Prognostic significance of electrocardiographic site of infarction after correction for enzymatic size of infarction


ABSTRACT To assess whether the site of myocardial infarction is an independent prognostic indicator, the outcome of patients with anterior myocardial infarction was compared with that of patients with inferior infarction. A consecutive series of patients who had suffered their first myocardial infarction was analyzed (398 with anterior and 391 with inferior infarction). Patients with anterior myocardial infarction had a higher 1 year mortality than those with inferior infarction (18.3% vs 10.5%, p = .002). When patients were matched for infarct size determined by peak creatine kinase (CK) level expressed as a multiple of the upper limit of normal, those with anterior myocardial infarction tended to have a higher 1 year mortality than those with inferior infarction for all subgroups of peak CK. Early mortality (day 1 to 28 after myocardial infarction) was greater in the anterior than in the inferior myocardial infarction group (10% vs 6.4%, p = .03); this was most significant when peak CK was greater than four times normal (12.4% vs 7.0%, p = .04). Late mortality was also higher in the anterior (8.4% vs 4.1%, p = .04) than the inferior infarction group and this was most significant when peak CK was less than two times normal (15.2% vs 0%, p = .02) or greater than eight times normal (10.6% vs 4.1%, p = .04). Multivariate analysis with proportional-hazards regression confirmed the prognostic significance of location of infarction independent of peak CK level. Thus, infarct location was found to be a predictor of prognosis that is independent of infarct size based on peak CK levels.

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THE PROGNOSIS of patients with anterior myocardial infarction is significantly worse than that of patients with inferior myocardial infarction.1-5 Anterior infarction is associated with more myocardial damage than inferior infarction.5,6 It remains unclear whether this difference in survival is due to the site or the size of myocardial infarction.

Goldberg et al.7 concluded that the poorer prognosis for patients with anterior myocardial infarction was probably related to the extent of myocardial damage rather than the location of the injury. Strauss et al.8 demonstrated a poorer prognosis (both early and late) for patients with anterior than for those with inferior infarction of similar size. However, they found no difference in the extent of infarction with either location of infarction, a finding that differs from other reports.5,6 Thanavarro et al.5 concluded that peak enzyme level and the location of the infarct each have independent influence on in-hospital prognosis of patients with myocardial infarction.

In this study we sought to clarify the influence of site of myocardial infarction on both early and late mortality. To assess the independent contribution of location of infarction to prognosis, the patients were grouped according to peak serum enzyme levels, since these reflect the extent of myocardial necrosis.9-13 Since previous studies14-17 have documented that prognosis is not only dependent on the size of the most recent infarction, but also on whether the patient has had previous infarctions, we prospectively studied the outcome of patients experiencing their first myocardial infarction.

Methods

Patient population. All patients less than 70 years of age who were admitted to the Sir Charles Gairdner Hospital Coro-
nary Care Unit between January 1973 and December 1981 with definite acute myocardial infarction by the World Health Organization criteria of 1969\textsuperscript{18} were prospectively evaluated.

Patients excluded from the study were (1) those who died on the first hospital day, because their peak serum enzyme levels may not have been obtained, (2) those in whom the site of infarction could not be located electrocardiographically, i.e., those with bundle branch block or without electrocardiographic changes, (3) those with previously documented myocardial infarction, and (4) those with true posterior myocardial infarctions.

There were 1401 patients initially enrolled in the study. After the exclusion criteria were applied 789 patients remained. Of these 398 had anterior or anterolateral myocardial infarction and 391 had inferior or inferolateral myocardial infarction.

**Clinical data.** Clinical, serum enzyme, and electrocardiographic data were recorded prospectively, as described previously.\textsuperscript{9}

Clinical data were recorded in a standardized format suitable for computer analysis. Age, sex, past history of angina, and presence or absence of diabetes mellitus were recorded. Blood pressures were recorded by cuff sphygmomanometer; the earliest measurement of blood pressure on admission to the hospital was recorded. Past history of myocardial infarction was documented if there was a history of typical pain supported by typical electrocardiographic or enzyme abnormalities.

Complications occurring during the patient's hospital stay were recorded. Conduction disturbances and arrhythmias were detected by continual observation of the electrocardiographic monitor by a member of the nursing staff while the patient was in the coronary care unit. When possible the abnormality was recorded on electrocardiographic paper. Pulmonary edema was considered present when the full clinical syndrome of marked dyspnea, tachypnea, and widespread rales throughout the chest was observed. Basal lung crepitations were defined as crepitations persisting after coughing. Cardiac failure was defined as persistent basal lung crepitations associated with a third heart sound and/or radiologic evidence of left heart failure during the patient's hospital stay. Reinfarction in the hospital was considered to have occurred if, after recovery from the documented admission myocardial infarction, there was a further episode of chest pain associated with further serial increases in cardiac enzymes.

