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SIGNIFICANCE OF HYPERCHOLESTEROLEMIA IN THE DEVELOPMENT OF ATHEROSCLEROTIC PLAQUE AT THE SITE PROXIMAL TO THE MYOCARDIAL BRIDGE

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ABSTRACT

Objective: The main aim of this study was to investigate whether myocardial bridge (MB) is an independent risk factor for the development of atherosclerotic plaque (AP) proximal to the bridge site in the left anterior descending coronary artery (LAD), and the significance of increased levels of cholesterol in the formation of AP in LAD coronary artery. **Methods:** This is a retrospective study performed with data from January 2015 to June 2017 in Zhongnan Hospital of Wuhan University. Our study had a total of 83 adult patients. Patients were subdivided into MB, MB & AP and AP groups. The relationship between MB and coronary atherosclerosis was compared with serum levels of lipid profile parameters. **Results:** Among the total 83 patients, 40 patients had MB only, 19 patients had MB&AP and 24 patients had AP only. TC (MB only 4.21 ± 0.55mmol/L, MB&AP 4.90 ± 0.74mmol/L, and AP only 5.05 ± 0.91mmol/L; P < .001), LDL-C (MB only 2.53 ± 0.58mmol/L, MB&AP 3.20 ± 0.60mmol/L, and AP only 3.41 ± 0.78mmol/L; P < .001), and TG (MB only 1.32 ± 0.50mmol/L, MB&AP 1.85 ± 0.73mmol/L, and AP only 2.08 ± 1.00mmol/L; P < .001) were significantly higher in patients with MB&AP and AP only compared to MB only. TC, LDL-C, and TG were significantly correlated with the type of coronary artery disease (CAD) in correlation analysis, while LDL-C and TG were significantly correlated with the type of CAD in regression analysis. **Conclusion:** In patients with hypercholesterolemia, atherosclerosis was more susceptible in the segment proximal to MB in the LAD, and MB in the mid-LAD is an independent risk factor for coronary atherosclerosis in the proximal LAD.

KEYWORDS: Myocardial Bridge, Coronary Artery Disease, Hypercholesterolemia, Atherosclerotic Plaque.

INTRODUCTION

The usual course of the coronary arteries and their major branches have an extramural sub epicardial course, but in the myocardial bridge, the coronary artery dips down into the myocardium and reappears in the epicardium along its course,[1] which may be of varying depth and length. The most common site of the myocardial bridge is the middle segment of the left anterior descending coronary artery (LAD). However, the posterior descending right coronary artery, diagonal branches as well as marginal branches of the circumflex artery are occasionally involved.[2] The artery coursing into the myocardium and overlain by a layer of muscle is also called a tunneled artery, which during systole can be characterized by a varying amount of lumen narrowing and compression of the tunneled segment with a 'milking' effect. MB is a congenital anomaly which is relatively benign and silent in most of the cases but sometimes it may cause symptoms such as myocardial infarction, syncope, atrioventricular blocks, ventricular tachycardia and sudden death.[3,4]

Atherosclerosis is considered as a pathologic process that causes the disease of the arterial wall, which is among the leading cause of death worldwide.[5] It is associated with genetic predisposition and multiple risk factors such as social & job stress,[6] high-fat diets, hypertension,[7] smoking,[8] hyperglycemia, hypercholesterolemia,[9] low physical activity,[10] genetic factors and bacterial & viral infections.[11] Atherosclerosis involves lipid accumulation, chronic inflammation, thrombosis and cell death.[12] The distribution of atherosclerotic plaque is non-random in manner around the different part of the coronary artery branches. The role of Endothelial Shear Stress (ESS) and blood flow disturbances are long been recognized as the most significant factor for the development of atherosclerotic plaque. Disturbed, low and low-oscillatory ESS subsequently acts as proatherogenic gene expression by the mechanism of

