria were: (1) recurrent angina pectoris, prolonged and intense, not related to effort; (2) absence of extracardiac accessory factors; (3) normal or slightly increased levels of enzymes, up to 50 percent above normal or basal levels; and (4) absence of severe pump failure or severe and prolonged arrhythmias. The minor criteria for intermediate syndrome were: (1) little or no response to administration of nitrates; (2) transitory changes of ventricular repolarization; (3) transitory cardiac arrhythmias; and (4) evolution in less than one month.

On the other hand, we considered that a patient had progressive angina when, during the last three months, his angina showed a change characterized by an increase in intensity or frequency, or both, of the crises, with a decrease in tolerance to effort and without filling the necessary characteristics for the diagnosis of intermediate syndrome.

Plan of Study

Phase A. This phase comprises three stages.

Stage 1. Any patient fulfilling the necessary clinical conditions was admitted to the coronary care unit for a complete clinical examination, electrocardiogram, chest roentgeno-
gram, phonocardiogram (in some cases), multistage exercise test (when indicated), and laboratory tests (serial determinations of levels of creatine phosphokinase, serum glutamic oxaloacetic transaminase, and lactic dehydrogenase). If the criteria for admission to the study were fulfilled, the patient was included in the medical or surgical plan according to the result of a random choice.

In 158 cases out of 163, the type of treatment was assigned by lot (Fig 1), while the remaining five patients (one with intermediate syndrome and four with progressive angina) were directly included in the surgical group. This happened at the beginning of this experience; in the original working plan (1970), if a case with therapy already suggested was referred to us by a physician not related to our group, the case was considered as included at random choice, since (1) no previous experience existed and (2) the decision as to type of treatment was made before the angiographic study. A year later, we waived this policy because no case was referred to us with an indication for angiographic studies and subsequent medical treatment and because methodologic analysis suggested the necessity of avoiding this policy. Because the evolution of the five cases admitted under this policy was known, we decided that they could remain in the study. The 17 cases of acute myocardial postinfarctional angina are not considered in this report; therefore, it is based on the results in 146 patients with intermediate syndrome or progressive angina.

Stage 2. In each patient an angiographic study was performed using Sones' technique, with 35-mm coronary cineangiographic studies and left ventriculographic studies. The coronary lesions (only those with greater than 70 percent obstruction of the vessel's lumen), the ventriculogram, and the collateral circulation were separately analyzed and also were analyzed as a whole on the basis of an appropriate index.16

In order to classify the ventriculograms, we adopted morphologic criteria based on changes in motility (hypo- kinesia, akinnesia, or dyskinesia), according to the extent and quality of the change. Thus, we designated as type A the ventriculograms that were normal and those with a minimal lesion of one wall, and type B referred to the more damaged or those ventriculograms that showed marked abnormalities of at least two walls.

The collateral circulation was classified as good, poor, or absent.

Stage 3: The patient was presented to the surgical staff. This group, unaware of the raffle's results, decided if the patient was a suitable candidate for direct revascularization surgery. If he was considered inadequate, he was excluded from the plan and assigned to the group of "excluded" patients. Otherwise, if the patient was considered to be a surgical candidate, he was admitted to the medical or surgical plan according to the raffle's results.

In surgical cases, the moment of surgery was considered as the definitive time of admission into the study. In the medical group, each case was definitively admitted to the study after the same time had elapsed as in the previous surgical patient. For example, surgical patient 50 underwent surgery after 30 hours. The next medical patient (No. 27 of the raffle) was definitively incorporated into the study 30 hours after his admission to the coronary care unit.

For medical treatment of the patients with the intermediate syndrome, the following procedures were used: (1) admission of the patient to the coronary care unit for at least five days, and not less than 96 hours after last significant complication; and (2) administration of nitroglycerin and fast-acting nitrates, analgesics (including opiates, when necessary), sedatives (diazepines), oxygen, anticoagulant drugs (heparin or dicumarinics, especially in obese patients and in those with a history of venous disease or myocardial infarction, unless contraindicated), digitalis and diuretics (only if there were signs of left ventricular failure), and β-adrenergic blocking agents (propranolol, 40 to 100 mg daily, or prad tolol, 200 to 400 mg daily unless cardiac failure was suspected). In progressive angina a similar therapeutic approach was used, but not all patients required a long stay in the coronary care unit.

