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Diabetes mellitus and female gender are the strongest predictors of poor collateral vessel development in patients with severe coronary artery stenosis

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Abstract

Background Coronary collateral vessel development (CVD), i.e., arteriogenesis, is regarded as one of the most important mechanisms—along with angiogenesis—to result in protection of the myocardium. Coronary CVD is associated with a reduction in infarct size, future cardiovascular events and improved survival in patients with occlusive coronary artery disease by enhancing regional perfusion in the chronically ischemic myocardium. In the present study, we aimed to investigate the relation of cardiovascular risk factors and hematological parameters with collateral development in patients with severely stenotic (≥95 %) and totally occluded coronary artery disease including at least one major coronary artery.

Materials and methods The study population was selected from the patients who underwent coronary angiography between January 2008 and March 2009. Five hundred and two patients who had at least one coronary artery stenosis ≥95 % (368 men; mean age 59 ± 10 years) comprised the study population. Of the 502 patients, 228 had total occlusion in at least one major epicardial coronary artery. Collateral artery grading was performed by using Cohen–Rentrop method to the vessel with coronary artery stenosis of ≥95 % and patients with chronic total occlusions (CTO). Patients with grade 0–1 collateral development were regarded as the poor collateral group, and patients with grade 2–3 collateral development were regarded as the good collateral group.

Results Two hundred and fifty-eight (51 %) of 502 patients had poor collateral development, and 244 (49 %) had good collateral development. Logistic regression analysis revealed that DM was independently associated with poor CVD in patients with ≥95 % stenosis ($p < 0.001$). Additionally, female gender and DM were found to be independently associated with poor CVD in patients with CTO ($p = 0.005$ and $p < 0.001$, respectively). Monocyte count was found to be independent of CVD neither in patients with ≥95 % stenosis nor in patients with CTO.

Conclusion Our data show that DM is an independent factor for poor coronary CVD both in patients with severe coronary artery stenosis and in patients with CTO. Female gender or being in post-menopausal period is another negative risk factor for poor CVD in addition to DM in patients with CTO.

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Introduction

Arteriogenesis, i.e., the growth of collateral arteries, is regarded as one of the most important mechanisms along with

angiogenesis to enhance regional perfusion in the chronically ischemic myocardium [1, 2]. Coronary collateral vessel development (CVD) has been shown to be potentially protective with regard to infarct size, ventricular aneurysm formation, ventricular function, future cardiovascular events and survival in patients with occlusive coronary lesions due to atherosclerosis [3–5]. Cardiovascular risk factors affecting CVD have been evaluated in several clinical studies [6–8]. Diabetes mellitus (DM) has been found to be a negative predictor for the development of functional collateral arteries in patients with coronary artery stenosis >75 % [6].

Monocytes play a pivotal role in arteriogenesis at the cellular level by releasing growth factors, proteases and chemokines, hence mediating cell proliferation and migration as well as structural remodelling of the extracellular compartment [9]. Recently, it has been documented that monocyte number is an independent factor for the development of good collateral arteries in patients with severe coronary artery stenosis ≥95 % in a study with patients without DM [10]. In the present study, we investigated the relation of cardiovascular risk factors and hematological variables—mainly focusing on blood monocyte count—with collateral development in coronary artery disease (CAD) patients with (at least one) severely stenotic (≥95 %) or totally occluded coronary artery (CTO).

Materials and methods

The study population was selected from the patients who underwent coronary angiography bet at the University hospital in Bolu and IMC Hospital in Mersin, Turkey. All patients with at least one major coronary artery stenosis of ≥95 % or with a CTO were consecutively included in the study. Their coronary angiograms were examined for CVD by two experienced interventional cardiologists.

Five hundred and two selected patients who had at least one coronary artery stenosis ≥95 % (368 men; mean age 59 ± 10 years) comprised the study population. Of the 502 patients, 228 had a CTO in at least one major epicardial coronary artery. Total and differential leukocyte counts and biochemical markers obtained at most 2 days before or on the day of coronary angiography were used for analysis. Patients with previous revascularization history of either surgical bypass or percutaneous intervention, evidence of ongoing infection or inflammation, recent acute coronary syndrome either with or without ST-segment elevation (3 months before enrollment), hematological disease or known malignancy were excluded from the study. Biochemical assessments were performed using standard methods. Total and differential leukocyte counts were measured by an automated hematology analyzer (Coulter Gen-S, COULTER Corp, Miami, USA).

Standard selective coronary angiography with at least four views of the left coronary system and two views of the right coronary artery was performed using the Judkins technique. For the analysis of the effect of multivessel disease on coronary CVD, the number of the diseased vessels was identified according to the number of the major coronary arteries having ≥70 % stenosis by eyeballing.

