Long-term Prognosis for Patients With Variant Angina and Influential Factors

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Two hundred forty-five patients with variant angina were followed for an average of 80.5 months (range, 36–184 months). Survival rate at 1, 3, 5, and 10 years was 98%, 97%, 97%, and 93%, respectively. Survival rate without myocardial infarction at 1, 3, 5, and 10 years was 86%, 85%, 83%, and 81%, respectively. By univariate analysis, ST segment elevation in both the anterior and inferior electrocardiographic leads was the most important factor influencing survival, followed by use of calcium antagonists, left ventricular function, smoking, and alcohol intake. The variables that significantly correlated with survival without myocardial infarction were use of calcium antagonists, left ventricular function, extent and severity of coronary artery disease, coronary artery bypass surgery, and disease activity. Multivariate analysis using the Cox proportional hazards model showed that intake of calcium antagonists, extent and severity of coronary artery disease, and ST segment elevation in both the anterior and inferior leads were significant independent predictors of survival without myocardial infarction. We conclude that long-term prognosis for patients with variant angina is relatively good and that use of calcium antagonists improves it. (Circulation 1988;78:1–9)

Variant angina is characterized by recurrent attacks of chest pain occurring at rest and associated with ST segment elevation on ECG, and its cause is now established to be spasm of a major coronary artery. Calcium antagonists have been shown to be effective and are currently widely used for its treatment. However, the long-term prognosis of this syndrome and factors affecting it are less clear. Several studies have examined the clinical characteristics and the long-term prognosis of patients with variant angina. However, these studies are limited because of either the small number of patients or the short follow-up period or both. Only three studies included more than 100 patients, and even in these studies survival rates were reported for up to only 3–5 years. These studies show that the important factor affecting prognosis for patients with variant angina is the extent and severity of coronary artery disease and that patients are at the highest risk of cardiac death or acute myocardial infarction during the early phase of the follow-up period when disease activity is high.

However, it is not clear from these studies whether the use of calcium antagonists is an important factor in the long-term prognosis for patients because most of the patients in each study either received calcium antagonists or did not; there was no basis for comparison. Moreover, there are still some controversies as to the indication and timing of coronary artery bypass surgery for variant angina, and there are few reports studying the long-term prognosis for patients with variant angina who underwent coronary artery bypass surgery as compared with those who received only drug treatments.

In the present study, we followed 245 consecutive patients with variant angina for periods of 3–15 years (average, 7 years) and examined the factors influencing the long-term prognosis for patients with variant angina, including the use of calcium antagonists and coronary artery bypass surgery. The results show that in addition to the extent and severity of coronary artery disease, intake of calcium antagonists and multivessel coronary spasm are the most important factors influencing the long-term prognosis for patients with variant angina.
Patients and Methods

Patients

Of the 2,087 patients admitted to our hospital who underwent coronary arteriography for suspected ischemic heart disease between August 1971, and September 1983, those who met the following criteria were consecutively included in the present study. These criteria were that 1) the attack occurred at rest and was associated with ST segment elevation of more than 0.2 mV on the ECG, 2) the attack was relieved by sublingual administration of nitroglycerin, and 3) the attack was not associated with elevation of serum cardiac enzymes. Two hundred forty-five patients (12%) met this criteria and were the subjects of the present study. Two hundred fourteen were men and 31 were women, their ages ranging from 34 to 70 years with a mean age of 54.4 years. Fifteen patients had had a myocardial infarction. ST segment elevation on the ECG was noted in the anterior leads in 124 patients, in the inferior leads in 94, and in both the anterior leads and the inferior leads either simultaneously or at different times in the remaining 27. Spontaneous attacks were detected in 211 patients during hospitalization, and attacks were documented only after ergonovine, hyperventilation, treadmill exercise, or methacholine20 during hospitalization at our hospital in the remaining 34 patients.

