The "Natural" History of Severe Angina Pectoris with Intensive Medical Therapy Alone: A Five Year Prospective Study of 133 Patients

Henry I. Russek, M.D., F.C.C.P.*

A prospective study utilizing a comprehensive medical regimen is reported in 133 patients with severe angina pectoris due to coronary artery disease. Marked amelioration of pain, increase in exercise tolerance and improvement in ischemic exercise-electrocardiographic patterns were observed in 90.2 percent of the patients in response to titrated doses of propranolol and sublingual isosorbide dinitrate administered concomitantly. The prospects for five-year survival were found to be excellent in patients with good left ventricular function and no adverse clinical signs. The annual mortality in a group of 102 "good risk" patients was only 1.2 percent. In sharp contrast, the yearly attrition rate in subjects with poor left ventricular function approximated 25 percent. The findings indicate that severe angina pectoris which is refractory to casual methods of management frequently responds to an intensive program of optimal medical care. It is only when medical therapy has been pursued with a high degree of enthusiasm and intensity of purpose that the attending physician can gain insight into the true indications for surgical intervention in the various clinical subsets of angina pectoris. Surgical revascularization would appear to have limited application in the treatment of this disease.

In the present era of revascularization surgery, the physician is hampered by a lack of knowledge concerning the natural history of angina pectoris. Currently, two divergent views are readily found in the literature: (1) that angina pectoris is a highly lethal disease; and (2) that it is a benign disorder compatible with long survival in the majority of cases. Although a number of authors1-4 have reported on mortality in large groups of patients observed for one, two, or more decades (Table 1), the relevance of their data to patient populations under treatment today with modern drugs and new perspectives in management may be readily challenged.

With no specific regimen of therapy, Zukel et al., for example, reported the annual mortality in a large series of patients with angina pectoris to be only about 3 percent, while Kannel et al.12 found the yearly attrition rate in their patients at Framingham to approximate 4 percent. Today, with modern therapeutic approaches consisting of dietary management, weight reduction, hypocholesterolemic drugs, control of hypertension and diabetes, curtailment of

**Table 1—Mortality in Angina Pectoris**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Annual Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zukel et al.1</td>
<td>3</td>
</tr>
<tr>
<td>Kannel et al.1</td>
<td>4</td>
</tr>
<tr>
<td>Parker et al.1</td>
<td>6</td>
</tr>
<tr>
<td>Block et al.1</td>
<td>6</td>
</tr>
<tr>
<td>Moberg et al.1</td>
<td>6.4</td>
</tr>
<tr>
<td>Sheldon et al.4</td>
<td>3.3 (1 vessel)</td>
</tr>
<tr>
<td></td>
<td>6.7 (2 vessels)</td>
</tr>
<tr>
<td></td>
<td>10.5 (3 vessels)</td>
</tr>
</tbody>
</table>

- **Clinical Professor of Medicine, Research Professor in Cardiovascular Disease, New York Medical College, New York, N.Y.; Visiting Professor of Cardiovascular Disease, Hahnemann Medical College and Hospital, Philadelphia, Pa.**
- Manuscript received April 6; revision accepted August 8.
- Reprint requests: Dr. Russek, 176 Hart Boulevard, Staten Island, New York 10301.
stress and tobacco, exercise training, and the use of such agents as propranolol and isosorbide dinitrate, it does not seem unreasonable to expect that the outlook has become more favorable. At present, however, it cannot be stated peremptorily that the prognosis in 1973 is appreciably better for the anginal patient than it was in former years because the availability of comprehensive measures, even of established value, can afford no assurance of application on a wide scale and in an effectual manner. The status of treatment for arterial hypertension in this country, for example, provides adequate insight into the wide gulf that may exist between actual results of casual management and those potentially attainable under optimal therapy. A similar disparity may exist with respect to angina pectoris, since many physicians appear to rely on nitroglycerin alone despite dramatic advances in treatment. This narrow approach has not only contributed appreciably to the incidence of "refractory" patients but has also led to premature or needless referral for surgical revascularization.

It should be evident that even if accurate statistics were now available to indicate the average annual mortality in anginal patients receiving optimal medical care, the physician would gain little in assessing the prognosis for the individual case and in rendering a decision with regard to surgery. Just as the average mortality for acute myocardial infarction tells little about the actual risk with a mild first attack or with a massive recurrent episode associated with cardiogenic shock, average annual attrition rates for patients with angina pectoris as a group must similarly mask the mortality risk prevalent in various clinical subsets of this syndrome. At present, therefore, there is urgent need not only to seek out clinical profiles that may identify anginal patients at varied risk but also to record the natural hazards in these categories under the best available medical care.

