

# Comparison of the Long-Term Prognosis between Coronary Vasospasm and Intermediate Vasoconstriction Induced by the Administration of Acetylcholine

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## ABSTRACT

**Background and Objectives :** The degree of coronary vasoconstriction induced by acetylcholine administration can vary. We compared the prognosis between coronary vasospasm and intermediate vasoconstriction, which were both induced by acetylcholine administration. **Subjects and Methods :** The subjects were 156 patients with the coronary vasospasm or intermediate vasoconstriction, as observed on the acetylcholine provocation tests that were performed from January, 2000 to January, 2004. The patients with a spasm showing greater than 90% reduction of vessel diameter along with chest pain or ST changes or both were classified as having 'strong positive vasospasm' (n=113). The patients with 70-90% reduction of diameter were classified as having 'intermediate vasoconstriction' (n=43). The mortality, frequency of chest pain and clinical events were then analyzed. **Results :** A smoking history ( $p<0.001$ ) and multivessel involvement ( $p=0.02$ ) were more frequent in the strong positive group. We compared the mortality and clinical events due to chest pain during the average  $26.4 \pm 14.1$  months of follow-up. There were 5 patients (4.4%) who incurred cardiac death in the strong positive group as compared with none in the intermediate group. The total clinical events were more frequent in the strong positive group ( $p<0.001$ ). Also, the strong positive group showed a significantly higher frequency of chest pain ( $p<0.001$ ). **Conclusion :** The long-term prognosis of the intermediate vasoconstriction was better than that of strong positive vasospasm. Thus, the intermediate vasoconstriction must be ruled out by strict application of the positive criteria for the acetylcholine provocation test. (Korean Circulation J 2006;36:503-509)

**KEY WORDS :** Vasospasm ; Vasoconstriction ; Prognosis.

## Introduction

The degree of coronary vasoconstriction that's induced by such common constrictor stimuli as acetylcholine can vary.<sup>1)2)</sup> For normal healthy persons, mild vasoconstriction can physiologically occur in response to acetylcholine, and this is usually diffuse and it does not exceed a 30% reduction of the coronary vessels' diameter.<sup>2)3)</sup> At the other extreme, patients with vasospastic angina can

show severe vasoconstriction, which induces total occlusion of the involved vessels, and this can play an important role as a cause of acute myocardial ischemia.<sup>2)4)</sup> Because of this wide spectrum of coronary vasoconstriction in response to acetylcholine, the positive criteria for confirming the diagnosis of vasospastic angina have been strictly defined as the total occlusion or severe vasoconstriction with more than a 90% reduction of vessel diameter with ischemic episodes that include chest pain or ischemic electrocardiographic (ECG) changes.<sup>5-7)</sup>

It's interesting that the intermediate form of coronary vasoconstriction is sometimes observed even on a drug provocation test, i.e., between the mild physiologic degree of vasoconstriction and the severe occlusive vasospasm.<sup>2)6)</sup> Furthermore, some of the patients showed vasoconstriction with more than a 70% reduction of vessel diameter, but they did not match the positive criteria of the ace-

