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Thirty-Six Month Observation of 33 Coronary Vasospastic Angina (VSA) Patients Undergoing a Combination Therapy With a Calcium Channel Antagonist and a Statin : Clinical Evaluation With an Emphasis on the Etiology of Refractory VSA

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Combination therapy with a calcium channel antagonist, such as benidipine hydrochrolide, and a HMG-CoA reductase inhibitor, such as pravastatin, which can improve lipid metabolism and reduce oxidative stress, may attenuate coronary vasoconstriction in patients with coronary spastic angina (VSA). The present study enrolled 33 patients with positive findings of the acethylcholine provocation test without coronary organic lesions in whom coronary angiography revealed no significant organic stenosis. In these patients, benidipine hydrochrolide or diltiazem hydrochrolide and an HMG-CoA reductase inhibitor (mainly pravastatin) were administered for 36 months following the acechylechline provocation test. The total serum cholesterol level, serum HDL cholesterol level, and serum LDL cholesterol level were evaluated at the baseline, 6, 12, and 36 months after the treatment started.

The mean blood pressure was also measured at the baseline, 6, 12, and 36 months. Of 33 patients, refractory VSA were recognized in seven. In evaluating these seven patients, the lipid profile and mean blood pressure were within normal limits. However, it was demonstrated that 6 of 7 of these patients were habitual smokers and alcohol drinkers. Accordingly, to prevent refractory attacks of VSA, the patients were required to cease consuming cigarettes and alcohol to prevent refractory VSA attacks.

These results indicated that the results indicate that lifestyle modification is an extremely important factor, as is the drug administration of calcium channel antagonists and HMB-CoA reductase inhibitors in preventing refractory VSA attacks. The present results show that the relaxation of coronary vessels as a result of a calcium channel antagonist in addition to the improvement of the lipid metabolism, especially increasing the HDL cholesterol level, and reduction of the LDL cholesterol level, might inhibit vascular contractility.

The precise mechanism of the inhibition of recurrent VSA by benidipine hydrochrolide and statin was not clearly identified in the present study. However, there was a very strong association between cigarette smoking and a pure coronary spasm.

In summary, a decrease of serum LDL cholesterol, an increase in serum HDL cholesterol, and an improvement in lifestyle habits, including the cessation of smoking, might be effective in inhibiting refractory VSA during treatment with calcium channel antagonists and statins.

Key Words: Calcium channel antagonist, HGM-CoA reductase inhibitor, Coronary vasospastic angina, Smoking cessation

INTRODUCTION

Vasospastic angina (VSA) is very rare. When angina-like symptoms occur at rest, mostly at a specific hour in the early morning, together with transient ST segment elevations and angiographically normal arteries, provocative tests with acetylcholine should be performed [1]. Endothelial dysfunction, a strong thrombotic tendency, and an increased platelet

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aggregation with changes in autonomic tone can induce coronary vasospasm. Once patients are treated with calcium antagonists or nitrates, their prognosis is excellent, and severe complications, such as arrhythmias, myocardial infarction, or sudden death, are extremely rare. Coronary stenting could also be useful for refractory coronary spasm [2].

The frequency of VSA in Japan is said to be higher than that in Western countries [2]. In addition to its central mechanism of variant angina, coronary spasm has also been demonstrated to play an important role in some cases of exertional angina, acute myocardial infarction (AMI), or sudden cardiac death [3, 4].The long-term prognosis of patients with VSA has been shown to be better than that in patients with organic stenosis; however, reports in which fatal cardiac events developed despite treatment with a calcium channel antagonist have been published in some VSA cases [1-4]. It was recently reported that benidipine hydrochrolide, a calcium channel antagonist, can increase the production of nitric oxide (NO) via an increment of endogenous NO synthetase (eNOS) protein in vessels and seems to exert antioxidant actions [5].

Moreover, the tissue levels of (6R)-5, 6, 7, 8-tetrahydrobiopterin (BH4), an important allosteric effector of NOS, were found to be reduced, but, in a type Ⅱ diabetic rat model, treatment with benidipine hydrochrolide maintained the BH4 levels without affecting blood pressure, suggesting that it was one of the mechanisms for increasing NO production.

Benidipine hydrochrolide has been reported to have concentration-dependent antioxidant effects in a rat brain homogenate [6]. In contrast, diltiazem hydrochrolide and verapamil had little inhibitory effect on lipid peroxidation [7, 8, 9]. These results suggest that the structure of dihydropyrimidine (DHP) is important for the antioxidant properties of DHP calcium antagonists. Thus, it was suspected that benidipine hydrochrolide might be superior to other calcium channel antagonists for obtaining improvement in the long-term prognosis of patients with VSA.

