The Influence of Location and Extent of Myocardial Infarction on Long-term Ventricular Dysrhythmia and Mortality

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SUMMARY Although the extent of enzymatically estimated infarct size appears to be an important determinant of morbidity and mortality early after infarction, its influences on long-term survival and late ventricular dysrhythmia have not yet been characterized. Accordingly, we prospectively studied 173 patients younger than 66 years of age without evidence of prior myocardial infarction, who survived acute myocardial infarction for at least 24 hours. Infarct size was estimated enzymatically and dysrhythmia quantified by computer from two-channel, 24-hour ambulatory ECGs. The mean infarct size index (ISI) of those who died was significantly larger than that of survivors (46.5 ± 5.8 (SEM) vs 21.1 ± 1.4 CK-g-Eq/m², p < 0.001). Overall survival was significantly better after small (ISI < 15 CK-g-Eq/m²) or modest infarcts (15 ≤ ISI < 30) than after large infarcts (ISI ≥ 30) (p < 0.01, p < 0.05, respectively). Regardless of the locus of the infarction, patients with small infarcts had a better prognosis than those with larger infarcts. Late mortality was comparable after transtural and subendocardial infarction, but higher after anterior than after inferior infarction (15% vs 6%; p < 0.05). Among the 10 clinical and hemodynamic variables evaluated with multivariate analysis, ISI (but not infarct locus), peak plasma creatine kinase, congestive failure at the time of admission, age and gender were significantly related to mortality. Premature ventricular complexes were more frequent among patients with modest or large infarcts (ISI ≥ 15) throughout the follow-up (p < 0.05), regardless of infarct locus. Thus, the extent of infarction is a strong determinant of both ventricular dysrhythmia and mortality, late as well as early after acute myocardial infarction.

MORTALITY EARLY after acute myocardial infarction is related to age, the presence or absence of old myocardial infarction, and the site and extent of myocardial infarction sustained.1-5 In addition, the incidence and severity of ventricular dysrhythmia during the first 24 hours after infarction reflect the amount of myocardium damaged.6,7 Long-term survival appears to reflect in part the severity of the infarct based on indirect criteria, such as the presence of congestive heart failure, depressed ejection fraction and dyskinesis.8-11 Further, late ventricular dysrhythmia appears to correlate not only with the severity of coronary artery disease but also with left ventricular contraction abnormalities, which in turn reflect the extent of injury.12,13 This study was designed to determine whether the extent of infarction is an important determinant of the incidence and severity of ventricular dysrhythmia and mortality late after infarction. Because potential relationships might be obscured by advanced age or old infarcts,8 only patients aged 65 years or younger and without historical or electrocardiographic evidence of previous myocardial infarction were studied.

Methods

Patients

The objective of this study was to evaluate the influence of the extent of infarction on long-term as well as early prognosis. There were 173 patients aged 65 years or younger at the time of infarction, who survived for at least 24 hours with initial, acute myocardial infarction manifested by chest pain, serial changes in the activity of conventionally measured plasma enzymes, and evolving electrocardiographic changes diagnostic of either transmural or subendocardial infarction. Infarct size was estimated enzymatically based on analysis of serial changes in plasma creatine kinase (CK) activity for 96 hours, as previously described.14 Samples were obtained hourly for 10 hours, every 2 hours for the next 14 hours, every 4 hours for the subsequent 48 hours, and twice daily for 72 hours thereafter. Results were expressed as infarct size index (ISI) (CK-g-Eq/m² body surface area). Patients admitted with cardiogenic shock were excluded because potentially spurious enzymatic estimates of infarct size could occur due to alterations in enzyme release or clearance.15 Follow-up evaluations were obtained every 3 months for the first year and yearly thereafter to verify survival and to characterize functional class. The cause of death was determined by review of hospital records and personal communication with the patient's physician, family and, when necessary, friends. Sudden death was defined as death occurring within 1 hour of the onset of symptoms. All patients were followed successfully for at least 3 months. Fourteen of the 173 patients were lost to follow-up after 3 months.
Assessment of Ventricular Dysrhythmia

Ventricular rhythm was recorded and quantified with double-channel, 24-hour, continuous electrocardiographic Holter tape recordings and digitized and processed on the Argus/H computer system, which permits high-speed analysis of ventricular rhythm and human verification of all computer-detected, anomalous QRS complexes. The system's performance has been documented to include detection of more than 90% of all premature ventricular complexes (PVCs), with a false-positive rate of less than 1% and a reproducibility after digitization of 99%. Follow-up 24-hour Holter recordings were obtained from as many patients as possible who survived for at least 2 months; 101 recordings were obtained from 81 patients (47%) at defined intervals (2–38 months) after infarction. Only data derived from the first post-discharge recording are included in the analysis presented.

