Clinical Studies

Factors Influencing the Clinical Course and the Long-term Prognosis of Patients with Variant Angina

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SUMMARY

The purpose of this study was to clarify the factors influencing the clinical course and prognosis in variant angina. Also, the mechanism of acute myocardial infarction in variant angina is reviewed. The subjects were 110 patients with variant angina who, after the initial visit or admission, were observed for a period of at least 2 months, the average observation period being 68 ± 49 months (range: 2 months–16 years). The incidence of acute myocardial infarction was 21.8% of these patients and 87.5% of the infarctions occurred within 1 month of the initial visit or admission. In variant angina, the average rate over 1 year was 2.2%; however, in classical angina the rate was 3.7% and in postinfarction angina 5.0%. The mortality rate was 5.5%, with death in the majority of cases occurring within 1 month, as in myocardial infarction. When treatment was stopped, spontaneous remission occurred in at least 26 of the 110 cases (23.6%). Beyond 3 months, the remission continued in 19 of these 26 cases. Seven cases had acute myocardial infarction in spite of the suppression of anginal attacks with administration of calcium antagonists. Apparently coronary spasm is the cause of anginal attacks, and the cause of acute myocardial infarction in patients with variant angina appears to be coronary thrombus formation.

Additional Indexing Words:

Mortality rate Cardiac events Acute myocardial infarction
Spontaneous remission Calcium antagonists Postinfarction
angina Classical angina

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IN variant angina, acute myocardial infarction and life-threatening arrhythmia occur in the early stage.¹⁾⁻⁷⁾ Conversely, after a course of treatment passes a certain stage, conditions improve. Symptoms usually disappear and medical treatment can be discontinued for many patients. Therefore, it has been reported^{3),8),9)} that the clinical course and prognosis of variant angina are different from those of other types of angina pectoris. In this regard, it appears that calcium antagonists are markedly effective in suppressing anginal attacks^{10),11)} and that variant angina is characterized by spontaneous remission.^{8),12),13)}

The purpose of this study was to clarify the factors influencing the prognosis of this disease. For this purpose we studied patients with variant angina, including those with acute myocardial infarction and with spontaneous remission. The clinical features studied included the natural history of the disease, the results of treatment and future therapeutic strategies.

SUBJECTS AND METHODS

1. Patients

The subjects were 110 patients (92 males and 18 females) hospitalized at the Nippon Medical School and diagnosed as having variant angina. Their ages ranged from 29-84 years (mean 57.1 ± 10.1 years). Variant angina was defined as a transient ST-segment elevation of over 0.1 mV in any lead during a spontaneous anginal attack. Patients with a history of myocardial infarction were excluded. The period of observation was from 2 months to 16 years (mean 68.1 ± 48.9 months). All of the observations were made by the same physician over the entire period. The observations started the day of the patients' initial visit or admission. To compare the cardiac events in variant angina with those in patients with other types of angina pectoris, we included 185 patients with classical angina showing ST-segment depression during attacks (118 males and 67 females, average age 59.8 ± 10.0 years) and 91 with angina and a history of myocardial infarction (hereafter referred to as postinfarction angina, 79 males and 12 females, average age 59.0 ± 8.6 years). Cardiac events included acute myocardial infarction, recurrent infarction, cardiac death, aorto-coronary bypass graft surgery (ACBG) and percutaneous transluminal coronary angioplasty (PTCA).

2. Coronary arteriography

Coronary arteriography was carried out on 82 cases (72 males and 10 females, average age 53.9 ± 10.9 years) and the average observation period was 73.1 ± 45.1 months. A significant coronary artery lesion was defined as a luminal diameter stenosis of 75% or greater. No significant stenosis was

found in 30 cases; 40 cases had single vessel disease and 12 had multivessel disease. Of 82 cases in whom coronary arteriography was performed, 18 had acute myocardial infarction in addition to variant angina. Sixteen of the 18 cases had coronary arteriography after the myocardial infarction. Left ventriculography was carried out on 79 of the same patients who underwent coronary arteriography and the findings classified according to American Heart Association standards as hypokinesis, akinesis, dyskinesis and aneurysm, all regarded as "left ventricular wall motion abnormality". Nineteen of 79 cases had motion abnormalities. The left ventricular ejection fraction was calculated using the area-length method in the 30° right anterior oblique projection of the left ventriculography. The normal ejection fraction was defined as more than 60%. Eleven out of 58 cases in whom ejection fraction was calculated showed less than 60%.

