Digitalis-associated Cardiac Mortality After Myocardial Infarction

ARTHUR J. MOSS, M.D., HENRY T. DAVIS, PH.D., DAVID L. CONARD, M.D., JOHN J. DECAMILLA, B.S., AND CHARLES L. ODOROFF, PH.D.

SUMMARY The effect of digitalis therapy on 4-month posthospital cardiac mortality was investigated in 812 patients who survived the hospital phase of acute myocardial infarction. A stepwise multiple logistic regression analysis was used to identify variables associated with increased mortality and to adjust for differences in confounding variables between digitalis and nondigitalis patients. The major 4-month mortality (10 of 26 patients [38.5%]) occurred in digitalis-treated patients with congestive heart failure in the coronary care unit and complex ventricular premature depolarizations (VPDs) on a predischarge Holter recording. Logistic analyses that controlled for confounding variables indicated that digitalis use contributed to the increased mortality rate in this high-risk subset. The predicted mortality difference due to digitalis in patients with congestive heart failure and complex VPDs, adjusted for relevant nondigitalis risk factor variables, was 30% (90% confidence interval 18–42%). This retrospective study suggests that digitalis use increases the early posthospital mortality of myocardial infarction patients with combined electrical and mechanical dysfunction.

DIGITALIS THERAPY has been a mainstay in the treatment of left ventricular failure in patients with and without coronary heart disease. Some caution has developed regarding the use of cardiac glycosides in patients with acute myocardial infarction because of the hazards of arrhythmic toxicity and the potentially harmful effect of enhanced myocardial oxygen consumption.1,2 Katz3 suggested that the diseased heart operates under optimal conditions, and further inotropic stimulation (as with digitalis) could have adverse effects. Katz warned that drugs that increase contractility in the diseased heart may produce a benefit at the expense of life-shortening myocardial damage.

Digitalis is most useful in controlling the ventricular response rate to atrial fibrillation. The clinical efficacy of long-term digitalis therapy in patients with chronic left ventricular dysfunction and sinus rhythm has been questioned.4,5 Some physicians believe from their own clinical experience that digitalis therapy may increase the short-term mortality of convalescent myocardial infarction patients beyond that expected on the basis of the patients' anticipated clinical course. We analyzed the data base of the Rochester Heart Research Follow-Up Program6,7 to determine whether postinfarction patients treated with cardiac

glycosides have a higher mortality than comparable patients not given digitalis.

Methods

Population

The study population consisted of 978 residents of Monroe County, 798 men and 180 women who were younger than 66 years of age, who entered coronary care units (CCU) in two Rochester community hospitals between January 1, 1973 and December 31, 1976 with a definite or probable acute myocardial infarction and survived hospitalization. Definite myocardial infarction was substantiated by the presence of any two of the following: typical coronary-type chest pain, serial acute myocardial enzyme changes or ECG documentation (an evolving Q-wave abnormality with acute ST- and T-wave changes). Patients with probable myocardial infarction had typical coronary-type chest pain with minor enzyme changes and/or ECG-documented acute ST- and T-wave changes. Both the patient and the private physician gave informed consent before the study.

Data Acquisition

Nurse investigators interviewed the patients and reviewed their hospital charts during the last week of hospitalization. The patients' medical history before entry and their clinical course in the CCU and during hospitalization were recorded on prospectively designed forms as previously described.7 Clinical variables used in this study included demographic data; historical comorbidity, such as prior myocardial infarction, hypertension, angina pectoris and diabetes mellitus; the severity of the acute coronary event in terms of left ventricular dysfunction as manifest by pulmonary congestion or congestive failure* in the CCU; and myocardial infarct location as determined by Minnesota classification* of a 12-lead ECG categorized into anterior (Q/QS = 1.11-1.12), posterior (Q/QS = 1.14) and other (non-Q/QS abnormality) locations. Six-hour Holter ECG tape recordings were obtained during the last 3 days of hospitalization before discharge. These recordings were analyzed using a rapid 60:1 scan technique to identify ventricular premature depolarizations (VPDs). VPDs were categorized in terms of bigeminal, multiform, repetitive (two or more consecutive VPDs), or early-cycle (RR'/QT ≤ 1.00) beats. Complex VPDs were defined by the presence of one or more of the following patterns: bigeminal, multiform, repetitive or early-cycle VPDs. A medication history obtained at discharge ascertained whether the patient was or was not taking each of the following category of drugs: digitalis (digoxin or digitoxin), antiarrhythmic agents (procainamide or quinidine), diuretic agents and β blockers (propranolol).