During the initial 72 to 96 hr in the hospital serum levels of creatine kinase (CK) and aspartate transaminase (AST) were estimated daily and peak levels were recorded. The peak CK levels were then expressed as multiples of the upper limit of normal (i.e., less than two times normal, two to four times normal, four to eight times normal, and greater than eight times normal).

Electrocardiographic site of myocardial infarction was assessed from 12-lead electrocardiograms recorded at least daily for the first 3 days of the patient's hospital stay. Anterior myocardial infarction was defined as new Q waves and/or sequential ST segment elevations or T wave changes in leads V\textsubscript{1} to V\textsubscript{4}. Inferior myocardial infarction was defined as new Q waves and/or sequential ST segment elevations or T wave changes in leads II, III, and aVF. Anterolateral or inferolateral infarction was diagnosed if in addition there were new Q waves or sequential ST segment elevations or T wave changes in leads V\textsubscript{5}, V\textsubscript{6}, and/or I and aVL. After 1978, patients with only T wave changes on the electrocardiogram were excluded from the study. The site of infarction was determined by two scientific research officers experienced in electrocardiographic coding using the well-established above-mentioned criteria for site of infarction.

**Follow-up.** The date of death of patients was determined from review of death certificates in the Registrar General's office, review of the hospital case notes (for in-hospital deaths), or by contact with the local general practitioner or the family. Follow-up was 100\% for 1 year after the time of myocardial infarction.

In this study early mortality is defined as death within the first 28 days after myocardial infarction. Late mortality is defined as death after this period up until 1 year from the date of infarction.

**Analysis of data.** Differences between characteristics (including early and late death rates) of patients with infarcts in the two locations were examined. Discrete variables were tested against the chi-square distribution, using Yates correction where appropriate. For continuous variables the two tailed t test was applied. A p value of less than or equal to .05 was considered indicative of statistical significance.

Survival curves for the two groups were estimated by the Kaplan-Meier method\textsuperscript{19} for various groups of peak CK levels and equality of the curves was tested with log-rank test.\textsuperscript{20, 21} Curves were also estimated separately for 1 to 28, 29 to 90, and 91 to 365 day survival to investigate possible time dependency of the difference in death rates. Relative risks were estimated from these curves with the use of a proportional-hazards regression model.\textsuperscript{22} To examine possible confounding effects with other prognostic indicators, proportional-hazards regression analysis with the use of the computer program "RISK"\textsuperscript{23} was performed. Peak CK as a measure of size of infarction and the electrocardiographic location of infarction, as well as other clinical variables, were used in this multivariate analysis.

**Results**

Patients in the inferior and anterior infarct groups had similar mean peak CK and AST levels. The groups were also matched for age, sex, past history of angina, non–Q wave infarction, hypertension, and diabetes mellitus (table 1). When matched for size of infarction by peak CK level expressed as a multiple of the upper

<table>
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<th>TABLE 1</th>
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<tr>
<td><strong>Characteristics of patient population studied</strong></td>
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<tr>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Male:female ratio</td>
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<tr>
<td>PH angina (%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
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<tr>
<td>Diabetes mellitus (%)</td>
</tr>
<tr>
<td>Mean peak CK (U/l)</td>
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<tr>
<td>Mean peak AST (U/l)</td>
</tr>
<tr>
<td>Non–Q wave MI (%)</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
</tr>
<tr>
<td>2 or 3 degree AV block (%)</td>
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<tr>
<td>Reinfarction (%)</td>
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<tr>
<td>Cardiogenic shock (%)</td>
</tr>
<tr>
<td>Basal creatinase (%)</td>
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<tr>
<td>Pulmonary edema (%)</td>
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<td>Cardiac failure (%)</td>
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MI = myocardial infarction; n = number of patients; NS = not significant (p value > .05); PH = past history; U/l = units per liter; AV = atrioventricular.
limit of normal, the similarities with respect to age, sex, and past history of angina, non–Q wave infarction, and hypertension held true for each subgroup of peak CK level. The number of patients with diabetes mellitus in each subgroup was too small to statistically evaluate.

The 1 year mortality for patients with anterior myocardial infarction was 18.3% and that for those with inferior infarction was 10.5% (p = .002). Patients with anterior myocardial infarction had a significantly higher early mortality than those with inferior infarction (10% vs 6.1%, p = .03) and also had a higher late mortality (8.9% vs 4.2%, p = .04; table 2). The better 1 year survival of the patients with inferior myocardial infarction is demonstrated in figure 1.

One year survival of the four subgroups of patients matched for peak enzyme levels is illustrated in figure 2. Patients with inferior infarction had significantly better 1 year survival than those with anterior infarction in whom peak CK was less than two times normal (96.5% vs 83.6%, p = .04) or greater than eight times normal (81.6% vs 76.4%, p = .02). In the groups with two to four times normal and four to eight times normal peak CK, patients with inferior myocardial infarctions had a better survival but this difference was not statistically significant.

