The Posthospital Phase of Myocardial Infarction

Identification of Patients with Increased Mortality Risk

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SUMMARY
A prospective follow-up study was carried out on 100 patients recovering from acute myocardial infarction in order to develop a method for identifying those patients who are at high risk of late cardiac death. Variables, which were recorded just prior to the patient’s hospital discharge after the acute attack, included six rhythm parameters from a six-hour tape ECG recording, three indices of severity of the acute coronary event, and seven nonspecific variables. Seventy-nine of the 100 patients survived a two-year follow-up, and 17 of 21 patients who died succumbed from cardiac-related problems. A stepwise discriminant analysis program was used to derive a formula which would predict the likelihood of surviving two years after a myocardial infarction. The population was divided into two groups on the basis of the presence (Group A, N = 67) or absence (Group B, N = 29) of ventricular premature beats on the initial ECG tape recording. In Group A, 91% of both the survivors and nonsurvivors were correctly identified by a discriminant combination of three arrhythmia parameters and age. In Group B, 75% of the survivors and 100% of the nonsurvivors were properly classified simply from age and one index of severity.

Additional Indexing Words:
Ventricular premature beats        Bigeminy    Discriminant analysis    Survival probability

ROGNOSTICATION is assuming increasing importance in the evaluation of patients with coronary heart disease. With the advent of coronary artery bypass surgery, the need for an accurate determination of the prognosis for survival or cardiac death over a specific time duration in an individual patient has become apparent. The risks of surgical intervention must be evaluated in the light of the expected clinical course of the disease process. Presently, prognosis is usually made in gross qualitative terms (good, fair, poor) on the basis of subjective clinical experience. Recently, more quantititative methods have been applied to follow-up studies of patients with preinfarction angina, unstable angina, angina pectoris, and prior myocardial infarction, and more accurate and precise risk categorizations are emerging.

The purpose of the present study was to develop a quantitative prognostic index that would be applicable to individuals who were recovering from an acute myocardial infarction. The index or score was derived from specific clinical measurements which were made during the in-hospital convalescent phase after an acute myocardial infarction. A stepwise discriminant analysis technique was used to find out how much was added to the accuracy of a prediction by each of several parameters possibly affecting the long term outcome of acute myocardial infarction. From this discriminant index or score, the probability of survival and death from cardiac causes was derived.

Methods

Study Population
One hundred patients, aged 33 to 82 years, who were admitted to the Strong Memorial Hospital between January 1969 and October 1970 with acute myocardial infarction were the subjects of this study. The diagnostic criteria for an acute myocardial infarction included a typical clinical history and either 1) a
characteristic series of elevations in SGOT activity or 2) the development of new Q waves or significant ST and T wave changes on serial ECGs. The medical therapy and date of hospital discharge on each patient were determined by the patient's primary physician. Within three days prior to contemplated discharge a portable electrocardiographic tape recorder* was attached to each patient. A 6-hour ECG tape record was obtained during the patient's ordinary convalescent daytime activity using a modified bipolar $V_5$ lead as previously described from this laboratory.\(^8\)

Measurements

The ECG tape was analyzed by the Avionic rapid scan technique\(^*\) for: 1) basic rhythm; 2) average heart rate (HR); and 3) premature beats or rhythm of atrial, A-V junctional or ventricular origin. All ventricular premature beats (VPBs) were identified on each patient's record and categorized as follows: 1) VPB frequency (VPB\(_f\))—the number of VPBs/1000 normal beats; and 2) VPB prematurity (VPB\(_p\))—the earliest VPB coupling interval (R-R') divided by the Q-T duration, i.e., RR'/QT. In addition, identification was made of VPBs which were multifocal (VPB\(_m\)), those which occurred in bigeminal runs or pairs (VPB\(_b/p\)) and those which occurred in a sequence of ventricular tachycardia (VT), i.e., three or more VPBs in a row.

