European Review for Medical and Pharmacological Sciences 2023; 27: 6256-6263

A new marker of coronary collateral flow in patients presenting with acute myocardial infarction

A. DEMIRKIRAN[1], C. AYDIN[1], A. YILMAZ[2], A. ÇELIKKOL[3], Ş. ALPSOY[1], O. DONBALOĞLU[4], B. TOPÇU[5], F. BÖYÜK[6], D.T. ÇINAR[1]

[1]Department of Cardiology, Faculty of Medicine, Tekirdag Namık Kemal University, Tekirdag, Turkey
[2]Department of Medical Biochemistry, Cerrahpasa Faculty of Medicine, Istanbul University, Istanbul, Turkey
[3]Department of Medical Biochemistry, Faculty of Medicine, Tekirdag Namık Kemal University, Tekirdag, Turkey
[4]Department of Cardiac Surgery, Faculty of Medicine, Tekirdag Namık Kemal University, Tekirdag, Turkey
[5]Department of Biostatistics, Faculty of Medicine, Tekirdag Namık Kemal University, Tekirdag, Turkey
[6]Department of Cardiology, Yedikule Chest Diseases And Thoracic Surgery Training And Reseaerch Hospital, Istanbul, Turkey

Abstract. – OBJECTIVE: Multimerin-2 is an adhesion substrate between pericytes and basal membranes during angiogenesis. The present study aimed to assess the relationship between serum Multimerin-2 and coronary collateral flow grade.

PATIENTS AND METHODS: Between April 2022 and August 2022, 88 patients with subacute ST-elevation myocardial infarction were included in this study. The main inclusion criteria were patients who present 12-48 hours after symptom onset and aged between 18 and 90 years. The patients were divided into two groups according to the Rentrop classification: poor collateral group (Rentrop grade 0-1) and good collateral group (Rentrop grade 2-3). Biochemical and hematological parameters were measured before coronary angiography.

RESULTS: Serum Multimerin-2 levels were found to be significantly different between the two groups, and levels were higher in the Rentrop 2-3 group than in the Rentrop 0-1 group (3,527.9 ± 1,194.2 pg/ml and 946.7 ± 249.1 pg/ml; $p < 0.00$). Receiver operating characteristic curve analysis indicated that the area under the curve was 0.918 ($p = 0.001$), and the best cut-off value of 849 pg/ml had a sensitivity of 90.1% and a specificity of 84.1% for predicting Rentrop grade 2-3 coronary flow. The number of patients with low left ventricular ejection fraction (LVEF) by echocardiography at 30 days was significantly higher in patients with poor collateralization.

CONCLUSIONS: Multimerin-2 levels were found to be higher in patients with Rentrop grade 2-3 coronary flow than Rentrop grade 0-1 coronary flow after myocardial infarction. We detected a potential relationship between MMR-2 and good coronary collateral formation.

Key Words:
Multimerin-2, Coronary collateral flow grade, Myocardial infarction, Rentrop classification.

Introduction

Collateral vessels in the heart serve as conduits that bridge severe stenosis and can develop as an adaptation to ischemia[1,2]. According to previous studies[3,4], 40% of patients with myocardial infarction had collateral circulation to the artery that caused the infarct during the acute phase. The coronary collateral formation is a process of passive dilation of pre-existing collateral channels and active proliferation of arteriolar connections[5,6]. The formation of new vessels is regulated by several cell types, cytokines, growth factors, and extracellular matrix[7]. Sprouting angiogenesis ensured by the emergence of new capillaries from existing vessels is triggered by hypoxia which releases angiogenic factors[8]. The levels of vascular endothelial growth factors (VEGF) are high in the ischemic tissue[9-11]. VEGF and VEGF receptor (VEGFR2) expression are critical for vascular development from the endocardium[12]. Newer studies[13,15] continue to implicate new molecular signals possibly involved in coronary arteriogenesis, and this is an active area of investigation. Multimerin-2 (MMR-2) is an extracellular glycoprotein deposited along the basal membrane of the blood vessels and a ligand for the endothelial-specific

Corresponding Author: Aykut Demirkıran, MD; e-mail: aykutdemirkiran@nku.edu.tr

transmembrane glycoproteins (CLEC14A and CD93). MMR-2 provides the adhesion of pericytes to the basement membrane and regulates the VEGFA/VEGFR2 signaling axis[14,15]. Plasma MMR-2 levels increase during the disintegration of intercellular connections. CLEC14A and CD93 are overexpressed in tumor endothelium, and studies[16] confirm a role in both endothelial migration and tube formation. CLEC14A was previously shown to bind MMR-2, and antibodies disrupting this interaction retard angiogenesis[16]. MMR-2 was studied mainly in cancer cases. Studies[17,18] have been conducted to suppress the expression of Multimerin-2 to disrupt cancer angiogenesis.

