Sympathetic Nerve Activity in the Spasm-Induced Coronary Artery Region Is Associated With Disease Activity of Vasospastic Angina

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Objectives. We assessed the relation between sympathetic nerve activity and disease activity of vasospastic angina.

Background. The autonomic nervous system has been proposed to play a key role in attacks of vasospastic angina. A unique feature of vasospastic angina attacks is periodic fluctuation, which complicates the assessment of disease activity.

Methods. Twenty-five patients with left anterior descending coronary artery (LAD) spasm were studied: 12 with recent onset of chest pain (group 1) and 13 free of angina for more than 3 months after discontinuing medication (group 2). Group 1 underwent iodine-123 metaiodobenzylguanidine (MIBG) imaging (in the active phase) and atropine-stress MIBG imaging early after diagnostic angiography, and repeat MIBG imaging when they were free of angina for more than 3 months with medication (in the stable phase). Group 2 also underwent MIBG imaging (in remission). On a bull's-eye map, quantitative analysis of percent uptake and washout rate of MIBG was performed regionally.

Results. In group 1 in the active phase, the washout rate of the LAD territory was significantly lower than the rates in the stable phase, in remission and during atropine-stress MIBG imaging. The regional washout rate of the territories of the right coronary artery and the circumflex artery in the active phase was also significantly lower than that during atropine-stress MIBG imaging. The washout rate of the LAD territory in the active phase was significantly lower than the rates of the other two regions. In contrast, there were no significant differences in the distribution of regional percent uptake in every image. A similar distribution of washout rate was observed among group 1 patients in the stable phase, in group 1 patients during atropine-stress MIBG imaging and in group 2 patients.

Conclusions. The MIBG washout rate of the spasm-induced coronary artery territory changed according to the degree of disease activity. Thus, sympathetic nerve activity could reflect disease activity of vasospastic angina.

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four patients had mild arteriosclerotic plaque at the site of spasm (<50%). In group 2, 10 patients had completely normal coronary arteries, and the remaining three patients had mild arteriosclerotic plaque at the site of spasm (<50%). All patients had normal left ventricular function and demonstrated >99% vasoconstriction accompanying ischemic electrocardiographic (ECG) changes and chest pain by acetylcholine infusion only in the proximal portion of the left anterior descending coronary artery. All patients with vasospastic angina usually had chest pain occurring at rest and at least once a week before taking antianginal drugs. However, we could not document spontaneous ischemic attacks with ischemic ST segment changes in any of the patients with vasospastic angina. None of the patients had any chest pain after taking antianginal drugs. None of the patients had a history of myocardial infarction, diabetes mellitus or any other diseases affecting the autonomic nervous system. Informed consent was obtained from each patient. This study protocol was approved by the hospital's ethics committee.

Coronary angiography. After discontinuing antianginal drugs for several days, except for sublingual nitroglycerin, coronary angiography was performed. Before coronary angiography, a temporary pacing catheter was inserted into the right ventricle through the femoral vein; this was connected to the patient. This study protocol was approved by the hospital's ethics committee.

Figure 1. Definition of the territories of the three major coronary arteries on a polar map for iodine-123 metaiodobenzylguanidine imaging. LAD = left anterior descending coronary artery; RCA = right coronary artery; LCX = left circumflex artery.

Coronary angiography. After discontinuing antianginal drugs for several days, except for sublingual nitroglycerin, coronary angiography was performed. Before coronary angiography, a temporary pacing catheter was inserted into the right ventricle through the femoral vein; this was connected to a pulse generator with a demand-driven rate of 40 beats/min. Standard 12-lead ECGs were recorded continuously with a six-channel recorder. After control coronary arteriograms were obtained, acetylcholine, which had been dissolved in saline solution, was injected in incremental doses of 20 and 100 μg directly into the right coronary and subsequently the left coronary artery through a Judkins catheter. Coronary angiography was performed 1 min after acetylcholine was injected over 1 min. Acetylcholine administration was stopped and coronary angiography was performed immediately after the onset of chest pain accompanied by ischemic ECG changes. Chest pain was relieved promptly, either spontaneously or by intracoronary injection of nitroglycerin. After the acetylcholine provocation test, coronary angiography was performed after intracoronary injection of 0.3 mg of nitroglycerin. The results of coronary angiography after injection of nitroglycerin were classified according to the reporting system of the American Heart Association. Coronary artery spasm induced by acetylcholine was considered present if total or subtotal occlusion (>99% vasoconstriction) of the involved artery occurred in association with chest pain and ischemic ST segment changes (>0.1-mV ST segment elevation or depression from the control level). After coronary angiography, patients with coronary artery spasm resumed taking antianginal drugs.

