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Increased TIMI frame count of coronary arteries in patients with myocardial bridging

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ABSTRACT

Objectives: Myocardial bridging (MB) is associated with recurrent chest pain and cardiovascular events. Recently it has been proposed that MB has the features of vasospastic coronary artery characterized with reduced coronary flow reserve and endothelial dysfunction. In this study, an evaluation was made of the angiographic Thrombolysis in Myocardial Infarction (TIMI) frame counts (TFCs) of patients with normal angiogram and those with MB.

Methods: The study was conducted as a retrospective analysis of the demographic, laboratory, and angiographic features of consecutive patients who underwent coronary angiography between January 2014 and December 2017 in Necip Fazıl City Hospital and Sütçü Imam University, Kahramanmaraş, Turkey.

Results: The except for age (51.1 ± 11.6 years vs 56.8 ± 11.4 years) ($p = 0.011$), no difference was determined between the groups in respect of laboratory parameters and demographic features. TFCs of LAD (42.9 ± 6.1 vs 54.5 ± 11.5. $p < 0.001$), Cx (19.4 ± 4.5 vs 24.4 ± 7.1, $p < 0.001$), and RCA (26.8 ± 6.2 vs 32.5 ± 8.9, $p < 0.001$), and corrected TFC of LAD artery (25.2 ± 3.6 vs 32.0 ± 6.8, $p < 0.001$) were observed to be significantly increased in patients with MB compared to patients with normal coronary flow. Multiple regression analysis revealed that MB was the only determinant of increased corrected TFC of LAD artery (r=0.537, Adjusted r=0.281, $p < 0.001$).

Conclusions: Patients with MB had abnormally slow coronary flow demonstrated by increased TFC. This finding may explain the recurrent angina and cardiovascular events of patients with MB. It may also explain the reversible myocardial perfusion defects which are associated with recurrent cardiovascular events in patients with MB.

Keywords: Myocardial bridging, thrombolysis in myocardial infarction, TIMI frame count, coronary flow, recurrent angina

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Myocardial bridging (MB) of coronary artery disease may be associated with widely varying signs and symptoms of myocardial ischemia. Those signs and symptoms may develop due to either systolic compression of the coronary artery that can be detected on angiography or various hemodynamic abnormalities of coronary flow which can be documented on intracoronary Doppler assessment [1]. Abnormally increased pressure gradient during the systolic and diastolic period of coronary flow on the arterial segment proximal to the MB is the essential hemodynamic abnormality. Coronary flow reserve is

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also reduced due to those intracoronary hemodynamic abnormalities induced by MB [2].

Recent studies have documented that the response to the acetylcholine test was more pronounced in patients with MB and caused diffuse spasm of the coronary artery where MB was present [3]. This is probably associated with the recurrence of signs and symptoms and cardiovascular events in those patients with MB. Postmortem studies have documented that the proximal arterial segments of a bridged coronary artery were stripped of endothelial lining compared to the other arterial walls [4]. Thus, endothelial dysfunction is a significant pathophysiological abnormality observed in patients with MB [5]. An abnormally paradoxical vasospastic response to adenosine infusion detected on angiography is significant evidence of endothelial dysfunction [6]. Therefore, MB may be one of the significant causes in the etiology of angina pectoris and myocardial ischemia in non-obstructive coronary artery disease [7]. All these hemodynamic and pathological abnormalities inevitably produce coronary flow abnormalities which can be assessed by the coronary flow quantification method defined as Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) [8]. Quantifying the coronary flow with TFC may allow the cardiologist to decide whether there is an underlying coronary flow abnormality in the etiology of signs and symptoms and to predict the long-term outcomes for patients with MB [8].

In this study it was aimed to evaluate the coronary flow properties by assessing the TFC of the coronary arteries on the coronary angiography of patients with MB.

METHODS

The study was conducted as a retrospective analysis of the demographic, laboratory, and angiographic features of consecutive patients who underwent coronary angiography between January 2014 and December 2017 in Necip Fazıl City Hospital and Sütçü İmam University, Kahramanmaraş, Turkey. Informed consent was obtained from all the patients. Approval for the study was granted by the Local Ethics Committee of Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey.

Study Groups

All the patients were applied with coronary angiography for a diagnosis of stable coronary angiograph due to a positive treadmill test, recurrent chest pain despite medical therapy, previous dynamic ECG changes during chest pain, and patient request. The control group comprised patients with no apparent coronary artery stenosis as luminal irregularities, < 20% stenosis or normal coronary anatomy [9]. Patients with systolic compression of at least 25% luminal narrowing due to myocardial bridging in the proximal or middle segments of the left anterior descending artery were assigned to the myocardial bridging group.

