Airway Hyperresponsiveness in Patients With Coronary Spastic Angina

Relationship Between Coronary Spasticity and Airway Responsiveness

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Background Several reports have suggested a possible link between bronchial asthma and coronary spasm, but the possibility of a relationship in coronary spastic angina (CSA) has not been clarified.

Methods and Results Airway responsiveness to methacholine and coronary spasticity to acetylcholine were examined in 42 patients with CSA and 36 patients with chest pain syndrome (CP). Furthermore, 18 control subjects were examined and their airway responsiveness compared with that of the CSA and CP patients. The incidence of airway hyperresponsiveness was significantly higher in the CSA group (74%) than in the CP (19%) and control (17%) groups (p<0.0001). The geometric mean of the log minimum dose (Dmin), defined as the cumulative dose at the point at which respiratory conductance began to decrease, was significantly lower in the CSA group (0.75 log units) than in the CP (1.20 log units) and control (1.38 log units) groups (p=0.004).

Conclusion These results demonstrate that acetylcholine-induced coronary spasticity is significantly related to methacholine-induced airway responsiveness in patients with CSA. A generalized hyperresponsiveness of the vascular and nonvascular smooth muscles, including that through cholinergic mechanisms, may exist in patients with CSA.

Key Words: Airway responsiveness; Coronary spastic angina; Coronary spasticity

Coronary spasm plays an important role in the pathogenesis and pathophysiology of ischemic heart diseases, including variant angina (VA) and coronary spastic angina (CSA). In patients with VA, the coronary artery constrictor response to diverse constrictor stimuli is enhanced, and occlusive constriction is readily induced upon exposure to such stimuli.

Several complications of VA have been reported. The incidences of both migraine and Raynaud’s phenomenon may be as high as those in control subjects. In addition, enhanced esophageal motility in patients with VA has been reported. These findings strongly suggest the presence of a generalized disorder of smooth muscle contraction in VA.

Several reports have suggested a possible link between bronchial asthma and CSA both of which have the following similar clinical features. First, attacks of bronchial asthma or CSA frequently occur in the early morning. At that time of day, parasympathetic nerve activity is increased, and acetylcholine (ACh), a parasympathetic nerve neurotransmitter, provokes bronchospasm or coronary spasm through muscarinic receptors. Second, exercise and hyperventilation and exposure to cold can all induce episodes of asthma or CSA.

The relationship between airway responsiveness and coronary spasticity in CSA has not yet been clarified. Saitoh et al found airway hyperresponsiveness to ACh in patients with CSA, but not in those with chest pain syndrome (CP). However, they did not find a correlation between ergonovine-induced coronary spasticity and ACh-induced airway responsiveness.

Determination of whether a generalized hyperresponsiveness of smooth muscles exists in CSA may help in elucidating the mechanism of coronary spasm and identifying possible therapeutic targets. Although the occurrence of coronary spasm appears to be related to endothelial dysfunction with reduced endothelial vasodilator function or smooth muscle hypercontraction, the precise mechanism remains unclear. Anecdotal cases of refractory CSA resistant to intensive medical treatment have been reported. However, once the mechanism of coronary spasm has been clarified, it may be possible to treat CSA selectively.

In the present study, we examined airway hyperresponsiveness in patients with CSA to determine whether there is a relationship between airway responsiveness to methacholine (MCh) and ACh-induced coronary spasticity.

Methods

Patient Selection

Between February 1999 and March 2001, a total of 78 consecutive patients (45 men, 33 women; age range, 31–71 years) who complained of chest pain and showed ischemic changes as described below during treadmill exercise tests or Holter monitoring without significant stenosis (≥75%) at
coronary angiography were enrolled. Patients whose spontaneous attacks were diagnosed as VA and those with a positive response to ACh (>90% stenosis of any segment at coronary angiography) with chest pain or ischemic changes on ECG were defined as CSA. The remaining patients who had non-VA and a response of >90% stenosis were defined as CP. VA was defined as angina pectoris occurring in association with a transient ST-segment elevation of ≥0.2 mV during spontaneous angina attacks. Non-VA was defined as anginal chest pain without ST-segment elevation during spontaneous attacks. The other ischemic changes on ECG during treadmill exercise tests or Holter monitoring were ST-segment depression of >0.1 mV as a horizontal or down-sloping type, or more than 0.2 mV as a junctional type. The CSA group consisted of 26 men and 16 women (mean age, 57 years; age range, 31–70 years), and the CP group consisted of 19 men and 17 women (mean age, 58 years; age range, 31–71 years) (Table 1). A total of 18 control subjects, who were selected to match the risk factors for atherosclerosis of the CSA and CP patients, were also enrolled (Table 1). None of the patients in the CP and CSA groups had taken any bronchodilators or steroids before this study. The baseline data and airway hyperresponsiveness were compared among the CSA, CP and control groups.