Phase B. This phase included strict control of the hospitalized patient, whether he was assigned to the medical or to the surgical group, until he returned home. The patient was reevaluated every four months with a complete study that included clinical and electrocardiographic examination and, at variable intervals, an exercise test with an ergometric bicycle. In order to simplify the statistical analysis of the results, the following clinical follow-up index (point system) was used:

- Infarction
  - ST-T: +3
  - QR: +7
  - QS: +10

- Conduction defects
  - First-degree atrioventricular block; left anterior hemiblock: +1
  - Second-degree atrioventricular block; right bundle-branch block: +2
  - Left posterior hemiblock: +3
  - Third-degree atrioventricular block: +6

- Arrhythmias (all types except conduction defects): +2

- Heart failure
  - Grade 1: +1
  - Grade 2: +3
  - Grade 3: +5
  - Grade 4: +9

- Angina
  - 1+: +2
  - 2+: +4
  - 3+: +6
  - 4+: +8
Increasing diabetes +2
Blood pressure more than 200/120 mm Hg +2
Weight increase of more than 30 percent +2
Serum cholesterol level more than 350 mg/100 ml +2
Physical incapacity
Slight +1
Moderate +3
Severe +5

A year later, a new hemodynamic study was performed, whenever possible.
In summary, the plan of study was as follows:

Phase A
Stage 1
Clinical diagnosis
Random choice of treatment (medical or surgical)
Stage 2
Hemodynamic study
Stage 3
Acceptance of case by surgical group
Medical or surgical treatment (random choice)

Phase B
Follow-up at four-month intervals
Clinical evaluation
Basal ECG and effort test (twice yearly)
Updating of follow-up index
Hemodynamic study after a year, if possible

Finally, a statistical analysis of all data was performed to establish (1) if the groups were homogeneous, (2) if there were differences in their natural evolution, and (3) if surgery modified that evolution.

RESULTS

One hundred forty-six patients were admitted to the study as having intermediate syndrome or progressive angina, 33 of whom were excluded in phase A for the reasons previously stated. Therefore, our study is based on 113 patients with a mean follow-up of 32 months.

The mean age of the patients under medical treatment was 54 years for those with intermediate syndrome and 55 years for those with progressive angina (P > 0.80). The mean age of the patients who underwent surgery was 53 years for those with intermediate syndrome (P > 0.60) and 51 years for progressive angina (P > 0.45).

Four risk factors were taken into account: hypertension, diabetes, tobaccoism, and hypercholesterolemia. Their incidence was similar to that found in other types of coronary disease. Differences were not statistically significant.

There were no significant differences in the incidence of previous myocardial infarction; it was 42 percent (26/62) for all patients undergoing surgery and 45 percent (23/51) for medically treated patients. In the different subgroups, the incidence for previous infarction was as follows: intermediate syndrome treated surgically, 43 percent (12/28) vs 54 percent (13/24) in those treated medically (P > 0.40); and progressive angina treated surgically, 41 percent (14/34) vs 37 percent (10/27) in those treated medically (P > 0.70).

Electrocardiographic Findings

Changes were observed in basal findings as well as during the anginal episode.

Basal ECG. No differences were found between patients with the intermediate syndrome and those with progressive angina; changes of ventricular repolarization were common in both entities. In those patients with a history of previous infarction, the sequela of necrosis was detected in the tracing.

ECG during Pain: The most frequent electrocardiographic changes during an anginal attack were (1) depression of the S-T segment; (2) elevation of the S-T segment; (3) arrhythmias due to electrical instability and transitory changes in intraventricular conduction; and (4) changes in the T wave, which can become negative during variable lapses of time.

Angiographic Findings

All patients included in this study had obstructive lesions with luminal narrowing of 70 percent or more in at least one coronary artery. The left anterior descending coronary artery was the most frequently involved (110 of 113 cases).

Table 1 shows the results of the angiographic studies and the statistical analysis did not show any significant difference among the considered variables. In the intermediate syndrome, we observed a greater incidence of the type B ventriculogram in patients under medical treatment.