Patients with previous myocardial infarction, atherosclerotic coronary artery disease, hypertension, diabetes, acute coronary syndromes including unstable angina pectoris, non-ST/ST segment elevated myocardial infarction, myocarditis, acute or chronic systemic inflammatory disease, chronic liver disease, and also congestive heart failure with reduced or preserved ejection fraction, or chronic renal failure were excluded from the study. In addition, patients with a moderate or higher daily alcohol intake, age < 25 years or > 70 years, were excluded from the study.

Laboratory Measurements

Serum levels of laboratory parameters were measured from the venous blood samples obtained at 08.00 in the morning after a 12-hour fasting period. Samples collected in tubes containing K^3 EDTA were rested for 20 minutes and then centrifuged at 3500 rpm for 15 minutes. Total plasma cholesterol, triglyceride, and high-density lipoprotein [HDL] cholesterol, uric acid and glucose concentrations were measured with the Cobas c501 (Roche Diagnostics, USA) using the spectrophotometric technique. Low density lipoprotein [LDL] cholesterol levels were calculated with the Friedwald formula.

Complete blood count measurement and cell differentiation were performed by Sysmex XE-5000 using the diode laser bench and fluorescent flow cytometry technique. Leukocytes, neutrophils, lymphocytes, and monocytes were presented as ($nx10^3/mm^3$). Hemoglobin (Hb) and Hematocrit (Hct) were presented as g/dL and %, respectively. Platelet count (Plt) were presented as $nx10^3/mm^3$.

Coronary Angiography Procedure

The standard angiographic procedure was applied to all patients. With the patient in a supine position, a 6F arterial sheath was introduced to the femoral artery using the Seldinger technique. 6F right and left Judkins catheters were used to image the coronary arteries. Angiography was performed as a standardized procedure including coronary imaging from 4 positions (left caudal, right caudal, and left cranial, right cranial) for the left coronary system and from 2 positions (left and right cranial) for the right coronary artery. The contrast media used during angiography was Iohexol (Omnipaque-350/100 ml, Opakim, Turkey) which was injected as 6-8 mL during each image shot.

TIMI Frame Count (TFC)

TFCs of LAD, Cx, and RCA arteries were calculated as the difference of the last and first frames of those arteries. The first frames of the arteries were accepted as the entrance of the contrast dye to at least 70% of the arterial lumen. The last landmarks were the opacification of the distal branching for LAD, and the first branching of the posterolateral artery for RCA, and the distal branching for Cx artery on the left lateral wall [11]. The LAD and Cx arteries were assessed on the angiographic projection of the right anterior oblique with caudal angulation and the RCA was assessed on the angiographic projection of the left anterior oblique with cranial angulation. TFC of LAD was corrected with a factor of 1.7 which had been previously defined [10].

The angiographic images were analyzed by two independent cardiologists blinded to the study project. The interobserver variability of the two cardiologists was tested using the results of the TFC calculations from the LAD artery recordings of the first fifteen patients. Cronbach's Alpha was calculated as 0.976 and intraclass correlation of analyses was 0.975 ($p < 0.001$).

Statistical Analysis

Statistical analyses of the study data were applied using IBM SPSS 15.0 software (IL, USA). The conformity to normal distribution of the data was tested using the Kolmogorov Smirnov test. Continuous variables with normal distribution were compared with parametric tests e.g. Independent Samples *t* test while those variables without normal distribution were compared with non-parametric tests. The distribution of categorized variables was analyzed using the Chi-Square test. Correlation analysis of continuous and categorized variables was applied by the Pearson and Spearman tests, respectively. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

Demographic features of body weight and height, systolic and diastolic blood pressure, and BMI were not different between the groups. Age was determined to be significantly higher in patients with MB (51.1 ± 11.6 years vs 56.8 ± 11.4 years, $p = 0.011$) (Table 1). Complete blood count and laboratory parameters were not different in the comparison of the two groups, with

Table 1. Demographic characteristics of the patients

Characteristics	Patients with normal coronary angiography (n = 62)	Patients with MB on angiography (n = 54)	*p*
Age (years)	51.1 ± 11.6	56.8 ± 11.4	**0.011**
Weight (kg)	82.5 ± 8.9	84.2 ± 9.7	0.361
Height (cm)	170.0 ± 4.3	171.5 ± 5.3	0.119
BMI (kg/m^2)	28.6 ± 3.4	28.6 ± 3.3	0.959
SBP (mmHg)	125.6 ± 5.3	127.2 ± 7.8	0.233
DBP (mmHg9	74.9 ± 6.7	76.2 ± 7.5	0.350

Data are shown as mean±standard deviation. BMI = body mass index, DBP = diastolic blood pressure, MB = myocardial bridging, SBP = systolic blood pressure

