Journal of Disease Markers

Austin Publishing Group

Open Access Full Text Article

Research Article

Impacts of Established Cardiovascular Risk Factors on the Development of Collateral Circulation in Chronic Total Occlusion of Coronary Arteries

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Received: September 19, 2014; **Accepted:** September 24, 2014; **Published:** September 25, 2014

Abstract

Background: Presence and magnitude of coronary collateral circulation, as an adaptive mechanism has been shown to affect prognosis in patients with ischemic coronary artery disease. Thus far, the clinical determinants of the coronary collateral circulation were not well-established.

Objective: The objective of the study is to determine possible relationship between medical history, clinical findings and angiographic evidences of collateral coronary blood flow.

Methods: In an observational study, all patients who underwent coronary angiography for the first time with total occlusion in at least one coronary artery were participated in the study from February 2012 to February 2013. To determine the status of collateral flow, patients were divided into 4 groups according to Rentrop classification to detect possible factors that may influence collateral formation.

Results: A total of 52 patients met the inclusion criteria and entered the study. Statin therapy (67%), smoking (58%) and a positive family history (19%) were the most frequent findings. According to Rentrop classification, 7 (13.5%) patients were in grade 0, 17(32.7%) in grade 1, 21(40.4%) in grade 2, and 7(13.5%) were classified in grade 3 (Table1). There was significant association between myocardial performance and angiographic findings. There was no statistically significant difference between the grades for any of the risk factors (p value >0.05).

Conclusion: Although large epicardial or septal collateral vessels has been stated to become visible within two weeks after a complete occlusion of a major coronary vessel, our findings suggest that this vessel formation could not be related to medical history and clinical findings of patients.

Keywords: Collateral circulation; Coronary artery disease; Myocardial infarction; Angiogenesis

Introduction

Coronary artery disease (CAD) is the leading cause of death in the current century. Development of coronary collaterals in patients with CAD as an alternative source of blood supply has been hypothesized to decrease the infarct size, increase electrical stability, increase myocardial viability and ventricular function after acute and chronic coronary artery occlusion for future ischemic events. In fact, presence and extent of coronary collateral circulation have been shown to affect outcome of patients with CAD by reducing cardiovascular events [1-7].

There is a considerable variation of collateral formation in CAD patients. Thus , certain variables have been proposed to be related to the development of coronary collateral circulation such as patient's age, body mass index, gender, smoking status, history of diabetes mellitus, hypertension, hyperlipidemia, pre- infarction angina, use of beta-blockers, nitrates, antioxidants, angiotensin-converting enzyme inhibitors, serotonin blockers and alcohol consumption. This may explain considerable variability between the studies. There are few studies to report the same set of variables as predictors of collateral circulation [3-9]. Since the underlying molecular mechanism for collateral coronary vessel formation are not directly related to the clinical risk factors, there is still a need for well-designed studies with homogenous participants to show possible predictors of collateral circulation formation.

This prospective study tends to investigate impacts of established CAD risk factors as well as the effect of two common prescribed drugs on formation of coronary collateral circulation in patients with chronic total occlusion of the coronary artery.

Methods

Study participants

After approval of Ethics Committee of Shahid Beheshti University of Medical Sciences, this cross -sectional study was performed from February 2012 to February 2013 in the cardiac ward of Modarres hospital_ a training tertiary hospital, Tehran, Iran. All participants

Citation: Ansari ZA, Foroughi M. Impacts of Established Cardiovascular Risk Factors on the Development of Collateral Circulation in Chronic Total Occlusion of Coronary Arteries. J Dis Markers. 2014;1(3): 4.

Table 1: Distribution of patients with complete coronary occlusion based on demographic data; risk factors and the Rentrop classification.

Variable	Rentrop grade 3 (n=7)	Rentrop grade 2 (n=21)	Rentrop grade 1 (n=17)	Rentrop grade 0 (n=7)	P value
Smoking	4	13	9	4	0.23
Diabetes mellitus	1	5	6	1	0.76
Hypertension	3	12	6	5	0.34
Beta-blocker therapy	6	17	10	4	0.3
Obesity	2	8	2	2	0.27
Hyperlipidemia	2	8	7	6	0.11
Previous MI[α]	2	10	11	4	0.41
Statin therapy	4	13	12	6	0.62
Family history of premature CAD[β]	6	6	1	3	0.06
Male gender	1	4	2	1	0.94

[α]:Myocardial infarction, [β]:Coronary artery disease.

gave written informed consent. Study population consisted of patients being admitted with both elective and emergency condition for the first time coronary angiography. Coronary angiography was performed in the presence of acute coronary syndrome and in stable patients when non invasive tests were in favor of myocardial ischemia.

Chronic total occlusion in at least one of the three main coronary arteries was considered as an inclusion criterion. Chronic total occlusion was defined as 100% luminal diameter stenosis without a visible lumen and lack of antegrade flow. Patients with subtotal coronary occlusion and those who had acute occlusion were excluded.

