Influence of Myocardial Bridge On Atherosclerotic Plaque Distribution and Characteristics Evaluated By Near-Infrared Spectroscopy Intravascular Ultrasound

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Abstract

Purpose

This study aims to clarify whether myocardial bridge (MB) could influence atherosclerotic plaque characteristics assessed by using near-infrared spectroscopy-intravascular ultrasound (NIRS-IVUS) imaging.

Methods

One hundred and sixteen patients who underwent percutaneous coronary intervention (PCI) using NIRS-IVUS imaging were included. MB was defined as an echo-lucent band surrounding left anterior descending artery (LAD). In MB patients, LAD was divided into 3 segments: proximal, MB, and distal segments. In non-MB patients, corresponding 3 segments were defined based on the average length of the above segments. Segmental maximum plaque burden and lipid content derived from NIRS-IVUS imaging in the section of maximum plaque burden were evaluated in each segment. Lipid content of atherosclerotic plaque was evaluated as lipid core burden index (LCBI) and $\text{maxLCBI}_{4\text{mm}}$. LCBI is the fraction of pixels indicating lipid within a region multiplied by 1000, and the maximum LCBI in any 4-mm region was defined as $\text{maxLCBI}_{4\text{mm}}$.

Results

MB was identified in 42 patients. MB was not associated with maximum plaque burden in proximal segment. LCBI and $\text{maxLCBI}_{4\text{mm}}$ were significantly lower in patients with MB than those without in proximal segment. Multivariable analysis demonstrated both MB and maximum plaque burden in proximal segment to be independent predictors of LCBI in proximal segment.

Conclusion

Lipid content of atherosclerotic plaque assessed by NIRS-IVUS imaging was significantly smaller in patients with MB than those without. MB could be considered as a predictor of lipid content of atherosclerotic plaque when assessed by NIRS-IVUS imaging.

Introduction

Myocardial bridge (MB) is a common anatomic variant of muscle bundle overlying the intramyocardial segment of an epicardial coronary artery. The prevalence of MB varies based on the detection methods, such as autopsy, angiography, computed tomography, and intravascular imaging, and its location is mostly in the left anterior descending artery (LAD) [1,2]. It has been previously reported that MB

accelerates coronary atherosclerosis in the segment proximal to MB, whereas the development of atherosclerosis is significantly suppressed in LAD intima beneath MB [2]. On the other hand, several studies with multi-slice computed tomography have demonstrated that MB has no relationship with the progression of atherosclerotic plaque [3,4]. Thus, controversy about the association between MB and atherosclerotic plaque formation exists. Moreover, it is unclear whether MB has an impact on plaque characteristics in the segments proximal to and beneath MB.

Intravascular imaging, such as intravascular ultrasound (IVUS), can directly observe atherosclerotic plaque and estimate plaque vulnerability in vivo [5-7], and there are a few studies investigating the association of MB with plaque distribution and characteristics [8,9]. However, these studies utilized only gray-scale IVUS imaging. Near-infrared spectroscopy (NIRS)-IVUS consists of an ultrasound transducer and a scanning near-infrared laser to detect the lipid content of atherosclerotic plaque. Previous studies have shown that a large amount of lipid core plaque (LCP) detected by NIRS-IVUS can predict future adverse cardiovascular events [10,11]. Thus, the aim of this study was to clarify whether MB could influence atherosclerotic plaque characteristics as assessed by using NIRS-IVUS.

Methods

Study Population

The present study was a single center, retrospective observational analysis, conducted between March 2017 and May 2019 at Chiba University Hospital. Patients who underwent percutaneous coronary intervention (PCI) for any coronary artery disease with NIRS-IVUS imaging of LAD were considered eligible for the present study. Patients were excluded if NIRS-IVUS imaging analysis of the segment proximal to MB was not available for reasons of pre-existing coronary artery stent or severe calcification. Written informed consent for examination was obtained from all patients, and the ethical committee of Chiba University approved this study.