Patients were scheduled for clinical follow-up evaluation every 4 months during the first 2 years after hospital discharge. A detailed medication history was obtained at each follow-up visit. At the first 4-month follow-up visit, 21% (29 of 137) of the patients discharged on digitalis had discontinued this medication and 7% (46 of 648) of the nondigitalized patients had begun taking digitalis. An increasing crossover in digitalis use and discontinuance occurred after the first 4-month posthospital interval. For this reason the analysis of the effect of digitalis use on cardiac mortality was ascertained only for the first 4-month period.

Six of the 978 patients in the study population had missing values regarding the use of digitalis at discharge. These patients were excluded from analysis, and the net study population was 972 patients.

Mortality

All patients who died during the first 4-month posthospital interval were identified. Information about the terminal event was obtained from immediate family members, the personal physician, witnesses, and the hospital chart in patients who died in-hospital. Medication usage in the week before death was ascertained from these sources. This terminal event information was evaluated by a mortality review committee and a cause of death was assigned to each nonsurvivor, as previously described.8 During the 4-month posthospital interval, 42 patients died, 41 from cardiovascular causes. Among the patients who received digitalis at hospital discharge, 21 died, all from cardiovascular causes.

Statistical Analysis

The principal point of interest in this study is the rate of survival for patients treated with digitalis compared with those not treated with digitalis. Digitalis-treated patients can be expected to have more serious heart disease, and such was the finding in the present study. The digitalis patients had more severe cardiovascular comorbidity than the remainder of the population (table 1). Statistical techniques were used to adjust for differences between the digitalis and nondigitalis groups so that the effect of digitalis on mortality could be evaluated.

A stepwise modification of the multiple logistic regression technique was used to choose an appropriate model for mortality prediction. A discussion of this method including the situations in which it is applicable is provided by Cox,9 and a brief summary is presented in the Appendix. The parameters of the logistic model were fitted using GLIM.10 Two optimal logistic models were chosen from selected clinical variables. Digitalis, 16 clinically meaningful covariates from table 1, all two-factor interactions, and selected three-factor interactions were considered for inclusion in logistic model 1. The model that best described the observed data permitted evaluation of the strength of the association between digitalis usage at discharge (as well as other clinical variables) and 4-

*Pulmonary congestion was defined as roentgenographic evidence of interstitial or alveolar edema; congestive heart failure was defined as significant pulmonary rales and/or pitting edema.
month mortality. A second logistic model (model II) was fitted with the aforementioned variables except that digitalis was excluded from consideration. Logistic model II permitted the prediction of 4-month mortality in the digitalis and non-digitalis patients on the basis of non-digitalis variables. (This approach to fit model II is similar to age adjustment by the indirect method.) A comparison of the mortality rates predicted in various subgroups by models I and II provides an estimate of the effect of digitalis on mortality while simultaneously adjusting for the confounding effects of nondigitalis variables. Patients with missing values for any of the 17 variables were excluded from the analyses. The logistic analysis sample consisted of 812 patients; 134 patients were receiving digitalis. This sample contained 39 of 41 patients who died of cardiovascular causes in the first 4 months after hospital discharge.

Confidence limits for the differences in mortality between patients receiving digitalis and those not taking digitalis, adjusted for the concomitant variables, were determined by the "bootstrap" technique described by Efron14 (see Appendix).