The hospital chart on each patient was reviewed in detail by two of the authors. Sufficient information was accumulated from the chart to obtain a Peel index\(^*\) of severity of myocardial infarction as well as the Norris indices of short\(^-10\) and long-term\(^11\) survival. Additional variables that were obtained from chart review included age, sex, lowest systolic blood pressure (SBP), highest serum glutamic oxaloacetic transaminasi (SGOT) activity, highest blood urea nitrogen (BUN), highest white blood count (WBC), and highest rectal temperature. Thus, the 16 variables which were measured included six rhythm parameters from the ECG tape recording (HR, VPB\(_f\), VPB\(_p\), VPB\(_m\), VPB\(_b/p\), VT), three standard severity indices (Peel, Norris short, Norris long), and seven nonspecific variables.

Follow-up

Between one and one half and two years after the initial predischarge recording and chart review, all 100 patients were traced and their subsequent clinical course validated. Twenty-one patients died during this follow-up period, and the cause of death was ascertained from autopsy examination in six patients, from hospital record review in 13 patients, and from private physician and spouse interview in the remaining two patients.

Statistical Analysis

The prospective data obtained just prior to hospital discharge were related to the subsequent outcome (survival or cardiac death) during the two-year follow-up period. The multiple variables were entered into a stepwise discriminant analysis program (BMD-07M)\(^12\) to obtain the most accurate separation of those who survived and those who died from heart-related causes. An IBM 360 model 65 computer was utilized for high-speed analysis. The BMD-07M program performed multiple discriminant analyses in a stepwise manner. At each step, one variable was entered into the set of discriminating variables. The variable entered was selected by the first of the following equivalent criteria: 1) the variable with the largest discriminating power (F value); 2) the variable which when partitioned on the previously entered variables had the highest multiple correlation with the groups; and 3) the variable which gave the greatest decrease in the ratio of within to total generalized variances. A variable was not entered or deleted from the discriminating set if its F value was below a preset statistically significant level. The program also computed the canonical correlations and coefficients for canonical variables. The first two canonical variables were plotted on X-Y axes to give an optimal two-dimensional picture of the dispersion between survival and death. The coefficients for the first canonical variables were the coefficients in the linear discriminant function. These coefficients quantified the relative contribution to the discriminant function. In addition, the program computed for each case the probability of correct classification for survivors and nonsurvivors based on the value of the square of the Mahalanobis distance from the center of each group. The confidence intervals for the probability of misclassification were computed using the method of Lachenbruch.\(^13\) In this method each patient is sequentially removed, and the discriminant function is determined from the remaining patients. The (N-1) index is then applied to the patient removed. This method, popularly known as "jacknifing," gives an unbiased estimate of the error rate for discriminant function analysis.

Results

Seventy-nine patients survived and 21 died during the follow-up period of 1.8 ± 0.3 (SEM) years. Seventeen patients died from cardiac causes (recurrent myocardial infarction, 8; power failure syndrome, 5; sudden death, 4) within 0.5 ± 0.1 years after entry into the study. Four patients died of noncardiac causes, and these patients were not included in the subsequent analyses. The results of the stepwise discriminant analysis performed on all the variables from the entire population indicated significant predictive value for certain types of VPB. For this reason the population was divided into two groups. Group A included 67 patients who had one or more VPBs on the 6-hour ECG tape recording at entry into the study; the 12 cardiac deaths in the group were due to additional myocardial infarctions in six, power failure syndrome in two, and sudden death in four. Group B

*Avionics Electrocardiocorder and Electrocardioscanner, Avionics Corporation, Los Angeles, California.
consisted of 20 patients without tape recorded VPBs.

Group A (67 patients with VPBs)

A comparison of the mean values of the 16 variables in the 55 patients who survived and the 12 who died of cardiac causes is presented in table 1. A significant difference ($P < 0.05$) exists with a univariate comparison for mean values for Peel, Norris long, short, age, WBC, VPBP, VPBF, and VPBB/P. Ventricular tachycardia was not included in subsequent analyses because this arrhythmia occurred in only four patients.

