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Relation Between Preexistent Coronary Collateral Circulation and the Incidence of Restenosis After Successful Primary Coronary Angioplasty for Acute Myocardial Infarction

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Objectives. **The purpose of this study was to test the hypothesis that the incidence of restenosis after primary percutaneous transluminal coronary angioplasty for acute myocardial infarction is largely influenced by the preexistent coronary collateral circulation to the infarct-related coronary artery.**

Background. **The occurrence of restenosis after coronary angioplasty is the most serious limitation of this procedure. However, prediction of restenosis is difficult. Severe preexistent stenosis of the infarct-related coronary artery causing the development of collateral circulation may result in a high frequency of restenosis.**

Methods. **The study group consisted of 152 consecutive patients undergoing primary coronary angioplasty within 12 h after the onset of a first acute myocardial infarction. Of this group, 124 patients were angiographically followed up during the convalescent period of infarction and were classified into two groups according to the extent of preexistent collateral circulation to the infarct-related coronary artery.**

Results. **Restenosis occurred in 26 (38%) of 69 patients with poor or no collateral circulation (group A) in contrast to 35 (64%) of 55 patients with good angiographic collateral circulation (group B, $p < 0.005$). The frequency of preinfarction angina was significantly lower ($p < 0.05$) in group A (26% [18 of 69]) than in group B (44% [24 of 55]).**

Conclusions. **These findings indicate that the presence of well developed collateral circulation to the infarct-related coronary artery predicts a higher frequency of restenosis after primary coronary angioplasty. The difference in restenosis rates observed between the patients with and without good collateral circulation probably reflects the impact of underlying severity of stenosis on the long-term outcome after coronary angioplasty.**

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Although percutaneous transluminal coronary angioplasty is an established treatment for coronary artery disease, restenosis will develop over the ensuing 3 to 6 months in 30% to 50% of patients with successfully treated coronary lesions (1–3). Among numerous risk factors for restenosis, severe stenosis before angioplasty is frequently reported (4,5). Estimation of the extent of preangioplasty stenosis appears to be difficult in cases of primary angioplasty for acute myocardial infarction. In the present study, we hypothesized that the presence of high grade stenosis before angioplasty of the infarct-related coronary artery is associated with the presence of collateral circulation to the area perfused by the completely obstructed infarct-related coronary artery (6). Accordingly, we attempted to compare the restenosis rate between patients with and without well developed collateral circulation to the area perfused by the infarct-related coronary artery.

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Methods

Study group. This study group comprised 152 consecutive patients with a first acute myocardial infarction who underwent successful primary coronary angioplasty (residual stenosis ≤50%) for a complete occlusion of the infarct-related coronary artery (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0) within 12 h after the onset of symptoms. There were 110 men and 42 women; the mean age was 62 years. All patients had ≥30 min of chest pain accompanied by ST segment elevation ≥0.1 mV in two or more leads of the standard 12-lead electrocardiogram. There were no age restrictions, but patients with prior coronary angioplasty or bypass surgery, or both, were excluded.

Treatment protocol. All patients were given 10,000 U of intravenous heparin and transported promptly to the catheterization laboratory. A second 10,000-U bolus of heparin was administered intravenously after access was obtained. Coronary angiography was first performed on the non-infarct-related artery to evaluate the extent of collateral circulation to

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the area perfused by the completely occluded infarct-related artery. Angioplasty was performed in a routine manner with the use of appropriately sized angioplasty balloon catheters. Repeated balloon inflations were performed in an attempt to decrease the residual stenosis to ≤50%. Intracoronary urokinase at a dose of up to 480,000 U was permitted after angioplasty if there was definitive angiographic evidence of persistent intracoronary thrombus. A continuous intravenous infusion of heparin and nitroglycerin was given for 24 to 72 h after the procedure. Written informed consent was obtained from each patient.

End points. The primary end point of this study was angiographic restenosis, defined as stenosis >50% 6 months after an initially successful procedure.

