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Predictors of Coronary Collateral Vessels at the Time of Primary Percutaneous Intervention: Is there any?

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Abstract

Background: Coronary collateral vessel development (CCV) is an adaptive response of the coronary vascular system to arterial occlusion and one of the most important mechanisms to salvage myocardium at risk. During the early phase of acute myocardial infarction (AMI), patients will show marked angiographic heterogeneity in collateral formation that is independent of the status of coronary artery occlusion. In our study we aimed to assess presence and confounders of CCV in the early setting of myocardial infarction with ST elevation (STEMI) in patients undergoing percutaneous coronary intervention.

Materials and Methods: Collateral artery grading was performed by using Cohen-Rentrop method to the culprit vessel with total occlusion. Patients with grade 0 collateral development were regarded as absence of collateral vessels and patients with grade 1, 2 or 3 collateral development were regarded as presence of collateral vessels. Age, gender, DM, hypertension, hyperlipidemia, smoking, pain-PCI time, family history of coronary artery disease, patients' medications, systolic blood pressure, were included in regression analysis.

Results: There were not statistically significant differences in terms of Diabetes Mellitus, hypertension, smoking, family history of coronary artery disease, gender, medications (nitrates, beta blockers, antiplatelets, renin-angiotensin system blockers, and statin).

Conclusion: We have not documented any parameters associated with development of CCV in the setting STEMI. Beyond the clinical or environmental factors contributing to formation of collateral vessel development, some patients seem to be unlucky or genetically are not prone to have a pre-existed arteriolar connection.

Keywords: Atherogenesis; Coronary artery disease; Coronary collateral blood flow; Collateral circulation; Collateral development

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Introduction

Coronary Collateral Vessel development (CCV) *i.e.* arteriogenesis has been intensively studied for several decades. Despite of our increased understanding of the cellular and molecular processes involved in collateral development, the mechanism underlying these large differences between individual patients in the extent and adequacy of collateralization remains unclear. It is an adaptive response of the coronary vascular system to arterial occlusion and one of the most important mechanisms along with angiogenesis to enhance regional perfusion in the chronically ischemic myocardium [1-3]. Coronary collateral vessel 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 [4-6].

After an acute occlusion of coronary artery, restoration of coronary blood flow through arteriogenesis takes a long time duration from days to weeks at four different stages. During the early phase of Acute Myocardial Infarction (AMI), patients will show marked angiographic heterogeneity in collateral formation that is independent of the status of coronary artery occlusion [7]. The sudden occlusion of an epicardial coronary artery result in a dramatic fall in coronary perfusion and creates a pressure gradient between the arteries proximal to the occlusion and distal from the occlusion, and this increases the blood flow through the preexisting arterioles [8]. In our study we aimed to assess presence and confounders of CCV in the early setting of myocardial infarction with ST elevation

Table 1: Clinical characteristics of patients.

Variables	Present CCV (n=40)	Absent CCV (n=74)	P value
Age	62±11	58±9	0.02
Gender	30(75%)	54(73%)	0.89
Smoking	18(45%)	40(54%)	0.81
Hypertension	16(40%)	23(31%)	0.36
Diabetes Mellitus	10(25%)	16(22%)	0.34
Hyperlipidemia	9(22%)	20(27%)	0.81
Pre-infarction angina	16(40%)	23(31%)	0.34
Nitrate	4(10%)	9(12%)	0.62
Beta-blocker	9(22%)	13(18%)	0.34
Statins	6(15%)	18(24%)	0.24
Renin angiotensin system blockers	13(32%)	21(29%)	0.95
Aspirin	12(30%)	18(24%)	0.34
Pain-PCI time	218 ±112	213±142	0.19
Sistolic blood pressure	121±32	115±14	0.84

CCV: Coronary Collateral Vessels; PCI: Percutan Coronary Intervention

(STEMI) in patients undergoing percutaneous coronary intervention.

Materials and Methods

The study population was recruited from the patients who underwent primary coronary intervention due myocardial infarction with ST elevation (STEMI). STEMI was defined as typical chest pain with ≥ 2 mm ST elevation in 2 contagious precordial leads or ≥ 1 mm ST elevation in other leads or new left bundle brunch block. One hundred and fourteen patients with STEMI comprised the study population. Patients with renal failure, malignancies and acute infections were not included in the study. Patients who had thrombolytic treatment or who underwent rescue PCI were not included in the study. Total and differential leukocyte counts and biochemical markers were obtained at admission. Total and differential leukocyte counts were measured by an automated hematology analyzer (Coulter Gen-S, COULTER Corp, Miami, USA). Pain-PCI time was defined as the time from onset of chest pain to first visualization of coronary arteries.

The following clinical and demographic 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), hypercholesterolemia (known treated hypercholesterolemia or serum total cholesterol concentrations higher than 200 mg/dl). Current cigarette smoking was defined as active smoking of at least 5 cigarettes per day within the past 12 months. Family history was considered as positive if a first-degree blood relative has had coronary heart disease or stroke before the age of 55 years (for a male relative) or 65 years (for a female relative).

Collateral vessel development grading

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. The number of the diseased vessels was identified according to the number of the major coronary arteries having ≥70% stenosis by eye-balling. Collateral artery grading was performed by using Cohen-Rentrop method to the culprit vessel with total occlusion [9]. Patients who had TIMI 1 or 2 flows distal to the culprit lesion were not included in the study. 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. Intra- and inter-observer variability of coronary collateral vessel grading was 2% and 3%, respectively. Patients with grade 0 collateral development were regarded as absence of collateral vessels and patients with grade 1, 2 or 3 collateral development were regarded as presence of collateral vessels.