![Figure 1. Survival after initial myocardial infarction in patients with infarct size index (ISI) < 15 CK-g-Eq/m² (solid line) vs ISI ≥15 CK-g-Eq/m² (interrupted line). Brackets indicate the standard error of survival. Above) Survival curves for all patients who survived 24 hours. Below) Survival curves for patients who survived at least 21 days after infarction. Survival was significantly different between those with large and small infarcts for all patients (p < 0.01) and for 21-day survivors (p < 0.05).](image)

Statistics

Survival data were computed with the use of Statistical Analysis System (version 76.5) and a product-limited estimate of cumulative survival (Kaplan, Meier), a procedure based upon individual survival time. This procedure provides an estimate of the standard error of the probability of survival. Equality of survival between groups of patients was evaluated with the use of the Mantel-Cox test, a non-parametric rank test. This procedure compares survival curves in their entirety rather than survival at selected, isolated times, as with some actuarial methods.

For statistical analysis of survival and arrhythmias, patients were segregated according to infarct size. For comparison of arrhythmia data, patients were separated at a cut-off for ISI of 15 CK-g-Eq/m². When the survival data were analyzed, the group with ISI ≥ 15 was further divided into patients with ISI < 30 and ≥30, because an ISI of 30 is approximately equivalent to 33% of estimated left ventricular mass index in normal subjects, and because infarcts involving larger amounts of the left ventricular mass are associated with a grave prognosis. All three groups were not used in every analysis, because in some instances they would have contained too few patients to permit adequate statistical analysis.

Relationships between infarct size and clinical variables, including age, gender, coronary risk factors and physiologic and laboratory parameters measured during the first 24 hours of hospitalization, were assessed with the use of standard regression procedures because of the continuous nature of these variables. Since survival is a discontinuous variable, other techniques were required for its analysis. Accordingly, maximum-likelihood estimation (a form of multivariate analysis) using multiple combinations of variables was used to identify the best predictors of death. Maximum-likelihood estimation serves the same purpose as regression analysis, but is necessary because of the lack of normality among the independent variables. Standard regression techniques were used to assess the relationships between selected historical and physiological variables and PVC frequency. However, since PVC frequency conforms more closely to a log-normal (ln) than to a normal dis-

*Maximum-likelihood estimates were obtained by means of a procedure developed for application with the Statistical Analysis System by Miller et al. based on the following considerations: Associated with every random sample of patients from the entire study population is a probability, p, of choosing a sample with the observed characteristics with respect to identified variables used to predict mortality. The value of p depends upon the frequency of occurrence of values of all the variables of interest in the population. If a sample is used to estimate the probability of death, the estimate is a maximum-likelihood estimate if it assigns to the actual sample chosen the highest possible value for p. The maximum-likelihood technique was used in lieu of discriminant analysis because the latter requires that the predictors be normally distributed, unlike the maximum-likelihood technique, which does not entail such a requirement.
tribution, statistical analysis was performed on transformed (ln) values for PVC frequency. Simple comparisons between groups were performed with the unpaired t test and the chi-square test with the Yates correction.

Results

Mortality

One hundred seventy-three patients (125 male and 48 female) were followed for a minimum of 3 months. The mean follow-up was 21.7 months (range 3–58 months). The patients were 26–65 years old (averaging 53.8 ± 0.6 years [SEM]). Twenty-five patients (15 males and 10 females) died during the follow-up, five suddenly and six after overt reinfarction. Forty-four percent (11 of 25) of those who died succumbed during the first 3 months.

Relation of Estimates of Infarct Size to Mortality

Infarct size (ISI) among patients who died was larger than that among survivors (46.5 ± 5.8 vs 21.1 ± 1.4 CK-g-Eq/m²; p < 0.001). Even when patients who died during the initial 21 days after infarction were excluded, the ISI of those who succumbed was significantly greater than the ISI in survivors (49.1 ± 0.7 vs 22.2 ± 1.6; p < 0.001). When patients were divided according to estimates of infarct size, the 70 patients with small infarcts (ISI < 15 CK-g-Eq/m²) had a significantly higher survival rate than the 103 patients with larger infarcts (p < 0.01) (fig. 1). When deaths during the first 3 weeks after infarction were excluded, the difference remained significant (p < 0.05) (fig. 1). When patients with larger infarcts were divided into those with moderate (15 ≤ ISI < 30 CK-g-Eq/m²) and those with large (ISI ≥ 30) infarcts, patients with larger infarcts had a poorer prognosis throughout the follow-up, even when those who died early were excluded (p < 0.05) (fig. 2).