NIRS-IVUS Imaging and Analysis

Systematic NIRS-IVUS imaging of the LAD was performed using the Makoto™ Intravascular Imaging System (NIPRO Corporation, Osaka, Japan), and was acquired from as distal as possible, with motorized transducer pullback speed of 0.5 mm/second. In cases where PCI for LAD was indicated, NIRS-IVUS imaging was acquired before any intervention if the severity of lesion allowed crossing of the imaging catheter or after balloon dilatation if needed. MB was defined as an echo-lucent band partially surrounding the LAD. In MB patients, LAD was divided into 3 segments: proximal segment (LAD ostium to MB entrance), MB segment, and distal segment. In non-MB patients, corresponding 3 segments were defined based on the average length of the above segments. To quantify the amount of lipid content of atherosclerotic plaque, lipid core burden index (LCBI) was evaluated in each segment. LCBI is the fraction of pixels indicating lipid within a region multiplied by 1000 and LAD was scanned for the maximum LCBI in any 4-mm region, which was defined as $\text{maxLCBI}_{4\text{mm}}$.

Grayscale IVUS Analysis

All grayscale IVUS images were analyzed using echo Plaque 3.0 (INDEC Systems, Los Altos, CA, USA) by experienced investigators, and all measurements were conducted in each of the 3 segments. Vessel and lumen areas were measured at the leading edge of the external elastic membrane (EEM) and luminal borders. Plaque area was calculated as vessel area minus lumen area. Plaque burden was calculated as plaque area divided by vessel area. Maximum plaque burden, and vessel and lumen areas in the cross-section of maximum plaque burden were obtained. In patients with MB, thickness of MB halo and maximum arterial compression were evaluated. Arterial compression was calculated as a decrease in EEM-cross sectional area (CSA) at systole divided by EEM-CSA at end-diastole, which was represented as a percentage. Atherosclerotic plaque calcification severity was assessed as the largest arc of calcium in the cross-section of maximum plaque burden, then further classified as calcification score: zero-point (0°), one-point (1° to 90°), two-point (91° to 180°), three-point (181° to 270°) or four-point (271° to 360°).

Statistical Analysis

Statistical analysis was performed with JMP® 13.2.0 (SAS Institute Inc., Cary, NC, USA). Data are expressed as mean $\pm$ SD or frequency (%). Difference between baseline characteristics was assessed by Student t-test or Wilcoxon rank sum test and Fisher's Exact test or Pearson's χ^2 test in terms of continuous variables and categorical variables, respectively. Univariable analysis was performed using linear regression analysis of rank-transformed outcomes. The associated variables on univariable analysis ($p < 0.10$) were included in multivariable analysis. Multiple linear regression analysis of rank-transformed outcomes was used for multivariable analysis. A value of $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 136 patients underwent PCI using NIRS-IVUS imaging during the study period. Among these, NIRS-IVUS imaging of the proximal segment was not available in 20 patients because of the severe calcification and pre-existing coronary artery stent. Thus, 116 patients were included in this study (male, 80%; age, 69.4 ± 10.9 years). MB was identified in 42 out of 116 patients (36%). Baseline characteristics are shown in Table 1. Patients with MB were significantly younger and had less NIRS-IVUS imaging for LAD as a culprit vessel of PCI performed. Other characteristics were similar between patients with and without MB.

Table 1
Baseline Characteristics

	MB n=42	Non-MB n=74	P value
Age (years)	66.8 ± 11.4	70.9 ± 10.5	0.051
Male	37 (88%)	56 (76%)	0.107
BMI	25.0 ± 3.9	24.0 ± 3.7	0.177
Hypertension	32 (76%)	45 (61%)	0.092
Diabetes mellitus	16 (38%)	33 (45%)	0.496
Dyslipidemia	33 (79%)	49 (66%)	0.160
Current smoker	5 (12%)	14 (19%)	0.327
Prior myocardial infarction	8 (19%)	19 (26%)	0.417
Prior PCI	13 (31%)	20 (27%)	0.653
Prior CABG	1 (2%)	1 (1%)	0.682
eGFR (ml/min/1.73 m ²)	71.5 ± 21.5	68.6 ± 21.0	0.496
BNP (pg/ml)	50.3 ± 99.5	156.8 ± 406.1	0.098
Admission LVEF (%)	58.5 ± 10.5	56.0 ± 13.7	0.333
Acute coronary syndrome	9 (21%)	21 (28%)	0.411
Target vessel for PCI	21 (50%)	57 (77%)	0.003
Medical treatment at discharge			
Antiplatelet	42 (100%)	74 (100%)	0.682
Anticoagulant	4 (10%)	8 (11%)	0.827
Statin	38 (90%)	68 (92%)	0.794
ACE-I or ARB	26 (62%)	40 (54%)	0.412
β blocker	19 (45%)	24 (32%)	0.170
Calcium channel blocker	21 (50%)	35 (47%)	0.780
Diuretic	2 (5%)	13 (18%)	0.048
MRA	1 (2%)	6 (8%)	0.213