Meanwhile, it has also been reported that diverse oxidative stresses are involved in the onset of VSA [10-12]. In regard to statins, which are HMG-CoA reductase inhibitors, it has been shown that, in addition to improving the lipid profile, statins can also exert antioxidant activity [11]. Statins have been reported to have the potential to suppress vasoconstriction by exerting antioxidant activity and, thereby, improving endothelial dysfunction, which has been pointed out as one of the possible mechanisms of VSA [12].

From these facts, it may be considered that combined treatment with a calcium channel blocker and statins may be more effective in the treatment of VSA. The present examination was designed to investigate the effects of combined treatment with a calcium channel blocker and an HMG-CoA reductase inhibitor on coronary vasospasm in patients with VSA who were diagnosed as positive through acethylcholine provocation tests.

PATIENTS AND METHODS

From January 2000 to April 2008, 95 cases of coronary artery disease (CAD) identified at the at Nagami Clinic, Unnan city, Shimane prefecture were referred to the department of circulatory medicine of Matsue Red Cross Hospital, Shimane Medical University Hospital, or Shimane Prefectural Central Hospital for the examinations of the CAD lesions. Of the 95 cases, 33 revealed positive acethylcholine provocation test without coronary organic lesions (≦ 25% stenosis of the luminal diameter).

A positive coronary vasospasm test was defined as a transient narrowing to at least 90%, determined by comparison with the normal control coronary angiogram. Before participating, the patients and their families received a full explanation of the purpose of the present study, and written informed consent was obtained from each participant. Furthermore, each patient was informed that the clinical data obtained during the course of this study would not be used for any purpose other than for the present study.

In the present study, as a calcium channel antagonist, either benidipine hydrochrolide or diltiazem hydrochrolide was used at random. In contrast, as an HMG-CoA reductase inhibitor, a statin was used according to the serum value of the total cholesterol.

Patients with positive acetylcholine provocation

test in coronary angiography participated in the present study. The drug was changed to benidipine hydrochrolide or diltiazem hydrochrolide for patients with hypertension, who were treated with a single antihypertensive drug. The initial dose of benidipine hydrochrolide was 4mg/day, which was gradually increased as needed to the maximum dose of 8mg/day. Meanwhile, the initial dose of diltiazem hydrochrolide was 90mg/day, which was gradually increased as needed to the maximum dose of 180mg/day. The statins used in the present study were pravastatin in 19 cases, simvastatin in 5 cases, pitavastatin calcium in 5 cases, and rosuvastatin in 4 cases. The initial dose of the HMG-CoA reductase inhibitor was in accordance with the levels of the total serum cholesterol levels and LDL cholesterol levels of each patient. Even if the lipid profiles were within normal limits, a minimum dose of a statin was administered. The dose of an HMG-CoA reductase inhibitor, such as pravastatin, was subsequently set so as to keep the total cholesterol levels below 200mg/dl, the LDL cholesterol levels, below 100mg/dl, and the HDL cholesterol levels, above 45mg/dl. During the 36-month follow-up, patient lifestyles choices were examined.

Of special interest were tobacco habits, alcohol use, sleeping, and body mass index (BMI). If an episode of angina or elevated blood pressure occurred, the patients were treated by increasing the dose of benidipine hydrochrolide or diltiazem hydrochrolide or by administering an additional dose of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker, as necessary. Fortunately, none of the patients required drugs in addition to binidipine hydrochrolide or diltiazen hydrochrolide for the treatment of angina or elevated blood pressure. In addition, none of the patients experienced an acute coronary syndrome, congestive heart failure, or other serious diseases during the follow-up periods. Furthermore, if a patient had an elevated level of total cholesterol or LDL cholesterol, the first therapy focused on the improvement of life style before any other drugs were prescribed. The details of the patient profiles in the present study are shown in Table 1.

Measurement of the Blood Biochemical Parameter

All laboratory measurements, which were conducted after the patients had fasted overnight, included measurements of the serum lipid profile after 12, 24, and 36 months from starting the treatment with an HMG-CoA reductase inhibitor, including the measurement of the baseline value. Total cholesterol was enzymatically measured, and HDL and LDL cholesterols were measured by homogeneous assays.