The remaining 15 variables were entered into the stepwise discriminant analysis program. The sequence in which the first five variables were combined to form the discriminant function together with the F values for entry and group discrimination and the respective levels of significance are presented in table 2. The first four variables separate the outcomes survival and death with reasonable accuracy, and inclusion of the remaining 11 variables did not significantly improve the accuracy of the separation. Thus, an F value of 2.1 was selected and only four variables were entered into the discriminant function. Using the first canonical coefficients of the four variables, the following function for the Group A discriminant score ($DS_A$) was obtained:

\[ DS_A = -1.72 \text{ VPB}_{B/P} - 0.065 \text{ Age} + 1.78 \text{ VPBF} - 0.01 \text{ VPBB/P} + 3.0 \]

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>$n = 55$ Survived</th>
<th>$n = 12$ Died</th>
<th>$P$ level*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peel</td>
<td></td>
<td>11.7</td>
<td>15.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Norris long</td>
<td></td>
<td>5.6</td>
<td>7.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Norris short</td>
<td></td>
<td>6.3</td>
<td>8.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>57.6</td>
<td>67.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>M = 1, F = 2</td>
<td>1.2</td>
<td>1.2</td>
<td>—</td>
</tr>
<tr>
<td>SBP</td>
<td>mmHg</td>
<td>141</td>
<td>141</td>
<td>—</td>
</tr>
<tr>
<td>SGOT</td>
<td>Karmen units</td>
<td>152</td>
<td>162</td>
<td>—</td>
</tr>
<tr>
<td>BUN</td>
<td>mg/100 ml</td>
<td>25</td>
<td>34</td>
<td>—</td>
</tr>
<tr>
<td>WBC</td>
<td>$\times 10^6$ cells/mm$^3$</td>
<td>14.8</td>
<td>12.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Temp.</td>
<td>°F</td>
<td>101.4</td>
<td>101.3</td>
<td>—</td>
</tr>
<tr>
<td>HR</td>
<td>beats/min</td>
<td>78</td>
<td>80</td>
<td>—</td>
</tr>
<tr>
<td>VPBP</td>
<td></td>
<td>1.22</td>
<td>1.02</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VPBF</td>
<td>no./1000</td>
<td>5.7</td>
<td>34.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>VPBM</td>
<td>Absent = 0, Present = 1</td>
<td>0.40</td>
<td>0.50</td>
<td>—</td>
</tr>
<tr>
<td>VPBB/P</td>
<td>Absent = 0, Present = 1</td>
<td>0.14</td>
<td>0.75</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VT</td>
<td>Absent = 0, Present = 1</td>
<td>0.07</td>
<td>0.00</td>
<td>—</td>
</tr>
</tbody>
</table>

* $P$ level using a two-tailed test.

Abbreviations: Peel = Peel index; Norris long, short = Norris indices of short- and long-term survival; SBP = systolic blood pressure; SGOT = highest serum glutamic oxaloacetic transaminase activity; BUN = highest blood urea nitrogen; WBC = highest white blood count; Temp. = highest rectal temperature; VPBP, VPBF, VPBB/P = ventricular premature beat prematurity, frequency, multifocal, bigeminal runs or pairs; VT = ventricular tachycardia.

Table 2

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Variable</th>
<th>$F$ (df)*</th>
<th>Entry values</th>
<th>$P$ level</th>
<th>$F$ (df)*</th>
<th>Group discrimination</th>
<th>$P$ level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>VPBP</td>
<td>25.7(1,65)</td>
<td>&lt;0.0001</td>
<td>25.7(1,65)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Age</td>
<td>9.5(1,64)</td>
<td>&lt;0.005</td>
<td>19.3(2,64)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>VPBF</td>
<td>6.5(1,63)</td>
<td>&lt;0.025</td>
<td>16.2(3,63)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>VPBP</td>
<td>2.2(1,62)</td>
<td>&lt;0.20</td>
<td>12.9(4,62)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Norris short</td>
<td>2.0(1,61)</td>
<td>&lt;0.20</td>
<td>10.9(5,61)</td>
<td>&lt;0.005</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(df) = degrees of freedom.

See table 1 for explanation of abbreviations.
POSTMYOCARDIAL INFARCTION

A DS A greater than zero included 50 of 55 (91%) survivors (average score +1.1) and a DS A less than zero identified 11 of 12 (91%) nonsurvivors (average score −1.2). Increasing positivity and negativity increased the likelihood of properly classifying survivors and nonsurvivors, respectively. The probability of survival as a function of the DS is presented in figure 1. The probability of misclassification was 0.13 ± 0.04 (SE) with a 95% confidence range from 0.00 to 0.31.

Group B (29 patients without VPBs)

A comparison of the mean values of the 11 variables in the 24 patients who survived and the five who died of cardiac causes is presented in table 3. A significant difference (P < 0.05) exists in univariate comparisons of mean values for Norris short, age, and SGOT.

