Protection of Ischemic Myocardium During or After Convalescence From Acute Myocardial Infarction*

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While all patients who have sustained an acute myocardial infarction are at risk of recurrent myocardial infarction, congestive heart failure and sudden death due to ventricular arrhythmias, some are at higher risk than others. In recent years, particular emphasis has been placed on identification and therapy in such patients to avert, delay, or assuage these eventualities.

The goals in these patients at high risk might be as follows: (1) To identify the high risk patient as one who has the potential for electrical instability or who has ventricular dysfunction. The potential for electrical instability includes ventricular fibrillation, ventricular tachycardia, premature ventricular arrhythmias of high grade,1 bradyarrhythmias or asystole; (2) To develop a rational approach to therapy, possibly including quinidine, procainamide, disopyramide, phentoin, beta blockers, possibly preload and afterload reduction, or surgery.

Clinical Evaluation of Patients at High Risk

Patients can be identified as being at high risk from any aspect of the total clinical evaluation. From the history, we can learn of fatigue, dyspnea, orthopnea, palpitations, and chest discomfort. From the physical examination, we can discern an abnormal left ventricular impulse, an S-3 gallop, rales, or edema. In addition, a perceptive overall general clinical impression may be very helpful.

The standard ECG may show left or right ventricular hypertrophy, pathologic Q-waves, conduction abnormalities, ST-T wave changes, or arrhythmias.

Ambulatory 24-hour monitoring or extended monitoring systems ("event recorders") can reveal supraventricular tachycardia, premature ventricular contractions of ominous types,1 bradyarrhythmias, episodes of bradycardia combined with bursts of tachycardia, (the "brady-tachy syndrome"), ventricular tachycardia, or even fibrillation.

Exercise testing can detect high-risk patients as those with reduced duration of exercise, those who develop angina, ST shift, or dysrhythmia. Echocardiograms will discover dilated ventricular chambers and abnormal ventricular wall motion. Vital to such an overall evaluation is coronary arteriography which identifies patients who may be at high risk having left main or triple or double, or even high grade single vessel coronary artery disease or abnormal ventricular wall motion.

Once apprised of all or selected portions of this evaluation, we must then focus the data to develop a clinical profile for the high-risk patient. The patient may have one or a combination of several clinical findings. The patient may be one who has survived an acute myocardial infarction but who has had congestive heart failure in the coronary care unit. He or she may be identified as one who has a depressed or moderately depressed left ventricular ejection fraction—probably the single best predictor. The patient may be older, or have multivessel disease, or an increased left ventricular end-diastolic volume, bundle branch block, a previous myocardial infarction, ventricular tachyarrhythmia, or second or third degree atrioventricular block. The patient may have a combination of depressed ejection fraction and late hospital phase premature ventricular contractions of Lown class 3 to 5,1 or a combination of previous myocardial infarction and depressed ejection fraction of less than 40 percent—the best combination predictor by multivariate analysis.2,6

We have found by thallium exercise tests in patients three weeks following myocardial infarction that we could identify 83 percent of patients having myocardium jeopardized by a 70 percent or greater coronary arterial narrowing.7 Jeopardized myocardium was defined as normal or hypokinetic region wall motion in zones supplied by a stenotic coronary artery of 70 percent or more.

Rogers et al8 found that after myocardial infarction, patients with a left ventricular ejection fraction of greater than 40 percent had a 95 percent survival at three years, whereas those with an ejection fraction of

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40 percent or less had a three-year survival of only 76 percent—a statistically significant difference. Patients studied with coronary arteriography within 30 days of a myocardial infarction had a 73 percent incidence of multivessel coronary artery disease, i.e. left main or triple or double vessel disease. It was not possible to predict coronary arteriographic findings by the clinical course, whether uncomplicated or complicated by congestive failure, dysrhythmias, recurrent ischemic pain, or infarction.8 Nor could multivessel disease be predicted by limited exercise testing soon after myocardial infarction.9

