Angiology: Open Access
ISSN: 2329-9495

Teragawa et al., Angiol 2017, 5:3
DOI: 10.4172/2329-9495.1000202

Research Article Open Access

What Factors Contribute to Chest Symptoms during Exercise in Patients with Vasospastic Angina?

Teragawa H*, Fujii Y, Oshita C, Uchimura Y and Ueda T

Department of Cardiovascular Medicine, JR Hiroshima Hospital, Hiroshima, Japan

***Corresponding author**: Hiroki Teragawa, Department of Cardiovascular Medicine, JR Hiroshima Hospital, 3-1-36 Futabanosato, Hiroshima-732-0057, Japan, Tel: +81822621171; E-mail: hiroteraga71@gmail.com

Received date: 27 July, 2017; **Accepted date:** 06 August, 2017; **Published date:** 10 August, 2017

Abstract

Objective: Chest symptoms in patients with vasospastic angina (VSA) typically occur during rest. However, we have occasionally experienced patients with VSA who have had chest symptoms even during exercise. However, factors contributing to the chest symptoms during exercise in patients with VSA remain unclear. Therefore, we investigated this relationship.

Methods: We investigated 101 patients with VSA (median age: 69 years, 51 males and 50 females). We completed detailed chest symptom examinations at rest (n=85), during exercise (n=2), and both at rest and during exercise (n=14). Patients were divided into the two groups: Group I consisted of patients with VSA whose chest symptoms occurred only at rest (n=85, 84%) and Group II consisted of patients with VSA whose chest symptoms occurred during exercise (n=16, 16%). On a coronary angiography, the presence of atherosclerosis (% stenosis>25%), significant coronary stenosis (% stenosis>50%), and myocardial bridging (MB), defined as the narrowing of the coronary artery during systole, were checked. Clinical parameters, including angiographic findings, were assessed in the two groups.

Results: There were no significant differences in coronary risk factors between the two groups. The presence of atherosclerosis (Group I: 58% vs. group II: 75%) and significant coronary stenosis (Group I: 10% vs. group II: 25%) did not differ between-groups. The presence of MB was significantly higher in Group II (50%) than in Group I (12%, p=0.0002). Logistic regression analysis showed that the presence of MB was associated with patients in Group II.

Conclusions: MB, rather than coronary atherosclerosis or significant coronary stenosis, may contribute to chest symptoms during exercise in patients with VSA.

Keywords: Coronary spasm; Myocardial bridging; Exercise-induced myocardial ischemia

Introduction

Vasospastic angina (VSA) is characterized by transient vasoconstriction of the epicardial coronary arteries leading to myocardial ischemia [1-3]. Chest symptoms in patients with VSA typically occur at rest and from midnight to early morning. Many reports also show chest symptoms during exercise [4-12]. These reports identify clinical characteristics in patients with chest symptoms during exercise such as the presence of severe of coronary stenosis or impaired fibrinolysis [5-7,9,12], however, it is unclear if other characteristics are present, or not.

The myocardial bridge (MB), which is characterized with the systolic narrowing of epicardial coronary artery due to myocardial compression during systole, is reportedly associated with abnormalities of cardiovascular system, including exertional angina or acute coronary syndrome [13,14]. The presence of MB is associated with coronary spasms [15-19]. Thus, it is possible that MB may influence chest symptoms during exercise in VSA patients. In the present study, we focused on the presence of MB on coronary angiography (CAG) and investigated the relationship between the presence of MB and chest symptoms during exercise in VSA patients.

Patients and Methods

In this observational and retrospective study, 101 patients (51 males and 50 females, median age, 69 years) with VSA, diagnosed on the basis of the positive spasm provocation test (SPT) results were studied. Because coronary spasm can occur in patients who underwent percutaneous coronary intervention (PCI) and such patients without obvious significant coronary stenosis with a positive SPT result were included in the present study. Patients with moderate chronic kidney disease (estimated glomerular filtration ratio<45 mL/min/1.73 m^2) or with severe coronary stenosis (% stenosis ≥ 75%) were excluded from the study. The protocol was approved by the Ethics Committee of our institution and written informed consent was obtained from all patients.

The procedure of CAG and SPT at our institution was reported previously [20,21]. All coronary vasodilators were discontinued at least 48 h before catheterization, with the exception of sublingual nitroglycerin (NTG). We performed the diagnostic coronary angiography using the percutaneous brachial approach and, thereafter, performed the SPT.

