Long-Term Prognosis of Vasospastic Angina without Significant Atherosclerotic Coronary Artery Disease

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SUMMARY

Long-term prognosis of 90 patients with vasospastic angina without significant coronary artery disease (less than 50% reduction in luminal diameter) was examined for a mean follow-up period of 4 years. All patients had episodes of angina at rest and were treated with calcium antagonists. One patient developed myocardial infarction and 2 died suddenly during the follow-up period. In the patient with myocardial infarction, there was an abrupt worsening of angina prior to the infarction despite therapy with a calcium antagonist. One of the sudden death patients discontinued his calcium antagonist before his death. Of the sudden death patients, one had ventricular tachycardia and the other had a complete atrioventricular block during an anginal attack. The incidence of such serious arrhythmias was higher (p<0.01) in sudden death patients (2/2) than that in survivors (6/88). The treatment with calcium antagonists reduced the severity and frequency of angina in all patients. These results suggest that long-term prognosis of vasospastic angina without significant coronary artery disease is good as characterized by the low incidence of myocardial infarction and death and the favorable response to treatment with calcium antagonists.

Additional Indexing Words:
Vasospastic angina Coronary artery spasm Prognosis No significant coronary artery disease

Many studies have considerably increased our understanding of the clinical and coronary arteriographic characteristics and treatment of patients with vasospastic angina.1-8 Recently, the long-term prognosis of large numbers of patients with vasospastic angina has been reported by several
investigators.9)-11) These reports have identified the presence of atherosclerotic coronary artery disease as the strongest prognostic factor in patients with vasospastic angina. Since a large proportion of these patients had significant coronary artery disease, results of previous studies cannot be applied to patients with vasospastic angina without significant coronary artery disease. In addition, these reports involved considerable numbers of patients who were not treated with calcium antagonists. With more recent reports on the effects of calcium antagonists on reduction of complications in patients with vasospastic angina,10),22) the long-term prognosis of vasospastic angina may now be greatly improved by treatment with calcium antagonists over that previously reported.9)-11)

In the present study, we describe the long-term prognosis of medical treatment of vasospastic angina without significant coronary artery disease in 90 patients admitted to our hospital during a recent 9-year period. All of these patients were initially treated with calcium antagonists such as diltiazem, nifedipine or verapamil, after coronary spasm diagnosis. The incidences of myocardial infarction and death were considerably lower in our patients compared to those reported in previous comparably sized studies.9)-11)

**Methods**

**Study patients:**

In the present study, diagnosis of coronary artery spasm without significant coronary artery disease was made in patients meeting all of the following criteria: 1) typical anginal pain occurring at rest that was relieved spontaneously or promptly after sublingual nitroglycerin, 2) anginal pain with transient electrocardiographic ST elevation of more than 0.2 mV from the base line level, or with ergonovine-induced coronary diameter reduction by over 50% compared to coronary diameter after intravenous nitroglycerin, 3) angiographically, no significant organic coronary stenosis (<50% narrowing of luminal diameter) and no evidence of previous myocardial infarction. Between January 1977 and December 1985, 90 consecutive patients meeting the criteria were admitted to Kyushu Kohsei-Nenkin Hospital. The clinical features of the patients are summarized in Table I. The mean age of the patients was 58 years (range 38 to 70) with 76 men and 14 women. Rest angina was present in all patients; effort angina was also present in 26 of the 90 patients. The ECG at rest was within normal limits in 76 patients. During angina transient ST elevation was noted in 59 patients (27 in anterior leads, 28 in inferior leads and 4 in both areas). In another 31 patients, significant ECG-ST changes were not documented during episodes of angina,
but angina with coronary spasm was provoked after ergonovine administration. Serious arrhythmia such as ventricular fibrillation, ventricular tachycardia and advanced atrioventricular block were documented during anginal attack in 8 patients. Treadmill exercise testing revealed ST elevation of more than 0.2 mV in 2, ST depression of more than 0.1 mV in 10 and a normal pattern in 78 patients.

**Patient management:**

All patients were admitted to the coronary care unit and underwent continuous ECG monitoring. Medical treatment with calcium antagonists, with or without nitrates, was immediately started and continued until cardiac catheterization. A 12 lead ECG was recorded during episodes of angina when possible.