Recent advances in MMR-2 and angiogenesis research have impacted the treatment of non-malignant diseases. MMR-2 was found to play an important role in the pathological vascularization of macular degeneration[19]. The purpose of the present study was to investigate the relationship between the degree of coronary collateral circulation and plasma levels of MMR-2 that regulate angiogenesis. Although MMR-2 plays an important role in angiogenesis, to our knowledge there is no study in the literature on MMR-2 in patients with coronary collateral circulation, and our study is the first. Here, we investigate the involvement of MMR-2 in the neovascular progression after acute coronary occlusion. We demonstrate the important role of MMR-2 in the formation of coronary collateral circulation.

Patients and Methods

Patients

Our study is a prospective study in which each patient was included in the study after evaluating the collateral status in coronary angiography. Between April 2022 and August 2022, 88 patients presented with subacute ST-elevation myocardial infarction included. The main inclusion criteria were patients who present 12-48 hours after symptom onset and aged between 18 and 90 years. We excluded patients with coronary artery bypass surgery, coronary stent, renal failure, significant stenosis in non-infarct related arteries, and hematologic, and oncological diseases.

Procedures

Collateral circulation was assessed in coronary cine angiograms by two cardiologists. The Rentrop-Cohen method was used to evaluate and categorize coronary collateral circulation[20]. Patients were included in the study according to the coronary collateral flow and divided into two groups: The poor collateral group included patients with Rentrop 0-1 collateral flow grade and the good collateral group included patients with Rentrop 2-3 collateral flow grade.

Biochemical, and hematological parameters were measured before coronary angiography. Serum samples were allocated and preserved at -80°C till the time of MMR-2 measurement. MMR-2 was measured using an ELISA kit (ELK Biotechnology CO., Ltd. Wuhan, China).

The primary efficacy endpoint was the MMR-2 levels and extent of visible collaterals assessed by angiography.

Statistical Analysis

The software SPSS, (version 18.0, SPSS Corp., Chicago, IL, USA), was used for statistical analysis. The Kolmogorov-Smirnov test was used to determine whether the data were appropriate for a normal distribution. Numerical values with normal distribution were indicated as mean ± standard deviation and categorical variables as percentages. Student *t*-test or Mann-Whitney U test was used for the analysis of numerical variables, and the Chi-square test was used for categorical variables. ROC curve was used to determine the cut-off value of serum MMR-2 in the prediction of Rentrop class 2-3 collateral flow. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Study Population Characteristics

A total of 88 patients presented with subacute-ST myocardial infarction were enrolled. The study population was divided into two subgroups. The poor collateral group consisted of 44 patients with Rentrop grade 0 or 1 collateral blood flow in the infarct territory. The good collateral group consisted of 44 patients with Rentrop grade 2 or 3 collateral flow. There were no statistically significant differences in baseline clinical characteristics (Table I). The comparison of laboratory parameters is summarized in Table II. Serum MMR-2 levels were found to be significantly different between the two groups, and levels were higher in the Rentrop 2-3 group than in the Rentrop 0-1 group (3,527.9 ± 1,194.2 pg/ml and 946.7 ± 249.1 pg/ml; $p < 0.00$). Receiver

Table I. Comparison of baseline clinical variables between poor collateral and good collateral groups.