Patients who suffered from allergies, including bronchial asthma, other pulmonary diseases or respiratory tract infections within 1 month prior to the study and had a past history of bronchial asthma were excluded. The present study was approved by the Ethical Committee of the Cardiovascular Disease Center of Sendai and Tokyo Women’s Medical University. All the patients and control subjects gave fully informed consent before participating in the study.

### Coronary Angiography and Spasm Provocation Tests

Coronary angiography was performed in the morning using the Judkins technique. All vasodilatory drugs, including calcium-channel antagonists and nitrates, were discontinued at least 48 h before cardiac catheterization, with the exception of sublingual nitrates. Angiography was performed using a Philips cine angiography system (OPTIMUS 1050C) and recorded on 35 mm cine film at 48 frames/s. Control coronary angiograms of the left coronary artery in the right anterior oblique projection and the right coronary artery in the left anterior oblique projection were obtained after injection of 6–8 ml of Omnipaque (Daichi Seiyaku, Tokyo, Japan). A USCI bipolar electrode catheter was inserted into the right ventricular apex via the femoral vein and connected to a temporary cardiac pacemaker (5330; Medtronic, Minneapolis, MN, USA) at a pacing rate of 40 beats/min. Intracoronary injection of ACh was performed after a lack of significant stenosis was confirmed using a similar method to that reported previously by Okamura et al. ACh chloride (Daichi Seiyaku) was dissolved in 5 ml of 0.9% saline solution and injected into the left coronary artery at incremental doses of 20, 50, and 100 mg for 30 s each. ACh was also injected into the right coronary artery at incremental doses of 20 and 50 mg in a similar manner. The time interval between each injection was 3 min. When a coronary spasm of >90% was induced and did not resolve spontaneously within 3 min after the ACh injection, 2.5 mg of isosorbide dinitrate was injected into the coronary artery. During the study, arterial blood pressure and 12-lead ECG were continuously monitored on an oscilloscope using a Nihonen-Kohden poligraph system (RMC-2000). After the intracoronary injection of ACh, left ventriculography was performed in the right anterior oblique projection and the ejection fraction was measured.

### Quantitative Coronary Angiography

The luminal diameter of the coronary artery was measured quantitatively by means of the edge detection method (CCIP-310; Cathex Inc, Tokyo, Japan) at end-diastole in each of segments 1–14 according to the American Heart Association Classification, after calibration of the catheter tip. The segments were excluded from the measurements if they were <1.0 mm in diameter on control angiograms.

The changes in the coronary artery diameter after ACh injection were calculated as the percentage change relative to control coronary angiograms. At least 2 experienced cardiologists measured the coronary artery diameter and calculated the changes in the diameter in a blinded manner. The averages of these percentage changes were obtained, and the interobserver variance was found to be <10%. Four indices were used to evaluate the degree of coronary spasticity in each subject: (1) maximum reduction of the coronary diameter, defined as the percentage change in diameter of the most constricted coronary segment in response to ACh injection in the CSA and CP groups; (2) mean reduction of the coronary diameter, defined as the average percentage change in diameter of all the coronary segments in response to ACh injection in the CSA and CP groups; (3) number of vessels induced to undergo >90% stenosis in response to ACh injection, including single-vessel or multi-vessel coronary spasm (multivessel coronary spasm was defined as >90% stenosis induced by ACh in 2–3 of the left descending artery, left circumflex artery, and right coronary artery), in the CSA group; and (4) minimum ACh dose, defined as the minimum dose of ACh that induced >90% stenosis in the CSA group. The relationships of these 4 indices with those of airway responsiveness (described below) were also analyzed.

### Holter Monitoring

All patients underwent Holter monitoring using Nihon Kohden RAC2101 or 3103 recorders (Nihon Kohden Co, Tokyo, Japan). CM5, the standard V5 lead position, and NASÁ, a modified inferior lead position, were monitored for 24 h. During the monitoring, all medications were withheld except for sublingual nitroglycerin. The monitoring tapes were analyzed using a Nihon Kohden DSC-3100 Holter tape analyzer (Nihon Kohden Co).