Table 1:This table demonstrated the precise data of the present enrolled patients

1) Age: 37~84 years old (mean age 62.4 years old)	
2) Sex: male ;24 cases female;34 cases	**58 caces**
3) Numbers of spastic vessels:	
・One branch	**23 cases**
・Two branches	**16 cases**
・Three branches	**8 cases**
・Four branches	**5 cases**
・More than five branches	**6 cases**
4) Chief complaint	
・Chest pain (at night)	**21 cases**
・Chest pain (at rest)	**12 cases**
・Chest pain (at exercise)	**6 cases**
・Syncope	**8 cases**
・Uncomfortable feeling after drinking cold drink	**5 cases**
・Uncomfortable feeling at rest	**8 cases**
・Weakened strength of extremity	**5 cases**

Statistical Analyses

Data were expressed as the mean ± standard deviation for continuous variables. The paired t-test was used to compare the differences in the serum lipid concentrations between the baseline and after treatment. $P < 0.05$ was considered to be statistically significant.

RESULTS

Of the present 33 patients, 2 required the additional use of benidipine hydrochrolide because of unsatisfactory management of blood pressure. Among the 33 patients examined, a coronary vasospasm was completely suppressed in 26 patients for 36 months after the start of the above-reported treatment, and the remaining 7 patients showed a coronary vasospasm more than 1 time/year for a maximum of 6 times/year during the 36 months. The mean doses of benidipine hydrochrolide and diltiazem hydrochrolide were 8.2±3.0 mg/day and 96.5±12.4mg/day, respectively. In the present study, 26 patients were treated with benidipine hydrochrolide. In contrast, the remaining 7 patients were treated with diltiazem hydrochrolide. Two were treated with benidipine hydrochrolide and had refractory VSA; on the other hand, 5 patients were treated with diltiazem hydrochrolide and had refractory VSA. The incidence of refractory VSA in the patients treated with benidipine hydrochrolide was lower during the 36-month follow-up, although there were no significant differences.

Time Course of Changes in Blood Pressure and Serum Lipid Profiles

During the follow-up period, the blood pressure gradually decreased from the baseline value (133±11 mm Hg). Blood pressure was 113±11 mm Hg at 6 months, 124±11 mm Hg at 12 months, 120±11 mm Hg at 24 months, and 118±10 mmHg at 36 months after enrollment in the study. As shown in Table 2, the serum total cholesterol level at 12, 24, and 36 months significantly decreased ($P < 0.01$ versus baseline values).

However, there was no significant difference between the value at 12 months and that at 36 months. The LDL cholesterol level also decreased significantly ($p< 0.01$ versus baseline values). In addition, there was a significant difference between the value at 12 months and that at 36 months ($P<0.05$) (Table 3). The serum HDL cholesterol level rose dramatically ($p < 0.01$ versus baseline values). However,

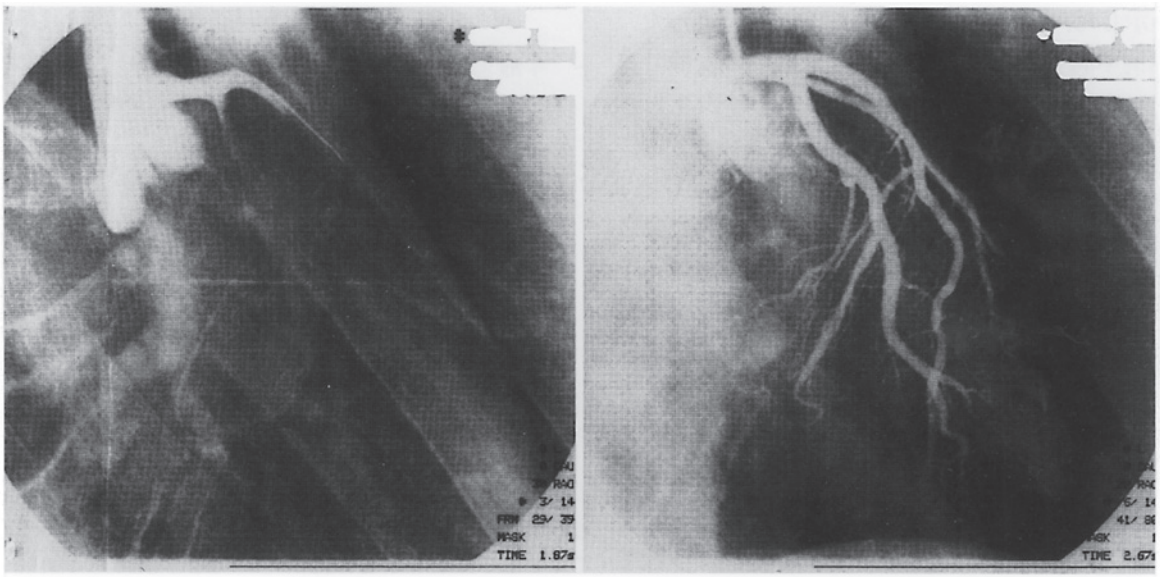


Fig. 1. This case was a 53 years-old man with chief complaint of syncope and incontinentia urinae. The cardiogram of this patient demonstrated that complete Obstruction of left descending branch and circumflex branch of the left coronary artery by Acechylcholine provocation test(left side). And complete obstruction of the coronary artery was clearly relieved by intravenous administration of nitroglycerine(right side).
This was a very sever case of VSA.

there was not a significant difference between the value at 12 months and that at 36 months (Table 4).

