Time Course of Restenosis During the First Year After Emergency Coronary Stenting

Adnan Kastrati, MD; Albert Schömig, MD; Rainer Dietz, MD; Franz-Josef Neumann, MD; and Gert Richards, MD

Background. Prevention of abrupt vessel closure after percutaneous transluminal coronary angioplasty (PTCA) represents one of the current indications for intracoronary stent implantation. After the procedure, the stented segment undergoes luminal changes that may lead to late restenosis. This study was undertaken to assess the time course of luminal changes during the first year after emergency placement of coronary stents.

Methods and Results. Coronary stenting was indicated in patients with present or threatened vessel closure secondary to large dissections after PTCA. From June 1989 to May 1991, 82 patients who received Palmaz-Schatz stents and did not have early vessel occlusion after stenting were enrolled into a serial angiographic follow-up study. Coronary normal reference diameter and minimal luminal diameter were measured with an automated edge detection technique. Patients who underwent repeat PTCA for restenosis were excluded from further serial angiography. The restudy rate at 3, 6, and 12 months was 96%, 81%, and 90% of the eligible patients, respectively. The incidence of restenosis (defined as a diameter stenosis ≥50%) was 22.0% at 3 months, 31.9% at 6 months, and 33.2% at 12 months. Minimal luminal diameter was increased from 0.66±0.32 mm before to 2.85±0.43 mm immediately after stenting. It was 0.46±0.31 mm smaller than the diameter of the maximally inflated balloon during the procedure. The reduction in minimal luminal diameter was 0.80±0.69 mm (p=0.0001) for the first 3 months, 0.29±0.52 mm (p=0.0001) between 3 and 6 months, and 0.13±0.32 mm (p=0.01) for the last 6 months. The percentage of patients who presented a significant change in minimal luminal diameter (defined as >0.60 mm) declined from 50.6% during the first 3 months and 18.9% between 3 and 6 months to 6.5% for the period between 6 and 12 months.

Conclusions. The incidence and the time course of restenosis after emergency coronary stenting are similar to that reported for conventional PTCA. Coronary lumen dimensions demonstrated a peak change at 3 months and remained mostly stable after the first 6 months. (Circulation 1993;87:1498–1505)

Key Words • stents • coronary angioplasty • coronary dissection • coronary occlusion

Coronary stenting is currently used for circumventing two major limitations of percutaneous transluminal coronary angioplasty (PTCA): early acute occlusion and restenosis of the dilated vessel. Abrupt vessel closure after PTCA occurs in 2–9% of the cases. It is often associated with acute ischemic complications and/or the need of emergency aorto-coronary bypass surgery. Extensive coronary dissection of the dilated vessel has been found to be the most frequent precursor of this complication. Restenosis involves one third of the patients undergoing PTCA. The process of restenosis seems to begin as early as immediately after the procedure. Elastic recoil, vasospasm, platelet aggregation, and thrombus formation are factors that alone or in combination contribute to the early luminal diameter reduction of the dilated vessel. Smooth muscle cell proliferation, migration, and elaboration of extracellular matrix later become the dominant mechanisms of the restenosis. Two well-designed angiographic studies have found that most of the narrowing of the dilated coronary arteries occurs within the first 3 months, and only minimal changes develop after 6 months. Accordingly, the process of restenosis after PTCA seems to be a time-limited phenomenon, and the 6-month restenosis rate has been accepted to represent the definitive incidence of this complication.

Implantation of coronary stents is also associated with the occurrence of early occlusion secondary to stent thrombosis and late restenosis. Experimental animal studies and pathological data in humans have shown that in addition to the mechanisms acting after PTCA, the interactions between stent and vessel wall affect the phenomenon of restenosis after the procedure. The presence of a foreign body in the vascular wall may influence the time course of restenosis in a way that is still unclear. Observations made in a porcine model demonstrate that progression of intimal hyperplasia after stenting continues for a much longer period than after balloon injury alone. Yet, the poten-
tional influence of the atherosclerotic plaque on the response to injury is usually absent in animal studies, and great care must be taken in extrapolating these findings to humans.\textsuperscript{34} The knowledge of the temporal sequence of restenosis after coronary stenting is important not only for scheduling the follow-up of the patients but also for planning possible preventive measures. This study was designed to assess the time of luminal changes after emergency coronary stenting by means of serial quantitative angiography.