### Treadmill Exercise Tests

Treadmill exercise tests were performed in the morning according to the Bruce protocol after the patients had fasted for >4 h. All medications were withheld except for sublingual nitroglycerin for 48 h before the tests. Signals from 12-lead ECG were displayed continuously during the observation period and recorded at regular intervals, as well as when chest pain occurred during exercise or the recovery phase.

### MCh Inhalation Challenge

All the subjects were studied from 13.00–14.00 h on a separate day within 3 days of the coronary angiography. The forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) were measured using a dry-seal spirometer (OST 80A; Chest Co, Tokyo, Japan) in all subjects.
at 30 min before the study. An arterial blood gas analysis was also carried out (170 pH/Blood Gas Analyzer; Corning, Medfield, MA, USA). MCh (Sigma Chemical Co, St Louis, MO, USA) inhalation tests were performed using a device (Astograph TCK-6100H; Chest Co) that displayed a respiratory resistance (Rrs) dose–response curve measured by the forced oscillation method during tidal breathing with continuous inhalation of aerosolized MCh. This system was previously described by Takishima et al \(^{28}\) and has been used in both clinical settings and clinical studies. \(^{29,30}\) Briefly, it consists of an aerosol delivery system, a loudspeaker box system generating a constant amplitude sine wave pressure at 3 Hz and a system for automatically measuring Rsrs from the mouth flow and mouth pressure. Rrs was continuously displayed against time on an X–Y recorder (Watanabe WX-441; Graphtec Corp, Tokyo, Japan). Aerosols were generated by 12 Bird nebulizers (Bird Corp, Palm Springs, CA, USA) connected to the main tube near the mouthpiece, each of which contained 4 ml of MCh solution at different concentrations, at a constant airflow of 6 L/min controlled by an air compressor to elicit an output of approximately 0.15 ml/min. The subjects wore a nose-clip and inhaled the aerosols by tidal breathing through the mouthpiece. MCh was prepared in 0.9% saline in 2-fold increasing concentrations ranging from 0.049 to 25 mg/ml. After confirmation that inhalation of saline for 1 min did not change the baseline Rsrs, each concentration of MCh solution was inhaled for 1 min until the Rsrs reached approximately 2-fold the baseline value or until the maximum concentration was administered. A solution of 0.5% salbutamol was inhaled as a bronchodilator for 2 min after the provocation was stopped.

Three indices \(^{28}\) were used to evaluate airway responsiveness in each subject: (1) baseline value of Rsrs (Rsrs cont), defined as the mean value of Rsrs obtained graphically during inhalation of saline for 1 min; (2) minimum dose (Dmin) of MCh, defined as the cumulative dose at the point at which respiratory conductance (Grs), obtained graphically as the reciprocal of Rsrs, started to decrease linearly and calculated in terms of 1 unit = 1 min inhalation of 1 mg/ml of MCh during tidal breathing; and (3) linear slope of the decrease in Rsrs (Grss), defined as \(\Delta\)Grs/\(\Delta\)t (in L·s\(^{-1}\)·(cm\(^2\)H2O/min)\(^{-1}\)·min\(^{-1}\)).

Because an inverse relationship was found between the slope and Rsrs cont, we used the normalized slope (Grss/Grs cont) in order to compensate for differences in the initial airway caliber among the subjects. We considered the subjects to have airway hyperresponsiveness when the Rsrs increased by >100% from the baseline value after inhalation of MCh at doses below the total cumulative dose (50 units). A log Dmin value of 1.70 or a log Dmin value <1.70 with the Rsrs increased by <100% was used for subjects without airway hyperresponsiveness.

### Statistical Analysis

Normality was evaluated by normal distribution plots and histograms for the variables. Analyses were performed on the natural logarithm of the Dmin values to improve normality. Continuous variables were calculated as the mean ± SD and compared using the unpaired t-test or analysis of variance. When significant differences were detected by the analysis of variance, individual groups were compared using Scheffé’s test. Categorical variables were calculated as frequencies and analyzed by the chi-square test or Fisher’s exact test, depending on the numbers involved. Linear regression analysis was performed to examine the relationships of the coronary diameter reduction with Rsrs, log Dmin and Grss/Grs cont. Correlation coefficients between the minimum ACh dose that induced >90% stenosis and log Dmin in patients with CSA were calculated using Spearman’s rank correlation coefficients. A value of p<0.05 was considered to indicate statistical significance.
Results