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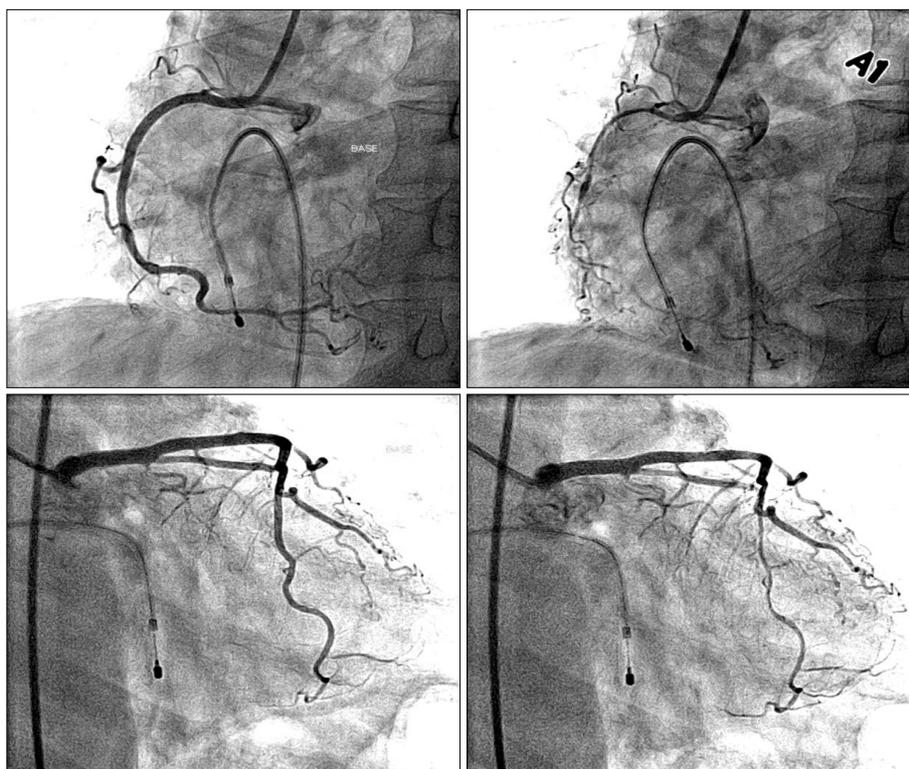
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**Fig. 1.** Definitions of the 'strong positive vasospasm group' and the 'intermediate vasoconstriction group'. Those patients with greater than a 90% reduction of vessel diameter that was accompanied by chest pain or ECG changes were classified as having 'strong positive vasospasm' (upper half). Those patients with 70-90% reduction of vessel diameter were classified as having 'intermediate vasoconstriction' (lower half). ECG: electrocardiographic.

tylcholine provocation test, and these patients will occasionally exhibit ischemic chest pain during the provocation test and also during the follow-up period.<sup>2)</sup> So, they are sometimes inappropriately regarded as patients with true coronary vasospasm. However, the long-term prognosis and the clinical course of these patients have not been reported on.

Thus, we conducted this study to evaluate the patients who showed vasoconstriction with more than a 70% reduction of vessel diameter, but they did not match the positive criteria of the acetylcholine provocation test, and we wanted to determine if they had the same clinical characteristics and a similar long-term prognosis as compared to that of the patients suffering with classical vasospastic angina.

## Subjects and Methods

### Definitions

'Strong positive vasospasm' was defined as a coronary spasm with greater than a 90% reduction of vessel diameter on the acetylcholine provocation test with typical chest pain or ST segment changes being seen on the standard 12-lead ECG or both. Those patients who showed vasoconstriction with more than a 70% reduction of vessel diameter, but they did not match the positive criteria of the acetylcholine provocation test (a vessel dia-

meter reduction of 70-90%), were defined as having 'intermediate vasoconstriction' (Fig. 1). Multivessel vasospasm was defined as strong positive vasospasms in more than 2 of the major epicardial coronary arteries. Furthermore, 70-90% vasoconstriction in more than 2 of the major epicardial coronary arteries was defined as multivessel vasoconstriction. The patients who showed multivessel vasospasm or multivessel vasoconstriction were classified as patients with multivessel involvement. Significant atherosclerosis was defined as over 50% of fixed vessel diameter stenosis.

### Patient group

224 patients suffering with typical chest pain that was suspected of being vasospasm underwent intracoronary acetylcholine provocation testing from January, 2000 to January, 2004 at the Kangnam St. Mary's Hospital, the Catholic University of Korea. The included patients were divided into two groups: the strong positive vasospasm group and the intermediate vasoconstriction group. The patients with diameter reductions of less than 70% and the patients with significant atherosclerosis (>50% diameter stenosis) on the preceding coronary angiography were excluded from the study. For all the patients of both groups, their medical treatment with such vasodilators as calcium antagonists, nitrate or nicorandil was started just after the provocation test.

