Programmed ventricular stimulation in survivors of an acute myocardial infarction

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ABSTRACT The prognostic significance of programmed ventricular stimulation and its usefulness in relation to other forms of invasive and noninvasive testing was evaluated in 150 survivors of acute myocardial infarction. Ventricular tachyarrhythmias of 6 beats or more were induced in 35 (23%) patients. No significant differences existed between patients with inducible ventricular tachyarrhythmias and those without inducible ventricular tachycardia with respect to occurrence of spontaneous ventricular arrhythmias in the acute and early recovery phase of infarction or predischarge exercise-induced ischemia or arrhythmias, severity of coronary artery disease, or degree of left ventricular dysfunction. A higher incidence of inferior myocardial infarction was observed in patients with inducible ventricular tachycardia when compared with those without inducible ventricular tachycardia (66% vs 41%, p < .01). During a mean follow-up of 10 ± 5 months (range 2 to 19), there were two sudden deaths, three nonsudden deaths, and two additional patients developed sustained ventricular tachyarrhythmias. There was no significant difference between patients with and those without inducible ventricular tachyarrhythmias with respect to the occurrence of these events. In this study population, a lower mean ejection fraction (p < .01), the presence of a ventricular aneurysm (p < .05), and exercise-induced ventricular premature contractions (p < .05) were predictors of sudden death and of spontaneous ventricular tachycardia. Thus, the findings of this study do not support the hypothesis that the induction of ventricular tachyarrhythmias in patients recovering from acute myocardial infarction identifies a group at high risk for sudden cardiac death.


SURVIVORS OF MYOCARDIAL INFARCTION represent a large and easily identifiable population of patients at risk for sudden cardiac death and considerable efforts have been made to identify in this group those patients at highest risk for subsequent fatal arrhythmic events. Although it has been demonstrated that frequent and repetitive ventricular premature complexes during ambulatory electrocardiographic monitoring are associated with increased mortality, the predictive accuracy of this marker of risk for sudden death and its relationship to left ventricular dysfunction are still somewhat controversial. Furthermore, trials of class I antiarrhythmic drug therapy after myocardial infarction have produced discouraging results.

Programmed electrical stimulation has been used effectively in the diagnosis and management of patients with life-threatening ventricular arrhythmias. More recently, it has been suggested that this technique could accurately predict patients at risk for sudden death after myocardial infarction. However, this finding has not been substantiated by other investigators, and the relationship between the information obtained by electrophysiologic testing and other prognostic indicators has not yet been evaluated.

This prospective study was undertaken to evaluate the prognostic significance of programmed ventricular stimulation in patients with recent myocardial infarction. In addition, the prognostic value of results of programmed ventricular stimulation was compared with that of the site and size of myocardial infarction, the incidence of spontaneous arrhythmias observed during both the acute and early recovery phase of infarction, the severity of coronary artery disease, and the degree of left ventricular dysfunction.

Methods

**Patient population.** The study population was selected from 320 patients admitted to the coronary care unit of the Montreal Heart Institute between May 1983 and October 1984 for acute
myocardial infarction and who satisfied the following criteria: (1) age 65 years or less, (2) absence of uncontrolled angina or heart failure, (3) absence of sustained ventricular tachycardia 72 hr or more after the onset of infarction, and (4) absence of significant nonischemic heart disease. Of these patients, 150 gave written informed consent to undergo treadmill exercise testing, 24 hr ambulatory electrocardiographic monitoring, coronary angiography, left ventricular radionuclide angiography, and programmed ventricular stimulation.

Clinical evaluation. A detailed clinical history and physical examination were obtained from each patient. On admission, patients were assigned by clinical criteria to Killip classes I through IV. Serum creatine kinase and MB isoenzyme levels were measured at 8 hr intervals for the first 24 hr and then daily for the next 48 hr. The criteria for acute myocardial infarction included at least two of the following: myocardial ischemic pain lasting more than 30 min., serum levels of creatine kinase elevated at least twice above the upper limit of normal with presence of the MB fraction, and Minnesota code-electrocardiographic criteria for acute infarction.

Programmed ventricular stimulation. All patients underwent programmed ventricular stimulation while in the postab-sorptive state and while receiving no antiarrhythmic medication for at least 72 hr before the study. The tests were performed a mean of 12 ± 2 days (range 8 to 20) after myocardial infarction. A quadrupolar electrode catheter was inserted percutaneously and positioned at the right ventricular apex under fluoroscopic guidance. Stimulation was performed with a programmable stimulator and an isolated constant current source.

