Recurrent Ischemia More Than 1 Year After Successful Percutaneous Transluminal Coronary Angioplasty
An Analysis of the Extent and Anatomic Pattern of Coronary Disease

Randy K. Bottner, MD, FACC, Curtis E. Green, MD, FACC, Carolyn J. Ewels, BS, Evelyn Recientes, BS, Geoffrey A. Patrissi, MA, and Kenneth M. Kent, MD, PhD, FACC

Of 1,181 consecutive patients who underwent successful percutaneous transluminal coronary angioplasty (PTCA) as an initial revascularization procedure and who had at least 1 year of asymptomatic follow-up, 66 (6%) underwent repeat angiography because of recurrent symptoms or evidence of exercise-induced ischemia. Patients who had revascularization procedures within 1 year of PTCA were not included in the analysis. Mean time to recurrent ischemia was 30.8±17.4 months (range 12–89 months). At follow-up, 47 patients had angina, 13 had atypical chest pain, two had acute myocardial infarction, and four had positive exercise tests without symptoms. No patient showed spontaneous regression in the extent of coronary artery disease (CAD). As compared with the extent of CAD immediately after PTCA, the extent of CAD at follow-up did not change in 26 patients (39%); it increased by one vessel in 30 (45%), by two vessels in seven (11%), and by three vessels in three (5%). The pattern of CAD seen at follow-up compared with that seen after PTCA was as follows: 18 patients (27%), no change; seven (11%), restenosis only; 30 (45%), progression of CAD at other sites only; and 11 (17%), a combination of restenosis and progression of CAD at other sites. The time to recurrence of ischemia was significantly different between those with restenosis only versus those with progression only (20.1±9.2 vs. 38.3±18.5 months) (p<0.009). Progression of CAD was equally distributed between dilated and nondilated vessels; however, when progression occurred in the PTCA vessel, it was significantly more likely to be distal to the PTCA site (p<0.008). (Circulation 1989;80:1580–1584)

Percutaneous transluminal coronary angioplasty (PTCA) is an effective alternative to coronary artery bypass grafting (CABG) as a method of coronary revascularization in selected patients. Both procedures alleviate signs and symptoms of ischemia in the majority of patients.1–3 Neither CABG nor PTCA, however, alter the progressive nature of the atherosclerotic disease process. Thus, it is expected that after either of these palliative procedures, recurrent signs or symptoms of ischemia will develop in some patients. Recurrent ischemia within 6 months of PTCA occurs in up to 40% of patients and is usually due to restenosis.4–7 Recurrence of ischemia beyond 6 months is usually due to progression of coronary artery disease (CAD) at other sites,8 but the extent and pattern of CAD in patients with late recurrent ischemia after PTCA has not been rigorously assessed. To more fully understand the long-term implications of PTCA as a revascularization strategy, we have analyzed a consecutive group of patients who underwent PTCA as an initial revascularization procedure and who developed recurrent evidence of ischemia after a prolonged asymptomatic period.

Methods
Consecutive patients undergoing PTCA from February 1979 until April 1987 were screened retrospectively to identify all patients who met the following criteria: 1) successful PTCA, 2) no prior CABG or
PTCA, 3) recurrent evidence of myocardial ischemia after a symptom-free interval of 1 year or more, 4) no revascularization procedures within 1 year of PTCA, and 5) angiographic follow-up.

Angiograms before and after PTCA were evaluated by two or more experienced PTCA technicians, cardiac angiographers, or cardiac radiologists. Lesion severity was calculated by manual caliper measurement, averaging the percent reduction of luminal diameter in two orthogonal views in comparison with adjacent "normal" segments in the artery. Significant disease was defined as more than 50% luminal diameter stenosis. The extent of CAD was defined as one-, two-, or three-vessel disease if a significant stenosis involved any portion of the body or a significant branch of a major epicardial vessel.

