Characteristics of Symptomatic and Asymptomatic Myocardial Ischemia during Ambulatory Electrocardiographic Monitoring in Patients with Angina Pectoris

Hiroshi KISHIDA, M.D., Takeshi SUZUKI, M.D., Tsutomu SAITO, M.D., Fumio OTSU, M.D., Noritake HATA, M.D., Jun NEJIMA, M.D., Yoshiki KUSAMA, M.D., HIROKO YASUTAKE, M.D., and Naomi INOKUCHI, M.D.

SUMMARY

The purpose of the present study was to clarify the characteristics of myocardial ischemic attacks in patients with exertional angina (EA, 56 cases), exertional and rest angina (ERA, 28 cases), rest angina (RA, 4 cases), and variant angina (VA, 39 cases). The Holter electrocardiographic findings were compared among the four types of angina pectoris. The frequency of symptomatic ischemic attacks in descending order was 46.0% in EA, 29.0% in ERA, 28.1% in RA, and 21.6% in VA, while the frequency of asymptomatic ischemic attacks was in the reverse order. The maximal heart rates during symptomatic ischemic attacks were in descending order, EA, ERA, RA, and VA. The maximal heart rate during ischemic attacks was significantly lower in patients with spontaneous angina than in those with exercise-induced ischemia for all types of angina (p<0.05, respectively). Further, the difference in maximal heart rate during ischemic attacks between the ambulatory electrocardiogram and exercise test was greater in patients with RA and VA than in those with EA. Therefore, this suggests that increased coronary vascular tone is a cause of spontaneous ischemic attacks in each type of angina pectoris.

Additional Indexing Words:
Asymptomatic ischemia Holter monitoring Exertional angina Rest angina Variant angina Coronary tone Exercise test

IN recent years the diagnosis of coronary artery disease and myocardial ischemia has been greatly facilitated by various modern techniques including exercise testing, Holter electrocardiography, radionuclide studies and
coronary arteriography. They provide powerful tools especially for detecting asymptomatic coronary artery disease and making a definitive diagnosis of silent myocardial infarction. On the other hand, it has been reported\(^1\)-\(^3\) that not only ischemic attacks that are consistent with subjective symptoms but also asymptomatic ones occur during episodes of transient myocardial ischemia.

The purpose of the present study is to clarify the clinical significance of symptomatic and asymptomatic ischemic attacks in patients with angina pectoris using ambulatory electrocardiography. Further, ambulatory electrocardiographic findings were compared with exercise electrocardiographic and coronary arteriographic findings to study the mechanisms of different anginal syndromes.

**Subjects and Methods**

Studies were carried out on 127 patients (96 males and 31 females, aged 58±9 years) who had been diagnosed as having angina pectoris, who were divided into a group of 88 patients with transient ST-segment depression on the electrocardiogram during an anginal attack and a group of 39 patients with ST-segment elevation on the electrocardiogram. The patients in the former group were further divided into three groups, 56 patients with exertional angina (EA, 38 males and 18 females, aged 57±9 years), 28 patients with exertional and rest angina (ERA, 20 males and 8 females, aged 61±10 years), and 4 patients with rest angina (RA, 3 males and 1 female, aged 63±10 years). The disease in the latter group (35 males and 4 females, aged 58±10 years) was defined as variant angina (VA). The ambulatory electrocardiographic findings were compared among these four types of angina.

Patients with a history of myocardial infarction and those with equivocal ST-segment changes on the electrocardiogram were excluded from the study, and antianginal agents were withdrawn on the days of observation by ambulatory electrocardiography.

Twenty four-hour ECG was recorded with an Avionics Holter electrocardiograph. ECG was recorded through 2 channels, one of them where the maximum ST-segment deviations were observed. ST-segment deviations were considered abnormal in cases where ischemic ST-segment depression or elevation of 0.1 mV or greater at 80 msec after the J point lasted 1 min or more in real time.\(^4\)-\(^5\) Such ischemic attacks were divided into symptomatic and asymptomatic types. Symptomatic and asymptomatic types were distinguished by the presence or absence of subjective symptoms recorded on daily cards. All subjective symptoms associated with transient ST-seg-
ment deviations fulfilling the above criteria were regarded as symptomatic attacks. The duration of ST-segment deviation during an ischemic attack was defined as the time lapsed from the time ST-segment deviation appeared on the real-time electrocardiogram to the time the ST-segment returned to baseline.