Regarding collateral circulation, the most important difference was observed between progressive

<table>
<thead>
<tr>
<th>Angiographic Findings</th>
<th>Intermediate Syndrome</th>
<th>Progressive Angina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary lesions</td>
<td>Surgical Medical</td>
<td>Medical Surgical</td>
</tr>
<tr>
<td>One artery</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Two arteries</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Three arteries</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Left ventriculogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Type B</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Coronary collaterals</td>
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<td></td>
</tr>
<tr>
<td>Good</td>
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<td>10</td>
</tr>
<tr>
<td>Poor</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Absent</td>
<td>7</td>
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angina and intermediate syndrome. In patients with progressive angina, collateral circulation was present more often and was of better quality than in patients with intermediate syndrome.

The angiographic index in the various subgroups was as follows: intermediate syndrome treated surgically, 14.3 points; intermediate syndrome treated medically, 16.0 points; progressive angina treated surgically, 14.3 points; and progressive angina treated medically, 14.2 points. There were no significant differences among the values for the angiographic index.

Excluded Patients

This is a heterogeneous group that includes the patients who, although fulfilling the clinical requirements, were later withdrawn from the study because of any of the reasons detailed in Table 2.

Follow-Up Study

The mean follow-up for the 113 patients was 32 months (range, 24 to 56 months). The evolution of the groups under medical treatment will be analyzed first; the differences between surgical and medical subgroups will be discussed later.

We decided to consider preferably those factors that are more objective and less related to the observer's point of view, such as myocardial infarction, mortality, clinical follow-up index, and finally, the changes in the anginal pattern.

Medical Treatment. The incidence of acute myocardial infarction in the subgroups treated medically was 38 percent (9/24) in the patients with intermediate syndrome and was 7 percent (2/27) in those with progressive angina (P < 0.01) (Table 3). In six out of the nine patients with intermediate syndrome who had an acute myocardial infarction, necrosis occurred during the acute stage (with four deaths, all due to pump failure); and in the remaining three, necrosis occurred during the follow-up period (at two, three, and eight months), with two deaths (acute pulmonary edema and sudden death after 15 days). In eight cases the necrosis was anterior, and in one, it was diaphragmatic. In those with progressive angina, we observed one patient with necrosis in the acute stage (who died because of pump failure) and one patient with necrosis after two months. Both of the cases of necrosis were anterior.

Mortality in medically treated patients with the intermediate syndrome was 46 percent (11/24) and with progressive angina was 7 percent (2/27) (P < 0.005) (Table 3). Deaths were classified as either related (cardiac and extracardiac) or unrelated.

Five of the deaths in medically treated patients with the intermediate syndrome occurred during the acute stage, and six occurred during the follow-up

### Table 2—Number of Excluded Patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>Intermediate Syndrome</th>
<th></th>
<th>Progressive Angina</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Surgical</td>
<td>Medical</td>
<td>Surgical</td>
<td>Medical</td>
</tr>
<tr>
<td>Insufficient angiographic lesions</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single lesions of circumflex artery</td>
<td>1</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hyperthyroidism and coronary spasm</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Subaortic stenosis</td>
<td>...</td>
<td>...</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>Aneurysm of coronary artery</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Normal coronary arteries</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Excessive severe angiographic lesion</td>
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<td>...</td>
<td>2</td>
</tr>
<tr>
<td>Refused study</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other causes</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>1</td>
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</table>

### Table 3—Incidence of Myocardial Infarction and Mortality in Various Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total No. of Patients</th>
<th>Myocardial Infarction</th>
<th>Mortality</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Patients</td>
<td>Percent</td>
<td>No. of Patients</td>
<td>Percent</td>
</tr>
<tr>
<td>Intermediate syndrome</td>
<td>28</td>
<td>4</td>
<td>14*</td>
<td>3</td>
<td>11**</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical treatment</td>
<td>24</td>
<td>9</td>
<td>38*†</td>
<td>11</td>
<td>46**†</td>
</tr>
<tr>
<td>Progressive angina</td>
<td>34</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>34</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>27</td>
<td>2</td>
<td>7†</td>
<td>2</td>
<td>7†</td>
</tr>
</tbody>
</table>

*χ² = 3.715; P < 0.056. **χ² = 8.099; P < 0.005. †χ² = 6.804; P < 0.01. ‡χ² = 9.877; P < 0.005.
period. Of those patients who died during the acute stage, four deaths were due to myocardial infarction (after two, five, seven, and eight days) and one was due to sudden death occurring 20 days after the patient's discharge from the coronary care unit. Of the patients who died during the follow-up period, four died suddenly (3, 8, 12, and 16 months after their inclusion in the study), and two died from acute pulmonary edema after 2 and 40 months, respectively.