Coronary arteriography was done with either Sones or Judkins technique. No premedications, including atropine, were given before arteriography to avoid a possible effect on coronary spasm or vasoconstriction.20 After provocation tests for coronary spasm by either ergonovine,5,6 hyperventilation,21 arm exercise,22 methacholine,20 epinephrine,3 or cold pressor test were done, nitroglycerin was given, and coronary arteriography was again performed in multiple projections to evaluate organic stenosis after eliminating the effect of vasoconstriction. Significant organic stenosis was defined as more than 75% stenosis of luminal diameter of three major coronary arteries and more than 50% stenosis of luminal diameter of the left main trunk. A left ventriculogram was filmed in the 30° right anterior oblique projection in all patients.

Ninety-seven patients had no fixed coronary stenosis of more than 75% luminal diameter, 108 had one-vessel disease, 24 had two-vessel disease, 13 had three-vessel disease, and 3 had left main trunk disease. The left ventriculogram was normal in 230 patients and revealed segmental wall motion abnormalities in 15 patients. Coronary spasm occurred spontaneously in 22 patients and was induced by either ergonovine, methacholine, epinephrine, hyperventilation, arm exercise,22 or cold pressor test in 158 patients during coronary arteriography. Of the 27 patients with ST segment elevation in both the anterior and inferior leads, eight patients had one-vessel disease, and the remaining 19 patients had no fixed stenosis of more than 75% luminal diameter. Spasm in more than one major coronary artery was demonstrated in 22 patients by coronary arteriography.

Treatment

Drug treatment was applied initially to all patients. Sixty-nine patients did not receive calcium antagonists but did receive long-acting nitrates or so-called coronary vasodilators such as dipyridamole or trimetazidine as the initial treatment because calcium antagonists were either not available or not known to be effective for the treatment of variant angina during the first part of this study or because spontaneous attacks were infrequent. The remaining 176 patients were treated initially with diltiazem (n = 120), nifedipine (n = 20), or a combination of diltiazem and nifedipine (n = 36). Thirty-four patients underwent coronary artery bypass surgery because of the presence of more than 90% organic stenosis of luminal diameter. They also received drug therapy (19 received calcium antagonists, and the remaining 15 received other drugs) as the initial treatment. The usual drug doses were 120–360 mg daily for diltiazem and 40–80 mg daily for nifedipine.

Follow-up

After discharge, the patients were followed at our hospital or at related clinics every 1–2 months. At each visit, standardized questions were asked, physical examinations were done, and a standard 12-lead ECG was taken at 3-month intervals. Those who did not come for a follow-up check were followed by telephone interviews with the patients or with their family. Five patients underwent percutaneous transluminal coronary angioplasty (PTCA) during the follow-up period. Two patients who were taking nifedipine switched to diltiazem because of

| Table 1. Clinical and Angiographic Variables of 245 Patients With Variant Angina |
|-----------------------------|-----------------------------|-----------------------------|
| Variables                   | Subsets                     | No. of patients %            |
| Coronary artery disease     | No stenosis >75%            | 97                          |
|                             | One-vessel disease          | 108                         |
|                             | Multivessel disease         | 40                          |
| Calcium antagonist           | Yes                         | 176                         |
|                             | No                          | 69                          |
| Site of ST elevation         | Anterior                    | 124                         |
|                             | Inferior                    | 94                          |
|                             | Both                        | 27                          |
| Disease activity             | Spontaneous attacks         | 211                         |
|                             | Provoked attacks only       | 34                          |
| Left ventricular function    | Normal                      | 230                         |
|                             | Abnormal                    | 15                          |
| Smoking                     | Yes                         | 79                          |
|                             | No                          | 154                         |
| Alcohol                     | Yes                         | 128                         |
|                             | No                          | 105                         |
| Coronary artery bypass surgery | Yes                        | 34                          |
|                             | No                          | 211                         |
pitting edema, and two patients who were taking diltiazem switched to nifedipine because of brady-cardia and atrioventricular block.

