Clinical Characteristics Associated with Sudden Death in Patients with Variant Angina

D. Douglas Miller, M.D., David D. Waters, M.D., Jadwiga Szlachcic, M.D., and Pierre Théroux, M.D.

SUMMARY After hospital discharge, 114 patients with variant angina were followed for a mean period of 26 months. Six died suddenly and 13 others were resuscitated from sudden cardiac death. The extent of coronary artery disease and the prevalence of left ventricular dysfunction in these 19 “sudden death” patients were similar to those in the patients who did not experience sudden death (“survivors”). During spontaneous episodes of ST elevation recorded in hospital, 56 of the 114 patients had serious arrhythmias: ventricular fibrillation in two, ventricular tachycardia in 28, ventricular couplets or bigeminy in 17, second- or third-degree atrioventricular block in six and asystole in three. Patients with and those without these arrhythmias during attacks were similar with respect to extent of coronary artery disease, left ventricular function and most other clinical variables. The maximal ST elevation, however, was higher in the arrhythmia group (7.4 ± 5.7 vs 3.3 ± 2.3 mm, p < 0.01). Serious arrhythmias were detected in 16 of the 19 sudden death patients, compared with 36 of the 86 survivors (p < 0.01). Sudden death occurred during follow-up in 15 of the 36 patients (42%) with ventricular fibrillation, ventricular tachycardia, high-degree atrioventricular block or asystole during attacks, compared with only four of 69 (6%) without these arrhythmias (p < 0.001).

We conclude that variant angina patients with serious arrhythmias during spontaneous attacks differ from other variant angina patients only in the degree of ischemia during attacks, as reflected by maximal ST elevation, but are at a much higher risk for sudden death.

SUDDEN DEATH is a frequent complication in most subsets of coronary artery disease. Severe multivessel involvement and left ventricular dysfunction are usually present both in patients who die suddenly1,2 and in those resuscitated from sudden death,3,4 and various clinical factors that correlate with sudden death have been identified.5–8

Variant angina is a rare diagnosis in sudden death patients, but sudden death is a common complication of variant angina. Variant angina patients who die suddenly or are resuscitated probably differ from other sudden death patients and other variant angina patients, but the differences between these groups have never been described. The identification of factors associated with sudden death in variant angina could have important therapeutic implications and would also permit stratification of these patients into high- and low-risk subsets. In this study, we compared the clinical characteristics of variant angina patients who died suddenly or were resuscitated with the clinical characteristics of variant angina patients who did not experience sudden death (“survivors”).

Methods

Patients

Variant angina was defined as spontaneous angina at rest with transient ST-segment elevation, rapidly relieved by nitroglycerin, without evidence of myocardial necrosis. The study population consists of 114 consecutive patients who met these criteria and were hospitalized between 1975 and 1981 in the coronary care unit of the Montreal Heart Institute. Forty-seven patients who had ergonovine-induced variant angina attacks but no spontaneous episodes documented during hospitalization were excluded. 
Sudden death was defined as death within 1 hour after the onset of symptoms. In five of the six deaths classified as sudden, the event was witnessed and began as an episode of angina at rest; the other patient died in his sleep without premonitory symptoms. Nine patients who were rehospitalized and died during the acute phase of a well-documented myocardial infarction were excluded from both the sudden death and the survivor groups. Thirteen patients had cardiovascular collapse that necessitated cardiopulmonary resuscitation: Ventricular fibrillation was documented as the cause in six patients and asystole in four; in three patients the exact arrhythmia was not determined. These 13 patients were counted as resuscitated sudden deaths. All patients were classified into these categories by one observer on the basis of a complete description of the event without knowledge of the clinical history.

Patient Management

All patients were hospitalized in the coronary care unit. A 12-lead ECG was recorded during episodes of rest angina and the ECG lead with the highest ST elevation was monitored continuously for at least 3 days. ST-segment elevation was measured to the nearest 0.5 mm (0.05 mV) at 0.04–0.08 second after the peak of the R wave or nadir of the S wave. The ECG lead that showed the highest ST elevation was used for measurement, and the mean of three consecutive beats was calculated to correct for possible respiratory variation or alternans. Measurements derived from the monitoring lead were corrected by calibrating the baseline R-wave amplitude between attacks to the R-wave amplitude in the same lead on the standard ECG.