A 5-Fr pacing catheter (Bipolar Balloon Catheter, Bebrawn, Melsungen, Germany) was inserted into the right ventricle via the interjugular vein or median cubital vein, and set to 50 beats/min. We

continuously monitored the arterial pressure, heart rate, and ECG readings and these results were recorded using a multichannel recorder (Polygraph 1600; Nihon Electric Corporation, Tokyo, Japan).

After the diagnostic coronary angiography, incremental doses (30 and 50 μg) of acetylcholine (ACh) were infused into the right coronary artery (RCA) for 20 s, with 3- min intervals between consecutive doses. If coronary spasms were not induced by 50 μg of ACh doses, 80 μg of ACh was infused into the RCA. When coronary spasms were provoked or the infusion of maximum ACh dose was completed, a coronary angiography was immediately performed. When coronary spasms were provoked but spontaneously relieved, we did not administer an intracoronary infusion of NTG into the RCA and moved to the SPT of the left coronary artery (LCA). In such cases, we again performed coronary angiograms after an NTG infusion into the RCA after the SPT for the LCA was finished. When coronary spasms were prolonged or were severe to cause unstable hemodynamics, 200 μg of NTG was administered by an intracoronary injection to relieve coronary spasms. Even after the intracoronary NTG injection into the RCA, we performed a subsequent SPT for the LCA because we have experienced many patients with positive spasm provocation under such condition. When the RCA was small, or when we could not engage the catheter into the RCA, we skipped the SPT for the RCA.

After the SPT for RCA was finished, incremental doses of 50 and 100 μg of ACh were infused into the LCA for 20 s, with 3-min intervals between consecutive doses. When coronary spasms were not provoked by 100 μg of ACh, 200 μg of ACh and/or 20, 40, and 60 μg of ergometrine maleate (EM) was infused into the LCA. When coronary spasms occurred or provocation tests using the maximum ACh dose were finished, we immediately performed a coronary angiography. After we administered NTG injections of 200 μg, we performed the final coronary angiography for the LCA. Each coronary angiogram was performed using an autoinjection device (ZoneMaster, Sheen Man, Osaka, Japan) with contrast medium of 2.5 mL/s, up to a total volume of 5 mL per injection.

During SPTs, if systolic blood pressure reduced<90 mmHg and/or a continuation of ST segment elevations on ECG occurred, we increased the speed of the intravenous volume injection, up to the maximum speed and/or added another intracoronary NTG injections. Even after such countermeasures, if unstable hemodynamics and ST segment elevations on ECG continued, we infused small doses (2-10 μg) of adrenaline intracoronarily or intravenously [22].

How to measure the coronary artery diameter on coronary angiograms has been previously described [20,21]. First, we selected the spastic segments, atherosclerotic segments and MB segments for quantitative analysis. Two investigators (O.C and U. Y) blinded to the clinical data, measured the luminal diameters of selected segments, using an end-diastolic frame by a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR; Siemens, Berlin, Germany). When the results reported by two investigators were coincident, the results, especially the presence of MB, were adopted in the present study. For the MB segments, the measurements were performed both at end-diastolic and end-systolic frames. Measurements at the selected segment were performed three times, and the average value of three measurements was used for the analysis. The changes in the diameter of coronary artery, in response to each drug, were expressed as percentage changes from the baseline values. Both intraobserver and interobserver variabilities of the measurement shown here are excellent [22,23]. Lesions with more than 20% stenosis and with more than 50% were defined as atherosclerotic lesions and significant coronary stenosis, respectively. The myocardial bridging was defined as more than 20% reduction in the coronary diameter during the systole.

VSA was defined as ≥ 90% narrowing of the epicardial coronary arteries on angiography, in response to ACh and/or EM, during the SPT, presence of characteristic chest pain, and/or ST segment deviation on ECG [24]. We defined a focal spasm as >90% discrete transient vessel narrowing, localized in one coronary segment of major and branch coronary arteries. We defined a diffuse spasm as 90% transient diffuse vasoconstriction observed in more than two adjacent coronary segments of the major coronary arteries and branches [25]. If the patient had a focal spasm occurred in one vessel and a diffuse spasm occurred in another vessel, we defined that this patient belongs to the focal spasm group.

We also defined the presence of multivessel spasms as coronary spasms that occur in more than and equal to two major coronary arteries. The presence of multivessel spasm was not assessed as following cases: 1) cases in which the SPT was not performed for the RCA, because of inability to engage the catheter into the RCA ostium or a small RCA, or 2) cases in which NTG was intracoronarily infused to relieve coronary spasm and the following SPT was negative.