Data Analysis

Myocardial infarction was diagnosed by ischemic chest pain lasting more than 30 minutes followed by appearance of a new Q wave or ST-T waves changes on the ECG and elevation of serum cardiac enzymes. Sudden death was defined as death within 1 hour after the onset of symptoms or, in the case of unwitnessed death, after the victim has been seen to be well within the preceding 12 hours. Follow-up time was calculated from the date of hospital admission. The outcome events considered were cardiovascular death (sudden death and death due to acute myocardial infarction) and total cardiac events (cardiovascular death and nonfatal myocardial infarction). During the study, one patient was unavailable for follow-up, eight patients died from noncardiac causes, and five patients underwent PTCA. These patients were considered to be unavailable for follow-up at the time of death or PTCA. Eight variables were selected for analysis based on their possible relevance to survival and survival without myocardial infarction as judged from previous studies\textsuperscript{16–19} and our clinical experiences. These variables were extent and severity of coronary artery disease, use of calcium antagonists, site of ST segment elevation, disease activity, left ventricular function, smoking of more than one pack of cigarettes per day during the follow-up, alcohol intake of more than 28 g/day during the follow-up, and coronary artery bypass surgery. Table 1 shows these variables and the incidence of their subsets. We grouped the patients according to who was treated with calcium antagonists initially and who was not. To determine disease activity, we grouped the patients into those who had had spontaneous attacks during hospitalization and those who had had only provoked attacks during hospitalization. Curves for both sur-

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
Variables & $\chi^2$ & df & $p$ \\
\hline
Site of ST elevation & 15.75 & 2 & 0.0004* \\
Calcium antagonist & 9.19 & 1 & 0.0024* \\
Left ventricular function & 9.16 & 1 & 0.0025* \\
Smoking & 7.66 & 1 & 0.0056* \\
Alcohol & 7.23 & 1 & 0.0072* \\
Disease activity & 2.15 & 1 & 0.1427 \\
Coronary artery disease & 0.85 & 2 & 0.6532 \\
Coronary artery bypass surgery & 0.00 & 1 & 0.9855 \\
\hline
\end{tabular}
\caption{Predictors of Survival in Patients With Variant Angina (Log Rank Test)}
\end{table}
FIGURE 2. Plots of five variables correlated significantly with survival by univariate analysis. Panel A: ST segment elevation in both the anterior and inferior leads. Panel B: Intake of calcium antagonists. Panel C: Left ventricular function. Panel D: Smoking during follow-up. Panel E: Alcohol intake during follow-up. Vertical bars indicate standard errors; anterior, patients with attack with ST segment elevation in anterior ECG leads; inferior, patients with attack with ST segment elevation in inferior ECG leads; both, patients with attack with ST segment elevation in both anterior and inferior ECG leads; LV, left ventricle. (See text for further details.)
Figure 3. Plots of five variables correlated significantly with survival without myocardial infarction by univariate analysis. Panel A: Intake of calcium antagonists. Panel B: Left ventricular function. Panel C: Extent and severity of coronary artery disease. Panel D: Coronary artery bypass surgery. Panel E: Disease activity. Vertical bars indicate standard errors; LV, left ventricle; MI, myocardial infarction. (See text for further details.)
survival and survival without myocardial infarction rates were constructed by means of the standard Kaplan-Meier life-table analysis. The influence of potentially important prognostic variables was assessed with a univariate analysis using log rank test. A multivariate analysis with Cox proportional hazards model was done to determine whether the variables that significantly correlated with outcome were independent or interdependent. \( p<0.05 \) was considered significant.

### Results

#### Clinical Characteristics of Patients

Clinical patient characteristics selected as possible factors influencing long-term prognosis are shown in Table 1. As compared with previous studies, there were fewer patients with multivessel disease and far fewer patients with previous myocardial infarction or left ventricular dysfunction in our series. The ratio of patients who were not treated initially with a calcium antagonist (diltiazem or nifedipine) was also lower. To be noted is that 27 out of the 245 patients (11%) had an attack with ST segment elevation in both the anterior and inferior electrocardiographic leads either simultaneously or at different times.