Angina with ST depression or pseudonormalization of a negative T wave occurred occasionally in these patients but was not counted as variant angina episodes and was almost never associated with arrhythmias. When more than one type of arrhythmia occurred during attacks, only the most advanced grade was counted. For comparison, patients with ventricular fibrillation, ventricular tachycardia, ventricular couplets or bigeminy, second- or third-degree atrioventricular block, or asystole during attacks were arbitrarily classified prospectively into a separate group.

Coronary arteriography was performed in 110 of the 114 study patients. A percutaneous transfemoral approach was used, and views with cranial angulation were routinely filmed. Care was taken to avoid catheter-induced coronary artery spasm, and no attempt was made to induce coronary spasm by the administration of ergonovine during catheterization. Nitroglycerin was not given before the initial injections; however, when a lesion was noted, the vessel was filmed again in multiple views after nitroglycerin administration. A left ventricular angiogram was filmed in the 30° right anterior oblique view. Left ventriculography was not done in 10 cases. All angiographic documents were interpreted independently by an experienced cardiovascular radiologist.

After hospital discharge, all patients returned for regular visits to a special clinic for variant angina patients. No patient was lost to follow-up. For patients hospitalized more than once, the duration of follow-up was calculated from the admission during which variant angina was first diagnosed.

Statistical Analysis

Paired dimensional data were analyzed using either the paired t test or Wilcoxon signed-rank test, where appropriate, for parametric and nonparametric distributions. Unpaired dimensional data were analyzed using either the unpaired t test or the Mann-Whitney U test where appropriate. Proportional data were analyzed using the chi-square test. A p value < 0.05 (two-tailed) was considered significant. When multiple variables were compared between two groups, a level of p < 0.01 was required to reject the null hypothesis.

Results

During a mean follow-up of 26.2 ± 18.1 months, six patients died suddenly and 13 were resuscitated from sudden cardiac death. Table 1 shows the clinical and angiographic features of these 19 patients and the 86 survivors. Nine other patients who died during a subsequent hospitalization for myocardial infarction were excluded from both groups, but their data are also listed in table 1. The age, sex distribution, baseline ECG, site of ST elevation, extent of coronary disease, presence of left ventricular dysfunction and length of follow-up for the sudden death patients and survivors were similar. During hospitalization, both groups had an equal number of variant angina attacks per day, but the maximal ST elevation was higher in the sudden death group than in survivors (7.26 ± 6.5 vs 4.8 ± 4.1 mm, p < 0.01).

Serious ventricular arrhythmias or conduction disturbances were documented in the hospital during ST elevation in 16 of the 19 sudden death patients (84%) and in 36 of the 86 survivors (42%, p < 0.01). The specific arrhythmias are listed in table 2 for each group. Overall, ventricular fibrillation was recorded in two patients, ventricular tachycardia in 28, ventricular couplets or bigeminy in 17, second- or third-degree atrioventricular block in six and asystole in three. If ventricular couplets and bigeminy were not counted as serious arrhythmias, the difference between the two groups became more pronounced; the remaining arrhythmias were found in 15 of 19 patients (79%) in the sudden death group and in 21 of 86 survivors (24%). Thus, sudden death occurred during follow-up in 15 of 36 patients (42%) with ventricular fibrillation, ventricular tachycardia, high-degree atrioventricular block or asystole documented during attacks, compared with only four of 69 patients (6%) without these arrhythmias (p < 0.001).

Table 3 presents a comparison of the 56 patients with and the 58 patients without arrhythmias during attacks. The extent of coronary disease and most other clinical variables were similar in the two groups. The maximal ST elevation was higher in the patients with arrhythmias than in those without (7.4 ± 5.7 vs 3.3 ± 2.3 mm, p < 0.01).

