CLINICAL CHARACTERISTICS OF PATIENTS WITH SPONTANEOUS REMISSION OF VARIANT ANGINA

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SAMON KOYANAGI, M.D. AND AKIRA TAKESHITA, M.D.

To determine the factors influencing the spontaneous remission of variant angina, clinical characteristics were examined in 75 Japanese patients with variant angina. Spontaneous remission was defined as an absence of angina at rest for at least 3 months after withdrawal of treatment with calcium antagonists. This remission occurred in 12 patients (16%) (remission group), while angina persisted despite treatment with calcium antagonists and nitrates in 33 patients (44%) (persistent angina group). The remaining 30 patients (40%) were angina-free under treatment with calcium antagonists and/or nitrates (angina-free on treatment group).

The prevalence of significant coronary artery stenosis (>75%) was significantly higher in the remission group than in the persistent angina group (44% vs 7%, p<0.05). The prevalence of cessation of smoking was significantly higher in the remission group than in the persistent angina group (92% vs 39%, p<0.01). Age, gender, other coronary risk factors, disease activity of variant angina and site of myocardial ischemia during anginal attacks were not statistically different among the 3 groups.

There data indicate that remission of variant angina occurs more frequently in patients with than in those without significant coronary artery stenosis and that cessation of smoking is an important factor for remission of variant angina.

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Since the first report by Prinzmetal et al., several studies have been performed on the clinical characteristics and the long-term prognosis of patients with variant angina. In patients with variant angina, treatment with calcium antagonist and/or nitrate is effective in reducing the frequency of anginal attacks. In many cases the attacks disappear while the treatment is continued. However, it is difficult to predict how long the disease activity will continue in each patient. Indeed, after withdrawal of medical treatment, variant angina recurs and even causes sudden death in some patients. In contrast, spontaneous remission is also a characteristic outcome of variant angina in some patients. Therefore, the present study was designed to examine the clinical characteristics of patients with spontaneous remission of variant angina in order to elucidate the factors influencing the duration of disease activity.

METHODS

Patients

The diagnosis of variant angina was made by the following criteria: (1) history of chest pain at rest, (2) spontaneous or

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Key words:
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Spontaneous remission
Coronary artery spasm

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nitroglycerin-induced relief of the pain in less than 10 min, (3) ST-segment elevation of at least 2 mm not present in the baseline electrocardiogram but documented during pain and disappearing with relief of pain at least 1 occasion, and (4) no subsequent evidence of acute myocardial infarction.

Follow-up data were obtained from 93 patients with variant angina by mail questionnaire followed by telephone interview, contact with the patient and his/her family, and contact with the patient's personal physician. Eighteen patients were excluded for the following reasons: cardiac death or sudden death in 7 patients, non-cardiac death in 8, and coronary bypass surgery or angioplasty in 3. The remaining 75 patients were entered in the present study. Mean age on admission was 58 years (range 31 to 76); 62 patients were men and 13 were women. Forty-three had a history of effort angina, 6 a previous myocardial infarction and 22 a history of progressive angina. Risk factors for ischemic heart disease were present in 36 with hypertension, in 8 with diabetes mellitus, in 5 with hypercholesterolemia (>225 mg/dl) and in 63 with history of smoking.

Initial management
After admission, patients underwent continuous electrocardiographic monitoring without medication for at least 3 days. They were told to report all chest symptoms and a complete electrocardiogram was recorded during the episodes. After the diagnosis of variant angina was made, medical treatment with calcium channel blockers, without nitrates, was immediately started and continued until cardiac catheterization.

Cardiac catheterization
All drugs except sublingual nitroglycerin were discontinued at least 8 h before cardiac catheterization. Coronary arteriography was performed by a percutaneous transfemoral or transbrachial approach in multiple views. Since coronary arteriography became available at our hospital in 1977, it was not performed in 4 patients. Coronary arteriography could not be performed in another 2 patients in whom there was life-threatening non-cardiac illness or informed consent was not given. The ergonovine provocative test was performed during coronary arteriography in 42 patients who had no significant coronary artery stenosis (>75%). Ergonovine was administered intravenously or intracoronarily in a cumulative manner. Aortic pressure and 12-lead electrocardiograms were recorded at 30 sec intervals, until the occurrence of angina or electrocardiographic ST-T changes. Coronary artery spasm was defined as a more than 50% reduction in coronary luminal diameter compared with that after nitroglycerin administration. The results were reviewed by more than 3 senior angiographers in a conference during the week of catheterization.