**Results**

**Multiple Logistic Analysis**

Seventeen clinically important variables were analyzed by the stepwise multiple logistic regression technique (see Methods) using 4-month mortality/survival as the binary outcome event. The variables included in the multiple logistic model (model I) together with the relevant chi-square statistics for deletion from the model are presented in table 2. Variables of clinical interest excluded from the model on the basis of small chi-square values for inclusion are listed at the bottom of table 2. Digitalis therapy was associated with increased mortality only in patients with congestive heart failure, and especially in those with congestive heart failure and complex VPDs on a predischarge Holter recording.

The observed number of 4-month mortality events, the number of patients at risk and the associated mortality rates classified by the presence of congestive heart failure, complex VPDs and the use of digitalis are presented in table 3. The fitted mortality percentages provided in table 3 for model I are computed from the multiple logistic model using the digitalis- and non-digitalis-related variables (the full 10-variable model) presented in table 2. The predicted mortality percentages for model I are in excellent agreement with the observed rates. This concordance of observed and predicted mortality rates substantiates the predictive accuracy of logistic model I. Model I, which incorporates two- and three-factor digitalis interaction terms, suggests synergism in the effects of congestive heart failure, complex VPDs, and digitalis on mortality.

The major 4-month mortality (38.5%) occurred in the digitalis-treated patients with congestive heart failure and complex VPDs. To adjust for the differences in the relative severity of the underlying cardiac disease in the digitalis and nondigitalis patients,
further logistic analyses were carried out using the 16 nondigitalis variables from table 2. The resulting logistic model (model II, table 3) included the seven nondigitalis variables from model I plus congestive heart failure and complex VPDs. In essence, model II predicts the mortality rates for various digitalis subgroups solely on the basis of nondigitalis variables. Model II indicates that the digitalis-treated patients have roughly twice the predicted mortality of nondigitalis-treated patients in all categories, which suggests an increased concentration of non-digitalis-related risk factors in the digitalis subgroup. However, the adjustment made by model II does not adequately describe the observed 4-month mortality in digitalis-treated patients with congestive heart failure and complex VPDs (model II vs observed: 7.7% vs 38.5%).

A comparison of the predicted mortality rates between model I (full 10-variable model with digitalis terms) and model II (alternate model without digitalis terms) for digitalis-treated patients with congestive heart failure and complex VPDs is presented in table 4. This comparison indicates that digitalis use in these high-risk patients is associated with a fivefold increased mortality. The difference in the mortality rates between models I and II in this subset is 30.8% (90% confidence interval 18.2–42.3%) (table 4). This mortality difference represents our best estimate of the digitalis contribution to early posthospital mortality in this high-risk subset when adjusting for the relevant non-digitalis risk factor variables.

Characteristics of the Mortality Events

The characteristics of the terminal event in the digitalis and nondigitalis patients who died were scrutinized (table 5). All the digitalis-associated deaths were of cardiovascular cause. A majority of the digitalis deaths were in-hospital and were not sudden (> 24 hours), and the reverse was true for non-digitalis patients. In both groups of patients the predominant cause of death was acute myocardial infarction, as previously defined. Twenty of the 21 patients discharged from the hospital on digitalis were still taking digitalis in the week before death, but only five of 20 non-digitalis patients were receiving digitalis at the time of death.

Discussion

Our analysis suggests that digitalis therapy increased the mortality of some coronary patients in the early posthospital phase of myocardial infarction, i.e., those with congestive heart failure and complex VPDs. These results are particularly disconcerting because patients with cardiac mechanical dysfunction are the ones most likely to be treated with digitalis.