ACE-I angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BNP* brain natriuretic peptide, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonist, *OHA* oral hypoglycemic agent, *PCI* percutaneous coronary intervention

	MB n=42	Non-MB n=74	P value
OHA	17 (40%)	31 (42%)	0.563
<i>ACE-I</i> angiotensin converting enzyme inhibitor, <i>ARB</i> angiotensin receptor blocker, <i>BNP</i> brain natriuretic peptide, <i>LVEF</i> left ventricular ejection fraction, <i>MRA</i> mineralocorticoid receptor antagonist, <i>OHA</i> oral hypoglycemic agent, <i>PCI</i> percutaneous coronary intervention			

Grayscale Ivus Analysis

IVUS findings are shown in Table 2. Maximum plaque burden was significantly greater in the proximal segment than other segments. In comparison between patients with and without MB, maximum plaque burden was similar in the proximal and distal segments, whereas it was significantly smaller in the MB segment compared with the corresponding mid segment in patients without MB (Fig. 1).

Table 2
NIRS-IVUS Findings

	MB n=42	Non-MB n=74	P value
Proximal segment			
Vessel area (mm ²)	13.9 ± 4.5	13.8 ± 4.5	0.940
Lumen area (mm ²)	4.5 ± 2.3	4.2 ± 2.3	0.462
Maximum plaque burden (%)	67.4 ± 11.4	69.5 ± 11.9	0.364
LCBI	101.5 ± 81.6	151.8 ± 103.7	0.009
MaxLCBI _{4mm}	338.1 ± 231.1	429.1 ± 212.6	0.034
Calcification Score	1.0 ± 0.8	1.3 ± 1.0	0.130
MB segment			
Vessel area (mm ²)	8.6 ± 2.9	9.0 ± 2.8	0.504
Lumen area (mm ²)	5.0 ± 2.0	4.5 ± 2.7	0.288
Maximum plaque burden (%)	40.6 ± 12.9	51.4 ± 18.1	0.001
LCBI	19.1 ± 44.1	87.7 ± 97.1	<0.001
MaxLCBI _{4mm}	44.1 ± 98.5	219.2 ± 203.7	<0.001
Calcification Score	0.4 ± 0.6	0.6 ± 0.7	0.296
Distal segment			
Vessel area (mm ²)	8.4 ± 2.5	7.2 ± 2.1	0.039
Lumen area (mm ²)	4.5 ± 1.9	3.7 ± 1.7	0.085
Maximum plaque burden (%)	45.9 ± 16.3	47.5 ± 19.8	0.737
LCBI	42.1 ± 70.8	70.1 ± 87.9	0.165
MaxLCBI _{4mm}	108.7 ± 177.3	172.0 ± 208.9	0.202
Calcification Score	0.2 ± 0.4	0.5 ± 0.7	0.012
<i>LCBI</i> /lipid core burden index, <i>MB</i> myocardial bridge			

In patients with MB, the distance from LAD ostium to MB entrance was 39.0±9.8 mm and the length and maximum thickness of MB halo were 19.7±10.5 mm and 0.54±0.24 mm, respectively. Arterial compression of the MB segment was 18.6±12.7% on average. There were no significant correlations between maximum plaque burden in the proximal segment and MB parameters evaluated by grayscale

IVUS, such as MB length ($r=-0.24$, $p=0.12$), halo thickness ($r=-0.23$, $p=0.15$), arterial compression ($r=-0.08$, $p=0.62$), and the distance from LAD ostium ($r=0.05$, $p=0.73$). Calcification scores in the cross-section of maximum plaque burden in the proximal and MB segments were similar between patients with and without MB, but it was significantly lower in the distal segment in patients with MB compared to those without.

