ORIGINAL ARTICLES

The High-risk Angina Patient
Identification by Clinical Features, Hospital Course, Electrocardiography and Technetium-99m Stannous Pyrophosphate Scintigraphy

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SUMMARY We evaluated 193 consecutive unstable angina patients by clinical features, hospital course and electrocardiography. All patients were managed medically. Of the 193 patients, 150 (78%) had a technetium-99m pyrophosphate (Tc-PYP) myocardial scintigram after hospitalization. Of these, 49 (33%) had positive scintigrams. At a follow-up of 24.9 ± 10.8 months after hospitalization, 16 of 49 patients (33%) with positive scintigrams died from cardiac causes, compared with six of 101 patients (6%) with negative scintigrams (p < 0.001). Of 49 patients with positive scintigrams, 11 (22%) had nonfatal myocardial infarction at follow-up, compared with seven of 101 patients (7%) with negative scintigrams (p < 0.01). Age, duration of clinical coronary artery disease, continuing angina during hospitalization, ischemic ECG, cardiomegaly and a history of heart failure also correlated with cardiac death at follow-up. Ischemic ECG and a history of angina with a crescendo pattern also correlated with nonfatal infarction at follow-up. Patients with continuing angina, an ischemic ECG and a positive scintigram constituted a high-risk unstable angina subgroup with a survival rate of 58% at 6 months, 47% at 12 months and 42% at 24 and 36 months. We conclude that the assessment of clinical features, hospital course, ECG and Tc-PYP scintigraphy may be useful in identifying high-risk unstable angina patients.

ONE OF THE MAJOR FUNCTIONS of the coronary care unit is to identify high-risk patients for cardiac morbidity and mortality during and after hospitalization. Unstable angina patients continue to be ideal patients for risk evaluation because they represent a large proportion of the coronary care unit population, they do not have new significant myocardial necrosis at the time of diagnosis, and they have a high incidence of cardiac death and nonfatal myocardial infarction during follow-up.1-3 In 1973, Gazes and associates reported a high-risk subgroup of unstable angina patients for cardiac morbidity and mortality.4 Their high-risk unstable angina group included patients with continuing angina after hospitalization associated with ECG changes of myocardial ischemia and a history of angina.

Technetium-99m pyrophosphate myocardial scintigraphy has been shown to be a sensitive method for the diagnosis of acute myocardial infarction.6-12 Properly performed, this technique can diagnose myocardial infarction in more than 95% of patients with transmural myocardial infarction and in 38-100% of patients with nontransmural myocardial infarction.4-12 Of interest, 25-42% of patients with unstable angina pectoris have positive myocardial scintigrams.5, 8, 10, 12-15 It has been suggested that these patients may have clinically undetected myocardial necrosis.5, 16

The natural history of unstable angina patients with positive scintigrams is unknown. The purpose of the present investigation was to assess the natural history of patients with unstable angina pectoris, especially those with positive myocardial scintigrams; and to assess the prognostic value of technetium-99m pyrophosphate scintigraphy, by itself, and in combination with other clinical measurements in a large population of patients admitted to the coronary care unit with a diagnosis of unstable angina.

Materials and Methods

From July 1975 to March 1977, 250 consecutive patients admitted to the coronary care unit of the Long Beach Veterans Administration Medical Center met our criteria for unstable angina: (1) prolonged angina at rest lasting more than 15 minutes. (2) No evidence of acute myocardial infarction after a 3-day observation period, as determined by serial ECGs and serum enzyme determinations. (During the observation period, none of the patients had new Q waves on their ECGs or an abnormal rise in serum creatine kinase enzyme (CK) or CK-MB isoenzyme.) (3) No documented myocardial infarction within 3 months of the present admission.

Of the 250 patients, 57 (23%) had coronary artery bypass graft surgery, 3.1 ± 3.7 weeks (range 4 days to 12 weeks) after hospital admission. The selection of patients for surgery was based on physician and
patients' preferences. The remaining 193 patients who received medical therapy for unstable angina form the basis of this study.

There were 192 men and one woman, ages 29–82 years (mean 57.3 ± 9.7 years). In all 193 patients, ECGs were obtained daily and during recurrent attacks of chest pain. All the ECGs were reviewed and interpreted as showing either an ischemic or nonischemic pattern. An ischemic ECG pattern had either transient horizontal or down-sloping ST-segment depression of at least 0.1 mV, transient ST-segment elevation of at least 0.1 mV or transient symmetrical T-wave inversion in multiple leads. ECGs with none of these features were considered nonischemic. Patients who had recurrent episodes of rest angina after 24 hours of hospitalization (≥ 3 attacks) with or without ECG changes requiring nitroglycerin or narcotics for relief were defined as continuing angina patients. Patients without recurring episodes of angina were defined as patients without continuing angina. The number of anginal attacks in each patient was determined from the patient's nursing notes.

Of the 193 patients, 150 (78%) had a technetium-99m pyrophosphate myocardial scintigram 2.1 ± 1.1 days (range 1–4 days) after their admission to the coronary care unit. The criterion for myocardial scintigraphy was based solely on radionuclide and scintillation camera availability. Of the 150 patients, 27 (18%) had a second scintigram 15 ± 7.1 days after their initial scintigram.