Clinical variables. The presence or absence of a history of preinfarction angina before the acute infarction was documented. Preinfarction angina was defined as typical anginal chest pain occurring >1 week before the onset of acute myocardial infarction (7). A history of hypertension was defined as systolic pressure ≥160 mm Hg, diastolic pressure ≥95 mm Hg or currently treatment for hypertension. The diagnosis of diabetes mellitus was established on the basis of any one of the following three factors: history of taking insulin or an oral hypoglycemic agent, abnormal preinfarction fasting glucose levels (≥120 mg/100 ml) and positive results on a 75-g oral glucose tolerance test.

Coronary angiographic and procedural characteristics. The infarct-related artery, the severity of coronary artery disease and the extent of residual stenosis were determined with coronary angiography at the onset of acute myocardial infarction. We also documented complications related to the primary angioplasty procedure, such as coronary dissection, hemodynamic instability requiring the use of intraaortic balloon pumping, distal coronary embolism or no reflow phenomenon.

Follow-up coronary angiography was conducted by the Judkins technique in 124 patients 173 days (range 96 to 210) after the onset of acute myocardial infarction. Quantitative analysis of the percent lumen diameter stenosis of the infarct-related artery was performed by using a caliper on adequately magnified 35-mm cine frames at end-diastole in multiple projections. The projection showing the most severe coronary narrowing was selected.

Collateral circulation. Collateral circulation was graded on a scale of 0 to 3, depending on the degree of opacification of the occluded vessel. The score of the collateral index was based on the injection that best opacified the occluded vessel: 0 = no opacification; 1 = filling of side branches of the artery to be perfused by way of collateral vessels without visualization of the epicardial segment; 2 = partial filling of the epicardial segment by way of collateral vessels; and 3 = complete filling of the epicardial segment by way of collateral vessels (8).

Clinical follow-up. During the in-hospital convalescent period, aspirin, 81 mg orally, was administered daily. Oral calcium channel antagonists, nitrates and beta-adrenergic blocking agents were given at the discretion of the attending physician. Clinical events, including recurrent ischemia, reinfarction, death from all causes and treatment with repeat coronary angioplasty or bypass grafting, or both, were also recorded.

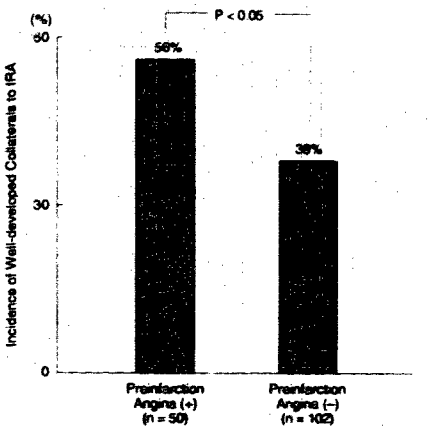

Figure 1. Incidence of well developed collateral circulation to the infarct-related artery (IRA) at the onset of acute myocardial infarction. Such circulation was more frequently observed in patients with (+) than without (−) preinfarction angina.

Patient subgroups. The 124 patients who underwent follow-up coronary angiography were classified into two major subgroups according to the extent of collateral circulation to the infarct-related artery at the onset of infarction. Group A comprised 69 patients without significant collateral perfusion (collateral index 0 or 1) and group B comprised 55 patients who had well developed collateral circulation to the infarct-related artery (collateral index 2 or 3).

Statistical analysis. Results are presented as mean value ± SD. Proportional data were analyzed by the chi-square test, with the Yates correction if one of the frequencies in the 2 × 2 contingency table was <5. Parametric comparisons were performed with use of the unpaired Student *t* test. Collateral index was compared with the Wilcoxon signed rank test. A backward elimination procedure in a multiple regression analysis was used to identify important predictors of restenosis at follow-up coronary angiography. Results were considered significant at the 5% critical level.

Results

Relation of preinfarction angina to collateral circulation. The incidence of well developed collateral circulation to the infarct-related artery at the onset of infarction was significantly higher in patients with than in those without preinfarction angina (56% vs. 38%, $p < 0.05$) (Fig. 1).

