Factors influencing the long-term prognosis of treated patients with variant angina

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ABSTRACT To determine the prognosis of variant angina and the factors influencing it, 169 consecutive patients hospitalized in our coronary unit were followed for a mean of 15.3 months (range 1 to 68). Survival at 1, 2, and 3 years was 95%, 90%, and 87%, respectively; survival without myocardial infarction was 80%, 78%, and 75%. Twenty of the 22 myocardial infarctions and eight of the 14 deaths occurred within the first 3 months. Mantel-Haenszel log-rank analysis demonstrated that coronary disease, ventricular function, and the degree of disease activity were significant interdependent variables that influenced both survival and survival without infarction. At 1, 2, and 3 years, survival for patients with multivessel disease was 81%, 76%, and 66%; for patients with one-vessel disease, 97%, 92%, and 92%; and for patients without stenoses ≥ 70%, 98% at each year (p = .0003). Survival without infarction at 1 year was 88% in patients with no stenoses ≥ 70% and 82% in patients with single-vessel disease; it did not change thereafter in either group, but was 62%, 58%, and 50% at 1, 2, and 3 years in patients with multivessel disease (p = .001). Treatment did not influence survival in any subgroup (only 14 patients died overall) or survival without infarction in patients with multivessel disease. However, in patients without multivessel disease, treatment with nifedipine, diltiazem, and verapamil improved survival without infarction compared to treatment with perhexiline maleate or long-acting nitrates alone (92% vs 67% at 1, 2, and 3 years; p < .005). Thus in addition to preventing angina, nifedipine, diltiazem, and verapamil appear to reduce complications in patients with variant angina without multivessel disease.


PROGNOSIS has been well defined in most subgroups of patients with coronary artery disease. However, the natural history of variant angina is unclear because the syndrome is characterized by frequent spontaneous exacerbations and remissions and because, except for the series described by Maseri et al.1 and Severi et al.,2 most reports involve small numbers of patients, heterogeneous treatment, or different selection criteria.3–14 During a recent 5 year period, 169 patients with variant angina were hospitalized at our institution. All but seven underwent coronary arteriography and all survivors were seen at regular intervals after discharge at our variant angina clinic. The purpose of this article is to describe the prognosis of these patients and to define the factors that influence prognosis.

Methods

Patients. The diagnosis of variant angina was made in patients meeting all of the following criteria: (1) burning or squeezing retrosternal chest pain at rest, (2) relief of the pain by nitroglycerin in less than 5 min, (3) ST segment elevation of at least 2 mm not present on the baseline electrocardiogram (ECG) but documented during pain and disappearing with relief of pain, and (4) no subsequent evidence of myocardial necrosis. Between March 1976 and August 1981, 169 patients meeting these criteria were hospitalized at the Montreal Heart Institute.

The mean age of the patients was 51 years (range 24 to 71); 117 were men and 52 were women. Thirty patients had previously had a myocardial infarction, 11 had undergone coronary artery bypass surgery,15 and six had had percutaneous transluminal coronary angioplasty.16 Effort angina was present in 89.17 ST segment elevation was noted at the anterior electrocardiographic leads in 96 patients and at the inferior leads in 73. Attacks were documented in 47 patients during hospitalization only after ergonovine administration; spontaneous attacks were detected in hospital in the other 122 patients.

Patient management. Patients were hospitalized in the coronary care unit, where they underwent continuous electrocardiographic monitoring for at least 3 days. A complete ECG was recorded during episodes of angina at rest when possible. Coro-
Coronary arteriography was performed by a percutaneous transfemoral approach with preformed catheters, and routine filming of sagittally angulated views of the left coronary artery. Patients were not routinely given nitroglycerin before angiography, but if coronary stenoses were present, the involved vessels were restudied in multiple views after nitroglycerin administration. Coronary arteriography was not performed in seven patients who either had associated life-threatening noncardiac illness or developed myocardial infarction soon after admission to hospital. In all but eight of the patients who underwent coronary arteriography, a left ventricular angiogram was filmed in the 30 degree right anterior oblique view.