Since a variety of factors are known to influence the prognosis in angina pectoris, the classification, intensive treatment and follow-up of patients in relatively high and low risk categories could provide useful data for weighing the hazards of operation against the natural consequences of the disease. Insight gained from long clinical experience shows that among the major factors contributing to risk in this disorder are cardiac enlargement, congestive heart failure, multiple myocardial infarctions, hypertension, atrial fibrillation, valvular heart disease and diabetes mellitus. Since patients suffering from severe angina pectoris frequently possess none of these poor prognostic signs, it seems possible to identify "good risk" subjects who, despite severe initial symptoms, could have excellent prospects, with appropriate medical therapy, for both dramatic clinical improvement and relatively long survival. It is interesting that similar classification proved useful in selecting patients for anticoagulant therapy in acute myocardial infarction. Thus, we have reported that the low morbidity and mortality in patients initially classified as "good risk" on the basis of clinical prognostic signs did not justify even the small hazard attending the use of anticoagulant drugs during the acute phase of myocardial infarction. In contrast, the reverse was found to be true for "poor risk" patients. The question we sought to answer with respect to severe angina pectoris, therefore, was whether or not similar classification and follow-up could prove helpful in establishing criteria for or against surgical intervention. From the prospective study beginning in November, 1966 and continuing to the present, useful data appear to be emerging.10-12

MATERIAL AND METHODS

In all, a total of 133 patients with severe forms of angina pectoris, unresponsive to conventional treatment, were followed under a well defined and intensive therapeutic program. Their ages ranged from 29 to 80 years. Of the total, 102 patients were men and 31 were women. In each instance slight to moderate physical or emotional stress regularly evoked classic episodes of angina pectoris which, until the time of study, could not be adequately controlled or prevented despite the customary use of nitroglycerin, long-acting nitrates, sedatives, and other measures. As a consequence, in many activities of daily living, occupational performance and even sleep were frequently disturbed. Alterations in lifestyle also had limited influence on disability in these patients. Among the measures tried were reduction in the speed of walking; reserving more time for dressing in the morning; a change in the manner of transportation; avoidance of overloading the stomach and of walking after meals or in cold weather; and the elimination of emotional outbursts, prolonged conversation, straining at stool, or watching competitive sports. The average number of nitroglycerin tablets used per day varied from 5 to 50 in these patients. None in the series was treated with β-blocking agents prior to this study. The diagnosis was confirmed in each patient by an unequivocal history of the classic symptoms, present for one year or more, and typical ischemic electrocardiographic (ECG) patterns after exercise, previous episodes of myocardial infarction, or cinecoronary angiographic evidence of advanced disease. Within the three-month period preceding this study, 32 patients in the series were studied by angiography, and 26 of this number were found to have severe triple coronary artery disease. A history of one or more myocardial infarctions requiring hospitalization was elicited in 55 of the 133 patients and confirmed by electrocardiography. Seventeen patients in the series were on digitalis therapy prescribed for previous congestive heart failure. Eight suffered from other complications such as cerebrovascular insufficiency, previous stroke, or severe and uncontrolled diabetes. Twelve patients were over the age of 70 years.

CLASSIFICATION OF PATIENTS

Although all patients suffered from severe and refractory...
forms of angina pectoris, they were classified as "good risk" or "poor risk" at the time of their initial examinations on the basis of certain clinically recognized poor prognostic signs. Such classification was maintained unaltered throughout the period of study regardless of events occurring during the course of follow-up. Thus, a patient was considered a poor risk for relatively long survival if he had any one of the following unfavorable criteria:

**Congestive Heart Failure, Past or Present**

Congestive heart failure at any time is an important prognostic sign. It was elicited by means of carefully recorded history to determine the occurrence of effort dyspnea, paroxysmal nocturnal dyspnea and edema, and by physical examination and roentgenography.

**Significant Enlargement of the Heart**

Clinical evidence of cardiac enlargement was presumed present when the maximal apical impulse was accentuated or diffuse and situated lateral to the midclavicular line and when the area of cardiac dullness on percussion extended well beyond 10 cm to the left of the midsternal line in the fifth interspace. In all instances confirmation was required by fluoroscopic and roentgenologic examination prior to final classification. From fluoroscopic study important information was also obtained concerning left ventricular function and asynergy.

