Myocardial Bridging Increases the Risk of Coronary Spasm

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Summary

Background: Myocardial bridging (MB) has been associated with cardiac events. Whether coronary spasm is one factor contributing to those events is unknown.

Hypothesis: This study investigated whether the likelihood of coronary spasm is increased in patients with MB.

Methods: A spasm-provocation test was performed by infusing acetylcholine into the left coronary artery in 114 Japanese patients with chest pain. The test result was defined as positive when the diameter of the coronary artery was reduced by $\geq 50\%$ and ST-segment changes were documented. Myocardial bridging was defined as a $> 15\%$ reduction in coronary arterial diameter during systole after intracoronary injection of nitroglycerin.

Results: Myocardial bridging was identified in 41 patients (36%) and was located in the mid-segment of the left anterior descending coronary artery (LAD) in all patients. Patients with MB experienced coronary spasm more frequently than patients without MB (MB+: 73%; MB–: 40%, $p = 0.0006$). Furthermore, among patients with a positive spasm-provocation test, coronary spasm occurred more frequently in the mid-segment of the LAD in patients with MB than in those without MB (MB+: 73%; MB–: 45%, $p = 0.0259$). Multivariate regression analysis demonstrated that MB was a predictor of coronary spasm (odds ratio: 3.478, $p = 0.0088$).

Conclusions: These results suggest that MB increases the risk of coronary spasm and that coronary spasm may be the proximate etiology of cardiac events associated with MB.

Key words: vasospastic angina, coronary artery, cardiac sudden death

Introduction

Myocardial bridging (MB) is an anomaly in which myocardium overlies the intramural course of segments of the epicardial coronary arteries. Its typical angiographic presentation is the systolic “milking” effect due to transient vascular compression.^{1–3} The frequency of MB has been reported to range from 5.4 to 85% in autopsy series^{4–6} and from 0.5 to 29.4% on coronary angiography.^{1,6–11} Although it remains to be determined how MB affects the cardiovascular system, MB has been associated with myocardial infarction^{12–17} and sudden cardiac death,^{18–21} and coronary spasm is thought to be one factor connecting cardiac events and MB.^{13, 22, 23} However, it has yet to be verified that coronary spasm is more frequent in patients with MB. This study attempted to determine whether MB increases vulnerability to coronary spasm in patients who underwent a spasm-provocation test.

Methods

Study Population

We studied 114 Japanese patients (65 men and 49 women, mean age 60 years) who underwent coronary angiography and a spasm-provocation test for the first time to evaluate chest pain. Sixty-five patients (57%) had chest pain at rest, 23 patients (20%) had exertional chest pain, and the remaining 26 patients (23%) had chest pain both at rest and during exercise. Treadmill exercise electrocardiograms (ECG) were performed in 101 patients (89%), and 46 (46%) had positive results. Stress myocardial perfusion imaging was performed in 29 patients (26%), and 16 (56%) were judged abnormal. Patients with organic coronary stenosis ($> 50\%$), prior myocar-

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dial infarction, cardiomyopathy including hypertrophic cardiomyopathy, or any other serious medical condition were excluded from the study. Written informed consent was obtained from all patients prior to the study. The protocol was approved by the Ethics Committee of our institution.

Study Protocol

All antianginal agents were withheld for at least 48 h prior to catheterization, except for the unrestricted use of sublingual nitroglycerin, which was withheld for 1 h prior to catheterization. Diagnostic left heart catheterization and coronary angiography were performed using the standard percutaneous brachial approach. A 5F temporary pacing electrode catheter (Bard, Tewksbury, Mass., USA) was placed in the right ventricular apex via the right internal jugular vein and connected to a temporary pacemaker set at a rate of 50 beats/min.

After baseline conditions had been established, incremental doses of acetylcholine (ACh) were infused into the left coronary artery (3, 30, and 100 $\mu\text{g}/\text{min}$) for 2 min, with 5-min intervals between consecutive doses until the induction of coronary spasm. Once coronary spasm was induced, the next infusion of ACh was withheld. If coronary spasm was not induced by ACh, then incremental doses of methylergometrine maleate were infused into the left coronary artery (10, 20, and 30 $\mu\text{g}/\text{min}$) for 1 min with 1-min intervals between consecutive doses. If coronary spasm was not induced by this infusion, incremental doses of methylergometrine maleate were infused into the right coronary artery (RCA, 15 and 25 $\mu\text{g}/\text{min}$) using the same protocol as for the left coronary artery. When coronary spasm was induced, nitroglycerin (200 μg) was given by intracoronary injection. The intracoronary infusions of ACh and methylergometrine maleate were administered using an infusion pump (TE-311, Terumo, Tokyo, Japan) set at a rate of 1 ml/min. We have adopted this protocol because (1) we can observe coronary endothelial function and induce coronary vasospasm with an intracoronary infusion of ACh, and (2) the ability to induce coronary spasm seems to be greater with intracoronary infusion of methylergometrine maleate than with ACh.²⁴ Therefore, we initially infused ACh and methylergometrine maleate only when the ACh-provocation test was negative.