Evaluation of the lifestyle of the sever six patients with refractory VSA

In 26 patients, refractory VSA was completely suppressed during the 36-month follow-up. However, seven patients experienced refractory VSA. The lifestyle choices and administration of drugs for preventing VSA were investigated. With regard to the administered drugs, there was not a particular problem. However, with regard to lifestyle choices, 6 of the 7 patients did not quit smoking, and 3 of the 7 did not reduce their BMI. Four of the 7 drank alcohol two or three times weekly. Three of 7 had inadequate sleep. These results suggest that lifestyle choices had a negative impact on patients with refractory VSA. (Table 5).

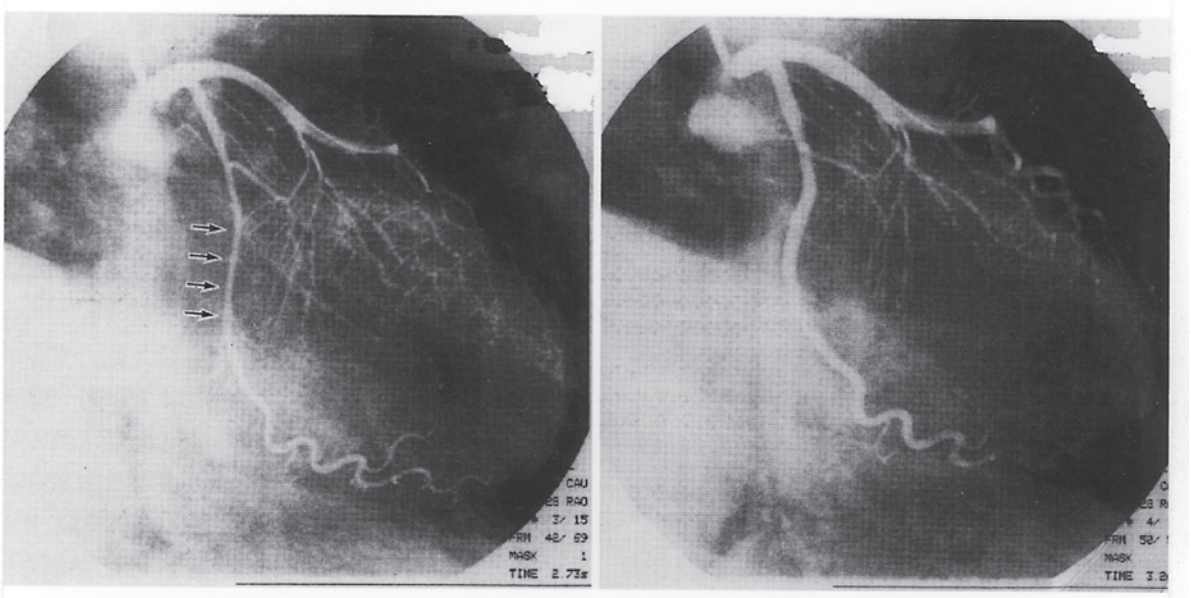
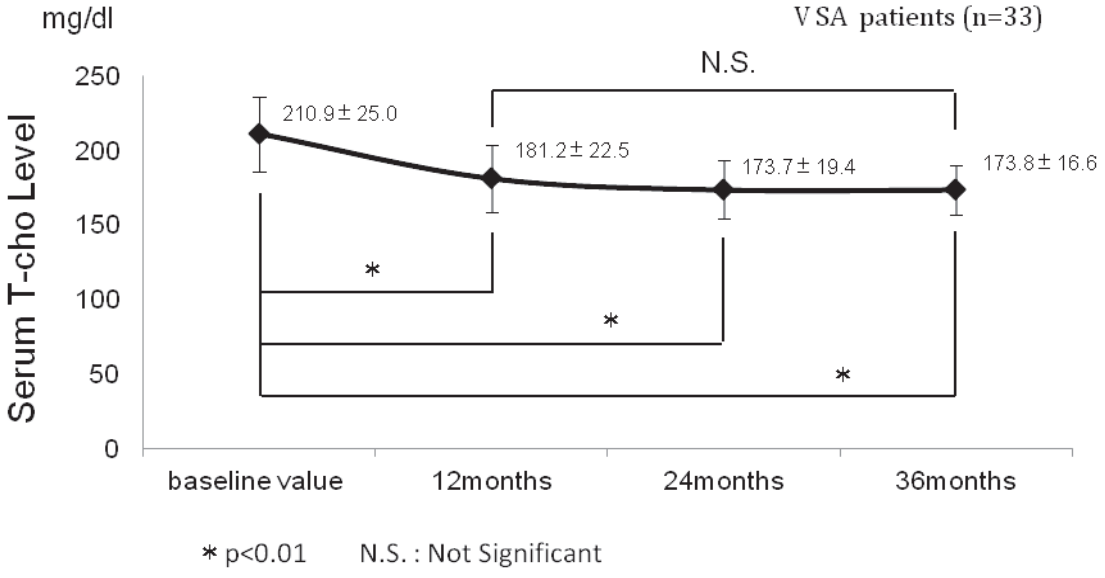