**Multiple Myocardial Infarctions**

In all instances documentation of such events was obtained by carefully recorded history, reference to records of previous hospitalizations, and detailed electrocardiographic study.

**Gallop Rhythm**

Each patient was auscultated sitting, supine, and after mild exercise in the left lateral position. The presence of a protodiastolic (third) heart sound at the apex on auscultation was recorded as a sign of serious ventricular impairment.

**Refractory Hypertension**

Levels of blood pressure persisting above 170 mm Hg systolic, and 100 mm Hg diastolic, despite adequate and vigorous therapy were considered to exert an adverse influence on prognosis.

**Atrial Fibrillation**

In the presence of severe angina pectoris, atrial fibrillation, with its impairment of stroke volume and potential for complications, was deemed an unfavorable prognostic criterion.

**Severe and Uncontrolled Diabetes**

Diabetic patients refractory to vigorous therapy or nonoperative in its administration and showing persistent glycosuria and hyperglycemia were assumed to have a guarded prognosis.

**Previous "Stroke" or Cerebrovascular Insufficiency**

The complication of "stroke" or cerebrovascular insufficiency in the presence of severe angina pectoris was accepted as evidence of diffuse atheromatosis with poor outlook for survival.

**Advanced Age**

Considering the limitations of the normal lifespan, "advanced age" was arbitrarily classified as "over the age of 70 years."

Of the 133 patients in the series, 102 qualified as "good risk" by manifesting none of the predesignated unfavorable indices, while 31 were identified as "poor risk" on the basis of these criteria (Table 2). Fifteen of 28 patients with findings of severe triple coronary artery disease on angiography were classified in the "good risk" group because of good left ventricular function and no adverse clinical signs. All 11 patients with angiographic evidence of significant left ventricular asynergy would have also been classified as "poor risk" from the clinical criteria alone.

When judged by functional status (New York Heart Association Classification), 87 of the patients were found to be in class 3, and 46 were in class 4.

**Therapeutic Management**

All patients were placed on a regimen designed to achieve or maintain optimum weight. Serum lipid abnormalities were treated by means of diet and often by hypcholesterolemic agents. Hypertension and diabetes were managed with appropriate drugs with the aim of careful control. Use of tobacco and stimulants was proscribed. Alterations in lifestyle to minimize stress were adopted where feasible. When left ventricular function was not impaired, graduated exercise on a daily basis, always preceded by prophylactic medication, was encouraged.

Medicinal treatment in all cases consisted of the combined administration of propranolol and isosorbide dinitrate (ISDN). The dosage of propranolol was determined in each patient by careful titration to discover the amount needed to reduce resting heart rate to a frequency of 55 to 60 beats per minute. The daily dosage of propranolol varied from as little as 10 mg twice daily to 160 mg four times daily. Sixty-two percent of the patients required 40 mg, 20 percent 60 to 80 mg, 10 percent 100 to 160 mg and 8 percent 20 mg or less, as a single dose three or four times daily. Isosorbide dinitrate was administered *sublingually* in a dosage varying between 2.5 and 10 mg, according to individual tolerance and response. Seventy-four percent of the patients took 5 mg of ISDN, 6 percent 2.5 mg and 20 percent 10 mg as their usual sublingual dose. The dosage of propranolol was taken orally *before* each meal and that of ISDN sublingually *after* each meal in order to obtain the longest possible period of synergistic activity during expected times of physical stress. When congestive heart failure was detected or even suspected, digitalis and an orally administered diuretic were prescribed prior to the use (or continuation) or propranolol therapy.

**Table 2—Classification and Characteristics of 133 Patients with Severe Angina Pectoris**

<table>
<thead>
<tr>
<th>Type</th>
<th>No.</th>
<th>Age</th>
<th>Yr.</th>
<th>CHF*</th>
<th>Prev. Com-MI**</th>
<th>plc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Good risk&quot;</td>
<td>102</td>
<td>58.8</td>
<td>0</td>
<td>0</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>&quot;Poor risk&quot;</td>
<td>31</td>
<td>65.2</td>
<td>12</td>
<td>17</td>
<td>27</td>
<td>8</td>
</tr>
</tbody>
</table>