Myocardial imaging was performed 2 hours after the injection of 20 mCi of technetium-99m pyrophosphate that contained less than 0.15 mg of tin. Chromatography, as previously described, was performed before each study to document the binding efficiency of the radiopharmaceutical. Myocardial scintigrams were recorded using a scintillation camera fitted with a Devcon collimator in a converging mode (82 patients) or a high-resolution collimator (68 patients). Imaging was performed in anterior, 45° left anterior oblique and left lateral views. Each view contained 500,000 counts with the Devcon collimator or 400,000 counts with the high-resolution collimator with the 20% window and the photopeak centered on 140 keV. Serial studies on individual patients were performed with the same camera and collimator. Delayed imaging was performed at 4 hours in all patients suspected of having persistent blood pool activity.

Myocardial scintigrams were interpreted using our previously reported grading system. The intensity of radioactivity in the area of the left ventricle was graded from 0 to 3+: 0 = no activity in region of the left ventricle; 1+ = activity less than that of rib; 2+ = activity equal to or greater than rib activity; and 3+ = activity equal to or greater than sternal activity. A scintigram of 2+ or greater was considered positive. Our grading system differs from that proposed by Parkey and Willerson. A 2+ scintigram in our system corresponds to a 3+ scintigram in their system. This is important because some investigators have considered a 2+ diffuse scintigram, according to Parkey-Willerson classification as equivocal, but not a diagnostically positive scintigram. In patients undergoing bone scintigraphy who had normal ECGs and no history of heart disease, the incidence of a 2+ scintigram by our classification was 2%. Myocardial scintigrams were also characterized by the distribution of activity. Regional uptake was considered when activity could be localized to an area of the left ventricle. Diffuse uptake was assigned when anatomic location was considered indeterminant. The myocardial scintigrams were interpreted by two experienced observers without knowledge of the patient's diagnosis. When there was disagreement between the observers in the interpretation of a scintigram, the lower score was assigned. There was complete agreement between the observers in 90% of the scintigrams interpreted. At the time of scintigraphy, none of the patients had pericardial disease, recent transthoracic cardiorenal, calcified cardiac valves or myocardial contusion, which are clinical disorders reported to be associated with false-positive myocardial scintigrams.

Of 193 patients, 78 (40%) had cardiac catheterization and coronary angiography by either the Sones or Judkins techniques 8.2 ± 6.8 days (range 4–22 days) after their hospital admission for unstable angina pectoris. Forty-two (22%) of the remaining patients had a cardiac catheterization 2.1 ± 2.0 years before their admission to the hospital for unstable angina. Coronary artery disease was considered present if the patient had coronary angiographic evidence of at least 75% luminal diameter stenosis of a major coronary artery or a well-documented myocardial infarction.

After hospital discharge, the surviving patients were followed in our cardiology clinic at a minimum of 3-month intervals. Medical therapy was individualized and included nitrates, propranolol, digitalis, diuretics and antiarrhythmics as indicated. The follow-up period terminated on October 1, 1978 (150 patients), at the time of cardiac death (31 patients), at the time of late coronary artery bypass surgery (six patients), at the time of death from noncardiac causes (four patients), and at the time of last known follow-up (two patients). The average follow-up time was 24.9 ± 10.8 months (range 1 week to 40 months). Follow-up data were obtained from patient interviews, hospital records, telephone interviews with patients' relatives, and from results of autopsy studies. Follow-up end points included cardiac death and nonfatal myocardial infarction. Cardiac death was classified as sudden death within 6 hours after the onset of symptoms, assumed to be due to a cardiac arrhythmia, death from acute myocardial infarction, and death from intractable congestive heart failure during hospitalization. The diagnosis of acute myocardial infarction was based on typical history, ECG changes with new Q waves or new persistent ST-segment abnormalities, and classic serial cardiac enzyme alterations.

The data were presented as mean ± SD. The UCLA Biomedical Computer Programs were used in the data analysis, which included chi-square, contingency-table analysis and multiple stepwise regression analysis.
All tests of significance are based on two-tailed tests. Survival rate estimates and standard errors were computed using the life-table method of Cutler and Ederer. 24

Results

The clinical features of the 193 patients, mean age 57.3 ± 9.7 years, upon entering the study are shown in table 1. The mean duration of clinical coronary artery disease was 54.7 ± 66.4 months. Coronary artery disease was documented in 167 of 193 patients (86%) with documentation by coronary angiography in 43 patients (22%), by coronary angiography and history of myocardial infarction in 74 patients (38%), and by history of myocardial infarction in 50 patients (26%). Three patients (2%) had normal coronary angiography. Twenty-three patients (12%) had no history of myocardial infarction and did not undergo coronary angiography. Some of these patients may not have had coronary artery disease.

Of the 193 patients, 81 (42%) had an ischemic ECG during their hospitalization. Of the 81 ischemic ECG patterns noted, one patient (1%) had transient ST-segment elevation on his ECG, 61 (75%) had transient ST-segment depression on their ECGs, and 19 (24%) had transient symmetric T-wave inversions on their ECGs. Of the 193 patients, 73 (38%) had continuing rest angina during their hospitalization. Forty-three of these 73 patients (65%) also had transient ischemic ECG changes during attacks of chest pain.

