Risk factors for recurrent stenosis following successful coronary angioplasty

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■ The major limitation of coronary angioplasty is recurrent stenosis. Patient, clinical, and procedural factors at the time of angioplasty were correlated with the presence or absence of angiographically documented recurrent stenosis or continued patency. Patients with single-vessel, multilesion disease had a lower incidence of recurrence than those with single-vessel, single-lesion disease (22.2% v 37.3%). Patients with multivessel disease had the highest rate of recurrent stenosis (45%). Sex and age did not predict recurrence. Patients with more severe symptoms, patients without prior myocardial infarction (MI), and insulin-dependent diabetic patients were more likely to have recurrent stenosis. Of the lesion variables, a severe stenosis or a low gradient before angioplasty, the absence of an intimal tear after angioplasty, and left anterior descending artery lesions correlated with a higher recurrence rate. Inflation times ≥30 seconds and a greater total number of inflations correlated with a higher recurrence rate. Multivariate analysis showed the following variables to be important predictors of recurrence: Canadian Heart Class, history of myocardial infarction, gradient before angioplasty, artery dilated, number of inflations, severity of stenosis before angioplasty, and insulin-dependent diabetes mellitus.
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RECURRENT stenosis after initially successful percutaneous transluminal coronary angioplasty (PTCA) is the greatest limitation of this technique. While the recurrent stenosis can be safely dilated and primary success rate is high,[1] the recurrent lesion may be more severe than the original lesion.[2] Thus, the possibility of recurrence restricts the indications for this method.

Two previous large studies[3,4] analyzed clinical data present at the time of initial angioplasty and attempted

to correlate demographic and procedural factors with recurrent stenosis. In the present study we used a computer database to analyze patient, procedural, and lesion factors present at initial angioplasty to see if any of these variables correlated with recurrent stenosis.

METHODS

There were 729 patients in this study and a total of 871 native vessel segments. Of these, 601 patients had single-vessel, single-lesion angioplasty. Due to a difference in defining recurrence in multivessel and multilesion cases, only patients with single-vessel, single-lesion disease were analyzed to determine factors associated with recurrence. These patients had a mean age of 56 years (range 30–80 years). Their PTCA procedures were

TABLE 1
LESION RECURRENCE RATE BY GROUP

	Single-vessel, single-segment	Single-vessel, multi-segment	Multiple vessels
Number of lesions with success	377	70	99
Number of lesions with recurrence	224	20	81
Total number of lesions	601	90	180
Recurrence rate (%)	37.3	22.2	45.0

TABLE 2
DEMOGRAPHIC VARIABLES AND RECURRENCE

Variable	Number at risk	Recurrence rate (%)	P
Age (years)			
≤40	28	39.3	.13
41–50	125	28.8	
51–60	228	38.2	
61–70	178	38.8	
>70	42	50.0	
Sex			
Female	144	33.3	.32
Male	457	38.4	

TABLE 3
RISK FACTOR VARIABLES BY RECURRENCE

Variable	Number at risk	Recurrence rate (%)	P
Canadian Heart Class			
Class I	57	25.0	.006
Class II	274	38.0	
Class III	112	41.1	
Class IV	57	56.1	
History of congestive heart failure			
No	542	36.9	.69
Yes	53	39.6	
Number of previous myocardial infarctions			
None	421	40.6	.009
≥1	180	29.4	
Number of previous revascularization surgeries			
None	536	36.4	.20
≥1	65	44.6	
History of hypertension			
No	374	35.8	.34
Yes	224	39.9	
History of hyperlipidemia			
No	507	36.0	.47
Yes	88	40.9	
Diabetes			
No diabetes	519	36.0	.04
Non-insulin-dependent	54	38.9	
Insulin-dependent	26	61.5	
Postmenopausal (women only)			
No	71	39.4	.16
Yes	71	28.2	
History of smoking			
No	199	40.7	.25
Yes	383	35.9	
If previous smoker			
Quit (>1 mo prior to PTCA)	220	37.3	.40
Still smoking	276	33.5	
Family history of coronary artery disease			
No	294	36.1	.55
Yes	307	38.4	
ECG results			
Normal	276	38.0	.76
Abnormal	323	36.8	
"Q" wave infarct			
None of possible	515	37.6	.62
Definite	86	34.9	

performed from December 30, 1980 to September 4, 1985. The data at initial PTCA and at recurrence were entered into the PTCA Registry and stored on a Vax 11/780 computer.