3. Patient management

Of the 110 cases, 92 received drug therapy. Of these, 14 had acute myocardial infarction after drug therapy. After hospitalization, 10 patients were found not to need drug therapy as they were angina-free, but 1 of the 110 patients had to have urgent coronary bypass graft surgery. Also, immediately after hospitalization 7 patients had acute myocardial infarction, and 3 of these died. Three of the remaining 4 cases required treatment. Thus, 21 patients had acute infarction in the acute phase of this disease. Ninety-two patients were treated with drugs: 59 with calcium antagonists only, 12 with anticoagulants, 11 with nicorandil,¹⁴⁾ 4 with, initially, continuous nitroglycerin infusion, 3 with isosorbide, 1 with calcium antagonist-isosorbide combined, 1 with topical nitroglycerin and 1 with a continuous intravenous infusion of diltiazem.

4. Drugs

Nifedipine was the most frequently used calcium antagonist, the daily dose being 30–60 mg (40 mg in most cases). Other calcium antagonists used (and their daily doses) were diltiazem, 90–180 mg (usually 120 mg), verapamil, 120–240 mg (usually 160 mg) and perhexiline, 300–400 mg (usually 300 mg). Nicorandil was used in 20–50 mg doses (usually 20 mg) and long-acting oral nitrates in doses of 60–120 mg (usually 120 mg). The drugs were administered every 4–6 hours. Continuous intravenous infusions of nitroglycerin and diltiazem were used to treat uncontrolled anginal attacks.

5. Statistical analysis

Statistics were analyzed using the Chi-square test. For analysis of prognosis of each type of angina pectoris, curves for cardiac events were constructed using standard life-table analysis. The results were considered significant at $p < 0.05$.

RESULTS

Clinical course

Fig. 1 shows a summary of the clinical course of the disease following hospitalization. Of the 110 cases, 21 (19.1%) had infarction, 89 did not. Of the 89 cases without infarction, 78 had initially received treatment, while 10 had no attacks after admission and were discharged without medication. The remaining case required urgent aorto-coronary bypass graft surgery. Of those treated initially, 52 continued receiving treatment during the ensuing clinical course of their disease, while 6 required no further treatment; however, during the clinical course, cardiac events such as acute myocardial infarction, cardiac death and aorto-coronary bypass graft surgery occurred in 4 of them. Of the 10 who had received no drug treatment, 4 were able to continue without treatment and 1 underwent aorto-coronary bypass graft surgery. No "follow-up" was possible with the remaining 5 after their discharge from hospital.

Of the 21 cases with acute myocardial infarction, 14 had infarction despite medical treatment. Seven had the infarction immediately after entering hospital and 3 of them suffered cardiac death. During a follow-up period after initial treatment, 9 of the 14 cases still receiving treatment con-

Fig. 1. Clinical course after initial treatment in patients with variant angina pectoris.

* Aorto-coronary bypass graft surgery.

** One patient who had cardiac death.

*** Patients in whom we could not follow the clinical course at the time of this study.

tinued with the treatment. Later, the treatment was discontinued in 2 of these 9 patients. Of the 4 cases with infarction immediately after admission, 2 received treatment subsequently, and 1 thereafter stopped having anginal attacks and so treatment was also stopped.

Of the 110 cases with variant angina during the follow-up period, 24 had acute myocardial infarction, 21 (87.5%) of them within 1 month. The remaining 3 developed acute myocardial infarction 4, 18 and 53 months after initial diagnosis. Nine patients died during the follow-up period. Six were cardiac deaths, 3 were non-cardiac. Three of the cardiac deaths occurred within 6 days after admission and the others were 3, 4 and 53 months after initial diagnosis. Accordingly, the incidence of cardiac death within 1 year was 4.5%.