Classification of patients according to collateral circulation. Characteristics of the same 124 patients with follow-up angiography who did (group B) and did not (group A) have

JACC Vol. 27, No. 7
June 1996:1688–92

Table 1. Characteristics of 124 Patients With and Without Well Developed Collateral Circulation at the Onset of Acute Myocardial Infarction

	Group A: CI = 0, 1 (n = 69)	Group B: CI = 2, 3 (n = 55)	p Value
Age (yr)	62 ± 12	61 ± 12	NS
Male	45 (65%)	48 (87%)	< 0.05
Preinfarction angina	18 (26%)	24 (44%)	< 0.05
Hypertension	31 (45%)	23 (42%)	NS
Diabetes mellitus	19 (28%)	11 (20%)	NS
Cigarette smoking	49 (71%)	43 (78%)	NS
Total cholesterol (mg/dl)	200 ± 43	199 ± 43	NS
LAD	30 (43%)	30 (55%)	NS
Multivessel disease	27 (39%)	19 (35%)	NS
Residual stenosis >25%	14 (20%)	13 (24%)	NS
Coronary dissection	17 (25%)	8 (15%)	NS
IABP	6 (9%)	8 (15%)	NS
Distal embolism/no reflow	3 (4%)	8 (15%)	NS
Recurrent ischemia	18 (26%)	10 (18%)	NS
Reinfarction	3 (4%)	0 (0%)	NS
Death	1 (1%)	1 (2%)	NS
Repeat PTCA	17 (25%)	21 (38%)	NS
CABG	1 (1%)	8 (15%)	< 0.05
CI at follow-up coronary angiography	0.2 ± 0.6	0.4 ± 0.8	NS

Data are presented as number (%) of patients or mean value ± SD. CABG = coronary artery bypass grafting; CI = collateral index (see Methods for definition); IABP = intraaortic balloon pumping; LAD = left anterior descending coronary artery; PTCA = percutaneous transluminal coronary angioplasty.

well developed collateral circulation at the onset of acute myocardial infarction are summarized in Table 1. The two groups were well balanced with respect to all cardiovascular risk factors, coronary angiographic and procedural characteristics and clinical events during the follow-up period. Collateral index at follow-up coronary angiography was also comparable between groups. However, preinfarction angina occurred more frequently in group B patients with well developed collateral circulation than in group A patients. There was also a significant difference in male predominance between the two groups. The restenosis rate was significantly lower ($p < 0.005$) in group A (26 [38%] of 69) than in group B (35 [64%] of 55) (Fig. 2).

Classification of patients according to restenosis. Characteristics of the same 124 patients according to the presence or absence of restenosis at follow-up coronary angiography are shown in Table 2. Sixty-one (49%) of these 124 patients had restenosis of the infarct-related artery. Patients with restenosis had preinfarction angina more frequently than those without restenosis (48% vs. 21%, $p < 0.005$) and also had a higher collateral index at the onset of infarction (1.4 ± 1.0 vs. 0.9 ± 0.9, $p < 0.01$). They had a significantly higher frequency of residual stenosis >25% (31% vs. 13%, $p < 0.05$), and a greater incidence of recurrent ischemia (36% vs. 10%, $p < 0.005$). They also underwent coronary angioplasty or bypass grafting, or both, more frequently (angioplasty, 61% vs. 2%, $p < 0.005$; bypass grafting 14% vs. 0%, $p < 0.005$). Collateral index at follow-up coronary angiography was significantly higher in patients with than in those without restenosis (0.6 ± 0.9 vs. 0, $p < 0.01$); however, the two groups were comparable with respect to other variables.

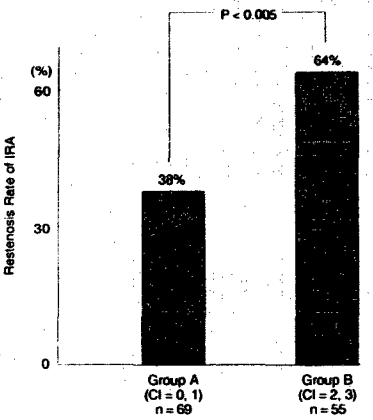

Figure 2. Rate of restenosis of the infarct-related artery (IRA). Restenosis occurred more frequently in patients with well developed collateral circulation. CI = collateral index (see Methods for definition).

