Coronary collateral vessel development after acute myocardial infarction

Ersan Tatli MD, Armağan Altun MD, Mutlu Büyüklü MD, Ahmet Barotçu MD

E Tatli, A Altun, M Büyüklü, A Barotçu. Coronary collateral vessel development after acute myocardial infarction. Exp Clin Cardiol 2007;12(2):97-99.

OBJECTIVE: The aim of the present study was to assess the factors affecting collateral vessel development in patients with acute myocardial infarction.

METHODS AND RESULTS: Between May 2001 and April 2004, coronary angiography was performed on 74 patients following myocardial infarction. Only patients with total proximal occlusion in the left anterior descending coronary artery (LAD) or right coronary artery (RCA) in angiography were included in the study. Patients were separated into two groups according to the development of coronary collateral circulation (CCC). In group 1, CCC was inadequate (Rentrop 0, 1 and 2); and in group 2, CCC was adequate (Rentrop 3). Although CCC was adequate in 20 of 28 (71%) patients who had RCA occlusion (P=0.015), it was adequate in only 14 of 46 (30%) patients who had LAD occlusion (P>0.05). The presence of angina pectoris was positively correlated with the development of CCC (P=0.03). Diabetes mellitus (DM) was present in 14 of 40 (35%) patients with inadequate CCC and four of 34 (11%) patients with adequate CCC. The presence of DM was significantly higher in the group with inadequate development of CCC (P=0.017).

CONCLUSIONS: While DM was associated with an inadequate development of CCC, the presence of angina pectoris and RCA occlusion were associated with an adequate development of CCC.

Key Words: *Acute myocardial infarction; Coronary collateral circulation; Diabetes mellitus*

Coronary collateral vessels (CCV) are the remnants of the embryonic arterial system and develop under various stimuling factors. Normally, there are many anastomosing vessels that connect big coronary arteries to each other in humans. Many of these vessels are less than 200 µm in diameter and are the precursors of coronary collateral circulation (CCC).

CCV of patients with normal or mild coronary artery disease cannot be seen in coronary angiography because they are very small and carry an insignificant volume of blood. Coronary arteries must be occluded 99% or 100% for CCV to be visible (1). The most important stimulating factor in the development of CCV is the pressure gradient between normal and occluded vessel areas (2). This pressure gradient causes the opening of CCV by increasing the rate of blood flow in collateral circulation, activation of endothelium and stimulation of growth factors (3,4). In addition, there are important differences in ischemic heart disease for the collateral circulation development, and factors that create these differences are not clearly known (5).

The present study was designed to detect various factors that affect the development of CCV in patients with totally occluded single-vessel disease, detected by coronary angiography after myocardial infarction.

METHODS

Patient population

Between May 2001 and April 2004, 1236 patients who had coronary angiography performed in a hemodynamic laboratory were evaluated for the present study. Eighty-four of the 1236 patients who had acute myocardial infarction and total proximal occlusion in only the left anterior descending coronary artery (LAD) or the right coronary artery (RCA) were selected. However, of the 84 patients, seven were excluded from the study because of chronic obstructive pulmonary disease and three were excluded because of severe anemia; thus, 74 patients were included (49 men, 25 women) in the present study. All patients were receiving streptokinase infusion therapy. None of the patients had reperfusion criteria (ie, decrease in early ST elevation and reperfusion arrhythmia).

Body mass index (BMI), age, sex, hypertension (HT), diabetes mellitus (DM), smoking, preinfarction angina (PIA), time of coronary angiography after myocardial infarction, oral use of beta-blockers and nitrates were recorded for all patients. Development of CCV and coronary artery localization were scored by using angiographic analyses.