We defined the presence of variant angina (VA) as angina that was documented with spontaneous ST elevation on ECG. On admission before the SPT, we assessed chest symptoms, especially when chest symptoms occurred, via a detailed interview with patients and their family members. We estimated their chest symptoms at rest, rest and exercise, and only exercise. Regarding we determined presence of chest symptoms during exercise, when chest symptoms occurred with reproducibility. According to the chest symptoms at rest and during exercise, we divided the patients into the following 2 groups: Group I (n=85) consisted of VSA patients, whose chest symptoms occurred only at rest. Group II (n=16) consisted with VSA patients, whose chest symptoms occurred during exercise: at rest and during exercise (n=14) and only during exercise (n=2). Furthermore, we confirmed administered medications from their medication notebook, both at admission for CAG and SPT at one-year follow-up after discharge. At follow-up, we also assessed the number of angina attacks, which was the mean occurrence over the preceding 3 months.

Fasting blood samples were obtained on the day of the CAG. We questioned to all patients about their smoking status and classified as a current smoker, past smoker (who had stopped smoking for at least 1 month), or nonsmoker. The presence of hypertension was defined as a systolic blood pressure of ≥ 140 mmHg, a diastolic blood pressure of ≥ 90 mmHg, and/or the patient was on antihypertensive drugs. For the blood chemical parameters, we measured the total cholesterol level, triglycerides, high-density lipoprotein cholesterol, fasting blood sugar, hemoglobin A1C, creatinine, C-reactive protein (CRP) and brain natriuretic peptide (BNP). The estimated glomerular filtration rate (mL/min/1.73 m^2) was calculated using the standard formula [26] and the presence of chronic kidney disease (CKD) was defined using standard criteria [27]. We calculated low-density lipoprotein cholesterol using the Friedewald equation [28]. We defined dyslipidemia as low-density lipoprotein cholesterol of ≥ 120 mg/dL and/or the patient was on medication for the condition. We defined diabetes mellitus as fasting blood sugar levels of ≥ 126 mg/dL and hemoglobin A1C ≥ 6.5%, and/or the patient was on medication. The presence of metabolic syndrome (MtS) was also defined as per standard criteria [29]. We also evaluated family history of coronary

artery disease (CAD), left ventricular ejection fraction (LVEF) and left ventricular wall motion abnormalities on echocardiography.

Statistical Analysis

All data are expressed as median (quartiles). The comparisons for baseline characteristics of the two groups were performed using Wilcoxon signed-rank test or $\chi 2$ analysis, as appropriate. The logistic regression analysis, using factors with a $p<0.2$, was used to clarify factors associated with the presence of chest symptoms during exercise. A p value of <0.05 was considered statistically significant.

Results

There were 85 patients (84%) in Group I and 16 patients (16%) in Group II (Table 1). In Group II, chest symptoms during exercise were observed in the morning in 10 (63%) of 16 patients and symptoms were at various times in the remaining 6 patients The patients' characteristics, including conventional coronary risk factors, family history of CAD, MtS, CKD, and VA did not differ between the two groups. History of PCI was similar in the two groups (7% in the Group I vs. 13% in the Group II), and the use of drug-eluting stents was not different in the two groups (5% in Group I vs. 13% in Group II).

	Group I	Group II	p value
Numbers (%)	85 (84)	16 (16)	
Age (yrs)	69 (61-76)	70 (64-74)	0.7908
Male / Female	42 / 43	08-Aug	0.9656
Body mass index	24.3 (21.9-26.5)	24.4 (22.7-28.0)	0.3547
Coronary risk factor (%)			
Smoking (%)	21 (25)	2 (13)	0.2855
Current / Past	21 / 22	02-Apr	0.5135
Hypertension	55 (65)	11 (69)	0.7552
Dyslipidemia	49 (58)	11 (69)	0.4067
Diabetes mellitus	23 (27)	6 (38)	0.3971
Family history of CAD (%)	15 (18)	4 (25)	0.4899
Metabolic syndrome (%)	26 (31)	6 (38)	0.6068
Chronic kidney disease (%)	26 (31)	8 (50)	0.1317
Variant angina (%)	4 (5)	1 (6)	0.7939
Preivous PCI (%)	6 (7)	2 (13)	0.4691
Use of DES (%)	4 (5)	2 (13)	0.3319

Values are presented as numbers (%) or median (quartiles).
CAD: coronary artery disease; PCI: percutanous coronary intervention; DES: drug-eluting stent.

Table 1: Patient characteristics.