**Cardiac catheterization:**

All medications except sublingual nitroglycerin were withheld for at least a day before cardiac catheterization. Coronary arteriography was performed in all 90 patients by Sones’ technique in multiple views after intravenous bolus administration of nitroglycerin (0.25 mg). Ergonovine testing was routinely
done in cases with suspected but unproven angina before nitroglycerin administration. Serial intravenous ergonovine in doses of 0.05 and 0.15 mg (total 0.2 mg) was administered at 3 to 5 min intervals. Coronary angiograms were performed after each ergonovine injection. If anginal pain associated with reductions in coronary artery diameter by over 50%, compared with that after intravenous nitroglycerin, were documented after ergonovine, we considered the test as positive and intravenous nitroglycerin was given without delay. A left ventriculogram was filmed in biplane projections (right anterior oblique 30° & left anterior oblique 60°). Left ventriculography was not done in 6 patients.

**Therapy and follow-up:**

Soon after the diagnosis of coronary spasm, all patients were treated with a calcium antagonist such as verapamil (n=14), nifedipine (n=20), diltiazem (n=52), or combinations of nifedipine and diltiazem (n=4). Long-acting nitrates were added if needed to control angina. The usual doses of drugs were 120 to 240 mg/day for verapamil, 40 to 80 mg/day for nifedipine and 120 to 240 mg/day for diltiazem. All patients became asymptomatic upon discharge from the hospital. Following discharge, each patient was followed as an outpatient, usually by the same physician, at 1 month intervals. Questionnaires were made regarding the frequency, duration and severity of anginal pain. A standard chest X-ray and ECG were obtained at intervals of at least 6 months. The mean follow-up period was 4 years (range 6 to 108 months).

**Statistical analysis:**

Distribution of clinical characteristics in patients with and without serious events was analyzed by Fisher’s exact test. Probabilities of less than 5% were considered significant.

**Results**

No patient died during the hospitalization period. One patient developed myocardial infarction and 2 died during the follow-up.

**Myocardial infarction and death:**

One patient developed inferior myocardial infarction, diagnosed by typical symptoms and serial electrocardiographic changes, 8 months after discharge from the hospital. During his hospitalization, spontaneous attacks did not occur but transient 90% luminal narrowing of the right coronary artery was provoked by ergonovine administration. Coronary arteriography after
nitroglycerin revealed 25% organic stenosis at the site of the induced spasm and no stenosis in the left coronary artery. Thus, the electrocardiographic site of the infarction corresponded to the site of the previously provoked coronary artery spasm. After discharge, he had been asymptomatic for 8 months with diltiazem (240 mg/day). Worsening angina pectoris was present for a few days prior to the infarction.

One patient died suddenly at midnight shortly after the onset of chest pain and before he could take nitroglycerin while travelling during the 3rd year of his follow-up period. He personally discontinued verapamil for 2 days prior to his death, as he had forgotten to bring it with him. During initial hospitalization, his ECG showed transient ST elevation in inferior leads that were associated with advanced atrioventricular block. Spontaneous spasm with transient 80% luminal reduction along the right coronary artery was found on arteriography during his hospitalization. The patient had been asymptomatic with verapamil therapy just before discontinuation of the drug. A second patient died suddenly during the 2nd year of his follow-up period. He had been asymptomatic on nifedipine 80 mg/day and long-acting nitrate 80 mg/day, and continued his medication up to his death. He was found dead in bed in the early morning by his family. During his hospitalization, transient ST elevation in anterior leads with ventricular tachycardia had been documented.

Comparison of clinical characteristics:
Clinical characteristics of the patients who died or experienced myocardial infarction were compared with those of the patients who did not. There was no difference in age distribution, sex ratio, history of effort angina, normal ECG findings, location of spasm and so on. A statistically significant difference between the 2 groups was noted only in the presence of serious arrhythmia during angina; serious arrhythmia was documented in both sudden death patients (100%), and only 6 of the 88 survivors (7%, p<0.01).

Effects of calcium antagonist drugs on treatment:
During the follow-up period, angina became less frequent and less severe in all patients, although a few patients showed fluctuations in symptoms while on therapy. Two patients were readmitted to the hospital because of recurrent episodes of angina despite therapy. One of them became asymptomatic with increased diltiazem dosage and the other responded when long-acting nitrates were added. Calcium antagonists were eventually discontinued in 7 patients. No serious drug related side effects were observed during the follow-up period.
DISCUSSION

This study may define the long-term prognosis for Japanese patients with vasospastic angina without significant coronary artery disease. The present study included a relatively large number of patients with vasospastic angina without significant atherosclerotic coronary artery disease, all of whom had been medically treated with calcium antagonists. To our knowledge, no published reports have included this number of patients with vasospastic angina without significant coronary artery disease.