Lesions on follow-up angiography were measured in multiple projections and averaged. Recurrence in a lesion was defined as a loss of greater than 50% of initial gain if the site had been subjected to balloon angioplasty at the time of initial PTCA. Progression in uninjured vessel segments was not counted as a recurrence. Angiograms obtained at other institutions were mailed to the Cleveland Clinic for review and measurement. The interval between PTCA and restudy was at least one month.

The overall restudy rate (those with a follow-up angiogram) was 32.4% of 2253 procedures. The specific restudy rates were: 34.2% of 1758 procedures in single-vessel, single-lesion disease; 16% of 275 procedures in multilesion, single-vessel disease; 38.2% of 220 procedures in multilesion, multivessel disease.

The chi-square test was used to test for a difference between the recurrence rates for categorical variables. The two-sample t-test was used for continuous variables to compare the means in those with recurrence to the means in those with no recurrence. If a continuous variable had a highly skewed distribution, a nonparametric

Wilcoxon rank sum test was used instead of the t-test. Logistic regression was used to evaluate all factors simultaneously with regard to their association with recurrence or no recurrence.[5] A P value less than or equal to 0.05 was considered significant in all analyses.

RESULTS

The recurrence rate in patients with single-vessel, single-segment PTCA was 37.3% (*Table 1*). The recur-

TABLE 4
ANGIOGRAPHIC AND HEMODYNAMIC VARIABLES IN RELATION TO RECURRENCE

Variable	Number at risk	Recurrence rate (%)	P
Vessel			
Right coronary artery	189	21.5	<.0001
Left anterior descending artery (includes Dg)	306	45.1	
CFX	105	43.8	
Intimal tear			
No	406	39.7	.05
Yes	187	31.0	
Preoperative stenosis			
40–79%	239	31.8	.03
80–89%	149	36.9	
≥90%	213	43.7	
Postoperative stenosis			
<10%	120	38.3	.62
10–19%	169	37.7	
20–29%	180	35.0	
30–39%	90	34.4	
≥40%	35	48.6	
Preoperative gradient			
<40 mmHg	120	45.8	.04
≥40 mmHg	415	35.3	
Postoperative gradient			
<10 mmHg	294	35.7	.62
10–20 mmHg	156	39.0	
≥20 mmHg	72	32.9	
Morphology			
Concentric	281	35.9	.89
Eccentric	232	35.3	
Morphology			
Discrete	431	33.4	.27
Multiple	59	40.7	

TABLE 5
PTCA PROCEDURAL VARIABLES IN RELATION TO RECURRENCE

Variable	Number at risk	Recurrence rate (%)	P
Maximum inflation pressure			
<8 atm	55	45.5	.15
≥8 atm	444	37.2	
Maximum time of inflation			
<30 sec	152	30.3	.04
≥30 sec	196	40.8	
Number of inflations			
<5	246	33.7	.03
≥5	223	43.5	

A severe lesion, as judged by greater than 80% diameter narrowing, was more likely to recur ($P=.02$). However, a severe lesion as judged by pressure gradients, ie, a high initial pressure gradient (≥40 mmHg), was less likely to recur (35.3% v 45.8%, $P=.04$). Patients with intimal tears were also less likely to have recurrence (31.0% v 39.7%, $P=.05$).

Procedural variables are summarized in *Table 5*. Longer inflation times (≥30 seconds) are associated with a higher recurrence rate (40.8% v 30.3%, $P=.04$). A higher number of inflations was associated with a higher recurrence rate ($P=.03$).

Table 6 contrasts the three major studies of recurrent stenosis using angiographic criteria.[3,4] In order to assume that these patients are a representative cross-section of the total patient population, the study patients were contrasted with patients not undergoing follow-up angiography. Factors that differed significantly between the two groups are shown in *Table 7*.

All variables that were significantly associated with recurrence (*Tables 2–5*) were allowed as potential factors in a stepwise logistic model. A total of 347 persons with a complete set of data on all potential factors were analyzed by this method. The most significant factor was vessel location (right coronary artery v left anterior descending artery and circumflex). Terms in the final model that contained seven significant factors are given in *Table 8*. These results support the previous findings that many different factors are associated with recurrence. However, intimal tear, time of inflation, and lesion crossing time are no longer important in the presence of other factors. The odds ratio and its interpretation for each factor (expressed in terms of a positive association) are given in *Table 8* as well. An odds ratio measures the relative risk of recurrence in one group compared to another group. An odds ratio of 1.0 means the risk of recurrence is the same in the two

rence rate per lesion was 22.2% for single-vessel, multilesion PTCA and 45.0% in multivessel angioplasty. The majority of patients with multivessel disease (53/84, 63%) had angiographic recurrence at one or more sites, a higher recurrence rate than in patients with single-vessel, single-segment disease. The recurrence rate in single-vessel, multilesion PTCA would be expected to be higher than for single-vessel, single-lesion angioplasty if there were a positive association of recurrence at different segments within the same vessel. However, the above results show the reverse trend.