Equipment used to perform the PTCA was standard for the time at which the procedure was performed. The medical regimen employed after PTCA varied to some degree over this 8-year period; however, most patients received aspirin, dipyridamole, and a calcium channel blocker. Because of the nature of the practice, many patients received follow-up care by the referring physician. Exercise testing and cardiac catheterization were performed at 6 months in 64 and 28 patients, respectively. Of the 28 patients who had 6-month angiography, 21 underwent routine cardiac catheterization as participants in the two phases of the National Heart, Lung, and Blood Institute PTCA Registry or as determined by the referring physician, and seven underwent cardiac catheterization based on exercise test results.

All patients were contacted by phone on an annual basis to determine symptomatic status, intervening coronary events (e.g., hospitalization, myocardial infarction, death), or revascularization procedures. The details of interim exercise tests, cardiac catheterizations, or intervening coronary events were obtained from the referring physician. Angina was considered present if a symptom complex similar to that before PTCA recurred. Atypical chest pain was defined as the occurrence of a chest pain syndrome that was different from that before PTCA. A positive exercise tolerance test in an asymptomatic patient was defined as 1 mm or more ST depression (horizontal or down-sloping) from the ST segment baseline. On development of evidence of recurrent ischemia, all patients underwent angiographic restudy.

Restenosis was defined as either a recurrent stenosis more than 50% at the PTCA site or as a loss of 50% of the gain achieved by PTCA. The morphology of the restenotic lesion was characterized as discrete (less than 1 cm in length), tubular (more than 1 cm in length), complex (ulcerated or eccentric), or occlusive.

Progression of CAD was defined as an increase of at least 20 percentage points since PTCA was performed and a stenosis severity more than 50% at follow-up. Progression was characterized as to whether it involved the dilated vessel or a nondilated vessel. When progression occurred in the dilated vessel, it was further categorized as to whether it was proximal or distal to the PTCA site.

Data were analyzed with standard statistical techniques. Categorical variables were analyzed with a two-tailed Fisher’s exact test or χ² analysis. Continuous variables were analyzed with the Mann-Whitney U test. An α level of 0.05 was considered to be significant.

**Results**

Of 1,181 patients who underwent at least one successful PTCA procedure, 66 (5.6%) met the inclusion and exclusion criteria for the present study. Fifty (76%) were men, similar to the gender distribution of the initial cohort. The average age at the time of the index PTCA was 52.9±9.8 years (range, 34–78 years). One-vessel PTCA was performed in 60 patients (91%) and two-vessel PTCA in six (9%).

Sixty-four patients (97%) underwent routine exercise testing at 6 months after PTCA. Exercise tests were negative in 57 patients, positive in two, and equivocal in five. Cardiac catheterization was performed in 28 patients 6 months or more (range, 6–10 months) after PTCA, either as a routine part of follow-up or as guided by exercise test results. No patient demonstrated progression of CAD or restenosis at this time.

At a mean follow-up time of 30.8±17.4 months, typical angina recurred in 47 patients (71%), 13 (20%) had atypical chest pain, four (6%) were asymptomatic but had positive exercise tests, and two (3%) presented with new infarctions.

Table 1 compares the extent of CAD before PTCA with that immediately after PTCA. At entry, 37 patients had one-vessel disease, 23 had two-vessel disease, and six had three-vessel disease. After PTCA, 39 patients had no significantly diseased vessels, 19 patients had one-vessel disease, and eight patients had two-vessel disease. Six patients (four with one-vessel disease and two with two-vessel disease at the time of PTCA) had undilated, significantly diseased branch vessels (i.e., more than 50% luminal diameter stenosis) after dilation of the main epicardial vessel, accounting

<table>
<thead>
<tr>
<th>Diseased vessels at entry</th>
<th>Patients (n)</th>
<th>Diseased vessels after percutaneous transluminal coronary angioplasty (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>37</td>
<td>33 4 0 0</td>
</tr>
<tr>
<td>Two</td>
<td>23</td>
<td>6 15 2 0</td>
</tr>
<tr>
<td>Three</td>
<td>6</td>
<td>0 0 6 0</td>
</tr>
</tbody>
</table>
for the apparent lack of change in the number of diseased vessels in these six patients.