The treadmill exercise test was performed on 99 patients according to the Bruce protocol, and the patients were considered positive for abnormal ST-segment deviation when they had ischemic ST-segment depression or elevation of more than 0.1 mV or greater at 80 msec after the J point.

Coronary cinearteriography was performed on 90 of 127 patients with angina pectoris. A fixed narrowing of more than 50% of the luminal diameter was defined as significant coronary artery stenosis. According to this criterion, 10 patients had normal or nearly normal coronary arteries, 36 patients single-vessel disease, and 44 patients multi-vessel disease. Of the patients with EA, 1 had normal coronary arteries, 10 had single-vessel disease, and 21 had multi-vessel disease. Of the patients with ERA, 0, 5, and 15 had normal coronary arteries, single-vessel disease, and multi-vessel disease, respectively. Of the patients with RA and those with VA, 0, 2, and 0, and 9, 19, and 8 had normal coronary arteries, single-vessel disease, and multi-vessel disease, respectively.

The results were evaluated statistically using Student’s t-test. All average values were expressed as mean ± standard deviation. Differences were considered significant when $p < 0.05$.

**Results**

Table I shows the frequency of ischemic attacks with and without subjective symptoms. Symptomatic ischemic attacks were frequent in angina with attacks on exertion, their frequency being 46.0%, or 110 of 236 attacks, for EA, 29.0%, or 89 of 307 attacks, for ERA, 28.1%, or 9 of 32 attacks, for RA, and 21.6%, or 78 of 338 attacks, for VA, while the frequency of asymptomatic ischemic attacks was high in angina with attacks at rest. There was a significant difference between these four types of angina ($p < 0.001$). Further, whereas the mean frequency of symptomatic ischemic attacks was about the same for all types of angina, asymptomatic ischemic attacks were more frequent than symptomatic ones in all but EA, and the difference was statistically significant for RA ($p < 0.05$) and for ERA and VA ($p < 0.001$, respectively).

The favored time of occurrence of ischemic attacks varied with each type of angina, as shown in Fig. 1, being the daytime for EA, 7:00–8:00 a.m.
Table I. Frequency of Symptomatic and Asymptomatic Ischemic Attacks in Each Type of Angina Pectoris

<table>
<thead>
<tr>
<th>Type of Angina</th>
<th>Number of cases</th>
<th>Mean frequency of ischemic attacks (attacks/day/patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exertional angina</td>
<td>56</td>
<td>3.6±3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(236) ***</td>
</tr>
<tr>
<td>Exertional and rest angina</td>
<td>28</td>
<td>8.3±8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(307) **</td>
</tr>
<tr>
<td>Rest angina</td>
<td>4</td>
<td>6.4±3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(32) **</td>
</tr>
<tr>
<td>Variant angina</td>
<td>39</td>
<td>7.9±8.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(336) **</td>
</tr>
</tbody>
</table>

( ): Total number of ischemic attacks in all cases of each type of angina pectoris.
* p<0.05, ** p<0.01, *** p<0.001.

Fig. 1. Circadian variation of ischemic attacks in each type of angina pectoris. The parentheses show the percent of asymptomatic ischemic attacks.

for ERA, 2:00–3:00 a.m. for RA, and 3:00–6:00 a.m. for VA. Symptomatic and asymptomatic ischemic attacks showed a similar tendency with respect to the favored time of occurrence in all but VA.

Table II indicates the magnitude of ST-segment deviation in each type of angina in relation to symptomatic and asymptomatic ischemic attacks. In
Table II. Magnitude of ST-segment Deviation in Each Type of Angina Pectoris