We are concerned about sources of systematic error that may have contributed to the findings. Because the digitalis effect on mortality was observed primarily in patients with congestive heart failure and complex VPDs, the categorization of this subgroup warrants comment. We used a standard clinical definition of congestive heart failure — significant auscultatory pulmonary rales and/or pitting leg edema recorded by

<table>
<thead>
<tr>
<th>Table 2. Variables Included in Logistic Model I for Predicting 4-month Posthospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Digitalis-related variables</strong></td>
</tr>
<tr>
<td>Digitalis, CHF and complex VPD interaction</td>
</tr>
<tr>
<td>Digitalis and CHF interaction</td>
</tr>
<tr>
<td>Digitalis and diuretic interaction†</td>
</tr>
<tr>
<td><strong>Non-digitalis variables</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>ECG heart rate</td>
</tr>
<tr>
<td>Anterior myocardial infarction</td>
</tr>
<tr>
<td>Cigarette smoking</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>NYHA functional class</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
</tr>
</tbody>
</table>

Variables not included in the model: digitalis, CHF, pulmonary congestion, shock, any VPD, multiform VPD, complex VPD, hypertension, diuretic therapy, social class rank, and digitalis and complex VPD interaction.

*Chi-square statistics are for variable deletion. All chi-square values used 1 degree of freedom. A large chi square for deletion indicates the variable is necessary in the model.

†Presence of this variable is associated with reduced four-month mortality.

Abbreviations: NYHA = New York Heart Association; VPD = ventricular premature depolarization; CHF = congestive heart failure.

the CCU physician in the medical chart. Although this definition lacks quantitative precision, it reflects qualitative impairment of left ventricular function. However, because congestive heart failure was diag-

<table>
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<tr>
<th>Table 3. Observed and Predicted 4-month Mortality in Patients with Various Combinations of Congestive Heart Failure, Complex Ventricular Premature Depolarizations and Digitalis Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congestive heart failure Absent Present</strong></td>
</tr>
<tr>
<td>Digitalis absent</td>
</tr>
<tr>
<td>Observed</td>
</tr>
<tr>
<td>2.6%</td>
</tr>
<tr>
<td>Model I*</td>
</tr>
<tr>
<td>Model II†</td>
</tr>
<tr>
<td>Digitalis present</td>
</tr>
<tr>
<td>Observed</td>
</tr>
<tr>
<td>0%</td>
</tr>
<tr>
<td>Model I*</td>
</tr>
<tr>
<td>Model II†</td>
</tr>
</tbody>
</table>

The numbers in parentheses represent the observed 4-month mortality divided by the patients at risk. The percentages refer to the 4-month mortality rates either observed or predicted by models I and II.

*Model I: Full fitted model using digitalis-related variables and nondigitalis variables listed in table 2.
†Model II: Alternate model using the seven non-digitalis variables listed in table 2 plus congestive heart failure and complex VPD.

Abbreviation: VPD = ventricular premature depolarization.
nosed clinically, considerable variability may exist in the degree of left ventricular dysfunction and the severity of coronary artery disease in this high-risk sub-
group. Such variability may influence the results, especially if the digitalis-treated patients had more severe myocardial and coronary disease. Complex VPDs were identified on the predischarge Holter recording according to predetermined criteria. At the time of data collection, the digitalis hypothesis had not been considered. Digitalis therapy at discharge was ascertained from the discharge prescriptions given to the patient, and a meaningful error seems unlikely. Patient compliance is difficult to evaluate from the collected data, but some information is available from the terminal event record regarding use of digitalis in those who died. Twenty of 21 digitalis patients were taking digitalis within the week before death. In contrast, among 20 nondigitalis patients who died of cardiovascular cause within 4 months after discharge, only five patients were taking digitalis at the time of death. This crossover would dilute the magnitude of the digitalis effect on mortality.