Differences in survival between all patients with large vs small infarcts (p < 0.001), 21-day survivors only (p < 0.005), or 90-day survivors (p < 0.02), were all significant. Patients with large infarcts had a marked decrease in survival rate during the first 6 months, after which the survival rate declined less rapidly (fig. 2) compared with the rate in patients with small infarcts. An intermediate early decline in survival rate occurred in patients with moderate infarcts.

Relation of the Site of Infarction to Mortality

Among the 61 patients who sustained anterior transmural myocardial infarction, 13 succumbed during the follow-up. However, only nine of the 79 patients with inferior transmural myocardial infarction succumbed (χ² = 1.86; p > 0.1). Mean age, sex distribution, and duration of follow-up were comparable in both groups. Survival rates for these groups are shown in figure 3. Survival curves for all patients were not significantly different, although survival associated with anterior infarction appears to decline more rapidly during later portions of the follow-up. When patients who died during the first 3 weeks after infarction were excluded, the survival associated with anterior transmural myocardial infarction was diminished compared with survival after inferior infarction (p < 0.05) (fig. 3).

The difference in survival with anterior vs inferior infarction may reflect the significant difference in ISI between the two groups. The mean ISI in patients with transmural anterior myocardial infarction was 33.2 ± 3.3 vs 23.6 ± 1.9 CK-g-Eq/m² in those with inferior infarction (p < 0.01). When the survival of patients with small (ISI < 15) or large (ISI ≥ 30) inferior infarcts was compared with survival of those with anterior infarcts of comparable extent, no significant differences were evident. The results were analogous when patients who died within 3 weeks were excluded.

![Survival curves for patients with infarct size index (ISI) < 15 (circles) vs ISI < 30 (triangles) vs ISI ≥ 30 CK-g-Eq/m² (squares). Brackets indicate the standard error of the probability of survival. Above) Survival curves for all patients who survived 24 hours. Below) Survival curves for patients who survived at least 21 days after infarction. Survival curves were not significantly different between those with small and moderate-sized infarcts whether or not early deaths were excluded. All other comparisons were significant. See text for details.](http://circ.ahajournals.org/)

Figure 2.
Among patients who died after anterior infarction, those with ISI ≥ 50 CK-g-Eq/m² died significantly earlier than those with smaller infarcts (mean survival 3.9 ± 2.1 vs 18.7 ± 12.2 months; p < 0.05). A similar trend, though not statistically significant, was noted with inferior infarction.

Thirty-one patients had subendocardial infarction, of whom two died during the follow-up. Of the 142 patients with transmural infarction, 23 died. Survival was slightly but not significantly better after subendocardial than after transmural infarction (p = 0.19); but when early deaths were excluded, the slight difference in survival narrowed further (fig. 4). These results differ from those obtained among groups including patients older than 65 years of age, in whom survival after subendocardial infarction appears to be more likely than after transmural infarction.  

ISI with transmural infarction averaged 27.7 ± 1.8 vs 10.5 ± 1.7 CK-g-Eq/m² with subendocardial infarction (p < 0.001). The apparent disparity between the large difference in infarct size and the lack of a significant difference in survival may result, in part, from the small number of patients with subendocardial infarction.

Descriptors Associated with Mortality

To assess the significance of demographic and physiologic parameters as descriptors associated with mortality after infarction, 10 variables were investigated in combinations of 2–10 variables. For each combination of variables, the strength of the association of the combination with mortality was assessed. In some sets of combinations, the sample was evaluated both with and without exclusion of patients who died within the first 21 days or patients younger than 50 years of age.

Table 1 lists the variables tested. The only variables found to be significant descriptors alone or in any combination with one or more of the other variables were ISI, the presence of moderate or severe congestive heart failure at the time of hospital admission,
peak plasma CK activity, gender and age. ISI was a significant predictor of mortality in every trial in which it was tested, whether alone or in combination with one or more of the other nine variables, and whether the entire sample or only one of the subsets was used. The presence or absence of congestive heart failure at the time of hospitalization was a significant predictor in 68% of the trials in which it was tested, but it was not significant when patients who died within the first 21 days were excluded from the analysis. Age was significant only when patients younger than age 50 years of age were excluded from the analysis and when the presence or absence of congestive heart failure was not a variable in combination with age. In the entire sample, 10 of 48 women died, in contrast to 15 of 110 men (χ² = 2.19; p = 0.14); but gender was significant only when patients younger than 50 years of age were excluded, and was most significant among patients who survived for at least 21 days. Thus, among patients older than 50 years of age, 10 of 38 women but only 11 of 94 men died (χ² = 4.32; p < 0.05).

