International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Relation between severity of myocardial bridge and vasospasm☆

Yuichi Saito *, Hideki Kitahara, Toshihiro Shoji, Satoshi Tokimasa, Takashi Nakayama, Kazumasa Sugimoto, Yoshihide Fujimoto, Yoshio Kobayashi

Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, Chiba, Japan

ARTICLE INFO

Article history:
Received 12 May 2017
Received in revised form 29 June 2017
Accepted 3 July 2017
Available online xxxx

Keywords:
Myocardial bridge
Vasospastic angina
Coronary artery disease

ABSTRACT

Background: Myocardial bridge (MB) has been reported to induce cardiac complications including coronary vasospasm. Although MB has some anatomical and morphological variations, the association of these variations with vasospasm is unclear. The aim of this study was to investigate the relation between morphological severity of MB and vasospasm induced by acetylcholine (ACh) provocation test.
Methods: A total of 392 patients without coronary stent in the left anterior descending artery (LAD) undergoing intracoronary ACh provocation test were included. Angiographic coronary artery vasospasm was defined as total or subtotal occlusion induced by ACh provocation. MB was identified on coronary angiography as a milking effect. Total bridged length and maximum percent systolic compression of MB in the LAD were analyzed quantitatively.
Results: MBs in the LAD were identified in 140 patients (36%), mostly in the mid segment. Patients with MB in the LAD had greater number of provoked vasospasm in the LAD and positive ACh provocation test compared to those without. The bridged length positively correlated with percent systolic compression of MB ($r = 0.37$, $p < 0.001$). In the receiver operating characteristic curve analysis, both bridged length and percent systolic compression of MB significantly predicted the provoked LAD spasm (AUC 0.74, $p < 0.001$, and AUC 0.68, $p < 0.001$). Multivariate regression analysis demonstrated these factors as independent predictors for provoked LAD spasm.
Conclusion: MB, especially morphologically severe MB, may induce greater coronary vasospasm.

1. Introduction

Myocardial bridge (MB), partially overlying the coronary artery, is a congenital anatomical variant, and it mostly involves the left anterior descending coronary artery (LAD) [1–3]. Although MB has been traditionally considered a benign anatomy [4], the association of MB with cardiac complications has been reported in many cases, such as coronary atherosclerosis [5], myocardial ischemia [6,7], acute coronary syndrome [8], and sudden cardiac death [9]. On the other hand, vasospastic angina is also an important cardiac disorder that causes adverse events [10,11], and intracoronary acetylcholine (ACh) provocation test is useful to diagnose vasospastic angina [12,13]. MB is known to increase the risk of coronary vasospasm by endothelial dysfunction [14–16]. Furthermore, patients with MB were reported as being predisposed to severe and diffuse long coronary artery spasm [17]. However, MB has some anatomical and morphological variations, including location, length, depth, and degree of compression [2,18], and the association between these variations of MB and vasospasm are not fully understood. Thus, the aim of this study was to investigate the relation between morphological severity of MB and coronary artery vasospasm induced by ACh provocation test.

2. Methods

2.1. Study population

From April 2012 to July 2016, a total of 446 patients underwent intracoronary ACh provocation test at Chiba University Hospital. Patients with ACh provocation only for the right coronary artery (RCA) ($n = 3$), and coronary stent in the LAD ($n = 51$), were excluded. Thus, 392 patients were included in the present study. Written informed consent for examination was obtained from all patients, and the ethical committee of Chiba University approved this study.

2.2. Intracoronary acetylcholine provocation test

Intracoronary ACh provocation tests were performed according to the guidelines for diagnosis and treatment of patients with vasospastic angina by the Japanese Circulation Society Joint Working Group in the clinical settings [13], as previously reported [19–21]. Briefly, all vasodilators, such as calcium channel blockers and long-acting nitrates, were discontinued at least 48 h before the examination in elective cases, except for sublingual nitroglycerin as needed. After insertion of a temporary pacing electrode in the right ventricle, control angiography of the left coronary artery (LCA) and RCA was performed. ACh was injected in incremental doses of 20 and 50 μg into the RCA, and 20, 50 and 100 μg into the LCA, over a period of 20 s. There were some exceptions with other injection doses of ACh, such as 10 ($n = 2$) and 80 μg ($n = 5$) into the RCA, and 150 ($n = 1$) and 200 μg ($n = 3$) into the LCA. Coronary angiography was performed 1 min after the start of each injection. Doses of ACh were given at 5 min intervals. After ACh provocation test, 1–2 mg of isosorbide dinitrate was administered into the RCA and the LCA, and coronary angiography was then performed.

