CLINICAL CHARACTERISTICS AND POSSIBLE ROLE OF
CORONARY ARTERY SPASM IN SYNCOPE
AND/OR ABORTED SUDDEN DEATH

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We investigated the clinical and pathophysiologic characteristics in patients with
vasospastic angina who developed syncope and/or experienced aborted sudden
death (SD). Vasospastic angina was diagnosed using the methylergonovine test.
Syncope was found in 32 (10.4%) patients among 309 who were admitted to our
institute in a one-year period. The most frequent cause of syncope was ven-
tricular tachycardia which was found in 10 (31.2%) of the 32 patients. The next
important cause of syncope was vasospastic angina which was found in 7 pa-
tients (21.8%). Among the 7 patients with vasospastic angina who experienced
one or more syncopal episodes, there were 3 patients with aborted SD, 3 with
syncope and one with shock. Cardiovascular collapse was observed in 4. In-
terior wall ischemia was found in 5 and anterior wall ischemia in 2 during the
methylergonovine test. None of the 7 patients had significant coronary stenosis.
Two patients had no prodromal symptom such as chest pain. Our results sug-
gest that coronary artery spasm may be one of the most frequent cardiovascular
diseases that causes syncope which is not always accompanied by a prodromal
symptom. Therefore, coronary spasm should be distinguished in patients with
unexplained syncope or aborted SD.

VASOSPASTIC angina is characterized by re-
current chest pain occurring at rest
without an increase in myocardial oxygen
consumption.1–2 Vasospastic angina is now
established as being the dynamic obstruction
of one or more epicardial coronary
arteries.3–4 The long-term prognosis has been
reported to be relatively good with medical
treatment during the follow-up period of
several years.5–7 However, it is well known
that one of the major complications of vaso-
pastic angina is sudden death. Cardiac death
has been reported to occur in patients with
vasospastic angina and many of these deaths
have occurred suddenly.5–8 Therefore, sud-
den death is an important factor related to
prognosis in patients with vasospastic angina.

As syncope can be followed by sudden
death, it is important to understand the
pathophysiology and the characteristics of
patients with syncope and/or aborted sudden
death for patient management, as well as for
the prevention of sudden death. Therefore,
we investigated the clinical and pathophy-
siologic characteristics in patients with vasos-
pastic angina who developed syncope and/or

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TABLE I CLINICAL DIAGNOSIS IN PATIENTS WITH SYNCOPE

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>(n)</th>
<th>(%)</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained VT</td>
<td>7</td>
<td>21.8</td>
<td>7 *</td>
</tr>
<tr>
<td>Vasoospastic angina</td>
<td>7</td>
<td>21.8</td>
<td>2 *</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>3</td>
<td>9.4</td>
<td>3 *</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>2</td>
<td>6.3</td>
<td>2</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>2</td>
<td>6.3</td>
<td>0</td>
</tr>
<tr>
<td>Complete AV block</td>
<td>2</td>
<td>6.3</td>
<td>2</td>
</tr>
<tr>
<td>Micturition syncope</td>
<td>2</td>
<td>6.3</td>
<td>2 *</td>
</tr>
<tr>
<td>WPW syndrome</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>1</td>
<td>3.1</td>
<td>1</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>1</td>
<td>3.1</td>
<td>1 *</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>1</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>2</td>
<td>6.3</td>
<td>2 *</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>100</td>
<td>23 (19 *)</td>
</tr>
</tbody>
</table>

VT = ventricular tachycardia; AV = atrioventricular; EPS = electrophysiologic study; * = EPS included VT induction

experienced aborted sudden death. In addition we also examined the frequency of syncope in cardiovascular disease and the role of vasoospastic angina.

