EXCELLENT PROGNOSIS OF JAPANESE PATIENTS WITH CHEST PAIN AND NORMAL OR NEARLY NORMAL CORONARY ARTERIES — 2- to 13-Year Follow-Up of 274 Patients After Coronary Cineangiography —

YUZO HIROTA, M.D., HARUHIKO OHNACA, M.D., RYOICHI TSUJI, M.D. KATSUHISA ISHII, M.D., YOSHIO KITA, M.D., MICHIHIRO SUWA, M.D. AND KEISHIRO KAWAMURA, M.D.

Although the prognosis of patients with chest pain and normal coronary arteries is reportedly good in the Western literature, it is unclear in Japan. The purpose of this study was to examine the natural history of 274 consecutive patients with chest pain and normal or nearly normal coronary arteries, and to determine whether the possibility of minor coronary artery disease has clinical implications as a prodromal factor of other heart diseases.
Six of the patients died during the mean observation period of 6 years (74.5 ± 35.4 months): 2 cancer, 3 cerebro-vascular accident, and 1 renal failure death. Three additional patients suffered from nonfatal cerebro-vascular accidents. Eleven patients were readmitted for evaluation of chest pain, and 4 of these were diagnosed as having vasospastic angina. Progression of significant coronary artery disease was not detected in these 11 patients with repeated coronary angiography. None of the patients in this study developed fatal or nonfatal myocardial infarction. A small number of patients (36/240, 15.0%) continued to suffer from chest pain. None of the patients developed cardiomyopathies or valvular heart diseases. Our observations indicate that the prognosis of chest pain with normal or nearly normal coronary arteries is better than that presented in the Western reports. (Jpn Circ J 1994; 58: 43-48)

MANY patients undergo coronary angiography because of chest pain indicative of coronary artery disease. However, the coronary arteries of a significant percentage of these patients appear to be normal. Several long-term studies have reported that 10% to 30% of patients undergoing coronary angiography fall into this category!—6 Such patients are diagnosed as having chest pain syndrome when the presence of coronary spasm of the epicardial artery is ruled out. Earlier reports from western countries have indicated that these patients experience a good prognosis!—11 Some of the patients in this category have repeated episodes of chest pain and ECG changes identical to those found in angina pectoris. These patients are diagnosed as having syndrome X!2,13 Recently, “microvascular angina” has been proposed as an

Key words:
- Chest pain syndrome
- Syndrome X
- Microvascular angina
- Vasospastic angina
- Natural history
- Cerebrovascular accident

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The Third Division, Department of Internal Medicine, Osaka Medical College, Takatsuki Japan
Mailing address: Yuzo Hirota, M.D. The Third Division, Department of Internal Medicine, Osaka Medical College, 2-7 Daigakucho, Takatsuki-City, Osaka 569, Japan

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TABLE I PATIENT PROFILE

<table>
<thead>
<tr>
<th>Total No.:</th>
<th>274</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male(%)/Female:</td>
<td>143 (52.2)/131</td>
</tr>
<tr>
<td>Age (years, mean±SD):</td>
<td>38–75 (55.5±7.8)</td>
</tr>
<tr>
<td>Follow-up Period:</td>
<td>10–160 (74.5±35.4)</td>
</tr>
</tbody>
</table>

FOUR MAJOR RISK FACTORS of CORONARY ARTERY DISEASE

- smoking(%): 112 (40.9%)
- hypertension: 127 (46.4%)
- hyperlipidemia: 67 (24.5%)
- glucose intolerance: 79 (28.8%)
- no risk factor: 70 (25.5%)
- one risk factor: 76 (27.7%)
- two risk factors: 82 (29.9%)
- three risk factors: 40 (14.6%)
- four risk factors: 6 (2.2%)

alternative name for syndrome X based on observations of reduced coronary artery reserve and/or minor artery disease as a possible cause of chest pain.14,15 When these patients have persistent or repeated myocardial ischemia with minor coronary artery disease, their conditions might progress to cardiomyopathies, or some other cardiac disease. Indeed, instead of the good prognosis reported previously11–11 recent investigations have indicated that some of these patients develop dilated cardiomyopathy-like features.16–18

On the other hand, if these patients remain healthy without cardiac disease for a long time, coronary cineangiography should be of great help to them. Unfortunately, no report to date has adequately described the natural history of such patients with an acceptable study population in Japan. This clinical observation describes a 2- to 13-year follow-up of 274 patients with chest pain and apparently normal coronary arteries in the absence of vasospastic angina.