☆ Statement of authorship: The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Cardiovascular Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba, Chiba 260-8677, Japan.
E-mail address: policemaccho@yahoo.co.jp (Y. Saito).

http://dx.doi.org/10.1016/j.ijcard.2017.07.002
0167-5273/

Angiographic coronary artery vasospasm was defined as total or subtotal occlusion induced by ACh provocation test. It was evaluated by 2 experienced cardiologists, who were unaware of the patients' clinical characteristics. The positive diagnosis of intracoronary ACh provocation test was defined as angiographic coronary artery vasospasm accompanied by chest pain and/or ischemic electrocardiographic changes, such as transient ST elevation ≥ 0.1 mV, ST depression ≥ 0.1 mV, or new appearance of negative U waves, recorded in at least 2 contiguous leads on the 12-lead electrocardiogram [13]. Multivessel spasm was defined as ACh-induced coronary artery vasospasm of ≥2 major epicardial arteries. Based on the American Heart Association classification [22], vasospasm in the proximal area was defined as vasoconstriction occurring in segment 6, and that in the mid area was in segment 7 without proximal vasospasm, whereas vasospasm in the distal area was defined as that only occurring in segments 8, 9, or 10 in the LAD [23]. Types of vasospasm were divided into focal and diffuse spasm in the LAD. The focal type was defined as the LAD narrowing within the borders of 1 isolated or 2 neighboring coronary segments, and diffuse type as the LAD narrowing observed in ≥2 adjacent coronary segments [23].

2.3. Myocardial bridge

Angiographic MB was identified by 2 independent cardiologists as the systolic narrowing of coronary vessels that was more pronounced than in neighboring normal vessels, with partial or complete decompression during diastole (i.e. milking effect) [24,25]. Angiograms acquired after administration of intracoronary isosorbide dinitrate were analyzed based on previous reports that systolic LAD compression by MB could be accentuated by intracoronary nitrates [18]. Quantitative coronary angiography analysis in the LAD was conducted for evaluating the severity of MB with QAngio XA (Version 7.1, Medis Medical Imaging System BV, Leiden, The Netherlands) by an automated program [26]. Each LAD was examined for total bridged length, minimum lumen area, reference vessel diameter, and maximum percent systolic compression of the bridged segment in end-systole [24,27]. Location of MB was classified as proximal, mid, and distal, as with that of coronary vasospasm as previously described. Positional relation of vasospasm to MB was defined as follows: segment proximal to MB, in the segment ≥5 mm proximal to MB; MB segment, within MB or 5 mm proximal and distal margins; and segment distal to MB, in the segment ≥5 mm distal to MB. Cardiac event was defined as a composite of cardiac death, myocardial infarction, ventricular fibrillation (VF) or sustained ventricular tachycardia (SVT), and readmission due to chest pain, reviewed by medical record.

2.4. Statistical analysis

Statistical analysis was performed with SAS statistical software package version 9.4 (SAS Institute, Cary, NC). Data are expressed as mean ± SD or frequency (%). Continuous variables were compared using Student's *t*-test, and categorical variables were compared with Fisher's exact test. The receiver operating characteristic curve analyses and logistic regression analyses were conducted based on the provoked angiographic LAD spasm. Separate logistic regression analyses were performed to identify univariate predictors of LAD spasm, and the associated variables were included in the stepwise backward selection method in the model of multivariate logistic regression analysis, presented as an odds ratio with 95% confidence intervals. A value of $p < 0.05$ was considered significant.

3. Results

MBs were identified in 140 patients (36%) in the LAD, and 1 patient (0.3%) in the RCA and in the left circumflex, respectively. Table 1 lists baseline characteristics divided into 2 groups according to the presence of MB in the LAD. Patients with MB in the LAD had greater number of provoked vasospasm in the LAD, which most frequently occurred in the mid segment. Consequently, the rate of positive ACh provocation test was significantly higher in patients with MB compared to those without. On the other hand, there were no significant differences of characteristics ACh provocation test except for the location of LAD spasm in the subjects accompanied by LAD spasm with or without MB in the LAD. In the present study, there were 16 out of 392 patients (4%) with cardiac events, which were defined as a composite of cardiac death (n = 1), myocardial infarction (n = 2), VF or SVT (n = 5), and readmission due to chest pain (n = 8) during the mean follow-up period of 14.9 ± 16.6 months. There were no significant differences in the incidence of cardiac events between patients with and without MB in the LAD (2.9% vs. 4.8%, p = 0.43), and between patients with and without LAD spasm (5.4% vs. 2.9%, p = 0.21). The differences in each component of cardiac events were not significant between patients with and without MB in the LAD (cardiac death: 0% vs. 0.3%, p = 1.00; myocardial infarction: 0.7% vs. 0.4%, p = 1.00; VF or SVT: 0% vs. 2.0%, p = 0.17; readmission due to chest pain: 2.1% vs. 2.0%, p = 1.00). In addition, readmission due to chest pain in patients with or without LAD spasm was not significantly different (3.3% vs. 1.0%, p = 0.15).