Clinical variables	Poor collateral (n = 44)	Good collateral (n = 44)	*p*-value
Age, years	64.7 ± 4.9	62.1 ± 8.7	0.102
Male, n (%)	34 (77)	37 (84)	0.091
Body mass index, kg/m^2	25.0 ± 2.1	26.2 ± 1.5	0.765
Smoking, n (%)	12 (27)	15 (34)	0.139
Hypertension, n (%)	33 (75)	35 (79)	0.088
Diabetes mellitus, n (%)	21 (47)	18 (40)	0.048
Initial HR, beat/min	72 ± 8	74 ±6	0.215
Initial SBP, mm Hg	130 ± 14	134 ± 17	0.316
Initial DBP, mm Hg	75 ± 4	82 ± 8	0.733
Pain-to-balloon time (hour)	31.2 ± 11.1	32.4 ± 12.4	0.266
Door-to-balloon time (minute)	20.5 ± 9.2	23.2 ± 11.6	0.324
LV < 50% by echocardiography after PCI	19 (43.1)	17 (38.6)	0.081
Killip class			
I-II	35 (79.5)	38 (86.3)	0.061
III-IV	9 (20.4)	6 (13.6)	0.054
Previous use of drugs, n (%)			
Beta-blocker	11 (25)	14 (31)	0.432
Nitrate	5 (11)	4 (9)	0.931
Renin-angiotensin system blockers	21 (47)	24 (54)	0.341
Calcium channel blockers	9 (20)	10 (22)	0.214
Aspirin	14 (31)	18 (40)	0.334
Oral anti-diabetics	13 (29)	14 (31)	0.113
Statin	8 (18.1)	10 (22.7)	0.145

Data are given as mean ± standard deviation or percentages (%).

operating characteristic curve analysis indicated that the area under the curve for adequate neovascularization was 0.918 (p = 0.001), and the best cut-off value of 849 pg/ml had a sensitivity of 90.1% and a specificity of 84.1% for predicting adequate neovascularization (Figure 1). The Troponin T and BNP values obtained from the same sample with MMR-2 samples were found to be higher in the poor collateral group than in the good collateral group.

Angiographic and Procedural Findings

There were no significant differences according to pain-to-balloon time and door-to-balloon time in both groups. The difference in the TIMI 0 and 1 flow grades was not statistically significant between the groups. 40 (90.9%) patients in the poor collateral group and 37 (84%) patients in the good collateral group underwent stent implantation (Table III).

Forty-six (52%) had total occlusion of the left anterior descending artery (LAD), and forty-two

Table II. Comparison of laboratory parameters between Poor collateral and Good collateral groups.

	Poor collateral	Good collateral	*p*-value
Hemoglobin (g/dL)	13.9 ± 1.4	14.1 ± 1.4	0.609
Platelet (10^3/mm^3)	232 ± 37	227 ± 49	0.254
White blood cell (10^3/mm^3)	8.1 ± 1.3	7.8 ± 1.2	0.216
Fasting blood sugar (g/dL)	100 ± 15.2	96 ± 9.1	0.123
Creatinine (mg/dL)	0.88 ± 0.4	0.89 ± 0.2	0.458
Total cholesterol (mg/dL)	177 ± 34	183 ± 21	0.192
HDL-cholesterol (mg/dL)	42 ± 9	44 ± 8	0.201
LDL-cholesterol (mg/dL)	115 ± 25	124 ± 31	0.215
Triglyceride(mg/dL)	162 ± 43	174 ± 21	0.815
hs-CRP (mg/L)	4.9 ± 1.1	3.2 ± 1.1	0.362
Peak Troponin T (hs)(ng/L)	1,252.25 ± 323	972.5 ± 231	0.044
Brain natriuretic peptide (pg/mL)	4,096.27 ± 972	1,798.10 ± 492	0.023
Multimerin-2 (pg/mL)	946.7 ± 249.1	3,527.9 ± 1,194.2	0.000

Data are given as mean ± standard deviation or percentage (%). HDL: High-density lipoprotein; LDL: Low-density lipoprotein; CRP: C-reactive protein; hs: high-sensitive.