The 11 variables were entered into the stepwise discriminant analysis program. The sequence in which the first three variables were combined to form the discriminant function together with the F values for entry and group discrimination and the respective levels of significance are presented in table 4. Age was the single most important variable and properly categorized 17 of 24 (70%) survivors and four of five (80%) nonsurvivors. When other individual variables were combined with age, the Peel index of severity, which incidentally includes age in its index, contributed most to improving the correct categorization of survivors and nonsurvivors. However, the improvement in group separation was significant at only the 7% level. Inclusion of one or more of the remaining variables did not significantly improve the separation. Thus, an F value of 1.0 was selected and only two variables were entered into the discriminant function. Using the first canonical coefficients of the age and Peel variables, the following function for the Group B discriminant score (DSB) was obtained:

\[
DS_B = -0.078 \text{ Age} - 0.085 \text{ Peel} + 5.8
\]

A DS B greater than zero identified 18 of 24 (75%) survivors (average score +0.62), and a DS B less than zero included five of five (100%) nonsurvivors (average score −0.66). Increasing positivity and negativity enhanced the likelihood of properly classifying survivors and nonsurvivors, respectively. The probability of misclassification was 0.34 ± 0.09 (SE) with a 95% confidence of 0.00 to 0.72.

Discussion

A quantitative method for identifying the important determinants of long-term survival and late death after recovery from acute myocardial infarction is presented. The approach utilizes stepwise discriminant analysis for optimal combination of variables that will predict who will survive and who will die in a two-year follow-up period. The analytic techniques applied in this prospective study are considerably different from the methods used in the coronary prognostic indices of Peel and Norris. The former is a retrospective study in which arbitrary values for selected variables were based on the authors’ clinical impression of their

Table 3

| Variable | Units | n = 24 Survived | n = 5 Died | P_level*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Peel</td>
<td></td>
<td>10.4</td>
<td>15.8</td>
<td>—</td>
</tr>
<tr>
<td>Norris</td>
<td></td>
<td>5.4</td>
<td>8.5</td>
<td>—</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>54.6 ± 65.0</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>M = 1, F = 2</td>
<td>1.08</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>SBP</td>
<td>mm Hg</td>
<td>147 ± 135</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>SGOT</td>
<td>Karmen units</td>
<td>149</td>
<td>76</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BUN</td>
<td>mg/100 ml</td>
<td>24</td>
<td>28</td>
<td>—</td>
</tr>
<tr>
<td>WBC</td>
<td>×10⁶ cells/mm³</td>
<td>14.1</td>
<td>11.5</td>
<td>—</td>
</tr>
<tr>
<td>Temp</td>
<td>°F</td>
<td>101.2 ± 100.6</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>beats/min</td>
<td>78</td>
<td>78</td>
<td>—</td>
</tr>
</tbody>
</table>

*P level using a two-tailed test.
See table 1 for explanation of abbreviations.
importance for prognosis. The latter utilized a semiquantitate approach in which weighted factors were subjected to discriminant analysis to obtain a score bearing on hospital survival. The Norris prognostic index was subsequently applied to patients surviving hospitalization. The present study utilizes stepwise discriminant analysis methods similar to those reported by Shubin et al. and Affi et al. in their prognostication of survival from shock.

In both groups A and B, age is an important factor which bears on the posthospital clinical course. Age is the most important variable in Group B and actually appears twice in the discriminant function. It is the first entered variable, and it is also included as an item in the second variable, the Peel Index. In patients with VPBs (Group A), age takes priority over all parameters except the VPB pattern of bigeminy and/or pairs. These age findings are not surprising since a variety of studies have shown an increasing mortality with age.

In patients with VPBs (Group A) the presence of bigeminy and/or pairs is an ominous finding. However, this variable is either present or absent. VPB prematurity and frequency have a range of values, and shorter coupling intervals and more frequent VPBs indicate a progressively adverse prognosis. Although the importance of these VPB characteristics in acute myocardial infarction is well recognized, a quantitation of their prognostic significance in the recovery phase has not been documented previously. Also, it is extremely interesting that these VPB variables have considerably higher discriminating value with regard to survival and death than the standard indices of Peel and Norris or the individual variables of heart rate, sex, SBP, SGOT, BUN, WBC, or temperature. The high discriminating value of the VPB variables suggests that a major mechanism of cardiac death in Group A may be related to cardiac arrhythmias. It is estimated that six of 12 cardiac deaths in Group A were secondary to cardiac arrhythmias (three of six with recurrent myocardial infarction and three of four sudden deaths). Whether or not these deaths could be prevented by the prophylactic use of antiarrhythmic measures is speculative at this point.