Methods

Patients

During a 24-month period from June 1989 to May 1991, emergency placement of a Palmaz-Schatz stent (Johnson & Johnson) was attempted in 111 of 2,052 patients submitted to PTCA. The indication for emergency stent implantation was extensive coronary dissection during PTCA with present or threatened vessel closure despite multiple balloon dilations in a patient without major contraindications to anticoagulation therapy. All patients gave written informed consent before the intervention.

Coronary stents were successfully delivered in 107 (96\%) of the patients (Figure 1). Twenty patients belonging to our early experience underwent elective bypass surgery within 1 week from the procedure in accordance with our initial policy to use stent implantation as a bridge to surgical intervention. The target lesion in most of these patients was situated proximally in the left anterior descending coronary artery, and no clinical signs of stent occlusion were observed up to the day of the bypass operation. Because of the short time delay, they had no angiographic control before surgery and were excluded from the follow-up protocol of the present study. Five additional patients who had clinical and angiographic evidence of early thrombotic stent occlusion within the first 2 weeks after the procedure were also excluded. The remaining 82 patients were enrolled into a prospective follow-up study including

### Table 1. Main Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
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<tr>
<td>No. of patients</td>
<td>82</td>
</tr>
<tr>
<td>Sex (M/F)</td>
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<tr>
<td>Age (years)</td>
<td>58.9±9.3</td>
</tr>
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<td>Angina pectoris</td>
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<td>Unstable</td>
<td>35</td>
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<td>Stable</td>
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<td>Active smokers</td>
<td>17</td>
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<td>Systemic hypertension</td>
<td>46</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Single-vessel disease</td>
<td>39</td>
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<tr>
<td>Multivessel disease</td>
<td>43</td>
</tr>
<tr>
<td>Prior PTCA</td>
<td>27</td>
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<tr>
<td>Coronary dissection associated with total occlusion before stenting</td>
<td>10</td>
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<tr>
<td>Stent localization</td>
<td></td>
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<tr>
<td>LAD</td>
<td>19</td>
</tr>
<tr>
<td>LCx</td>
<td>16</td>
</tr>
<tr>
<td>RCA</td>
<td>44</td>
</tr>
<tr>
<td>Bypass graft</td>
<td>3</td>
</tr>
<tr>
<td>Single-stent patients</td>
<td>77</td>
</tr>
<tr>
<td>Multiple-stent patients</td>
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</table>

PTCA, percutaneous transluminal coronary angioplasty; LAD, left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

serial angiographic control at 3, 6, and 12 months. Clinical events were recorded, and patients presenting with recurrent anginal symptoms were recatheterized before the preset time. Baseline characteristics of the patients are listed in Table 1.

Stent implantation was performed using the technique described previously.\textsuperscript{18} Anticoagulation was instituted according to the following regimen: 1) 15,000 units of heparin and 500 mg of aspirin were administered intravenously during the procedure. 2) Immediately after the procedure, an oral vitamin K antagonist (Marcumar, Hoffmann-La Roche AG) and aspirin (100 mg per day) were started. Heparin infusion was adjusted according to the activated partial thromboplastin time and continued until stabilization of the therapeutic level of oral anticoagulation (generally for 7–10 days). Patients were usually discharged after 2 weeks. Oral anticoagulation was discontinued 2 months after the procedure.

Quantitative Coronary Angiography and Definitions

Coronary arterial dimensions were assessed in a single matched "worst view." The same projection that showed the most severe stenosis before the intervention was used throughout the study. The selected cineframe was digitized with a spatial resolution of 1,850 dots per inch and 256 gray levels by means of a ScanMaker 1850S slide scanner (Microtek International, Inc., Taiwan) connected to a Macintosh Quadra 900 computer (Apple Computer, Inc.). The edge detection software was developed in our laboratory and based on the weighted sum of the first and second derivative applied to the digitized brightness information.\textsuperscript{25} The contour was automatically detected after choosing the region of
interest and an approximate centerline of the arterial segment containing the stenosis. The same software was used for measuring the actual balloon size used during stent placement. The absolute dimensions of the vessel and the diameter of the final stent expansion balloon were computed using the guiding catheter as a scaling device. Percent diameter stenosis was calculated using minimal luminal diameter and interpolated reference diameter. In a few patients in whom opacification distal to the stenosis was too poor to allow normal contour detection, the diameter of the normal segment proximal to the stenosis was used as normal reference diameter. Because of the poor visibility of Palmaz-Schatz stents, no attempts were made to distinguish whether restenosis lay within or in the proximal or distal segments adjacent to the stent. The quantitative assessment was carried out on frames before PTCA, immediately after stent placement, and at each follow-up angiographic control. There were no measurements made immediately after PTCA because of the presence of large dissections in our patients (as per indication) would preclude any exact analysis. The difference, if any, between the diameter of the final stent expansion balloon and the resulting minimal luminal diameter was considered to be caused by elastic recoil of the stented coronary segment.