The results of the technetium-99m myocardial scintigrams obtained in the 150 patients during their coronary stay are shown in table 2. Of the 150 patients, 49 (33%) had positive scintigrams. Of the 49 patients who had positive scintigrams, 39 patients (80%) had a diffuse abnormality and 10 (20%) had a regional abnormality. One patient had a 3+ regional abnormality. Figures 1 and 2 are abnormal scintigrams from two patients during unstable angina pectoris.

Of the 27 patients who had repeat scintigraphy, eight of 15 patients (53%) who had initially positive scintigrams and 11 of 12 patients (92%) who had initially negative scintigrams had negative scintigrams at follow-up scintigraphy. The four patients with a worse scintigram at follow-up scintigraphy all sustained an acute myocardial infarction at repeat scintigraphic study.

Of the 49 patients with positive scintigrams, 27 (55%) had an ischemic ECG during unstable angina, compared with 32 of 101 patients (32%) with negative scintigrams (p < 0.01). Also, 40 of the 49 patients (82%) with positive scintigrams during unstable angina had a history of myocardial infarction, compared with 55 of 101 patients (55%) with negative scintigrams (p < 0.01).

Four patients died during initial hospitalization, all from acute myocardial infarction, yielding a hospital mortality of 2%. Twenty-seven other patients died from cardiac causes during follow-up. Of these cardiac deaths, 14 (52%) were sudden deaths, 10 (37%) were due to acute myocardial infarction, and three (11%) were from intractable congestive heart failure. Of the 193 patients, four (2%) had a nonfatal myocardial infarction during initial hospitalization and 17 (9%) after hospital discharge. The survival curve for the 193 patients is shown in figure 3. The survival rate was 94% at 1 month, 89% at 6 months, 86% at 12 months, 85% at 18 months, 84% at 24 months, 83% at 30 months and 83% at 36 months.

Table 3 shows that the incidence of cardiac death and nonfatal myocardial infarction at follow-up correlated with the presence or absence of continuing angina and a presence or absence of an ischemic ECG during hospitalization for the 193 patients with unstable angina. The presence of either continuing angina during hospitalization or an ischemic ECG correlated with an increased incidence of cardiac death or nonfatal myocardial infarction.

Figure 4 shows the survival curves for the 43 patients with continuing angina during hospitalization and ischemic ECGs and in the 82 patients with no continuing angina during hospitalization and nonischemic ECGs. The survival curves show a significantly greater mortality in patients with continuing angina during hospitalization and ischemic ECGs. The survival of patients with continuing angina during hospitalization and ischemic ECGs was 77% at 1 month, 65% at 6 months, 58% at 12 months and 56% at 24 and 36 months.

Table 4 indicates the results of myocardial scintigrams in the 150 patients who had the study performed.
HIGH-RISK UNSTABLE ANGINA PATIENT/Olson et al.

Figure 1. (upper) A 2+ abnormality (positive scintigram) during unstable angina. (lower) A negative scintigram in the same patient at follow-up 14 days later. A = anterior view; O = 45° left anterior oblique view; L = left lateral view.

Figure 2. (upper) A 2+ abnormality (positive scintigram) during unstable angina. (lower) A 3+ abnormality (worse scintigram) at follow-up 3 weeks later, when the patient had an acute myocardial infarction. A = anterior view; L = lateral view.

formed during unstable angina correlated with the incidence of cardiac death and nonfatal myocardial infarction at follow-up. Patients with positive scintigrams were more likely to have cardiac death or nonfatal myocardial infarction than patients with negative scintigrams. Twelve of the 16 cardiac deaths (75%) and seven of the 11 nonfatal myocardial infarctions (64%) in the positive scintigram group occurred within 6 months after hospital entry for unstable angina pectoris. Figure 2 is a scintigram during unstable angina in one patient who had a nonfatal myocardial infarction during follow-up.

Figure 5 shows the survival curves for the 49 patients with positive scintigrams and the 101 patients with negative scintigrams during unstable angina. The survival curves show a significantly greater mortality in patients with positive scintigrams at all the time intervals. Of the four patients with cardiac deaths during their initial hospitalization for unstable angina, three had myocardial scintigrams, and all three had a positive scintigram before they died. Of the four patients with nonfatal myocardial infarction during their hospitalization, three had positive scintigrams before the onset of infarction.

Chi-square values and contingency coefficients of correlation between cardiac death and nonfatal myocardial infarction and the 13 clinical variables thought to have prognostic value are shown in table 5. For cardiac death, a positive scintigram was the best predic-
tor, followed by continuing angina during hospitalization, ischemic ECG, history of congestive heart failure, and cardiomegaly by chest x-ray. Bypass graft surgery was negatively correlated with cardiac death. For nonfatal myocardial infarction, the ischemic ECG was the best predictor, followed by a positive scintigram, and history of angina with a crescendo pattern. Recent onset angina and a history of hypertension were negatively correlated with nonfatal myocardial infarction.

Coefficients of correlation between cardiac death and age and duration of clinical coronary artery disease were 0.21 and 0.22, respectively ($p < 0.05$). Neither age nor duration of clinical coronary artery disease correlated significantly with nonfatal myocardial infarction.