Early mortality of patients matched for peak enzyme levels is shown in table 2. In every subgroup of CK level, those with anterior myocardial infarction had a higher early mortality compared with those with inferior myocardial infarction, although this difference did not reach statistical significance. In the population in which peak CK was more than four times normal, mortality after anterior infarction was significantly greater than that after inferior infarction (12.4% vs 7.7%, p = .04).

Late mortality of patients matched for peak enzyme levels is also outlined in table 2. Patients with anterior myocardial infarction had a significantly higher fatality rate when their peak CK was less than two times normal (15% vs 0%, p = .02) or greater than eight times normal (10.6% vs 4.1%, p = .04). Analysis of

![FIGURE 1. Survival curve for patients who have suffered their first myocardial infarction (MI). n = number of patients.](http://circ.ahajournals.org/Downloadedfrom)
the population in which peak CK was less than four times normal showed that those with anterior myocardial infarction had a late mortality of 9% and those with inferior infarction a late mortality of 2% (p = .03). In the group in which peak CK was greater than four times normal late mortality after anterior infarction (9.2%) was greater than that after inferior infarction (5.4%), but this difference did not achieve statistical significance.

Multivariate analysis with a proportional-hazards regression analysis model confirmed the difference in survival between patients with anterior and those with inferior myocardial infarction independent of the peak CK level. When other risk factors were included (i.e., previous infarction, age, sex, past history of angina, hypertension, diabetes, atrioventricular block, atrial fibrillation), the estimated relative risks calculated with a model including location (anterior vs inferior) and size (peak CK) of infarction changed only slightly after adjustment for each of the other variables in turn.

The relative risk of death in the first year after anterior myocardial infarction was 1.89 times that after inferior infarction. The relative risk of death was higher for patients with anterior myocardial infarction at all levels of infarct size (table 3). There was little difference between the risk ratios for different time periods after infarction (table 4), implying that 1.89 is a valid estimation of the risk ratio for the whole year after infarction.

Included in table 1 are the in-hospital complications observed. Patients with inferior myocardial infarctions had a higher incidence of second- and third-degree atrioventricular block (9.4% vs 3.5%, p = .0003). However, those with anterior infarctions had a significantly higher incidence of pulmonary edema on admission to the hospital (8% vs 3.5%, p = .01) and a higher incidence of cardiac failure during the hospital

TABLE 3

<table>
<thead>
<tr>
<th>Relative risk (anterior vs inferior MI)</th>
<th>95% confidence levels</th>
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<tbody>
<tr>
<td>All patients</td>
<td>1.89</td>
</tr>
<tr>
<td>CK &lt; 2 x normal</td>
<td>4.79</td>
</tr>
<tr>
<td>CK 2 – 4 x normal</td>
<td>1.83</td>
</tr>
<tr>
<td>CK 4 – 8 x normal</td>
<td>1.38</td>
</tr>
<tr>
<td>CK &gt; 8 x normal</td>
<td>1.93</td>
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</tbody>
</table>

Population is subgrouped into multiples of upper limit of normal range of peak CK levels.

FIGURE 2. Survival curves for patients who have suffered their first myocardial infarction (MI) by subgroups according to enzymatic size of infarction. n = number of patients; Normal = upper limit of normal range of CK levels.
stay (30.6% vs 17.6%, p = .0001). Otherwise the groups were similar with respect to incidence of atrial fibrillation, reinfarction in hospital, cardiogenic shock, and basal crepitations on admission to the hospital. The above differences and similarities held true when the groups were stratified as previously described.

Discussion

The size of myocardial infarction is well recognized as an important prognostic indicator. The influence of site of myocardial infarction has not been clearly defined. Goldberg et al. concluded that the larger infarct size associated with anterior infarction in their study was the probable reason for the poorer prognosis of this group of patients. Other studies have demonstrated the tendency for anterior infarcts to be larger than inferior infarcts. Thanavaro et al. concluded that location of infarction had an independent influence on in-hospital prognosis after stratifying patients according to peak AST level to control for infarct size. Strauss et al. demonstrated a poorer prognosis (both early and late) for patients with anterior myocardial infarctions compared with those with inferior infarctions of equivalent size, based on the fact that the two groups of patients had similar peak release of serum enzymes.