Electrocardiographic monitoring. All patients were observed with continuous visual electrocardiographic monitoring assisted by rate alarms for the first 4 days in the coronary care unit. A two-channel 24 hr Holter recording was obtained in 147 patients a mean of 11 ± 9.5 days (range 5 to 90) after myocardial infarction. Counts were made of the total number of ventricular premature complexes during each hour and the arrhythmias were also graded according to the system devised by Lown and Wolf.

Exercise testing. Exercise testing was performed as previously described in 148 patients a mean of 9 ± 2 days (range 6 to 17) after myocardial infarction by the Naughton protocol. End points were 70% of age-predicted maximal heart rate, workload of 5 mets, appearance of limiting symptoms, severe ventricular arrhythmias, and greater than 5 mm of ST segment depression. A test result was considered abnormal if 1 mm or more of ST segment depression developed compared with the baseline tracing and with the use of a minimum of three and in most instances 12 electrocardiographic leads.

Catheterization and angiographic procedures. Selective coronary arteriography was performed as previously described in all patients a mean of 10 (range 7 to 19) days after myocardial infarction. Each patient was classified as having one-, two-, or three-vessel coronary artery disease based on the presence of a 75% or more reduction of the internal vessel diameter of the main arteries or branches. Left ventricular ejection fraction was calculated in each patient from a radionuclide-gated scan obtained with the use of technetium perchlorate.

Follow-up. Patients were followed up to 19 months at 3 to 6 month intervals. No patient was lost to follow-up and follow-up data were complete in all patients. A clinical history, physical examination, and electrocardiogram were obtained during each visit. For the purpose of this report, January 31, 1985 was determined a common termination date and follow-up information was obtained in all patients during the 6 weeks preceding this date.

The end points of the study were death or the development of documented sustained ventricular tachyarrhythmias. Death was defined as sudden if it occurred within 1 hr of the onset of symptoms.

Although the results of the programmed ventricular stimulation study were available to the treating physician, they did not influence treatment since this technique was considered as a research procedure. Only one patient was discharged on antiarrhythmic drug therapy. This patient, who had inducible sustained ventricular tachycardia, did not undergo stimulation-guided antiarrhythmic therapy and drug therapy had been discontinued at the time of last follow-up.

Differences among continuous variables were analyzed by the unpaired Student t test. Discrete variables were compared with the chi-square test. For 2 × 2 tables with cell frequencies of less than 5, analysis was performed with Fisher’s exact probability test. All values are expressed as mean ± 1 SD. A p value of less than .05 was considered indicative of a significant difference.

Results

Response to programmed ventricular stimulation (table 1). Ventricular fibrillation during programmed ventricular stimulation occurred in two patients. Sustained ventricular tachycardia was induced in 16 patients. The arrhythmia had a right bundle branch block morphology in 10 patients and a left bundle branch block morphology in six. The mean cycle length of the tachycardia was 246 msec (range 200 to 330) and its mean duration was 40 sec (range 13 to 180). Nonsustained ventricular tachycardia was initiated in 17 patients. The tachycardia was polymorphic in 13 patients and had a right bundle branch block morphology in four. The mean cycle length of the tachycardia was 214 msec (range 175 to 300) and its duration was 16 complexes (range 6 to 43). Two ventricular extrastimuli were required to initiate all sustained and nonsustained ventricular tachyarrhythmias. External countershock was required to terminate sustained ventricular tachyarrhythmia in 10 patients.
TABLE 1

Response to programmed ventricular stimulation

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n = 35)</td>
<td></td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>2</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
<td>16</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>17</td>
</tr>
<tr>
<td>Group B (n = 115)</td>
<td></td>
</tr>
<tr>
<td>Repetitive ventricular responses</td>
<td>85</td>
</tr>
<tr>
<td>No response</td>
<td>30</td>
</tr>
</tbody>
</table>

Repetitive ventricular responses were induced in 85 patients. Thirty patients had no extra response to programmed ventricular stimulation.

On the basis of programmed stimulation, the patients were divided into two groups. Group A consisted of the 35 patients (23%) with inducible ventricular tachycardia or ventricular fibrillation. Group B comprised the remaining 115 patients (77%), who had either one to five repetitive ventricular responses or no extra response to programmed ventricular stimulation at all.

Seventeen patients belonging to group A and 56 patients in group B were receiving ß-blockers at the time of programmed ventricular stimulation (p = NS). The mean stimulation threshold was 0.71 ± 0.18 among patients in group A and 0.62 ± 0.24 in group B (p < .05). However, ventricular refractory periods were similar between the two groups (252 ± 20 vs 259 ± 22 msec; p = NS).