In 63 patients no fixed coronary stenosis > 70% of the luminal diameter was seen at coronary arteriography; 59 patients had one- vessel disease > 70% and 40 had multivessel involvement. Results of left ventriculography were normal in 114 patients and revealed a segmental wall motion abnormality in 40, hypokinesis in 16, akinesis in 20, and dyskinesis in four. Coronary artery spasm developed spontaneously during arteriography in 31 of the 162 patients. Ergonovine testing was rarely done during coronary arteriography. After arteriography an ergonovine test was performed in the coronary care unit according to a defined protocol in patients with suspected but unproven variant angina. Patients with documented variant angina did not undergo ergonovine testing for diagnostic purposes; however, to assess the effect of treatment with calcium antagonist drugs, some of these patients underwent testing before and during treatment according to a research study protocol.

Coronary artery bypass surgery, with or without plexectomy, was performed as initial treatment in 11 patients and was done during the follow-up period in seven others. Drug treatment was applied initially to the other 158 patients. During the first part of the study period, perhexiline maleate was the only calcium antagonist drug available to us; therefore, 45 patients were initially treated with this drug24 (n = 29) or with long-acting nitrates alone (n = 16). The remaining 113 patients were initially treated with nifedipine (n = 38), diltiazem (n = 32), or verapamil (n = 17) or with combinations of these drugs (nifedipine and diltiazem, n = 25; nifedipine and verapamil, n = 1). Long-acting oral or topical nitrates were added if symptoms persisted on treatment. The usual drug doses were 100 to 400 mg twice daily for perhexine maleate, 20 mg four times daily for nifedipine, 120 mg three times daily for diltiazem, 160 mg three times daily for verapamil, 30 mg four times daily for isosorbide dinitrate, and 2 inches four times daily for nitroglycerin ointment.

After discharge, each patient returned to a special hospital clinic at 1 month, 3 months, and every 3 months thereafter. At each visit a standardized questionnaire, physical examination, and ECG were recorded. Calcium antagonists were eventually discontinued in 45 patients, because of serious side effects from perhexiline maleate in eight24 and because no angina had occurred during several months of treatment in 37 others.

Data analysis. Myocardial infarction was diagnosed in patients who developed symptoms of definite or probable infarction (Minnesota code criteria26.27) or who experienced myocardial ischemic pain lasting longer than 30 min followed by confirmatory cardiac enzyme or isoenzyme abnormalities. During the study, four patients were unavailable for follow-up; another patient who died from a noncardiac cause (suicide) was also considered to be unavailable for follow-up.

For the entire population, curves for both survival and survival without myocardial infarction were constructed by means of the standard life-table analysis.28 The influence of clinical and angiographic variables on prognosis was assessed with a Mantel-Haenszel log-rank analysis.29 A multivariate analysis was performed to determine whether the variables that significantly correlated with outcome were independent or interdependent.

Table 1 lists the variables that were studied and their subsets. As an index of disease activity, we classified patients into three groups: those in whom attacks were rare and could only be documented by ergonovine provocation, and those with and without serious arrhythmias during attacks, since such arrhythmias may be an indicator of more severe ischemia and a worse prognosis.30 Serious arrhythmias were defined as ventricular fibrillation, ventricular tachycardia, ventricular couplets or bigeminy, second or third degree atrioventricular block, and asystole.30