METHODS

Study Population
Between August 1978 and September 1990, we performed 2,161 cardiac catheterizations and coronary cineangiograms. Seventy percent (1,655/2,161) of these patients underwent these procedures for evaluation of possible coronary artery disease. The study population of this report consists of 274 (16.6%) consecutive patients who underwent coronary cineangiography for the evaluation of chest pain and were found to have no significant coronary artery disease. Patients with previous history of myocardial infarction, abnormal Q wave in standard ECG, rhythm disturbances, cardiomyopathies, valvular heart diseases, or other significant heart diseases were excluded. Patients with hypertension who had symptoms of congestive heart failure or left ventricular hypertrophy with ST-T abnormalities were also excluded. The patients consisted of 140 males and 134 females who ranged in age from 38 to 75 (mean±SD : 55.5±7.8) years (Table I).

Clinical Evaluations
In addition to complete physical, chest X-ray, echocardiographic and blood examinations, all 274 patients underwent repeated ECG recordings and 24-h Holter monitorings to document anginal attacks. Exercise stress ECG test was performed with a bicycle ergometer or treadmill in 231 patients. Exercise stress ECG was interpreted as positive when it showed ≥0.1 mV horizontal or sagging ST depression, or ≥0.2 mV ST elevation, and as equivocal when it showed ≥0.1 mV junctional or <0.1 mV horizontal ST depression. The coronary cineangiograms were performed via the brachial or femoral approaches under fasting conditions. All cardiac medications were withheld for at least 16 h before the procedure. Pressure measurements and left ventricular cineangiograms were performed first. Left ventricular volumes were calculated with the area-length method in 266 patients (97.1%) whose cineangiograms were good enough for the analysis. An ergonovine provocation test was performed in 226 patients (82.5%). After the control cineangiography, 0.4 mg of ergonovine maleate was given intravenously by 3 divided doses, and angiography was repeated 5 min after the last administration. Cineangiography was repeated after 0.3 to 0.6 mg nitroglycerin sublingual or 2 to 3 mg isosorbide dinitrate intravenous administrations.

Patients who had one of the following findings were excluded on the basis of having...
significant coronary artery disease or vasospastic angina: 1) presence of ≥75% luminal narrowing in one of the major coronary arteries (≥50% in the left main trunk) as judged by nitroglycerin angiography, 2) documentation of ≥0.2 mV horizontal or sagging ST depression, or ≥0.2 mV elevation with chest pain at rest by standard or Holter ECG, or 3) appearance of focal narrowing of ≥90% with ST deviations in a 12-lead ECG by ergonovine angiography which disappeared after administration of nitroglycerin. Asymptomatic ST deviations alone in the standard or Holter ECGs, and diffuse coronary spasm without ECG changes induced by ergonovine maleate were not considered to be positive for the diagnosis of vasospastic angina.

Four major coronary risk factors were evaluated from histories, physical examinations, and blood chemistries. Smokers included persons who had quit smoking within 1 year prior to admission. Hypertensives were defined as having a history of hypertension (systolic ≥160 mmHg or diastolic ≥95 mmHg) and who were receiving antihypertensive medications, or who had documented hypertension (systolic ≥160 mmHg or diastolic ≥95 mmHg) on at least 2 occasions at our outpatient department or after admission. Hypercholesterolemia was diagnosed in patients who showed an elevated fasting total cholesterol level (≥240 mg/dl) during admission or who had a history of hypercholesterolemia and were receiving oral lipid-reducing medications. Patients with overt diabetes or abnormal oral glucose tolerance tests were classified as glucose intolerance.

**Follow Up Data**

Most of the patients were followed at our outpatient department, affiliated hospitals or the private clinics of the referring doctors. Clinical information was obtained from outpatient records and primary physicians. The remaining information was obtained by telephone interviews. By the end of August 1992, 28 patients (28/274, 10.2%) were lost to follow-up by moving at least twice and failing to leave forwarding addresses. The actual follow-up period ranged from 10 to 160 (74.5 ± 35.4) months (Table I).

**RESULTS**

**Clinical Profile (Table I)**

Of these 274 patients, 112 were smokers (40.9%), and 127 were hypertensives (46.4%). Seventy had none of the 4 major risk factors for coronary artery disease (25.5%). Those who had 1, 2, or ≥3 risk factors were evenly distributed among the remaining 204 patients. Hemodynamic data are shown in Table II. Left ventricular filling pressure was elevated in 54 patients (≥14 mmHg, 19.7%). The mean value (10.8 ± 4.3 mmHg) was slightly higher than our previous normal data (9 ± 3 mmHg) probably due to the inclusion of 30 (55.6%) hypertensive patients. None showed global or regional wall motion abnormalities by left ventricular cineangiography. Ejection fraction ranged from 52 to 87% (68.1 ± 7.1%, n = 266).