Table 4. The Magnitude and the Significance of the Predicted Mortality Difference Between Logistic Models I and II for Digitalis Patients with Congestive Heart Failure and Complex Ventricular Premature Depolarizations

<table>
<thead>
<tr>
<th>Model</th>
<th>Mortality (%)</th>
<th>Difference</th>
<th>90% confidence interval*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>38.5</td>
<td>7.7</td>
<td>30.8</td>
</tr>
</tbody>
</table>

*Confidence interval obtained by the "bootstrap" technique.14

The digitalis-treated patients had more severe underlying heart disease than those who did not receive digitalis (table 1). We attempted to evaluate the relative severity of the underlying heart disease in the digitalis and nondigitalis patients in model II of the logistic analysis. Within model II, the high-risk (congestive heart failure and complex VPDs) digitalis patients had twice the mortality of nondigitalis patients. Nevertheless, the predicted mortality rate in model II in the highest risk digitalis-treated patients (7.7%) is far below the observed mortality rate (38.5%). This finding suggests a mortality difference due to digitalis even when adjusting for the severity of the underlying cardiac disease.

The patient's physician was solely responsible for the decision to initiate digitalis therapy. We are concerned that the physicians selected patients with more severe cardiac disease for digitalis therapy, and this increased severity was not identified by the clinical variables such as congestive heart failure, pulmonary congestion, hypotension and shock. An underesti-
mation of the true severity of the cardiac disease in the digitalis patients would contribute to an erroneously increased mortality in this group compared with the nondigitalis patients. Although an error of this type is possible, its magnitude is probably small, as judged by the prognostic value of these variables in other studies.5,15

We selected the posthospital interval of 4 months in which to evaluate the effects of digitalis therapy on mortality for a variety of reasons. Davis et al.18 showed that the early posthospital period was when the majority of deaths occurred in the first 2 years after discharge. If digitalis contributes to increased posthospital mortality, it should be evident within the first 4 months after discharge. Also, patient compliance is likely to be maximal and crossover and discontinuance of prescribed therapy are likely to be minimal in the early posthospital interval. Thus, by choosing this time period, the "contamination" effect of digitalis drop in and drop out would be reduced. Further, the prospective study design used 4-month follow-up intervals, and during this period 100% follow-up of the study population was achieved.

How can the findings of this study be reconciled with the known physiologic effects of digitalis and existing clinical studies? The cost of the positive inotropic effect of digitalis therapy is increased myocardial oxygen consumption.1,2 Stimulation of the diseas-
ed heart by digitalis has questionable long-term hemodynamic benefit,++ and the stimulation may enhance myocardial damage.5 Also, in the presence of acute and subacute coronary heart disease, the potential for digitalis-induced ventricular arrhythmias may be increased as a result of myocardial ischemia, reduced cardiac output and diminished renal func-
tion.16,17 The evidence suggests that the therapeutic-toxic margin for digitalis is relatively narrow, especially in patients with compromised left ventricular function. In this regard, logistic model I indicated that the increased mortality associated with digitalis therapy occurred primarily in patients with congestive heart

Table 5. Characteristics of the Terminal Event in Digitalis and Non-digitalis Patients Who Died Within 4 Months After Hospital Discharge

<table>
<thead>
<tr>
<th>Digitalis</th>
<th>Nondigitalis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 21)</td>
<td>(n = 20)</td>
</tr>
<tr>
<td>Location of death</td>
<td></td>
</tr>
<tr>
<td>Out-of-hospital or emergency ward</td>
<td>8</td>
</tr>
<tr>
<td>In-hospital</td>
<td>13</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
</tr>
<tr>
<td>Definite or possible acute myocardial infarction</td>
<td>17</td>
</tr>
<tr>
<td>Chronic coronary heart disease</td>
<td>3</td>
</tr>
<tr>
<td>Other cardiovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Suddenness of death</td>
<td></td>
</tr>
<tr>
<td>Less than 1 hour</td>
<td>6</td>
</tr>
<tr>
<td>1-24 hours</td>
<td>2</td>
</tr>
<tr>
<td>More than 24 hours</td>
<td>12</td>
</tr>
<tr>
<td>Unwitnessed</td>
<td>1</td>
</tr>
<tr>
<td>Digitalis therapy in the week before death</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
</tr>
</tbody>
</table>

*One non-digitalis patient died of noncardiovascular causes and is not included in this table.
failure and coexisting complex VPDs. The role of complex VPDs in this interaction is speculative. In the patients with congestive heart failure, complex VPDs may have been enhanced by digitalis. Alternatively, complex VPDs may be a marker of more severe myocardial disease, thereby selecting out the patients at an increased mortality risk from digitalis.