Clinical features in cases with and without acute myocardial infarction

As shown in Table I, the duration of a history of angina pectoris is shorter, there is a greater incidence of rest and exertional angina and of unstable angina, and there is a greater prevalence of ST-segment elevation in the anterior lead and more frequent occurrence of arrhythmias during attacks in the infarction group when compared to the non-infarction group.

Occurrence of cardiac events in variant angina

Fig. 2 shows the frequency of occurrence in a 10-year period of cardiac events in patients with variant angina, classical angina and infarction angina, according to a life-table analysis. In classical angina there were 43 cases of acute myocardial infarction of which 5 had recurrences of infarction, 19 suffered cardiac death, 8 had ACBG surgery (1 case twice) and 1 had PTCA. With variant angina, there were 24 cases of acute myocardial infarction. Of these, 6 suffered cardiac death, 3 had recurrence of infarction and ACBG was performed in 3 cases. In postinfarction angina, 19 cases had a second infarct. Of these, 6 suffered cardiac death, 3 had a third infarct and ACBG was performed in 12 cases.

Three months after initial diagnosis, the frequency of cardiac events was 20.7% in variant angina, 8.1% in classical angina and 2.1% in postinfarction angina (Fig. 2). There were significant differences between the former and the latter 2 types of angina ($p < 0.01$, $p < 0.001$, respectively). However, the average annual rate of cardiac events from 6 months to 10 years after admission was 2.2% in variant angina, 3.7% in classical angina and 5.0% in postinfarction angina. Thus, the rate was higher in the latter 2 types of angina than in variant angina.

In summary, the incidence of cardiac events in variant angina is high

Table I. Clinical Features of Groups with and without Acute Myocardial Infarction in Patients with Variant Angina Pectoris

	Acute myocardial infarction		p Value
	Present	Absent	
Number of patients (male: female)	24 (19 : 5)	86 (73 : 13)	—
Duration of angina (months)	9.3±21.8	17.7±27.8	NS
Predominant symptom			
Angina at rest	2 (8.3%)	34 (39.5%)	p<0.01
Angina at rest & of effort	16 (66.7%)	40 (46.5%)	NS
Angina of effort	6 (25.0%)	12 (14.0%)	NS
Unstable angina	22 (91.7%)	64 (74.4%)	NS
Associated disease	16 (66.7%)	49 (57.0%)	NS
Electrocardiogram			
Abnormal rest ECG	13 (54.2%)	32 (37.2%)	NS
Sites of ST-segment elevation			
Anteroseptal	15	39	NS
Anterolateral	2 ¹⁷	6 ⁵⁰	
Anterior & inferior	0	5	
Inferior	7	36	
Arrhythmias during attacks	17 (70.8%)	41 (47.7%)	p<0.05
Coronary arteriography			
No fixed lesions <75%	1/18(5.6%)	29/64(45.3%)	p<0.01
Single vessel disease	11/18(61.1%)	29/64(45.3%)	
Multivessel disease	6/18(33.3%)	6/64(9.4%)	
Involved vessel			
Left anterior descending artery lesion	13/18(76.5%)	25/64(39.1%)	p<0.01
Circumflex artery lesion	5/18(29.4%)	9/64(14.1%)	NS
Right coronary artery lesion	4/18(23.5%)	10/64(15.6%)	NS
Abnormal ventriculogram	12/15(80.0%)	7/64(10.9%)	p<0.001
Left ventricular ejection fraction less than 60%	5/ 8(62.5%)	6/50(12.0%)	p<0.001

in the acute phase and the rate increases slightly thereafter, but in classical and postinfarction angina the annual rates increase by stages. Thus, it appears that the mode of occurrence of cardiac events is different in the latter 2 types of angina from that in variant angina. In order to determine why the course of variant angina proceeds satisfactorily, the factors influencing the effects of treatment were examined.

Effects of treatment and spontaneous remission

In order to examine the effects of treatment in variant angina, the treated patients were classified into 2 groups: those who continued to experience

Fig. 2. Probability of cardiac events in each group with classical angina, variant angina or postinfarction angina after initial visit or admission.

attacks (group A) and those whose attacks had completely disappeared for a long period (group B). In addition, the patients who had not had long-term treatment and had been angina-free were classified as group C. The clinical characteristics in these 3 groups were compared.