Table 2 compares the extent of CAD after PTCA and at follow-up. Fifteen patients had no vessels with significant stenoses, 21 had one-vessel disease, 22 had two-vessel disease, and eight had three-vessel disease. No patient demonstrated spontaneous regression of CAD. The extent of CAD did not change in 26 patients (39%); it increased by one vessel in 30 (45%), by two vessels in seven (11%), and by three vessels in three (5%).

When evaluated as a function of the manifestation of recurrent ischemia, the average change in extent of CAD from immediately after PTCA to follow-up was 0.96±0.80 vessels per patient for patients with recurrent angina, myocardial infarction, or asymptomatic positive exercise tests versus 0.15±0.36 vessels per patient for patients with atypical chest pain (<0.0004).

Table 3 demonstrates the pattern of CAD found at follow-up. No change in anatomy was found in 18 patients (27%), 10 of whom presented with atypical chest pain. In seven patients (11%), restenosis was the only change in anatomic pattern from immediately after PTCA; 30 (45%) manifested progression of CAD in one or more vessels without restenosis; and 11 (17%) demonstrated a combination of restenosis and progression of CAD. The average time to evidence of recurrent myocardial ischemia for the entire group was 30.8±17.4 months (range, 12–89 months). In patients with no change in coronary anatomy, the time to evidence of recurrent ischemia was 25.1±14.7 months; in patients with restenosis only, the time to recurrence was 20.1±9.2 months; in patients with progression of CAD only, the time to recurrence was 38.3±18.5 months. In patients with both restenosis and progression of CAD, the time to recurrence was 26.8±12.8 months. The difference in time to recurrence between those with restenosis only and those with progression of CAD only was significant (<0.009).

Figure 1 demonstrates the distribution of new disease for the 41 patients with progression of CAD. In nine patients (22%), progression involved the dilated vessel only, in 23 (56%) a nondilated vessel only, and in nine (22%) both the dilated vessel and a nondilated vessel. Progression occurred in 18 of 72 dilated vessels (25%) and 36 of 119 (30%) nondilated vessels (p=NS). In the 18 patients with progression of CAD involving the dilated vessel, progression occurred proximal to the PTCA site in three (17%) and distal to the PTCA site in 15 (83%) (<0.008).

In the 18 patients with restenosis at follow-up, 14 (78%) had a negative exercise test, one (5%) had a positive exercise test, and two (11%) had equivocal exercise tests at 6 months. Eight of these patients, including all three with equivocal or positive exercise tests, underwent repeat coronary angiography within 3 months of the exercise test without evidence of restenosis. The morphology of the restenotic lesion was discrete in nine patients (50%), tubular in five (28%), complex in one (5%), and totally occlusive in three (17%). In only one of the three patients with total occlusion was angiography performed at 6 months.

Table 4 lists the therapy used after follow-up. In the seven patients with restenosis only, five had successful repeat PTCA, one had unsuccessful repeat PTCA followed by elective CABG, and one was treated medically. In the 30 patients with progression of CAD only, 15 had successful PTCA of a new

<table>
<thead>
<tr>
<th>Disease vessels after percutaneous transluminal coronary angioplasty</th>
<th>Patients (n)</th>
<th>Disease vessels at follow-up (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>39</td>
<td>15 15 6 3</td>
</tr>
<tr>
<td>One</td>
<td>19</td>
<td>0 7 11 1</td>
</tr>
<tr>
<td>Two</td>
<td>8</td>
<td>0 0 4 4</td>
</tr>
</tbody>
</table>