Demographic variables for single-vessel, single-lesion angioplasty are summarized in *Table 2*. Patient factors, ie, data gathered during the history and physical examination, are summarized in *Table 3*. Lesion factors, ie, factors obtained from the angioplasty images and from hemodynamic measurements, are summarized in *Table 4*. The most striking difference is that the recurrence rate in the right coronary artery (21.2%) is half the recurrence rate in the left coronary vessels (45.1%, $P<.001$).

TABLE 6
OVERVIEW OF THREE MAJOR STUDIES

	NHLBI	P	EMORY	P	Cleveland Clinic	P
Total patients restudied	557		998		731	
Single vessel, single segment	529		998		601	
Restudy rate	84%		54%		34%	
Recurrence rates by:						
Sex						
Female	22%	.01	25%	.08	33%	.37
Male	36%		32%		38%	
Duration of angina						
≤2 months	44%	.01	35%	.01	38%	.71
>2 months	29%		27%		37%	
Vessels dilated						
Right coronary artery	(110)N/A-NS		(262) 27%	.01	(189) 21%	<.0001
CS	(23)		(123) 18%		(105) 44%	
Left anterior descending artery	(373)		(613) 34%		(306) 45%	
Intimal tear						
Yes	N/A		26%	.7	31%	.05
No	N/A		32%		40%	
History of myocardial infarction						
Yes	(126) 26%	.05	N/A-NS		29%	.01
No	(412) 37%				41%	
History of diabetes						
Yes	(431) 47%	.05	N/A-NS		46%	.07
No	(496) 32%				36%	
Final gradient						
<20 mmHg	31%	.01	<15 mmHg 27%	.01	<10 mmHg 36%	.62
20–39 mmHg	41%		≥15 mmHg 38%		10-20 mmHg 39%	
≥40 mmHg	57%				≥20 mmHg 33%	

N/A-NS = not available but not significantly different.
N/A = not available.

groups being compared (eg, previous MI *v* no previous MI). For example, a person with no previous MI has a 2.14 times higher risk of having a recurrence than a person with a previous MI.

DISCUSSION

The actual recurrence rate in this study is unknown because of the relatively low restudy rate. Recurrence rate depends on restudy rate since those not restudied may have a different rate from those restudied. In general, studies with higher restudy rates tend to have a lower recurrence rate.[3] Definitions of restenosis vary; however, the definition used in this study, 50% loss of initial gain, is consistent with other large studies.[3,4] Holmes et al[4] contrasted four definitions of recurrent stenosis and found that the recurrence rates were similar regardless of the definition used.

The recurrence rate in multivessel disease is higher than that in single-vessel disease when one considers the recurrence of any stenosis as recurrence per patient. This is logical since multivessel disease is more extensive and more lesions are dilated. In this respect, Cleveland Clinic data conflict with a preliminary report from Emory University suggesting that recurrence rate is no higher in multivessel disease.[6] This issue should be studied carefully in a cohort with a high restudy rate. If recurrence rate is excessive in multivessel disease, then the cost-effectiveness of PTCA over coronary bypass graft surgery is seriously compromised,[7] particularly in centers where large numbers of internal mammary artery grafts are used.[8]

The failure to show any higher recurrence rate when multilesion, single-vessel cases were compared to single-lesion, single-vessel cases encourages the use of angioplasty in a vessel with more than one stenosis.

The findings in single-vessel, single-lesion angioplasty are similar to those in the two other large studies from the National Heart Lung Blood Institute (NHLBI)[4] and from Emory University[3] in many respects (*Table 6*). The two other studies have shown a higher recurrence rate among patients with a short duration of symptoms. The data from Emory also showed a higher recurrence rate among the patients with unstable angina. Our data do not confirm this.