Prognosis of vasospastic angina without significant coronary artery disease:

The results of our study indicate that long-term prognosis of medically treated patients with vasospastic angina without significant coronary artery disease is apparently good, as evidenced by the low overall mortality rate, the rare incidence of myocardial infarction, and steady tendency toward improvement of symptoms after therapy with calcium antagonists. A large incidence of myocardial infarction and death especially during the first 3 or 6 months after the diagnosis of vasospastic angina has been reported in previous studies. This trend however, was not evident in our patients.

The number of patients with sudden death was small in our study, which may present difficulties in analyzing the risk factor of sudden death. However, serious arrhythmias during anginal episodes were documented in both sudden death patients. The incidence of such arrhythmias in the sudden death patients was significantly higher (p<0.05) than that in the survivors. Thus, our results may suggest that the presence of serious arrhythmias during angina may be an important prognostic factor in vasospastic angina with no significant coronary artery disease. Miller et al also reported that the occurrence of serious arrhythmias during coronary spasm may be an indicator of a worse prognosis.

Comparison with previous studies:

Sudden death and myocardial infarction occurred in 2 and 1 of our patients, respectively. These incidences are considerably lower than those in the previous comparably sized follow-up studies where the rates of cardiac death were 8–11% and those of myocardial infarction 13–23%. One of the major factors likely to have contributed to the differences in the rate of cardiac events is that none of the patients in the present study had significant coronary stenosis of more than 50%. The other likely factor is treatment with calcium antagonists. Significant reduction in rate of cardiac events following treatment with calcium antagonists has been reported. However, the re-
relative contributions of the two factors is unknown.

There are two previous follow-up studies of the long-term prognosis of vasospastic angina without significant coronary artery disease, although the numbers of patients included were small. In a study by Bott-Silverman et al., no cardiac death and 11 myocardial infarctions (19%) occurred in 59 patients after treatment with long-acting nitrate during an average follow-up period of 5.9 years. In addition, Freedman et al.12) reported that no death or myocardial infarction occurred during a follow-up period of 3 years in 37 patients treated with calcium antagonists. Thus, our current results may confirm those preliminary observations that vasospastic angina patients without significant coronary artery disease are basically at low risk for cardiac events when given calcium antagonist therapy.

**Effects of treatment:**

In the present study, treatment with calcium antagonists did improve symptoms of angina. It is notable that angina pectoris in the patient with myocardial infarction has been under control with diltiazem but there was an abrupt worsening of angina prior to his infarction. It should also be noted that one patient died suddenly despite therapy with calcium antagonists and another died suddenly when angina recurred after accidental discontinuation of a calcium antagonist. In both sudden death patients, angina pectoris appeared to be well controlled just prior to the occurrence of the events. These findings might imply that the disappearance of subjective symptoms with calcium antagonist therapy is not necessarily a definite indicator of adequate treatment in patients with vasospastic angina. Egashira et al.22) reported the occurrence of acute myocardial infarction following painless ST elevation despite diltiazem therapy. However, it is suggested that all patients with coronary spasm should be treated with calcium antagonists independently of the presence of coronary artery disease, since long-term effects of calcium antagonists on the reduction of complications have been reported by several investigators.9),10),12),14),15),17),18)

Whether or not lifelong therapy is required in asymptomatic patients has not been elucidated at the present time.19) In this study, one of the 2 sudden deaths occurred soon after withdrawal of calcium antagonist therapy. Thus, it should be considered that when the reduction or discontinuation of medical therapy is attempted in asymptomatic patients, the decision should be made with caution, especially in patients with documented serious arrhythmias during angina.
CONCLUSIONS

A limitation of this study was that it was retrospective and uncontrolled. However, despite these limitations, the clinical implication of our current results which is worth emphasizing is that the long-term prognosis of Japanese patients with vasospastic angina without significant coronary artery disease is considerably better under treatment with calcium antagonists, than that reported for patients with significant coronary disease. Thus, it may be suggested that coronary arteriography is required for accurate prognostic classification of patients as there are no other consistent factors reported so far that permit adequate discrimination between the 2 groups.11,21

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REFERENCES