Results

During a mean follow-up period of 15.3 months (range 1 to 68), 14 of the 169 patients died and 22 others developed myocardial infarction. Twenty of the 22 myocardial infarctions and eight of the 14 deaths occurred during the first 3 months, including seven deaths and 12 infarctions within 1 month. Six of the 14 deaths were sudden and eight were in-hospital complications of myocardial infarction. Figure 1 illustrates the curves for survival and survival without myocardial infarction.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subsets</th>
<th>Patient/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery</td>
<td>Disease</td>
<td>Subsets</td>
</tr>
<tr>
<td>No stenosis &gt; 70%</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Disease activity</td>
<td>Arrhythmias during attacks</td>
<td>57</td>
</tr>
<tr>
<td>No arrhythmias during attacks</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Provoked attacks only</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>Normal</td>
<td>114</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>40</td>
</tr>
<tr>
<td>Initial treatment</td>
<td>Nifedipine, diltiazem, verapamil</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>Other medical treatment</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>Bypass surgery ± plexectomy</td>
<td>11</td>
</tr>
<tr>
<td>Age</td>
<td>20-39 yr</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>40-59 yr</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>60-79 yr</td>
<td>41</td>
</tr>
<tr>
<td>Duration of rest angina</td>
<td>&lt; 1 mo</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>1 to 3 mo</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 mo</td>
<td>47</td>
</tr>
<tr>
<td>Site of ST elevation</td>
<td>Anterior</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Inferior</td>
<td>73</td>
</tr>
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</table>

A The total for each variable is not 169 because of seven patients without coronary arteriography, 15 without left ventriculography, and four in whom the duration of rest angina could not be accurately determined. The classification of disease activity is based on our previous study, which showed that arrhythmias during attacks were an indicator of more severe ischemia.30

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FIGURE 1. Survival and survival without myocardial infarction for the entire patient population. The number of patients completing each follow-up interval without an end-point event are listed. Eight of the 14 deaths and 20 of the 22 myocardial infarctions occurred within the first 3 months.

Survival. The clinical and angiographic factors that correlated with survival and survival without infarction and the statistical significances of the observed differences are listed in table 2. The strongest predictor of survival was coronary artery disease. Thirteen deaths occurred in the 162 patients who had coronary arteriography: one in the 63 with no stenoses $\geq 70\%$ (1.6%), three in the 59 with single-vessel disease (5.1%), and nine in the 40 with multivessel disease (22.5%). Left ventricular function and the degree of disease activity also correlated with survival by univariate analysis, but a multivariate analysis indicated that these two variables correlated significantly with coronary artery disease and were thus not independent predictors of survival.

Survival curves are illustrated for each of these three variables in figure 2. At 1, 2, and 3 years, survival for patients with multivessel disease was 81%, 76%, and 66%, respectively; for patients with one-vessel disease, 97%, 92%, and 92%, respectively; and for patients without stenoses $\geq 70\%$, 98% at each year. The degree of disease activity correlated with survival because no deaths occurred in the subset of 47 patients in whom attacks could be documented only by provocative testing; only four of these 47 had multivessel disease, 19 had single-vessel involvement, and 24 had no stenoses $\geq 70\%$. Survival was similar in patients with and without arrhythmias during attacks. Patients with normal left ventricular function had survival rates of 97%, 95%, and 91% at 1, 2, and 3 years compared with 88%, 84%, and 84% in those with abnormal left ventricular function.

Survival without myocardial infarction. Coronary artery disease, the degree of disease activity, and left ventricular function also correlated with the other end-point studied, survival without myocardial infarction (table 2). Again, coronary artery disease was the strongest predictor statistically. Multivariate analysis indicated that disease activity and left ventricular function were dependent on coronary artery disease and were thus not independent predictors of survival.

Curves for survival without infarction are illustrated for each of these three variables in figure 3. Survival without infarction at 1 year was 88% in patients with no stenoses $\geq 70\%$ and 82% in patients with single-vessel disease; it did not change thereafter in either group, but was 62%, 58%, and 50% at 1, 2, and 3 years in patients with multivessel disease. Myocardial infarction occurred in only two of the 47 patients whose attacks could be documented only by provocative testing. Survival without infarction at 1 year was 87% with normal and 71% with abnormal ventricular function.

The risk of myocardial infarction with survival for at least 1 month thereafter was 6/63 (9.5%) for patients without stenoses $\geq 70\%, 7/59$ (11.9%) for patients with one-vessel disease, and 8/40 (20%) for those with multivessel disease (one tail, $p < .05$). As noted previously, all but two of the myocardial infarctions occurred within the first 3 months of follow-up.