endothelial mechanotransduction. The arterial segments which are usually straight where the flow is undisturbed there the ESS vary within a physiological range, the endothelial cells express atheroprotective genes. The preferred location of atherosclerotic lesions is near branch ostia, lateral wall of bifurcation and curvatures of arteria. The role of Tensile Stress (TS) also known as circumferential stress, TS is higher at the segment proximal to the bridge than at the tunneled artery might be contributing in the development of AP in artery proximal to MB and atheroprotection in the tunneled artery segment. Other contributing factors for localization of AP includes septal perforators, coronary wall motion, wall thickness, blood pressure and heart rate.[13-18] There have been several studies suggesting excessive amounts of cholesterol, an abundant and fundamental lipid molecule in human cells, as a recognized risk factor and its role in triggering in the development and progression of atherosclerotic plaque as well as making the plaque more complex.[16,19]

As the main purpose of this study was to find out the significant relation between myocardial bridge with the development of atherosclerosis in the segment proximal to the bridge site, and the role of increased levels of cholesterol in the formation of atherosclerosis in the coronary artery. We retrospectively evaluated if hypercholesterolemia and the anatomical location of MB itself were the risk factor for the development of AS on the proximal segment of coronary artery diagnosed by multislice computed tomography-coronary angiography (MSCT-CA).

Table. 1: Localization of Atherosclerotic Plaques and Myocardial Bridging on LAD Coronary Artery in Patients with MB only, MB&AP, AP only and Classification of MB by Characteristics of Deep Seated MB and Superficial MB.

Localization of AP on LAD Coronary Artery				
		Proximal	**Middle**	**Total**
MB & AP		17	2	19
AP only		20	4	24
Localization of MB on LAD Coronary Artery				
	Proximal	**Middle**	**Distal**	**Total**
MB only	5	32	3	40
MB & AP	0	17	2	19
		Arterial stenosis due to AP		
		<25%	>25%	Total
MB & AP		16	3	19
AP only		21	3	24
MB Classification by characteristics of deep-seated MB and Superficial MB				
		MB&AP	**MB only**	**Total**
Deep		16	18	34
Superficial		3	22	25

Abbreviations: MB, myocardial Bridging; AP, atherosclerotic plaque; LAD, left anterior descending.

MATERIALS AND METHODS

Study Design

The present study was carried out in Zhongnan Hospital of Wuhan University. This is a retrospective study performed with data of two and half years from January 2015 to June 2017. This study consists of a total number of 83 adult patients. Patients included were diagnosed as having MB and/or AP by MSCT-CA. The group was further divided into three subgroups as the presence of MB (n=40), MB&AP (n=19) and AP (n=24). The detailed clinical history, general examination and all laboratory and radiological investigations and the required data were gathered from the digital recordings of medical archives of the patients included in this study.

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Table. 2. Comparison of Clinical Features of Patients with MB, MB & AP and AP.

Category	**No. of Cases**	**Gender**		**Heart Rate**	**HTN (%)**	**Smoking (%)**
		Male (%)	**Female (%)**			
MB	40	17 (42.5%)	23 (57.5%)	74.50 ± 11.18	6 (15.0%)	9 (22.5%)
MB & AP	19	12 (63.2%)	7 (36.8%)	73.11 ± 11.51	8 (42.1%)	8 (42.1%)
AP	24	15 (62.5%)	9 (37.5%)	71.71 ± 6.80	16 (66.7%)	7 (29.2%)

Abbreviations: MB, myocardial Bridging; AP, atherosclerotic plaque; HTN, hypertension.

Exclusion Criteria: Patients with the history of previous percutaneous coronary intervention and/ or coronary artery bypass grafting and/or Supra-arterial myotomy, coronary anomalies other than myocardial bridging, renal failure, congestive heart failure or ongoing antidyslipidemic therapy.