MIBG scintigraphy. One week after coronary angiography, all patients in group 1 underwent cardiac MIBG imaging while taking antianginal drugs (active phase). During follow-up, all patients in group 1 underwent repeat MIBG scintigraphy when their attacks disappeared with drug administration for >3 months (9 ± 3 months after onset; stable phase). At this time, chest pain and ischemic ST-T segment changes on the ECGs had disappeared completely in all patients. All patients in group 2 underwent MIBG scintigraphy at least 3 months (4 ± 1 months) after discontinuing antianginal drugs (in remission). None of the patients in group 2 demonstrated ischemic changes on the ECGs or chest pain after discontinuing drugs.

A dose of 111 MBq of commercially available MIBG (Daichi Radioisotopes Labs., Ltd., Tokyo, Japan) was administered intravenously from 9 to 10 AM after undisturbed supine bed rest for 15 min. Cardiac single-photon emission computed tomographic (SPECT) images were acquired 15 min (initial image) and 3 h (delayed image) after the injection of MIBG, using a three-head gamma camera (Toshiba GCA 9300A/HG, Tokyo, Japan) with 120° rotation per head in 3° increments, 30 s per step and a 128 × 128 matrix. The data were reconstructed by filtered backprojection (Shepp-Logan) on a Toshiba GMS 5500A system. Neither scatter correction nor attenuation correction was performed.

Oblique tomographic slices on the short, vertical long and horizontal long axes were computed and displayed. For semi-quantitative analysis, relative MIBG uptake of the left ventricle was calculated in all short-axis slices using a modified three-dimensional region of interest algorithm (20) and setting the maximal MIBG uptake at 100%. On a polar map representation, the territory in each of the three major coronary arteries is demonstrated in Figure 1.

Quantitative analysis of the washout rate of MIBG was also performed. Regional washout rates from the heart were calculated using initial and delayed images. The regional washout rate was obtained using the following formula: Regional washout rate (%) = (A - B)/A × 100, where A = average counts in a region on the initial image; and B = average decay-corrected counts at the same region on the delayed image. Decay correction was performed assuming that the half-life of radionuclide (iodine-123) was 13 h.

Atropine-stress test. One week after the first MIBG imaging scans were taken, all patients in group 1 underwent atropine-stress MIBG imaging. Electrocardiographic monitoring was performed throughout the test. Blood pressure was recorded before and every 1 min after atropine injection until the injection of MIBG. After supine bed rest for 15 min, 1 mg of atropine was injected intravenously. This dose of atropine has been reported to suppress coronary artery spasm (10).
Figure 2. Polar maps for iodine-123 metaiodobenzylguanidine (MIBG) depicting regional percent uptake and regional washout rate of MIBG in the territory of the three major coronary arteries in patients with left anterior descending coronary artery spasm. Scans were performed at the various stages of disease activity. Group 1 = 12 patients with chest pain within 3 months of admission; Group 2 = 13 patients with no chest pain for >1 year during antianginal drug therapy and no recurrence for >3 months after discontinuing antianginal drugs; Atropine = MIBG imaging after 1 mg of atropine injection. #p < 0.05; ##p < 0.01; *p < 0.02; **p < 0.001 versus active phase. Results shown are mean value ± SD.

MIBG was injected 3 min after the atropine injection. MIBG images were obtained 15 min and 3 h after the injection of 111 MBq of MIBG.

Statistical analysis. Results are expressed as mean value ± SD. Two-way repeated measures analysis of variance (ANOVA) was used to compare the regional percent uptake and regional washout rate of each region in the serial imaging and within three regions in each image by one-way ANOVA followed by a Bonferroni multiple comparison test. Significant differences were recognized at p < 0.05.

Results

Regional MIBG uptake. The results of the regional MIBG uptake in patients with coronary artery spasm are illustrated in Figure 2. As shown in Figure 2, uptake of MIBG in the left ventricle shows a similar heterogeneous distribution in both groups. There were no significant differences in the regional MIBG uptake between group 1 in the active phase or in other phases and group 2.

Regional washout rate. Figure 2 also shows the regional washout rate in the two groups. In group 1 in the active phase, the regional washout rate of the territory of the left anterior descending coronary artery was significantly lower than the rates of the circumflex artery territory (p < 0.02) and the right coronary artery territory (p < 0.05). However, there were no significant differences among the three regions in the other phases. The regional washout rate of the territory of the left anterior descending coronary artery in the active phase was significantly lower than that in the other phases (p < 0.01 compared with the value in the stable phase, p < 0.01 compared with the value in remission and p < 0.001 compared with the value in the atropine-stress test). Also, the regional washout rates of the territories of the right coronary artery and the circumflex artery in the active phase were significantly lower than those in the atropine-stress test (p < 0.02 and p < 0.05, respectively).