#### Long-term Prognosis

All patients were followed for at least 3 years or until death. During the follow-up period of 36–184 months (mean, 80.5 months), 12 of the 245 patients died of cardiovascular disease. Seven of these patients died suddenly, and the remaining five died of acute myocardial infarction. Thirty-two patients developed nonfatal acute myocardial infarction. Fifteen of the 32 myocardial infarctions (47%) and five of the 12 deaths (42%) occurred during the first 3 months of follow-up.

Figure 1 shows the survival and survival without infarction rates for the whole group. The overall survival rate was 98%, 97%, 97%, and 93% at 1, 3, 5, and 10 years, respectively. The survival without infarction rate was 86%, 85%, 83%, and 81% at 1, 3, 5, and 10 years, respectively.

#### Survival

The variables that correlated with survival and the statistical significance of the observed differences by univariate analysis are shown in Table 2. The variable that predicted survival best was the appearance of ST segment elevation in both the anterior and inferior electrocardiographic leads during the attack. Five of the seven sudden deaths occurred in patients who had an attack with ST segment elevation in both the anterior and inferior leads. Intake of calcium antagonists, left ventricular function, smoking, and intake of alcohol also correlated with survival by univariate analysis. Survival curves for each of these variables are shown in Figure 2. Four of the seven sudden deaths occurred after taking large amounts of alcohol.

It was not possible to determine which of these variables were independent predictors of survival because the number of cardiac deaths was small (12 patients) and multivariate analysis could not be done.

#### Survival Without Myocardial Infarction

The variables that correlated with survival without myocardial infarction and the statistical significance of the observed differences by univariate analysis are shown in Table 3. Intake of calcium antagonists, left ventricular function, extent and severity of coronary artery disease, coronary artery bypass surgery as the initial treatment, and disease activity were predictors of survival without myocardial infarction. Figure 3 illustrates the survival without myocardial infarction rate for each of these variables. Myocardial infarction occurred in 11 of the 34 patients who underwent coronary artery bypass surgery as an initial treatment, and nine of the 11 (82%) developed myocardial infarctions during or within 1 week of the operation and were thus perioperative. Thereafter, only two nonfatal myo-

### Table 3. Predictors of Survival Without Myocardial Infarction in Patients With Variant Angina (Log Rank Test)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survival without myocardial infarction</th>
<th>( \chi^2 )</th>
<th>df</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium antagonist</td>
<td></td>
<td>8.79</td>
<td>1</td>
<td>0.0030*</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td>5.90</td>
<td>1</td>
<td>0.0152†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td>7.81</td>
<td>2</td>
<td>0.0201†</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td></td>
<td>5.13</td>
<td>1</td>
<td>0.0236†</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td>3.84</td>
<td>1</td>
<td>0.0498†</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>2.85</td>
<td>1</td>
<td>0.0913</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td>1.86</td>
<td>1</td>
<td>0.1729</td>
</tr>
<tr>
<td>Site of ST elevation</td>
<td></td>
<td>1.63</td>
<td>2</td>
<td>0.4431</td>
</tr>
</tbody>
</table>

df, degrees of freedom.