Coronary Artery Imaging

Medical recordings of the patients with coronary artery disease were retrospectively reviewed from the medical archive for MSCT-CA report. Among the total eighty-three patients we had, they were further divided into three subgroups according to the MSCT-CA report as the patient having MB only, the patient having MB&AS and patient having AS only on LAD. The patient underwent MSCT-CA due to chest discomfort, suspected coronary artery disease or inconclusive stress test result.

Laboratory Data

Lipid profiles of all participants were available on medical files. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentrations were analyzed by a Beckman Coulter AU5800 Analyzer after overnight fasting, all samples were received from the serums derived from the venous blood. Hypercholesterolemia was defined as TC> 5.18 mmol/L, LDL-C > 3.63 mmol/L, HDL-C < 1.04 mmol/L, TG> 1.70 mmol/L, or ongoing antidyslipidemic therapy.

Statistical Analysis: All data were tested by Shapiro-Wilk test to find the normality of study groups. Data with normal distribution were compared with parametric tests (ANOVA), while those without the normal distribution were compared with nonparametric tests (Kruskal-Wallis test). Post hoc analysis was performed by Tamhane test for data with inhomogeneous variances and Tukey's test for homogenous variances. The data were reported as mean ± standard deviation for those analyzed by parametric tests, whereas data with non-normal distribution were reported as the number of patients (percentage). Correlation analysis of variables was performed by Spearman correlation test. The P-value <.05 were considered as statistically significant. All the obtained data were subjected to statistical analysis by applying above mentioned statistical tests using IBM SPSS 23.0 for Windows (Chicago, Illinois) software.

Table. 3. Comparisons of laboratory Parameters among patients with Myocardial bridging, Myocardial bridging & Atherosclerotic plaque and Atherosclerotic plaque.

	Patient with MB (n=40)	Patient With MB & AP (n=19)	Patient with AP (n=24)	P value
Age in years	55.03 ± 10.35	56.89 ± 9.41	59.88 ± 8.81	.161
Heart Rate per minute	74.50 ± 11.18	73.11 ± 11.51	71.71 ± 6.80	.572
TC mmol/L	4.21 ± 0.55	4.90 ± 0.74	5.05 ± 0.91	<.001
LDL-C mmol/L	2.53 ± 0.58	3.20 ± 0.60	3.41 ± 0.78	<.001
HDL-C mmol/L	1.30 ± 0.26	1.31 ± 0.16	1.20 ± 0.26	.112
TG mmol/L	1.32 ± 0.50	1.85 ± 0.73	2.08 ± 1.00	<.001

Abbreviations: TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein; TG, triglyceride.

RESULTS

During the study period of two and half years selected for our study, we had total (n=83) patients, whose age ranged from 27 years to 78 years. They were further divided into three groups as MB, MB&AP, AP. In cases with MB(n=40), cases with MB&AP (n= 19), cases with AP (n=24). The different features of AP and MB and their localization were described in the (Table 1). TC (MB only 4.21 ± 0.55mmol/L, MB&AP 4.90 ± 0.74mmol/L, and AP only 5.05 ± 0.91mmol/L; P < .001), LDL-C (MB only 2.53 ± 0.58mmol/L, MB&AP 3.20 ± 0.60mmol/L, and AP only 3.41 ± 0.78mmol/L; P < .001), and TG (MB only 1.32 ± 0.50mmol/L, MB&AP 1.85 ± 0.73mmol/L, and AP only 2.08 ± 1.00mmol/L; P < .001) were significantly higher in patients with MB&AP and AP only compared to MB only. (Table 3). Correlation coefficient (C.C)- Spearman's rho: [TC: C.C= .462 P<.001, LDL-C: C.C= .509 P<.001, T.G: C.C= .373 P .001]. TC, LDL-C, and TG were found to be significantly correlated with the type of coronary lesion of patients in the correlation analysis, however only LDL-C and TG were found to be significantly correlated with the type of CAD in regression analysis (Table 4). However mean age of patients and heart rate with MB&AP, AP and MB were not significantly different among the groups (Table 3). Gender distribution and distribution of patients in presence of HTN and smoking history among three different groups are shown in (Table 2).