Digoxin was the predominant cardiac glycoside prescribed in this population. Drug dosage and blood levels were not part of the data base, and the prevalence of digitalis toxicity cannot be determined. Recent studies suggest that the concomitant administration of quinidine increases the blood level of digoxin.\(^5\) Thirty-four percent of the digitalis-treated patients were receiving antiarrhythmic agents (propranolol or quinidine) at discharge, but information is not available about the use of individual antiarrhythmic drugs. Although the digitalis-quinidine interaction may have been involved in the increased digitalis-associated mortality, we cannot isolate the importance of this drug combination in the observed results. Similarly, serum potassium levels were not part of the original study protocol, and the confounding effect of hypokalemia cannot be ascertained. A favorable digitalis-diuretic interaction was observed (table 2), and it is unlikely that diuretic-induced hypokalemia contributed to the increased mortality among the high-risk digitalis-treated patients.

The magnitude of the risk posed by digitalis in the subset of patients with congestive heart failure and complex VPDs is marked (mortality difference estimated at 30%), and one might ask why such a large effect had not been recognized previously. The increased digitalis risk is concentrated in 3% of the postcoronary population (digitalis and congestive heart failure and complex VPDs, 26/812), and the high 4-month mortality of 38.5% (10 of 26) in this subgroup could be overlooked as a result of the dilution effect from the relatively low mortality of 8.7% (nine of 108) in the remaining digitalis-treated patients. Further, because it is anticipated that patients with left ventricular dysfunction will have an increased mortality, the augmented lethality with digitalis might not be appreciated except when specific analyses are carried out, i.e., looking at the variables jointly, as in table 3.

To our knowledge, this is the first large-scale study in which retrospective analysis of prospectively accumulated data has identified digitalis therapy as a factor contributing to increased mortality. The observed effect was limited to a subset of the postcoronary patients who had clinical evidence of congestive heart failure in the CCU and complex VPDs on a predischARGE Holter recording. The implications of these findings are quite profound, for postinfarction survival may be increased by not prescribing or by discontinuing the use of digitalis in these patients. A prospective digitalis withdrawal trial is needed to answer this question.

Acknowledgement

The authors thank Nancy Kellogg for her secretarial assistance.

References


Appendix

Two principal statistical techniques are used in the analysis of this study: stepwise multiple logistic analysis\(^24\) and the bootstrap.\(^25\) A multiple logistic model assumes that the probability an individual will die within 4 months is \(F(x) = [1 + \exp(-[\alpha + \beta x])^{-1}]^{-1}\) where \(x = (x_1, \ldots, x_n)\) is a vector containing the values of \(N\) prognostic variables and \(\alpha, \beta = (\beta_1, \ldots, \beta_k)\) are parameters of the model. When \(\alpha\) and \(\beta\) are unknown, they can be estimated by maximal likelihood using the information contained in a random sample from the population. When it is also necessary to determine which prognostic variables are important in predicting mortality, a stepwise procedure can be used for variable selection. The stepwise procedure we used was the "step-up, step-down" method.\(^26\) Each step of this procedure has two parts. In the first part, we select the variable that causes the greatest increase in the likelihood when added to the model. This variable is then added to the model if its contribution to the likelihood is greater than 1.0; otherwise, the procedure is terminated. In the second part of the step, all variables whose contribution to the overall
log-likelihood is less than 1.0 are removed from the model.