The following clinical and demographical parameters were recorded: age, sex, hypertension (known hypertension treated with antihypertensive drugs, two or more blood pressure recordings greater than 140/90 mm Hg), diabetes mellitus (known diabetes treated with diet or drugs or both; or either a fasting serum glucose of more than 126 mg/dl or random plasma glucose >200 mg/dl in persons with symptoms of hyperglycemia) and hypercholesterolemia (known treated hypercholesterolemia or serum total cholesterol concentrations higher than 200 mg/dl). All the diabetic patients had been receiving oral anti-diabetic drugs and/or insulin for at least 6 months. Current cigarette smoking was defined as active smoking of at least five cigarettes per day within the past 12 months.

Collateral vessel development grading

Collateral artery grading was performed by using Cohen–Rentrop method [11] to the vessel with coronary artery stenosis of ≥95 %. Collateral grades according to Cohen–Rentrop method were defined as: grade 0, no filling of any collateral vessels; grade 1, filling of side branches of the artery to be perfused by collateral vessels without visualization of epicardial segment; grade 2, partial filling of the epicardial artery by collateral vessels; and grade 3, as complete filling of epicardial artery by collateral vessel. If the patient had more than one vessel with severe stenosis ≥95 %, the highest CVD score was recorded for statistical analysis. Patients with grade 0–1 collateral development were regarded as poor collateral group, and patients with grade 2–3 collateral development were regarded as good collateral group. Of the 122 female patients, 111 (91 %) were in post-menopausal period and 45 (90 %) out of 50 (90 %) female patients in the CTO group were in menopause. Since most of the female patients were in post-menopausal period, all female patients were included in the regression analysis.

Statistical analysis

Continuous variables were given as mean ± SD; categorical variables were defined as percentage. Continuous variables and categorical variables were compared by using unpaired t test and Chi-square test, respectively. Distribution of continuous variables was tested by Kolmogorov–Smirnov test. All continuous variables were shown to be normally

distributed. Logistic regression was used to analyze the possible association of cardiovascular risk factors and hematological variables with CVD both in patients with coronary stenosis ≥95 % and in subgroup of patients with chronic total occlusion. Age, gender, DM, hypertension, hyperlipidemia, smoking, whole blood neutrophil, lymphocyte, monocyte, platelet count, mean platelet volume and hemoglobin were included in regression analysis. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (SPSS for windows 15, Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

Two hundred and fifty-eight (51 %) of 502 patients had poor CVD, and 244 (49 %) had good CVD (Figs. 1, 2). The clinical, hematological and biochemical characteristics of the patients are shown in Table 1. There were no statistically significant differences in terms of cardiovascular risk factors, biochemical and hematological parameters except DM, which was significantly higher in patients with poor CVD (43 %) than in good CVD (23 %; $p < 0.001$; Table 1). Logistic regression analysis revealed that DM was the only variable independently associated with poor CVD (Table 2).

The same analysis was carried out for patients with CTO in at least one epicardial coronary artery. Two hundred and twenty-eight had CTO (mean age 59 ± 12 years, Table 3). Of whom, 61 patients had poor CVD and 167 patients had good CVD. Comparison of baseline characteristics and laboratory parameters between two groups (poor and good CVD) showed that presence of diabetes mellitus ($p < 0.001$) and female gender ($p = 0.002$) were significantly higher in patients with poor CVD than in patients with CTO (Table 3). These parameters were also found to be independently associated with poor CVD in patients with CTO (Table 4). The number of single-vessel, two-
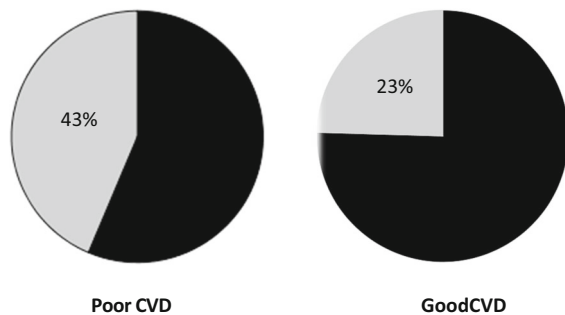

Fig. 1 Presence of diabetes mellitus in patients with poor and good collateral vessel development (CVD)
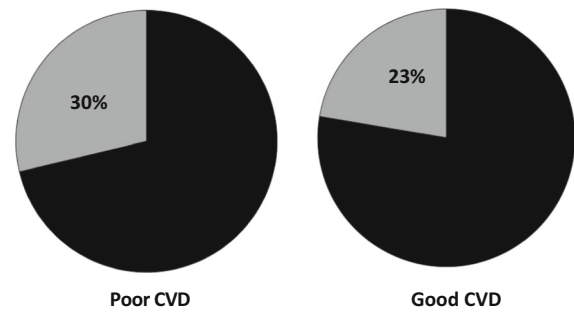