The results of a multiple stepwise regression analysis for cardiac death and nonfatal myocardial infarction with the clinical variables are shown in tables 6 and 7. For cardiac death, continuing angina during hospitalization, duration of clinical coronary artery disease, ischemic ECG, prior bypass graft surgery, age, history of congestive heart failure, history of hypertension and positive scintigram were the best linear combination of predictor variables (multiple $R = 0.484$). The above variables are listed in the order of

![Figure 4](http://circ.ahajournals.org/)

**Figure 4. Survival curves for the 43 patients with continuing angina and ischemic ECGs and the 82 patients with no continuing angina and nonischemic ECGs during unstable angina. $p < 0.001$.**

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### Table 3. Incidence of Cardiac Death and Nonfatal Myocardial Infarction at Follow-up Correlated with the Presence or Absence of Continuing Angina and the Presence or Absence of an Ischemic ECG During Hospitalization for Unstable Angina in 193 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of pts</th>
<th>Cardiac death</th>
<th>Nonfatal myocardial infarction</th>
<th>Either cardiac death or nonfatal myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing angina during hospitalization</td>
<td>73</td>
<td>23 (32%)§</td>
<td>11* (15%)</td>
<td>29 (40%)§</td>
</tr>
<tr>
<td>No continuing angina during hospitalization</td>
<td>120</td>
<td>8 (7%)</td>
<td>10† (8%)</td>
<td>17 (14%)</td>
</tr>
<tr>
<td>Ischemic ECG</td>
<td>81</td>
<td>22 (27%)¶</td>
<td>15* (19%)¶</td>
<td>32 (40%)¶</td>
</tr>
<tr>
<td>Nonischemic ECG</td>
<td>112</td>
<td>9 (7%)</td>
<td>6† (5%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Continuing angina and ischemic ECG</td>
<td>43</td>
<td>18 (42%)**</td>
<td>9* (21%)†</td>
<td>22 (51%)**</td>
</tr>
<tr>
<td>No continuing angina and nonischemic ECG</td>
<td>82</td>
<td>4 (5%)</td>
<td>6† (7%)</td>
<td>9 (11%)</td>
</tr>
</tbody>
</table>

*Five patients subsequently died from cardiac causes.
†One patient subsequently died from cardiac causes.
§$p < 0.001$, continuing angina during hospitalization vs no continuing angina during hospitalization.
¶$p < 0.001$, ischemic ECG vs nonischemic ECG.
**$p < 0.001$, continuing angina and ischemic ECG vs no continuing angina and nonischemic ECG.
their relative contribution to the multiple-R value.

For nonfatal myocardial infarction, ischemic ECG, history of angina with crescendo pattern, history of hypertension, history of smoking, cardiomegaly, age, history of diabetes and a positive scintigram were the best linear combination of predictor variables (multiple R = 0.400). The above values are listed in the order of their relative contribution to the multiple-R value. The correlation coefficients in tables 6 and 7 are not exactly the same as the contingency coefficients in table 5 because the two methods used are based on different concepts for establishing statistical relationships, and sample size was different for each group.

Table 8 depicts the incidence of cardiac death and nonfatal myocardial infarction in the 150 patients in whom hospital course, ECG and technetium-99m pyrophosphate scintigraphy were assessed. A high-risk subgroup for cardiac death and nonfatal myocardial infarction could be identified by the combined presence of continuing angina during hospitalization, ischemic ECG and a positive myocardial scintigram (subgroup H). A low-risk subgroup (subgroup A) for cardiac death and nonfatal myocardial infarction could be identified by the combined absence of these three variables. At follow-up, of the 19 subgroup H patients, 15 (78%) had cardiac death or nonfatal myocardial infarction, compared with four of 51 subgroup A patients (7%) (p < 0.001).

Figure 6 shows the survival curves for subgroup A and H patients. For the 19 subgroup H patients, the survival rate was 63% at 1 month, 58% at 6 months, 47% at 12 months and 42% at 24 and 36 months. For the 51 subgroup A patients, the survival rate was 100% for the first 24 months and 95% at 30 and 36 months (p < 0.001).

The combined presence of all three parameters was a better predictor for cardiac death and the combined incidence of cardiac death and nonfatal myocardial infarction at follow-up compared with patients with continuing angina and ischemic ECG during hospitalization and a negative myocardial scintigram (subgroup E). At follow-up, of the 19 subgroup H patients, 11 (57%) had a cardiac death, compared with two of 12 subgroup E patients (16%) (p < 0.05). Of the 19 subgroup H patients, 15 (78%) had either cardiac death or nonfatal myocardial infarction, compared with three of 12 subgroup E patients (25%) (p < 0.01).

Discussion

Previous studies have shown that unstable angina patients at high risk for morbidity and mortality include those with advanced age, those who have ischemic ECG changes and continuing rest angina after hospitalization, and those who have left ventricular dysfunction or a history of angina or myocardial infarction. The findings of the present investigation support these observations and indicate that patients with abnormal technetium-99m pyrophosphate myocardial scintigrams during unstable angina also have an increased risk of cardiac morbidity and mortality. Forty-six percent of the patients with a positive scintigram during unstable angina had cardiac death or nonfatal myocardial infarction during a follow-up period of 24.9 ± 10.8 months after the diagnosis of unstable angina was established.