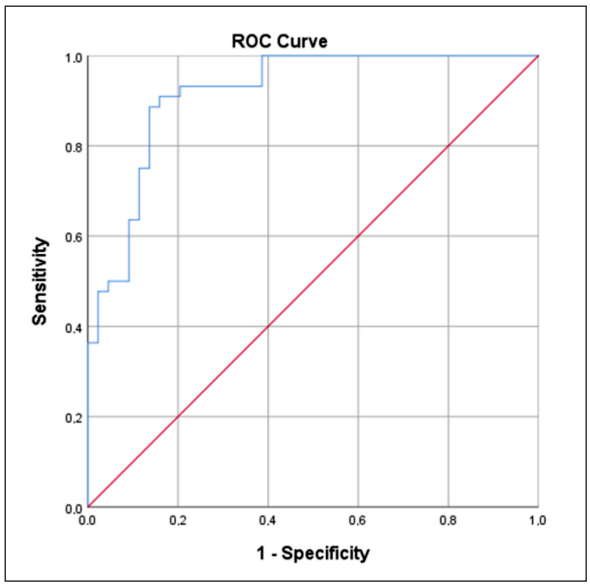

Figure 1. Receiver operating characteristic (ROC) curve testing the accuracy of multimerin-2 levels in the prediction of adequate neovascularization. The optimal serum multimerin-2 cutoff value of 849 pg/ml provided the highest sensitivity (90.1%) and specificity (84.1%). The area under the curve for apical rotation was 0.918 ($p = 0.001$).

(48%) had total occlusion of the right coronary artery (RCA). Adequate visible collateral development was found significantly more frequently in RCA occlusion than in LAD occlusion. Visible collateral development was found to be adequate in seventeen patients (36.9%) who had LAD occlusion and also twenty-seven patients (64.2%) who had RCA occlusion ($p = 0.010$). MMR-2 levels were also higher in total RCA patients than in total LAD patients (2,755.2 ± 1,205.1 pg/ml and 1,989.8 ± 671.3 pg/ml; $p = 0.018$) (Table IV).

Clinical Outcome at 30-Day Follow-Up

A total of 83 patients were alive at the 30-day follow-up. The number of patients with low left ventricular ejection fraction (LVEF) by echocardiography at 30 days was significantly higher in patients with poor collateralization. No significant differences were shown concerning myocardial re-infarction, or cardiovascular death (Table V).

Discussion

Although there are studies[21,22] on the inhibition of MMR-2 expression to block cancer neovascularization, we highlighted the relevance the MMR-2 levels in myocardial infarction-associated angiogenesis. According to this study, MMR-2 levels were found to be higher in patients with adequate coronary collateral development. However, to our knowledge, this study is the first clinical study demonstrating the relationships between MMR-2 and visible collateral vessels in patients presenting with MI. The plasma MMR-2 level during angiogenesis may affect coronary collateral formation. We intend to explore its potential as a coadjuvant therapy for coronary reperfusion with further studies.

Angiogenesis is a complex process that requires coordinated interaction between endothelial cells, and extracellular matrix under the control of many factors that we have not demonstrated yet with research. Given the impact of MMR-2 in angiogenesis, the loss of expression may significantly impact angiogenesis and chemotherapy efficacy. MMR-2 expression levels were demonstrated by Pellicani et al[14] to be essential to proper

Table III. Angiographic and procedural data.

	Poor collateral	Good collateral	*p*-value
Infarct-related coronary artery, n (%)			
Right	15 (35.7)	27 (64.2)	
Left anterior descending	29 (63.2)	17 (36.9)	
Left circumflex	0	0	
TIMI flow before percutaneous coronary intervention			
0	43 (97.7)	41 (93.1)	
1	1 (2.3)	3 (6.9)	
GP IIb/IIIa administration, n (%)	18/44 (40.9)	26/44 (36.3)	0.143
Stent insertion, n (%)	40 (90.9)	37 (84)	0.121
TIMI flow after percutaneous coronary intervention			
0	6 (13.6)	3 (6.8)	
1	7 (15.9)	5 (11.3)	
2	7 (15.9)	4 (9)	
3	24 (54.5)	32 (72.7)	

Table IV. Comparison of findings between anterior and inferior wall myocardial infarction.

	Anterior wall MI N = 46	Inferior wall MI N = 42	*p*-value
Multimerin-2 (pg/mL)	1,989.8 ± 671.3	2,755.2 ± 1,205.1	0.018
Rentrop 2-3 n (%)	17 (36.9)	27 (64.2)	0.010

MI: myocardial infarction.

Table V. Comparison of laboratory parameters between Poor collateral and Good collateral groups.