The variability of coronary measurements inherent to our method was assessed in 23 stented patients who had angiograms with matching projections performed at our institution at two different times (diagnostic and immediately preceding PTCA). The size of the catheters used for most of the analyzed angiograms was 6F for the diagnostic and 8F for the intervention session. The median interval between the two angiographies was 21 days. The difference (mean±SD) between the two measurements was 0.06±0.30 mm for minimal luminal diameter and 0.09±0.28 mm for the normal reference diameter. Any change in minimal luminal diameter more than double of the standard deviation (0.60 mm) during follow-up studies was considered as significant. Restenosis was defined as a percent diameter stenosis ≥50% found at control angiography.

**Angiographic Follow-up**

As shown in Figure 2, 79 patients (96%) had angiography at 3 months (median, 100 days); 13 patients with restenosis who had repeat PTCA were excluded from further follow-up. Six-month angiography (median, 192 days) was performed on 56 of the remaining 69 patients (81%), and six other patients were submitted to PTCA. Fifty-seven of the 63 patients without prior PTCA (90%) had angiographic study at 12 months (median, 368 days). All 82 patients had at least one control angiography, and the reason for missing studies was always patient refusal. The three patients with missing angiographic study at 3 months had angiography at both 6 and 12 months (except one who underwent repeat PTCA at 6 months). Eleven of the 13 patients without angiography at 6 months and four of the six patients with no angiography at 12 months had already completed two of the three required controls.

**Statistical Analysis**

Values are expressed as mean±SD. Restenosis rate was calculated according to the actuarial method and expressed in percent±1.96 SEM. Two-tailed t test and ANOVA followed by Scheffe’s test were used to check for significant differences between the means of continuous variables. Values of p<0.05 were considered significant.

**Results**

Before the intervention, the patients presented a coronary normal reference diameter of 3.26±0.64 mm, a minimal luminal diameter of 0.66±0.32 mm, and a diameter stenosis of 79.5±9.6%. The size of the balloon used for stent deployment was 3.31±0.38 mm.

Coronary stenting was associated with an increase in minimal luminal diameter from 0.66±0.32 mm to 2.85±0.43 mm and a marked reduction in percent diameter stenosis from 79.5±9.6% to 17.4±6.9%. Normal reference diameter did not change during the study period (3.25±0.5 mm at 1-year control versus 3.26±0.64 mm before stent implantation).

Cases of death or myocardial infarction were not observed during the study period. Figure 3 illustrates the time course of restenosis during the entire period of the study. Restenosis rate was 22.0±7.9% at 3 months. It increased to 31.9±9.5% at 6 months and showed only a minimal further rise to 33.2±10.4% at 12 months (Figure 3). The cumulative number of patients with restenosis was 18, 26, and 27 at 3, 6, and 12 months, respectively. During the study period, five of the 10 patients with vessel wall dissection and total occlusion after PTCA had restenosis after stenting. Fifteen of the 27 patients with angiographic restenosis had recurrent angina pectoris during follow-up.
The difference between diameter of the final stent expansion balloon and minimal luminal diameter immediately after stent placement was $0.46 \pm 0.31$ mm (Figure 4); 14% of the lumen diameter was lost because of elastic recoil of the stented segment.

Minimal luminal diameter demonstrated a change of $-0.80 \pm 0.69$ mm from immediately after stenting to 3 months ($p=0.0001$); during the same interval, percent diameter stenosis was augmented by $19.6 \pm 20.2\%$ ($p=0.0001$). Seven patients met the criteria of restenosis after 6 months but did not do so at 3 months. These patients, however, tended to have more reduction in minimal luminal diameter during the first 3 months than the other 42 patients without restenosis in both studies ($-0.78 \pm 0.42$ mm versus $-0.46 \pm 0.44$ mm, $p=0.08$). From 3 to 6 months, the change in minimal luminal diameter was $-0.29 \pm 0.52$ mm ($p=0.0001$), and the change in percent diameter stenosis was $7.8 \pm 12.9\%$ ($p=0.0001$). The changes were much lower between 6 and 12 months: $-0.13 \pm 0.32$ mm for minimal luminal diameter ($p=0.01$) and $3.2 \pm 9.5\%$ for percent diameter stenosis ($p<0.05$). Five patients with restenosis at 6 months who did not require repeat PTCA showed a change in minimal luminal diameter between 6 and 12 months comparable to that of patients without restenosis ($0.08 \pm 0.28$ mm versus $-0.16 \pm 0.32$ mm, $p=NS$).