\*\( p<0.01; \) †\( p<0.05. \)

### Table 4. Predictors of Survival Without Myocardial Infarction in Patients With Variant Angina (Cox Proportional Hazards Model)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survival without myocardial infarction</th>
<th>( \chi^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium antagonist</td>
<td></td>
<td>8.95</td>
<td>0.0028*</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td></td>
<td>7.04</td>
<td>0.0080*</td>
</tr>
<tr>
<td>Site of ST elevation</td>
<td></td>
<td>3.99</td>
<td>0.0459†</td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td>2.53</td>
<td>0.1118</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td>1.44</td>
<td>0.2301</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>1.28</td>
<td>0.2587</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td></td>
<td>0.83</td>
<td>0.3616</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td>0.71</td>
<td>0.4004</td>
</tr>
</tbody>
</table>

\*\( p<0.01; \) †\( p<0.05. \)
cardiac infarctions occurred in this group during the entire follow-up period. However, multivariate analysis using the Cox proportional hazards model indicated that only intake of calcium antagonists, extent and severity of coronary artery disease, and ST segment elevation in both the anterior and inferior electrocardiographic leads were significant independent predictors of survival without myocardial infarction when all of the eight variables were analyzed jointly (Table 4).

Discussion

The present study provides the clinical characteristics and long-term prognosis of Japanese patients with variant angina. Both survival and survival without myocardial infarction rates in our series were better than those reported previously by Severi et al,16 Waters et al,17 Mark et al,18 and Walling et al.19 In these previous studies, the survival rate at 1 and 3 years ranged from 88% to 95% and from 84% to 92%, respectively, and the survival without myocardial infarction rate at 1 and 3 years ranged from 70% to 83% and from 63% to 77%, respectively. This difference is probably due to the fact that the percentage of patients with multivessel disease and/or impaired left ventricular function was smaller, and the percentage of patients who received a calcium antagonist (diltiazem or nifedipine) as the initial treatment was higher in our series. Our results are in agreement with those of the recently published multicenter study from Japan.26 However, our study cannot be accurately compared with the Japanese multicenter study because the latter did not estimate survival and survival without myocardial infarction rates with a life-table analysis.

The 5-year survival rate in our series was better than the 92% survival rate of medically treated patients with stable angina from the Coronary Artery Surgery Study (CASS) registry27 and was substantially better than the 78% survival rate of medically treated patients with coronary artery disease from the Duke data bank.28 The 5-year survival without myocardial infarction rate in our series was comparable with the 82% rate from the CASS registry27 and was substantially better than the 64% rate from the Duke data bank.28 Mark et al18 reported that patients with variant angina had a higher probability of death and nonfatal myocardial infarction than did patients with nonvariant coronary disease if other prognostic factors were constant, but our study could not address this problem because important prognostic factors, including extent and severity of coronary artery disease and intake of calcium antagonists, were different in our series from those in the CASS registry or Duke data bank.

Both cardiac death and nonfatal myocardial infarction occurred most often in the first 3 months of follow-up in our series. This pattern is similar to those reported by other investigators. Severi et al16 Waters et al17 and Mark et al18 observed 42%, 57%, and 50% of deaths before hospital discharge and during 3 and 6 months of follow-up, respectively, and 87%, 91%, and 86% of nonfatal infarctions during 1 month, 3 months, and 1 month of follow-up, respectively. The result from the Japanese multicenter study26 is also similar. Thus, the patient with variant angina is at the highest risk of both cardiac death and nonfatal myocardial infarction within the first few months after being hospitalized for evaluation. This is probably due to the fact that most patients had increasing severity or frequency of angina, or "unstable angina," when they were admitted to the hospital.

It is to be noted that this initial high-risk period in variant angina is similar to that following acute myocardial infarction29 or coronary angioplasty.30

Factors Influencing Survival

In our series, ST segment elevation in both the anterior and inferior electrocardiographic leads during an attack was the most significant predictor of survival by univariate analysis. Five of the seven sudden deaths occurred in patients with ST segment elevation in both the anterior and inferior leads, and spasm of both the right and left coronary artery was demonstrated by coronary arteriography in four of the five patients. Thus, sudden death in these patients probably resulted from severe and extensive myocardial ischemia associated with lethal arrhythmias due to multivessel coronary spasm.31 Survival was better in patients who were initially treated with a calcium antagonist (diltiazem or nifedipine) than those who were not treated with these drugs. Survival also correlated with left ventricular function.