Figure 1 compares survival with regard to sudden...
death for the patients with and those without arrhythmias, excluding the nine patients who died during a myocardial infarction. At 6, 12 and 24 months, survival in the arrhythmia group was 76%, 71% and 64%, respectively, compared with 96% in the group without arrhythmias. The difference between the curves is statistically significant (p < 0.001).

The influence of treatment on the risk of sudden death could not be evaluated because patients were treated in a nonstandardized way with a variety of drugs, often given in combination. During the study, nifedipine, diltiazem and verapamil became available and ß-blockers or perhexiline maleate were no longer used. Coronary bypass surgery was performed in 19 of the 114 patients. At the time of sudden death, treatment consisted of long-acting nitrates in six cases, ß-blockers in four, coronary bypass surgery in three and calcium-antagonist drugs in six (nifedipine and verapamil in two patients each and diltiazem and perhexiline maleate in one patient each). Eight of the 19 patients who died suddenly or were resuscitated from sudden death were free of angina at rest during the preceding month; the 11 other patients had rest angina and were using sublingual nitroglycerin regularly. In nearly all patients for whom an adequate history was available, the episode of sudden death began with rest angina.

**Discussion**

This study indicated that the risk of sudden death during the 2 years after hospital discharge increases from 6% to 42% for variant angina patients with documented ventricular fibrillation or tachycardia, high-degree atrioventricular block or asystole during spontaneous variant anginal attacks. This high-risk subgroup included one-third of the study patients.

Moreover, most other clinical features, including the extent of coronary disease or the presence of left ventricular dysfunction, were not predictive of sudden death. This finding was unexpected. In patients without variant angina, sudden death is usually associated with severe coronary disease and left ventricular dysfunction.1 2 In the variant angina populations described by Maseri et al.11 and Severi et al.,12 only nine of their 107 patients studied by coronary arteriography did not have stenoses > 50%. Overall mortality and myocardial infarction were both more common in patients with multivessel disease. At least five of the 12 deaths in their study12 could be classified as sudden; one of

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**Table 1. Clinical and Angiographic Features of Sudden Death Patients Compared with Survivors**

<table>
<thead>
<tr>
<th></th>
<th>Sudden death* (n = 19)</th>
<th>Survivors (n = 86)</th>
<th>Death during MI (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>47.7 (24-68)</td>
<td>52.5 (32-71)</td>
<td>58.3 (45-68)</td>
</tr>
<tr>
<td>Male/female</td>
<td>14/5</td>
<td>61/25</td>
<td>7/2</td>
</tr>
<tr>
<td>Normal ECG</td>
<td>7 (37%)</td>
<td>36 (42%)</td>
<td>1 (11%)</td>
</tr>
<tr>
<td>Variant angina attacks/day</td>
<td>0.43 ± 0.46</td>
<td>0.45 ± 0.58</td>
<td>2.0 ± 3.4</td>
</tr>
<tr>
<td>Anterior ST elevation</td>
<td>11 (58%)</td>
<td>49 (57%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Maximal ST elevation (mm)</td>
<td>7.2 ± 6.5†</td>
<td>4.8 ± 4.1</td>
<td>6.5 ± 5.3</td>
</tr>
<tr>
<td>Arrhythmias during ST elevation</td>
<td>16 (84%)‡</td>
<td>36 (42%)</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>Length of follow-up (months)</td>
<td>32.7 ± 22.1</td>
<td>24.8 ± 16.9</td>
<td>24.7 ± 13.8</td>
</tr>
<tr>
<td>Coronary arteriography:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No stenosis ≥ 70%</td>
<td>8 (42%)</td>
<td>32 (39%)</td>
<td>0</td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>5 (26%)</td>
<td>27 (33%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>6 (32%)</td>
<td>24 (29%)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>Artery to ischemic zone ≥ 70% stenosed</td>
<td>10 (53%)</td>
<td>46 (55%)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>Abnormal left ventriculogram</td>
<td>3/17 (18%)</td>
<td>24/82 (29%)</td>
<td>3/5 (60%)</td>
</tr>
</tbody>
</table>

*Includes 13 patients resuscitated from sudden cardiac death.
†p < 0.01 vs survivors (all other comparisons NS).
‡Data are given for patients who died during a myocardial infarction, but the group was too small for statistical comparisons to be made.