Fig. 2. This case was a 64-years-old woman with chief complaint of uncomfortable felling at rest. The cardiogram showed that narrowing of the circumflex branch of the left coronary artery by Acechylcholine provocation test (left side:→) and narrowing portion of the coronary artery was relieved by orally administration of nitroglycerine (right side).

Table 2: The serum total cholesterol level at baseline, 12,24,36 months.



Finally, Figs. 1 and 2 are the results of cardioangiograms of the two typical clinical cases of VSA in which coronary vasospasm was induced during the acetylcholine provocation test. The patient represented in Fig. 1 had a severe case of VSA with complete obstruction of the left descending artery of the left coronary artery, and, as a result, benidipine hydrochrolide and pravastatin were used. However, he had 3 episodes of refractory VSA over the follow-up period. The case in Fig. 2 is one without refractory VSA in the follow-up period, and the patient was treated with benidipine hydrochrolide and simvastatin.

DISCUSSION

Neurohumoral substances or autocoids act on the vascular endothelium, inducing the production of an

Table 3: The serum LDL level at baseline, 12,24,36 months.

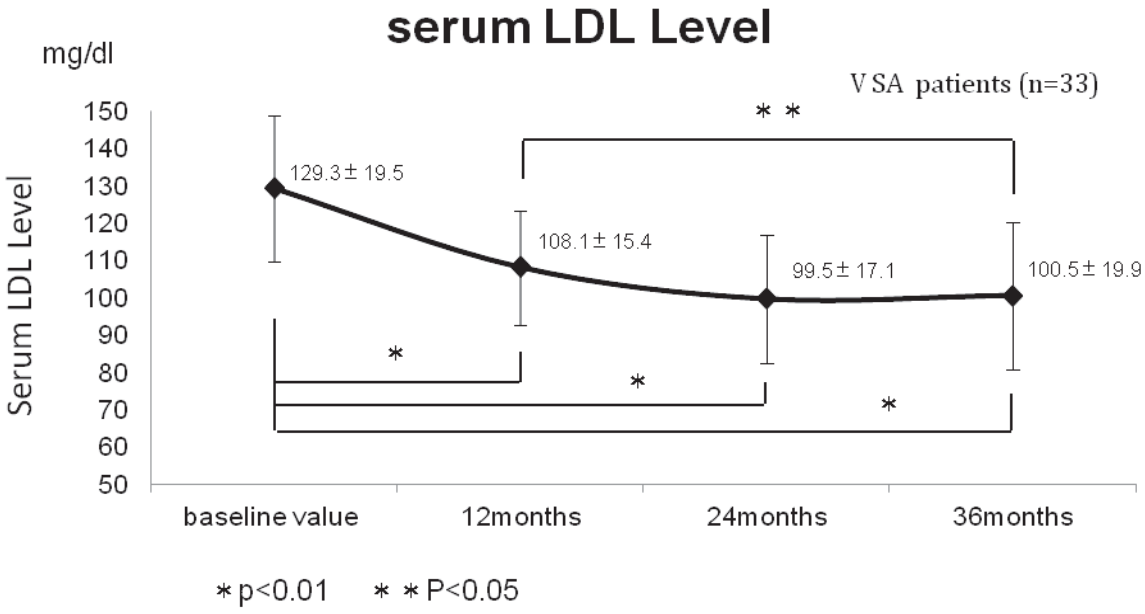


Table 4: The serum total serum HDL level at baseline, 12,24,36 months.