Serial MIBG scintigraphy: case report (Fig. 3). A 58-year-old man was referred to our hospital for chest pain occurring from midnight to early morning. Coronary angiography revealed acetylcholine-induced spasm in the left anterior descending coronary artery. He was given antianginal drugs immediately after angiography and the anginal attacks disappeared. One week after the diagnostic angiogram, he underwent MIBG imaging. Thereafter, his anginal attacks completely disappeared. Approximately 1 year later, he underwent follow-up MIBG imaging. The washout rate in the left anterior descending coronary artery territory was markedly higher than that seen on the first MIBG imaging scan. In early August 1995, chest pain between midnight and early morning recurred. One month after reemergence of chest pain, he underwent MIBG imaging. At this time, the increased washout rate in the left anterior descending coronary artery territory on the second MIBG imaging scan was markedly reduced.
Discussion

The present study demonstrates that patients with left anterior descending coronary artery spasm showed a reduced washout rate of MIBG early after the onset of chest pain, which subsequently increased with disappearance of anginal attacks, especially in the spasm-induced coronary artery territory.

**Contradiction to previous studies.** Using MIBG imaging, the integrity of the myocardial sympathetic nervous system has been studied in various heart diseases (15–19). Reduced MIBG uptake and enhanced MIBG washout have been shown in ischemic heart disease. Both reduced MIBG uptake and enhanced MIBG washout are considered the result of disinnervation or denervation of sympathetic nerve endings, or both, mainly due to myocardial ischemia. Recently, patients with vasospastic angina have been shown to have regional sympathetic dysinnervation by visual assessment of MIBG imaging (20). However, sympathetic dysinnervation from cardiac ischemia is not negligible. In addition, it is sometimes difficult to assess MIBG imaging visually, especially in the inferior wall (15). Furthermore, gender- and age-related heterogeneous distribution of MIBG has been reported (21). Thus, it is important to consider these factors in the MIBG studies. Therefore, we limited our study to patients with left anterior descending coronary artery spasm and normal left ventricular function, whose chest pains had been suppressed by antianginal drugs. In addition, the study subjects matched the factors noted above. Under these conditions, quantitative analysis of MIBG imaging showed that MIBG uptake in the heart was preserved in all study patients with coronary artery spasm, even in the active phase. However, regional washout rates of the spasm-induced coronary artery territory in the active phase were apparently reduced compared with those in the other stages.

**Atropine-stress MIBG scintigraphy.** In the present study, atropine-stress MIBG imaging was performed to assess a mechanism of reduced washout rates in the active phase of vasospastic angina. As a result, atropine, an antimuscarinic drug, could enhance washout rates in each region, prominently in the spasm-induced coronary artery region, in the active phase of vasospastic angina. Given that atropine blocks presynaptic muscarinic receptors (22) and removes the inhibitory influence on the release of norepinephrine, one possible mechanism of the reduced washout rate of MIBG in the active phase of vasospastic angina is considered to be an inhibition of norepinephrine release from the presynaptic site. Considering the cardiac sympathetic–parasympathetic interactions at sympathetic nerve terminals and the effects of atropine on the parasympathetic nervous system, we speculate that the sympathetic nervous system in patients with vasospastic angina in the active phase might be suppressed by the parasympathetic nervous system, especially in the spasm-induced territory. This is partially supported by the reports that the parasympathetic nervous system is enhanced in vasospastic angina in the active phase (14,23). In contrast, atropine is well known to suppress acetylcholine-induced spasm clinically (10). Therefore, the MIBG images obtained after atropine injection were considered to represent the sympathetic nerve activity in the heart, under which coronary spasm is difficult to induce. In the present study, this was clinically demonstrated by the fact that the results of atropine-stress MIBG imaging were similar to those of MIBG imaging performed in the stable phase and remission. Thus, atropine-stress MIBG imaging may provide us with some important clinical information on vasospastic angina.

**Clinical implications.** Fluctuation of ischemic attacks in vasospastic angina makes it very difficult to assess disease activity of vasospastic angina. Until now, exercise test (4),
ergonovine provocation alone (5,6) or combined with hyperventilation (7), ambulatory ECG monitoring (8) and measurement of blood components (9) have been proposed as means of assessing disease activity in vasospastic angina. However, the shortcomings of these tests make assessment of disease activity incomplete. In the present study, we demonstrated that noninvasive MIBG imaging, which can be easily and safely performed in patients with vasospastic angina in various clinical states, could provide a useful tool to assess disease activity. In fact, as shown in a case with recurrence of ischemic attacks, the washout rate in the spasm-induced coronary artery territory was reduced again when anginal attacks recurred, even though the patients continued taking antianginal drugs. Thus, MIBG imaging could help monitor disease activity of vasospastic angina.

However, it has been suggested that the parasympathetic nervous system plays a major role in coronary spasm. Given that a period of marked imbalance of the sympathetic and parasympathetic nervous systems has been shown to have a close relation to vasospastic angina activity (24), the sympathetic nerve activity in the spasm-induced coronary artery territory could reflect the disease activity of vasospastic angina.

Conclusions. Using serial MIBG imaging, the present study showed that sympathetic nerve activity in the spasm-induced coronary artery territory changed according to disease activity in vasospastic angina. The present study suggested that serial MIBG imaging, including atropine-stress MIBG imaging, could help determine disease activity and the territory of the spasm-induced coronary artery in vasospastic angina, even though the study was limited to spasm in the left anterior descending coronary artery.

References