Only two (7 percent) of the 27 medically treated patients with progressive angina died, one from myocardial infarction and cardiogenic shock (during the acute stage) and the other dying suddenly after 12 months.

In spite of the different natural evolution regarding the incidence of acute myocardial infarction and mortality, no significant differences were found in medically treated patients between both subgroups (intermediate syndrome and progressive angina) on the basis of the analyzed data, risk factors, age, sex, angiographic lesions, ventriculograms, angiographic index, and incidence of previous infarction.

Table 4 shows the mortality in medically treated patients with intermediate syndrome and with progressive angina, relating the mortality to the number of involved vessels and the condition of the ventriculogram. To date, no patient with a lesion of only one vessel has died.

Surgical Treatment. Surgery was performed on 62 patients (28 with intermediate syndrome and 34 with progressive angina). Ninety-nine bypasses and three related aneurysmectomies were performed. Of the 28 patients with intermediate syndrome, one, two, and three bypasses were performed in 15, eight, and five patients, respectively. In progressive angina, one bypass was performed in 17 patients, two bypass operations in 15 patients, and three bypass operations in two patients. Of the three patients undergoing aneurysmectomy, two had progressive angina, and one had the intermediate syndrome.

In surgical patients, the incidence of acute myocardial infarction, the mortality, the follow-up index, and angina must also be analyzed. In each case the data are compared with the results in the respective clinical control group.

In the 28 patients with intermediate syndrome treated surgically, four patients (14 percent) developed myocardial infarction (all of them in the acute stage); the necrosis was anterior in two patients and diaphragmatic in the other two. There were no significant differences compared to the medically treated group (P > 0.55). Only one patient died because of an inferior necrosis.

In patients with the intermediate syndrome treated surgically, three deaths were classified as related (11 percent) and one as unrelated (bronchopneumopathy three months after surgery). Of the three cases of related death, two patients died during surgery, and one died ten days after surgery from septic shock. The difference in mortality between medically and surgically treated subgroups with the intermediate syndrome is statistically significant (P < 0.005) (Table 3).

Of the 34 surgically treated patients with progressive angina, three deaths were classified as related (9 percent) and one as unrelated (neoplasm 14 months after surgery). Of the patients who died during the acute stage, two died during surgery, and one died from acute renal failure that followed cardiogenic shock. In this subgroup, there were no significant differences between the medically and surgically treated patients.

Table 4 shows the relationship between mortality and the number of involved vessels, ventriculogram, collateral circulation, and angiographic index.

Follow-Up Index

Patients with intermediate syndrome who were surgically treated showed a more favorable long-term evolution than those medically treated (P < 0.011) (Fig 2). This difference is not apparent in the

| Table 4—Mortality of Patients Related to Findings on Angiographic Studies* |
|---------------------------------|----------------|----------------|----------------|
|                                | Intermediate Syndrome | Progressive Angina |
| Angiographic Findings | Surgical | Medical | Surgical |
| Coronary lesions            |              |          |              |
| One artery                  | 1           | 1       | 1             |
| Two arteries                 | 2           | 6       | 1             |
| Three arteries               | 5           | 1       | 3             |
| Left ventriculogram         |              |          |              |
| Type A                       | 2           | 3       | 1             |
| Type B                       | 1           | 8       | 2             |
| Coronary collaterals        |              |          |              |
| Good                         | 1           | 2       | 1             |
| Poor                         | 2           | 5       | 1             |
| Absent                       | 4           | 4       | 1             |
| Angiographic index, points  | 11.3        | 17.9    | 20.0          | 20.3 |

*Table values (except angiographic index) are numbers of patients who died.
patients with progressive angina, although a remarkable tendency to a better evolution is recognizable (Fig 2).