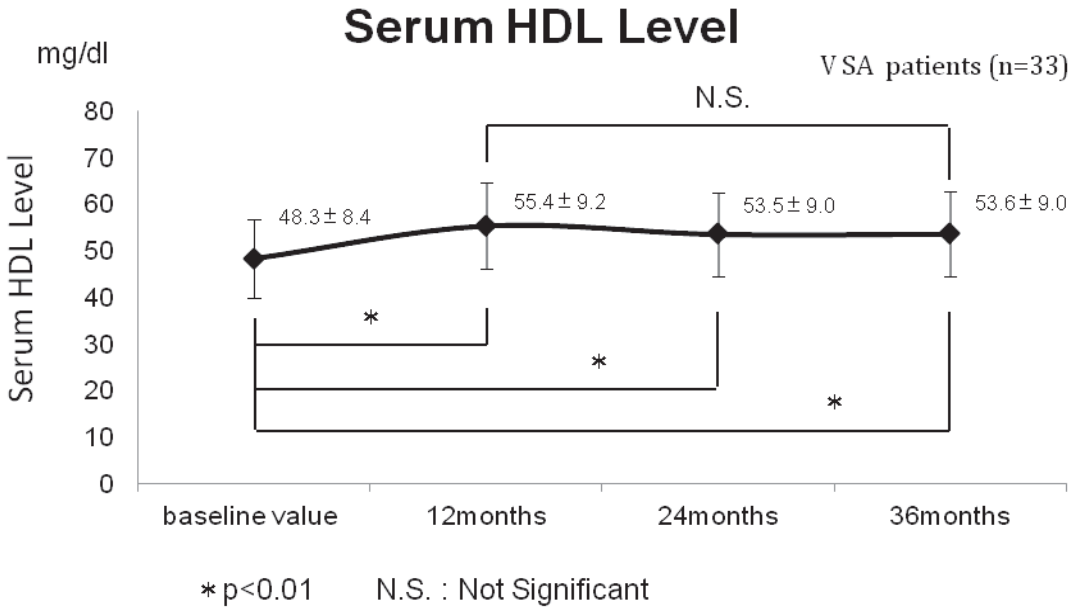


Table 5: Characteristics of the lifestyle modification of the patients with refractory VSA

Characteristics of refractory VSA patients (n=7)

Patient	Smoking	Drinking	BMI:25%≦	Much work	Sleeping time
No1	○	○	○	○	
No2	○				Short time
No3	○	○	○	○	
No4	○				Short time
No5		○		○	
No6	○		○	○	
No7	○	○			Short time

endothelium-derived relaxation factor (EDRF) or NO, which has an impact on coronary vessel tone [1]. A coronary spasm may result from an impaired EDRF release by dysfunctional endothelium. On the other hand, a coronary spasm itself induces the release of a potent vasoconstrictor, such as a platelet-derived growth factor, which further aggravates spasms and, therefore, plays a role in the unstable nature of VSA. The normal endothelium-dependent vasodilator mechanisms are greatly impaired in the setting of atherosclerosis [4]. Indeed, most spasms occur at the site of an organic stenosis, but spasms can occur in vessels with extreme variability in the extent of coronary atherosclerosis [6]. Although there is a strong thrombotic tendency at the time of a spasm, thrombus formation alone does not induce spasms because thrombolytic agents cannot relieve them. The reduction in blood flow together with increased platelet aggregation and endothelial dysfunction during vasospasm plays an important role in the progression of atherosclerosis[6]. Changes in automatic tone can trigger spasms or contribute to their constriction in patients with VSA [7]. Multi-vessel spasms occur in 43% of patients with VSA. In those patients, spontaneous episodes are more frequent, and no significant coronary lesions are often found. Multi-vessel spasms are associated with an increase in sudden death [9].

VSA attacks can be provoked by a variety of physiological stimuli, including cold temperatures, ice water or alcohol consumption, REM sleep, atrial pacing, consumption of acetylcholine, cocaine, or nicotine, alpha adrenergic stimulation, hyperventilation, and exercise. Potentially fatal arrhythmias, such as complete AV block, ventricular tachycardia or fibrillation, and electromechanical dissociation occur in 16-63% of patients and tend to recur [1, 9, 10]. Ventricular arrhythmias occur in as many as 50% of patients with documented coronary artery spasm and are unrelated to the site of ischemia, the presence of coronary lesions, age, and sex. Thus, clinical and angiographic features are of limited value in recognizing patients at risk for ventricular arrhythmia. Severe ventricular arrhythmias occur during maximal ST segment elevation, in association with hemodynamic signs of acute ischemic cardiac dysfunction or during reperfusion after the administration of nitrates. Ventricular arrhythmia during ischemia is much more frequent than it during reperfusion because coronary spasms are generally short in conjunction with VSA [13]. In untreated patients, acute myocardial infraction (AMI) has been described in as many as 20% of patients within the first three months following symptoms, even in patients with normal coronaries or non-significant lesions [14]. There is no correlation between the risk of AMI and the severity of VSA. Once treated, the risk for AMI in coronary spasm with normal coronary arteries is low [15].