As shown in Table II, group A consisted of 44 cases, group B of 43 and group C of 19, and their respective incidence rates of acute myocardial infarction were 40.9%, 4.7% and 0%, with the incidence of cardiac death being, respectively, 6.8%, 0% and 0%, giving group A the highest rates of cardiac events. In group A, 20 of 44 cases (45.5%) were treated exclusively with calcium antagonists, while 13 (29.0%) were treated with a combination of antianginal drugs; the corresponding figures, respectively, for group B were 28 of 43 (65.1%) and 8 of 43 (18.6%), indicating less use of the combined drugs with group B. With group C, 11 of the 19 received initial treatment. Of these, 7 were treated exclusively with calcium antagonists with marked effectiveness, 2 cases with anticoagulants and 1 case each with nicorandil and a combination of drugs. The remaining 8 did not receive any treatment following initial diagnosis.

The effects of treatment in group A were not good and the prognosis was poor. On the other hand, of the other 62 cases (groups B and C), a large majority had no attacks at all over a long period whether they received medical treatment or not. The cause of satisfactory prognosis may be attributed to the effectiveness of calcium antagonists, but spontaneous remis-

Table II. Clinical Features of Groups with Persistent Angina and Angina-free on Treatment and Those with Spontaneous Remission without Treatment

	With treatment		Without treatment	Comparison	p Value
	Persistent angina	Angina-free	Remission		
Number of patients (male : female)	44 (37 : 7)	43 (36 : 7)	19 (17 : 2)	—	—
Duration of follow-up (Mo)	65.3±45.0	69.8±47.0	97.7±46.9	AP (+) : AP (-)	p<0.001
Acute myocardial infarction	18 (40.9%)	2 (4.7%)	0 (0%)	AP (+) : RM	p<0.001
Cardiac death	3 (6.8%)	0 (0%)	0 (0%)		NS
Duration of angina (Mo)	9.7±18.5	19.8±30.6	11.8±18.7		NS
Predominant symptom					
Angina at rest	7 (15.9%)	20 (46.5%)	11 (57.9%)	AP (+) : AP (-)	p<0.01
Angina at rest & of effort	30 (68.2%)	20 (46.5%)	5 (26.3%)	AP (+) : RM	p<0.001
Angina of effort	7 (15.9%)	3 (7.0%)	3 (15.8%)		NS
Unstable angina	40 (90.9%)	32 (74.4%)	11 (57.9%)	AP (+) : AP (-)	p<0.05
Associated disease				AP (+) : RM	p<0.01
Electrocardiogram	27 (61.4%)	23 (53.5%)	8 (42.1%)		NS
Abnormal rest ECG	18 (40.9%)	13 (30.2%)	9 (47.4%)		NS
Site of ST-segment elevation					
Anteroseptal	18 (40.9%)	23 (53.5%)	8 (42.1%)		NS
Anterolateral	6 (13.6%)	2 (4.6%)	0		NS
Anterior & inferior	2 (4.6%)	3 (7.0%)	0		NS
Inferior	18 (40.9%)	15 (34.9%)	11 (57.9%)		NS
Arrhythmias during attacks	29 (65.9%)	23 (53.5%)	9 (47.4%)		NS
Coronary arteriography					
No fixed lesions <75%	8/35 (22.9%)	16/31 (51.6%)	5 (41.7%)	AP (+) : AP (-)	p<0.05
Single vessel disease	20/35 (57.1%)	14/31 (45.2%)	4 (33.3%)		
Multivessel disease	7/35 (20.0%)	1/31 (3.2%)	3 (25.0%)		
Abnormal ventriculogram	13/35 (37.1%)	4/31 (12.9%)	2/12 (16.7%)	AP (+) : AP (-)	p<0.05
Left ventricular ejection fraction less than 60%	7/27 (25.9%)	2/26 (7.7%)	0/16 (0%)		NS

Four patients were excluded from Table II because they had acute myocardial infarction immediately after admission.