Coronary angiography was performed immediately after the occurrence of chest symptoms and/or ST-segment changes, or after each dose of ACh administration and after only the last dose of methylergometrine maleate when neither chest symptoms nor ST-segment changes were induced, and 2 min after nitroglycerin injection. Arterial pressure, heart rate, and ECG were monitored continuously and recorded on a multichannel recorder (Polygraph 1600, Nihon Electric Corporation, Tokyo, Japan).

Quantitative Coronary Angiography

The arterial diameters were measured by angiographers blinded to the patients' clinical characteristics. Coronary diameter was measured on an end-diastolic frame, and both

end-diastolic and end-systolic frames were selected for analysis of MB. All images were analyzed using a computer-assisted coronary angiographic analysis system (CAAS II/QUANTCOR, Siemens AG, Berlin and Munich, Germany). The average of three measurements of luminal diameter was used for analysis. Changes in the coronary diameter in response to drug infusion were expressed as the percent change from the baseline on the angiogram taken prior to infusion. In patients with negative provocation tests, we measured ACh-induced changes in the diameter of the proximal, mid, and distal segments of the coronary artery over which MB was located in patients with MB and compared them with those of the same segments in patients without MB. The intraobserver reproducibility was excellent ($r = 0.997$), and interobserver reproducibility was similarly high ($r = 0.985$).

Definitions

Myocardial bridging was defined as a $> 15\%$ reduction in the diameter of the coronary artery in systole after intracoronary injection of nitroglycerin. It was at times observed during the initial coronary angiogram before spasm-provocation tests or during the coronary angiogram prior to injection of nitroglycerin. However, we frequently observed that injection of nitroglycerin exacerbated systolic narrowing of MB segments, which is consistent with other reports,^{25,26} and the injection of nitroglycerin facilitates the identification of MB. Therefore, the final diagnosis of MB was made after injection of nitroglycerin.

One problem with research into MB has been the lack of uniformity in the definition of MB. Several studies have defined MB as coronary artery narrowing of $> 50\%$.^{27–29} However, we have adopted this less restrictive definition for the following reasons: (1) We usually used the right anterior oblique caudal view to monitor changes in coronary diameter in response to drug infusion. Because MB is frequently present over the mid segment of the left anterior descending coronary arteries (LAD), apparent systolic narrowing of the MB segment may be less in the right anterior oblique caudal view than in the cranial views. However, the right anterior oblique caudal view affords a better view of both the entire LAD and the left circumflex artery (LCx). (2) In our preliminary study, systolic narrowing of the mid segment of the LAD was $-0.3 \pm 5.6\%$ (range, -10 to 8.9%) in 30 subjects without MB in the right anterior oblique caudal view. The straight cranial view was used only to measure the length of the MB segments.

A positive spasm-provocation test was defined as a $\geq 50\%$ reduction in arterial diameter, associated with ST-segment changes and/or typical chest pain after intracoronary drug injection.³⁰ The length of the spastic segment was also defined as the length with a $\geq 50\%$ reduction in diameter. The diameter of the totally occluded spastic segments was defined as 0 mm.

The trunks of the LAD, LCx, and right coronary artery (RCA) were divided into proximal, mid, and distal segments of equal lengths. The locations of the MB and spastic segment were expressed in terms of these three segments. When coronary spasm occurred diffusely from the proximal to the distal

segment of a coronary artery, the location was defined as proximal, mid, and distal.