Assessment of predictors of restenosis by multivariate analysis. Multivariate stepwise logistic regression analysis was performed on the 124 patients with repeat coronary angiography to identify predictors of restenosis. Variables examined

Table 2. Characteristics of 124 Patients With and Without Restenosis at Follow-Up Coronary Angiography

	With Restenosis (n = 61)	Without Restenosis (n = 63)	p Value
Age (yr)	62 ± 12	62 ± 11	NS
Male	47 (77%)	46 (73%)	NS
Preinfarction angina	29 (48%)	13 (21%)	< 0.005
Hypertension	31 (51%)	23 (37%)	NS
Diabetes mellitus	14 (23%)	16 (25%)	NS
Cigarette smoking	45 (74%)	47 (75%)	NS
Total cholesterol (mg/dl)	201 ± 46	200 ± 39	NS
CI at initial coronary angiography	1.4 ± 1.0	0.9 ± 0.9	< 0.01
LAD	31 (51%)	29 (46%)	NS
Multivessel disease	26 (43%)	20 (41%)	NS
Residual stenosis >25%	19 (31%)	8 (13%)	< 0.05
Coronary dissection	9 (15%)	16 (25%)	NS
IABP	9 (15%)	5 (8%)	NS
Distal embolism/no reflow	5 (8%)	6 (10%)	NS
Recurrent ischemia	22 (36%)	6 (10%)	< 0.005
Reinfarction	3 (5%)	0 (0%)	NS
Death	2 (3%)	0 (0%)	NS
Repeat PTCA	37 (61%)	1 (2%)	< 0.005
CABG	9 (14%)	0 (0%)	< 0.005
CI at follow-up coronary angiography	0.6 ± 0.9	0	< 0.01

Data are presented as number (%) of patients or mean value ± SD. Abbreviations as in Table 1.

Table 3. Characteristics of 152 Patients With and Without Follow-Up Coronary Angiography*

	With Follow-Up Coronary Angiography (n = 124)	Without Follow-Up Coronary Angiography (n = 28)
Age (yr)	62 ± 12	64 ± 12
Male	93 (75%)	17 (61%)
Preinfarction angina	42 (34%)	8 (29%)
Hypertension	54 (44%)	11 (39%)
Diabetes mellitus	30 (24%)	8 (29%)
Cigarette smoking	92 (74%)	19 (68%)
Total cholesterol (mg/dl)	201 ± 42	192 ± 47
CI at initial coronary angiography	1.0 ± 1.0	1.[illegible] ± 1.1
LAD	60 (48%)	11 (39%)
Multivessel disease	46 (37%)	9 (32%)
Residual stenosis >25%	29 (23%)	9 (32%)
Coronary dissection	25 (20%)	5 (18%)
IABP	15 (12%)	6 (21%)
Distal embolism/no reflow	11 (9%)	2 (7%)

*There were no significant differences between groups in any of the studied variables. Data are presented as number (%) of patients or mean value ± SD. Abbreviations as in Table 1.

were a) age (dummy coding for nominal variables <60 = 0, ≥60 = 1); b) gender (female = 0, male = 1); c) preinfarction angina (− = 0, + = 1); d) history of hypertension (− = 0, + = 1); e) presence of diabetes mellitus (− = 0, + = 1); f) history of smoking (− = 0, + = 1); g) serum level of total cholesterol (≤220 mg/dl = 0, >220 mg/dl = 1); h) collateral index at the onset of infarction (0, 1 = 0, 2, 3 = 1); i) infarct-related coronary artery (left circumflex or right coronary artery = 0, left anterior descending coronary artery = 1); j) presence of multivessel disease (− = 0, + = 1); k) residual stenosis (≤25% = 0, >25% = 1); l) coronary dissection (− = 0, + = 1); m) use of intraaortic balloon pumping (− = 0, + = 1); n) distal embolism or no reflow phenomenon, or both (− = 0, + = 1). This analysis revealed that the presence of preinfarction angina (r = 0.1700, p = 0.0083), higher collateral index at the onset of infarction (r = 0.1334, p = 0.0245) and more severe residual stenosis (r = 0.1876, p = 0.0046) were significant predictors of restenosis.