Fig. 2 Ratio of female gender in patients with poor and good collateral vessel development (CVD)

vessel and three-vessel disease was comparable between patients with good and poor CVD (Table 5). The overall severity of the each coronary artery stenosis was comparable between male and female patients (Left anterior descending % stenosis: 73 ± 33 vs. 76 ± 30; $p = 0.38$, left circumflex % stenosis: 59 ± 40 vs. 52 ± 42; $p = 0.10$, right coronary artery % stenosis: 66 ± 340 vs. 60 ± 41; $p = 0.19$, respectively).

As monocytes have been demonstrated to play a role in collateral formation, we have investigated the monocyte count of our patients with high-grade coronary artery stenosis. The monocyte count was found to be independent of CVD both in patients with ≥95 % stenosis and in patients with CTO (Tables 2, 4, respectively).

Discussion

There are several main findings of our study: (1) There is an independent association between the presence of DM and poor collateral arteries in both patients with ≥95 % stenosis and patients with CTOs, (2) female gender and history of MI are the other independent associates of poor collateral vessel development in patients with CTO along with DM, and (3) monocyte count is independent of the presence of coronary collateral arteries in both patients with ≥95 % stenosis and in patients with CTO.

DM is one of the best documented negative risk factors for the development of collateral arteries. Poor coronary collateral development has been documented in DM by Abaci et al. [6] in patients with more than 75 % stenosis. Moreover, metabolic syndrome was found to be associated with poor CVD [7]. In our study, we have shown that in patients with severe coronary stenosis (≥95 %) and in patients with CTO, DM is a major predictor for poor coronary CVD. On the contrary, Zbinden et al. [8] have reported that the coronary collateral flow index does not differ between diabetic and non-diabetic patients. However, it cannot be excluded that the patient groups differed

Table 1 Comparison of characteristics of patients with poor and good collateral vessel development (CVD) in severe coronary stenosis (≥95 %)

	Poor CVD (258)	Good CVD (244)	p value
Age (mean/median)	60 ± 10/59	60 ± 10/60	0.66
Gender (female)	77 (30 %)	57 (23 %)	0.10
Female after menopause (>50 years)	70 (27 %)	54 (22 %)	0.27
Diabetes mellitus	112 (43 %)	57 (23 %)	<0.001
Smoking	85 (33 %)	72 (30 %)	0.40
Hypertension	130 (50 %)	127 (52 %)	0.71
Hyperlipidemia	71 (29 %)	72 (28 %)	0.62
Neutrophil (10^3/ml) (mean/median)	5.2 ± 1.7/5.2	5.0 ± 1.7/5.0	0.10
Lymphocyte (10^3/ml) (mean/median)	2.3 ± 0.8/2.3	2.3 ± 0.7/2.3	0.83
Monocyte (10^3/ml) (mean/median)	0.59 ± 0.24/0.59	0.56 ± 0.23/0.57	0.59
Platelet count (10^3/ml) (mean/median)	242 ± 59/242	232 ± 59/234	0.07
Mean platelet volume (fl) (mean/median)	9.1 ± 1.42/9.1	9.1 ± 1.32/9.07	0.90
Hemoglobin (g/dL) (mean/median)	13.9 ± 1.4/13.9	13.7 ± 1.4/13.7	0.27

Table 2 Logistic regression analysis in patients with severe coronary artery stenosis (≥95 stenosis)

	Odds ratio	Confidence interval	p value
Age	1.00	0.98–1.02	0.69
Female gender	0.66	0.42–1.03	0.07
Diabetes mellitus	0.37	0.24–0.55	<0.001
Hypertension	1.30	0.88–1.90	0.19
Smoking	0.76	0.50–1.14	0.19
Hyperlipidemia	1.27	0.83–1.94	0.27
Neutrophil count	0.94	0.84–1.05	0.31
Lymphocyte count	1.01	0.80–1.30	0.89
Monocyte count	0.93	0.39–2.22	0.87
Hemoglobin	0.94	0.83–1.08	0.44
Platelet count	0.99	0.99–1.00	0.12
Mean platelet volume	1.00	0.88–1.15	0.90

Table 4 Logistic regression analysis in patients with chronic total occlusion (CTO)

