Multiple Coronary Angioplasty: A Model to Discriminate Systemic and Procedural Factors Related to Restenosis

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To assess the interrelation of clinical and procedural factors responsible for restenosis, 119 patients undergoing coronary arteriography were studied a mean of 5.8 ± 3 months after successful multiple percutaneous transluminal coronary angioplasty. In all clinical, angiographic and procedural variables, the 119 patients undergoing repeat catheterization were similar to the 87 patients that did not. Overall, restenosis occurred in 74 (34%) of 215 lesions. Sixty-three patients had no restenoses, 44 had at least one restenosis and 12 had restenosis at all angioplasty sites. The statistical distribution of restenosis did not follow a binomial model, suggesting that restenosis is more than a lesion-specific phenomenon.

Of all the clinical and procedural variables assessed by multivariate logistic regression analysis, only percent stenosis before angioplasty (p < 0.01), diabetes mellitus (p < 0.01) and percent stenosis after angioplasty (p < 0.05) were predictive of restenosis in the entire group. Patients with no restenoses and patients with restenosis at all sites were not different with respect to procedural variables; however, patients with restenosis at all sites more often (p < 0.05) had diabetes and recent onset angina. In contrast, patients with no restenoses differed from patients with isolated restenosis with respect to procedural variables: severity of stenosis before and after angioplasty, balloon/artery lumen ratio and maximal inflation pressure. Thus, procedural factors may be more related to isolated restenosis, but patient-related factors such as diabetes and recent onset angina may play a more important role in patients with multiple restenoses.

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Multivessel coronary angioplasty is now used to treat more patients (1,2), but restenosis remains the major limitation of the procedure. Medical trials to prevent restenosis have been disappointing (3), probably partly because of the multiplicity of recurrent-related factors. Balloon/artery lumen ratio (4), maximal inflation pressure (5-8) and stenosis after angioplasty (4,7,9) have been demonstrated to influence restenosis. Likewise, reports have suggested that diabetes mellitus (6,10), unstable angina (9) and hyperlipidemia (6) also play a role. However, the respective importance of these procedural and clinical factors remains undetermined.

An approach to assess the relative influence of systemic versus local factors would be to compare patients with multiple restenoses with patients with isolated restenosis after multiple coronary angioplasty. Thus, we tested the hypothesis that systemic or patient-related factors might be more common with restenosis at all sites, and that lesion-related or procedure-related factors might be more frequent in association with an isolated restenosis. The pattern of restenosis after multiple coronary angioplasty was also examined to determine whether it followed the expected binomial distribution.

Methods

Study patients. Between December 1981 and January 1986, 1,448 patients underwent a first elective coronary angioplasty at the Montreal Heart Institute. At least two lesions were dilated in 206 of these patients, who form our study group; primary success rate and complication rate in these patients have previously been published (11). Not included were patients who had a repeat procedure for restenosis or who underwent angioplasty of saphenous vein...
grafts or coronary angioplasty during acute myocardial infarction.

Angioplasty procedure. All dilated segments were studied prospectively by measuring arterial diameter proximal and distal to the stenosis to determine optimal balloon size. The degree of stenosis was measured with a caliper in the view showing the most severe stenosis and was expressed as a percent of luminal narrowing as compared with the closest normal segment. All measurements were made by an independent experienced radiologist. All angioplasty procedures were performed by way of a percutaneous femoral approach as previously described (4). Since April 1983, all angioplasty procedures were performed by way of a percutaneous femoral approach as previously described (4).

Follow-up. Coronary arteriography was recommended to all patients at 6 months but was done earlier in those with recurrent angina. The average time to angiographic follow-up was 5.8 ± 3 months after angioplasty.

Data analysis. Severity of angina was graded according to the Canadian Cardiovascular Society classification (13). Unstable angina was defined as angina of increasing severity, including pain at rest, or new onset angina (<1 month). Diabetes was diagnosed if the fasting blood sugar, measured in all patients, was >140 mg/dl or if insulin or oral hypoglycemic drugs were already prescribed. Intimal dissection was defined according to National Heart, Lung, and Blood Institute criteria (14). Primary angioplasty success was defined as a stenosis reduction >20% with a residual stenosis diameter <50% in the absence of major complications (electrocardiographic or enzymatic evidence of myocardial infarction or repeat catheterization after coronary angioplasty).