*Congestive heart failure
**Myocardial infarction

CHEST, VOL. 65, NO. 1, JANUARY, 1974
“NATURAL” HISTORY OF SEVERE ANGINA PECTORIS

COMPARATIVE EKG RESPONSES (lead V2) TO STANDARD EXERCISE (35 min) FOLLOWING PROPRANOLOL AND/or ISOSORBIDE DINITRATE. (A.S., 60 yr. o.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time (min)</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>EKG Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>2 min</td>
<td>70</td>
<td>120/80</td>
<td>Normal</td>
</tr>
<tr>
<td>ISO</td>
<td>2 min</td>
<td>70</td>
<td>120/80</td>
<td>Normal</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4 min</td>
<td>70</td>
<td>120/80</td>
<td>Normal</td>
</tr>
<tr>
<td>ISO</td>
<td>4 min</td>
<td>70</td>
<td>120/80</td>
<td>Normal</td>
</tr>
</tbody>
</table>

RESULTS

Clinical Manifestations

The striking clinical response to propranolol and isosorbide dinitrate therapy observed among subjects in this series has been previously reported. In 90.2 percent of the 133 patients, marked amelioration of angina pectoris associated with significant increments in exercise tolerance have been documented by controlled observations. In these patients, there has been not only a reduction of 50 percent or more in the frequency of anginal episodes and in nitroglycerin requirements but also a striking increase in the ability to exercise without pain (p<0.01). The favorable clinical responses correlate closely with improvement in ischemic ECG patterns evoked by standard exercise. In 50 percent of 62 patients so tested, there has been complete reversal of ECG abnormalities due to exercise when evaluations were performed during periods of combined pharmacologic activity of these agents (Fig 1). It is of interest that no tendency has been observed toward an attenuation of effect with the passage of time.

Improvement in functional class following the administration of propranolol-isosorbide dinitrate therapy has been most significant (Table 3). Twenty of the 87 patients originally in class 3 showed sufficient improvement to be grouped in class 1, while 63 shifted to class 2. Of the 46 patients in class 4 at commencement of this study, 18 were judged to be in class 2, and 19 were in class 3 after the institution of therapy.

Myocardial Infarction

Over the six-year period, 25 of the 102 “good risk” patients suffered attacks of acute myocardial infarction, and of these 19 recovered and 6 died. In the “poor risk” group, myocardial infarction occurred in 24 patients, with the death of 17 of the 31 patients during the same period.

Mortality

Only 6 of the 102 “good risk” patients observed from three to six years have died. None of the 102 died during the first year, two of the 102 patients died during the second year, one of the 100 surviving patients died during the third year, two of 94 patients died during the fourth year and one of 85 patients died during the fifth year. A small number was observed through the sixth year during which there were no deaths. From the mortality experience in this study, the probability of death in “good risk” and “poor risk” patients was plotted (Fig 2). It can be seen that 6 percent of “good risk” patients may be expected to die by the end of the fifth year of follow-up, indicating an average annual mortality of 1.2 percent for this group. In sharp contrast, in “poor risk” patients it may be anticipated to approximate 25 percent. These differences are highly significant statistically (p<.001). Although only one-third of

Table 3—Comparison of New York Heart Association Functional Class Before and After Propranolol-ISDN Therapy

<table>
<thead>
<tr>
<th>Functional Class</th>
<th>Pretreatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>9</td>
</tr>
</tbody>
</table>

CHEST, VOL. 65, NO. 1, JANUARY, 1974
our "poor risk" patients survived to the end of the fourth year, it is of interest that none in this group died during the fifth year of observation. Since all of the survivors in the "poor risk" group were patients over the age of 70 years, with good left ventricular function and no adverse clinical signs, it seems apparent that old age per se should not have been used as one of the indices for an unfavorable five-year prognosis. These data make it clear that overall mortality in any reported series will depend on the composition of the sample with respect to the numbers of "good risk" and "poor risk" patients.