Table 2. Laboratory findings of the patients

	Patients with normal coronary angiography (n = 62)	Patients with MB on angiography (n = 54)	*p*
Hb (g/dL)	13.4 ± 1.3	14.1 ± 1.7	**0.030**
Hct (%)	41.1 ± 3.5	42.2 ± 4.8	0.200
Leukocyte (x10^3)	7.9 ± 2.2	8.0 ± 1.6	0.850
Neutrophil (x10^3)	5.0 ± 1.9	4.8 ± 1.5	0.461
Lymphocyte (x10^3)	2.2 ± 0.7	2.1 ± 0.6	0.355
Monocyte (x10^3)	0.6 ± 0.2	0.7 ± 0.3	0.079
Platelet (x10^3)	237.9 ± 65.0	230.0 ± 52.2	0.485
Glucose (g/dL)	93.8 ± 10.2	92.1 ± 9.9	0.388
Urea (mg/dL)	28.9 ± 10.4	28.7 ± 6.3	0.953
Creatinine (mg/dL)	0.8 ± 0.2	0.8 ± 0.1	0.527
AST (IU/L)	23.2 ± 6.3	24.0 ± 6.7	0.504
ALT (IU/L)	23.1 ± 9.9	23.4 ± 7.9	0.880
Total cholesterol (mg/dL)	179.4 ± 37.0	179.2 ± 42.6	0.974
LDL cholesterol (mg/dL)	112.4 ± 29.5	114.9 ± 39.9	0.697
HDL cholesterol (mg/dL)	45.3 ± 15.8	37.8 ± 7.2	**0.002**
TG (mg/dL)	153.8 ± 101.3	188.7 ± 105.6	0.082
Na (mEq/L)	140.7 ± 2.3	140.0 ± 2.3	0.107
K (mEq/L)	4.5 ± 0.4	4.4 ± 0.4	0.106

Data are shown as mean±standard deviation. ALT = alanine aminotransferase, AST = aspartate aminotransferase, Hb = hemoglobin, Hct = hematocrit, HDL = high-density lipoprotein, K = potassium, LDL = low density lipoprotein, Na =sodium, TG = triglyceride

the exception of Hb (13.4 ± 1.3 vs 14.1 ± 1.7, p = 0.030) and serum levels of HDL (45.3 ± 15.8 vs 37.8 ± 7.2, p = 0.002) (Table 2).

TFCs of LAD (42.9 ± 6.1 vs 54.5 ± 11.5, $p < 0.001$), Cx (19.4 ± 4.5 vs 24.4 ± 7.1, $p < 0.001$), and RCA (26.8 ± 6.2 vs 32.5 ± 8.9, $p < 0.001$), and corrected TFC of LAD artery (25.2 ± 3.6 vs 32.0 ± 6.8, $p < 0.001$) were significantly increased in patients with MB compared to patients with normal coronary flow (Table 3).

Table 3. TIMI frame counts of the patients

TIMI frame counts	Patients with normal coronary angiography (n = 62)	Patients with MB on angiography (n = 54)	*p*
Corrected TFC	25.2 ± 3.6	32.0 ± 6.8	**< 0.001**
LAD TFC	42.9 ± 6.1	54.5 ± 11.5	**< 0.001**
Cx TFC	19.4 ± 4.5	24.4 ± 7.1	**< 0.001**
RCA TFC	26.8 ± 6.2	32.5 ± 8.9	**< 0.001**

Data are shown as mean±standard deviation. Cx = circumflex coronary artery, LAD = left anterior descending coronary artery, TFC = TIMI frame count, TIMI = Thrombolysis in Myocardial Infarction, RCA = right coronary artery

In correlation analysis, corrected TFC was positively correlated with the presence of MB (r=0.537, p = 0.537) and Hb (r=0.212, p = 0.027), and male gender (r=0.240, p = 0.012). In multivariate linear regression analysis with a stepwise model, only the presence of MB was determined to be significantly correlated with corrected TFC of LAD artery (r=0.537, Adjusted r=0.281, p < 0.001) and no correlation was determined in respect of gender and Hb level.

DISCUSSION

The most significant result of this study was that coronary flow quantified by TFC was observed to be reduced in patients with MB compared to patients with normal coronary anatomy. TFC is a well validated technique to quantify coronary flow in angina or chest pain syndromes associated with non-obstructed coronary artery disease. TFC may quantify not only the epicardial coronary flow but also distal microvasculature and resistance, providing an objective and sensitive evaluation of the flow changes of the coronary artery [11]. The most interesting result of this study was that the slowing of the coronary blood flow was not limited only to the coronary artery where there is MB. Increased TFC is a global abnormality of coronary arteries in both the right and left coronary system. Although similar findings were reported by Barutcu *et al*. [12], they stated that TFC was significantly increased only on the LAD artery associated with MB but not on the RCA or Cx artery. On close examination of the results of that study, cTFC was seen to be significantly higher (24.7 ± 2.1 vs 22.1 ± 1.9, p = 0.001) in the LAD artery while TFC tended to be higher in the Cx artery (22.1 ± 2.4 vs 21.3 ± 2.3, p = 0.18) and was no different in the RCA (23.1 ± 2.2 vs 23.4 ± 2.1, p = 0.7) in patients with MB in the LAD artery. Coronary flow was significantly decreased irrespective of the degree of systolic narrowing and other clinical and echocardiographic features of the patients. That the number of patients was limited in that study may have been the reason why the results did not reach a level of statistical significance. In the current study, a larger population was evaluated, which may have contributed to the statistical significance of the data.