Echocardiography

M-mode echocardiography of the left ventricle was performed by one experienced physician who was blinded to the other data of the patients. Left ventricular dimensions (inter-ventricular septal thickness, posterior wall thickness, and left ventricular end-diastolic diameter) were measured at the end of diastole using the leading-edge-to-leading-edge convention. Duplicate measurements were obtained, and their average value was used to calculate the left ventricular mass according to the formula of Devereux and Reichek,³¹ and the left ventricular mass was expressed as the left ventricular mass index (LVMI) to minimize the effect of variations in body size. Left ventricular hypertrophy (LVH) was defined as LVMI $> 110 \text{ g/m}^2$ for women and $> 134 \text{ g/m}^2$ for men.³²

Statistical Analysis

All data are expressed as the mean $\pm$ standard deviation. Baseline characteristics between the two groups were compared by Student's unpaired *t*-test and chi-square analysis, as appropriate. Serial changes in hemodynamic variables and changes in coronary diameter in response to drug infusion were compared using one-way analysis of variance. Serial percent changes in the coronary diameter with Ach infusion between subgroups with and without MB in patients with negative spasm-provocation tests were compared using two-way analysis of variance. We performed multivariate logistic regression analysis to identify factors predicting a presence of MB and positive spasm-provocation tests. A *p* value of < 0.05 was considered statistically significant.

Results

Frequency and Angiographic Findings of Myocardial Bridging

Myocardial bridging was observed in 41 patients (36%) and was located at the mid segment of the LAD in all cases (Table I). The age, incidence of coronary risk factors, and left ventricular ejection fraction were similar in patients with and without MB. The percentage of men was greater and the body mass index was smaller in patients with than in those without MB. The LVMI was $116 \pm 28 \text{ g/m}^2$ for women and $118 \pm 30 \text{ g/m}^2$ for men in patients with MB, and $116 \pm 31 \text{ g/m}^2$ for women and $131 \pm 41 \text{ g/m}^2$ for men in patients without MB. Left ventricular hypertrophy tended to be less common in patients with than in those without MB ($p = 0.0707$). Based on multivariate logistic regression analysis using male gender, body mass index, and the presence of LVH, male gender ($p = 0.0034$, odds ratio 3.863) and body mass index ($p = 0.0401$, odds ratio 0.856) were associated with MB.

The lumen diameter of MB segments was $2.15 \pm 0.39 \text{ mm}$ in diastole and $1.48 \pm 0.44 \text{ mm}$ in systole, and the percent systolic narrowing of MB segments was $32 \pm 13\%$ (range 15–71%). The length of the MB segment was $16.3 \pm 5.7 \text{ mm}$ (range 8.2–34.7 mm). No atherosclerotic changes were observed at MB segments.

Coronary Spasm

There were 59 patients (52%) with a positive spasm-provocation test. Coronary spasm was induced by Ach at a dose of $30 \mu\text{g/min}$ in 15 patients (25%) and at a dose of $100 \mu\text{g/min}$ in 32 patients (54%), and by methylergometrine maleate in 12

TABLE I Characteristics of the study patients

	MB (+) (n = 41)	MB (–) (n = 73)	p Value
Age (years)	59 ± 8	61 ± 11	NS
Men/women	32 / 9	33 / 40	0.0007
Body mass index (kg/m^2)	23.6 ± 2.1	25.1 ± 3.6	0.0169
Coronary risk factors			
Cigarette smoker (%)	14 (34)	20 (27)	NS
Systemic hypertension ^a (%)	20 (49)	38 (52)	NS
Hypercholesterolemia ^b (%)	10 (24)	24 (33)	NS
Diabetes mellitus (%)	6 (15)	12 (16)	NS
Presence of any risk factors (%)	32 (78)	61 (84)	NS
Left ventricular hypertrophy (%)	12 (29)	34 (47)	NS
Left ventricular ejection fraction (%)	70 ± 7	71 ± 8	NS
Positive spasm-provocation test (%)	30 (73)	29 (40)	0.0006

^a On therapy and/or blood pressure $\geq 140/90 \text{ mmHg}$.

^b On therapy and/or total cholesterol $\geq 240 \text{ mg/dl}$.

Data are expressed as the mean $\pm$ standard deviation.

Abbreviations: MB = myocardial bridging, NS = not significant.

patients (20%). Coronary spasm was induced in the LAD in 44 patients (75%), in the LCx in 8 patients (14%), in both the LAD and LCx in 4 patients (7%), and in the RCA in 3 patients (5%). The spastic segments were located in the proximal LAD in 11 patients (19%), the mid LAD in 35 patients (59%), the distal LAD in 21 patients (36%), the proximal LCx in 7 patients (12%), the mid LCx in 10 patients (17%), the distal LCx in 6 patients (10%), the mid RCA in 1 patient (2%), and the distal RCA in 3 patients (5%).