Effect of treatment. Treatment did not influence over-

### TABLE 2

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Survival</th>
<th>Survival without infarction</th>
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</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
<td>$\chi^2$</td>
<td>p value</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14.7</td>
<td>.0003</td>
</tr>
<tr>
<td>Disease activity</td>
<td>5.7</td>
<td>.03</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td>3.0</td>
<td>.04</td>
</tr>
<tr>
<td>Initial treatment</td>
<td>0.89</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of rest angina</td>
<td>0.81</td>
<td>NS</td>
</tr>
<tr>
<td>Site of ST elevation</td>
<td>0.17</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mantel-Haenszel log-rank analysis. Degrees of freedom = 2 for all variables except left ventricular function and site of ST elevation, in which degrees of freedom = 1. One-tailed p values are listed for coronary artery disease, disease activity, and left ventricular function; two-tailed p value for treatment. NS = p > .1.*
all survival but significantly affected survival without infarction (figure 4). The number of patients treated initially with bypass surgery was too small to assess. Survival without infarction at 1 year was 87% in patients treated with nifedipine, diltiazem, and verapamil, compared with 61% in patients treated with perhexiline maleate or nitrates alone. In patients with multivessel disease, treatment did not influence survival without infarction (χ² = .17, p = NS). In patients without stenoses ≥ 70%, survival without infarction at 1, 2, and 3 years was 93% with nifedipine, diltiazem, and verapamil, compared with 77% with perhexiline maleate or nitrates alone. Although the risk ratio between the two groups is greater than 3:1, this difference does not attain statistical significance (χ² = 2.85; two tail, p = .09). In patients with one-vessel involvement, survival without infarction at 1, 2, and 3 years was 90% with nifedipine, diltiazem, and verapamil compared with 50% with other medical treatment (χ² = 9.11, p < .005). Similarly, when all patients without multivessel disease are combined, the difference between the two groups at 1, 2, and 3 years is 92% vs 67% (p < .005). The other variables did not account for these differences.

Discussion

This study defines prognosis and the factors influencing prognosis for patients with variant angina. Survival at 1, 2, and 3 years for all patients was 95%, 90%, and 87%; however, by 1 year 20% of the group had suffered a myocardial infarction or death. Twenty of the 22 infarctions occurred within the first 3 months and none occurred after the first year. In a comparably sized series of variant angina patients, Maseri et al.¹ and Severi et al.² observed a similar pattern: five of their 138 patients died and 28 others developed myo-
cardiac infarction during the first month, but thereafter only seven cardiac deaths and four infarctions occurred during a follow-up of at least 2 years.

In most subsets of patients undergoing coronary arteriography, particularly those with stable angina, the subsequent risk for infarction or death remains relatively unchanged from year to year. The huge decrease after 3 months in the risk of infarction for variant angina patients suggests that some factors active early in the disease later disappear or that the population is composed of two subgroups with markedly different outcomes, with the smaller subgroup invariably progressing to infarction.

The extent and severity of organic coronary stenoses influence survival after myocardial infarction and in stable and unstable angina. This variable was also the strongest predictor of survival and survival without infarction in this study. The outcome for patients with one-vessel disease was similar to that for patients with no stenoses $\geq 70\%$ and markedly better than that in patients with multivessel disease, both for death and myocardial infarction. These results cannot be accurately compared with those of the study of Severi et al. because they considered a stenosis $\geq 50\%$ as significant, because 31 of their 138 patients did not undergo coronary arteriography, and because only nine of the 107 with arteriography had no lesions $\geq 50\%$. Nevertheless, their patients with multivessel disease had a higher incidence of both death and myocardial infarction than their combined group with one-vessel disease or no significant stenoses.