The results of blood chemical and echocardiographic parameters are shown in Table 2. The lipid and diabetic parameters and BNP levels were similar in the two groups, however the CRP level was significantly higher in Group II, compared to Group I (p=0.0465), and eGFR tended to be lower in Group II than in the Group I (p=0.0726). LVEF and the presence of left ventricular wall motion abnormalities did not differ between the two groups.

	Group I	Group II	p value
Blood chemical parameters			
Total cholesterol (mg/dL)	187 (163-209)	184 (155-205)	0.5895
Triglyceride (mg/dL)	126 (91-147)	120 (106-158)	0.622
HDL-cholesterol (mg/dL)	54 (46-67)	52 (44-62)	0.6285
LDL-cholesterol (mg/dL)	103 (85-129)	92 (81-124)	0.3844

Fasting blood sugar (mg/dL)	98 (91-115)	106 (89-115)	0.2531
Hemoglobin A1C (%)	5.9 (5.6-6.5)	6.0 (5.7-6.7)	0.3101
C-reactive protein (mg/dL)	0.05 (0.02-0.11)	0.11 (0.03-0.54)	0.0465
eGFR (ml/min/1.73 m2)	69.6 (63.0-81.3)	63.2 (56.7-75.1)	0.0726
Brain natriuretic peptide (pg/mL)	22 (13-38)	22 (12-94)	0.6653
Echocardiographic parameters			
LVEF (%)	67 (62-72)	67 (64-71)	0.5955
LV wall motion abnormality (%)	7 (8)	1 (6)	0.7783
Values are presented as numbers (%) or median (quartiles). HDL: high-density lipoprotein; LDL: low-density lipoprotein; eGFR: estimated.			

Table 2: Blood chemical parameters and echocardiographic parameters.

Regarding the medications taken at admission for CAG and SPT (Table 3), medications, besides anti-platelet drugs, did not differ between the two groups, however, the frequency anti-platelet drug administration tended to be higher in Group II (50%), compared to Group I (27%, p=0.068).

On CAG (Table 4), the presence of atherosclerosis (58% in the Group I, 75% in the Group II, p=0.2103) and significant coronary stenosis (11% in the Group I, 25% in the Group II, p=0.1194) did not differ between the two groups. Maximum coronary stenosis was similar in the two groups. The presence of MB was significantly higher in Group II (50%), compared to Group I (12%, p=0.0002). On SPT, the types of diffuse/focal spasms did not differ between the two groups (p=0.1423), nor was the presence of multivessel spasms (58% in the Group I, n=73 vs. 75% in the Group II, n=12, p=0.5839). A representative case is shown in Figure 1.

Logistic regression analysis using study variables (p<0.2) demonstrated that the presence of MB (Odds ratio: 11.83, p=0.0006) as well as elevated CRP (Odds ratio: 7.51, p=0.0061) and low eGFR (Odds ratio: 3.91, p=0.0478) were significantly associated with chest symptoms during exercise (Table 5).

	Group I	**Group II**	**p value**
Before admission			
Nitroglycerin (%)	28 (33)	4 (25)	0.2809
Calcium-channel blocker (%)	37 (44)	4 (25)	0.1662
ACI/ARB (%)	25 (29)	8 (50)	0.1164
Beta-blocker (%)	8 (9)	2 (13)	0.7544
Anti-platelet drug (%)	23 (27)	8 (50)	0.068
Statin (%)	30 (35)	9 (56)	0.1191
Anti-diabetic drugs (%)	12 (14)	2 (13)	0.8636
Anti-diabetic drugs (insulin, %)	1 (1)	1 (6)	0.1814
One year follow-up			
Numbers of coronary vasodilators (%)	1 (1-2)	1 (1-2)	0.5955
Calcium-channel blocker (%)	76 (89)	16 (100)	0.1726
Beta-blocker (%)	5 (6)	4 (25)	0.0138
Values are presented as numbers (%) or median (quartiles). ACI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.			

Table 3: Contents of medications taken before admission and at one-year follow-up.