The hospital mortality for the 193 unstable angina patients treated medically in our study was 2%. The hospital deaths were all due to myocardial infarction. Previous studies on unstable angina reveal a hospital mortality of 0–60%. The incidence of nonfatal myocardial infarction during hospitalization in our study was 2%. Previous studies have reported an in-

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Survival curves for the 49 patients with positive scans and the 101 patients with negative scans during unstable angina. *p < 0.01; † p < 0.001.

![Table 4](http://circ.ahajournals.org/)

**Table 4. Incidence of Cardiac Death and Nonfatal Myocardial Infarction at Follow-up Correlated with the Results of Scintigraphy During Unstable Angina Pectoris**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of pts (n = 150)</th>
<th>Positive scintigram (n = 49)</th>
<th>Negative scintigram (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>22</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>18</td>
<td>12</td>
<td>11‡</td>
</tr>
<tr>
<td>Either cardiac death or nonfatal myocardial infarction</td>
<td>35</td>
<td>23</td>
<td>23</td>
</tr>
</tbody>
</table>

*p < 0.01, positive scintigram vs negative scintigram.
†p < 0.001, positive scintigram vs negative scintigram.
‡Four patients also had subsequent cardiac death.
§One patient also had subsequent cardiac death.
The difference in mortality and nonfatal myocardial infarction between our study and the previous studies is probably because of differing definitions of unstable angina and patient selection. Patients who received coronary artery bypass graft surgery within 3 months of the onset of unstable angina were excluded from our study population. In addition, patients with myocardial infarction within 3 months of admission to the coronary care unit were also excluded. The Unstable Angina Pectoris National Cooperative Study Group reported a hospital mortality of 3% for patients treated medically. Their study also indicated an incidence of 8% for nonfatal myocardial infarction during hospitalization.  

Despite the reasonably good prognosis during hospitalization for our unstable angina pectoris patients, the incidence of 7–80%, 1–3, 25, 28, 30, 31 the difference in mortality and nonfatal myocardial infarction between our study and the previous studies is probably because of differing definitions of unstable angina and patient selection. Patients who received coronary artery bypass graft surgery within 3 months of the onset of unstable angina were excluded from our study population.

**Table 5. Chi-square Values and Contingency Coefficients of Correlation Between Cardiac Death and Nonfatal Myocardial Infarction and the 13 Clinical Variables in 193 Patients with Unstable Angina**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death χ²</th>
<th>C</th>
<th>Nonfatal myocardial infarction χ²</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent onset angina</td>
<td>1.510</td>
<td>-0.088</td>
<td>4.838*</td>
<td>-0.156</td>
</tr>
<tr>
<td>History of angina with a crescendo pattern</td>
<td>1.510</td>
<td>0.088</td>
<td>4.838*</td>
<td>0.156</td>
</tr>
<tr>
<td>Continuing angina during hospitalization</td>
<td>20.77†</td>
<td>0.312</td>
<td>0.488</td>
<td>0.050</td>
</tr>
<tr>
<td>Ischemic ECG</td>
<td>12.75‡</td>
<td>0.249</td>
<td>7.198†</td>
<td>0.190</td>
</tr>
<tr>
<td>Positive scintigram§</td>
<td>18.81†</td>
<td>0.334</td>
<td>7.134†</td>
<td>0.189</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>4.962*</td>
<td>0.158</td>
<td>2.592</td>
<td>-0.116</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>1.590</td>
<td>0.090</td>
<td>0.175</td>
<td>-0.030</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>7.859†</td>
<td>0.198</td>
<td>1.889</td>
<td>-0.099</td>
</tr>
<tr>
<td>History of bypass graft surgery</td>
<td>5.749*</td>
<td>-0.170</td>
<td>0.815</td>
<td>1.065</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>1.633</td>
<td>0.092</td>
<td>3.853*</td>
<td>-0.140</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>0.474</td>
<td>-0.050</td>
<td>0.248</td>
<td>0.036</td>
</tr>
<tr>
<td>History of smoking</td>
<td>0.188</td>
<td>-0.031</td>
<td>0.961</td>
<td>-0.070</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>1.330</td>
<td>0.083</td>
<td>2.520</td>
<td>0.114</td>
</tr>
</tbody>
</table>

* p < 0.05.
† p < 0.01.
‡ p < 0.001.
§ Based on the 150 patients in the group who had scintigrams.