**Beta Blocking Agents in Protection of Ischemic Myocardium**

Several studies in postmyocardial infarction patients utilizing beta-adrenergic blocking agents have been performed to determine the effect on mortality and reinfarction. Agents have included propranolol,10 propranolol or atenolol,11 alpenolol,12 practolol,13 oxprenolol, or disopyramide.14 Alpenolol was associated with a reduction in sudden death,15 and in mortality rate in patients 65 years of age and younger,16 while practolol provided a significant reduction in mortality of 38 percent, especially in patients having anterior infarction with a diastolic blood pressure of 78 mm Hg or below.15 However, neither is available in the United States, and the other agents are no longer commercially available because of side effects.15 Some of the trials did not show the anticipated results of reduced mortality,12,13,15 though treated patients who remained on therapy fared better than those who started and then discontinued therapy.16 Early use of intravenous atenolol within 12 hours of chest pain decreased enzyme release, enhanced R-wave preservation, and may have averted infarction in patients entering with chest pain but without evidence of infarction at entry.16

Recent large prospective randomized population studies have shown improved survival following recovery from a myocardial infarction from administration of beta blocking agents. Still other investigations have shown considerable benefit from a reduced saturated fat diet and cessation of smoking or antiarrhythmic agents in certain groups of patients.

The beta-blocker timolol has been found in Norway to reduce mortality and reinfarction in patients surviving myocardial infarction.17 Timolol was started orally as 5 mg twice daily and increased to 10 mg twice daily. Therapy was started 7 to 28 days after myocardial infarction. There were 945 patients receiving timolol and 939 patients treated with placebo. Patients were followed 12 to 33 months with a mean of 17 months. Group 1 consisted of patients with recurrent myocardial infarction. Group 2 included patients with first myocardial infarction but who were at high risk, and group 3 were patients who were at low risk.

Timolol reduced overall mortality in risk group 2 as well as all groups combined (p<0.001). The cumulative mortality rates for all causes of death at 33 months were 10.6 percent for timolol-treated patients and 17.5 percent for patients treated with placebo for a 39.4 percent reduction (p = 0.0005). The cumulative sudden death rates for the same period of follow-up were 7.7 percent in the timolol group and 13.9 percent in the placebo group for a 44.6 percent reduction in sudden deaths (p = 0.0001).

The cumulated reinfarction rates at 33 months were for timolol treated patients 14.4 percent and for placebo treated patients 20.1 percent for a 25.4 percent reduction in reinfarction (p = 0.0006). Importantly mortality was reduced in patients below and above 65 years of age.

Metoprolol was studied in Sweden for its effect on mortality after acute myocardial infarction.18 It was begun at 15 mg intravenously and changed to 100 mg orally twice daily. Therapy was started as soon as possible after myocardial infarction (the mean time was 11.3 hours) and was continued for 90 days. There were 698 metoprolol patients and 697 placebo patients. Cumulative mortality rates for 90 days were for patients receiving metoprolol, 5.7 percent, and for patients taking placebo, 8.9 percent, for a 36 percent reduction in mortality (p<0.03). Mortality was reduced in patients below and above 65 years of age.

The effect of propranolol on mortality after acute myocardial infarction was studied in this country—the beta blocker heart attack trial (BHAT).18 Propranolol was started at 20 mg and advanced to 40 mg, then 60 mg every eight hours in 82 percent of patients and 80 mg every eight hours in 18 percent of patients. Therapy was started from 5 to 21 days after myocardial infarction. There were 1,916 propranolol-treated patients and 1,921 placebo patients. Patients were followed for 25 months. They were divided into groups 1, 2, and 3, comparable to the timolol study, and in each, propranolol reduced the relative risk.

The total mortality in the propranolol-treated patients was 7.2 percent and in placebo-treated patients, 9.8 percent, for a 26.5 percent reduction in total mortality (p<0.005). The cardiovascular disease mortality was 6.6 percent in propranolol patients and 8.9 percent in placebo patients for a reduction of 25.8 percent (p<0.01). The arteriosclerotic heart disease mortality was 6.2 percent in patients receiving propranolol and 8.5 percent in patients given placebo, resulting in a 27.1 percent reduction in mortality for this subgroup (p<0.01). Sudden death was similarly reduced with 3.3 percent of propranolol patients dying suddenly, whereas 4.6 percent of placebo patients died suddenly for a 28.3 percent reduction in propranolol-treated patients (p<0.05). Propranolol reduced mor-
tality risk in all age groups and in anterior and inferior myocardial infarction.