Study variables

In this study positive history of smoking was limited to the current smokers. Patients would be assumed as hypertensive if their blood pressure was ≥140/90 mmHg on two separate readings, or if they were taking any antihypertensive medications. Obesity was defined as a body mass index of > 30 kg/m^2. Diabetes mellitus was defined as the presence of history of antidiabetic medication, or a fasting glucose level above 126 mg/dL. Patients were considered to have hyperlipidemia if their total cholesterol was ≥200 mg/dL, or if they were taking lipid-lowering medication. Previous history of documented myocardial infarction (MI) in patients and a positive family history of the premature CAD in their family members were carefully obtained. History of receiving two widely prescribed drugs including beta-blockers and statins was recorded.

Coronary angiography and grading of coronary collaterals

All patients underwent selective coronary angiography in multiple orthogonal projections by the Judkins technique. Angiograms were reviewed by an experienced cardiologist who was blinded to the study objectives. Presence and extent of the coronary collateral vessels were graded according to a visual assessment, the Rentrop scoring system: 0= no filling; 1= filling of the small side branches; 2 =partial filling of the epicardial artery by collateral vessels; 3= complete filling of the epicardial artery by collateral vessels [9, 10]. The same physician performed echocardiographic evaluation of the patients, while their angiographic data were masked.

Statistical analysis

Continuous data were expressed as mean± standard deviation and categorical data was given in number and percentage. Comparison of the continuous data between the two collateral groups (presence and absence of collateral circulation) was evaluated by independent samples t-test, if there was no normal distribution, via the Mann-Whitney U test. Categorical data were evaluated by a Chi-square or Fisher's exact test as appropriate. In this study p value < 0.05 was accepted as significant. All statistical analyses were carried out via SPSS version 20.0 for Mac OS (SPSS, Inc., Chicago, Ill, USA).

Results

Study subjects

A total of 52 patients met the inclusion criteria and were included in statistical analysis. Eighty-five percent of the participants were male with the mean age of 62.6 ± 9.9 years (39 - 84). Descriptive analysis of the clinical and demographic data in recruited patients revealed that positive history of previous treatment with beta-blockers (71%) and Statins (67%) were the most prevalent findings. Of the established risk factors of CAD, presence of smoking (58%), previous MI (52%), hypertension (50%), hyperlipidemia (42.5%), obesity (29%), diabetes mellitus (25%) and positive family history of CAD (19%) were shown to be present in our patients. The interval between MI and coronary angiography was from 3 months to 5 years. Results of the study indicated there was no statistically significant difference between males and females in terms of the presence of any studied risk factors (chi-square p>0.05 for all variables). Moreover, age distribution between the presence and absence of the risk factors was not statistically significant for any of the variables (Mann-Whitney U test p>0.05 for all risk factors).

Presence of collateral circulation according to rentrop classification

Results showed that in 7 patients (13.5%), there was no collateral flow (grade 0). Seventeen patients (32.7%) were classified as grade one, 21 patients (40.4%) had partial collateral flow (grade 2) and in 7 patients (13.5%), complete collateral perfusion was noted (grade 3). To understand possible association between the studied variables and collateral circulation formation, at the first stage of our analysis, coronary collateral were treated as a four-level variable. Table 1 summarizes status of each variable according to Rentrop classification. Left anterior descending artery was the most occluded artery in this population (Table 2). There was significant association between echocardiographic left ventricular ejection fraction (EF) and angiographic findings mean EF in grade 0:28%, grade1:46%, geade 2:51% and grade 3:53%, p value= 0.01.

Table 2: Distribution of coronary arteries with total occlusion.

Occluded coronary artery	Patients number
Circumflex	5
Right coronary	14
Left anterior descending	32
Left anterior descending+ Circumflex	1

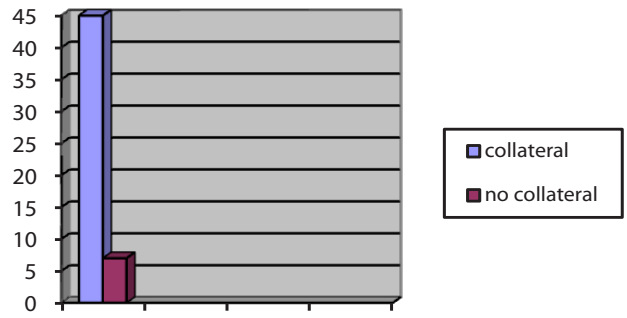

Figure1: Representation of total occluded vessels with and without collaterals.

Predictive factors for coronary collateral formation

At the second stage of analysis, presence of coronary artery circulation was treated as a binary variable. Rentrop grade 1, 2 and 3 were accepted as presence of collateral development (group 1, n= 45), and Rentrop grade 0 was accepted as no collateral development (group 2, n= 7) (Figure1). Table 3 shows baseline characteristics according to the presence of the coronary collaterals. History of hyperlipidemia is the only factor that shows statistically different proportion between those with collateral vessels and those who have not developed such arteries. However, when all variables entered a stepwise logistic model, no variable was shown to be independently able to (after adjusting for other variables in the equation) predict formation of collateral circulation (logistic model p-value>0.05). Patients in group2 had less myocardial function in the word of left ventricular ejection fraction (p value: 0.01).