Table. 4. Analysis of Correlation Between the Coronary Arterial Lesion Type of Patients and Serum Levels of TC, LDL-C, and TG.

	Bivariate Analysis		Linear Regression Analysis	
	CC	**P**	**β**	**P**
TC	.462	<.001	-.112	.584
LDL-C	.509	<.001	.521	.010
TG	.373	.001	.296	.004

Abbreviations: CC, correlation coefficient; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

DISCUSSION

Our study is a retrospective study, which is among one of the few studies conducted in this group of patients with MB and/or AP. The finding of this study could be very useful in recognition, prevention and management of hypercholesterolemia as a risk factor for atherosclerosis in the patient who has MB. Atherosclerosis is known as a disease of chronic inflammation of atrial wall that ultimately results in tissue damage and fibrosis. The study of atherosclerosis and its risk factors is important as atherosclerosis remains the leading cause of death worldwide. As we have stated above multiple risk factors for atherosclerosis have been defined. Our study shows 22.5% MB only patient were smokers while 42.1% with MB&AP and 29.2% with AP only were smokers. 15% of MB only patients were hypertensive while 42.1% with MB&AP and 66.7% with AP only were hypertensive. (Table 2)

As we know 64-slice computed tomography angiography has emerged as a promising method for evaluating coronary artery disease, so in this study, we used 64-slice CTA to study the diagnosis of MB and distribution of atherosclerosis in coronary arteries. A large number of other studies shows that coronary atherosclerosis is found more frequently in LAD artery system than in other coronary arteries and in a majority of cases, it is in the proximal segment.[17,18] which is similar to the finding of our study as MB&AP group had 17 cases of proximal LAD atherosclerosis while AP only had 20 cases in proximal LAD. As shown in (Table.1)

In addition to systemic risk factors, the other factors such as local mechanical forces might also play a role in determining the rate of progression of atherosclerosis. Such factors as described earlier are ESS, blood flow disturbances, TS, septal perforators, coronary wall motion, locations such as branch ostea, the lateral wall of bifurcations and curvatures of arteria, blood pressure and heart rate.[13-19]

Myocardial bridging as a risk factor for the development of atherosclerosis and causing various types of cardiovascular events have been constantly studied. H. Duygu et al, they retrospectively analyzed 71 patients with MB found on coronary angiography and then the total group was subdivided into two groups as presence and absence of atherosclerotic lesion, their result suggests the ratio of systolic compression of the bridging segment may be related to atherosclerosis. They found that the degree of systolic compression was higher in the group of patients with atherosclerosis, so their suggestion was MB play the role to initiate the development of atherosclerotic lesion or help in the progression of AP in the segment proximal to the MB.[20]

The factors such as the degree of cardiac contractility along with the location, length and thickness of the muscle bridge were responsible for the degree of coronary obstruction by the MB. There was a finding of characteristic diastolic flow disturbance and high stress proximal to MB which was the main contributor for the development of atherosclerosis in the segment proximal to the MB according to studies done with coronary angiography, intravascular ultrasonography, and intracoronary doppler study. In some case, the pressure in the segment proximal to the MB was higher than the pressure in the aorta.[21-24]

In a study by Mustafa Aparci et al, they retrospectively analyzed 34 patients who were diagnosed as having coronary artery disease by MSCT-CA, the group was further divided by the presence of MB and/or AP on LAD artery. Serum levels of metabolic parameters were compared among study groups, they reported total cholesterol, LDL-C, VLDL-C, TG was significantly correlated with the type of coronary artery disease, they described in presence of hypercholesterolemia, MB had a significant role for the localization of AP in the proximal segment where the MB is located itself. Our finding is similar to their finding as in our result TG, LDL-C and TG were significantly correlated with the type of coronary artery disease.[9]