<table>
<thead>
<tr>
<th>Type of Angina</th>
<th>Number of cases</th>
<th>Exertional angina (mm/attack)</th>
<th>Exertional and rest angina (mm/attack)</th>
<th>Rest angina (mm/attack)</th>
<th>Variant angina (mm/attack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>57</td>
<td>-1.8±1.3</td>
<td>-1.6±1.0</td>
<td>-1.5±0.9</td>
<td>+3.5±2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>***</td>
<td>(66)</td>
<td>(74)</td>
<td>(49)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td>-1.3±0.6</td>
<td>-1.3±0.4</td>
<td>-1.4±0.7</td>
<td>+2.2±1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>***</td>
<td>(94)</td>
<td>(146)</td>
<td>(123)</td>
</tr>
<tr>
<td>Cases with symptomatic ischemic attacks alone</td>
<td>39</td>
<td>-1.5±1.0</td>
<td>-1.5±0.5</td>
<td>-1.0±0.1</td>
<td>+3.0±2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>***</td>
<td>(44)</td>
<td>(15)</td>
<td>(24)</td>
</tr>
<tr>
<td>Cases with asymptomatic ischemic attacks alone</td>
<td>31</td>
<td>-1.2±0.4</td>
<td>-1.3±0.5</td>
<td>-1.0±0.1</td>
<td>+2.3±1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>***</td>
<td>(72)</td>
<td>(146)</td>
<td>(142)</td>
</tr>
</tbody>
</table>

The number of cases with both symptomatic and asymptomatic ischemic attacks was 22 cases in exertional angina (EA), 17 cases in exertional and rest angina (ERA), 2 cases in rest angina (RA), and 16 cases in variant angina (VA). The number of cases with symptomatic ischemic attacks alone was 22 cases in EA, 7 cases in ERA, and 10 cases in VA. The number of cases with only asymptomatic ischemic attacks was 12 cases in EA, 4 cases in ERA, 2 cases in RA, and 15 cases in VA. ( ): The number of ischemic attacks. * p<0.05, ** p<0.01, *** p<0.001.

patients with EA or ERA who had both symptomatic and asymptomatic ischemic attacks, the magnitude of ST-segment depression was significantly greater in the group with symptomatic ischemic attacks than in that with asymptomatic ones (p<0.001), and patients with VA were found to have a similar tendency. In patients with either symptomatic ischemic attacks or asymptomatic ones alone, the magnitude of ST-segment deviation tended to be greater in patients with symptomatic ischemic attacks than in those with asymptomatic ones. These findings suggest that the extent of myocardial ischemia is more severe in patients with symptomatic ischemic attacks than in those with asymptomatic ones.

Table III indicates the duration of ST-segment deviation in different types of angina. In patients with both symptomatic and asymptomatic ischemic attacks the duration of ST-segment deviation was significantly longer in the group with symptomatic ischemic attacks than in that with asymptomatic ones for all types of angina (p<0.001). In patients with symptomatic ischemic attacks or asymptomatic ones alone, on the other hand, there was no difference in duration of ST-segment deviation for EA, but it was of significantly longer duration in patients with symptomatic ischemic attacks than in those with asymptomatic ones for ERA and VA (p<0.001). As was the case with the magnitude of ST-segment depression, therefore, it may also be said that the extent of myocardial ischemia is more severe in patients with
Table III. Duration of ST-segment Deviation in Each Type of Angina Pectoris

<table>
<thead>
<tr>
<th>Type of Angina</th>
<th>Number of cases</th>
<th>Exertional angina (min/attack)</th>
<th>Exertional and rest angina (min/attack)</th>
<th>Rest angina (min/attack)</th>
<th>Variant angina (min/attack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>57</td>
<td>17.9±10.3 (66) ***</td>
<td>18.6±14.6 (74) ***</td>
<td>15.7±26.1 (4) ***</td>
<td>8.3±7.6 (49) ***</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>39</td>
<td>13.4±8.6 (94) ***</td>
<td>9.7±7.4 (146) ***</td>
<td>7.4±0.6 (14) ***</td>
<td>3.1±2.8 (123) ***</td>
</tr>
<tr>
<td>Symptomatic attacks alone</td>
<td>39</td>
<td>15.9±11.6 (44) ***</td>
<td>24.5±14.5 (15) ***</td>
<td>*</td>
<td>*** 7.4±4.5 (24) ***</td>
</tr>
<tr>
<td>Asymptomatic attacks alone</td>
<td>31</td>
<td>16.8±15.1 (32) ***</td>
<td>7.5±5.6 (72) ***</td>
<td>11.3±7.0 (9) ***</td>
<td>4.3±2.5 (142) ***</td>
</tr>
</tbody>
</table>

The number of cases in each type of angina pectoris is the same as that of cases shown in Table II. ( ) is the number of ischemic attacks. * p<0.05, ** p<0.01, *** p<0.001.