The mean diameter of the spastic segments ($n = 95$) was 1.69 ± 0.60 mm at baseline and 0.54 ± 0.36 mm during coronary spasm (percent change: $-73.1 \pm 15.1\%$). After nitroglycerin infusion, the mean diameter of the spastic segments increased to 2.22 ± 0.60 mm (percent change: $33.2 \pm 22.7\%$).

Myocardial Bridging and Coronary Spasm

Coronary spasm was induced in 30 of 41 patients (73%) with MB and in 29 of 73 patients (40%) without MB ($p = 0.0006$) (Table I). The spastic segments were more frequently located in the mid LAD segment in patients with than in those without MB ($p = 0.0259$). The mid LAD was one of the spastic segments in all patients with MB (Table II).

Factors Associated with Coronary Spasm

Based on univariate analysis, the factors associated with a positive spasm-provocation test were the presence of MB ($p = 0.0005$), the absence of diabetes mellitus ($p = 0.0265$), and the body mass index ($p = 0.0360$). In addition, factors associated with a positive spasm-provocation test of $p < 0.2$ were male gender ($p = 0.1005$) and hypertension ($p = 0.1378$). Multivariate logistic regression analysis using these factors demonstrated that the presence of MB was associated with a positive

spasm-provocation test, as was the absence of diabetes mellitus ($R^2 = 0.146$) (Table III).

Acetylcholine-Induced Changes in Coronary Diameter of Myocardial Bridging Segments in Patients with Negative Spasm-Provocation Test

There were 11 patients with and 44 patients without MB who had negative spasm-provocation tests. Because all MB segments were located in the mid segment of the LAD, we compared the changes in the diameter of the proximal, mid, and distal segments of the LAD in response to Ach between the two groups. Heart rate and mean arterial pressure were unchanged in response to Ach infusion. Changes in the baseline diameter of the proximal (with MB: 3.26 ± 0.79 mm and without MB: 3.38 ± 0.65 mm), mid (with MB: 1.87 ± 0.32 mm and without MB: 2.04 ± 0.41 mm), and distal segments (with MB: 1.75 ± 0.42 mm and without MB: 1.62 ± 0.28 mm) were similar in the two groups. Acetylcholine-induced changes in the diameter of the mid segments tended to be more constricted in patients with than in those without MB ($p = 0.0676$), whereas Ach-induced changes at the proximal and distal segments were similar in the two groups. Because the clinical characteristics including gender, body mass index, and the incidence of LVH were not similar in the two groups, we selected 11 patients without MB, matched for those three variables. Baseline diameter of the proximal (without MB: 3.41 ± 0.63 mm), mid (without MB: 2.07 ± 0.54 mm), and distal segments (without MB: 1.54 ± 0.27 mm) in the two groups were similar. Acetylcholine-induced constriction of the mid segments was greater in patients with than in those without MB ($p = 0.0064$), whereas Ach-induced changes in the proximal and distal segments were similar (Fig. 1). Nitroglycerin-induced dilation in all three segments were similar in the two groups.

Discussion

The present study demonstrates that coronary spasm is more common in patients with than in those without MB, especially in the MB segments during spasm-provocation tests.

TABLE II Locations of coronary spasm in patients with a positive provocation test

Location	Frequency of coronary spasm (%)		p Value
	MB (+) (n = 30)	MB (–) (n = 29)	
LAD pro (%)	6 (20)	5 (17)	NS
LAD mid (%)	22 (73)	13 (45)	0.0259
LAD dis (%)	10 (33)	11 (38)	NS
LCx pro (%)	2 (7)	5 (17)	NS
LCx mid (%)	5 (17)	5 (17)	NS
LCx dis (%)	4 (13)	2 (7)	NS
RCA pro (%)	0 (0)	0 (0)	—
RCA mid (%)	0 (0)	1 (3)	NS
RCA dis (%)	0 (0)	3 (10)	NS

Abbreviations: LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery, pro = proximal segment, mid = mid segment, dis = distal segment, NS = not significant.

TABLE III Multivariate logistic regression analysis of variables associated with a positive spasm-provocation test

Variables	Odds ratio	95% CI	p Value
Presence of myocardial bridging	3.478	1.368–8.843	0.0088
Absence of diabetes mellitus	4.089	1.177–14.204	0.0267
Presence of hypertension	2.221	0.965–5.107	0.0605
Body mass index	0.912	0.797–1.044	0.1819
Male gender	1.627	0.674–3.924	0.2788

Abbreviation: CI = confidence interval.