Clinical Characteristics

No significant differences were found among the CSA, CP and control groups in terms of age, sex, blood gas and IgE value or coronary risk profiles such as hypertension, hyperlipidemia, diabetes mellitus and smoking (Table 1). Vasodilatory drugs were administered to 14 of the 42 CSA patients and 4 of the 36 CP patients before admission. In the CSA group, 13 patients were diagnosed as having VA, and the remaining 29 were diagnosed as having CSA by selective spasm provocation tests. Among the latter, 18 patients had spontaneous chest pain attacks accompanied by ST depression on ECG, and 11 had positive treadmill exercise tests. In the CP group, 7 patients had spontaneous chest pain attacks accompanied by ST depression, and 29 had positive treadmill exercise tests. There were no significant differences among the 3 groups for baseline pulmonary functions, such as FVC, percentage value of predicted FVC, percentage value of predicted FEV1 or arterial oxygen pressure (PaO2). Furthermore, no significant differences existed among the patients in the CSA and CP groups in terms of the left ventricular ejection fraction (Table 1).

Coronary Angiography and Spasm Provocation Tests

A coronary spasm of >90% was provoked in 10 of 13 patients with VA. Among the 42 CSA patients, 28 showed ST elevation and the remaining 14 showed ST depression during intracoronary administration of ACh. Despite the fact that 3 patients in the CP group had ST-segment depression with chest pain during ACh injection, they did not show >90% stenosis caused by coronary spasms. All the patients who showed >90% stenosis by coronary spasms had either chest pain or ST changes during intracoronary administration of ACh, and we classified these patients into the CSA group. The ACh-induced maximum and mean reductions of the coronary diameter were significantly higher in the CSA group than in the CP group (96±6% vs 56±18%, p<0.0001, and 59±15% vs 30±20%, p<0.0001, respectively). Among the CSA patients, smokers had slightly, but not significantly, higher coronary spasticity than non-smokers (maximum constriction: 99% vs 94%, average constriction: 55% vs 49%, respectively). During the ACh provocation tests, no asthmatic attacks were provoked.

Airway Hyperresponsiveness to MCh

The mean values of Rrs cont and SGrs/Grs cont did not differ significantly among the 3 groups. The geometric mean value of log Dmin was significantly lower in the CSA group (0.75 log units) than in the CP (1.20 log units) and control (1.38 log units) groups (p=0.004) (Fig 1). The incidence of airway hyperresponsiveness was significantly higher in the CSA group (74%) than in the CP (19%) and control (17%) groups (p<0.0001).

Among all the subjects, the airway hyperresponsiveness of smokers did not differ from that of non-smokers (log Dmin: 0.79 log units vs 0.75 log units, respectively). During the MCh inhalation tests, no asthmatic or anginal attacks were provoked.
Relationship Between Coronary Spasticity and Airway Hyperresponsiveness

No significant correlations were found for the ACh-induced maximum diameter reduction and Rrs cont or for the mean diameter reduction and Rrs cont in the CSA and CP groups. A significant inverse correlation was found between the ACh-induced maximum diameter reduction and log Dmin in the CSA group (r=−0.46, p=0.008; Fig 2), but not in the CP group. Similarly, a significant inverse correlation was found between the mean diameter reduction and log Dmin in the CSA group (r=−0.79, p=0.005; Fig 3), but not in the CP group.

There was no significant correlation between the maximum diameter reduction and SGrs/Grs cont in either the CSA group (r=0.21, p=0.089) or CP group (r=0.16, p=0.074; Fig 4).

The mean Rrs cont and SGrs/Grs cont in patients with multivessel coronary spasms did not differ significantly from those in patients with single-vessel coronary spasms. However, the geometric mean of log Dmin was significantly lower in patients with multivessel coronary spasms (0.30 log units) than in patients with single-vessel coronary spasms (0.98 log units, p=0.018; Fig 5). The minimum ACh dose was correlated to the log Dmin of MCh in CSA patients with airway hyperresponsiveness (r=0.87, p=0.007; Fig 6).

Discussion

The results of the present study demonstrate that CSA patients have a higher incidence of airway hyperresponsiveness than CP patients and control subjects, and that ACh-induced coronary spasticity is significantly correlated with MCh-induced airway responsiveness in CSA patients. Furthermore, the minimal dose of ACh that induced >90% stenosis in the coronary artery is significantly correlated with the log Dmin of MCh, defined as the cumulative dose at the point at which respiratory conductance begins to decrease, in CSA patients with airway hyperresponsiveness.