The ventricular stimulation studies caused no deaths. All sustained ventricular tachyarrhythmias were converted promptly to sinus rhythm, although conversion was complicated by persistent neurologic sequelae in one patient.

Clinical characteristics. The clinical characteristics of the patients in the two groups are summarized in Table 2. The average age of all patients was 52 years; 87% were men and 26% had suffered a previous myocardial infarction. The location of acute infarction was anterior in 45% of the patients and inferior in 47% of patients. Thirty percent of patients had non-Q wave infarction. The mean peak creatine kinase level for all patients was 1989 IU/liter. Most patients had no evidence of left ventricular failure at the time of admission. The incidence of inferior infarction was significantly higher in the patients in group A (66%) compared with those in group B (41%, p < .01) and anterior infarctions were more frequent in group B (51%) than in group A (26%, p < .01). There was no significant difference in age, sex distribution, incidence of prior myocardial infarction, incidence of non-Q wave infarction, peak creatine kinase levels, or Killip class between the two groups.

Comparison of the spontaneous ventricular arrhythmias in the acute (≤72 hr) phase of myocardial infarction and response to programmed ventricular stimulation (table 3). Thirty-eight (25%) of the 150 patients suffered from ventricular tachycardia or fibrillation in the first 72 hr after myocardial infarction. Twelve (8%) patients had a sustained ventricular tachyarrhythmia requiring cardioversion and 26 (17%) patients had nonsustained ventricular tachycardia. The proportion of patients having these arrhythmias was not significantly different between group A and group B.

Comparison of the arrhythmias recorded during 24 hr ambulatory electrocardiographic monitoring and response to programmed ventricular stimulation. The mean number of ventricular premature complexes per hour recorded during 24 hr Holter monitoring was 4.3 ± 10.9 among patients of group A compared with 2.4 ± 6.5 in patients of group B. Although a trend was present this difference was not significant and, as illustrated in figure 1, the number of ventricular premature complexes per hour was evenly distributed between the two groups. Only 11 (7%) patients in this study had more than 10 ventricular premature complexes per hour.

There was also no significant difference in Lown grade classification between patients in group A and group B. Thirteen patients (38%) in group A and 32 patients (28%) in group B had grade 3 or 4 arrhythmias.

Correlation of results of exercise testing with results of programmed ventricular stimulation (table 4). Forty-eight (32%) of the 148 patients who underwent exercise testing developed 1 mm or more ST segment depressions.
TABLE 3
Comparison of the arrhythmias recorded in the coronary care unit with the results of programmed ventricular stimulation

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 15)</th>
<th>Group B (n = 115)</th>
<th>Total (n = 150)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained VT/VF</td>
<td>5 (14%)</td>
<td>7 (6%)</td>
<td>12 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nonsustained</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT/VF</td>
<td>10 (28%)</td>
<td>21 (18%)</td>
<td>26 (17%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

VT = ventricular tachycardia; VF = ventricular fibrillation.

Coronary angiography and radionuclide ventriculography. As shown in table 5, no significant differences existed between the two groups with respect to the number of coronary vessels with a stenosis of 75% or more (1.5 ± 0.8 vs 1.6 ± 0.8), the mean ejection fraction measured by predischarge radionuclide gated scan (45 ± 12% vs 46 ± 12%), and the number of patients with a left ventricular aneurysm (three vs nine patients).

Follow-up. In table 6, the results of programmed ventricular stimulation are correlated with clinical outcome during the 10 ± 5 months (range 2 to 19) of follow-up evaluation. There were seven (5%) fatal or near-fatal cardiac events. Four of these seven events occurred within 3 months of infarction. There were two sudden deaths. One group A patient with inducible sustained ventricular tachycardia died suddenly at 15 months of follow-up and one patient belonging to group B died suddenly 15 days after hospital discharge. Three patients belonging to group B suffered nonsudden cardiac deaths. All three deaths were due to cardiogenic shock, two secondary to recurrent myocardial infarction and one related to coronary bypass surgery. Two patients, one in each group, were resuscitated from spontaneous sustained ventricular tachycardia. The arrhythmia occurred 1 week after hospital discharge in the patient in group A with inducible sustained ventricular tachycardia and developed in the late hospital course of a recurrent myocardial infarction in the patient in group B. There were no significant differences in the occurrence of sudden death, nonsudden death, and/or spontaneous sustained ventricular tachycardia between the two groups. There was also no significant difference in the occurrence of these events when the 18 patients with inducible sustained ventricular tachyarrhythmias were compared with the 132 patients without inducible sustained arrhythmias at the time of programmed ventricular stimulation. Patients with inducible sustained tachyarrhythmias had a lower mean ejection fraction than
TABLE 6
Correlation between results of programmed ventricular stimulation and clinical outcome (mean follow-up 10 ± 5 months)