### Coronary artery angiography and the acetylcholine provocation testing

All the patients included in the study had prior coronary angiography done by the standard Judkin's method after the injection of 3000 units of heparin. The provocation test was done with acetylcholine after a temporary pacemaker had been inserted through the femoral vein. The provocation test was carried out by the phased injection of 20, 50 and 100  $\mu$ G acetylcholine in the left coronary artery and also the phased injection of 20, 50  $\mu$ G acetylcholine in the right coronary artery with an interval between injections of 2 minutes until a spasm of greater than 90% reduction of the vessel diameter was induced in each of the epicardial coronary arteries. Once a positive provocation had been observed, 1000  $\mu$ G of nitroglycerin was injected into the coronary artery to normalize the spastic lesions, as was observed via performing angiography. The patients who did not display a greater than 90% spasm in spite of the maximal injected dose of acetylcholine were classified as the intermediate vasoconstriction group or they were excluded from the study according to the definitions. All the medications, except sublingual nitroglycerin, that could have an effect on vasomotor response were stopped at least for 3 days prior to the testing. The degree of coronary vasoconstriction or fixed stenosis was measured by quantitative coronary angiographic analysis (QCA).

### Variables

This study was carried out for an average of  $26.4 \pm 14.1$  months after the intracoronary acetylcholine provocation test by performing a retrospective analysis of the patients with using the clinical records and conducting individual phone interviews.

### Mortality

The deaths that occurred during the follow up period were divided into cardiac death, stroke and non-cardiac death, according to the cause of death. Subgroup studies were done to discover the specific cause of death, the interval between the diagnosis and death, and whether or not the patients' medical treatment was continued.

### Frequency of chest pain

The frequency of chest pain during the follow up period was compared and analyzed by using the criteria previously published by Sueda et al.<sup>8)</sup> Grade 1 meant near daily attacks of chest pain and grade 5 meant that no chest pain was felt. A higher number of the grade indicates that a lower frequency of chest pain was experienced by the patients.

Grade 1: Near daily attacks

Grade 2: 1-4 attacks per month

Grade 3: 1 attack per month but <4 attacks per month

Grade 4: <1 attack per month

Grade 5: No attacks

### Clinical events

To compare the clinical differences in both groups during the follow up period, the number of admissions or emergency room (ER) visits due to chest pain and also the need to increase the dosage of the initial medications or to change vasodilators for the uncontrolled chest pain were compared between the two groups.

### Statistical analysis

The variables displayed by both the groups were analyzed by using the statistical program SPSS (version 11.0). All the variables were recorded as average standard deviations or numbers and percentages (%), and the comparisons between the two groups were carried out by performing t-tests and correlation testing. p-values (p) less than 0.05 were considered statistically significant.

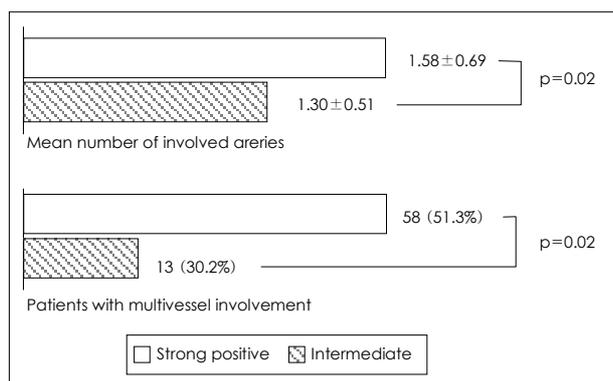
## Results

156 patients were included in the study out of a total of 224 patients. There were 113 patients (50.4%) in the strong positive vasospasm group and 43 patients (19.2%) in the intermediate vasoconstriction group. The patients in both groups were followed up for an average of  $26.4 \pm 14.1$  months.