METHOD

Subjects: (1) We determined the frequency of syncope among 309 patients with cardiovascular disease who were admitted to our institute between April 1988 and April 1989. (2) We evaluated the characteristics of patients with vasoospastic angina who developed syncope and/or aborted sudden death. Syncope was defined as a complete but transient loss of consciousness with a loss of postural tone. Aborted sudden death was defined as cardiovascular collapse of sudden onset without any evidence of acute myocardial infarction with successful resuscitation. The patients experiencing aborted sudden death became unresponsive, pulseless, apneic, and received cardiopulmonary resuscitation. A patient who developed shock with loss of postural tone was included in this study. Diagnosis of vasoospastic angina was based on at least one of the following criteria: (1) transient ST segment elevation of 0.2 mV or more on electrocardiogram (ECG) during a spontaneous attack without any evidence of acute myocardial infarction, and (2) a positive methylergonovine test.

For the differential diagnosis of syncope, all patients were interviewed and underwent complete physical examination. A 12-lead ECG, chest x-ray, routine laboratory testing, two dimensional echocardiography and at least 24-hour ambulatory ECG were performed on all patients with syncope as basic noninvasive evaluations. Electroencephalography, brain computed tomography, orthostatic blood pressure determination and bed-side carotid sinus massage were performed when a possible cause of syncope was not determined by basic evaluation. Electrophysiologic study (EPS) was also performed on 23 of 32 patients with syncope (Table I). The protocol of EPS was previously described? Sustained ventricular tachycardia (VT) was defined as lasting more than 30 sec or producing loss of consciousness, and non-sustained VT was defined as terminating spontaneously within 30 sec. EPS and spasm provocation test were performed on different days.

Methylergonovine test: A fully informed consent was obtained from each patient before cardiac catheterization and methylergonovine testing. Patients were studied in the fasting state and were premedicated with an intramuscular injection of 10 mg of diazepam one hour before catheterization. All drugs
<table>
<thead>
<tr>
<th>Case</th>
<th>Age &amp; Sex</th>
<th>Symptom (n)</th>
<th>Prodromal symptom</th>
<th>Rest ECG</th>
<th>Time</th>
<th>CVC</th>
<th>CPR</th>
<th>ECG during attack</th>
<th>EMT and coronary arteriographic findings</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>60M</td>
<td>aborted SD (3)</td>
<td>(-)</td>
<td>N</td>
<td>3:20</td>
<td>(+)</td>
<td>(+)</td>
<td>CS &amp; AVB</td>
<td>II, III, aVF ST† CS &amp; AVB</td>
<td>RCA (100)</td>
</tr>
<tr>
<td>2.</td>
<td>56M</td>
<td>aborted SD (1)</td>
<td>chest pain</td>
<td>N</td>
<td>10:30</td>
<td>(+)</td>
<td>(+)</td>
<td>NI</td>
<td>II, III, aVF ST†</td>
<td>RCA, CX (100)</td>
</tr>
<tr>
<td>3.</td>
<td>51M</td>
<td>aborted SD (1)</td>
<td>(-)</td>
<td>N</td>
<td>8:00</td>
<td>(+)</td>
<td>(+)</td>
<td>NI</td>
<td>V2~V4 ST↓</td>
<td>LAD (99)</td>
</tr>
<tr>
<td>4.</td>
<td>68M</td>
<td>shock (1)</td>
<td>epigastral discomfort</td>
<td>N</td>
<td>10:00</td>
<td>(-)</td>
<td>(-)</td>
<td>NI</td>
<td>II, III, aVF ST†</td>
<td>RCA (100)</td>
</tr>
<tr>
<td>5.</td>
<td>64F</td>
<td>syncope (4)</td>
<td>chest pain</td>
<td>N</td>
<td>7:40</td>
<td>NI</td>
<td>(-)</td>
<td>V3~V6 ST↓</td>
<td>V5~V6 ST↓</td>
<td>CX (86)</td>
</tr>
<tr>
<td>6.</td>
<td>59M</td>
<td>syncope (2)</td>
<td>chest pain</td>
<td>N</td>
<td>6:30</td>
<td>(+)</td>
<td>(+)</td>
<td>II, III, aVF ST†</td>
<td>II, III, aVF ST† AVB</td>
<td>CX (100)</td>
</tr>
<tr>
<td>7.</td>
<td>46M</td>
<td>syncope (1)</td>
<td>chest pain</td>
<td>N</td>
<td>8:15</td>
<td>NI</td>
<td>(-)</td>
<td>NI</td>
<td>II, III, aVF ST†</td>
<td>LAD (90), CX (100)</td>
</tr>
</tbody>
</table>