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 35)</th>
<th>Group B (n = 115)</th>
<th>Total (n = 150)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Nonsudden</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Spontaneous sustained VT</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Therapy at end of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>15</td>
<td>51</td>
<td>66</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary bypass surgery or coronary angioplasty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td>4</td>
<td>17</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>NS</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; VT = ventricular tachycardia.

those without inducible sustained arrhythmias (40 ± 12% vs 46 ± 11%, p < .05). There were no significant differences between patients with and those without inducible sustained tachyarrhythmias with respect to other clinical characteristics.

Six patients, all belonging to group B, experienced recurrent nonfatal myocardial infarction.

At the end of follow-up, 15 group A and 51 group B patients were receiving the pharmacologic equivalent of propranolol, 160 mg/day or less (p = NS). Four patients in group A and 17 patients in group B underwent coronary bypass surgery or coronary angioplasty for control of angina (p = NS). Two patients in group A and three patients in group B were receiving antiarrhythmic drug therapy (p = NS). Of these five patients, two were being treated for paroxysmal atrial fibrillation and antiarrhythmic therapy was initiated for premature ventricular complexes in three patients.

To determine if other factors could accurately identify high-risk patients, the subjects who died or experienced spontaneous sustained ventricular tachyarrhythmias were compared with those who did not experience these events during the follow-up period with respect to clinical characteristics and results of all available tests. The mean ejection fraction was significantly lower in the seven patients who died or had sustained ventricular tachyarrhythmias when compared with the remaining 143 patients (35 ± 14% vs 46 ± 11%, p < 0.01). Ventricular arrhythmias occurred during exercise testing in three of the seven patients suffering end point events (43%) as compared with 11 of 141 (8%) survivors (p < .05). When the analysis compared only the four patients who died suddenly or had sustained ventricular tachyarrhythmias with the patients who did not experience an arrhythmic event, the differences still attained statistical significance: the mean ejection fraction was 29 ± 12% in these four patients as compared with 46 ± 11% in the remaining 146 patients (p < .01) and exercise-induced ventricular arrhythmias were observed in two of four patients (50%) who died suddenly or later developed sustained ventricular tachyarrhythmias as compared with 12 of 144 patients (8%) who did not experience these events during follow-up (p < .05). Furthermore, the incidence of sudden death or spontaneous sustained ventricular tachyarrhythmias was significantly greater in patients with a left ventricular aneurysm than in patients without an aneurysm (17% vs 1%, p < .05). No statistically significant difference could be detected between survivors and patients who died and/or had spontaneous ventricular tachyarrhythmias in terms of history of prior myocardial infarction, site and extension of acute infarction, Killip class at admission, peak creatine kinase level, occurrence of ventricular arrhythmias in the acute phase of infarction, mean ventricular premature contractions per hour or Lown grade during Holter monitoring, exercise-induced angina or ST segment depression, two- or three-vessel coronary artery diseases, or medication at the time of follow-up.

The 170 nonassessed patients underwent a follow-up similar to that in the 150 assessed patients. There were eight (5%) deaths during a mean follow-up of 9 ± 5 months: four were nonsudden, two were sudden, and two were due to undetermined causes.

Discussion
This study was designed to test the hypothesis that the induction of ventricular tachyarrhythmias soon after a myocardial infarction could identify those patients at risk for subsequent serious arrhythmic events. In this prospective study, patients also underwent 24 hr Holter monitoring, exercise testing, coronary angiography, and radionuclide ventriculography before hospital discharge. There are three major findings: first, the response to programmed ventricular stimulation was unrelated to the indexes of infarct size or the severity of coronary artery disease, or to the occurrence of spontaneous ventricular arrhythmias in the acute and early recovery phase of myocardial infarction; second, the initiation of a ventricular tachyarrhythmia by electrophysiologic testing was a poor marker of risk for the occurrence of sudden death or...
spontaneous ventricular tachycardia during the 10 month follow-up period; third, prognosis was more related to ejection fraction, exercise-induced ventricular premature contractions, and presence of a left ventricular aneurysm.