**Table 1.** Baseline characteristics

	Strong positive (n=113)	Intermediate (n=43)	P
Age (years)	52 $\pm$ 12	51 $\pm$ 12	0.58
Male	66 (58.4%)	23 (53.5%)	0.58
Risk factors			
Family history	30 (26.5%)	9 (20.9%)	0.47
Hypertension	29 (25.7%)	18 (41.9%)	0.07
Smoking	69 (61.1%)*	11 (25.6%)*	<0.001
Diabetes	8 (7.1%)	7 (16.3%)	0.08
High-density lipoprotein <45 mG/dL	39 (34.5%)	15 (34.9%)	0.97
Pain duration (months)	17.76 $\pm$ 15.83	16.09 $\pm$ 12.13	0.73
Spasm site (artery)			
Left main	0 (0%)	0 (0%)	1.0
Left anterior descending	74 (65.5%)	24 (55.8%)	0.27
Left circumflex	43 (38.1%)	8 (18.6%)	0.12
Right coronary	68 (60.2%)	25 (58.1%)	0.82
Initial medication			
Calcium antagonist	111 (98%)	41 (95%)	0.79
Nitrate	83 (73%)	31 (72%)	0.93
Nicorandil	72 (64%)	27 (63%)	0.92

\*: the number of patients who had a history of smoking was significantly higher in the strong positive vasospasm group



**Fig. 2.** Multivessel involvement. The mean number of involved epicardial coronary arteries and the percentage of patients showing the multivessel involvement were higher in the strong positive vasospasm group.

**Table 2.** Mortality and causes of deaths

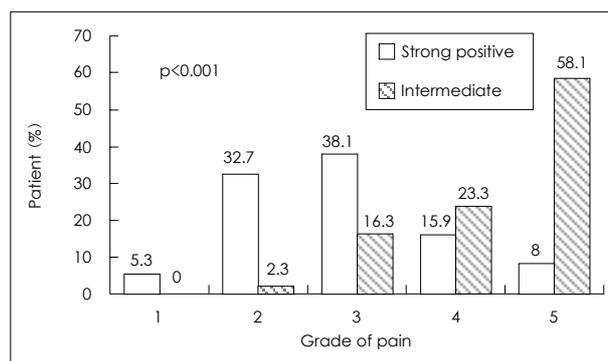
	Strong positive (n=113)	Intermediate (n=43)	p
Total death	12 (10.6%)	2 (4.7%)	0.25
Cardiac death	5 ( 4.4%)	0 ( 0%)	0.16
Stroke	4 ( 3.5%)	1 (2.3%)	0.70
Non-cardiovascular	3 ( 2.7%)	1 (2.3%)	0.91

### Baseline characteristics

There were no differences in both groups in regards to the patients' age, gender and duration of chest pain, but the smoking history was strongly correlated with the strong positive vasospasm group (69 patients, 61.1% vs 11 patients, 25.6%, respectively,  $p < 0.001$ ) (Table 1). The average number of involved vessels was significantly higher in the strong positive vasospasm group than in the intermediate vasoconstriction group ( $1.58 \pm 0.69$  vs  $1.30 \pm 0.51$ , respectively,  $p = 0.02$ ) (Fig. 2), and the number of patients with multivessel involvement was also higher in the strong positive vasospasm group (58 patients, 51.3% vs 13 patients, 30.2%, respectively,  $p = 0.02$ ) (Fig. 2).

### Mortality and the cause of death

Although there was no statistically significant difference between both groups, no cardiac deaths were observed in the intermediate vasoconstriction group, while there were 5 patients (a 4.4% cardiac death rate) who incurred cardiac death in the strong positive vasospasm group. The total death rate in the strong positive vasospasm group was relatively higher (12 deaths, 10.6%) than the total death rate in the intermediate vasoconstriction group (2 deaths, 4.7%) (Table 2). Of the 5 patients who incurred cardiac death, sudden cardiac arrest was observed in 3 patients; 2 out of these 3 patients, including 1 patient who had underlying dilated cardiomyopathy, died after cardiopulmonary resuscitation (CPR) was performed upon visiting our ER due to sudden loss of consciousness, and these 3 patients sho-



**Fig. 3.** Frequency of chest pain. A higher number of the grade indicates the lower frequency of chest pain experienced by the patients. During the follow-up period and with medical treatment, the patients in the intermediate vasoconstriction group showed less frequent chest pain than did the strong positive vasospasm group.