Symptomatic ischemic attacks than in those with asymptomatic ones.

Ambulatory electrocardiographic findings are compared with exercise electrocardiographic findings in Fig. 2. The positivity of exercise tests performed on patients with different types of angina, as shown on the left side of this figure, stood at 88.0% for EA and 94.4% for ERA. It was higher in patients with EA than in those with RA and VA. The maximal heart rate during ischemic attacks was significantly lower in patients with spontaneous angina on the ambulatory electrocardiogram than in those with exercise-induced ischemia on treadmill exercise testing for all types of angina (p<0.05) as shown on the right side. Further, the difference in maximal heart rate during ischemic attacks between the two tests was greater in patients with RA than in those with EA.

Figure 3 indicates the relationship between ambulatory electrocardiographic findings and coronary arteriographic findings. The magnitude of ST-segment depression is compared between symptomatic ischemic attacks and asymptomatic ones according to the number of diseased coronary arteries. The magnitude of ST-segment depression was greater in the group with symptomatic ischemic attacks than in that with asymptomatic ones in the group of patients with either normal and single vessel disease or multi-vessel disease, while no such difference was noted with the severity of coronary artery disease.

On the right side is shown the duration of ST-segment deviation, which showed a tendency similar to the magnitude of ST-segment depression. Accordingly, it may be said that there is no correlation of severity between


ischemic attacks and coronary artery disease.

**DISCUSSION**

*Reliability of ambulatory electrocardiography in ischemic heart diseases:*

Various factors including postural change, hyperventilation, and frequency response characteristics of the electrocardiograph can be causes of transient ST-segment deviation. Tanabe et al. found that when differentiating transient ST-segment depression from ischemic ST-segment depression, the time to reach maximum ST-segment and T-wave changes, and ST-segment and T-wave changes in Lead CM₅ before and after postural change were of use, along with the rate of increase in heart rate before the occurrence of ST-segment deviation. In the present study, the electrocardiographic changes in different postures were assessed according to the criteria of Tanabe et al.⁶

---

**Fig. 2.** Results of treadmill exercise testing and ambulatory ECG monitoring in each type of angina pectoris. The left side of Fig. 2 shows the positivity of exercise tests. The right side shows the comparison between maximal heart rate during spontaneous angina and exercise-induced ischemia. Rest angina was excluded from the results of the right side of this figure because of the small number of cases. A = exertional angina (50 cases); B = exertional and rest angina (18 cases); C = rest angina (3 cases); D = variant angina (28 cases). * p < 0.05, ** p < 0.01.
Deanfield et al.\(^7\) noted that ST-segment depression of 0.1 mV or greater lasting at least 30 sec was not seen in healthy persons. It has also been reported\(^2\) that ST-segment depression on the ambulatory electrocardiogram in patients with coronary artery disease is a sign of myocardial ischemia, and that since such ST-segment depression disappears with antianginal treatment, it can be considered indicative of a myocardial ischemic attack.\(^8\),\(^9\)

Some ambulatory electrocardiographs do not meet the AHA requirements.\(^10\) Ours were also somewhat below the AHA standards, but it has been reported\(^11\) that this poses no particular problem when used in clinical practice. We believe that our ST-segment deviation data bear analysis and, therefore, are of clinical significance, although obtained with such equipment.

**Mode of occurrence of ischemic attacks and its pathogenetic implications:**

It was found that the frequency of asymptomatic ischemic attacks was higher than that of symptomatic ones in patients with stable exertional angina,\(^11,12^-^14\) variant angina,\(^15,16\) and unstable angina.\(^17,18\) In the present study, the mean frequency of attacks in each type of angina was higher with asymptomatic ischemic attacks than with symptomatic ones, and this tendency was marked in patients with angina at rest in particular.

The favored time of occurrence of ischemic attacks in our series of patients was the daytime in patients with EA and early morning in patients with...
VA in accordance with other reports.\textsuperscript{16,19} The favored time of occurrence of ischemic attacks in ERA and RA has not yet been reported. In our study ERA was found to have a predilection for nearly a mid-point between EA and VA, and RA showed little difference from VA regarding the predilection for time of occurrence of ischemic attacks.