AP (+)=persistent angina ; AP (-)=angina-free ; RM=spontaneous remission ; Mo=months.

sion may also be involved. Moreover, it may also be that patients in groups B and C had much less severe disease.

There was a significantly higher frequency of rest angina in groups B ($p < 0.01$) and C ($p < 0.001$) than in A, but group A had a higher frequency of rest and exertional angina. Group A had a significantly greater frequency of unstable angina than group B or C ($p < 0.05$, $p < 0.01$, respectively). Only 22.9% of group A patients had no significant stenotic lesions, compared with 51.6% of group B and 41.7% of group C. The difference between groups A and B was significant ($p < 0.05$). The type responding to treatment or whose treatment could be stopped had more rest angina, and fewer unstable angina and coronary artery lesions.

Table III shows the clinical course of those 43 cases for whom temporary or long-term treatment was suspended. These patients were classified according to the length of time medication had been suspended: less than 3 months and 3 months or more. In the first group, 7 of 24 cases had no attacks. In the other group, none of the 19 had attacks. So there was remission in 26 cases in all. Accordingly, the frequency of spontaneous remission for all 110 cases was at least 23.6% and that of long-term remission for the 110 cases was 17.3%. However, of the group whose short-term treatment was stopped, 17 cases had recurrence of attacks and 2 had myocardial infarction, which resulted in sudden death in 1 of them. It was not possible to analyze the characteristics of the clinical features of the 17 cases in detail as the number was rather small, but they were similar to those cases still receiving treatment and having persistent angina.

Table III. Clinical Course of 43 Patients with No Medical Treatment

	No. of patients	Recurrence of attacks		Development into myocardial infarction	Cardiac death	Non-cardiac death
		Absent	Present			
Total	43	26	17	2	1	1
No treatment for a short period	24	7	17*	2**	1***	0
No treatment for a long period	19	19	0	0	0	1

* Rest angina recurred in 8 of 17 patients, rest and exertional angina in 3 and exertional angina in 6.

** Recurrence of myocardial infarction was present in 1 of 2 patients.

*** One patient had sudden death.

Remissions were considered short-term when they persisted for up to 3 months and long-term when they persisted for more than 3 months.

DISCUSSION

The cause of acute myocardial infarction in variant angina

As previously reported¹⁾⁻⁴⁾ myocardial infarction often occurs soon after variant angina appears. Prinzmetal et al¹⁾ noted that acute myocardial infarction occurred in 11 of 35 cases (31.4%). According to Severi et al,³⁾ 23.2% of 138 cases had infarctions, 87% of which occurred within 1 month after the angina appeared. According to Waters et al,¹⁵⁾ 13.0% of 169 cases, had infarctions, 91.0% of these occurred within 3 months. Mark et al⁹⁾ reported that myocardial infarction occurred in 14 of 62 cases (22.6%) with initial medical treatment and 85.7% of them occurred within 1 month. Similarly in our study, 24 of 110 cases (21.8%) had myocardial infarction, 87.5% of them within 1 month. Therefore, the importance of treatment during the initial phase must be emphasized.

In the acute phase of this disease, most cases appear to have unstable angina; however, it is unclear whether treatment should consist of a calcium antagonist alone as the drug of choice. The initial treatment with calcium antagonists as used in this study was markedly effective in a large number of cases. But of the 10 patients who had myocardial infarction during treatment with calcium antagonists, 7 had a decrease in anginal attacks to less than half of the initial rate. In 2 other cases, despite the complete disappearance of attacks, acute myocardial infarction occurred later with further anginal attacks. Waters et al⁴⁾ have reported similar cases.

It has been conjectured^{16),17)} that a prolonged coronary artery spasm precipitates acute myocardial infarction in variant angina, but our study and that of Waters et al⁴⁾ clearly indicate that factors other than spasm are more important in the pathogenesis of the infarction.