Clinical follow-up. Of 152 patients, 28 (18%) did not have repeat coronary angiography for the evaluation of restenosis of the dilated infarct-related artery. Fourteen patients refused repeat coronary angiography, and we could not get in touch with the remaining 14 patients. Patients with and without follow-up angiography were compared with respect to several variables, including collateral index at the onset of infarction (Table 3). No significant differences in these variables were observed between patients with and without repeat angiography.

Discussion

Previous studies. Urban et al. (9) showed, in an elegant study examining 100 vessels of 91 patients who had elective coronary angioplasty, that restenosis rate was significantly increased when coronary wedge pressure measured at the time of elective angioplasty was >30 mm Hg (52% vs. 23%). Probst et al. (10) also demonstrated that patients with angiographically demonstrable collateral circulation had a significantly higher incidence of restenosis than did those without such circulation (46% vs. 26%). Our data on the patients undergoing primary coronary angioplasty were quite in agreement with those just mentioned, although the rate of restenosis in our patients without collateral circulation was slightly higher than that in the earlier studies. The difference may be accounted for by the small number of patients in all three studies. A prospective study comprising a large cohort of patients may therefore be needed to conclude that the preexistent collateral circulation adversely influences restenosis of the dilated artery of patients undergoing primary balloon angioplasty for acute myocardial infarction.

Stenosis severity of the infarct-related coronary artery. In the present study, we presumed that angiographically demonstrable collateral circulation to the infarct-related coronary artery implies preexistent severe stenosis of the infarct-related coronary artery. This assumption is based on the important observations of Rentrop and colleagues (11). In their series of patients studied during elective coronary angioplasty, the magnitude of collateral circulation became greater as stenosis severity of the culprit lesion increased beyond 70% diameter narrowing, and collateral vessels could not be visualized in patients with a coronary stenosis of <70% narrowing. The higher frequency of preinfarction angina in this group of patients appears to support the linkage between the severity of stenosis and development of collateral vessels (7).

Mechanisms of restenosis. The precise mechanisms of restenosis after angioplasty are not clear. There are two possible explanations for the difference in restenosis rate between patients with and without collateral circulation. 1) Severe stenosis before angioplasty has been reported to be predictive of restenosis (4,5). In our group B patients who had the higher frequency of preinfarction angina and well developed collateral circulation, it is reasonable to assume that severe atherosclerotic stenosis already existed in the infarct-related artery at the onset of infarction. Because the restenosis process consists of an abnormal inward proliferation of intimal tissue as a result of balloon injury (12), it is logical that it would occur more frequently in lesions that had more severe stenosis initially. 2) The competitive collateral flow may negatively influence long-term results of angioplasty. A negative influence of competitive flow has also been demonstrated in the setting of coronary artery bypass surgery. Cashin et al. (13) reported on the fate of minimally obstructed coronary arteries that received bypass grafts. They found that perceptible progression of disease occurred within 3 years of bypass grafting in 38% of minimally diseased arterial segments in contrast to only 3% of comparable unbypassed coronary arteries.

Summary. The salient findings of our study are that 1) the patients with preinfarction angina had well developed collateral circulation to the infarct-related coronary artery more frequently than did patients without preinfarction angina; 2) the restenosis rate was significantly higher in patients with well developed collateral circulation at the onset of infarction than in those with poor or no collateral circulation; 3) the incidence of recurrent ischemia and revascularization procedure was significantly higher in patients with restenosis than in those without restenosis; and 4) the presence of preinfarction angina, well developed collateral circulation at the onset of infarction and more severe residual stenosis after successful primary coronary angioplasty were significant predictors of restenosis.

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