The results of exercise stress tests are presented in Table III. Stress tests were not performed in 43 patients for various reasons, such as possible unstable angina, chronic obstructive lung disease, or neuro-muscular or orthopedic problems. Fifty-four (23.4%) were diagnosed as positive, 10 (4.3%) as equivocal or nondiagnostic, and 167 as negative. Only 11 of the 54 patients (20.4%) with a positive exercise showed elevated left ventricular end-diastolic pressure.

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**TABLE II** HEMODYNAMIC CHARACTERISTICS

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP (n=274, mmHg, Mn±SD):</td>
<td>2–22 (10.8 ± 4.3)</td>
</tr>
<tr>
<td>LVEDP≥14 mmHg:</td>
<td>54 (19.7%)</td>
</tr>
<tr>
<td>LVEF (n=266, %, Mn±SD):</td>
<td>52–87 (68.1 ± 7.1)</td>
</tr>
<tr>
<td>LVEF&lt;60%:</td>
<td>33 (12.4%)</td>
</tr>
</tbody>
</table>

*abbreviations: LVEDP=left ventricular end-diastolic pressure, EF=ejection fraction*

**TABLE III** EXERCISE STRESS TESTS

<table>
<thead>
<tr>
<th>Type</th>
<th>Total No.</th>
<th>Positive</th>
<th>Equivocal</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>231</td>
<td>54 (23.4%)</td>
<td>10 (4.3%)</td>
<td>167 (72.3%)</td>
</tr>
</tbody>
</table>
TABLE IV PROGNOSIS

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Death:</td>
<td>6</td>
</tr>
<tr>
<td>cancer:</td>
<td>2</td>
</tr>
<tr>
<td>CVA:</td>
<td>3</td>
</tr>
<tr>
<td>renal failure:</td>
<td>1</td>
</tr>
<tr>
<td>Alive:</td>
<td>240</td>
</tr>
<tr>
<td>chest pain (+):</td>
<td>36 (15.0%)</td>
</tr>
<tr>
<td>chest pain (-):</td>
<td>200 (83.3%)</td>
</tr>
<tr>
<td>readmission:</td>
<td>11</td>
</tr>
<tr>
<td>VSA:</td>
<td>4</td>
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<tr>
<td>acute MI:</td>
<td>0</td>
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<tr>
<td>unstable angina:</td>
<td>0</td>
</tr>
<tr>
<td>nonfatal CVA:</td>
<td>3</td>
</tr>
<tr>
<td>Lost:</td>
<td>28</td>
</tr>
</tbody>
</table>

**Abbreviations:** CVA = cerebro-vascular accident, VSA = vasospastic angina, MI = myocardial infarction

**Follow-up data (Table IV)**

Six patients died during the observation period: 2 from cancer, 3 from cerebro-vascular accidents, and 1 from renal failure. Three additional patients experienced nonfatal stroke. All of the 6 patients who had cerebro-vascular accidents were hypertensives. Eleven patients were readmitted for an evaluation of chest pain, and coronary cineangiography was repeated. Four were diagnosed as having vasospastic angina without organic stenosis. Significant coronary artery disease or vasospastic angina could not be detected in the other 7 patients. None of our patients experienced fatal or nonfatal myocardial infarction. No cases of sudden death were observed. About one-half of the patients (115/237, 48.5%) received cardiac medications, mainly for the control of hypertension. Most of the patients (200/240, 83.3%) were free from chest pain for at least 1 year prior to September 1992, 4 were diagnosed as vasospastic angina later while 36 others (15%) continued to complain of chest pains of various intensity (Table V). A second exercise test was interpreted as positive in only 5 of these 36 patients.

**DISCUSSION**

Our investigation revealed an excellent prognosis for patients with chest pain and normal or nearly normal coronary arteries. There were no sudden deaths, or episodes of fatal or nonfatal myocardial infarction during the observation period of more than 6 years. Three patients died of stroke and 3 additional patients suffered from nonfatal stroke.

Although the study population of this investigation was heterogeneous and difficult to classify into discrete subgroups, the patients can be categorized into 4 overlapping subgroups. The first subgroup consists of patients with anxiety neurosis. Although cardiologists claim that the patient is apparently neurotic and free from coronary artery disease, they are obligated to perform coronary cineangiography at the request of either the patient himself or referring doctors. It is very difficult to reassure such patients that they are healthy even after angiography. Six of the patients in this study who are currently disabled by daily or weekly chest pain can be classified into this category.