The presence or absence of diabetes, angina pectoris, use of tobacco, and the site of infarction were not significant descriptors.

Based on analysis of all 10 variables and the 156 patients with complete sets of data available, survival in 135 of 137 and mortality in eight of 19 decedents could be discriminated accurately. When only three variables were used, optimum discriminating included ISI, the presence or absence of congestive failure, and gender; these variables accurately discriminated survival in 146 of 148 survivors, but discriminated mortality in only 11 of 25 nonsurvivors.

Regression analysis was applied to combinations of one to seven variables to assess the significance of the association of each variable with infarct size index after removal of the effects of all other variables in the trial. Each combination of variables was considered a trial. The probability value of greatest significance for each variable is listed in the second column. CHF = presence of congestive heart failure at the time of hospital admission. Systolic blood pressure (BP) and heart rate refer to values at the time of hospital admission.

### Table 1. Analysis of the Association Between Clinical Variables and Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum significance</th>
<th>Number of significant trials/total (p &lt;0.05)</th>
<th>Significant trials (p &lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISI</td>
<td>0.0001</td>
<td>50/50</td>
<td>100%</td>
</tr>
<tr>
<td>CHF</td>
<td>0.0001</td>
<td>15/22</td>
<td>68%</td>
</tr>
<tr>
<td>Sex</td>
<td>0.0384</td>
<td>4/40</td>
<td>10%</td>
</tr>
<tr>
<td>CK</td>
<td>0.0015</td>
<td>1/11</td>
<td>9%</td>
</tr>
<tr>
<td>Age</td>
<td>0.0170</td>
<td>2/30</td>
<td>5%</td>
</tr>
<tr>
<td>ANT/INF</td>
<td>0.1533</td>
<td>0/33</td>
<td>0</td>
</tr>
<tr>
<td>TM/SE</td>
<td>0.9241</td>
<td>0/25</td>
<td>0</td>
</tr>
<tr>
<td>Cig</td>
<td>0.1485</td>
<td>0/9</td>
<td>0</td>
</tr>
<tr>
<td>Angina</td>
<td>0.3236</td>
<td>0/26</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.3621</td>
<td>0/20</td>
<td>0</td>
</tr>
</tbody>
</table>

Maximum-likelihood estimation (a form of multivariate analysis) using combinations of two to 10 variables was used to estimate the probability of death. For every trial (combination of variables), the significance of each included variable in determining the maximum-likelihood estimate was found.

**Abbreviations:** ISI = infarct size index; CHF = congestive heart failure at the time of hospital admission; CK = plasma creatine kinase; ANT/INF = location of infarction (anterior vs inferior); TM/SE = location of infarction (transmural vs subendocardial); Cig = cigarette use before infarction.

### Table 2. Analysis of the Association Between Clinical Variables and Infarct Size Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum significance</th>
<th>Number of significant trials/total (p &lt;0.05)</th>
<th>Significant trials (p &lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>0.0074</td>
<td>8/8</td>
<td>100%</td>
</tr>
<tr>
<td>Age</td>
<td>0.2192</td>
<td>0/8</td>
<td>0</td>
</tr>
<tr>
<td>Sex</td>
<td>0.4089</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.6272</td>
<td>0/6</td>
<td>0</td>
</tr>
<tr>
<td>Angina</td>
<td>0.1313</td>
<td>0/10</td>
<td>0</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.3715</td>
<td>0/3</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.4429</td>
<td>0/3</td>
<td>0</td>
</tr>
</tbody>
</table>

Regression analysis was applied to combinations of one to seven variables to assess the significance of the association of each variable with infarct size index after removal of the effects of all other variables in the trial. Each combination of variables was considered a trial. The probability value of greatest significance for each variable is listed in the second column. CHF = presence of congestive heart failure at the time of hospital admission. Systolic blood pressure (BP) and heart rate refer to values at the time of hospital admission.