**Table 6. Multiple Stepwise Regression Analysis Results for Cardiac Death and Significant Clinical Variables for the 150 Patients Who Had a Scintigram During Unstable Angina**

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>R</th>
<th>R²</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuing angina during hospitalization</td>
<td>0.322</td>
<td>0.322</td>
<td>0.103</td>
<td>0.337</td>
</tr>
<tr>
<td>Duration of clinical coronary heart disease</td>
<td>0.215</td>
<td>0.393</td>
<td>0.154</td>
<td>0.328</td>
</tr>
<tr>
<td>Ischemic ECG</td>
<td>0.245</td>
<td>0.428</td>
<td>0.183</td>
<td>0.324</td>
</tr>
<tr>
<td>Prior bypass surgery</td>
<td>-0.163</td>
<td>0.454</td>
<td>0.206</td>
<td>0.320</td>
</tr>
<tr>
<td>Age</td>
<td>0.206</td>
<td>0.468</td>
<td>0.219</td>
<td>0.319</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>0.127</td>
<td>0.474</td>
<td>0.225</td>
<td>0.319</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.038</td>
<td>0.479</td>
<td>0.230</td>
<td>0.319</td>
</tr>
<tr>
<td>Positive scintigram</td>
<td>0.204</td>
<td>0.484</td>
<td>0.235</td>
<td>0.319</td>
</tr>
</tbody>
</table>

The remaining variables did not significantly increase R² (p < 0.01) or reduce the SEE.

Abbreviations: r = coefficient of correlation between each of the variables and death; R = multiple R; R² = the proportion of the variance in the criterion variable death, which is accounted for by the stepwise addition of each indicated variable.

**Table 7. Multiple Stepwise Regression Analysis Results for Nonfatal Myocardial Infarction and Significant Clinical Variables for the 150 Patients Who Had a Scintigram During Unstable Angina Pectoris**

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>R</th>
<th>R²</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic ECG</td>
<td>0.228</td>
<td>0.228</td>
<td>0.052</td>
<td>0.301</td>
</tr>
<tr>
<td>History of angina with a crescendo pattern</td>
<td>0.179</td>
<td>0.304</td>
<td>0.092</td>
<td>0.305</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>-0.147</td>
<td>0.329</td>
<td>0.108</td>
<td>0.303</td>
</tr>
<tr>
<td>Smoking</td>
<td>-0.051</td>
<td>0.348</td>
<td>0.121</td>
<td>0.302</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>-0.113</td>
<td>0.366</td>
<td>0.134</td>
<td>0.301</td>
</tr>
<tr>
<td>Age</td>
<td>0.071</td>
<td>0.382</td>
<td>0.146</td>
<td>0.300</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.137</td>
<td>0.392</td>
<td>0.154</td>
<td>0.299</td>
</tr>
<tr>
<td>Positive scintigram</td>
<td>0.104</td>
<td>0.400</td>
<td>0.160</td>
<td>0.299</td>
</tr>
</tbody>
</table>

The remaining variables did not significantly increase multiple R² (p < 0.01) or reduce the SEE.

Abbreviations: r = coefficient of correlation between each of the variables and nonfatal myocardial infarction; R = multiple R; R² = the proportion of the variance in the criterion variable nonfatal myocardial infarction, which is accounted for by the stepwise addition of each indicated variable.
patients treated medically, the survival rate was 94% at 1 month, 89% at 6 months, 86% at 12 months, 84% at 24 months, and 83% at 36 months. These survival data are compatible with previously reported series on the natural history of unstable angina pectoris. The cumulative survival of unstable angina patients in the classic study of Gazes et al. involving 140 patients was 82% at 12 months, 75% at 24 months, and 69% at 36 months. Krause and co-workers reported a 1-year survival of 85% in 100 patients with acute coronary insufficiency. Schroeder and associates, in a retrospective study involving 170 patients with prolonged ischemic pain at rest and transient ECG changes admitted to their coronary care unit, reported for their patients a 1-year cumulative survival rate of 90% and a 2-year survival rate of 80%. In the Unstable Angina Pectoris National Cooperative Study Group, the patients treated medically had a survival rate of 93% at 1 year and 91% at 2 years.

Patient selection may explain the differences in survival rates.

Our findings indicate that unstable angina patients at risk for cardiac death at follow-up include those patients who are older, have a long duration of clinical coronary artery disease, ischemic ECG changes and continuing angina during hospitalization, cardiomegaly by chest x-ray, and a history of congestive heart failure. Patients at risk for nonfatal myocardial infarction during the follow-up period include those with ischemic ECG changes and old angina with a crescendo pattern. These findings are consistent with previously reported studies.

It is not surprising that the 43 patients in our study who had the presence of both continuing angina and ischemic ECG changes during their hospitalization had an ominous clinical course, with a survival rate of 74% at 3 months, 65% at 6 months and 58% at 12 months. These survival data for the first year for these 43 patients were similar to the survival data of Gazes’ 56 high-risk patients. Gazes et al. reported a survival rate of 74% at 3 months and 57% at 12 months in their high-risk unstable angina patients, patients with continuing angina after hospitalization, ischemic ECG changes and a history of angina.

The major finding of the present investigation is that patients with positive technetium-99m pyrophosphate myocardial scintigrams during unstable angina have a greater incidence of cardiac death or nonfatal myocardial infarction during a 3-year follow-up period compared with patients with negative scintigrams. At follow-up, 46% of the patients with positive scintigrams had either cardiac death or nonfatal myocardial infarction, compared with 12% with negative scintigrams. Twelve of the 16 cardiac deaths (75%) and seven of the 11 nonfatal myocardial infarctions (64%) in the positive scintigram group occurred.