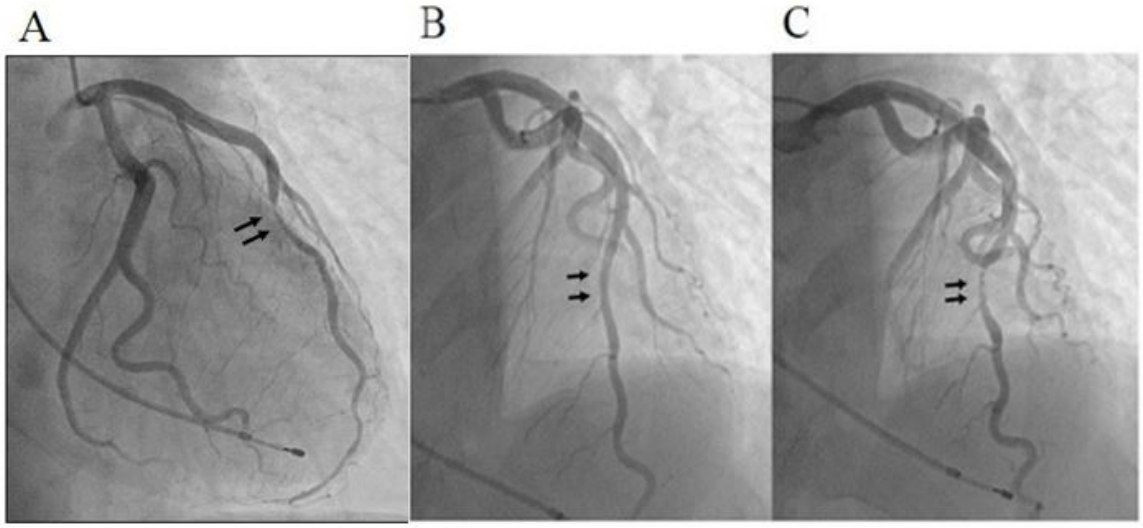

Figure 1: Coronary angiogram pictures in a representative case. The patient had chest symptoms at rest during the night and during exercise early in the morning. Coronary angiography showed a severe vasospasm, provoked by intracoronary infusions of acetylcholine, indicated by the arrows (A) and showed the presence of MB at spastic segment (B: diastole, C: systole), which was indicated by arrows.

	Group I	Group II	p value
Coronary angiography			
Atherosclerosis (%)	49 (58)	12 (75)	0.2103
Significant coronary stenosis (%)	9 (11)	4 (25)	0.1143
Maximum percent stenosis	23 (0-25)	24 (6-25)	0.2635
Myocardial bridging (%)	10 (12)	8 (50)	0.0002
Spasm provocation test			
Focal / diffuse spasm	38 / 47	4 / 12	0.1423
Multivessel spasm (%)	42 (58) (n=73)	9 (75) (n=12)	0.2524
Values are presented as numbers (%) or median (quartiles).			

Table 4: Results of coronary angiography and spasm provocation test.

At follow-up, the numbers of angina attacks were higher in the Group I than Group II (p=0.0135); 0 (0-1) in the Group I and 1 (0-2) in the Group II. The number of coronary vasodilators taken did not differ between the two groups. Group II took more beta blockers, compared to Group I (25% vs. 6 % in the Group I, p=0.0138, Table 3).

Presence of chest symptoms during effort		
Factor	**Odds ratio**	**p value**
Myocardial bridge	11.83	0.0006
Elevated CRP level	7.51	0.0061
Reduced eGFR	3.91	0.0478
Significant coronary stenosis	2.64	0.1043
Focal / diffuse spasm	2.17	0.141
CRP: C-reactive protein; eGFR: Estimated Glumerular Filtration ratio.		

Table 5: Logistic regression analysis for chest symptoms during exercise.

Discussion

In the present study, we focused on the presence of MB, which is characterized by transient narrowing of epicardial coronary artery during systole and is associated with cardiovascular system abnormalities, as a possible contributor to chest symptoms during exercise, in patients with VSA. We showed that MB was significantly higher in VSA patients with chest symptoms during exercise. Furthermore, we demonstrated MB was associated with chest symptoms in VSA patients. These findings may provide information regarding treatment in VSA patients with chest symptoms during exercise.

It is accepted that attacks of coronary spasms typically occur during periods of rest between night and early morning and are usually not induced by daytime exercise [24]. Vasospastic angina is often induced by even slight effort in the early morning, but is not typically induced by even strenuous effort in the afternoon or later in the day. Thus, there are VSA patients have chest symptoms during exercise; however, the frequency of chest symptoms during exercise is unclear. Ishii et al. [30] reported that 7.0-11.3% of VSA patients experienced chest symptoms at rest and during exercise while 61.9-70.3% of VSA patients had chest symptoms that occurred at rest. Takagi et al. [31] reported that chest symptoms at rest (50%), at rest and during effort (41%), and during effort alone (9%), in 1429 VSA patients. In the present study, we

reported chest pain frequencies during rest (84%), during rest and during exercise (14%), and only during exercise (2%). Our data were drawn from patients' and families' personal assessments, and were not based on the results of exercise ECG testing. The frequency of chest symptoms during exercise varies according to personal activities such as walking, or other means of commuting, in the morning, or according to ECG testing during exercise.