The second subgroup consists of patients with iatrogenic anxiety. These patients are usually middle-aged females, in whom ECG abnormalities at rest or during an exercise stress test were detected at an annual medical check-up as part of a factory- or community-based health care program. After being informed of the possibility of coronary artery disease based on abnormal ECG and/or abnormal exercise test, they become anxious about their heart conditions and begin to complain of chest pain. About one-third of our study population fell into this category. Normal findings on coronary angiography have an extremely beneficial effect in these patients, and chest pains eventually subside.

The third subgroup consists of patients with so-called syndrome X. This syndrome was first described by Likoff et al. and so named by Kemp several years later to describe patients who had typical exertional chest pain with ECG changes and normal
coronary arteries. The pathogenesis of chest pain in these patients is a current topic in cardiovascular medicine.21,22 Cannon et al.4,15 proposed the term "microvascular angina" for patients with indications of limited coronary reserve, stress-induced left ventricular wall motion abnormalities, and abnormal thallium imaging study. When chest pain and a positive exercise stress test are also observed, physicians usually recommend coronary cineangiography for these patients. About one-fourth of this study population with a positive stress test could be diagnosed as having syndrome X using the wider definition. However, only 5 patients had repeated chest pain and reproducible positive exercise stress test. Therefore, only 5 of the 274 patients in this study could be diagnosed as having syndrome X using the strict definition.

Patients in the fourth subgroup may have actual cardiac or noncardiac chest pain. They may have minor pulmonary emboli, pleuro-pericarditis, chest wall pain or upper gastro-intestinal disorders such as esophageal spasm.3 Patients with vasospastic angina are also included in this subgroup. Documentation of anginal attacks with ECG changes is very difficult in some patients with vasospastic angina, and the ergonovine test may produce a false negative when the disease activity is low.19 Although the presence of vasospasm of the epicardial coronary artery could not be detected during the initial observations, this condition was established during subsequent admissions in 4 cases.

Several prognostic studies have been published in patients with chest pain and normal or nearly normal coronary arteriograms from the United States and western Europe.1−11 However, there are no such reports dealing with an adequate study population from Japan. Our results differ from those of previous reports on several points. First, whereas almost all of the other investigators2−4,6−11 have reported small but significant numbers of fatal and nonfatal cardiovascular accidents, we encountered no cases of sudden death or myocardial infarction. Some of the study populations in these other reports have included patients with previous histories of myocardial infarction.2,8,9 Yasue et al.21 observed 12 cardiovascular deaths and 32 episodes of nonfatal myocardial infarction in 245 patients with variant angina during an observation period of 80.5 months. Although only 90 (40%) patients were free from significant coronary artery stenosis, the incidence of fatal and nonfatal cardiovascular accidents was very similar to that found in the larger studies of patients with chest pain and normal coronary arteries.6−8 Vigorous attempts to document vasospasm were not carried out in these studies. Therefore, although it has been generally said that the incidence of vasospastic angina is high in Japan and low in the United States, there remains a possibility of vasospastic angina among these study populations.

Another difference is that we observed 3 fatal and 3 nonfatal cerebrovascular accidents among hypertensives. Papanicolaou et al. from Duke University6 described 2 cerebro-vascular accident deaths among 1977 patients, while some papers have not reported any fatal or nonfatal cerebro-vascular accidents. This difference in the incidence of cerebro-vascular accidents might be related to differences in the study populations. About one-half of our patients were hypertensives, and almost all of them were receiving antihypertensive medications at the time of the evaluation. Although the 6 patients who experienced cerebro-vascular accident were also receiving medications, stroke could not be prevented.

The third difference is the incidence of continuing chest discomfort after angiography. In most of the other reports,4,6,9−11 more than 50% of the patients have disabling angina-like chest pain, and Bemiller and associates3 have reported that marked improvement of chest pain was seen in 80% of their study population. In our study, only 36 (15%) patients presently complain of chest pain.

Whereas recent observations have suggested that a subgroup of patients with syndrome X may experience repeated ischemia, and may also develop other heart disease16−18 none of the patients in our study developed congestive heart failure or cardiomyopathies. This difference might be related to the very small number of patients (5 out of 274) who had so-called syndrome X or microvascular angina in this study.

Our study suggests that coronary cine-
angiography is a good tool for predicting an excellent prognosis and for providing reassurances of health for Japanese patients with chest pain and normal or nearly normal coronary arteries.

REFERENCES

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