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**Table 2. Severe Arrhythmias and Conduction Disturbances Documented During Spontaneous Variant Angina Attacks**

<table>
<thead>
<tr>
<th></th>
<th>Sudden deaths* (n = 19)</th>
<th>Survivors (n = 86)</th>
<th>Death during MI (n = 9)</th>
<th>Total (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with arrhythmias</td>
<td>16</td>
<td>36</td>
<td>4</td>
<td>56</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>8</td>
<td>18</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Ventricular couplets/bigeminy</td>
<td>1</td>
<td>15</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Second- or third-degree AV block</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Asystole</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*Includes 13 patients resuscitated from sudden cardiac death.

Abbreviation: AV = atrioventricular; MI = myocardial infarction.
these five patients had normal coronary arteries, but the four others had three-vessel disease. The small number of patients and the rarity of cases without fixed lesions in their population make it difficult to evaluate the relationship of sudden death in variant angina to the extent of coronary disease.

Our patients had less extensive coronary disease: 40 of 110 patients had no stenosis $\geq 70\%$. As described elsewhere, myocardial infarction appeared to be more common in our patients with fixed lesions than in those without. However, the extent of coronary disease in sudden death patients and survivors was identical (table 1). We speculate that the main influence of fixed lesions in provoking sudden death probably occurs when they are multiple and critical or associated with severe left ventricular dysfunction. These underlying conditions are not present in most patients with variant angina.

Sudden death in patients with variant angina presumably occurs when a fatal arrhythmia is induced by severe transmural myocardial ischemia caused by transient coronary vasospasm. This study demonstrates that these arrhythmias can often be detected beforehand. In addition, in this study and in the 26 cases reported by Kerin et al., patients with serious arrhythmias had higher ST elevation during attacks than patients without arrhythmias. The magnitude of ST-segment elevation reflects the extent and severity of myocardial ischemia, although theoretical and practical considerations limit the usefulness of this correlation. Patients in our study with serious arrhythmias during attacks undoubtedly had worse ischemia than those without arrhythmias, because the mean maximal ST elevation was more than twice as high in the arrhythmia group as in the other group.

These findings have therapeutic implications. Sudden death should not occur in variant angina patients if the attacks of coronary vasospasm that provoke life-threatening arrhythmias can be eliminated. Variant angina episodes usually decrease markedly or disappear entirely during treatment with the calcium-antagonist drugs nifedipine, diltiazem or verapamil. Patients with serious arrhythmias during attacks should probably be treated more aggressively than other variant angina patients, with the goal of eliminating all attacks.

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Survival curves for sudden death comparing the patients with and those without documented arrhythmias during anginal attacks. Patients resuscitated from sudden death are included, but those who died because of a myocardial infarction during a subsequent hospitalization are excluded. The clinical and angiographic features of the two groups were similar except that maximal ST elevation during attacks was higher in the arrhythmia group. The difference between the curves is statistically significant ($p < 0.001$).
to reduce the risk of sudden death. As with other complications in variant angina, the risk of sudden death is highest soon after the diagnosis is made (fig. 1). Although treatment can eventually be safely discontinued in some patients with variant angina, this approach could be hazardous for those who have had serious arrhythmias during attacks.

Editorialists often speculate that coronary spasm may be an important cause of sudden coronary death, however, data to support this notion are scanty. Coronary spasm accounts for the clinical manifestations of variant angina and undoubtedly caused the sudden deaths in this study. The clinical characteristics, extent of coronary disease and degree of left ventricular dysfunction in variant angina sudden deaths differ from the clinical characteristics usually found in other sudden coronary deaths. In patients with critical fixed lesions and left ventricular dysfunction, minimal changes in coronary artery caliber might escape clinical detection, but could trigger fatal arrhythmias. A study of patients resuscitated from cardiac death should be undertaken to determine the role of coronary spasm in this syndrome.

References
13. Waters DD, Szlachcic J, Miller D, Théroux P: Clinical characteristics of patients with variant angina complicated by myocardial infarction or death within one month. Am J Cardiol 49: 658, 1982
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