Data analysis
The patients were divided into 3 groups. Spontaneous remission of variant angina was defined as an absence of angina at rest for at least 3 months after withdrawal of medical treatment (remission group). The patients under medical treatment were divided into 2 groups with respect to the presence or absence of angina at rest (persistent angina group and angina-free on treatment group). Intergroup differences were analyzed using an analysis of variance, a chi-square test or Fisher's exact probability test when appropriate. Since the main purpose of the present study was to elucidate the clinical characteristics influencing spontaneous remission of variant angina, comparisons of the clinical characteristics were made mainly between the remission group and the persistent angina group. Statistical significance was accepted when the p value was less than 0.05.

RESULTS
Among the 75 patients, 12 were completely free of rest angina for at least 3 months after withdrawal of medical treatment (remission group). Medical treatment was stopped following physician's advice in 9 patients and by the patient's own decision in the remaining 3 cases. In the remaining 63 patients, 30 were free of angina for at least 6 months with medical treatment (angina-free on treatment group). Angina persisted in 33 patients despite continued medical treatment (persistent angina group).

Age, gender and duration of rest angina before admission were similar among the 3
## TABLE I  CLINICAL CHARACTERISTICS OF PATIENTS WITH VARIANT ANGINA

<table>
<thead>
<tr>
<th></th>
<th>Remission</th>
<th>Angina-Free on treatment</th>
<th>Persistent Angina</th>
</tr>
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<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>12</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>60±11</td>
<td>58±7</td>
<td>58±10</td>
</tr>
<tr>
<td><strong>Sex (male/female)</strong></td>
<td>11/1</td>
<td>25/5</td>
<td>26/7</td>
</tr>
<tr>
<td><strong>Angina pre-admission (mo)</strong></td>
<td>27±49</td>
<td>45±71</td>
<td>49±60</td>
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**Variant angina attacks**

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<tbody>
<tr>
<td>Spontaneous (%)</td>
<td>58</td>
<td>73</td>
<td>61</td>
</tr>
<tr>
<td>Provoked only (%)</td>
<td>42</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td>Anterior (%)</td>
<td>58</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>Inferior (%)</td>
<td>25</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>Anterior and inferior (%)</td>
<td>17</td>
<td>3</td>
<td>12</td>
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**Coronary arteriography**

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<tr>
<td>Organic stenosis</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0−50 (%)</td>
<td>44*</td>
<td>72</td>
<td>81</td>
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<tr>
<td>51−75 (%)</td>
<td>11</td>
<td>10</td>
<td>13</td>
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<tr>
<td>&gt;75 (%)</td>
<td>44*</td>
<td>17</td>
<td>6</td>
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**Risk factors**

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<tbody>
<tr>
<td>Diabetes mellitus (%)</td>
<td>8</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>50</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>0</td>
<td>7</td>
<td>9</td>
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**Smoking**

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<tr>
<td>Non smoker (%)</td>
<td>8*</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>Habitual smoker (%)</td>
<td>0*</td>
<td>10</td>
<td>24</td>
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<tr>
<td>Former smoker (%)</td>
<td>92*</td>
<td>77</td>
<td>39</td>
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**Duration of follow-up period (mo)**

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<td></td>
<td>109±68*</td>
<td>56±36</td>
<td>60±31</td>
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*Mean ± SD, mo = months
*p<0.05, **p<0.01 vs persistent angina group.*

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**Fig.1.** The prevalence of patients with significant coronary stenosis (>75%) in remission group (Remission; n=9) and persistent angina group (Persistent angina group; n=31). The incidence of patients with significant coronary artery stenosis in the remission group was significantly higher than that in the persistent angina group.

The disease activity (spontaneous attacks vs provoked attacks only) and site of ST-segment elevation during attacks were also similar in the remission and the persistent angina groups (Table I). The prevalence of significant coronary artery stenosis (>75%) was significantly higher in the remission group than in the persistent angina group (Table I, Fig. 1).

Among the coronary risk factors, prevalence of diabetes mellitus, hypertension and hypercholesterolemia were not significantly different among the 3 groups. Prevalence of non-smoker was significantly lower in the remission group than in the persistent angina group (Table I). Incidence of cessation of smoking was significantly higher in the remission group than in the persistent angina group (Table I). In fact, all of the patients, who had previously smoked, stopped smoking in the remission group (Fig. 2).