### Relationships Between Ventricular Dysrhythmia and the Extent and Location of Infarction

Holter recordings during the follow-up were available in 81 of 173 patients (47%). Fifty-three recordings were obtained between 2–6 months after infarction, 18 between 6–12 months and 14 more than 12 months after infarction. There was no significant difference between patients from whom recordings were or were not obtained with respect to infarct location, gender, history of angina pectoris, heart rate or systolic blood pressure at the time of hospital admission. Patients from whom recordings were available for analysis were slightly but significantly younger (52 ± 0.9 vs 56 ± 0.8 years; p < 0.01), and had slightly but significantly lower admission diastolic blood pressure (86 ± 1.6 vs 91 ± 1.8 mm Hg; p < 0.05). They included a higher percentage of smokers (69 of 81 vs 62 of 91). Based on multiple regression analysis, no significant relationships were found between PVCs/24 hours and any of these.
TABLE 3. The Significance of Relationships Between Infarct Location, Infarct Size Index and the Frequency of Premature Ventricular Complexes

<table>
<thead>
<tr>
<th>Location of infarction</th>
<th>ln PVCs/24 hours</th>
<th>Time after infarction</th>
<th>ln PVCs/24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>4.17 ± 0.32</td>
<td>(n = 66)</td>
<td>4.06 ± 0.4</td>
</tr>
<tr>
<td>ISI &lt; 15</td>
<td>2.93 ± 0.61</td>
<td>(n = 20)</td>
<td>ISI &lt; 15</td>
</tr>
<tr>
<td>ISI ≥ 15</td>
<td>4.71 ± 0.39</td>
<td>(n = 46)</td>
<td>ISI ≥ 15</td>
</tr>
<tr>
<td>Inferior (transmural)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>4.52 ± 0.42</td>
<td>(n = 40)</td>
<td>6.0 ± 1.3</td>
</tr>
<tr>
<td>ISI &lt; 15</td>
<td>3.81 ± 0.74</td>
<td>(n = 14)</td>
<td>ISI &lt; 15</td>
</tr>
<tr>
<td>ISI ≥ 15</td>
<td>4.90 ± 0.50</td>
<td>(n = 26)</td>
<td>ISI ≥ 15</td>
</tr>
<tr>
<td>Anterior (transmural)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>3.64 ± 0.51</td>
<td>(n = 26)</td>
<td>3.7 ± 0.9</td>
</tr>
<tr>
<td>ISI &lt; 15</td>
<td>0.88 ± 0.34</td>
<td>(n = 6)</td>
<td>ISI &lt; 15</td>
</tr>
<tr>
<td>ISI ≥ 15</td>
<td>4.47 ± 0.57</td>
<td>(n = 20)</td>
<td>ISI ≥ 15</td>
</tr>
<tr>
<td>Subendocardial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>3.64 ± 0.88</td>
<td>(n = 15)</td>
<td></td>
</tr>
<tr>
<td>ISI &lt; 15</td>
<td>2.48 ± 0.88</td>
<td>(n = 11)</td>
<td></td>
</tr>
<tr>
<td>ISI ≥ 15</td>
<td>6.81 ± 1.38</td>
<td>(n = 4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Abbreviations: ISI = infarct size index; PVC = premature ventricular complex; ln = natural logarithm distribution.

The frequency of PVCs/24 hours differed substantially among groups of patients with small and larger infarcts. Thus, IN PVCs/24 hours was 2.8 ± 0.5 in patients with ISI < 15 in contrast to 4.9 ± 0.4 in those with ISI ≥ 15 CK-g-Eq/m² (p < 0.001). Expressed in arithmetic terms, patients with large infarcts had a mean of 1031 PVCs/24 hours compared with 602 PVCs/24 hours in those with small infarcts. When patients with ISIs ≥ 15 were further divided into those with ISI from 15–30, and those with ISI ≥ 30, both groups had significantly more PVCs/24 hours than patients with ISI < 15 (p < 0.01); but the two groups with larger ISI were not significantly different from each other. Because the frequency of PVCs varies as a function of time after infarction, recordings were obtained at several selected intervals. Patients with small infarcts had fewer PVCs/24 hours than those with large infarcts, whether their recordings were obtained 2–6 months, 6–12 months, or more than 12 months after infarction (table 3). However, there was no close correlation between the frequency of PVCs among patients in the first 24 hours after infarction and the frequency in the same patients during late follow-up. This may reflect the marked diminution of absolute PVC frequency late compared with early after infarction. Among the 14 recordings obtained more than 1 year after infarction, only four showed mean hourly PVC rates greater than 20, all in patients with ISI ≥ 15 CK-g-Eq/m² (x² = 4.3; p < 0.05 compared with patients with small infarcts).

When the PVC frequencies associated with inferior compared with anterior myocardial infarction were analyzed, there were no significant differences. Among patients with small infarcts (ISI < 15 CK-g-Eq/m²), significantly more PVCs occurred with inferior than with anterior infarcts. The cause of the difference is obscure, because no significant differences were found between these groups in mean age, ISI, heart rate or interval between infarction and Holter recording. However, infarct location had no apparent influence on the PVC frequency among patients with larger infarcts (table 3).