Medications. During the procedure, all patients received 5,000 U heparin. Administration of aspirin (650 mg/day) and dipyridamole (75 mg three times daily) was begun 1 day before angioplasty and continued for 6 months thereafter when the procedure was successful. Diltiazem (60 or 90 mg) was administered the evening before and the morning of angioplasty; in some patients, diltiazem was continued for 6 months (12).

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Restenosis was assessed using three definitions: 1) residual stenosis >50% of luminal diameter; 2) loss of ≥50% of the gain in vessel diameter achieved at angioplasty; and 3) increase >30% in the immediate postangioplasty stenosis.

Univariate analysis was performed with the chi-square test for categorical data and the unpaired t test for continuous variables. Multivariate analysis was performed by stepwise logistic regression to identify variables predictive of restenosis.

A chi-square goodness of fit test was employed to determine whether the restenosis data were compatible with a binomial distribution model (15). The binomial distribution defines the likelihood of an all-or-none event (that is, restenosis) occurring in a given number of trials (that is, angioplasty sites). The per lesion restenosis rate used in the model was 34% when restenosis was defined as residual stenosis >50% of luminal diameter (preceeding definition 1). This rate was derived from a nearly consecutive series of restudied patients who had undergone single vessel angioplasty at our institute during the same period as the study population. Only the 87 patients with two angioplasty sites successfully dilated were included in the binomial distribution model; separate models were not constructed for patients with three or more sites dilated because the numbers of patients in these groups were too small. A difference in the observed pattern of restenosis from that predicted by the binomial distribution implies that restenosis does not occur randomly but is influenced by patient-related factors.

Results

Incidence of restenosis. Two hundred fifteen lesions had been successfully dilated in the 119 patients with repeat catheterization. When defined by definition 2 (loss of ≥50% of the gain achieved), the restenosis rate was 38% (82 of 215). When defined as an increase in diameter stenosis >30% (definition 3), restenosis occurred in 66 lesions (31%). Restenosis defined as >50% diameter stenosis (definition 1) was present in 74 lesions (34%).

Statistical distribution. We tested the hypothesis that restenosis after double-lesion angioplasty followed the predicted binomial distribution (Fig. 1). The observed pattern of restenosis did not follow the expected distribution and the difference is statistically significant (p < 0.05).

Clinical, angiographic and procedural variables related to restenosis. Stepwise logistic regression analysis was performed on the 119 patients with repeat catheterization to identify restenosis-related factors (Table 2). In order of significance the factors were preangioplasty stenosis (p = 0.005), diabetes mellitus (p = 0.003) and residual stenosis (p = 0.046).

Our study group contained 12 patients (10%) in whom all dilated lesions developed restenosis. Seven of these patients had restenosis at both of two dilated sites, two patients at all of three dilated sites and three patients at all of four dilated sites. In 63 (53%) of the 119 restudied patients, all dilated lesions were patent at repeat catheterization. In the remaining 44 cases (37%), some lesions developed restenosis but others did not.

Diabetes mellitus and recent onset angina (≤1 month) were more frequent in patients with restenosis at all sites than in patients with no restenosis (Table 3). Among the 12 patients with multiple restenoses, 3 (25%) had diabetes versus 4 (6%) in the no restenosis group, and 5 (42%) had recent onset angina versus 9 (14%) of 63 (p < 0.05) in the no restenosis group. These two groups, however, did not differ with respect to any of the procedural variables listed in Table 3.

In contrast, the 44 patients with an isolated restenosis, when compared with the group without restenosis, had more severe lesions before angioplasty (79 ± 7% versus 69 ± 8%, p < 0.01), more severe stenoses after angioplasty (35 ± 3% versus...
versus 27 ± 8%, p < 0.01), a lower balloon/artery lumen ratio (p < 0.05) and higher maximal inflation pressures (p < 0.05). On the other hand, these two groups did not differ significantly with respect to any of the patient-related factors (Table 3).