In a study from England, oxprenolol was evaluated in 1,163 patients one to 90 months after acute myocardial infarction. A 4:3 randomization schema was utilized such that 632 patients received oxprenolol, 40 mg orally twice daily, and 471 received placebo. Ages ranged from 35 to 65, and follow-up averaged 48 months and ranged from six to 84 months. The major influence on prognosis was the time at which treatment was started after infarction. In 417 patients in whom treatment was started within four months of infarction, oxprenolol increased the six-year cumulative survival from 77 percent to 95 percent (p < 0.0001).

In 274 patients with treatment starting between five and 12 months of infarction, the survival rate was similar in the two groups. However, in 412 patients entered between one and 7½ years after their first infarction, oxprenolol reduced the six-year survival rate from 92 percent to 79 percent (p = 0.002). The increased mortality in this latter group mainly occurred late after withdrawal from active treatment. The value of low-dose oxprenolol in secondary prevention appeared to be confined to patients treated relatively soon after myocardial infarction. It was only the extended follow-up of these latter patients that pointed out the excess mortality in the oxprenolol group. While it was not clear how long the drug should be continued, survival curves for the two treatment groups entered soon after infarction were still diverging at six years. Because of this finding, the authors felt that it may be wise to continue these drugs for at least this length of time.

**Diet and Cessation of Smoking**

Information about diet and smoking in patients with heart disease, though not after a myocardial infarction, may also be useful in patients recovered from a myocardial infarction. The Norway diet-and-smoking five-year randomized intervention trial was a study of primary prevention for coronary heart disease in patients at high risk of developing a myocardial infarction. The study was in men 40 to 49, with a cholesterol level between 290 and 380 and an increased coronary risk score based on cholesterol, smoking, and blood pressure, with systolic blood pressure less than 150 mm Hg. In the intervention group, if the cholesterol was elevated, they were given a diet of reduced saturated fat and increased polyunsaturated fat. If the triglyceride value was elevated, they were given a diet of reduced total energy intake including a reduction in sugar, alcohol, and fat. Eighty percent smoked, and these were given individual anti-smoking advice. Wives were invited for the diet and smoking information.

In the intervention group, the percentage of caloric intake of total fat, saturated fatty acids, carbohydrates, and cholesterol was reduced significantly as was the polyunsaturated to saturated fat ratio. The mean serum cholesterol level fell 13 percent, and the mean fasting serum triglyceride value fell 20 percent in the intervention group as compared to the control group. The mean tobacco consumption per man fell 45 percent in the intervention group. In the intervention group, 25 percent stopped while 17 percent stopped in the control group.

The incidence of myocardial infarction—both fatal and nonfatal—and sudden death was 47 percent lower in the intervention group than in the control group (p = 0.028). The incidence of strokes was also significantly less. From this study, the authors concluded that in healthy, middle-aged men at high risk of coronary heart disease, advice to change eating habits and to stop smoking, significantly reduced the incidence of the first event of myocardial infarction and sudden death. This reduction in incidence in the intervention group is correlated with the reduction in total cholesterol and to a lesser extent, with smoking reduction.

In patients followed two years after myocardial infarction in Goteborg, Sweden, a reduced risk of death and of reinfarction was found in those stopping smoking. The study was performed in men surviving their first myocardial infarction as compared to population controls. Cardiovascular deaths in those who continued smoking was 17 of 174 or 10 percent as compared to 11 of 231 or 5 percent in those who stopped smoking (p < 0.05). Reinfarctions in those who continued to smoke occurred in 31 of 174 or 18 percent, while in those who stopped, reinfarction occurred in 20 of 231 or 9 percent (p < 0.01). In patients who stopped, there was less dyspnea on exertion but a higher incidence of hypertension. The recommendation from the study was that a high priority be given to anti-smoking measures after myocardial infarction.