Coronary spasms are a significant cause of sud-

den death, but, in treated patients, death is rare [13-15]. There is an excellent long-term outcome of treated VSA with 89-97% overall survival at five years, depending on the severity of disease, concomitant obstructive artery disease or arrhythmia, and number of vessels involved.

However, the clinical course is poor without treatment, with up to 30% of patients experiencing a cardiac arrest within 5 weeks of the onset of symptoms. In the great majority of patients, there is a tendency for symptoms to decrease, but the activity of coronary spasm can be waxing and waning during the follow-up as endothelial damage may sometimes heal over the course of several months. Therefore, medical therapy should not be withdrawn without careful follow-up over several years [16].

Calcium antagonists are standard treatment for all patients with VSA. All first generation calcium blockers are effective in relieving symptoms: nifedipine 40 mg/day in 94%, diltiazem 180 mg/day in 91%, and verapamil 240 mg/day in 86%, irrespective of eventual organic coronary artery stenosis. Second generation calcium antagonists, such as amlodipine 5-10 mg/day, also relieve angina [3]. The combination of different calcium antagonists may be helpful, but the side effects of those calcium antagonists may become more prominent. It has been reported that, among calcium antagonists, benidipine can increase the production of nitric oxide (NO) via increments of eNOS protein in vessels and seems to exert antioxidant actions. Moreover, the BH4 levels was found to be decreased in the type II diabetic rat model and treatment with benidipine maintained BH4 levels without affecting blood pressure, suggesting that benidipine is one of the most reliable mechanisms for increasing NO production.

Dihydropyrimidine (DHP) calcium antagonists, especially benidipine hydrochrolide, have been reported to have concentration-dependent antioxidant effects in a rat brain homogenate. In contrast, diltiazem and verapamil had little inhibitory effect on lipid peroxidation. These results suggest that the DHP structure is important for the antioxidant properties of DHP calcium antagonists. Meanwhile, it has also been reported that diverse oxidative stresses are involved in the onset of VSA. In regard to HMG-CoA reductase inhibitor represented by pravastatin, it has been shown that, in addition to improving the lipid metabolism, these drugs can also exert antioxidant activity. Statins have been reported to have the potential to suppress vasoconstriction by exerting antioxidant activity and thereby improving endothelial dysfunction, which has been pointed out as one of the possible mechanisms of VSA.

Although the present study was a small, its results indicated that coronary vasospasm was suppressed by treatment with a calcium channel blocker, such as benidipine hydrochrolide and HMG-CoA reductase inhibitors, and also showed improvements of the serum lipid metabolism, particularly in evaluating the serum HDL cholesterol level and reducing the serum LDL level.

In previous investigations, it was reported that improvement of oxidative stress could prevent coronary vasospasm from the viewpoint of the etiology of this disease [17-22]. This evidence demonstrated that suppression of oxidative stress by calcium channel blockers and HMG-CoA reductase inhibitors might prevent coronary vasospasm and, eventually, refractory VSA.

In the present study, the elevation of the serum HDL cholesterol level and reduction of the serum LDL cholesterol level were significant in all patients. In view of a report in which HDL cholesterol exerts antioxidant actions and improves vascular relaxation by improving the vascular endothelial dysfunction, it is possible that the elevation of the serum HDL cholesterol level resulted in the suppression of coronary vasospasm.

From these facts, it is probable that the greater elevation of the serum HDL cholesterol level and reduction of the serum LDL level showing suppression of coronary vasospasm is attributable to the HDL cholesterol-elevating effect of statins. However, 7 patients experienced refractory VSA because they made poor lifestyle choices, such as smoking tobacco, drinking excessive amounts of alcohol, or inadequately managing their body weight.

From the viewpoint of the lipid metabolism, use of HMG-CoA reductase inhibitors, such as pravastatin and aggressively advocating lifestyle modifications, such as quitting tobacco smoking and managing body weight, all play an important role in

preventing refractory VSA.

Tani et al. [23] demonstrated that combination therapy with benidipin hydrochrolide and pravastatin, which could improve the lipid metabolism and reduce oxidative stress, might attenuate coronary vasospasm in patients with VSA. They reported that reducing the serum MDA-LDL level and elevating the serum HDL cholesterol level might be useful for suppressing coronary vasospasm in patients with VSA. Furthermore, serum MDA-LDL and HDL cholesterol were demonstrated to exert antagonistic actions by causing progression and suppression of atherothrombosis, respectively.