FIG. 1 Percent change in coronary artery diameter in the proximal (A), mid (B), and distal (C) segments in response to intracoronary acetylcholine infusion in patients with (●) and without MB (○). Vertical bars represent standard deviation. Ach = acetylcholine, MB = myocardial bridging, NS = not significant.

Furthermore, multivariate logistic regression analysis showed that MB is a predictor of coronary spasm. These results suggest that coronary spasm is likely to occur clinically in patients with MB and may be a causal factor in cardiac events associated with MB.

Frequency of and Characteristics of Patients with Myocardial Bridging

The frequency of MB in the present study was 36%, which is higher than that reported in other studies in which the incidence ranged from 0.5 to 29.4%.^{1,6-11} As Angelini *et al.*⁶ reported, the frequency of MB differs according to the subgroup studied. Our patients were unique in that all had experienced chest symptoms but had no clinically significant coronary stenosis. In addition, we used a broader definition of MB, > 15% systolic narrowing, so that patients with a mild degree of MB may have been included in the study.

Myocardial bridging was more common in men and in patients with a low body mass index. The relationship between MB and these factors has received little attention; however, Angelini *et al.*⁶ also found that MB is more common in men. This finding is one indication that MB is congenital. However, acquired factors such as physical development may contribute to the development of MB, and one report has already shown that MB can be acquired.³³

Several papers have shown a relationship between MB and LVH.^{6,28,29,34} Mohiddin *et al.*²⁹ have shown that MB is associated with more severe septal hypertrophy in patients with hypertrophic cardiomyopathy. However, Angelini *et al.*⁶ have reported that the incidence of MB is increased in patients with hypertrophic cardiomyopathy but not in those with systemic hypertension. We found no increased frequency of MB in patients with LVH. Patients with hypertrophic cardiomyopathy were excluded from the present study, which may account in part for our different results.

Cardiac Events Associated with Myocardial Bridging

Some case reports have indicated that a relationship exists between MB and major cardiac events, such as myocardial infarction¹²⁻¹⁷ and cardiac sudden death.¹⁸⁻²¹ Several factors may account for MB-related myocardial ischemia. First, MB may cause coronary obstruction during systole. Intracoronary Doppler flow measurements have shown that the diastolic flow velocities are increased in MB segments,^{3,27,35} and the peak systolic intracoronary pressure has been reported to be elevated within MB segments.^{3,27,36} Intravascular ultrasonography has shown that the cross-sectional area in MB segments is reduced during systole and that this reduction continues into early diastole.^{3,25,27} In addition, other studies have shown reversible perfusion abnormalities during stress myocardial single-photon emission computed tomography in patients with MB.^{37,38} Together, these findings suggest that mechanical compression of the coronary artery directly causes myocardial ischemia in MB segments. Second, thrombus formation in MB segments has been reported in patients with MB-related cardiac events;^{16,19} however, it is unclear whether thrombus formation in MB segments was primary or secondary. It is possible that turbulent shear stress predisposed the vessel toward thrombus formation.³⁹ Therefore, a turbulent shear stress, which is caused by the milking of MB segments, may increase the risk of thrombus formation in MB segments. Finally, it has been reported that coronary spasm is associated with MB-related cardiac events.^{13,22,23} These publications were all case reports, and the effect of MB on coronary spasm has not been investigated in a series of patients. Although we showed that coronary spasm is induced more frequently in patients with MB, especially in the MB segments, we did not measure the intracoronary hemodynamics or perform stress myocardial imaging in all patients and therefore were unable to show a direct relationship between MB and myocardial ischemia. However, our results strongly suggest that coronary spasm is implicated in MB-related cardiac events.

As Kodama *et al.*²³ have reported, the clinical management of patients with MB and coronary spasm can be challenging. Use of nitroglycerin, which is very effective for relieving coronary spasm, may sometimes exacerbate systolic narrowing of MB segments.²⁵ On the other hand, use of beta blockers, which reduces systolic narrowing in MB segments,³ may worsen coronary spasm.⁴⁰ Therefore, patients with coronary spasm and MB should be monitored carefully when these drugs are administered.

Possible Mechanisms Accounting for the Increased Frequency of Coronary Spasm in Myocardial Bridging Segments

First, atherosclerotic lesions may be more common in MB segments, which would explain why coronary spasm is more likely to occur in MB segments. Miyao *et al.*⁴¹ have shown that coronary spasm tends to occur in areas with atherosclerotic lesions. However, no atherosclerotic changes were observed angiographically in the MB segments in the present study. In addition, using intravascular ultrasound techniques, Hongo *et al.*²⁵ and Ge *et al.*³⁶ have shown that atherosclerotic lesions are absent in MB segments. In a histopathologic study, Ishii *et al.*⁴² demonstrated that atherosclerosis is suppressed in the regions of MB. Therefore, sufficient evidence exists to exclude atherosclerotic lesions as the primary etiology of spasm in MB segments.