Nirs-ivus Analysis

In patients with MB, LCBI and $\text{maxLCBI}_{4\text{mm}}$ were significantly lower in the proximal segment ($p=0.0088$ and 0.034 , respectively. Representative cases were shown in Fig. 2) and in the MB segment ($p<0.0001$ and <0.0001 , respectively), compared with the corresponding segments in non-MB patients (Table 2). In the distal segment, on the other hand, LCBI and $\text{maxLCBI}_{4\text{mm}}$ were similar between the 2 groups.

In the univariable analysis, target vessel for PCI, lumen area, maximum plaque burden, and the presence of MB were significantly associated with LCBI in the proximal segment (Table 3). Multivariable analysis demonstrated maximum plaque burden and MB to be independent predictors of LCBI in the proximal segment. Regarding $\text{maxLCBI}_{4\text{mm}}$ in the proximal segment, significant associations were shown in current smoking, target vessel for PCI, lumen area, maximum plaque burden, and the presence of MB in the univariable analysis. Multivariable analysis demonstrated a tendency with MB to predict $\text{maxLCBI}_{4\text{mm}}$ and current smoking and maximum plaque burden as independent predictors for $\text{maxLCBI}_{4\text{mm}}$.

Table 3
Predictors of NIRS Findings in Proximal Segment

Variable	LCBI		MaxLCBI _{4mm}					
	Univariable		Multivariable		Univariable		Multivariable	
	r	P value	β	P value	r	P value	β	P value
Age (years)	0.133	0.159			0.128	0.172		
Male	0.044	0.646			-0.065	0.486		
BMI (kg/m ²)	0.029	0.760			-0.007	0.940		
Hypertension	0.018	0.850			0.055	0.554		
Dyslipidemia	0.017	0.858			-0.029	0.757		
Diabetes mellitus	0.002	0.984			-0.048	0.611		
Current smoker	-0.132	0.163			-0.202	0.030	-0.188	0.020
Prior MI	-0.106	0.265			-0.040	0.668		
UA	-0.013	0.891			0.077	0.412		
eGFR	-0.029	0.759			0.033	0.725		
LDL-C	0.029	0.757			0.016	0.866		
Initial TnI	-0.005	0.955			0.047	0.621		
BNP	0.062	0.512			0.086	0.356		
ACS	0.120	0.206			0.134	0.151		
Target vessel	0.294	0.002	0.049	0.628	0.314	<0.001	0.055	0.559
Vessel area	0.038	0.690			0.056	0.548		
Lumen area	-0.311	0.001	0.064	0.607	-0.389	<0.001	-0.050	0.681
Max PB in seg P	0.455	<0.001	0.465	<0.001	0.514	<0.001	0.418	<0.001
Calcification Score	-0.005	0.959			0.162	0.082	0.065	0.427
Presence of MB	-0.245	0.009	-0.203	0.022	-0.197	0.034	-0.151	0.071
Antiplatelet	0.089	0.350			0.107	0.253		
Beta blocker	0.012	0.899			-0.112	0.229		

ACS acute coronary syndrome, BMI/body mass index, LCBI/lipid core burden index, MB myocardial bridge, PB plaque burden, seg P proximal segment

	LCBI		MaxLCBI _{4mm}	
ACEI/ARB	0.024	0.800	0.100	0.286
Statin	0.084	0.378	0.042	0.657
<i>ACS</i> acute coronary syndrome, <i>BMI</i> body mass index, <i>LCBI</i> lipid core burden index, <i>MB</i> myocardial bridge, <i>PB</i> plaque burden, <i>seg P</i> proximal segment				

With regard to the MB segment, target vessel for PCI, lumen area, calcification score, maximum plaque burden, the presence of MB, and use of beta-blockers were significantly associated with LCBI and maxLCBI_{4mm} in the univariable analysis (Table 4). Multivariable analysis revealed maximum plaque burden and the presence of MB as independent predictors for both LCBI and maxLCBI_{4mm}.