Angina

In both surgically treated subgroups (intermediate syndrome and progressive angina), the evolution of angina was more favorable than that observed in the corresponding medically treated subgroups (Fig 3). A similar tendency observed through the ergometric evaluation of functional capacity confirmed this finding.

Hemodynamic Study after a Year

We could not achieve our purpose of performing repeat catheterization on all patients after one year. To date, we have restudied only 18 patients (three medically and 15 surgically treated). For this reason, we will not discuss these results.

DISCUSSION

Natural Evolution

Many authors agree that the term, "preinfarctional angina," comprises a great number of patients whose characteristics have not yet been fully defined. Moreover, some of these authors think that under this designation, it would be possible to identify groups with different clinical pictures and natural evolution.

In an excellent review of revascularization surgery, V. L. Gott said: "At the present time, probably no group of patients with coronary artery disease possess more of a therapeutic dilemma than the group with unstable or preinfarction angina."

Early in 1970, we decided to study unstable angina in detail, and we reached conclusions that, based on a thorough knowledge of the clinical picture and supported by prospective studies, allowed us to identify probable different entities. At the same time...
that we studied the natural evolution under medical treatment, we planned to evaluate the effects of revascularization surgery on each of the clinical syndromes taken into account.\textsuperscript{15}

According to our results, it seems possible to identify groups with similar angiographic lesions and different natural evolutions. In this way the mortality for patients with intermediate syndrome treated medically was 46 percent (11/24) and for those with progressive angina treated medically was 7 percent (2/27) (P < 0.005) after a mean follow-up of 32 months. Although this fact can be observed without difficulty, it is less easy to determine the reasons for such a difference.

We believe that when analyzing the degree of obstruction in a coronary artery, we are evaluating the most important, but not the only, factor that determines the perfusion of the cardiac muscle; at the same time, one must take into account the following factors: (1) the aortic pressure head; (2) the progression rate of the lesion; (3) the exact quantification of the degree of obstruction (between 70 and 80 percent, nonangiographically demonstrable small variations can induce great changes in flow); (4) the role played by spasm (demonstrated in Prinzmetal's angina, but observed with increasing frequency in the remaining clinical types); (5) the existence and efficiency of collateral circulation, as well as the indemnity of the efferent vessel; and (6) the cardiac muscle's metabolic conditions. To all this, we may add the questionable temporary relationship between thrombosis and myocardial necrosis. Studies by Roberts\textsuperscript{24,25} and by Vlodaver and Edwards\textsuperscript{26} support the belief that in some cases (particularly in nontransmural necrosis), the thrombosis is an epiphenomenon rather than the direct source of myocardial infarction.

In necropsy studies of cases with unstable angina, Caulfield et al\textsuperscript{27} identified a high incidence of multiple hemorrhages of variable date in two or more arteries, which suggested an evolutionary process frequently ending in thrombosis. This process, which resembles that postulated in point 2 (progression rate of lesion), may be fundamental in the pathogenesis of some unstable varieties of angina pectoris.

Our attempt to emphasize the importance of the clinical picture as a valuable index in ischemic cardiopathy does not mean we do not give actual significance to the angiographic findings. Let us remember that in stable angina the investigations of Oberman et al\textsuperscript{28} Friessinger et al\textsuperscript{29} Moberg et al.\textsuperscript{30} and others\textsuperscript{31,32} are already classics. These investigators found a direct relationship between the mortality per year and lesions of one, two, or three coronary vessels.

Whatever may be the physiopathologic mechanism involved, our assumption is that we would now be able to explain many disagreements between reports of carefully followed groups of patients. If patients with intermediate syndrome (high risk) are mixed with others of progressive angina (low risk), and we add to them other cases, such as angina of recent onset, acute persistent ischemia, postinfarctional angina, or Prinzmetal's type, it is reasonable to expect the final mortality to be more related to the percentage of prevalence of each subgroup in the sample than to the actual natural history of each one of them separately.