There have been reportedly mechanisms responsible for chest symptoms during exercise in VSA patients [1,4,7,8,32]. VSA attacks have circadian variation [1], and early in the morning, the tone on coronary artery is increased and any effort under such conditions may contribute to the occurrence of attacks of exercise-induced coronary spasms. In addition, hyperventilation and changes in autonomic nerves can cause coronary spasms [1,32,33]. Hyperventilation during exercise and/or autonomic nerve changes during recovery after exercise may contribute to chest symptoms during exercise. The concept of coexistent coronary spasms and organic coronary stenosis is likely [12]. Organic coronary stenosis, or the occurrence of mild to moderate coronary spasms with organic coronary stenosis, may contribute to the development of exercise-induced attacks of coronary spasms. Sakata et al. [12] reported that enhanced platelet activation and coagulation were present in VSA patients with exercise-induced ischemia, and they indicated that coagulation abnormalities and atherosclerotic changes were associated with exercise-induced attacks of coronary spasms. In the present study, the frequency of atherosclerosis (% stenosis>20%), organic coronary stenosis (% stenosis>50%) and the % stenosis did not differ between the two groups, suggesting that the underlying angiographic coronary stenosis might not be associated with chest symptoms during exercise. However, we found MB related to chest symptoms in VSA patients.

The presence of MB, characterized by the transient narrowing of the epicardial coronary artery, due to myocardial compression during systole, is associated with cardiovascular system abnormalities [13-19,34,35]. In the present study, MB was more frequently observed in VSA patients with chest symptoms during exercise, and this finding was confirmed using a logistic regression analysis. MB is one cause of exertional angina due to dynamic coronary obstruction and the presence of atherosclerotic lesions beneath MB [13,14,36]. In addition, coronary spasms are likely to occur at MB segments, probably due to vascular endothelial dysfunction [18]. Thus, coexistence of exertional angina due to MB, and coronary spasms at MB segments, may contribute to chest symptoms during exercise in VSA patients with MB, although it is unclear if coronary spasms occur at MB segments during exercise.

Elevated CRP and reduced eGFR contributed to chest symptoms during exercise in VSA patients. It is unclear how these factors relate to symptom occurrence, however it elevated CRP and reduced eGFR may cause endothelial dysfunction [37,38], leading to changes in intracoronary plaque composition, which is difficult to accurately assess on CAG [39,40]. CRP increases atherosclerotic changes at MB segments [41]. Thus, it is possible that these factors contribute to the occurrence of exercise-induced myocardial ischemia in VSA patients.

The present study has the following clinical implications. As Kodama et al. [16] have reported, the clinical management of patients with MB and coronary spasms can be challenging. Use of NTG, which is very effective at relieving coronary spasms, may exacerbate systolic narrowing of MB segments [35]. On the other hand, use of beta blockers, which reduce systolic narrowing in MB segments, may worsen coronary spasms [4,9,42]. In the present study, at 1-year follow-up, the frequency of coronary vasodilator use did not differ between the two groups; however, the frequencies of chest symptoms and beta-blocker use were significantly higher in VSA patients with chest symptoms during exercise. Beta-blocker monotherapy should not be administered in VSA patients to worsen attacks of coronary spasm [24]; however, taking beta blockers, as well as coronary vasodilators such as calcium-channel blockers, may potentially improve chest symptoms during exercise in VSA patients, especially with MB. Waters DD, et al. reported that VSA with exercise-induced coronary spasms produce high-activity coronary spasms [8]. Consequently, VSA patients with exercise-induced chest symptoms require careful monitoring, especially when these drugs are administered.

There are several limitations to the present study. First, this study was retrospectively performed, only at our institution. In addition, the number of studied patients, especially in the Group II, was small. These findings may contribute to the results of logistic regression analysis. Second, in the present study, having chest symptoms during exercise was judged based on self-assessments, not on the results of exercise ECG tests. Several studies report that asymptomatic myocardial ischemia was present in VSA patients [24], even in VSA patients with exercise-induced chest symptoms [11]. In addition, in VSA patients with significant coronary stenosis, who have chest symptoms during exercise, PCI can be performed immediately, without performing the SPT. Thus, it is possible that the present study underestimates the frequency of these symptoms. Third, as we suggested above, we did not confirm the presence of myocardial ischemia to perform exercise ECG test or exercise stress myocardial perfusion imaging. Thus, chest symptoms during exercise did not always coincide with the presence of myocardial ischemia.