Table 4
Predictors of NIRS Findings in MB Segment

Variable	LCBI		MaxLCBI _{4mm}					
	Univariable		Multivariable		Univariable		Multivariable	
	r	P value	β	P value	r	P value	β	P value
Age (years)	0.133	0.180			0.157	0.119		
Male	0.099	0.318			-0.055	0.587		
BMI (kg/m ²)	0.092	0.353			0.064	0.528		
Hypertension	0.006	0.952			0.052	0.610		
Dyslipidemia	-0.198	0.044	-0.076	0.355	-0.150	0.137		
Diabetes mellitus	0.113	0.253			0.117	0.245		
Current smoker	0.110	0.267			0.060	0.556		
Prior MI	0.119	0.228			0.086	0.394		
UA	-0.061	0.540			-0.075	0.456		
eGFR	-0.002	0.987			-0.017	0.869		
LDL-C	-0.060	0.543			0.009	0.931		
Initial TnI	-0.077	0.446			-0.097	0.344		
BNP	-0.020	0.837			0.043	0.668		
ACS	-0.003	0.973			0.024	0.813		
Target vessel	-0.239	0.015	0.071	0.418	0.226	0.024	0.012	0.881
Vessel area	-0.001	0.990			-0.011	0.912		
Lumen area	-0.345	<0.001	0.036	0.742	-0.413	<0.001	0.021	0.833
Max PB in seg P	0.578	<0.001	0.448	<0.001	0.673	<0.001	0.523	<0.001
Calcification Score	0.249	0.013	0.139	0.096	0.256	0.012	0.126	0.094
Presence of MB	-0.390	<0.001	-0.221	0.016	-0.461	<0.001	-0.287	<0.001
Antiplatelet	-0.069	0.489			-0.078	0.440		
Beta blocker	0.197	0.045	0.110	0.200	0.251	0.012	0.136	0.081

ACS acute coronary syndrome, BMI/body mass index, LCBI/lipid core burden index, MB myocardial bridge, PB plaque burden, seg P proximal segment

	LCBI		MaxLCBI _{4mm}	
ACEI/ARB	0.060	0.548	0.153	0.130
Statin	0.018	0.859	-0.019	0.848
ACS acute coronary syndrome, BMI body mass index, LCBI lipid core burden index, MB myocardial bridge, PB plaque burden, seg P proximal segment				

Discussion

In the present study, MB was identified in 42 out of 116 patients (36%). Maximum plaque burden was not different between patients with and without MB in the proximal and distal segments, whereas significantly smaller in the MB segment compared with the corresponding mid segment in patients without MB. LCBI and maxLCBI_{4mm} were significantly lower in both the proximal and MB segments in MB patients compared with the corresponding segments in non-MB patients. Multivariable analysis demonstrated MB and maximum plaque burden as independent predictors of LCBI and maxLCBI_{4mm} in both the proximal and MB segments, except for the tendency that MB predicted maxLCBI_{4mm} in the proximal segment.

MB was previously reported to accelerate atherosclerosis in the segment proximal to MB but not in the segment beneath MB, and to be associated with plaque rupture leading to myocardial infarction, especially in the younger population. These phenomena were supported by autopsy and clinical observational studies [2,12,13]. However, several studies using multi-slice computed tomography have demonstrated that MB has no association with the progression of atherosclerotic plaque [3,4]. In the present study, plaque progression in the proximal segment was not different between patients with and without MB, although it was significantly suppressed in the MB segment compared with the corresponding mid segment in non-MB patients. While MB was defined as any echo-lucent band detected by grayscale IVUS in the present study, it was unclear whether all of MB had a significant effect on coronary blood flow, leading to increased atherosclerosis. In addition, patients in the present study had relatively more comorbidities, such as diabetes (DM) and dyslipidemia (DLP), than those of previous studies [14]. Moreover, patients without MB tended to be younger than those with MB in the present study. These potential factors could make the effect of MB on atherosclerotic plaque formation in the segment proximal to MB equivocal between patients with and without MB.