Statistical analysis

Continuous variables were given as mean ± S.D.; categorical variables were defined as percentage. Continuous variables and categorical variables were compared by using unpaired t test and Chi-square test respectively. Logistic regression was used to analyze the possible association of cardiovascular risk factors and hematological variables with CCV. Age, gender, DM, hypertension, hyperlipidemia, smoking, pain-PCI time, family history of coronary artery disease, patients' medications, systolic blood pressure, 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

Forty (35%) of 114 patients had angiographycally visible CCV and seventy four (75%) had no CCV in the early setting of STEMI. The clinical, hematological and biochemical characteristics of the patients are shown in Table 1. There were not statistically significant differences in terms of Diabetes Mellitus, hypertension, smoking, family history of coronary artery disease, gender, medications (nitrates, beta-blockers, antiplatelets, renin-angiotensin system blockers, and statin). Patients who had angiographycally visible CCV were significantly older than those not having any CCV. However, logistic regression analysis revealed that none of the parameters showed significant association with the presence of CCV (Table 2).

Discussion

The severity of stenosis and the myocardial ischemic symptoms are the main driving forces that influence the development of coronary collaterals in patients with coronary artery disease [9-10]. Our understanding about the CCV is mostly based on the studies evaluating the severe stenosis or chronic total occlusion process. Collateral vessels occur briefly in 4 stages after an acute occlusion or severe stenosis of the coronary artery and it usually takes several weeks to months. After a silent phases of 2 days in which nothing happens in terms of blood flow increase, endothelial cells and smooth muscle cells turn into proliferative ones [11]. CCV developments takes place either through the maturation of preexisted arteriolar connections or through the capillaries recruiting smooth muscle cells named as denovo [11,12]. However during the acute occlusion of a coronary artery there is no time for arteriogenesis to salvage myocardium at risk. Collateral growth of an individual may vary from complete to absent during the early phase of AMI. So the preexisted collateral arteries if exists play a critical role during the early stage of myocardial infarction.

During the acute occlusion of coronary artery, majority of the

Table 2: Logistic regression analysis for the presence of coronary collateral vessels at the time of primary percutaneous interventions in patients with STEMI.

Variables	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Age	0.06	1.04	0.99	1.09
Gender	0.42	1.56	0.52	4.67
Smoking	0.24	0.59	0.24	1.43
Hypertension	0.41	1.53	0.54	4.3
Diabetes Mellitus	0.54	1.38	0.48	4
Hyperlipidemia	0.91	0.93	0.28	3.06
Pre-infarction angina	0.37	1.54	0.58	4.07
Family history	0.71	1.33	0.29	6.07
Nitrate	0.35	0.48	0.1	2.29
Beta-blocker	0.65	1.3	0.4	4.28
Statins	0.18	0.35	0.07	1.62
Renin-angiotensin system blockers	0.88	0.91	0.25	3.25
Aspirin	0.2	2.06	0.67	6.36
Pain-PCI time	0.81	1	0.99	1
Sistolic blood pressure	0.28	1	0.99	1.02

CI: Confidence Interval; PCI: Percutan Coronary Intervention

patients, approximately 65% of patients had lack of angiographically visible CCV. In contrast to chronic total occlusions or severe stenosis in which negative predictors of arteriogenesis have been documented, we could not demonstrate any clinical parameters associated with absence or presence of CCV during the early setting of STEMI. However 35% of patients had angiographycally visible CCV even after 3 hours of MI. Although CCV shear stress and factors such as monocytes VGEF-A main driving forces for arteriogenesis, it takes several weeks to months to establish a CCV [11]. Presence of CCV in the early setting of myocardial infarction suggests that these patients should have already pre-existed CCV which become visible or functional after sudden occlusion of coronary artery. The possible explanations are that [1] these patients might have long-term severe stenosis before the presentation of STEMI and so might had enough time to establish coronary collateral flow [2], these patients might have pre-existed arterio-arteriolar connection which became functional after acute occlusion.

Coronary collateral arterioles exist in the normal human hearts that are potentially able to save myocardium from necrosis. Seiler concluded that a well-trained normal human heart is able to survive an acute coronary occlusion with only minimal necrosis due to good collateralization [13,14]. Although capillaries may be able to recruit smooth muscle cell and that muscular collateral arteries can form denovo, pre-existent arteriolar connections exist that enlarge by growth in response to arterial occlusion, still stands today [12]. In fact, the significant variability of native collateral conductance in humans is well established [15]. Presence of collateral vessels in mice as different mouse strains show major differences with regard to the presence of collaterals [16-18]. The study by Chalothorn et al. [19], provides a potential explanation for the inter-individual variability of the presence of functional collateral vessels. The novel data from Chalothorn et al focus on differences in native collateral vessels. This refers to the process of creating arterio-arterial anastomoses during embryonic and early postnatal life in the absence of any existing pathology, a process described as vasculogenesis [20]. In conclusion we have not documented any parameters associated with development of CCV in the setting of STEMI. Beyond the clinical or environmental factors contributing to formation of collateral vessel development, some patients seem to be unlucky or genetically are not prone to have pre-existed arteriolar connections.

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