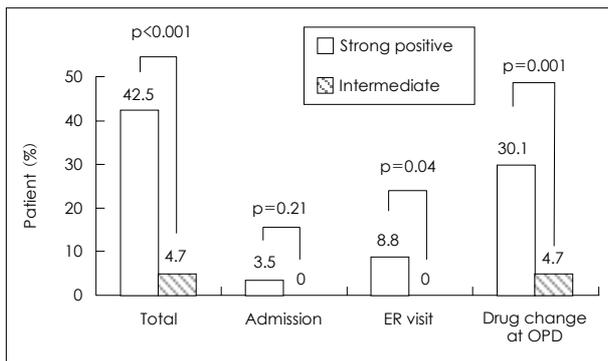
wed ventricular fibrillation on the ECG. The average time to death after the provocation testing for the 5 cardiac death patients was  $5.3 \pm 3.8$  months, and of these 5 patients, 4 patients stopped taking their medication without a doctor's order, including one patient who died due to ventricular fibrillation.

### Frequency of chest pain

A higher number of the grade with a lower frequency of chest pain was observed much more often in the intermediate vasoconstriction group than in the strong positive vasospasm group. From this observation, we could see a statistically significant correlation between the frequency of chest pain and the degree of vasoconstriction ( $p < 0.001$ ), so that the effectiveness of the medications for controlling chest pain was better for the intermediate vasoconstriction group than for the strong positive vasospasm group (Fig. 3). In other words, the symptom remission was significantly more frequent in the intermediate vasoconstriction group.

### Clinical events: admission or ER visits due to chest pain, changes of drugs or their dosage due to uncontrolled chest pain

To see the correlation between a statistically significant decrease of the frequency of chest pain in the intermediate vasoconstriction group and the clinical aspect of coronary vasoconstriction, and also to elucidate the clinical difference between the strong positive vasospasm group and the intermediate vasoconstriction group, we used the 'clinical events' variable, which was defined beforehand. The follow up of each of the specific clinical events showed no statistically significant difference for the hospitalization between the two groups (4 patients, 3.5% vs 0 patients, 0%, respectively,  $p = 0.21$ ). However, the number of patients who visited the ER in the intermediate vasoconstriction group was zero, while there were 10 patients (8.8%) who vi-



**Fig. 4.** Clinical events. Both groups showed no statistical difference for the number of patients who experienced admission due to chest pain. Yet the intermediate vasoconstriction group showed lower frequencies of ER visits and changes of their drugs due to uncontrolled chest pain. ER: emergency room, OPD: out-patient department.

sited the ER in the strong positive vasospasm group ( $p=0.04$ ). These 10 patients had an average of  $1.8 \pm 0.8$  visits to the ER during  $26.4 \pm 14.1$  months. In spite of continuous medication, more of the patients in the strong positive vasospasm group required more frequent changes of vasodilators or increases in the dosage of vasodilators as compared to the intermediate vasoconstriction group (34 patients, 30.1% vs 2 patients, 4.7%, respectively,  $p=0.001$ ). Thus, not only was a lower frequency of chest pain observed in the intermediate vasoconstriction group, but the patients in the intermediate vasoconstriction group had a better clinical prognosis as compared to the strong positive vasospasm group (Fig. 4).

## Discussion

### Intermediate vasoconstriction vs true vasospasm

This study showed that the intermediate vasoconstriction group had a better long-term prognosis than did the strong positive vasospasm group, although they both had similar baseline characteristics. In addition to fixed coronary stenosis, the use of calcium antagonist, ST elevations on both the anterior and inferior leads and the duration of pain before treatment, any multi-vessel involvement and a history of smoking were also predictive factors for a poor prognosis for patients suffering with vasospastic angina.<sup>5)8-15)</sup> Not only did the patients with intermediate vasoconstriction have a better response to medical treatment, they also showed lower frequencies of these poor prognostic factors.