In the proximal segment of LAD, a smaller amount of lipid content was observed in MB patients compared with non-MB patients whereas plaque burden was not different between the 2 groups. Wall shear stress (WSS) distribution is one of the considerable factors for plaque formation and subsequent vulnerability. In patients with MB, it has been reported that WSS at the segment proximal to MB is lower than that in the segment beneath MB [15,16]. A previous study has demonstrated the relationship between high WSS and progression of lipid-rich plaque assessed by NIRS-IVUS imaging [17]. Thus, it is possible that low WSS in the segment proximal to MB might be associated with less lipid content

observed in MB patients. However, since lower WSS was reported to have an impact on more plaque progression [18], the similar amount of plaque burden between patients with and without MB observed in the present study could not be explained from this point of view. Further examination is required to clarify this issue.

In the segment beneath MB, WSS should be higher than in other segments [15,16], and higher WSS possibly results in higher LCBI [17]. However, from the results of multivariable analysis in the present study, MB was associated with lower LCBI in the segment beneath MB. Multivariable analysis also demonstrated maximum plaque burden as a significant predictor for LCBI and maxLCBI_{4mm} in the present study. Plaque burden was reported to be positively correlated with LCBI in previous studies [19]. Therefore, less plaque burden in the MB segment might cause lower LCBI, despite possibly high WSS in the MB segment. In addition, a previous study with optical coherence tomography showed the absence of adventitial vasa vasorum formation in the segment beneath MB [20], which is involved in atherosclerotic plaque formation. This histological feature of MB may be associated with less plaque burden as well as lipid content in the MB segment.

Since patients with established CAD were included in the present study, it is conceivable that confounding risk factors, such as age, hypertension, DLP, and DM, could affect the lipid content of atherosclerotic plaque. Nevertheless, multivariable analysis demonstrated only maximum plaque burden (with a positive attitude) and MB (with a negative one) as independent predictors for lipid content in the proximal and mid segments of LAD. Although it is still uncertain whether MB has a significant effect on atherosclerotic plaque and its lipid content formation, patients with MB would not always have worse prognosis because of MB on atherosclerotic plaque vulnerability. However, further study is warranted to investigate what type of features of MB are associated with plaque stability or vulnerability, since previous reports suggest that MB can cause adverse events, such as arrhythmia, myocardial infarction, and sudden death in some patients with MB [21-23].

There are some limitations of the present study. This was a single-center study, and the number of subjects was small. The present study was a retrospective observational study and patient information was obtained from medical records only. Patients who have severe stenosis or coronary stent in the segment proximal to MB were excluded, and all remaining patients were Japanese with 80% being male. Thus, caution is warranted in applying the present study results to different populations.

In conclusion, lipid content of atherosclerotic plaque assessed by NIRS-IVUS imaging was significantly smaller in patients with MB than those without. MB could be considered as a predictor negatively associated with plaque vulnerability in the proximal and mid LAD.

Declarations

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Conflicts of interest

The authors declare that they have no conflict of interest.

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Figures

Maximum plaque burden

Figure 1

Maximum plaque burden in each segment. The vertical axis shows maximum plaque burden (%). Maximum plaque burden was similar in proximal and distal segment, but significantly lower in patients with MB in MB segment ($p=0.001$). MB myocardial bridge

Figure 2

Coronary angiogram and NIRS-IVUS images in proximal segments. Representative cases in patients with MB (A1-3) and with no MB (B1-3). The yellow dotted line in A1 (B1) showed proximal segment defined in methods. The green dotted line showed the segment of the coronary artery under MB. The white dotted line indicated the cross section of maximal plaque burden in proximal segment as shown in A2 (B2). A3 (B3) showed longitudinal IVUS images and chemogram derived from NIRS in proximal segment. LCBI is the fraction of pixels indicating lipid within a region multiplied by 1000 and LAD was scanned for the maximum LCBI in any 4-mm region, which was defined as maxLCBI_{4mm}. Patients with MB demonstrated similar maximum plaque burden but significantly lower LCBI and maxLCBI_{4mm} in proximal segment compared to those in patients with no MB. IVUS intravascular ultrasound, LCBI lipid core plaque burden, MB myocardial bridge, NIRS near-infrared spectroscopy