In so-called unstable angina, the results in the literature show remarkable discrepancies. In this sense, the mortality ranges from zero (according to Resnik\textsuperscript{4}) to 1.7 percent (Fulton et al\textsuperscript{19}), 15 percent (Krauss et al\textsuperscript{33}), 16.4 percent (Vakil\textsuperscript{45}), 26 percent (Gazes et al\textsuperscript{30}), 27 percent (Scanlon et al\textsuperscript{18}), 33.3 percent (Fischl et al\textsuperscript{35}), 36.3 percent (Goodin et al\textsuperscript{46}), 40 percent (Matloff et al\textsuperscript{18}), up to 50 percent (Eliot Corday, M.D., oral communication, 1971). The incidence of acute myocardial infarction also shows discrepancies that range from 3 to 91 percent according to these same authors.

Our study clearly shows that if we consider the patients as a whole (intermediate syndrome plus progressive angina), with medical treatment the mortality has a middle value (12 percent or six patients in the acute period, 22 percent or 11 patients after a year, and 24 percent or 12 patients after two years). These results are similar to those of Beamish and Storrie,\textsuperscript{10} of Krauss et al\textsuperscript{33} and of Gazes et al.\textsuperscript{30}

Gazes et al\textsuperscript{30} whose figures are very similar to ours, also distinguished two groups with very different evolution. Although these investigators\textsuperscript{30} did not perform angiographic studies, their patients were carefully selected on the basis of clinical examination, and a long-term ten-year follow-up has shown valid clinical evidence.

In our series, both groups of patients are also distinguished by the incidence of acute myocardial infarction; during the acute stage, it was 25 percent (13 patients) for intermediate syndrome and 4 percent (two patients) for progressive angina. Gazes et al\textsuperscript{30} reported 22 percent in the acute stage and 35 percent after a year for the high-risk patients, while for the whole group, they reported 12 percent in the acute stage and 21 percent after a year. Krauss et al\textsuperscript{33} reported an incidence of acute myocardial infarction of 17.6 percent in the acute stage for the highest risk group, against 6 percent for the whole group.

To date, we have not found reasons that justify
the division of cases with and without previous infarction, since both subgroups have identical evolutionary pattern and identical mortality.

We must remark that, notwithstanding such a dissimilar clinical behavior, we were not able to find any difference between the analyzed factors (age, sex, risk factors, coronary lesions, ventriculogram, and so on). The only point that deserves some comment is the greater frequency of collateral circulation in patients with progressive angina (it was absent only in five patients) compared with that in patients with intermediate syndrome (satisfactory in four patients). This tendency is not statistically significant.

The existence of a correlation between mortality and the size and extent of angiographic lesions is of particular interest. To date, no patient with lesions of only one vessel has died. Among those who did die, there was a tendency towards a poorer ventriculogram, and the angiographic index was also greater. Therefore, we may conclude that both the clinical picture and the angiographic findings have a significant prognostic value.

Surgery

Once we have recognized two different clinical entities, we must discuss the effects of surgery on each one of them.

Concerning the patients' admission to the plan, remember that it was based exclusively on clinical factors; on the other hand, every case (medical and surgical) was admitted by surgeons as suitable candidates for revascularization; and finally, patients who were rejected by the surgeons were definitely withdrawn from the study. This last point is important, because in some reports,14,18,98 patients rejected by the surgeon are included in the control group. This attitude may have a negative influence upon the results.

Approximately 7 percent (seven) of our patients were rejected because of normal coronary arteries or a minimal angiographic lesion. This agrees with some reports that found an incidence of about 10 to 15 percent.57

In the intermediate syndrome the incidence of definitely abnormal ventriculograms (called type B) is proportionally greater in the surgically treated group than in the medically treated one (Table 1). Nevertheless, we believe that this difference by itself does not justify the different values for mortality for the following three reasons. First, in Table 1, we see that the distribution of normal and abnormal ventriculograms between intermediate syndrome and progressive angina in medically treated patients is almost identical. Nevertheless, the mortality is quite different (46 percent or 11/24 vs 7 percent or 2/27). Secondly, the most altered ventriculogram necessarily is associated with a worse long-term natural evolution, but we do not believe that it is the only factor (not even the principal one) in the short-term evolution (days or weeks) of these cases. Thirdly, as in sudden death, this problem may be focused in a physiopathologic way. It is true that sudden death is nearly always associated with severe coronary myocardial lesions (mainly in patients more than 40 years old), but it is also true that if a patient is correctly treated and in time, he can survive for quite a long time. The anatomic substratum has not changed, but the fundamental mechanisms of the terminal arrhythmia have been controlled.