	Odds ratio	Confidence interval	p value
Age	1.02	0.99–1.05	0.15
Female gender	0.33	0.14–0.71	0.005
Diabetes mellitus	0.25	0.12–0.50	<0.001
Hypertension	1.50	0.74–3.05	0.26
Smoking	0.55	0.26–1.21	0.14
Hyperlipidemia	1.05	0.50–2.20	0.90
Neutrophil count	0.87	0.72–1.05	0.14
Lymphocyte count	1.28	0.78–2.10	0.34
Monocyte	0.70	0.24–2.00	0.50
Hemoglobin	0.95	0.76–1.20	0.69
Platelet count	1.00	0.99–1.01	0.94
Mean platelet volume	0.99	0.76–1.28	0.92

Table 3 Comparison of characteristics of patients with poor and good collateral vessel development in chronic total occlusion (CTO)

	Poor CVD (61)	Good CVD (167)	p value
Age (mean/median)	59 ± 13/59	60 ± 11/60	0.37
Gender (female)	23 (38 %)	31 (19 %)	0.003
Female after menopause (>50 years)	20 (33 %)	29 (17 %)	0.007
Diabetes mellitus	32 (53 %)	35 (22 %)	<0.001
Smoking	19 (31 %)	46 (28 %)	0.60
Hypertension	33 (57 %)	91 (56 %)	0.95
Hyperlipidemia	18 (30 %)	48 (29 %)	0.91
Neutrophil (10^3/ml) (mean/median)	5.4 ± 2.0/5.3	5.0 ± 1.7/5.1	0.08
Lymphocyte (10^3/ml) (mean/median)	2.2 ± 0.8/2.3	2.3 ± 0.7/2.3	0.38
Monocyte (10^3/ml) (mean/median)	0.57 ± 29/0.56	0.57 ± 0.22/0.56	0.86
Platelet count (10^3/ml) (mean/median)	243 ± 52/238	234 ± 60/235	0.29
Mean platelet volume (fl) (mean/median)	9.10 ± 1.39/9.2	9.19 ± 1,29/9.2	0.67
Hemoglobin (g/dL) (mean/median)	13.8 ± 1.2/14	13.7 ± 1.5/13.8	0.57

Table 5 Distribution and comparison of single-, double- and three-vessel disease

	Poor CVD*	Good CVD
Single vessel		
≥95 %	75/258 (29 %)	52/244 (21 %)
CTO	15/61 (25 %)	35/167 (21 %)
Two vessel		
≥95 %	93/258 (36 %)	106/244 (43 %)
CTO	19/61 (31 %)	71/167 (43 %)
Three vessel		
≥95 %	90/258 (35 %)	86/244 (36 %)
CTO	27/61 (44 %)	61/167 (36 %)

* versus good CVD, $p > 0.05$ for all

with regard to the severity of coronary stenosis, although the average stenosis grade was the same in both the diabetic and the non-diabetic cohort, namely 68 %. Therefore, when compared with our novel data presented in this paper, it appears that differences in collateralization between diabetic and non-diabetic patients can only be revealed, if patients with high-grade stenosis (95–100 %) are being compared. Additionally, the method of CVD assessment is another issue to be considered, while comparing the results of Zbinden et al, in which coronary collateral flow index has been used instead of the Cohen–Rentrop [11] coronary angiographic classification method.

Likewise, more controversial reports have been published in literature with different methodology assessing CVD. Werner et al. [12] have assessed the collateral function of CTO by intracoronary Doppler and pressure sensors before and after a balloon angioplasty and have reported no differences in parameters of collateral function between diabetic and non-diabetic patients indicating a similar development of collaterals in CTO. However, the acute recruitment of collateral function after recanalization as assessed during a balloon reocclusion was impaired in diabetic patients with an occlusion of <3 months duration. De Vries et al. [13] evaluated patients with stable CAD scheduled for elective PCI, found that 45 % have functional collaterals assessed by pressure monitoring guide-wire and reported no differences between patients with and without DM. History of angina pectoris and duration and severity of atherosclerotic burden rather than the presence of DM have been reported to be predictor of CVD [14, 15]. Moreover, Kyriakides et al. [16] have reported that type II diabetes does not prevent the recruitment of collateral vessels or the normal reduction in myocardial ischemia on repeated balloon inflations during coronary angioplasty. However, recruitment of collateral vessels during balloon inflation which is an acute situation mainly depends on the preexisted collateral vessels and is driven by shear stress. The most important

trigger of arterial remodelling in native as well as collateral vessels is increased tangential fluid shear stress at the endothelial surface. Fluid shear stress is the product of spatial velocity changes between different fluid layers or the fluid and the endothelium and blood viscosity increased adherence of monocytes, which transform into macrophages [17]. Werner et al. [18] have also detected that release of MCP-1 into the collateral circulation appears to be related to increased shear stress but release of bFGF into the collateral circulation is related to the duration of the occlusion and the quality of collateral function. However, release of bFGF is down-regulated in diabetic patients [18].