The basic concept of the technique as applied to the multiple logistic model is as follows. First, the parameters \( \alpha \) and \( \beta \) are estimated by maximal likelihood. If the vectors of prognostic variables for the \( M \) individuals in the sample used to estimate \( \alpha \) and \( \beta \) are respectively \( y_1, \ldots, y_M \) and then a series of random samples of Bennoulli random variables are generated such that \( Y_i \) is the \( i \)th random variable in the \( j \)th sample \( \Pr[Y_{ij} = 1] = F(x_i) \). For each random sample pseudo-maximal likelihood estimates of the parameters are obtained. The joint distribution of these pseudo-maximal likelihood estimates across the samples can then be used to form confidence limits for a test hypothesis about the parameters. The advantage of this technique over the usual maximal likelihood confidence intervals or the likelihood ratio test is that it does not rely on asymptotic distribution theory to determine confidence coefficients or significance levels. Asymptotic distribution theory may not be appropriate for small or moderate-sized samples.

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An Investigation in Patients with Previous Myocardial Infarction Who Present with Chest Pain

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TIMOTHY PRATT, M.SC., AND ROBERT STEINER, M.D.

SUMMARY Thirty-five patients who presented with chest pain underwent mapping of the ECG with exercise and angiocardiology. Krypton-81m was used to assess regional myocardial perfusion before, during and after atrial pacing.

Twelve of the 35 patients had negative exercise tests. Eight of these 12 had normal coronary arteries and four had \( \leq 50\% \) stenosis of at least one major coronary artery. All 12 patients had uniform increases in regional myocardial perfusion (98 \( \pm \) 14.0\%) during atrial pacing. Thirteen of the 35 patients had a history of myocardial infarction and precordial areas of Q waves. During exercise, all 13 patients complained of chest pain and showed precordial areas of both ST-segment elevation and depression. These 13 patients had \( \geq 70\% \) stenosis of at least one major coronary artery. Myocardial blood flow studies showed fixed defects of perfusion corresponding to the Q waves and ST-segment elevation. In addition, there were separate transient decreases of regional myocardial perfusion (70 \( \pm \) 9.0\%) during atrial pacing corresponding to ST-segment depression and chest pain. Ten of the 35 patients had a history of myocardial infarction and precordial areas of Q waves. During exercise, only two of these 10 complained of chest discomfort and all showed precordial areas of significant ST-segment elevation alone. All these patients had \( \geq 70\% \) stenosis of one or more major coronary arteries. Myocardial blood flow studies showed fixed defects of perfusion that corresponded to Q waves. These areas showed no changes during atrial pacing. All the patients showed at least one remote region of myocardium that increased perfusion (74 \( \pm \) 17.0\%) throughout pacing.

Patients with a history of myocardial infarction may present with chest pain. In this study, ST-segment elevation during an exercise ECG was not associated with chest pain or detectable myocardial ischemia. Regional perfusion in infarced segments of myocardium did not change with atrial pacing. However, separate precordial areas of ST-segment depression during exercise were associated with angina during exercise and pacing. ST-segment depression was also associated with the presence of a separate region of myocardium showing reversible disturbances of perfusion during pacing.

PATIENTS with a history of myocardial infarction may present with chest pain and the clinician needs objective evidence as to whether there is new myocardial ischemia. The complaint of chest pain may not be specific, and the ECG at rest may show only pathologic Q waves. The ECG during exercise may show ST-segment elevation or depression. The clinician must know what disturbances of regional myocardial perfusion occur in patients who have a history of myocardial infarction and who present with chest pain. In addition, diagnosis and management may be aided if the clinician knows what the ST-segment changes mean during stress in this situation.

We describe the exercise ECG and disturbances of regional myocardial perfusion during stress in a group of patients with a history of myocardial infarction who present with chest pain. Permanent and reversible disturbances of regional myocardial perfusion have been recorded in these patients and have been related to abnormal electrocardiographic signs. We examine the disturbances of myocardial perfusion in coronary artery disease (CAD) and its relation to the widely available and noninvasive use of the ECG.

Methods

Between January 1978 and December 1979, 23 patients (22 male and one female, ages 31–68 years,
Digitalis-associated cardiac mortality after myocardial infarction.
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The online version of this article, along with updated information and services, is located on
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http://circ.ahajournals.org/content/64/6/1150