Another study done by T. Nakaura et al had 188 total patients who were suspected to have coronary artery disease. Among the total patient who went for multi-detector computed tomography (MDCT), 50 patients had MB in the middle segment of the LAD. Their result showed that MB in LAD was significantly correlated with atherosclerosis in the proximal LAD. They suggested that MB in the mid LAD was an independent risk factor for the development of atherosclerosis in the segment proximal to MB.[23] Ding Shijun et al, they analyzed clinical variables and comorbidities of 1132 patients who underwent CTA and reported that 330 patients had MB at LAD. (42.6%) had Deep MB while (57.4%) had Superficial MB. They reported that the proximal segment of LAD was susceptible to atherosclerosis than the distal segment, and MB was an independent protective factor in the bridged segment. They suggested that the depth of MB and degree of compression of MB in diastolic phase are the independent factors related to atherosclerosis.[24] As many studies have suggested that MB is spared from atherosclerosis, although the exact mechanism responsible for this are not yet clear, various factors such as TS, high SS, and reduced phasic coronary motion have been identified for atheroprotection in the tunneled artery segment.[23,25,26] Their finding is similar to our finding as in our study among 59 patients with MB no one had AS in the tunneled segment.

As we know for the development of atherosclerosis, cardiovascular inflammation plays a key role. Some infectious organism such as viral and bacterial pathogens are associated for human atherosclerosis, in one study they suggested that atherosclerotic process is independent of an infectious organism and atherogenesis can be triggered by endogenous molecules such as

cholesterol, it was known to accumulate in AP in form of intracellular cholesterol esters in foam cells or as intra and extracellular crystalline material.[27] Hypercholesterolemia has a significant role in making plaque more complex, which is characterized by an increase in necrotic core volume in coronary artery plaque.[16]

In our study, we evaluated the laboratory data in patients diagnosed with MB only, MB&AP, and AP only on the LAD coronary artery by MSCT angiography. We found that the comparison of serum levels of TC, LDL-C, and TG was significantly different among patients with MB, MB&AP and AP (Table 3). In subgroup analysis, we observed that patients with AP and MB&AP had significantly higher serum levels of TC, LDL-C, and TG compared to those in patients with only MB. TC, LDL-C &TG was found to be positively correlated with the type of coronary disease in correlation analysis but only LDL-C and TG were significantly correlated with the type of CAD in regression analysis. Similarly, in a study by Gerald S Berenson et al serum concentration of TC, LDL-C, TG was significantly associated with the extent of lesions in the coronary arteries.[8] From our study, we can suggest that increased cholesterol in bloodstream acts as the promoting factor for atherosclerotic plaque in the arterial segment proximal to MB. We found that patients with MB had significantly lower serum levels of TC, LDL-C and TG compared to patients with MB&AP and AP only (Table 3).

As atherosclerosis is a slowly progressive disease, it may take decades to show clinical symptoms of cardiovascular events, but sometimes acute cardiac events occur in the context of plaque-related thrombus formation. As we know that hyperlipidemia correlates with necrotic core lesions and contributes to increased risk of coronary plaque vulnerability. We can suggest, the use of statin helps to prevent necrotic core plaque formation associated with hypercholesterolemia.[28] There are many studies suggesting the positive effect of lipid-lowering, especially LDL cholesterol lowering, for prevention of vascular events. In one study which had 174,000 patients, they demonstrated that the reduction in LDL cholesterol had a significant role in lowering major vascular events which were similar overall for man and woman. Even among the individuals who are at low risk of cardiovascular events, we can say, irrespective of sex, statins greatly help to reduce cardiovascular events and overall causes of mortality.[29]

CONCLUSION

In patients with hypercholesterolemia, atherosclerosis was more susceptible in the segment proximal to MB in the LAD, and MB in the mid-LAD is an independent risk factor for coronary atherosclerosis in the proximal LAD. We suggest close attention should be paid to prevent the development of coronary atherosclerosis in the segment proximal to the site of MB, especially in patients who do not have AP but have MB and hyperlipidemia.

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