Conclusion

MB on CAG contributes to chest symptoms during exercise in VSA patients. When such symptoms continue after administration of coronary vasodilators, careful administration of beta blockers may be helpful. Cardiologists should keep this consideration in mind.

Acknowledgments

We thank all staff members at the cardiac catheterization room and cardiovascular ward at JR Hiroshima Hospital.

References

1. Yasue H, Kugiyama K (1997) Coronary spasm: clinical features and pathogenesis. Intern Med 36: 760-765.
2. Yasue H, Nakagawa H, Itoh T, Harada E, Mizuno Y (2008) Coronary artery spasm-- clinical features, diagnosis, pathogenesis, and treatment. J Cardiol 51: 2-17.
3. Hung MJ (2010) Current advances in the understanding of coronary vasospasm. World J Cardiol 2: 34-42.
4. Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, et al. (1979) Circadian variation of exercise capacity in patients with Prinzmetal's variant angina: role of exercise-induced coronary arterial spasm. Circulation 59: 938-948.
5. de Servi S, Specchia G, Ardissino D, Falcone C, Mussini A, et al. (1980) Angiographic demonstration of different pathogenetic mechanisms in patients with spontaneous and exertional angina associated with S-T segment depression. Am J Cardiol 45: 1285-1291.
6. Matsuda Y, Ozaki M, Ogawa H, Naito H, Yoshino F, et al. (1983) Coronary arteriography and left ventriculography during spontaneous and exercise-induced ST segment elevation in patients with variant angina. American heart journal 106: 509-515.