In this context, the hypothesis that coronary flow abnormality or pressure gradients are due to anatomic restrictions induced by MB could not mechanistically explain why TFC significantly increased not only in the LAD artery but also in the Cx and RCA. Therefore, the global increase of TFC on LAD and remote coronary arteries could be explained by several hormonal or autonomic dysfunctıons triggered by MB. In several cases, it has been reported that MB is associated with paradoxically worsening of coronary vasospasm following intracoronary adenosine or nitroglycerine infusion [6, 13]. It has also been demonstrated that adding oral nitrate treatment worsened the stable angina of a subject with MB [10]. This phenomenon was attributed to the endothelial dysfunction due to pressure gradient and vascular shear stress induced by MB. Endothelial dysfunction is a significant cause of reversible myocardial perfusion defects detected in patients with non-obstructive coronary artery disease as in patients with MB [14]. MB is one of the significant causes of reversible myocardial perfusion defects. Although Brolin *et al*. [15] reported that prevalence of MB did not differ in patients with MINOCA (myocardial infarction due to non-critically obstructed coronary artery disease) or Takotsubo syndrome, recurrent sign and symptoms of ischemia, angina, and myocardial infarction in patients with MB renders the diagnosis of MB essential in the management of those patients. The results of the current study may highlight those recurrent clinical characteristics due to MB. Since slow coronary flow associated with MB is seen in all coronary arteries, it may explain why localization of reversible perfusion defects on the myocardium may vary and present heterogeneity on the perfusion tests in patients with MB. Those reversible and non-homogeneous defects which were formerly called "false positive" have been associated with endothelial and microvascular dysfunction which may be caused by myocardial bridging and not confined to the territory of one coronary artery [16]. Slow coronary flow on different remote coronary arteries may also partially explain the reason why reversible perfusion defects can be detected on irrelevant myocardial segments. This phenomenon may explain to critics why myocardial perfusion tests were not performed and ischemia not documented since those perfusion defects could not be induced on every test. This entity may be a unique clinical feature of endothelial and

microvascular dysfunction induced by MB. MB causes recurrent angina resistant to therapy and may be complicated with myocardial infarction or malignant arrhythmia.[17] Therefore, the signs and symptoms of patients with MB may be different from stable angina pectoris and not predictable or reproducible. Sometimes it may be diagnosed as variant angina due to recurrent coronary vasospasm in daily clinical practice [18]. The current authors have previously suggested that recurrent vasospasm may develop due to increased Ca accumulation on the arterial wall proximal to the coronary segment with MB, as documented in postmortem studies [4, 19]. Moreover, smooth muscle cells found in the subendothelial layers of pre- and post-MB segments of coronary artery have shown increased migratory and proliferative activity [20]. All those histolopathological findings may contribute to the increased vasospastic response of a coronary artery with MB and may account for the recurrent signs and symptoms and the cardiovascular events due to MB.

Limitations

The retrospective design of this study may be one of the limitations of this study. All the patients in the MB group had MB in the proximal or mid segment of the LAD artery, which is consistent with previously reported data [21]. Although it may appear to be a limitation of this study, the prevalences of MB in the Cx or RCA arteries reported in previous autopsy or angiographic studies have not been of sufficient significance to warrant the design of any groups of those coronary arteries with MB. Intracoronary pressure gradients could have been measured using intracoronary Doppler measurements and the comparison made according to the pressure gradient. However, this is an invasive method and may require a further prospective study with more complex hemodynamic monitoring. Challenge tests for coronary vasospasm (e.g. acetylcholine test, adenosine) could have been applied to evaluate the association between the vasospastic response of the coronary artery with MB and TFC, but this could be tested in another future prospective study. Although patients with acute or chronic systemic inflammatory diseases were excluded, no evaluation was made of the laboratory parameters of the systemic inflammatory state in this study.

CONCLUSION

Patients with myocardial bridging had significantly slower coronary flow compared to patients with normal coronary anatomy. Endothelial dysfunction, coronary hemodynamic abnormalities and pressure gradients induced by the presence of MB may account for this slow coronary flow. This finding may be one of the mechanisms accounting for the recurrent signs and symptoms of ischemia and cardiovascular events in patients with MB.

Author contributions

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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