Left ventricular function is an independent predictor of prognosis in medically treated patients with coronary disease; however, its influence is most marked when severe dysfunction is present, an uncommon finding in variant angina. In the study of Severi et al., the combined incidence of death and myocardial infarction was significantly greater in the 24 patients with diffuse hypokinesis, akinesis, or aneurysm compared with the 75 with localized hypokinesis or normal left ventriculograms. In our study, left ventricular function correlated weakly with both survival and survival without infarction, but this association was not independent of coronary artery disease.
PATHOPHYSIOLOGY AND NATURAL HISTORY—VARIANT ANGINA

A abrupt changes in the frequency of attacks and spontaneous remissions occur commonly in patients with variant angina. Disease activity is difficult to assess because electrocardiographic monitoring covers only brief periods and because coronary spasm often causes asymptomatic myocardial ischemia or angina without objective evidence of ischemia. Therefore, as an index of disease activity, we classified patients into three groups: those in whom attacks were rare and could not be documented in hospital except with ergonovine provocation, and those with and without serious arrhythmias during attacks. Previous studies suggest that the occurrence of arrhythmias during variant angina episodes may be an indicator of more severe ischemia and a worse prognosis. In this study, patients with and without arrhythmias during attacks had similar curves both for survival and survival without infarction. The third group, those with attacks documented only with provocative testing, had a much better outcome: no deaths and only two myocardial infarctions occurred in these 47 patients. The low prevalence of multivessel disease in this group (4/47) helps to explain their better prognosis.

Effect of treatment. Does treatment with calcium antagonists reduce the risk of myocardial infarction and death in variant angina? Variant angina episodes decrease markedly or disappear completely in most patients treated with these drugs. However, such clinical improvement does not remove the risk for myocardial infarction and death; in fact, variant angina attacks decrease in number or disappear entirely during treatment in most patients who develop these complications.

In the study of Severi et al., nearly all patients were treated with verapamil; their good long-term prognosis despite a high prevalence of organic coronary disease contrasts with the poor prognosis noted in reports in which calcium antagonists were not used. One possible explanation for this difference is that calcium antagonists reduce the incidence of myocardial infarction and death.

In this study, treatment with nifedipine, diltiazem, and verapamil did not improve survival alone but significantly improved survival without infarction compared to treatment with perhexiline maleate or nitrates alone (p = .008). Multivariate analysis demonstrated that this difference did not occur in patients with multivessel disease. In patients without stenoses ≥ 70% a greater than threefold difference was present but did not attain statistical significance (death or myocardial infarction occurred in only seven of the 63 patients without stenoses ≥ 70%). In patients with one-vessel disease the difference between the two treatment groups at 1, 2, and 3 years was 90% vs 50% (p < .005); in all patients without multivessel disease, the difference was 92% vs 67% (p < .005).

These findings should not be accepted as definitive because of limitations in our study. Patients were not randomly assigned to the treatment groups. Those who received perhexiline maleate or long-acting nitrates alone were treated during the first 2 years of the study; thereafter all medically treated patients received nifedipine, diltiazem, or verapamil. Thus the differences in prognosis between the two groups could theoretically have been caused by inapparent changes in the patient population or an overall improvement in patient management. On the other hand, larger numbers might show that treatment affects survival as well as survival without infarction; only 14 of our patients died and only six of these deaths were sudden. Effective treatment would logically be expected to prevent sudden deaths caused by arrhythmias during attacks. Conclusive proof that the newer calcium antagonists reduce complications compared with nitrates alone or no treatment would require a large randomized study.

Nevertheless, the available data suggest that all patients with newly diagnosed variant angina without multivessel disease should initially be treated with nifedipine, diltiazem, or verapamil, not only to prevent angina but also to reduce the risk of complications. The clinical efficacy of these three drugs seems approximately equal. Because complications usually

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occurs within the first 3 months after diagnosis and because symptoms often disappear spontaneously, lifelong treatment may not be required.

Our patients with multivessel disease had the most complications and their prognosis was not improved by the newer calcium antagonist drugs. In our opinion, coronary bypass surgery should be considered for this group. The number of patients in this study who underwent bypass surgery is too small to assess. The results of bypass surgery in variant angina are generally much worse than in stable or unstable angina, but some centers report excellent results when severe organic stenoses are present. Calcium antagonists should probably be administered postoperatively.

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Circulation. 1983;68:258-265
doi: 10.1161/01.CIR.68.2.258
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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