	Poor collateral	Good collateral	*p*-value
All-cause death	3 (6.8)	2 (4.5)	0.084
Cardiovascular death	2 (4.5)	1 (2.2)	0.112
Reinfarction	3 (6.8)	1 (2.2)	0.120
Target vessel revascularization	4 (9)	3 (6.8)	0.423
Stent thrombosis	1 (2.2)	1 (2.2)	0.921
LV < 50% by echocardiography at 30 day	32 (72.7)	18 (40.9)	0.043

angiogenesis and to predict the effectiveness of chemotherapy. In mice with suppressed MMR-2, tumor-associated vasculature was inadequate, and pericytic coverage was significantly reduced. In mice, chemotherapeutic efficacy was impaired, and perfusion of the arteries was decreased. Individuals can show different degrees of MMR-2 expression[23,24]. Low expression of Multimerin-2 after myocardial infarction may impair the development of new collaterals.

Greater lesion severity, proximal lesion location, and longer duration of lesion occlusion are correlated with increases in collateral flow[25,26]. In addition, a decrease in the development of coronary collateral was found in the elderly. The development of new collateral vessels may be diminished in older adults[26,27]. According to a previous study[27], the prevalence of collaterals was 48% in patients younger than age 50 years and only 34% in patients older than 70 years after acute myocardial infarction. In our study, factors such as age, male gender, body mass index, hypertension, smoking, and use of drugs did not have a significant effect on collateral vessel development. Although smoking increases collateral flow development in previous studies[28,29], it could not be shown in our study. There are contradictory results about the effects of diabetes mellitus on collateral vessel development[30-32]. One study of 306 patients with diabetes who underwent coronary angiography found that these patients had a lower mean collateral score compared with nondiabetics (2.4 *vs.* 2.6), suggesting that patients with diabetes may have poorer development of collaterals[33]. Fewer collaterals were also observed among patients with diabetes in a contemporary coronary intervention study[34] performed for chronic total occlusion. We observed that DM was present more commonly in the poor collateral group, in which coronary collaterals were inadequate, than in the good collateral group.

In a report of 1,059 patients presented with ST-elevation MI, the increased coronary collateral flow was associated with lower Killip class at presentation, less need for intraaortic balloon pumping, better myocardial blush grade after the intervention, and smaller enzymatic infarct size[35]. In our study, Killip classification at presentation was similar between the two groups. However, enzymatic infarct size assessed by high-sensitivity Troponin T value was higher in the poor collateral group at 48 h.

In our study, collateral development was more common in RCA than in LAD occlusions. The collateral formation is more prevalent in RCA occlusions was reported in many previous studies[36,37]. In addition, MMR-2 levels were found to be higher in the inferior wall compared to anterior wall myocardial infarction. However, narrowing was slightly more common in LAD in comparison to RCA.

Limitations

More detailed analysis of various factors or drugs that may have influenced the plasma levels

of MMR-2 could not be performed, because the number of ELISA kits and study population were small. One blood sample was collected from each participant, and the temporal variation of the MMR-2 level was not determined.

Conclusions

A higher rise in MMR-2 plasma level was associated with the presence of angiographically visible collateral connections in STEMI patients. We detected a potential relationship between MMR-2 and good coronary collateral formation. The detailed role of various angiogenic factors needs to be investigated in future studies.

Conflict of Interest

The authors declared no potential conflicts of interest for the research, authorship, and/or publication of this article.

Ethics Approval

The study protocol was approved by the ekirdag Namık Kemal University Ethics Committee (2022.81.05.08). Our research adhered to the tenets of the Declaration of Helsinki.

Informed Consent

All participants provided written informed consent.

Availability of Data and Materials

Data and materials are available and can be sent upon request.

Authors' Contribution

A.D., Ş.A., F.B.: conceptualization, methodology. A.D., Ş.A., F.B.: data curation, writing, and original draft preparation. B.T., C.A., A.Y., A.Ç.: visualization, investigation. B.T., O.D.: supervision and software. C.A., A.Ç., O.D.: reviewing, editing.

ORCID ID

Aykut Demirkıran: 0000-0001-8322-3514
Cihan Aydın: 0000-0002-1401-5727
Ahsen Yılmaz: 0000-0002-2270-2965
Aliye Çelikkol: 0000-0002-3799-4470
Doğa Tıraşoğlu Çınar: 0000-0003-2510-6867
Birol Topçu: 0000-0003-0771-2505
Şeref Alpsoy: 0000-0003-3720-0076
Okan Donbaloğlu: 0000-0001-5401-4772

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