7. Fuller CM, Raizner AE, Chahine RA, Nahormek P, Ishimori T, et al. (1980) Exercise-induced coronary arterial spasm: angiographic demonstration, documentation of ischemia by myocardial scintigraphy and results of pharmacologic intervention. Am J Cardiol 46: 500-506.
8. Waters DD, Szlachcic J, Bourassa MG, Scholl JM, Theroux P (1982) Exercise testing in patients with variant angina: results, correlation with clinical and angiographic features and prognostic significance. Circulation 65: 265-274.
9. Sato I, Shimomura K, Shiroeda O (1983) Exercise-induced cyclic episodes of S-T segment elevation in a patient with variant angina. Jpn Heart J 24: 739-746.
10. Kugiyama K, Yasue H, Okumura K, Goto K, Minoda K, et al. (1988) Suppression of exercise-induced angina by magnesium sulfate in patients with variant angina. J Am Coll Cardiol 12: 1177-1183.
11. Aoki M, Koyanagi S, Sakai K, Irie T, Takeshita A, et al. (1990) Exercise-induced silent myocardial ischemia in patients with vasospastic angina. American heart journal 119: 551-556.
12. Sakata K, Hoshino T, Yoshida H, Shugino H, Miura F, et al. (1996) Characteristics of vasospastic angina with exercised-induced ischemia--analysis of parameters of hemostasis and fibrinolysis. Jpn Circ J 60: 277-284.
13. Corban MT, Hung OY, Eshtehardi P, Rasoul-Arzrumly E, McDaniel M, et al. (2014) Myocardial bridging: contemporary understanding of pathophysiology with implications for diagnostic and therapeutic strategies. J Am Coll Cardiol 63: 2346-2355.
14. Hayashi T, Ishikawa K (2004) Myocardial bridge: harmless or harmful. Intern Med 43:1097-1098.
15. Ciampricotti R, el Gamal M (1988) Vasospastic coronary occlusion associated with a myocardial bridge. Cathet Cardiovasc Diagn 14: 118-120.
16. Kodama K, Morioka N, Hara Y, Shigematsu Y, Hamada M, et al. (1998) Coronary vasospasm at the site of myocardial bridge--report of two cases. Angiology 49: 659-663.
17. Munakata K, Sato N, Sasaki Y, Yasutake M, Kusama Y, et al. (1992) Two cases of variant form angina pectoris associated with myocardial bridge--a possible relationship among coronary vasospasm, atherosclerosis and myocardial bridge. Jpn Circ J 56: 1248-1252.
18. Teragawa H, Fukuda Y, Matsuda K, Hirao H, Higashi Y, et al. (2003) Myocardial bridging increases the risk of coronary spasm. Clin Cardiol 26: 377-383.
19. Teragawa H, Fujii Y, Ueda T, Murata D, Nomura S (2015) Case of angina pectoris at rest and during effort due to coronary spasm and myocardial bridging. World J Cardiol 7: 367-372.
20. Teragawa H, Fujii Y, Oshita C, Ueda T (2017) Importance of the spasm provocation test in diagnosing and clarifying the activity of vasospastic angina. Interv Cardiol J (in press).
21. Teragawa H, Fujii Y, Uchimura Y, Oshita C, Ueda T, et al. (2017) Usefulness of a pressure wire for the diagnosis of vasospastic angina during a spasm provocation test. J Clin Exp Res Cardiol (in press).
22. Teragawa H, Nishioka K, Higashi Y, Chayama K, Kihara y (2008) Treatment of coronary spastic angina, particularly medically refractory coronary spasm. Clin Med (Cardiology) 2:181-9.
23. Teragawa H, Kato M, Yamagata T, Matsuura H, Kajiyama G (2001) Magnesium causes nitric oxide independent coronary artery vasodilation in humans. Heart 86: 212-216.
24. Group JCSJW (2014) Guidelines for diagnosis and treatment of patients with vasospastic angina (Coronary Spastic Angina) (JCS 2013). Circ J 78: 2779-2801.
25. Sato K, Kaikita K, Nakayama N, Horio E, Yoshimura H, et al. (2013) Coronary vasomotor response to intracoronary acetylcholine injection, clinical features, and long-term prognosis in 873 consecutive patients with coronary spasm: analysis of a single-center study over 20 years. J Am Heart Assoc 2: e000227.
26. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, et al. (2009) Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982-992.
27. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. . Am J Kidney Dis 39: S1-S266.
28. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499-502.
29. Third Report of the National Cholesterol Education Program (NCEP) (2002) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106:3143-421.
30. Ishii M, Kaikita K, Sato K, Tanaka T, Sugamura K, et al. (2015) Acetylcholine-provoked coronary spasm at site of significant organic stenosis predicts poor prognosis in patients with coronary vasospastic angina. J Am Coll Cardiol 66: 1105-1115.
31. Takagi Y, Takahashi J, Yasuda S, Miyata S, Tsunoda R, et al. (2013) Prognostic stratification of patients with vasospastic angina: a comprehensive clinical risk score developed by the Japanese Coronary Spasm Association. J Am Coll Cardiol 62: 1144-1153.
32. Lanza GA, Pedrotti P, Pasceri V, Lucente M, Crea F, et al. (1996) Autonomic changes associated with spontaneous coronary spasm in patients with variant angina. J Am Coll Cardiol 28: 1249-1256.
33. Nakao K, Ohgushi M, Yoshimura M, Morooka K, Okumura K, et al. (1997) Hyperventilation as a specific test for diagnosis of coronary artery spasm. Am J Cardiol 80: 545-549.
34. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, et al. (2004) Acute myocardial infarction associated with myocardial bridging in a young adult. Intern Med 43: 1157-1161.
35. Hongo Y, Tada H, Ito K, Yasumura Y, Miyatake K, et al. (1999) Augmentation of vessel squeezing at coronary-myocardial bridge by nitroglycerin: study by quantitative coronary angiography and intravascular ultrasound. American heart journal 138: 345-350.
36. Berry JF, von Mering GO, Schmalfuss C, Hill JA, Kerensky RA (2002) Systolic compression of the left anterior descending coronary artery: a case series, review of the literature, and therapeutic options including stenting. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 56: 58-63.
37. Teragawa H, Fukuda Y, Matsuda K, Ueda K, Higashi Y, et al. (2004) Relation between C reactive protein concentrations and coronary microvascular endothelial function. Heart 90: 750-754.
38. Nakamura T, Obata JE, Hirano M, Kitta Y, Sano K, et al. (2011) Endothelial vasomotor dysfunction in the brachial artery predicts the short-term development of early stage renal dysfunction in patients with coronary artery disease. International journal of cardiology 148: 183-188.
39. Kelly CR, Weisz G, Maehara A, Mintz GS, Mehran R, et al. (2014) Relation of C-reactive protein levels to instability of untreated vulnerable coronary plaques (from the PROSPECT Study). Am J Cardiol 114: 376-383.
40. Miyagi M, Ishii H, Murakami R, Isobe S, Hayashi M, et al. (2010) Impact of renal function on coronary plaque composition. Nephrol Dial Transplant 25: 175-81.
41. Duygu H, Zoghi M, Nalbantgil S, Ozerkan F, Cakir C, et al. (2008) High-sensitivity C-reactive protein may be an indicator of the development of atherosclerosis in myocardial bridging. International journal of cardiology 124: 267-270.
42. Yasue H, Omote S, Takizawa A, Nagao M (1983) Coronary arterial spasm in ischemic heart disease and its pathogenesis. A review. Circ Res 52:I147-52.