Coronary angiography and grading of coronary collateral filling

Coronary angiography was performed on all patients using Philips Multidiagnosis C2 (Phillips, Netherlands) with the techniques of Judkins or Sones. Cineangiographical timing was taken during left coronary angiography for the evaluation of coronary collateral flow. Pressures were recorded before and after injection of contrast material during left ventriculography. Collateral vessels were graded according to the Rentrop classification: 0, no filling of any collateral vessels; 1, filling of side branches of the artery to be perfused by collateral vessels without visualization of the epicardial segment; 2, partial filling of the epicardial artery by collateral

Department of Cardiology, Trakya University School of Medicine, Edirne, Turkey
Correspondence: Dr Ersan Tatli, Department of Cardiology, Trakya University School of Medicine, Edirne, Turkey.
Telephone 90-284-235-7641/2150, fax 90-284-235-7652, e-mail ersantatli@yahoo.com
Received for publication October 30, 2005. Accepted for publication June 8, 2006

TABLE 1
Comparison of baseline clinical variables for matched patients

Clinical variables	Group 1 (n=40)	Group 2 (n=34)	P
Age, years	56.30±9.42	57.80±9.10	0.720
Male, n (%)	27 (68)	22 (65)	0.260
Body mass index, kg/m^2	28.01±4.1	28.34±4.0	0.140
Smoking, n (%)	29 (73)	27 (79)	0.200
Hypertension, n (%)	19 (48)	18 (53)	0.400
Diabetes mellitus, n (%)	14 (35)	4 (11)	0.017*
Preinfarction angina pectoris, n (%)	17 (43)	24 (71)	0.003*
Beta-blocker, n (%)	11 (20)	13 (38)	0.510
Nitrate, n (%)	10 (25)	16 (47)	0.400

**Statistically significant. Data given as mean ± SD when appropriate*

vessels; and 3, complete filling of the epicardial artery by collateral vessels. The reproducibility of the Rentrop grading system has previously been validated (6). All angiographies were evaluated by two cardiologists who were unaware of the study. Patients in Rentrop grades 0, 1 and 2 were classified as group 1 (CCV development inadequate), and patients in Rentrop grade 3 were classified as group 2 (CCV development adequate).

Statistical analysis

Continuous variables were expressed as mean ± SD. The relation between the continuous variables was evaluated with the unpaired Student's *t* test. The χ^2 test with Yates' continuity correction was used to assess the differences between dichotomous variables. Correlations between collateral score and other variables were analyzed by logistic regression analysis. For all tests, P>0.05 was designated nonsignificant, and P<0.05 was considered to be statistically significant. SPSS version 10.0 (SPSS, USA) was used to perform all statistical calculations.

RESULTS

Of the 74 patients, 46 (62%) had total occlusion of the proximal LAD and 28 (38%) had total occlusion of the proximal RCA. CCV development was found to be inadequate in 40 patients (54%) and well developed in 34 patients (46%). Groups were compared with respect to sex, age, BMI, HT, DM, PIA, smoking and oral use of beta-blockers and nitrates over the six months before myocardial infarction. Age, sex, BMI, HT, smoking, oral use of beta-blockers and nitrates, and the time between myocardial infarction and coronary angiography were statistically insignificant (P>0.05).

Twenty-four patients had a history of using beta-blockers and 26 patients had a history of using nitrates. There was no statistically significant relationship between CCV development and the use of these agents (Table 1). Twenty-eight patients had inferior and right ventricular myocardial infarction and 46 had anterior myocardial infarction. CCV development was found to be adequate in 14 patients (41%) who had LAD occlusion and also 20 patients (59%) who had RCA occlusion (P<0.05) (Table 2). CCV development was adequate in 24 of 41 patients (71%) with PIA (P=0.03). Twenty-four of 40 patients (35%) in group 1 and four of 34 patients (11%) in group 2 had DM. DM was found significantly more in group 1, which had inadequate CCV development (P=0.017).

TABLE 2
Comparison of angiographic findings between group 1 and group 2 patients

Angiographic variables	Group 1 (n=40)	Group 2 (n=34)	P
LAD total occlusion, n (%)	32 (80)	14 (41)	0.680
RCA total occlusion, n (%)	8 (20)	20 (59)	0.015*
Coronary angiography time after myocardial infarction (mean days)	20.4±2.1	21.1±1.8	0.640

**Statistically significant. LAD Left anterior descending artery; RCA Right coronary artery*

DISCUSSION

In the case of severe occlusion, which prevents blood flow in big epicardial coronary arteries, CCC gains importance in maintaining perfusion to myocardial tissues beyond the area of occlusion. There are many studies (5,7) that show the importance of the pressure gradient between open and occluded coronary arteries.