A slightly (but insignificantly) greater PVC frequency was associated with transmural as opposed to subendocardial infarction (table 3) (ln PVCs/24 hours = 4.2 ± 0.3 and 3.6 ± 0.9 for transmural and subendocardial infarction, respectively; p > 0.05). However, among patients subdivided according to ISI, no significant differences in PVC frequency were

three variables (smoking, age or diastolic blood pressure) among patients from whom recordings were obtained. Thus, it is unlikely that selective sampling substantially affected the findings regarding dysrhythmia.

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observed with the two types of infarctions.

When regression analysis was used to assess the contribution of selected parameters on ln PVCs/24 hours, the only significant variables were ISI and location of infarct (anterior vs inferior). Age, gender, or the nature of infarction (transmural compared with subendocardial) had no apparent independent effects on PVC frequency.

### Relationships Between MIRU* Class, ISI, and Survival

Patients without congestive heart failure at the time of hospitalization (MIRU class I) had smaller infarcts (ISI = 20.2 ± 1) than those with mild failure (MIRU class II; ISI = 30.7 ± 4; p < 0.01) and substantially smaller than those with severe failure (MIRU class III; 54.8 ± 10; p < 0.001). Among long-term survivors, significant differences remain between patients who are class I and II on admission. Overall survival was 92% for class I, 86% for class II, and 9% for class III (χ² = 54.6; p < 0.001). Among the nonsurvivors, 12 of 15 patients in classes I and II survived their initial hospitalization, in contrast to only three of 10 in class III (χ² = 4.34; p < 0.05). Among hospital survivors, 12 of 144 class I and II patients eventually died, compared with three of four in class III (χ² = 13.7; p < 0.001).

### Relation of Infarct Size to Other Clinical Parameters

The relationship between estimated infarct size and the incidence of reinfarction, development of new angina, and functional class at the time of admission were studied. The incidence of reinfarction was comparable for patients with ISI above and below 15 CK-g-Eq/m², as well as for patients with transmural compared with subendocardial infarction. Further, there was no significant difference in ISI between patients with and without reinfarction with a follow-up of at least 1 year.

### Discussion

Previous studies have shown that enzymatic measures are good indicators of the extent of myocardium lost due to infarction both in animals and in man. However, this method has limitations. Spurious enzymatic estimates of infarct size may be caused by several factors that affect enzyme release or clearance, including anesthesia, intramuscular injections, defibrillation and shock. In addition, for accurate estimates, patients must be studied promptly after the onset of infarction and must survive at least 24 hours to provide sufficient sampling time. Despite these limitations, estimates of myocardial damage obtained with this method are useful, as indicated by significant relationships between enzymatic estimates of infarct size and both survival and ventricular dysrhythmias early and late after infarction.

Among patients aged 65 years or younger, the extent of an initial myocardial infarction estimated enzymatically is an important determinant not only of early mortality but also of the rate of mortality for a prolonged interval after infarction, and hence for a significant long-term difference in overall mortality. Thus, in the population studied, the mean ISI of survivors was significantly less than that of the decedents. Further, among patients delineated according to ISI, those with small infarcts had better survival than those with modest or large infarcts. Even among patients grouped according to the locus of infarction, those with ISI ≤ 15 CK-g-Eq/m² had a better prognosis than patients with larger infarction in the same locus. In addition to overall survival, the duration of survival was significantly related to infarct size. Thus, patients

### Table 4. Relationship Between MIRU Class, Infarct Size Index and Survival

<table>
<thead>
<tr>
<th>MIRU class</th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>20.2 ± 1.5</td>
<td>30.7 ± 3.5</td>
<td>54.8 ± 9.7</td>
</tr>
<tr>
<td>(n = 119)</td>
<td>(p &lt; 0.01)</td>
<td>(n = 43)</td>
<td>(p &lt; 0.01)</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survivors</td>
<td>18.9 ± 1.5</td>
<td>27.8 ± 3.5</td>
<td>14</td>
</tr>
<tr>
<td>(n = 109)</td>
<td>(p &lt; 0.01)</td>
<td>(n = 37)</td>
<td>(n = 1)</td>
</tr>
<tr>
<td>Nonsurvivors</td>
<td>32.7 ± 9.2</td>
<td>42.8 ± 11.7</td>
<td>58.9 ± 9.7</td>
</tr>
<tr>
<td>(n = 10)</td>
<td>(p = NS)</td>
<td>(n = 6)</td>
<td>(NS)</td>
</tr>
<tr>
<td>p &lt; 0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values expressed are means of ISI ± SEm.
Abbreviation: ISI = infarct size index.