In the last decade, studies evaluating the effects of DM on development of CVD vessels have focused on monocyte-mediated mechanisms as monocytes are key players in arteriogenesis [19]. It is important to note that the function of monocytes appears to be critical. Monocyte dysfunction has been clearly demonstrated in patients with DM [20, 21]. As recently demonstrated, the cellular response of monocytes to VEGF-A is attenuated in diabetic patients secondary to a downstream signal transduction defect [21]. These data suggest that monocytes are important in arteriogenesis. The process of arteriogenesis seems to be critically dependent on monocytes and on proper monocyte function [1, 22, 23] as their ability to migrate might be critical for the arteriogenic response. Previous studies have shown that monocytes/macrophages in particular accumulate in the surrounding tissue of collateral vessels after arterial occlusion due to ICAM-1/Mac-1-dependent mechanisms [24, 25]. These macrophages are potent sources of cytokines and growth factors such as TNF-α, VEGF and FGF-2 [1, 26] that are required for natural adaptive arteriogenesis. Moreover, increased chemoattraction of monocytes/macrophages (e.g., by exogenously applied MCP-1) leads to an accelerated arteriogenic response, whereas lack of circulating monocytes reduces collateral artery growth [1, 27]. Recent experimental studies suggest a direct, functional correlation between collateral artery growth after occlusion of a main artery and the concentration of circulating monocytes [27, 28]. Moreover, Heil et al. [27] have reported that arteriogenesis is stimulated by increasing the number of circulating monocytes. However, almost all the studies documenting a direct correlation between monocyte number and arteriogenesis have evaluated this relation shortly after an acute occlusion of the infarct-related artery. Therefore, one interpretation could be that arteriogenesis might correlate with the number of monocytes recruited from the circulation. We have tested this hypothesis in the current study. We have to reject this hypothesis, as there was no correlation between monocyte number and coronary CVD.

On the other hand, the functional status of monocytes during the acute phase of arteriogenesis immediately

following the acute occlusion of the artery might be different from the chronic phase of occlusion. Since none of the patients had MI <3 months, our study population represents an established steady-state phase of arteriogenesis in which monocytes might be functionally more silent compared with acute occlusion phase of arteriogenesis. In essence, the arteriogenesis process has finished in our patients as the typical stimuli of arteriogenesis are absent under these conditions.

Another important finding of our study is that female gender is an independent factor for poor CVD in patients with CTO. In line with this observation, women are known to have a higher in-hospital mortality after MI and percutaneous coronary interventions than men [29, 30]. The differences in clinical course of women and men are not in the scope of our study. Meanwhile, it is important to note that women show another difference in terms of CVD. In accordance with previous reports [29, 30] showing that women have a poorer prognosis than men, female gender is an independent predictor of poor CVD in patients with CTO. This may partially explain why women have increased mortality after acute MI. A few animal studies tested the role of gender and estrogen on arteriogenesis. Kyriakides et al. [31] reported that gender does not influence angiogenesis and arteriogenesis in a rabbit model of chronic hind limb ischemia. However, they have found that estrogen withdrawal induced by oophorectomy negatively affects angiogenesis and arteriogenesis. Similarly, Lamping et al. [32] have found that ovariectomized rabbits had significantly impaired arteriogenesis, compared with ovariectomized rabbits with estrogen treatment. Recently, Mouquet et al. [33] reported that collateral circulation is less developed in women with CTO. Therefore, we speculate that withdrawal of estrogen due to menopause might have a negative effect on arteriogenesis. The exact pathophysiological mechanisms, however, remain to be elucidated.

There are some issues need to be addressed as limitations. We have assessed the severity and extent of CAD by eyeballing. Pressure and Doppler-derived intracoronary collateral measurements are regarded as the reference method for clinical assessment of coronary collateral flow [17]. Ineligibility of intravascular ultrasound and collateral flow measurement systems were the main reasons for not including those methods. However, considerable amount of patients with total occlusion has partially eliminated this limitation in terms of determining lesion severity. Another limitation is that type of DM, length of DM and treatment duration have not been recorded in our database, and therefore, further analysis regarding those variables could not be done.

In conclusion, we have demonstrated that DM is an independent denominator for poor CVD both in patients with severe coronary artery stenosis and in patients with CTO.

Besides DM, female gender in menopause is the other negative predictor of poor CVD in patients with CTO.

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