On the other hand, the hourly frequency ratio between symptomatic and asymptomatic ischemic attacks was nearly constant in patients with EA, but was variable in patients with VA. A probable explanation of this difference may be that ischemic attacks in patients with EA are common during the daytime and attributable to organic coronary artery lesions so that the anginal threshold remains nearly stable, thereby accounting for this high reproducibility, while ischemic attacks in patients with VA are common during the nighttime and early in the morning and attributable to coronary spasms so that the anginal threshold remains variable, thereby accounting for its low reproducibility. This presumptive explanation may be supported by the finding that the difference in maximal heart rate between exercise-induced and spontaneous attacks was much smaller in patients with EA than in those with ERA and VA.

Carboni et al\textsuperscript{13} reported that the anginal threshold in exertional angina was lower in the morning than in the afternoon. Fujita et al,\textsuperscript{20} on the other hand, reported that the coronary blood flow in conscious dogs was increased by 12.8\% in the afternoon, compared to its level in the morning. Further, it has been documented\textsuperscript{21–23} that vasoconstriction of a stenosed coronary artery can be an important mechanism in causing myocardial ischemia during dynamic exercise in patients with classic angina pectoris. \(\alpha\)-Adrenergic stimulation\textsuperscript{24} and endothelial injury, resulting in decreased endothelial-derived relaxing factor\textsuperscript{25} have been thought to be potential mechanisms of increased coronary arterial tone. According to our results, the maximal heart rate at the time of spontaneous angina was significantly lower than that at the time of exercise-induced ischemia. Therefore, it was suggested that although vasomotility is much more stable in patients with EA than in those with VA, increased vascular tone appears to be the mechanism for spontaneous ischemia rather than that for exercise-induced ischemia in patients with EA.

\textit{Comparison of symptomatic and asymptomatic ischemic attacks:}

ST-segment depression was greater, in both magnitude and duration, with symptomatic ischemic attacks than with asymptomatic ones. This tendency was common to all types of angina. Accordingly, it may be said that the extent of ischemia in angina pectoris is more severe with symptomatic ischemic attacks than with asymptomatic ones.

On the other hand, there was no correlation at all between the magni-
tude of ST-segment depression and the severity of coronary artery disease in either group of patients with symptomatic ischemic attacks or the group with asymptomatic ones during spontaneous attacks, as monitored by ambulatory electrocardiography. Nor was the duration of ST-segment depression correlated with the severity of coronary artery disease. These findings combine to suggest that myocardial ischemia is more severe with symptomatic ischemic attacks than with asymptomatic ones regardless of the severity of coronary artery disease.

Cecchi et al., however, contradict in stating that myocardial ischemia was more severe with symptomatic ischemic attacks than with asymptomatic ones in patients with both ischemic attacks, but there was no such difference between patients with symptomatic and asymptomatic ischemic attacks alone. Further, Hecht et al. who divided patients with exercise-induced ST-segment depression into a group with silent ischemia and a group with painful ischemia found that there was no difference between the 2 groups with respect to the amount of ischemia myocardium as determined by exercise tomographic thallium 201 imaging or the severity of angiographically documented disease.

As has been discussed, our findings are, in part, in agreement and, in part, in disagreement with the reported results from other investigators. This discrepancy may be accounted for by differences with respect to a disturbance in the anginal warning system, ambulatory electrocardiographic lead system, individual response to pain, and plasma endorphin secretion. In the present study the possibility of involvement of a disturbance in the anginal warning system was ruled out by the background factors of patients, and it was suggested that the differences between symptomatic and asymptomatic ischemic attacks were ascribable to the difference in the amount of myocardial ischemia. However, the influence of the remaining factors cannot be precluded and still remains to be clarified, since they were not examined in this study.

References

2. Lindsey HE, Cohn PF: "Silent myocardial ischemia" during and after exercise testing in patients with coronary artery disease. Am Heart J 95: 441, 1978
5. Kunkes SH, Pichard A, Meller J, Gorlin R, Herman MV, Kupersmith J: Use of the am-