AVB = complete atrioventricular block; CPR = cardiopulmonary resuscitation; CS = cardiac standstill; CVC = cardiovascular collapse; EMT = methylergonovine test; EPS = electrophysiologic study; † AVB = first degree atrioventricular block; ISDN = isosorbide dinitrate; LAD = left anterior descending coronary artery; N = normal; NI = no information; ND = not done; %DS = percent diameter stenosis; SD = sudden death; ST† and ↓ = ST segment elevation and depression; (-) = absent; (+) = present.
except for sublingual nitroglycerin were discontinued at least 24 h before the methylergonovine test. Methylergonovine testing was performed on 35 patients with rest angina, cardiac arrest or unexplained syncope and 21 of them had a positive result. Methylergonovine testing was not undertaken in 4 patients who developed spontaneous attack with ST segment elevation 2 h before the study. Overall, there were 25 patients with vasospastic angina in a year.

After control coronary arteriography of multiple views, methylergonovine testing was performed. We selected the method of intracoronary administration of methylergonovine for the provocation of coronary spasm. A pacing catheter was introduced into the right ventricle in order to maintain hemodynamic stability. Left and right Judkins catheters were introduced into the ostium of each coronary artery. Methylergometrine maleate (Teikoku Hormone MFG, Co., Japan) which has a potency similar to that of ergometrine maleate\cite{10,11} was dissolved in normal saline to the final concentration of 2 \( \mu \)g per milliliter. Methylergonovine was continuously administered by intracoronary administration at the speed of 10 \( \mu \)g/min for 5 min (maximal dose of 50 \( \mu \)g) at the initial provocation site. Coronary arteriograms were obtained 3 min after administration of methylergonovine if no change was observed in the ECG. When an ECG change of ST segment elevation or depression with or without chest pain appeared, coronary arteriography was immediately performed. When a subtotal or more severe spasm occurred at the initial site, 0.5 mg of isosorbide dinitrate (ISDN) was slowly administered for relief of the spasm. After provocation of one artery, the procedure was repeated in the other coronary artery using the same protocol. The two provocation studies were done over a span of 15 min or more. Finally ISDN (2 mg) was administered into each coronary artery and coronary arteriography was repeated to assess the severity of fixed coronary stenosis.

Two experienced cardiologists independently analyzed the coronary arteriograms. Coronary diameters were measured with an electronic caliper (Model: EC-1, Sandhill Scientific Inc., U.S.A.). A Judkins catheter was used for the calibration to determine the absolute coronary diameter. The methylergonovine test was considered positive if it produced a 75% or greater narrowing of the coronary artery accompanied by an ECG change of ST segment depression or elevation.

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RESULTS

Clinical diagnosis in patients with syncope (Table I): Syncope was found in 32 patients (10.4%) among 309 who were admitted to our institute in a one-year period. Sustained VT was found in 7 (21.8%) and non-sustained VT in 3 (9.4%) patients. Seven patients were diagnosed as having vasospastic angina by detection of ST segment shifts during a spontaneous attack and/or by a methylergonovine testing. Other causes of syncope are shown in Table I. Sustained VT, non-sustained VT, sick sinus syndrome, complete atrioventricular (AV) block, WPW syndrome, atrial flutter and long QT syndrome were already diagnosed before admission. Two patients with aortic stenosis displayed a pressure gradient across the aortic valve of more than 50 mmHg. Two patients had classical histories of micturition syncope, one patient displayed symptomatic postural hypotension and one patient demonstrated focal paroxysmal findings in the electroencephalogram. Monomorphic sustained VT was induced by EPS in 7 patients with clinical sustained VT. Sustained VT was not induced in the other 12 patients.

Clinical and angiographic characteristics in vasospastic angina with syncope and/or aborted sudden death (Table II): In 7 patients with syncopal episodes, there were 3 patients with aborted sudden death, 3 with syncope and one with shock. Multiple syncopal episodes were found in 3 patients. Two patients had no history of chest pain.
Fig. 4. Electrocardiograms recorded during the methylergonovine test. After intracoronary administration of methylergonovine, ST segment elevation, inverted T wave and first-degree atrioventricular block appeared.