Our study also demonstrated that patients with strong positive vasospasm showed a high rate of cardiac mortality, and this stands in contrast with the lack of cardiac death noted for the intermediate vasoconstriction group. Most of the cardiac deaths occurred within the early period after their discharge from the hospital and just after their arbitrary and foolish discontinuation of

their anti-spasmodic medications. Kishida et al. have found that 87.5% of myocardial infarctions occurred within one month of the patients' first hospital visit, and the patients with vasospastic angina experienced a decreased number of cardiac events as time went.<sup>16)</sup> Waters et al. and Severi et al. have also reported that a large portion of cardiac events occurred in the early period after the diagnosis of vasospastic angina.<sup>17)18)</sup> Thus, our study in concert with the previous reports suggests that the patients suffering with strong positive vasospasm show strong disease activity in the early period after the development of disease, and they need aggressive treatment once they are diagnosed because of the trend for cardiac deaths after the withdrawal from their medications. However, the patients suffering with intermediate vasoconstriction didn't have such early strong disease activity and the resultant high cardiac mortality.

Based on our findings, intermediate vasoconstriction could not be identified as true coronary vasospasm. The clinical course and prognosis of the patients suffering with intermediate vasoconstriction were completely different from the clinical course and prognosis of the patients suffering with coronary vasospasm. None of former experienced hospitalization, an ER visit due to chest pain and cardiac death during the follow-up period. Thus, the present study demonstrated that the strict positive criteria of the acetylcholine provocation test, defined as total or severe vasoconstriction of the involved vessels, had great value for the accurate diagnosis of the true coronary vasospasm. The intermediate vasoconstriction must be regarded as a non-specific vasomotor response to acetylcholine, according to the strict application of the positive criteria of the provocation test.

### Intracoronary acetylcholine administration

Directly measuring the diameter reduction on angiography after intracoronary injection of acetylcholine or ergonovine has high specificity and sensitivity for the diagnosis of coronary vasospasm.<sup>17)</sup> In many previous reports, acetylcholine showed the same or greater efficacy in inducing vasospasm when compared with ergonovine.<sup>19)20)</sup> Thus, intracoronary acetylcholine infusion is a generally accepted method to assess endothelial dysfunction, including vasoconstriction.<sup>21-23)</sup> Thus, the degree of the vasomotor response to acetylcholine could be a useful parameter, at least for confirming coronary vasospasm, which showed a worse prognosis than intermediate vasoconstriction.

### Different clinical course between both groups

There are no clear guidelines concerning the duration of medical treatment for vasospasm.<sup>24)</sup> One study suggested that it may be possible to decrease the dosage of drugs along with careful monitoring for any further

disease activity.<sup>25)</sup> However, when considering that a previous study showed that cardiac deaths occurred after withdrawal from their medication, the physician's careful consideration about the termination of treatment is surely necessary.<sup>26)</sup> Remission of vasospasm is defined as the patient showing no symptoms and negative findings on the follow-up provocation test even after the medication is terminated.<sup>24)</sup> In the west, remission of vasospasm via vasodilator therapy was a frequent outcome and was reported in up to 45% of patients.<sup>27)28)</sup> In present study, however, the occurrence of symptom relief (grade 5) was observed in only a small number of patients with positive vasospasm, and this could mean the patients suffering with true vasospasm have a low potential for achieving remission of their coronary vasospasm.

Yet many of the patients in the intermediate vasoconstriction group showed symptom relief during the follow-up period, and they demonstrated a significantly better clinical course and prognosis than did the patients suffering with true vasospasm.

In conclusion, the patients suffering with intermediate vasoconstriction have a better long-term prognosis and a significantly different clinical course as compared with the patients with the true coronary vasospasm. Thus, the strict positive criteria, which can effectively rule out intermediate vasoconstriction, must be applied for the accurate diagnosis of true coronary vasospasm and to prevent possible false positive results on the acetylcholine provocation test.

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