Some differences between the major studies can be explained in part by equipment changes during the course of these studies. The NHLBI study was the earli-

TABLE 7
COMPARISON OF PATIENTS RESTUDIED AND NOT RESTUDIED (ONLY VARIABLES WITH <0.05 LISTED)

Variable	Restudied	Not restudied	P
Mean (±SD) age	56.3 ± 9.3	57.9 ± 9.2	<.001
% Number of inflations <5	52.5	67.4	<.0001
% Maximum time of inflation <30 seconds	43.7	25.8	<.001
Mean (±SD) postoperative stenosis %	18.3 ± 12.6	15.8 ± 13.8	<.001
Mean (±SD) preoperative gradient (mmHg)	46.4 ± 14.1	49.7 ± 15.7	<.001

TABLE 8
LOGISTIC MODEL (n=347)

Variable	Coefficient	S.E.	P	Odds ratio
Canadian Heart Class				1.52
(I v II)	−0.21	0.19	.03	1.79
(I v III)	0.29	0.23		3.00
(I v IV)	0.55	0.26		
Number of myocardial infarctions (none v ≥1)	0.38	0.14	.007	2.14
Preoperative gradient (mmHg) (<40 v ≥40)	−0.37	0.15	.01	2.10
Artery (RCA v LAD and CFX)	0.68	0.15	<.0001	3.90
Number of inflations (<5 v ≥5)	0.31	0.12	.01	1.86
Preoperative stenosis				
(40–79% v 80–89%)	0.22	0.18	.007	1.49
(40–79% v ≥90%)	0.30	0.17		1.82
Insulin dependent (yes v no)	−0.61	0.31	.04	3.39

Categories at Risk

Canadian Heart Class II has 1.52 times higher probability of recurrence than Class I, Class III has 1.79 times higher chance than Class I, and Class IV has 3 times higher risk than Class I.

Patients with no myocardial infarction have 2.14 times higher risk than patients with myocardial infarction.

Preoperative gradient <40 mmHg has 2.10 times higher chance of recurrence than preoperative gradient ≥40 mmHg gradient

Left anterior descending artery and circumflex combined has 3.90 times higher risk of recurrence than right coronary artery.

Number of inflations ≥5 has 1.86 times higher probability of recurrence.

Preoperative stenosis 80–89% has 1.49 times higher chance of recurrence than 40%–79%, ≥90% has 1.82 times higher chance of recurrence than 40%–79%.

Preoperative stenosis ≥90% has 1.82 times higher probability of recurrence than 40%–79%

Insulin-dependent diabetics have 3.39 times higher chance of recurrence than non-insulin-dependent diabetics or non-diabetics.

est, the Emory study next, and the current study the last. During this time, smaller balloons with smaller lumens and more balloon sizes became available.

The NHLBI study and early analysis of the Emory data[9] showed that men were more likely than women to have recurrence. Later analysis of the Emory data showed these differences to be less striking.[3] Our study showed no significant differences in recurrence rates by sex. As mentioned earlier,[3] balloon sizes were limited in early studies to 3 mm diameter. This may well have been too small for many arteries in men and too large for some arteries in women. A larger balloon-to-distal artery ratio has been shown to affect recurrence rates favorably.[10,11] When the PTCA procedures from our study were done, beginning in 1983, there were a variety of balloon sizes available, including 3.7- and 3.5-mm balloons that were more appropriate for larger arteries.

Both earlier large studies documented a lower recurrence rate in patients with a lower residual gradient after PTCA. Our study failed to demonstrate these differences. This may be because residual gradient is no longer important or because our measurement of residual gradient was not as accurate. Mean residual (post-procedure) gradient was not available for the NHLBI patients; the mean residual gradient in the Emory group was 12 mmHg and in our study was 9.3 mmHg. The standard deviations among studies were also similar, 7–8 mmHg. The lower mean residual stenosis might have negated the earlier effect. However, most of the Emory patients had PTCA before the introduction of low-profile catheter, so that the lumen was compromised. Most of the patients in the current study had their PTCA procedures after the introduction of low-profile balloons. The smaller lumen collapses around the guidewire and

yields less reliable measurements. This means that lower-profile systems would give a less reliable pressure gradient, which in turn would yield less predictive information. Indeed recent studies comparing residual gradients with digital subtraction angiography and intracoronary flow reserve using Doppler flow probes show little correlation with recurrence.[12] Thus, residual gradient assessed with lower-profile catheters is no longer predictive of recurrent stenosis when efforts are made to lower mean residual stenosis to less than an average of 9 mmHg.