Table 1
Baseline characteristics.

Variable	All (n = 392)	MB (+) (n = 140)	MB (−) (n = 252)	p value
Age (years)	63.6 ± 12.1	63.7 ± 11.6	63.6 ± 12.4	0.97
Men	189 (48%)	70 (50%)	119 (47%)	0.60
Body mass index (kg/m^2)	23.8 ± 4.4	23.6 ± 4.0	23.8 ± 4.7	0.69
Hypertension	248 (63%)	76 (54%)	172 (68%)	0.006
Diabetes mellitus	68 (17%)	30 (21%)	38 (15%)	0.11
Dyslipidemia	256 (65%)	90 (64%)	166 (66%)	0.75
Current smoker	78 (20%)	27 (19%)	51 (20%)	0.82
Prior myocardial infarction	27 (7%)	15 (11%)	12 (5%)	0.03
Prior DES implantation	24 (6%)	12 (9%)	12 (5%)	0.19
Left ventricular ejection fraction (%)	60.4 ± 8.9	60.3 ± 8.8	60.5 ± 9.0	0.81
Medical treatment				
Calcium channel blocker	184 (47%)	64 (46%)	120 (48%)	0.72
Long-acting nitrate	66 (17%)	22 (16%)	44 (17%)	0.66
Antiplatelet	98 (25%)	36 (26%)	62 (25%)	0.81
Statin	117 (30%)	44 (31%)	73 (29%)	0.61
ACE-I or ARB	127 (32%)	37 (26%)	90 (36%)	0.06
β blocker	41 (10%)	11 (8%)	30 (12%)	0.21
Number of spasm vessels	0.92 ± 0.97	1.12 ± 0.99	0.81 ± 0.95	0.002
Provoked coronary artery				
Right	107 (29%)	48 (37%)	59 (25%)	0.02
Left anterior descending	184 (47%)	85 (61%)	99 (39%)	<0.001
Left circumflex	69 (18%)	24 (17%)	45 (18%)	0.83
Location of vasospasm in the LAD				
None	208 (53%)	55 (39%)	153 (61%)	<0.001
Proximal	62 (16%)	32 (23%)	30 (12%)	0.004
Mid	84 (21%)	46 (33%)	38 (15%)	<0.001
Distal	38 (10%)	7 (5%)	31 (12%)	0.02
Types of LAD spasm				0.26
Focal spasm	54 (29%)	21 (25%)	33 (33%)	
Diffuse spasm	130 (71%)	64 (75%)	66 (67%)	
Multivessel spasm	104 (27%)	47 (34%)	57 (23%)	0.02
Signs of ischemia				
Electrocardiographic change	147 (38%)	65 (46%)	82 (33%)	0.006
Chest pain	217 (55%)	90 (64%)	127 (50%)	0.008
Positive ACh provocation test	192 (49%)	83 (59%)	109 (43%)	0.002

Patients were divided into 2 groups according to the presence of MB in the LAD. ACE-I = angiotensin converting enzyme inhibitor; ACh = acetylcholine; ARB = angiotensin receptor blocker; DES = drug eluting stent; LAD = left anterior descending artery; MB = myocardial bridge.

In patients with MB in the LAD, characteristics of MB are shown in Table 2. The patients with provoked LAD spasm had greater total bridged length and maximum percent systolic compression of MB. MBs in the LAD were identified mostly in the mid segment (Fig. 1). In 81 out of 85 patients (95%) with LAD spasm, vasospasm occurred in

Table 2
Characteristics of MB in the LAD.

Variable	All (n = 140)	LAD spasm (+) (n = 85)	LAD spasm (−) (n = 55)	p value
Location of MB				
Proximal	1 (1%)	0 (0%)	1 (2%)	0.35
Mid	134 (96%)	81 (95%)	53 (96%)	
Distal	5 (4%)	4 (5%)	1 (2%)	
Positional relation of LAD spasm to MB				
Proximal to MB		49 (35%)		
On MB		32 (23%)		
Distal to MB		4 (3%)		
No vasospasm		55 (39%)		
Total bridged length (mm)	15.0 ± 6.9	17.2 ± 6.9	11.6 ± 5.4	<0.001
Minimum lumen area (mm)	1.50 ± 0.46	1.44 ± 0.47	1.61 ± 0.43	0.03
Reference vessel diameter (mm)	2.18 ± 0.43	2.20 ± 0.41	2.13 ± 0.46	0.36
Maximum percent systolic compression (%)	31.8 ± 15.1	35.4 ± 15.6	26.2 ± 12.6	<0.001

LAD = left anterior descending artery; MB = myocardial bridge.

Please cite this article as: Y. Saito, et al., Relation between severity of myocardial bridge and vasospasm, Int J Cardiol (2017), http://dx.doi.org/10.1016/j.ijcard.2017.07.002