The remission group had a longer duration of follow-up than the other 2 groups (Table
steno­sis and (2) cessation of smoking is very important for remission of the disease.

Limitation of study

A limitation of our study is that the dis­appearance of angina was a subjective end point not confirmed by objective evidence. However, it is often difficult to show objective­ly whether or not transient myocardial ischemia is present. Provocative tests may be useful in assessing disease activity in asymptomatic patients, but may not be more helpful than clinical evaluation of symptoms. Furthermore, it is possible that provocative tests reactivate disease activity in patients with spontaneous remission. A second limitation of the study is that 40% of the patients were entered in the angina-free on treatment group. It is reasonable to con­sider that this group includes patients with remission of variant angina and those with the active disease controlled under medica­tion. This notion is supported by the result that all of the clinical characteristics of this group are between those of the remission group and of the persistent angina group. In the previous study, attempts to taper or discontinue medication suggested that approximately half of the patients in this group belonged to the persistent angina group and the other half would likely belong to the remission group. A third limitation of the study is that the follow-up period was significantly longer in the remission group than in the persistent angina group. However, even when the duration of follow-up period was adjusted, the same tendencies were noted concerning the prevalence of cessation of smoking and significant coronary artery stenosis.

Coronary atherosclerosis and remission of variant angina

The present study has demonstrated that remission of variant angina occurs more frequently in patients with than in those without significant coronary artery stenosis. This finding is in agreement with that of Waters et al. However, they considered that this difference could be artificial because in their study many patients (at least 44 out of 168) were excluded in advance for cardiac events, such as myocardial infarction and coronary bypass surgery or angioplasty. In

DISCUSSION

The present study demonstrates; (1) spontaneous remission of variant angina occurs more frequently in patients with than in those without significant coronary artery
Remission of Variant Angina

contrast, in our study, only 10 patients were excluded in advance for those reasons (7 for cardiac or sudden death and 3 for coronary bypass surgery or angioplasty). Therefore, our finding is less biased in terms of the prevalence of patients with significant coronary artery stenosis. The mechanism for our finding remains to be elucidated. Kaski et al reported that coronary arteries with eccentric stenosis and normal coronary wall can more readily change their diameter in response to ergonovine than those with concentric stenosis but without normal coronary wall11. This is probably because eccentric stenosis retains a portion of normal vascular smooth muscle which is able to react to vaso-motor stimuli, whereas concentric stenosis tends to be fixed as vasomotion is limited by the involvement of the whole circumference of the artery by atherosclerotic process. Progress of atherosclerotic change and destruction of coronary artery smooth muscle would result in spontaneous remission of variant angina in some patients with significant coronary artery stenosis.

Smoking and remission of variant angina

Another important finding in our study was that cessation of smoking is very effective in obtaining remission of variant angina. Indeed, in the remission group all patients who had smoked stopped doing so. Patients with variant angina are often heavy cigarette smokers12 in whom smoking may play a role in inducing coronary artery spasm13. Maouad et al angiographically demonstrated diffuse or segmental narrowing of coronary arteries during smoking14. Smoking induces chest pain by increasing myocardial oxygen demand and by inappropriately decreasing coronary blood flow15,16. Prevalence of nonsmoker was higher in the persistent angina group than in the remission group. Therefore, it seems that 2 distinct groups of patients exist in variant angina; those with insignificant coronary artery stenosis, in whom smoking plays a relatively less important role and disease activity tends to be continued; and those with significant coronary artery stenosis, in whom smoking may play an important role and in whom disease activity tends to be diminished on cessation of smoking.

Other factors

The prevalence of other coronary risk factors (diabetes mellitus, hypertension and hypercholesterolemia) was not statistically different between the remission group and the persistent angina group, excluding their roles in sustaining the disease activity of variant angina. In contrast to previous reports10 in the present study disease activity was not a predictor of spontaneous remission of variant angina. In our hospital, an attempt to document spontaneous anginal attacks was routinely made after admission6. Therefore, the difference between the previous study10 and our study can not be explained by differences in monitoring.

Clinical implications

Variant angina is considered to be a temporary condition, which is observed during process of coronary atherosclerosis. The present study implies that when the patient has significant coronary artery disease, cessation of smoking is effective in reducing the disease activity and that when the patient has insignificant coronary artery stenosis, a longer period of medication and subsequent, careful withdrawal of drugs may be required.

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