**DISCUSSION**

In the present era of "coronary bypass" surgery for angina pectoris, justification for intervention by operation is often based on little more than the contention that there is an appalling mortality with any form of medical management. Thus, it was claimed that 50 percent of patients on conservative therapy die within five years, a decimation rate averaging 10 percent per year. In sharp contradiction to this alleged threat to life even under "optimal" medical care are the more favorable results reported by other investigators. Thus, Zukel et al. in a 15-year follow-up study, showed that about 3 percent of patients with angina pectoris die each year, while Kannel et al in the Framingham study indicated an annual mortality of approximately 4 percent in this disease. Moreover, since these more favorable results were reported in large series of patients at varied risk and under no specific program of therapy, an even better prognosis seemed likely for carefully selected "good risk" patients participating in a modern comprehensive medical regimen. This finding prevailed in the present study, which shows that in such patients the probability of death over a period of five years is only 6 percent, or approximately 1.2 percent per year. The mortality is not unlike that found in the general population in the same age groups. The significance of this observation is perhaps more meaningful when it is realized that it was made in patients who, at the time of entry into this study, were suffering from serious and refractory forms of angina pectoris often associated with severe two or three-vessel disease but with relatively normal left ventricular function. Inasmuch as coronary bypass surgery in similar patients is associated with an immediate mortality at operation ranging from 2.5 to 10 percent, as well as with a formidable incidence of nonfatal complications and graft failure, early and late, these data make it difficult to justify surgical intervention unless disabling symptoms persist despite optimal medical care.

The relatively favorable outlook for "good risk" patients in this study, despite symptoms of severe angina pectoris, is undoubtedly related to comparatively normal left ventricular function in all cases. Although angiography was obtained in only 20 percent of these patients, careful clinical assessment in conjunction with fluoroscopic and roentgenographic study disclosed normal heart size and function in all subjects. In this regard, the use of other noninvasive measures may prove valuable to identify or confirm those believed to be at minimal risk. In any case, in the event that some "poor risk" patients were inadvertently included in the "good risk" group, the conclusions to be drawn from this study would assume even greater validity. While careful selection was undoubtedly a crucial factor, the total medical regimen directed at the removal of coronary risk factors and the utilization of propranolol in combination with isosorbide dinitrate therapy for prevention of recurrent bouts of coronary insufficiency may have played an important, although presently undefined, role in determining the excellent prognosis in these patients.

These findings should not be construed to mean that coronary artery pathology demonstrable by coronary angiography has no prognostic importance. There is no conflict with the finding that morbidity and mortality are greater in patients with triple coronary artery disease than in those with single or double-vessel involvement (Table 1). It must be borne in mind, however, that triple coronary artery disease is also associated with a significantly higher incidence of congestive heart failure, cardiac enlargement, multiple infarctions and asynergy. Consequently, since the major determinant of survival is the status of left ventricular function, the probability of death when such function is relatively normal may not be appreciably increased even in the presence of triple-vessel disease (over a five-year period of intensive medical therapy).

When refractory angina pectoris is associated with impairment of left ventricular performance as observed in "poor risk" patients of this series, the prognosis appears grave whether medical or surgical therapy is adopted. In spite of excellent symptomatic response to medical treatment in most cases, 25 percent of these "poor risk" subjects died within the first year and 67 percent failed to survive to the end of the fourth year. Equally dismal, however, are the results of surgical therapy in which the immediate mortality has been reported as high as 40 percent or more, with the chances of salvage relatively poor. In this category too, therefore, intervention by operation should be considered only after the most careful clinical assessment.

CHEST, VOL. 65, NO. 1, JANUARY, 1974
The overall mortality for the 133 patients in this series was approximately 4 percent per year, which is strikingly similar to that reported by Kannel et al. in the Framingham study. When it is realized, however, that all of the patients in the present investigation suffered from severe symptoms often associated with one or more previous myocardial infarctions, whereas those in the Framingham study were selected anginal subjects without prior infarction, significant benefit from intensive medical therapy is suggested. In this regard, careful attention to risk factors and the administration of propranolol and sublingual isosorbide dinitrate to prevent pain and ischemic changes could prove to be of paramount importance.

Although the saphenous vein bypass operation is a potentially useful procedure in some cases of angina pectoris, it should be recognized that coronary disease is not necessarily ominous without heroic interventions. Indeed, it is possible to identify the large segment of patients who are not only responsive to antianginal therapy but in whom the prognosis for life and prolonged survival is often reasonably good. Certainly more harm than benefit is likely to ensue when operation is performed without prior consideration of the natural history of the disease and without meticulous selection of patients in whom the risks appear warranted and with whom technical success seems reasonably assured. More frequent and better utilization of available drugs and medical procedures would undoubtedly reduce the incidence of refractoriness and disability and thereby diminish the haste to seek often unattainable surgical solutions.

**REFERENCES**