In summary, reduction in the serum MDA-LDL level and elevation of the serum cholesterol level may be expected to suppress not only coronary vasospasm but also coronary atherosclerosis and thrombosis, possibly leading to the improvement of the long-term prognosis in patients with VSA.

Miwa et al. [24] followed up a series of patients with VSA and reported that the incidence of cardiac events was lower among patients showing greater elevation of the serum HDL cholesterol level over time than among those showing less marked elevation of the serum HDL cholesterol level in the suppression of coronary vasospasm.

Early atherosclerotic lesions have been enumerated as an etiologic factor for coronary spasm [25]. If coronary vasospasm is suppressed in response to coronary plaque regression, such a phenomenon is of great of interest. The findings in the present study suggest that elevating the serum HDL cholesterol level might be useful for suppressing coronary vasospasm in patients with VSA.

There were some limitations in the present study. First, coronary vasospasm was evaluated by using the acetylcholine provocation test, not spontaneous episodes of angina. If spontaneous angina was considered, more than 33 patients with VSA could be diagnosed among the 95 consecutive patients with CAD. Secondly, the sample size in the study was relatively small, and there was no control group regarding treatment with calcium antagonist or statin. However, there were 8 patients with VSA treated exclusively with a calcium antagonist without the use of a statin before the present study. Of those 8 patients, 5 had refractory VSA. This result revealed that it was necessary to treat VSA with a calcium antagonist and a statin. Thirdly, in the present investigation, the serum MDA-LDL level, which had a strong association with refractory VSA was not actually measured, and, instead of the serum MDA-LDL level, the serum LDL level was measured. Naturally, the serum MDA-LDL level did not coincide with the serum LDL level. Therefore, if the influence of the serum LDL-level on refractory VSA is necessary, the exact serum MDA-LDL measurement had to be performed in the present study. Therefore, it would be desirable to conduct a similar study with a larger number of subjects in the future and to explore additional factors that might be involved in the suppression of coronary vasospasm.

The present study showed that in order to prevent recurrent VSA attacks, it was necessary to manage with Ca antagonists, especially benidipine hydrochrolide, and statin. Furthermore, it was also demonstrated that improvement of lifestyle modification was key point in preventing recurrent VSA by stabilizing lipid metabolism.

From the information above, the stability of the coronary vessels must be maintained with a calcium channel antagonist and improvement of the lipid metabolism by statins to prevent the refractory VSA. In the present study, the patients with refractory VSA did not stop smoking cigarettes and drinking alcohol. Furthermore, they did not adequately manage their body weight and exercise. Smoking has been recognized as one of the major risk factors for myocardial infarction, sudden death, and angina pectoris; therefore, smoking tobacco may contribute to coronary ischemia, at least partly, by producing vasospasm. McKenna et al. [26] reported that smoking tobacco was the sole significant risk factor. They also described the postmortem findings of two patients who died of acute myocardial infarction, in whom they found occlusive coronary thrombosis without atheromatous changes. In another report, it was demonstrated that pathophysiological factors, such as hypoxemia, increased oxygen demand, the effect of nicotine on vascular tone, and the effects of carbon monoxide on oxygen delivery may be responsible for the excess coronary mortality because, among smokers, there is a reduc-

tion of coronary mortality risk, similar to that of never-smokers [27]. In addition, Caralis et al. [28] demonstrated that there was a very strong association between cigarette smoking and pure coronary spasm in young women. From these facts, it is possibly suspected that cessation of tobacco smoking must take place for the prevention of refractory VSA.

In conclusion, these results indicate that lifestyle changes can be as important as drug prescriptions, such as calcium channel antagonists and HMG-CoA reductase inhibitors, for preventing refractory VSA and the decrease of serum LDL cholesterol level and increase in the serum HDL cholesterol level may effectively inhibit refractory VSA during treatment by those medications. The precise mechanism of inhibiting recurrent VSA by calcium channel antagonists and HMG-CoA reductase inhibitors is not clearly demonstrated in the present study. So, double blinded-control study is must be done comparing the patients with VSA treated by calcium channel antagonists and HMG-CoA reductase inhibitors and the patients with VSA without treating by those two drugs in order to examine the precise mechanism of the present combination therapy from now on.

VSA presents a variety of symptoms, such as chest pain, discomfort in the chest after drinking cold water, or syncope. In our daily clinical work, patients with VSA may have their symptoms misdiagnosed by physicians. Therefore, we must consider the possibility of VSA early and treat the patients as soon as possible.

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