Discussion

This study showed in a subgroup of CAD patients who have chronic total occlusion of at least one of the coronary vessels, none of the established cardiovascular risk factors could independently predict formation of collateral circulation. There are some explanations for this finding. The timing of collateral development is not clear. Moreover, it is difficult to determine the ischemia related collateral formation in patients with multivessel disease. Specific inclusion criteria of the current study revealed new results as compared to the previously published data in this area.

Coronary collateral circulation has been recognized as an alternative source of blood supply to the myocardial area jeopardized by ischemia [1- 7]. Determinants of collateral development are the duration of coronary occlusion and the extent of preserved regional myocardial function [6]. Arteriogenesis is the remodeling process involved in this recruitment of already existing collateral vessels. Key cells in this process are endothelial cells, pericytes (for capillaries) and smooth muscle cells (for larger vessels) [1, 7, 8, 11]. Complete obstruction of coronary artery leads to a decrease in post-stenotic pressure and redistribution of blood to preexisting arterioles. The consequent sheer force may lead to an increased expression of certain endothelial chemokines and growth factors that help angiogenesis.

Patients with coronary collateral had significantly more preserved myocardial function in our study. This finding is comparable with the results of Werner et al, who showed coronary collateral function is less in patients with impaired regional function [6].

Some studies hypothesized that stenosis greater than 75% is sufficient for the development of coronary collateral vessels [9]. This study only included patients who had chronic total occlusion in at least one coronary artery. This different inclusion criterion might be the key explanatory cause of different results of this study. Although variables in various studies that are believed to exert influence on coronary collateral formation are inconstant, most of the previous reports have shown at least one cardiovascular risk factor as an independent predictor of this new vessel formation. In a similar study, Tatli et al. showed coronary collateral vessel formation was negatively affected in obese patients, although statistical significance was not identified [5]. Kornowsky had shown that collateral grade is associated with hyperlipidemia and myocardial blush is negatively associated with diabetes mellitus [7]. He et al. suggested higher fasting glucose levels and lower estimated glomerular filtration rate are

Table 3: Distribution of the study variables between the two groups.

Variables	Group1 (n=45)	Group2 (n=7)	P-value
Age (mean ± sd)	62.8 ± 9.5	61.3 ± 12.6	0.70
Male gender (%)	38 (84.4)	6 (85.7)	0.71
Smoking (%)	26 (57.8)	4 (57.1)	0.64
Diabetes mellitus (%)	12 (26.7)	1 (14.3)	0.43
Hypertension (%)	21 (46.7)	5 (71.4)	0.21
Beta-blocker therapy (%)	33 (73.3)	4 (57.1)	0.32
Obesity (%)	12 (26.7)	3 (42.9)	0.32
Hyperlipidemia (%)	17 (37.8)	6 (85.7)	0.024
Previous MI$^{\alpha}$ (%)	23 (51.1)	4 (57.1)	0.54
Statin therapy (%)	29 (64.4)	6 (85.7)	0.26
Family history (%)	7 (15.6)	3 (42.9)	0.12
EF $^{\beta}$ (%)	46 ±10	28±7.5	0.01

$^{\alpha}$: Myocardial infarction, $^{\beta}$: ejection fraction

independent predictors of poor collateral circulation in CAD patients [10]. Negative effects of diabetes mellitus are also encountered in some other studies, while our study failed to address this negative association after adjusting for other factors [8, 10]. This inconsistency might be due to the small proportion of diabetics in our study. In a more recent study, Xi et al. found no significant differences between the good collateral group and poor collateral group when compared with left ventricular ejection fraction, age, severity of angiographic disease and other cardiovascular risk factors, except plasma B-type natriuretic peptide levels that had a strong independent association with collateral Rentrop score[12]. Mouquet et al was found no relationship between the use of cardiac drugs and collateral formation whereas Scicchitano et al showed Ivabradine could improve coronary blood flow and microvascular function [13-14].

There are certain limitations to this study that should be taken into account. It was a single center study and its relatively small sample size may lead to a few numbers of patients in each Rentrop group. Prospective nature of this study was considered as superiority over previous reports, but it has significantly affected the sample size. Further studies with a larger sample size should be conducted to delineate possible interaction of cardiovascular risk factors and formation of coronary collateral flow in under study patients. Moreover, to obtain a clear result, the duration of presence of each risk factor should be considered.

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J Dis Markers - Volume 1 Issue 3 - 2014
ISSN : 2380-0682 | www.austinpublishinggroup.com

Citation: Ansari ZA, Foroughi M. Impacts of Established Cardiovascular Risk Factors on the Development of Collateral Circulation in Chronic Total Occlusion of Coronary Arteries. J Dis Markers. 2014;1(3): 4.