In patients without VPBs (Group B), the discriminant analysis found the Peel index a highly significant indicator of subsequent outcome. The Peel index was originally established to evaluate the severity of a myocardial infarction, and arbitrary weightings were assigned to age, sex, previous cardiac history, presence of shock, ECG pattern, and rhythm (normal sinus rhythm vs all other rhythms including extrasystoles) so that higher scores were associated with a greater chance of death. Our study substantiates the validity of the Peel index in patients without VPBs, yet certain VPB characteristics supercede the prognostic importance of the Peel index in patients with these extra beats.

Although stepwise discriminant techniques have unique applicability for prognostic data analysis, the limitations of this approach must be appreciated. Morgan and Sonquist and Feinstein pointed out a number of problems with discriminant analysis including its linearity, its use of individual variables rather than properties that demarcate a group of people, its computational peculiarities, i.e., "number crunching," and the clinician’s difficulty in comprehending the theoretical aspects of the mathematics. Despite these limitations, regressive discriminant techniques have found increasing usefulness in certain population studies, and their results (variable identification and risk categorization) have been validated. For example, a recent study investigating the predictive importance of the twelve-lead ECG successfully applied the discriminant risk scores derived from one population to a different group, and there was a high correlation.

Table 4
Sequence of Entry and Levels of Significance of Variables in Group B Discriminant Function

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Variable</th>
<th>Entry values</th>
<th>Group discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Age</td>
<td>5.4(1,27)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>2.</td>
<td>Peel</td>
<td>1.1(1,26)</td>
<td>&lt;0.40</td>
</tr>
<tr>
<td>3.</td>
<td>BUN</td>
<td>1.3(1,25)</td>
<td>&lt;0.30</td>
</tr>
</tbody>
</table>

*df = degrees of freedom.
BUN = blood urea nitrogen.
(r = 0.91) between predicted and actual mortality.\(^7\)
In the present study, the indices were tested by computing the probability of misclassification using the "jacknifing" technique of Lachenbruch.\(^13\)

The error rate for misclassification was much smaller in Group A (13%) than in Group B (34%). The large error rate in Group B reflects the small sample size of 27 patients and a very small mortality subgroup of five patients. The magnitude of the error rate in the Group B discriminant function indicates that the equation will have limited clinical usefulness.

A recent report by the Coronary Drug Project (CDP) describes their experience on the prognostic importance of premature beats following myocardial infarction.\(^25\)
The CDP identified 235 men among 2035 survivors of myocardial infarction (11.5%) who had one or more VPBs recorded in the resting 12-lead ECG. The ECG contained an average of 50 beats per recording. Increased long-term (three year) risk of death was associated with the frequency of VPBs, with VPBs in pairs or runs, and with early cycle VPBs.\(^25\)
The present study, in addition to substantiating the epidemiologic VPB findings of the CDP, provides individual patient risk categorization by means of a sustained six hour ECG recording. Approximately 25,000 beats per patient were recorded, 67% of the population had one or more VPBs, and more precise VPB characteristics with added risk of death over a shorter period of time were identified.

Classification of patients by means of prognostic indexing is an important step in the objective analysis of the clinical course of a complex disease process. Risk categorization and the identification of patients with increased mortality risk permit a more accurate evaluation of the effectiveness or ineffectiveness of new modalities of therapy. In addition, by identifying modifiable risk factors, such as certain VPB characteristics, it is hoped that therapy which is directed toward the control of these risk characteristics will reduce mortality and favorably influence the clinical course of patients with prior myocardial infarction.

Acknowledgment
The authors are indebted to the numerous physicians who allowed their patients to be entered into this study and thank Lizabeth Tiftt for her technical and secretarial assistance.

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Circulation. 1974;49:460-466
doi: 10.1161/01.CIR.49.3.460

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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