**Table 3. Pattern of Coronary Artery Disease Found at Follow-up Angiography**

<table>
<thead>
<tr>
<th>Pattern of CAD</th>
<th>Patients (n) (%)</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis only</td>
<td>7 (11)</td>
<td>20.1±9.2</td>
</tr>
<tr>
<td>No change</td>
<td>18 (27)</td>
<td>25.1±14.7</td>
</tr>
<tr>
<td>Restenosis + progression</td>
<td>11 (17)</td>
<td>26.8±12.8</td>
</tr>
<tr>
<td>Progression only</td>
<td>30 (45)</td>
<td>38.3±18.5</td>
</tr>
</tbody>
</table>

**Table 4. Treatment at Follow-up**

<table>
<thead>
<tr>
<th>Pattern of CAD</th>
<th>Patients (n)</th>
<th>PTCA</th>
<th>CABG</th>
<th>Medical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restenosis only</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Progression only</td>
<td>30</td>
<td>15</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Restenosis + progression</td>
<td>11</td>
<td>8</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No change</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>18</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.
site, two had elective CABG, and 13 were treated medically. In the 11 patients with combined restenosis and progression of CAD, eight had successful PTCA, one had elective CABG, and two were treated medically. All of the 18 patients with no change in coronary anatomy were treated medically. Of the 48 patients with new coronary lesions, 28 (58%) were successfully treated with a second PTCA, four (9%) by CABG, and 16 (33%) with medical therapy.

Discussion

The efficacy of PTCA as a short-term solution to ischemic symptoms in selected patients has been well documented.3,9-11 The efficacy of PTCA as a long-term revascularization strategy remains controversial.

In this report, we have analyzed the extent and pattern of CAD in patients who underwent an initial successful PTCA procedure and remained asymptomatic without evidence of recurrent ischemia until 1 year or more after the procedure. Although this represents a small percentage of our patients to this point (somewhat underestimated because of the selection criteria employed), it is an important subset to analyze as the number of patients undergoing PTCA and their follow-up duration increases.

The study is limited by the lack of angiographic follow-up at 6 months (42%), which introduces the possibility that some patients not presenting with evidence of recurrent ischemia until late after PTCA actually had some element of restenosis or progression that was clinically silent at an earlier time. Although neither highly sensitive nor specific for restenosis, exercise testing represents the best, widely available, noninvasive tool for the detection of restenosis in the majority of patients after PTCA. In this study, 96% of patients underwent exercise testing at 6 months, and 89% of the tests were negative. In the 11% of patients in whom exercise testing was either electrically positive or equivocal, coronary angiography was performed documenting the absence of restenosis or progression of CAD.

The extent of CAD increased by an average of 0.31±0.80 vessels per patient in the entire group over the 30.8±17.4 months of the follow-up period. When evaluated according to clinical presentation, the increase in the extent of CAD was significantly greater when patients presented with typical angina, a positive exercise test without angina, or a new myocardial infarction (0.96±0.80 vessels per patient) than when they presented with atypical chest pain (0.15±0.36 vessels per patient) (p<0.0004). The annualized rate of increase in the extent of CAD for these two groups is 0.40±0.38 versus 0.11±0.28 vessels/patient/yr, respectively (p<0.004). Thus, it can be expected that the recurrence of symptoms similar to those before PTCA, a new positive exercise test, or a new myocardial infarction heralds a significant increase in the extent of CAD at late follow-up.

At follow-up, 18 patients (27%) in the present study had no change in coronary anatomy from that observed immediately after PTCA. Of these, 10 patients presented with atypical chest pain, seven with angina, and one with an asymptomatic positive exercise test. At 6 months after PTCA, nine patients had negative exercise tests and nine had no change in anatomy by repeat angiography. The precise cause of recurrent symptoms in these patients is not known, but all were treated successfully with medications for presumed coronary spasm or noncardiac chest pain.