When there is severe occlusion in a big coronary artery, the volume of blood circulating through anastomosing vessels increases because of the pressure gradient between two ends of small vascular structures, which connect distal parts of the occluded vessel to other coronary arteries. As a result, the CCC progressively dilates and becomes visible in angiography (6). Besides the pressure gradient, there are many other factors that affect CCV development.

Ischemia and CCC

A strong relationship was reported (8) between PIA and CCC in which myocardial ischemia plays an important role. This relationship correlates with the results of the present study. In another study (9), it was reported that CCC depends on living myocardial cells in areas of infarction and that these ischemic cells secreted chemical agents (angiogenin, fibroblast growth factor, prostaglandin E2, thrombocyte-derived growth factor, etc) that stimulate CCV development.

CCV develops over time after an acute myocardial infarction. Collateral resistance rapidly decreases and collateral flow reaches 90% of maximal capacity in the first four weeks after acute occlusion, and CCC can be seen angiographically (10). In the present study, the time between coronary angiography and acute myocardial infarction was nearly 20.1±1.6 days in all patients, and CCC was observed in all patients included in the study.

Antianginal drugs and CCC

Although nitrates do not directly stimulate CCV development, it was shown by Kass et al (11) that some antianginal drugs promote the development of CCV.

This correlation could be explained by the increased use of antianginal drugs in patients with ischemic symptoms (ischemia increases collateral growth and development) (12). We also observed that CCC was adequate in the presence of PIA but antianginal drugs did not independently contribute to CCC development.

Localization of coronary artery occlusion and CCC

In our study, CCV development was significantly better in patients with total occlusion of the proximal RCA than in

patients with total occlusion of the proximal LAD. Similar findings are previously reported by Banerjee et al (13) and explained the improved CCC development by the presence of more potential collateral vessels in RCA occlusion.

DM and CCC

There are contradictory results about the effects of DM on CCC. Although Heinle et al (14) reported that collateral circulation does not decrease in DM, Abaci et al (15) (angiographic method) and Nisanci et al (16) (intracoronary pressure measurement method) showed that collateral circulation was decreased in DM. We also observed that DM was present more commonly in group 1, in which CCC was inadequate, than in group 2. These results correlate with the study results of Abaci et al (15).

Chronic hypoxia, anemia and CCC

In animal experiments by Eckstein et al (17), anemia stimulated the development of CCV, and these collaterals were not seen after blood transfusions. In addition, it was shown that chronic hypoxia and exercise also stimulate CCV development (18). For these reasons, we excluded 10 patients from the study who had anemia or chronic hypoxia (chronic obstructive pulmonary disease).

In our study, factors such as age, sex, BMI, HT and smoking did not have a significant effect on CCV development. Although smoking increases CCV development (19), it could not be shown in our study.

CCV development is affected by many factors. Recently, animal studies showed that factors such as vascular endothelial growth factor, fibroblast growth factor, angiopoietin and prostaglandin growth factor stimulate natural CCV development (20).

Study limitations

In the interpretation of our findings, several limitations must be considered. First, the number of patients was restricted because of selecting completely occluded single-vessel patients for explicitly evaluating coronary collateral flow. This situation is the most important limitation of our study. Second, angiography may not detect most collaterals situated intramurally. Therefore, the collaterals visualized by angiography may not accurately quantify collateral circulation. But the effect of this problem on collateral score would be the same in the two groups and thus should not change the interpretation of our results. Third, we did not measure ejection fraction by echocardiography before angiography. Our clinic did not have enough equipment and experience in primary percutaneous transluminal coronary angioplasty; thus, we were not able to perform it. Finally, the present study is a retrospective, observational one. However, the angiographic and clinical data belong to the same period and come from the same laboratory without substantial changes in management strategy.

CONCLUSION

Although we know many of the factors that affect the development of CCV, there are still some areas that are unclear and which on-going studies will help to clarify. According to our results, DM is associated with inadequate development of CCV. The presence of parameters such as angina and occlusion in RCA are asscoiated with adequate development of CCV.

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