While peak CK levels are an imperfect index of infarct size, they correlate well with total CK release, which in turn correlates with infarct size at autopsy. Thus, in this study, we used peak CK to estimate infarct size and found that infarct location was an independent predictor of early and late prognosis for patients suffering their first myocardial infarction. This was confirmed by two different methods of statistical analysis: first by stratifying patients with anterior and inferior myocardial infarction into subgroups according to peak CK level (and thus infarct size) and comparing the survival curves and early and late mortality among subgroups and second, by multivariate analysis with the proportional-hazards regression model. The effect of location of infarction on both early (less than 28 days after infarction) and late (28 to 365 days) mortality was important and was more significant for patients with larger infarcts. For those with small infarcts, there was an effect of location only on late mortality.

The most likely explanation for the poorer prognosis of patients with anterior myocardial infarction is that more extensive left ventricular damage occurs with anterior infarction than inferior infarction. Left ventricular function is an important, if not the major, determinant of prognosis after myocardial infarction. Peak levels of cardiac enzymes reflect the overall extent of myocardial necrosis with right and left ventricles contributing to enzyme release. However, after inferior infarction, the peak levels of cardiac enzymes may not accurately reflect the extent of damage to the left ventricle because a proportion of these patients may have right ventricular infarction contributing to enzyme release. This may particularly apply in the case of larger myocardial infarctions, where right ventricular infarction in patients with inferior infarction might be expected to contribute a greater proportion to enzyme release. Therefore, when comparing patients with anterior and those with inferior myocardial infarctions matched for infarct size based on peak enzyme release, it may be postulated that for each increment in serum enzyme level, those with anterior infarction have greater left ventricular dysfunction than those with inferior infarction. The pattern of early complications in our patients supports this hypothesis. The anterior infarct group had a greater incidence of pulmonary edema on admission to the hospital and of cardiac failure during the hospital stay; they therefore presumably had more impairment of left ventricular function compared with the group of patients with inferior infarcts of equivalent enzymatic size.

Other possible contributing factors ought to be considered. Bulkley et al. suggested that there may be qualitative differences in the anterior and inferior ventricular wall contributing to different prognoses after myocardial infarction. Eaton et al. in a limited series of 28 patients, suggested that patients with anterior infarcts, particularly those with high peak enzyme levels, were more at risk of “infarct expansion” with acute regional dilatation and thinning of the infarct zone. Infarct expansion may have immediate effects, leading to cardiac rupture. In addition, expansion of the infarcted zone may cause dysfunction of the noninfarcted myocardium and ventricular dilatation. A tendency for this to occur more readily after anterior infarction

<table>
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<tr>
<th>Time interval (after MI)</th>
<th>Relative risk (anterior vs inferior MI)</th>
<th>95% confidence levels</th>
</tr>
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<tbody>
<tr>
<td>Day 1–28</td>
<td>1.68</td>
<td>1.02–2.77</td>
</tr>
<tr>
<td>Day 29–90</td>
<td>2.17</td>
<td>0.88–5.38</td>
</tr>
<tr>
<td>Day 91–365</td>
<td>2.22</td>
<td>1.00–4.95</td>
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TABLE 4
Relative risk of death for patients with anterior and inferior infarction at various time intervals after myocardial infarction (MI)
would have an adverse effect since expansion of left ventricular volume worsens prognosis independent of ejection fraction.25

Other anatomic and functional differences between patients with anterior and those with inferior myocardial infarction may contribute to the differences in prognosis, but are probably of lesser importance. The pattern of atrial and ventricular arrhythmias in the two groups was no different in this study or in previous studies in which infarctions at different sites were compared.6 As would be expected from the blood supply to the ativoventricular node, there was a higher incidence of ativoventricular block in the patients with inferior infarction, but these are usually transient and rarely cause a fatal outcome. The effects of septal infarction complicating anterior myocardial infarction on intraventricular conduction disturbances could not be evaluated in this study since patients with bundle branch block were excluded because of concern about the reliability of localizing the infarction on the electrocardiogram in this situation. Thanavaro et al.3 confirmed a higher incidence of bundle branch block in those with anterior infarction, but the effect of this on prognosis remains undocumented.

In the present study there was particularly high late mortality of patients with anterior myocardial infarction compared with that of those with inferior infarction in the low enzyme elevation group (i.e., peak CK less than two times upper limit of normal). It might be postulated that, while many of the patients in the anterior infarction group suffered only a small infarction, it was associated with a high-grade obstructive lesion of the left anterior descending coronary artery, leaving a large area of myocardium at risk of reinfarction, and thus leading to subsequent poor prognosis.

The finding that the location of myocardial infarction, independent of size, is an important prognostic indicator warrants consideration in stratification of risk and clinical management of patients suffering their first myocardial infarction. Further investigations into the modes of death and differences in left ventricular function and volume expansion in patients with inferior and those with anterior infarctions of equivalent enzymatic size are needed to fully explain the reasons for the prognostic significance of the site of infarction. Studies currently underway suggest a greater degree of left ventricular dysfunction in patients with anterior infarcts compared with those with inferior infarcts of equivalent size.34

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