Second, vascular dysfunction at level of the endothelium and/or smooth muscle may occur in MB segments. Endothelial dysfunction⁴³ and/or dysfunction of smooth muscle cells⁴⁴ reportedly have been involved in the genesis of coronary spasm. We found that Ach-induced coronary constriction is more severe in MB segments. This finding suggests that some form of vascular dysfunction exists in MB segments. On the other hand, in an ultrastructural study, Ishii *et al.*⁴⁵ have demonstrated that endothelial cells and smooth muscle cells are preserved beneath MB, but not in the segments proximal and distal to MB. We did not find that the segments with the greatest degree of Ach-induced constriction were the same as the sites that had the greatest compression during systole within MB segments. Furthermore, the lengths of anatomic MB segments may not always coincide with angiographically determined MB segments. However, using an infusion of N^G-monomethyl-L-arginine, our previous study showed that the vascular response of MB segments to Ach is supranormal while the responses to N^G-monomethyl-L-arginine and nitroglycerin are unremarkable in the proximal and distal segments.⁴⁶ Furthermore, an immunohistochemical study has shown that the expression of endothelial nitric oxide synthase is suppressed beneath MB.⁴⁷ These findings support our hypothesis that vascular dysfunction occurs in MB segments.

It has been reported that turbulent flow may increase endothelial cell apoptosis or tumor necrosis factor- α -induced endothelial cell activation, whereas a steady laminar flow inhibits them.⁴⁸ These factors may cause vascular dysfunction, and therefore turbulent shear stress secondary to milking in MB segments may contribute to MB-induced vascular dysfunction.

Study Limitations

There were some limitations to our study. First, our spasm-provocation testing protocol was fairly aggressive; however, we have instituted several countermeasures to avoid serious adverse consequences of coronary spasm. First, we inserted a temporary pacing catheter into the right ventricular apex and connected it to a temporary pacemaker, because bradycardia sometimes occurs during Ach infusion or coronary spasm and prolonged bradycardia sometimes results in ventricular fibrillation. Second, at least two cardiologists reviewed each ECG to identify any ST-segment changes during spasm-provocation testing. Upon the detection of any ST-segment changes, the drug infusion was stopped, and coronary angiogram was performed immediately to look for areas of coronary spasm. In actuality, however, no patient suffered any serious adverse consequences related to coronary spasm during the implementation of this protocol. This protocol may increase the percentage of patients who developed coronary vasospasm without anginal symptoms or ECG changes. To exclude false-positives, we require that ST-T changes be present for a test to be considered positive. Second, MB is occasionally detected in patients who undergo electrophysiologic studies for the evaluation of arrhythmias, or in patients who undergo coronary angioplasty for organic coronary stenosis. It is unclear whether coronary spasm is more likely to occur in MB segments because we did not perform a provocation test in such patients. Third, the present study showed that coronary spasm occurs less frequently in the proximal LAD than in other segments in patients with and without MB. Because we did not perform intravascular ultrasonography, we are unable to say whether or not atherosclerotic plaques were present in the proximal LAD, or whether atherosclerotic plaques increase the likelihood of coronary spasm. However, the patients we studied had a history of chest pain without organic coronary sclerosis. The unusual characteristics of this study cohort may have contributed to the conclusion that coronary spasm occurs less frequently in the proximal LAD. Finally, we observed Ach-induced changes in the diameter of MB segments in patients whose provocation test was negative. Our results showed that Ach-induced changes in the coronary diameter of MB segments were constrictive but not spastic. Therefore, these findings do not directly support our hypothesis that vascular dysfunction leads to spasm of MB segments. However, this is not to say that MB segments, in which spasm was not induced in the present study, may not become spastic at a later date.

Conclusions

We demonstrated that MB increases the risk of coronary spasm, especially in the MB segments themselves. Vascular dysfunction may contribute to coronary spasm in MB segments, and coronary spasm may be proximate etiology of cardiac events associated with MB. Because a spasm-provocation test is not routinely performed in patients with chest pain, patients who have documented MB on routine coronary angiography should be closely monitored, since that coronary spasm may be the cause of their chest pain.

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