Coronary artery thrombi have been found by several investigators hours after the onset of myocardial infarction with unstable angina.¹⁸⁾⁻²¹⁾ It has been suggested by some that coronary artery spasm produces acute myocardial infarction in cases with normal coronary arteries.^{17),22),23)} But Heupler et al²⁴⁾ reported that an ergonovine test on such patients showed negative results. O'Reilly et al,²⁵⁾ Glancy et al²⁶⁾ and Bruschke et al²⁷⁾ found, using coronary arteriography, that myocardial infarction in patients with normal coronary arteries is produced by a thrombus or an embolism. In cases with unstable angina, including those showing ST-segment elevation during attacks, the rate of acute myocardial infarction was higher before calcium antagonists were introduced than after they were administered.²⁸⁾

If it is assumed that coronary artery spasm leads to anginal attacks and that intra-coronary thrombi precipitate acute myocardial infarction, it may

be that calcium antagonists inhibit anginal attacks and that they therefore can prevent myocardial infarction. However, as this study has indicated, although anginal attacks disappeared with calcium antagonist treatment and although calcium antagonists may inhibit coronary spasm caused by thrombus formation, these drugs may not affect the thrombus itself, and therefore myocardial infarction will proceed as the thrombus increases. Accordingly, it is suggested that the initial treatment of variant angina should combine antianginal agents with anticoagulants, antiplatelet agents or thrombolytic agents. We reported earlier¹⁰⁾ that anticoagulants were effective in some cases with variant angina.

We found that the cases with acute myocardial infarction were characterized by rest and exertional angina indicating unstable angina and multivessel disease.

Mark et al⁹⁾ compared mortality and infarction rates in groups of medically treated and surgically treated patients. The incidence of these complications was higher in the former than in the latter group. The reason for poor prognosis in the medically treated group was that these rates were very much higher in the group with significant coronary disease than in the group without significant coronary disease. In our experience also, over an average period of 5.3 years (4–7 years) of non-medication following ACBG, there was no occurrence of complication. Thus, it may be that calcium antagonists, anticoagulants and surgery are needed to prevent myocardial infarction. Furthermore, we need to study the connection between the mechanism of acute myocardial infarction and variant angina.

Remission in variant angina

Calcium antagonists are effective in preventing attacks of variant angina. In comparison with other forms of angina, this treatment has had extremely good long-term results with this disease. But according to the recent report of Girotti et al¹²⁾ even after treatment with antianginal agents was suspended, no attacks occurred in 4 cases over a long period. Apparently those patients had spontaneous remission. Accordingly, it is suggested that the preventive effect of calcium antagonists cannot be evaluated without considering spontaneous remission. Silverman et al²⁹⁾ using as subjects cases of variant angina with normal coronaries or slight stenosis, investigated the frequency of those who had no anginal attacks during a month or more without treatment. They defined such cases as spontaneous remission, and found 39% out of 59 cases experienced this remission. Of these, 15% showed no recurrence of symptoms within 2 years. This demonstrates the difficulty of evaluating the effects of medical treatment in this disease. Waters et al¹³⁾ reached the

same conclusion. Their frequency rate of spontaneous remission was 45%. Compared with patients with continuing attacks despite medical treatment, those with remissions had a short history of rest angina and a significantly lower frequency of coronary artery lesions.

The frequency of spontaneous remission in our studies was 23.6%, 17.3% of which were cases of long-term remission. The average angina-free period was 78 months. Although this remission rate cannot be precisely compared with those reported by other investigators, its frequency was lower than the others. Among our cases of spontaneous remission, many had rest angina and no significant stenotic lesions. Waters et al⁸⁾ performed ergonovine tests on patients with variant angina as a way of predicting spontaneous remission. They found that neither ST-segment elevation nor anginal pain occurred in 12 of 22 cases and that when treatment was discontinued, no attacks recurred. The spontaneous remission rate was not negligible, so it appears necessary, when estimating a long-term course of treatment or planning the future treatment of individual patients, to consider fully the possibility of spontaneous remission.

As long as the pathophysiology of spontaneous coronary spasm is unknown, the factors causing spontaneous remission will be unknown. But, there have been cases which suggest a link with other factors such as emotional stress, alcohol, seasonal change, cold, urination, blood pressure and β -receptor blocking agents. However, as this study has not dealt with such matters, it has not been possible to clarify this point further.

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