Saitoh et al.\textsuperscript{24} reported airway hyperresponsiveness to ACh in patients with CSA, but not in those with CP. However, they did not find a relationship between the bronchial provocative concentration of ACh that induced a 20% fall in the FEV\textsubscript{1} and the response threshold of ergonovine maleate that induced coronary spasms. The reason for this lack of relationship may be that they used ergonovine maleate, rather
than ACh, to provoke spasms. Both ACh and ergonovine have been used to induce coronary spasms in patients with CSA, but they act via different mechanisms. ACh, a neurotransmitter of the parasympathetic nervous system, has dual effects; namely, endothelium-dependent vasodilation at low doses and direct contraction of vascular smooth muscles at high doses, through muscarinic receptors on the endothelium and vascular smooth muscles. ACh elicits endothelium-dependent vasodilation in healthy controls, but this is impaired in arteries with atherosclerotic lesions and in hypercholesterolemia. In contrast, ergonovine maleate, an ergot alkaloid, elicits vasoconstriction through serotonergic receptors in human coronary arteries in vivo and in VA may induce coronary spasm directly, rather than via remote neurohumoral reflexes. Although ergonovine and ACh show similar sensitivities for identifying CSA, their provocation mechanisms differ in site, configuration and degree of coronary spasm. The differences between these 2 agents regarding their receptor distribution and ability to induce endothelium-derived vasodilation or constriction of arterial smooth muscles may be involved in the different results obtained in the present study and those of Saitoh et al. Because ACh and MCh challenges have been reported to yield similar high levels of sensitivity and specificity for revealing airway hyperresponsiveness, we consider that the differences between these 2 agents did not affect our results.

Fig 5. Distribution of log Dmin of methacholine in the coronary spastic angina patients with single-vessel and multi-vessel spasm. Solid lines indicate the median value for log Dmin in each group.

Mechanism cannot explain the present findings, because all the patients in the present CSA and CP groups had normal left ventricular ejection fractions.

Airway hyperresponsiveness is frequently encountered in patients with microvascular angina who experience breathlessness and anginal chest pain during physical or emotional stress with angiographically normal coronary arteries. The possibility that microvascular angina was included in the present CP group was not ruled out. In fact, the incidence of airway hyperresponsiveness in the CP group was slightly, but not significantly, higher than that in the control group. We did not discriminate microvascular angina from CP or compare airway hyperresponsiveness in microvascular angina with that in CSA, and these aspects remain to be investigated in future studies.

However, we report that patients with CSA show airway hyperresponsiveness, and that the complication of both CSA and bronchial asthma does not occur very frequently. Two possible reasons for this have been considered. The first is that airway hyperresponsiveness in CSA may be caused by hypersensitivity alone. Airway responsiveness comprises 2 elements: sensitivity and reactivity. Airway sensitivity is defined as Dmin, whereas airway reactivity is expressed as SGr/Grs cont. We found that the log Dmin was lower in CSA patients than in the CP patients and control subjects, whereas SGr/Grs cont did not differ among the 3 groups. These findings suggest that the CSA patients had a higher incidence of airway hypersensitivity than the other groups, but a similar incidence of airway hyperreactivity.

Inflences of age, sex, smoking habits, allergic factors, left ventricular ejection fraction and microvascular angina on airway hyperresponsiveness have been reported. However, no significant differences were observed among the present CSA, CP and control groups with respect to age, sex or coronary risk factors, including smoking and allergic factors.

Cabanes et al reported bronchial hyperresponsiveness to MCh in patients with impaired left ventricular function and indicated that the mechanism was likely to be related to elevated pulmonary venous pressure. However, this mechanism cannot explain the present findings, because all the patients in the present CSA and CP groups had normal left ventricular ejection fractions.

Airway hyperresponsiveness is frequently encountered in patients with microvascular angina who experience breathlessness and anginal chest pain during physical or emotional stress with angiographically normal coronary arteries. The possibility that microvascular angina was included in the present CP group was not ruled out. In fact, the incidence of airway hyperresponsiveness in the CP group was slightly, but not significantly, higher than that in the control group. We did not discriminate microvascular angina from CP or compare airway hyperresponsiveness in microvascular angina with that in CSA, and these aspects remain to be investigated in future studies.