*National Heart, Lung, and Blood Institute Myocardial Infarction Research Unit criteria.
with small infarctions who died survived significantly longer after infarction than those who died after large infarcts.

Because mortality after infarction appears to be related to the total mass of myocardium lost, it is likely that multiple infarctions in the same patient will have a cumulative effect on prognosis. The impairment of left ventricular function associated with an infarct of any given magnitude is greater in patients with prior than in those with initial infarction.26 Inclusion of patients with prior infarction may have obscured relationships between extent of infarction and long-term prognosis in some studies.12 In our own experience, inclusion of large numbers of patients with prior infarction reduces the significance of the extent of infarction in the index episode as a maximum-likelihood estimator of mortality (data not shown).

Although early mortality was not significantly different among patients with anterior compared with inferior transmural infarction, survival after 21 days was reduced among the former. This finding is in keeping with observations by others.3, 27 The poor prognosis is not attributable to differences in age or distribution of sex within the sample, but appears to depend on a larger mean ISI associated with anterior infarction. Because the estimate of infarct size is based on the total amount of CK released regardless of its source, and because right ventricular infarction often accompanies inferior myocardial infarction,28 infarct size in patients with inferior infarction reflects some damage to the right as well as to the left ventricle. It is likely that the electrophysiologic, hemodynamic, and hence prognostic implications of equal amounts of right and left ventricular injury differ. Thus, patients with equivalent overall infarct size reflecting some right ventricular involvement may have a better prognosis than those with anterior infarction and exclusively left ventricular involvement.

Although increased late mortality has been observed in patients with nontransmural as opposed to transmural infarction,29 the prognosis associated with transmural and subendocardial infarction is comparable for several years.29, 30 In fact, prognosis in patients with subendocardial infarction with modest enzyme elevations is substantially better than that in patients with subendocardial infarction and enzyme elevations comparable to the larger elevations typically seen in patients with transmural infarction.31 The increased late mortality (after 30 months) associated with subendocardial infarction in one report29 could reflect deleterious, arrhythmogenic effects of islands of viable but initially injured myocardium. However, this seems unlikely, because an early incidence of sudden death was not increased. It appears more likely that some patients with subendocardial infarction have an increased risk of late sudden death because of the nature and probable progression of underlying vascular disease responsible for the initial episode. An increased risk of late sudden death was not seen in the present study, possibly because the sample excluded patients with prior infarction. Differences in survival apparently dependent on the transmural site or transmural compared with subendocardial distribution of infarction may be attributable to differences in ISI.

The two variables most significantly associated with subsequent mortality in the multivariate, maximum-likelihood estimation analysis performed in this study were ISI and the presence or absence of severe pulmonary congestion at the time of hospital admission. These data are in agreement with results by others who have found a high pulmonary artery occlusive pressure to be a poor prognostic sign.32 Among the physiologic and clinical variables assessed, the only one significantly associated with ISI (alone or in combination with other variables) was the presence or absence of moderate-to-severe pulmonary congestion at the time of hospital admission. Thus, it appears that the extent of infarction was a determinant of early congestive heart failure as well as of early and late survival.

Most of our study patients were in MIRU classes I and II, and had a favorable prognosis. This probably results from the initial selection process, which eliminated patients with prior infarction. In addition patients who did not survive for at least 24 hours were excluded, which eliminated a significant proportion of patients who presented with severe congestive heart failure. The mortality we observed in patients in MIRU class III (pulmonary edema) was striking. This may result, in part, from vigorous treatment given to patients being held in our emergency room while awaiting a bed in the coronary care unit. This treatment could produce some clearing of pulmonary congestion in less resistant patients before presentation into our clinical investigation unit, thus shifting lower risk patients from MIRU class III to MIRU class II before admission to this study. The mean ISI of patients presenting in pulmonary edema was 55 CK-g-Eq/m², which corresponds to approximately 59% of the normal left ventricular mass index,20 an extent of injury associated with high mortality.

Although the multivariate analysis indicated that five variables were significantly related to survival after initial infarction, the best predictive power achieved correctly identified only 40% of the deaths. This is certainly not surprising in view of the obvious importance of the extent, distribution and progression of underlying coronary artery disease as determinants of mortality, particularly during long-term follow-up.33, 34 For the same reason, the most striking association between mortality rate (as opposed to overall mortality) and ISI was evident during the first 6 months after infarction.