The residual diameter was predictive of recurrent stenosis in the NHLBI study and in the Emory study. The lower the residual stenosis, the less likely was recurrent stenosis. Our study fails to confirm these results. Differences between studies due to differences in measurement are unlikely since our study and the Emory study used the same method of measurement. The mean (±S.D.) residual stenosis in the Emory study was 24% ± 13% compared to 18% ± 13% in our study. These differences among such a large number of patients are no doubt significant and may well explain the differences in results. When the average initial result is better, residual stenosis may well be of less value in predicting recurrence.

Both the Emory study and this study have shown that right coronary artery obstructions are less likely to recur. Reasons for this are uncertain, but it may be due to intrinsic differences between the right and left coronary arteries. Intimal tear was also associated with a lower recurrence rate in the Emory study and our study but not in the NHLBI study. Intimal tearing, however, is associated with a higher initial complication rate[13]; thus it has both advantages and disadvantages.

Drug therapy—antiplatelet agents and calcium channel blockers before, during, and after PTCA—was standard, and this study offers no information as to their value.

Clinical risk factors did not correlate with recurrence except for insulin-dependent diabetes mellitus. The Emory study did not show diabetes to be a risk factor for recurrence but the NHLBI study did. Excess risk for recurrence in diabetic patients in our study was confined to insulin-dependent diabetes. Others have also reported this correlation.[14] No attempt was made to correlate recurrence with degree of control of blood glucose levels. Perhaps improved glucose control during the months following PTCA would lower recurrence rates in insulin-dependent diabetic patients.

Other risk factors showed no correlation with recurrent stenosis in any of the three large studies. (This does not mean that risk factor modification during the healing period following PTCA is of no value in preventing recurrence.) All studies assessed the effect of the presence of risk factors at the time of PTCA on recurrence. A recent report[15] has shown that continued cigarette smoking after successful PTCA is associated with a higher recurrence rate. If this is true, perhaps lower cholesterol may also lower the probability of recurrent stenosis. Certainly a history of hyperlipidemia or history of increased cholesterol at the time of initial PTCA is a very inexact way to look at the effect of this potentially powerful risk factor.

A history of MI was predictive of nonrecurrence in both the NHLBI study and our patients. The reason is not obvious, but since all patients underwent PTCA for a single significant stenosis, MI may be a marker for disease that has been present for a longer period of time. This would imply that older lesions were less likely to recur.

Severity of stenosis as assessed by percent stenosis before PTCA and gradient before PTCA at first appear to be paradoxical. More severe lesions, as measured by diameter narrowing, were more likely to recur while lesions with lower initial gradients were more likely to recur. This apparent contradiction can perhaps be resolved by realizing that, in reality, initial gradient is the mean blood pressure at the guiding catheter minus the mean blood pressure at the balloon tip prior to any inflations. In most cases lesions are severe enough so that the balloon in fact totally occludes the artery; thus, the initial distal pressure represents balloon occlusion pressure. If one assumes the mean initial proximal pressure is the same for both recurrence and nonrecurrence groups (suggested by the fact that hypertensive and nonhypertensive patients were equally likely to have recurrence), then differences in initial pressure gradients must be due to differences in distal pressures. If this pressure is relatively high, as it frequently is with subtotal obstruction and the development of collaterals, then the initial gradient will actually be lower despite a more severe diameter narrowing. A higher balloon occlusion pressure is associated with a higher recurrence rate.[16] This observation is also in keeping with a higher recurrence rate in patients undergoing PTCA for total occlusion.

Canadian Heart Class showed a significant correlation with recurrence, however, conclusions must be guarded since the restudy group is not representative of the total group of patients on this factor.

Procedural variables are the easiest to manipulate since they can be operator-controlled. Longer inflation times and greater number of inflations were associated

with a higher recurrence rate. While this would seem to contradict reports that longer inflation times have a favorable effect on recurrence, it must be remembered that no attempt to control inflation time was made in our study. More inflations and longer inflation times might well have been used by the operator to improve an otherwise poor result. Determining optimal procedural variables will require a prospective randomized trial.

CONCLUSIONS AND CLINICAL IMPLICATIONS

This is the third large study of the effect of variables present at the time of initial PTCA on recurrent steno-

sis. Multivessel disease appears to have a higher recurrence rate, and thus should be approached more conservatively. Right coronary lesions and intimal tearing are associated with lower recurrence rates. Obtaining the best initial result is probably important for lower recurrence rates, but, as better equipment has allowed better initial results, the importance of this variable has lessened. Insulin-dependent patients are more likely to have recurrence. It would seem reasonable to make special efforts to optimize glucose control during the months following PTCA. The effects of risk factor modification after successful angioplasty have yet to be studied.

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