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Patients with bronchial asthma have been reported to show airway hyperresponsiveness because of enhancement of both sensitivity and reactivity. Because the present CSA patients had airway hyperresponsiveness related to hypersensitivity alone, they may not present any clinical signs and symptoms of bronchial asthma. The second possible reason is that the degree of airway hyperresponsiveness may be lower in CSA than in bronchial asthma. We did not include any patients with bronchial asthma or compare the airway hyperresponsiveness in CSA with that in bronchial asthma. The Dmin of patients with bronchial asthma in a previous report was lower than that of patients with CSA in our study. This lower degree of airway hyperresponsiveness in patients with CSA than in those
with bronchial asthma may also be one of the reasons why patients with CSA do not necessarily suffer such severe bronchospasm as do those with bronchial asthma.

CSA and bronchial asthma show similar clinical pathophysiology and pathogeneses, such as disturbances of the parasympathetic nervous system\(^\text{[16,17,49]}\) increases in the endothelin\(^\text{[50,51]}\) thromboxane A\(_2\)\(^\text{[52,53]}\) and serotonin\(^\text{[54,55]}\) levels, and involvement of inflammation\(^\text{[56-57]}\). However, the mechanisms of the linkage between the 2 diseases remain unknown.

Although the roles of polymorphisms in the endothelial nitric oxide synthase gene\(^\text{[58]}\) upregulated Rho-kinase\(^\text{[59]}\) and hypoadiponectinemia\(^\text{[60]}\) in coronary spasms have recently been reported, their mechanisms are unclear. Furthermore, no consensus has been reached for whether endothelial dysfunction with reduced endothelial vasodilator function\(^\text{[8,31,61,62]}\) or smooth muscle hypercontractility\(^\text{[63,64]}\) can induce a coronary spasm. Yokoyama et al reported that contractility of coronary smooth muscle cells was indeed augmented at the spastic coronary segment in a patient with VA\(^\text{[64]}\) Yamamoto et al\(^\text{[65]}\) and Egashira et al\(^\text{[66]}\) suggested that endothelial dysfunction is not necessarily the cause of coronary spasm, because the endothelium-dependent vasodilation induced by substance P is preserved, even in the sites of coronary spasticity induced by ergonovine\(^\text{[67]}\) or ACh\(^\text{[68]}\) at high doses in patients with VA. The latter study further demonstrated that low doses of ACh cause comparable vasodilation at the spastic site and control sites in normal coronary arteries, and suggested that ACh-induced coronary spasms in patients with VA result from hypercontractility of the vascular smooth muscles. Thus, hypercontractility of coronary smooth muscles may play an important role in coronary spasm.

Concerning the role of atherosclerosis in coronary spasm, the similar prevalences for the risk factors in the present patients with CSA and CP suggest that coronary spasms caused by ACh cannot simply be explained by endothelial dysfunction induced by atherosclerosis at variable degrees.

We have reported that hypersensitivity to cholinergic stimuli exists in the airways and coronary arteries of patients with CSA, suggesting that cholinergic hypersensitivity may modify and increase coronary spasms in these patients. We speculate that cholinergic hypersensitivity of nonvascular smooth muscles, as well as of the coronary arterial smooth muscles, exists systemically in patients with CSA. If we can elucidate the clinical significance and mechanism of the cholinergic hypersensitivity of smooth muscles in CSA, we may be able to identify therapeutic targets.

**Study Limitations**

The present study did not evaluate the relationship between coronary spasticity and airway hyperresponsiveness in normal control subjects, because it was ethically difficult for them to undergo coronary angiography. In addition, we did not include patients with bronchial asthma, because injection of ACh is contraindicated in them. Therefore, we could not clarify the incidence of the combination of CSA and bronchial asthma or determine the coronary spasticity in bronchial asthma. Further studies are needed to determine whether hyperresponsiveness of nonvascular smooth muscles, except for the bronchi, exists in CSA.

**Conclusions**

The results of the present study demonstrate that patients with CSA show airway hyperresponsiveness, and that coronary spasticity correlates with airway responsiveness in these patients. We speculate that a generalized hyperresponsiveness of vascular and nonvascular smooth muscles, including that through cholinergic mechanisms, may exist in patients with CSA. Further studies regarding the mechanisms are needed.

**Acknowledgment**

We thank Mrs Junko Sakuraba for her collaboration in this study.

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Airway Hyperresponsiveness in VA


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