The operative mortality in patients with unstable angina ranges from 5 to 10 percent in most of the

![Diagram](Figure 4. Survival curves (actuarial method) for subgroups of patients with intermediate syndrome and progressive angina receiving medical treatment (MT) and surgical treatment (ST). For intermediate syndrome, mortality is compared at acute period and at 8, 16 and 24 months (chi-square method).)

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reports, \(^1\)6-18, 38-40 although some investigators report a mortality of zero, \(^41\)42 and other surgical groups report a mortality of 20 percent and more. \(^43\)

In a group of cases strictly defined, by means of factors similar to those of the intermediate syndrome, Matloff et al. \(^14\) found a mortality of 40 percent in the medically treated group vs 3.4 percent in the surgically treated group. Long-term follow-up also showed differences in favor of the surgically treated patients. The findings of Vogel et al. \(^44\) are quite similar.

In our experience, by comparing the medical vs the surgical treatment of patients with intermediate syndrome, we can conclude that the incidence of acute myocardial infarction and the mortality are significantly different and that this difference persists in long-term follow-up (Fig 4).

Concerning the clinical status, there is also a clear difference when angina pectoris is considered. In the medically treated group, those patients who are still alive are asymptomatic, and many of them are in class 4; while in the surgical group, there is a higher percentage of asymptomatic patients, and none of them is in class 3 or 4.

In patients with progressive angina, there was no difference between the results of surgical or medical treatment; the mortality and the incidence of acute myocardial infarction are low in both subgroups. In this case, surgery does not seem to modify the natural evolution; however, the anginal status of the surgically treated patient is better than that of the medically treated patient.

The incidence of previous myocardial infarction was somehow higher in the unoperated patients with intermediate syndrome (54 percent or 13/24) than in the patients undergoing surgery (43 percent or 12/28), but this tendency does not seem to justify itself the very different evolution. Still more important is the fact that in the follow-up of medically treated patients, the mortality was the same for patients with (46 percent or 6/13) and without (45 percent or 5/11) previous infarction.

Considering what has been observed until now, we believe that it is no longer justifiable to speak generically of unstable angina. This term may be replaced by intermediate syndrome or progressive angina, since these are two entities with proper clinical and evolitional characteristics, and possibly with different therapeutic criteria. While intermediate syndrome is really a medical emergency that requires intensive care and angiographic study, once the clinical picture has persisted longer than 24 to 48 hours, progressive angina has a more benign natural evolution.

According to Theroux and Campeau, \(^46\) it may be advisable to reevaluate every patient after the acute episode has been controlled, that is, when the patient again shows stable angina. Fischl et al. \(^19\) were able to stabilize a group of patients who were defined according to strict criteria by the use of propranolol doses up to 400 mg.

In a recent paper, Selden et al. \(^47\) found a better prognosis in the high-risk group treated with \(\beta\)-adrenergic blocking agents. Nevertheless, two patients out of 19 suffered myocardial infarction, and another eight had to undergo surgery four months later because they were still highly symptomatic. Of the remaining nine patients, one died, and two others developed myocardial necrosis in the 21-month follow-up period. Besides, the low mortality in the acute stage could not be exclusively attributed to \(\beta\)-adrenergic blocking agents, since these drugs were administered only to 14 patients out of the 19. Let us remember that Fischl et al. \(^19\) reported a 12-month mortality of 33.3 percent.

The last point we wish to discuss is the best timing for surgery. In this regard, we believe that each institution has to solve the problem according to its own experience and to the following considerations: mortality and severe complications with surgery in the acute stage in the high-risk group vs mortality and severe complications in patients receiving medical treatment plus mortality and severe complications of surgically treated patients once the clinical syndrome has become stabilized.

The mortality that we observed in patients with the intermediate syndrome receiving medical and surgical treatment may be lower now. We must remember that the cases were admitted between 1970 and 1973. Since then, developments have occurred in the medical and surgical fields. In the medical field, the use of higher doses of \(\beta\)-adrenergic blocking agents, and in the surgical field, a better selection of cases, improved preoperative and postoperative care, and a better trained surgical team may contribute to the reduction in mortality; however, we do not believe that in either the medical or the surgical fields, changes have occurred that were important enough to modify the observed tendencies.

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