Fig. 5. Electrocardiograms recorded during the methylergonovine test. Soon after electrocardiographic changes appeared, cardiac standstill occurred for 5 sec. Right ventricular pacing was ineffective during cardiac standstill.

even when they developed cardiovascular collapse. One patient with shock also had no history of chest pain but had epigastric discomfort during the attack. The other 4 patients had a history of one or more episodes of chest pain occurring at rest. All syncopal episodes occurred in the early morning or morning. Cardiovascular collapse was found in 4 patients who required cardiopulmonary resuscitation. ECG changes were documented in 3 patients during the syncopal episode and/or spontaneous attack: cardiac standstill in one, and ST segment elevation or depression in 2. Serious arrhythmias were observed in 2 patients: cardiac standstill and complete AV block in one, and complete AV block in another. In one patient (case 6) with complete AV block during spontaneous attack, first degree AV block occurred during the provocation test. In patients in whom ECG was documented during a spontaneous attack, a similar ECG change was reproduced during the methylergonovine test. All patients had an ECG change during the provocation test. Inferior wall ischemia was seen in 5 patients (71%) during the methylergonovine test. Multivessel spasms were provoked in 2 patients. Mild coronary atherosclerosis was found in 3 patients and the other 4 patients had normal coronary arteries. EPS was performed on 2 patients the result of which was negative.

Presentation of a patient with aborted sudden death: A 60-year-old man (case 1 in Table II) was admitted to our institute for determination of the cause of an unconsciousness attack accompanied by cardiac arrest which occurred at night. He did not complain of chest pain during the attack. Twelve months before admission, he had experienced syncopal episodes on two occasions without chest pain after medical treatment with timolol (15 mg) for hypertension. After the syncopal episodes, timolol was stopped and treatment with nifedipine (40 mg) was begun. The patient did well over the next 12 months. After 24-hour discontinuation of the treatment with nifedipine, he suddenly developed cardiovascular collapse, and received cardiopulmonary resuscitation. ECG showed cardiac standstill and ventricular escape (Fig. 1a). During resus-
citation complete AV block appeared (Fig. 1b) and ECG returned to sinus rhythm after administration of atropine (Fig. 1c). On admission to our hospital, ECG showed no abnormality (Fig. 2). Physical and laboratory examinations were negative. We performed coronary arteriography and methylergonovine testing. No significant stenosis was found in the control coronary arteriogram (Fig. 3a). After 17 μg of methylergonovine was administered into the right coronary artery, ECG showed ST segment elevation in leads II, III, aVF (Fig. 4) and soon after the patient developed cardiac standstill (Fig. 5) and cardiovascular collapse and lost consciousness. Coronary spasm of the right coronary artery was demonstrated during the episode (Fig. 3b) but not in the left coronary arteries (Fig. 3c). Soon after 2 mg of ISDN was administered, ECG returned to normal sinus rhythm and blood pressure returned to the basal state. Coronary arteriograms after administration of ISDN showed mild coronary stenosis in the proximal right coronary artery (Fig. 3d) and normal left coronary arteries.

In the other 2 patients with aborted sudden, one patient (case 2) had a history of rest angina. He complained of chest pain and developed unconsciousness followed by apnea and pulselessness soon after swimming. Cardiopulmonary resuscitation was undertaken and he recovered about 10 min after resuscitation. The other patient (case 3) suddenly complained of general weakness at rest in the morning. He developed unconsciousness, apnea and pulselessness soon after the episode and received cardiac massage. He spontaneously recovered about 20 min after cardiac massage. When the 2 patients arrived at Hospital by ambulance, there was no evidence of ST segment shifts in the electrocardiography.