### Table 8. Incidence of Cardiac Death and Nonfatal Myocardial Infarction in the 150 Patients in Whom Hospital Course, ECG and Technetium-99m Pyrophosphate Scintigraphy Were Assessed

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Continuing angina</th>
<th>Ischemic ECG</th>
<th>Positive scintigram</th>
<th>No. of pts</th>
<th>Cardiac death</th>
<th>Nonfatal AMI</th>
<th>Cardiac death or nonfatal AMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>51</td>
<td>1 §</td>
<td>3 §</td>
<td>4 §</td>
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<tr>
<td>B</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>18</td>
<td>2 11§</td>
<td>0 §</td>
<td>2 11§</td>
</tr>
<tr>
<td>C</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
<td>9</td>
<td>1 11†</td>
<td>0 §</td>
<td>1 11§</td>
</tr>
<tr>
<td>D</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>20</td>
<td>1 5†</td>
<td>3* 15</td>
<td>3 15†</td>
</tr>
<tr>
<td>E</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>12</td>
<td>2 16‡</td>
<td>1 8</td>
<td>3 25§</td>
</tr>
<tr>
<td>F</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
<td>13</td>
<td>3 23</td>
<td>2* 15</td>
<td>4 30§</td>
</tr>
<tr>
<td>G</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>8</td>
<td>1 12‡</td>
<td>2 25</td>
<td>3 37‡</td>
</tr>
<tr>
<td>H</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>19</td>
<td>11 57</td>
<td>7† 36</td>
<td>15 78</td>
</tr>
</tbody>
</table>

*One patient also had a subsequent cardiac death.
†Three patients also had a subsequent cardiac death.
§p < 0.05 vs subgroup H.
¶p < 0.01 vs subgroup H.
*¶p < 0.001 vs subgroup H.

Abbreviations: AMI = acute myocardial infarction.

![Image of survival curves](http://circ.ahajournals.org/)

**Figure 6.** Survival curves for the 19 patients with the combined presence of continuing angina, ischemic ECG and positive scintigram and the 51 patients without these three variables during unstable angina. *p < 0.001.
within 6 months after the diagnosis of unstable angina was established.

The incidence of positive scintigrams during unstable angina in the present investigation was 33%. Investigators have reported an incidence of positive scintigrams varying from 25–42%.5, 6, 8, 10, 12, 15. The scintigraphic pattern of myocardial uptake of technetium-99m pyrophosphate during unstable angina is generally diffuse, similar to that of patients with sub-endocardial infarction.5, 15 Thus, a positive technetium myocardial scintigram with a diffuse abnormality by itself could not differentiate with certainty between patients with a classic subendocardial infarction and patients with unstable angina with no evidence of myocardial necrosis by ECG or enzyme determinations.

What causes positive scintigrams during unstable angina is not known, but may represent scattered areas of myocardial necrosis undiagnosed by serial ECG and routine serum enzyme determinations. Experimental studies indicate that myocardial uptake of technetium-99m pyrophosphate is always associated with myocardial necrosis.53–56 Jaffe et al.16 showed that many patients with positive scintigrams during unstable angina have enzymatic evidence of myocardial necrosis. Using frequent CK and CK-MB isoenzyme determinations, they showed that most patients with positive scintigrams during unstable angina have transient elevations of these enzymes during their hospital course. Also, in some patients, the technetium-99m pyrophosphate myocardial scintigram may be more sensitive for detecting myocardial necrosis than the enzyme diagnosis.

Our data indicate that some unstable angina patients with positive scintigrams probably do have clinically undetected myocardial necrosis. Sixty percent of the patients with positive studies during unstable angina who had serial scintigrams had a negative study at repeat scintigraphy 2–3 weeks later at a time when there was no clinical evidence of acute myocardial necrosis. In our experience, the demonstration of the resolution of an initial scintigraphic abnormality by serial scintigraphy supports the concept that the initial scintigraphic abnormality represents acute myocardial necrosis. We reported that 84% of patients with positive scintigrams during a documented myocardial infarction have an improved or negative scintigram in 2–3 weeks at follow-up scintigraphy.17

Patients with ECG evidence of myocardial ischemia in this study are more likely to have positive scintigrams. Berman and associates were unable to demonstrate positive scintigrams in patients with transient ST-segment depression on their ECGs which occurred during effort angina on the treadmill.20 Thus, patients with unstable angina have varying degrees of myocardial ischemia or injury as determined by the ST-segment shift on their ECGs. The myocardial scintigram may be useful in distinguishing patients with ST-segment depression on their ECGs who have myocardial necrosis during unstable angina from those with ST-segment depression without myocardial necrosis. Bodenheimer and associates20 could not show myocardial necrosis in seven patients with transient ST-segment changes on their ECGs during unstable angina at surgery by transmural biopsies. However, none of their patients had myocardial scintigrams before bypass graft surgery.20

Other mechanisms for positive scintigrams in our unstable angina pectoris patients include persistently positive scintigrams after myocardial infarction, ventricular aneurysm, and persistent blood pool activity.17, 18, 30, 46 A baseline scintigram or serial scintigraphy may be useful for assessing the significance of a positive scintigram in patients with ventricular aneurysm or a history of a myocardial infarction. Some of the positive scintigrams in our patients could have been caused by persistently positive scintigrams after acute myocardial infarction. Eighty-two percent of the patients with positive scintigrams during unstable angina had prior myocardial infarctions, compared with 55% of the patients with negative scintigrams. Patients with persistently positive scintigrams after acute myocardial infarction have a more fulminant clinical course than patients with negative scintigrams.30, 41