Also to be noted is that survival was better in patients who did not smoke or take alcohol during the follow-up period. This could be related to the fact that both smoking32 and alcohol intake33 may provoke coronary spasm in patients with variant angina.

Previous studies16-18 indicated that the extent and severity of organic coronary stenosis were the most important predictors of survival in patients with variant angina. However, in the present study, there was no significant association between extent and severity of coronary artery disease and survival. Indeed, six of the 12 deaths (50%) occurred in patients who had no significant coronary stenosis, and all of these deaths were sudden. Both the study by Miller et al34 and the Japanese multicenter study26 also indicated that there was no association between sudden death and extent and severity of coronary artery disease in patients with variant angina. Although there are some studies11,12 suggesting that prognosis for patients with variant angina without significant coronary stenosis is good, our study shows that this is not necessarily so, particularly in patients with multivessel coronary spasm.
Factors Influencing Survival Without Myocardial Infarction

Intake of calcium antagonists, left ventricular function, extent and severity of coronary artery disease, coronary artery bypass surgery, and disease activity were significant factors influencing survival without myocardial infarction rates by univariate analysis.

Survival without myocardial infarction rates were lower in patients who underwent coronary artery bypass surgery as the initial treatment compared with those who did not. This is probably in part because all of the patients who underwent surgery had significant coronary stenosis, while 56% of those who did not had no significant coronary stenosis. Thus, coronary artery bypass surgery was not a significant independent predictor of survival without myocardial infarction when assessed using multivariate analysis. Most myocardial infarction developed during the time of surgery, and prognosis after hospital discharge was good. A similar pattern has been noted in previous studies.18,35

Multivariate analysis indicated that only intake of calcium antagonists, extent and severity of coronary artery disease, and ST segment elevation in both the anterior and inferior leads were significant independent predictors of survival without myocardial infarction. The previous studies16–18 indicated that the single most important prognostic factor for survival without myocardial infarction in patients with variant angina was the extent and severity of coronary artery disease. Our present study confirms these results. In addition, our study shows that intake of calcium antagonists (diltiazem or nifedipine) is a significant independent predictor of survival without myocardial infarction and improves long-term prognosis in patients with variant angina, as suggested by the previous studies.14,26 Our study also reveals that multivessel coronary spasm as indicated by ST segment elevation in both the anterior and inferior leads during an attack significantly influences the long-term prognosis for patients with variant angina.

Limitations

In the present study, patients were not randomized with respect to intake of calcium antagonists. Most of the patients who did not take calcium antagonists belonged in the first part of the study. No other changes in therapy occurred over the study period except for the introduction of PTCA, which was done in only five of the study patients. These five patients were withdrawn from the follow-up at the time of the procedure. Nevertheless, unrecognized factors may have contributed to the differences observed between the two treatment groups. Because the number of patients with variant angina is not large and because short-term beneficial effects of calcium antagonists on variant angina are established,6–10 it is not feasible or necessary to do a prospective, randomized placebo-controlled study to prove that calcium antagonists improve the long-term prognosis for patients with variant angina.

Clinical Implications

Cardiac death and myocardial infarction occurred most often within 3 months of follow-up when disease activity was high. The incidence of perioperative myocardial infarction was also high during this period. Thus, aggressive therapy using calcium antagonists should be done during this period to prevent cardiac death and acute myocardial infarction. Coronary artery bypass surgery should not be done as the initial therapy during this period because of the danger of perioperative myocardial infarction. Calcium antagonists should not be discontinued, particularly in those patients with multivessel coronary spasm. And smoking and alcohol intake had adverse effects on survival in patients with variant angina; advice should be given to these patients regarding these habits.

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27. CASS principal investigators and their associates: Myocardial infarction and mortality in the Coronary Artery Surgery Study (CASS) randomized trial. N Engl J Med 1984;310:750–758

KEY WORDS • smoking • multivessel coronary spasm • calcium antagonists • sudden death
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