DISCUSSION

Several investigators have reported that syncope frequently occurs in 10-30% of patients with vasospastic angina. In the present study, 7 of 25 (28%) patients with vasospastic angina had a syncopal episode during the attack. However, the exact prevalence of vasospastic angina as a cardiovascular cause of syncope remains unknown. We examined the role of vasospastic angina in patients with syncope who were admitted to our cardiovascular center. Several investigators have reported that 26% to 36% of patients with syncope demonstrate cardiovascular causes. Bradyachyarrhythmia such as VT, sick sinus syndrome and AV block plays a great role in the genesis of syncope. Moreover, the role of electrophysiologic tests in the evaluation of patients with unexplained syncope has been emphasized. In the present study, the most frequent cause of syncope was VT. Our result was identical to those of previous reports but the most unusual finding was the high prevalence of vasospastic angina in the present study. Josephson et al reported that only one patient proved to have vasospastic angina out of 52 patients with syncope and/or cardiac arrest. In Japan, the frequency of vasospastic angina in patients with angina pectoris is higher than in other countries. Therefore, we suggest that vasospastic angina may be one of the most frequent cardiovascular diseases which can cause syncope in Japan.

The long-term prognosis of vasospastic angina has been reported to be relatively good. However, sudden death is one of the major complications in patients with vasospastic angina. During a follow-up period of several years, cardiac death occurred in 2% to 20% of patients with vasospastic angina, and 41% to 71% of cardiac deaths occurred suddenly. In the present study, 4 patients among 7 developed cardiovascular collapse and required cardiopulmonary resuscitation. We suggest that vasospastic angina may play a role in the pathophysiology of unexplained sudden death in Japan because of a high incidence of cardiovascular collapse requiring cardiopulmonary resuscitation as shown in this study. Many patients with vasospastic angina who develop sudden death in Japan have no significant coronary stenosis. Yasue et al reported that multivessel coronary spasm is the most important influencing factor on prognosis. In the present study, there was no patient with significant coronary stenosis and 2 patients were induced multivessel coronary spasm by the methylergonovine test. In contrast, several investigators have reported that a high frequency of significant coronary ste-

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nosis in one or more vessels is observed in vasospastic angina with sudden death in other countries. The cause of the difference between our result and that of other countries remains unknown.

In 3 patients among 7, aborted sudden death or shock was not accompanied by chest pain. This is an important point from both diagnostic and therapeutic standpoints. Meseri et al. reported that only 32% of 6,009 episodes of ischemic ECG change were accompanied by chest pain. Chest pain appeared two or more minutes after the onset of ST segment elevation. We suggest that a loss of consciousness may be preceded by chest pain because of the high prevalence of serious arrhythmia in patients suffering vasospastic angina with sudden death.

Ventricular tachycardia, atrioventricular block and electromechanical dissociation due to multivessel coronary spasm were suggested as pathophysiological factors of syncope in vasospastic angina. Our results suggest that vasospastic angina may be present in some patients who develop syncope or cardiovascular collapse even without chest pain. Therefore coronary spasm must be distinguished by a spasm provocation test.

We performed spasm provocation test by intracoronary injection of methylergonovine. It is suggested that persistent coronary spasm and multivessel coronary spasm which might produce cardiovascular collapse and even death could be prevented. Spasm provocation test must be carefully performed especially in patients with vasospastic angina who experienced syncope and cardiovascular collapse. In one patient among 7, cardiac standstill and cardiovascular collapse was reproduced by spasm provocation test, but the patient returned to a basal state soon after relief of the coronary spasm by intracoronary administration of ISDN. We suggest that the method of intracoronary administration of methylergonovine is effective and safer than intravenous injection.

CONCLUSIONS

Vasospastic angina is one of the most frequent cardiovascular causes of syncope. Multivessel coronary spasm and inferior wall ischemia are suggested to be involved in the pathophysiology of syncope and/or aborted sudden death. There may be a possibility of the existence of vasospastic angina in patients who develop syncope and/or experience aborted sudden death even in the absence of a prodromal symptom such as chest pain. Coronary spasm provocation testing should be performed in these patients because a high prevalence of syncope in patients with vasospastic angina and the risk of sudden death may be especially high in patients with aborted sudden death. A limitation of our study is the small number of patients studied, and further investigations with a large number of patients are necessary to discover the factors influencing the prognosis.

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