Comparison with previous studies. The ability to sustain reentrant circuits in areas of ischemic or infarcted ventricular tissue is believed to be a major mechanism causing sudden arrhythmic death. Programmed ventricular stimulation has been validated as a method of reproducing clinically occurring ventricular tachyarrhythmias.20-24 Because the capacity for such arrhythmias may exist in survivors of myocardial infarction, programmed ventricular stimulation has been proposed as a method for assessing electrical instability and for predicting sudden arrhythmic death after myocardial infarction. Green et al.34 reported that the induction of repetitive responses in postinfarction patients was predictive of future serious arrhythmias. However, the significance of repetitive responses has since been questioned and several studies have demonstrated that they are unrelated to outcome.35-38

Two recent reports25,26 have shown a correlation between the elicitation of sustained or nonsustained ventricular tachyarrhythmias and the occurrence of sudden death after myocardial infarction. Hamer et al.25 studied 70 patients with myocardial infarction complicated by heart failure or arrhythmia and found that four of 12 patients with inducible ventricular tachycardia of 5 beats or more died suddenly while only one of 25 patients without ventricular tachycardia after maximal provocation died suddenly (p < .05). Richards et al.26 evaluated 165 survivors of a myocardial infarction and found that 12 of 38 patients with electrical instability died suddenly or had spontaneous ventricular tachycardia compared with only two of the 127 stable patients. Our findings differ from these observations but extend those of Marchlinski et al.,27 who studied 46 patients after myocardial infarction and reported one sudden death among their 10 patients with inducible arrhythmias (≥4 beats) compared with five sudden deaths in the remaining 36 patients.

It is difficult to compare results between studies because methods of assessment differ. Our stimulation protocol consisted of up to two extrastimuli at twice diastolic threshold but did not include the high current intensities (up to 20 mA) tested by Hamer et al.23 and Richards et al.26 However, these latter two studies did not describe the relationship between the high current used and the induction of arrhythmias. We chose this stimulation protocol because its sensitivity and specificity have already been established for patients with clinically documented arrhythmias.39,40 The specificity of use of high current strength has yet to be determined and it has been shown that aggressive stimulation protocols can result in elicitation of ventricular tachyarrhythmias in patients without documented or suspected clinical arrhythmias.41 Furthermore, we were able to induce a ventricular tachyarrhythmia of 6 beats or more in a sizable proportion (23%) of patients. This rate of inducibility is similar to that obtained in the previous studies of patients after myocardial infarction.25-27 Therefore, it is unlikely that our results are due to the use of inadequate stimulation techniques.

End points and definitions of abnormal responses to programmed ventricular stimulation have also varied between studies. The end point of testing in our study was the induction of a sustained arrhythmia. We could not identify a specific response to programmed ventricular stimulation that could predict the subsequent occurrence of sudden death. Eighteen of our patients had electrical instability as defined by Richards et al.26 (ventricular arrhythmia lasting at least 10 sec). Sixteen of these patients (89%) have survived to follow-up without an arrhythmic event. None of 17 patients with nonsustained ventricular tachycardia died or experienced an arrhythmic event. One of the 85 patients with repetitive ventricular responses developed sustained ventricular tachycardia and one of the 30 patients with no extra response to programmed ventricular stimulation died suddenly.

Limitations. The overall prognosis for this study population was good: only seven patients (5%) suffered a fatal or near-fatal cardiac event during the 10 month follow-up period. Although programmed ventricular stimulation resulted in initiation of ventricular tachyarrhythmias in a significant proportion of patients (23%), the power of the study may have been decreased by the small numbers of patients who experienced either sudden death or serious arrhythmias. The exclusion of patients with severe heart failure and unstable angina undoubtedly accounts for the low mortality. In studies of nonselected postinfarction patients a 19% 1 year mortality has been reported.42 However, our rate is comparable to the 2% to 6% mortality in recent studies of more highly selected patients.43-47 Therefore, our data may not be applicable to the very high-risk subpopulation of survivors of myocardial infarction in whom no further tests may be necessary because their high risk is already clinically obvious.

The outcome in our patients may also have been influenced by information obtained from exercise testing or coronary angiography and the current attitudes about medical and surgical therapy of survivors of
myocardial infarction. At the final review over 40% of patients in both groups were being treated with β-blocking agents, which may also account for the low mortality and may have contributed to the lack of a significant difference in the incidence of cardiac events in the two groups. However, no attempt was made to suppress the arrhythmias induced by programmed ventricular stimulation and only five patients were receiving antiarrhythmic therapy at the end of follow-up.

Clinical implication. The findings of this study suggest that the induction of ventricular tachyarrhythmias in postinfarction patients does not identify a subgroup at high risk for sudden cardiac death. Because this invasive technique is associated with some morbidity and potential mortality, we do not recommend it for routine clinical risk stratification of patients recovering from an acute myocardial infarction.

We acknowledge the excellent technical assistance of Emma Lemire and Richard Carlier.

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