There was a significant relationship between the enzymatic estimates of infarct size and the frequency of PVCs detected 2 months to more than 1 year after myocardial infarction. Among patients compared after segregation according to the extent of infarction, those with smaller infarcts had a lower frequency of PVCs, a finding which is consistent with observations by Schultze and co-workers, who observed relationships between ejection fraction, wall motion abnormalities, and the frequency of late ventricular
dysrhythmia, even among a population of patients with prior myocardial infarction. These findings are also consistent with the association of PVC frequency early after infarction and ISI reported previously from our laboratory. Because ejection fraction early after infarction is significantly related to ISI, and because ejection fraction 1–3 weeks after infarction varies only modestly from ejection fraction early after the episode, relationships between PVCs late after infarction and ejection fraction may well reflect the amount of myocardium damaged.

Although both PVC frequency and total mortality are related to estimates of infarct size, neither relationship is linear. In fact, the patients with modest-sized infarcts (15 ≤ ISI < 30 CK-g-Eq/m²) responded disparately with respect to these two end points. The mortality of this group was similar to that of patients with smaller infarcts, while the incidence of dysrhythmia more closely resembled that in patients with the largest infarcts, further emphasizing the multifactorial nature of these variables.

We did not observe a significant difference in PVC frequency between patients with transmural and those with subendocardial infarction. However, PVC frequency was greater among patients with small inferior infarcts than among those with small anterior infarcts, results similar to those reported by Biddle et al. The factors responsible for this difference are not clear, but may include differences due to the underlying distribution of coronary arterial lesions, the relative predominance of sympathetic compared with parasympathetic responses to repetitive ischemia involving different regions of the heart, or differences in prevailing heart rate or the ranges of heart rate among patients in the two groups.

Our findings indicate a clear relationship between enzymatic estimates of infarct size and both ventricular dysrhythmia and long-term survival in the posthospital phase after infarction. Although a substantial proportion of the mortality can be accounted for in terms of the amount of myocardium undergoing infarction, the importance of other factors, such as the nature and progression of underlying coronary vascular disease, particularly late after infarction, is strongly suggested. The maximum-likelihood estimation multivariate analysis that we used tests variables that are readily measured in most institutions. Accordingly, we hope these criteria provided will be useful for prospective studies in test sets of control patients and those evaluated with interventions in many centers.

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creases in frequency of premature ventricular contractions at nine months following myocardial infarction. (abstr) Circulation 52 (suppl II): II-94, 1975

Evaluation of Warning Arrhythmias Before Paroxysmal Ventricular Tachycardia During Acute Myocardial Infarction in Man

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SUMMARY In order to determine the relationship of paroxysmal ventricular tachycardia (PVT) to any antecedent (premonitory) ventricular arrhythmias during the early phases of acute myocardial infarction, 24-hour Holter monitoring was begun on 52 male patients an average of 12.6 hours after the onset of prolonged chest pain that was documented as acute infarction. Twenty-four patients had PVT and 28 did not. We analyzed in detail the incidence of frequency of premature ventricular complexes (PVCs), prematurity and pairing during the 10 minutes immediately preceding PVT from a continuous 10-minute rhythm strip. There was no positive correlation between PVT and the number or complexity of PVCs in the 10 minutes immediately before ventricular tachycardia. These findings suggest that there is no consistent pattern or frequency of ventricular arrhythmia that could be identified as premonitory for PVT during the immediate pre-PVT period, even during the acute phase of myocardial infarction in man.

DURING acute myocardial infarction, ventricular tachycardia can degenerate into ventricular fibrillation.\(^1\) Paroxysmal ventricular tachycardia (PVT) has been reported to occur fairly frequently during the initial phases of acute myocardial infarction.\(^1\) Attempts to detect warning arrhythmias before ventricular fibrillation have generally not been successful; and several studies suggest that primary ventricular fibrillation is usually a sudden and un heralded catastrophe during the acute phase of myocardial infarction.\(^3\)\(^,\)\(^4\)

Other studies have reported that complex ventricular arrhythmias are noted frequently just before both ventricular tachycardia\(^5\) and ventricular fibrillation.\(^8\) Since PVT is a more common rhythm disturbance during acute myocardial infarction than ventricular fibrillation, and since ventricular tachycardia can degenerate into ventricular fibrillation, we examined the 10 minutes before episodes of PVT by Holter monitoring during the acute phase of myocardial infarction in man. We looked for a recurring pattern of ventricular arrhythmia that immediately precedes and might be predictive of PVT in these patients. We looked specifically at the incidence of three previously reported harbingers of PVT during acute myocardial infarction:\(^1\)\(^,\)\(^3\)\(^,\)\(^4\) the absolute frequency of premature ventricular complexes (PVCs), the in-
The influence of location and extent of myocardial infarction on long-term ventricular dysrhythmia and mortality.

E M Geltman, A A Ehsani, M K Campbell, K Schechtman, R Roberts and B E Sobel

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