We found a 27% overall occurrence of late restenosis in this patient population. This contrasts with the absence of restenosis reported by Rosing et al,12 the 1% rate reported by Cequier et al,13 and the 15% rate reported by Gruentzig et al14 but is probably explained by differences in the patient populations. In our study, patients were highly selected for angiographic restudy on the basis of recurrent ischemia as opposed to the cited studies in which consecutive patients underwent angiographic restudy as a routine part of the study protocol. In the study by Cequier et al,13 data regarding the incidence of recurrent ischemia at the time of angiographic restudy is not reported. In the study by Gruentzig et al14 only 21 of the 41 patients with late angiographic follow-up were restudied because of recurrent symptoms or signs of ischemia.

Morphologically, the restenotic lesions usually seen in our patients at late follow-up were either discrete or tubular rather than complex. This is similar to the morphologic appearance usually seen in early restenotic lesions.

Of interest is the significant difference in the time to evidence of recurrent ischemia found in patients in this study that was dependent on the pattern of disease at follow-up. It has been reported that patients with restenosis have recurrent ischemia earlier than those with progression of CAD.6 Our data support a similar relation even in patients with late recurrent ischemia. In this study, patients with restenosis as the only change in coronary anatomy manifested recurrent ischemia earliest, followed sequentially by those with a combination of restenosis and progression, and then by those with progression only. The difference between time to recurrence of ischemia in those with restenosis only versus those with progression only was highly significant (p<0.009). This suggests that the restenosis process may be indolent in a small percentage of patients but still occurs at a more rapid rate than progression of native disease.

In this study, 62% of patients demonstrated progression of CAD either alone or in combination with restenosis. Cequier et al13 observed progression in 31 of 85 patients (36%), a rate considerably lower than noted in our study but probably due to differences in the patient populations as noted above. They observed progression in 17% of dilated arteries and 14% of nondilated arteries and concluded
that PTCA does not induce the formation of new coronary lesions. In contrast, several case reports have demonstrated progression of CAD in the left main coronary artery after PTCA of the left coronary system.\textsuperscript{15-17} We found a 25% incidence of progression in dilated vessels and a 30% incidence in nondilated vessels (p=NS), supporting the conclusion of Cequier et al.\textsuperscript{13} To our knowledge, this is the largest reported series to date characterizing the pattern of progression when it does occur in the dilated vessel. In the 18 patients in whom progression occurred in the dilated vessel, it occurred proximal to the PTCA site in only three (17%) and distal to the site in 15 (83%) (p<0.008). This difference cannot be explained solely on the basis of the site of dilatation, as 50% of sites were in the proximal portion of the vessel and 50% were in the midportion or distal portion of the vessel. Although the reasons for this disparity are not clear, it is possible that the passage of the guide wire may result in more intimal damage than the passage of the balloon catheter. Because vessel caliber is usually smaller distally than proximally, distal intimal damage may be more likely to lead to significant stenoses than proximal intimal damage. Alternatively, given equal rates of spontaneous progression in these areas, significant obstruction will be manifest sooner distally than proximally because of the difference in vessel caliber.

With advances in technology, PTCA is becoming more widely applied. As the number of PTCA procedures performed increases and the duration of follow-up lengthens, the number of patients who are seen with recurrent evidence of ischemia after a prolonged asymptomatic interval will also increase. Based on the findings presented here, it is reasonable to expect that one of four of these patients will have some element of restenosis and that two of three will have progression of disease at other sites. Is the strategy of PTCA a failure in these patients? Our data would suggest otherwise. Only two patients presented with myocardial infarction, and neither of these involved the PTCA vessel. On recurrence, 42% of patients were treated successfully with a second PTCA procedure, and 52% were well controlled on medical therapy alone. Only 6% required CABG. On this basis, it would seem that PTCA offers the possibility of long-term survival with a low incidence of the morbid events of myocardial infarction or need for CABG, albeit with a significant chance of requiring future PTCA procedures or medical therapy.

References


KEY WORDS • angioplasty, transluminal • restenosis • coronary heart disease
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