**Nitrates, Anticoagulants and Antiarrhythmic Agents**

Prognosis after recovery from myocardial infarction was studied from 1978 to 1981 at the San Francisco General Hospital in 139 patients and reported by Rapaport and Remedios. High risk patients were those having complex ventricular ectopic rhythm and were older. In these patients, impaired global left ventricular function and in initial anterior myocardial infarction were both independently significant variables predictive of sudden death but not total mortality. However, failure to receive long-acting nitrates after hospital discharge was a risk for total mortality but not sudden death.

Pooling of results of secondary prevention trials after myocardial infarction to prevent mortality and rein-
infarction has definite hazards. Nevertheless, this technique has been done and allows certain insight. With regard to anticoagulants in the hospital phase of acute myocardial infarction, Chalmers et al. found that pooling of all randomized controlled trials gives a mean case fatality rate of 19.6 percent for the control group and 15.4 percent for the anticoagulated group—a relative reduction of 21 percent (p <0.05 or <0.001). Anticoagulants were given within a few hours of the diagnosis. Hemorrhagic complications were 3.8 times as frequent in patients receiving anticoagulants, but the risk:benefit ratio favored these same patients. He concluded that all patients who present no specific contraindication should receive anticoagulants during hospitalization for infarction. Pooling results of trials involving aspirin after myocardial infarction gives an estimate of reduction in mortality between 8.5 percent and 11 percent. Pooling results of physical exercise as an intervention indicates a 19 percent reduction in total mortality (p <0.05).

While there are no convincing data with regard to the efficacy of available antiarrhythmic agents in patients recovered from acute myocardial infarction, one must frequently take a pragmatic approach in the presence of serious ventricular arrhythmias. Electrophysiologic studies in specialized laboratories, administration of investigational pharmacologic agents in various doses, plus possibly surgery on the endocardium may become necessary in the presence of recurrent or refractory serious ventricular arrhythmias. However, Myerburg and colleagues found in survivors of prehospital cardiac arrest that adequate plasma levels of antiarrhythmic agents may protect against recurrent cardiac arrests despite failure to suppress ventricular ectopic depolarizations. Using either propranolol or quinidine gluconate, eight of 16 patients had unstable plasma levels of both agents, but both agents were subtherapeutic, and all had recurrent cardiac arrest. Eight of 16 patients did not have recurrent cardiac arrest. Six of these eight had consistently therapeutic levels. The difference in the groups was significant (p <0.01).

**Coronary Artery Bypass Surgery**

From our laboratory Rogers et al. investigated the effects of coronary bypass surgery in a prospective nonrandomized study on high risk patients recovered from a recent acute myocardial infarction. Patients had coronary arteriography and biplane left ventriculography within 60 days of myocardial infarction. Each view of the left ventriculogram was divided into five segments. At a mean follow-up of 23 ± 2 months after infarction, patients who had had four to ten residual jeopardized (ischemic) ventriculographic segments who were managed surgically had a 93 ± 5 percent survival as compared to those managed medically who had a 64 ± 11 percent mortality (p <0.05).

My interpretation of these data in the management of potentially high risk patients with ischemic myocardium following myocardial infarction is that the postmyocardial infarction patient should have a beta blocking agent. Timolol, metoprolol, and propranolol—all presently available in the United States—have been studied in this clinical setting, though other beta blockers may work as well. It would seem from the oxprenolol study that the beta blocking agent should be started within four months or less of acute myocardial infarction and though the data are only suggestive, might well be continued at least six years and perhaps longer. A concern regarding this recommendation exists, however, because of the reported reduction in high density lipoprotein (HDL) cholesterol concentration and increased triglyceride and urate concentration, in patients given propranolol.

In the male subject at high risk for coronary artery disease with or without a previous myocardial infarction, the presence of an elevated cholesterol level should cause initiation of a diet of reduced saturated fat and increased polyunsaturated fat and an elevated triglyceride level should initiate a diet of reduced total energy intake including sugar, alcohol, and fat. All patients should be advised to stop smoking. In the postmyocardial infarction patient with ischemic myocardium, data would seem to indicate an improved survival with coronary artery surgical revascularization.

**References**