**Discussion**

**Systemic factors influencing postangioplasty restenosis.** This study shows that restenosis after multiple coronary angioplasty does not follow the expected binomial distribution. Thus, the occurrence of restenosis at any site is not independent of the outcome of other lesions. This finding implies that systemic factors influence restenosis. By multivariate analysis, restenosis correlated with two procedural variables and one clinical variable, diabetes. In other studies, clinical factors such as diabetes (6,10), gender (5,9), smoking (6), dyslipidemia (6) and recent onset angina (5,6,9) have been associated with restenosis by univariate or multivariate analysis. The nonbinomial distribution of restenoses found in our study accented the potential importance of these systemic variables.

Systemic factors might be expected to be more evident in patients with restenoses at all sites and lesion-related or procedure-related factors more evident with isolated restenosis. Such a pattern was found in our study. Diabetes and recent onset angina were more frequent in the patients with restenosis at all sites. Patients with isolated restenosis and patients without restenosis did not differ with respect to clinical variables; however, procedural variables—severity of stenosis before and after angioplasty, balloon/artery lumen ratio and maximal inflation pressures—were significantly different in these two groups. These procedural variables did not distinguish patients with restenosis at all sites from those without restenosis. Myler et al. (6) also found that diabetes and a shorter duration of angina were more frequent in patients with restenosis at all sites. Hypercholesterolemia and smoking were also more prevalent in this group. Patients with no restenosis differed from patients with isolated restenosis with respect to procedural variables, as found in our study.

**Pathophysiology of restenosis.** The mechanisms whereby systemic factors contribute to restenosis are not known. Pathologic findings in patients who die after coronary angioplasty show a uniform proliferation of smooth muscle cells in the intima of the artery (16). Platelet-derived growth factors have been reported (17) to promote growth of cultured smooth muscle cells. Experimental studies (48,49) suggest that mural thrombus, platelet accumulation and release of platelet growth factors may be the predominant mechanisms causing restenosis. During unstable or recent onset angina, platelets release vasoactive substances, including growth factors (20). Likewise, proliferation of smooth muscle-type cells in the mesangium of the kidney in diabetic patients (21) bears some similarity to smooth muscle proliferation in restenosis. Ledet et al. (22) established that a factor capable of stimulating the proliferation of rabbit and human aortic smooth muscle cells is present in increased concentrations in
the serum of patients with non-normolipemic type I diabetes; this factor may be growth hormone (23). Furthermore, platelet abnormalities, including increased reactivity (aggregation and adhesion), spontaneous aggregation and diminished survival, were found in diabetics (24,25). Platelets from diabetic patients showed reduced prostacyclin production (26) and enhanced thromboxane A2 synthesis (27), a condition promoting platelet aggregation.

Limitations of the study. Only 64% of our patients with successful coronary angioplasty underwent repeat catheterization. Furthermore, more patients with than without recurrence of symptoms were restudied, probably biasing the restenosis rate. However, the main goal of this study was to examine the variables related to restenosis rather than to measure the rate of restenosis itself, and for this purpose the data are accurate.

All patients received aspirin and dipyridamole beginning 1 day before the procedure and continuing for 6 months thereafter. Although experimental work (28) suggested that antiplatelet agents influence restenosis, these drugs failed to reduce the rate of restenosis in two recent multicenter, double-blind, placebo-controlled trials (29,30) and were unlikely to have influenced the pattern of restenosis in our patients.

Conclusions. This study strongly suggests that multiple coronary restenoses after angioplasty are caused by patient-related factors. Under such conditions, interventions aimed at risk factor modification may be helpful. Isolated restenosis appears to be more influenced by procedural variables and thus may require a more mechanical solution, such as stents (31). These conclusions are speculative because the pathophysiologic mechanisms causing restenosis remain undefined.

References