Patients with persistently positive scintigrams have an increased incidence of cardiac death, nonfatal myocardial infarction and hospitalization for unstable angina and congestive heart failure.46 Buja et al.41 and Cowley et al.42 suggested that persistently positive scintigrams may be due to slow ongoing necrosis in the area of previous infarction. Patients who had a myocardial infarction within 3 months before admission were excluded from this study. This could exclude patients with recurring angina after infarction who might have had a much higher incidence of either negative or positive (probably negative) scintigrams, and could considerably have changed the look of the total group. Despite quality control of the radionuclide and delayed imaging techniques, some of the positive scintigrams in our patients may have been due to persistent blood pool activity. Nevertheless, the data indicate that a positive scintigram in patients with unstable angina is a marker for increased risk of cardiac death and nonfatal myocardial infarction at follow-up.

An important question raised by these new data is whether the scintigram is more useful prognostically in patients with unstable angina than history, clinical course, ECG and chest x-ray. Noting the contingency coefficients of correlations, the scintigram was the best predictor for cardiac death at follow-up. For nonfatal myocardial infarction, the scintigram was second only to the ECG as the best single predictor. The results of a multiple stepwise regression analysis indicated that the best linear combination of predictors for cardiac death in patients with unstable angina pectoris included patients with continuing angina during hospitalization, ischemic ECG and a long duration of clinical coronary artery disease. The best linear combination of predictors for nonfatal myocardial infar-
tion included patients with ischemic ECG changes and a history of angina with crescendo pattern. The myocardial scintigram added to these predictor variables but was of limited value.

When the results of scintigraphy were added to the two parameters, the presence of continuing angina and ischemic ECG during hospitalization, high- and low-risk unstable angina patients could be identified for cardiac death and nonfatal myocardial infarction at follow-up. The combined presence of continuing angina during hospitalization, ischemic ECG and positive scintigram define high-risk unstable angina patients for cardiac death and nonfatal myocardial infarction. Patients with the absence of these three parameters are low-risk patients. At follow-up, 78% of the high-risk patients had either cardiac death or nonfatal infarction, compared with 7% of low-risk patients. Thus, the scintigram combined with the hospital course and the ECG may be useful in identifying high- and low-risk patients for cardiac death and nonfatal myocardial infarction at follow-up.

Acknowledgment

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References

The Exercise Test in Variant Angina: Results in 114 Patients

Stefano de Servi, M.D., Colomba Falcone, M.D., Antonello Gavazzi, M.D., Antonio Mussini, M.D., Ezio Bramucci, M.D., Maria Teresa Curti, M.D., Carlo Vecchio, M.D., Giuseppe Specchia, M.D., and Piero Bobba, M.D.

Summary

One hundred fourteen patients with variant angina performed bicycle exercise stress tests, and were divided into three groups. Group 1 included 37 patients with a normal exercise test. Coronary arteriography revealed absence of significant coronary stenoses in 18 patients, one-vessel disease in 17 and involvement of two or more vessels in 2. Group 2 consisted of 40 patients who had ST-segment elevation during or just after exercise. Coronary arteriography in these cases revealed absence of significant coronary stenoses in nine patients, one-vessel disease in 18 and disease of two or more vessels in 13. Group 3 included 37 patients who had ST-segment depression during exercise. Absence of coronary artery disease was found in only two patients, one-vessel disease was found in 19 and disease of two or more vessels was found in 16.

Sixty-one patients repeated the exercise test after a mean of 18 months after hospital discharge. Exercise-induced ST-segment elevation was no longer present in surgically or medically treated patients; ST-segment depression was still evident in all the medically treated patients, but was absent in eight of 13 patients who underwent aortocoronary bypass surgery.

Exercise testing can be useful in the follow-up of patients with variant angina and in selecting patients most likely to be helped by bypass surgery.

No Reports in the literature describe the results of exercise testing in a large number of patients with variant angina.1-2 In a recent review of the literature, Weiner et al.8 concluded that half of the patients with variant angina have exercise-induced electrocardiographic changes diagnostic of ischemia; this conclusion challenges the prevailing belief that exercise tolerance is generally preserved in these patients.4-8 In this report, we present the results of exercise testing in 114 patients with variant angina.

Materials and Methods

Between January 1970 and April 1980, we observed 175 patients with Prinzmetal's variant angina. All patients presented with typical chest pain occurring at rest associated with transient ST-segment elevation. In the presence of an old myocardial infarction, as determined by the presence of Q waves on the ECG, the ST elevations were observed not in the leads showing signs of infarction, but in those leads not altered by the infarct.

One hundred fourteen patients could perform a bicycle exercise test in the supine position. Patients...
The high-risk angina patient. Identification by clinical features, hospital course, electrocardiography and technetium-99m stannous pyrophosphate scintigraphy.

H G Olson, K P Lyons, W S Aronow, P J Stinson, J Kuperus and H J Waters

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