The proportion of patients who demonstrated a significant lumen change ($>0.60$ mm) between two consecutive angiographic studies was decreasing from 3 to 12 months. From immediately after stenting to 3 months, 40 patients (50.6%) presented a reduction in minimal luminal diameter $>0.60$ mm (Figure 5). The same criterion was fulfilled by 10 patients (18.9%) between 3 and 6 months (Figure 6) and only by three patients (6.5%) from 6 to 12 months (Figure 7).

**Discussion**

Coronary stenting is one of the recent therapeutic and device-aided interventions aimed at reducing the incidence of abrupt vessel closure and late restenosis after PTCA. Restenosis after PTCA is a complex process not completely understood. It is thought, however, that lesion and regional flow characteristics are both major determinants of the degree of restenosis. The improvement of coronary stenosis geometry and flow characteristics with stents seems to be useful for preventing restenosis after PTCA. In addition to the improvement of flow characteristics, stents have been used successfully to tack up intimal and medial flaps. Both of these features have been the rationale for the management of patients with acute coronary occlusion after PTCA since 1986.

We resorted to emergency stent implantation in 5% of the total number of patients undergoing PTCA. All of them had either complete or impending vessel closure secondary to large wall dissections. The 5% rate in our
We used serial angiographic follow-up to assess the time course of luminal changes after emergency coronary stent implantation. The high angiographic restudy rate achieved at all three preset times in our patients avoids the selection bias that usually arises if only symptomatic patients are controlled. The assessment of coronary luminal changes was done by means of a quantitative angiographic system. Because of the proven superiority of the automated quantitative methods, they have become a widely accepted requirement for reporting the restenosis rate.12,21

The use of a single worst view to measure the coronary arterial dimensions in the present study may be arguable. A recent comparative study has found that coronary stenosis measurements made in the single worst view correlate very well with those obtained using two orthogonal views.32 Coronary stenting is known to remodel the stented segment into a more circular configuration,33 and further improvement of the reliability of single-view measurements is to be expected during follow-up studies.

The serial evaluation of coronary angiograms was preceded by a variability study performed in 23 patients. The difference in minimal luminal diameter obtained with a paired analysis of two separate coronary cineangiograms at a median of 21 days apart showed a standard deviation of 0.30 mm. This value differs somewhat from that of 0.36 mm reported by Reiber et al34 and of 0.25 mm found in the study of Nobuyoshi et al16 in a comparable number of patients. The time interval between the two angiograms was 90 days for the former and 9 days for the latter study. Differences in the time delay and those in the hardware and software features of the system used for the measurements may account for the differences in the variability limit obtained in these studies. We used the 0.60 mm value to distinguish the significant changes in coronary lumen between two consecutive angiographies because our main objective was the evaluation of serial changes. On the other hand, the presence of patients with repeat PTCA makes any further analysis difficult.

General consensus about the angiographic definitions of restenosis is lacking.28 To achieve comparability with other studies, we chose the most frequently used definition, that of a percent diameter stenosis ≥50%. Recently, the absolute change in luminal diameter was proposed as a more reliable index of restenosis.15 Definitions based on absolute changes reflect hyperplasia as an important component in the process leading to restenosis. Restenosis is, however, a wider concept that includes the initial result as well. This is particularly relevant in the case of stenting that achieves a larger lumen than PTCA alone. Coronary stenosis, on the other hand, and consequently all the interventional decisions taken in the clinical practice, are based on percent diameter stenosis. It is desirable to apply for restenosis the definitions that are similar to the one that led to the intervention.

Elastic Recoil

We assessed the elastic recoil phenomenon during the stent placement procedure. Whether the recoil process is extended beyond the time of the intervention is still unclear. Controls performed the day after PTCA yielded conflicting results in this regard. Nobuyoshi et

Figure 6. Scatterplot of progression of coronary luminal narrowing between 3 and 6 months after stent implantation in 53 patients with both angiographic controls. MLD, minimal luminal diameter. Solid lines represent twice the variability (0.60 mm) for repeated measurements of MLD of the same lesion during two separate angiographic studies.

Figure 7. Scatterplot of progression of coronary luminal narrowing between 6 and 12 months after stent implantation in 46 patients with both angiographic controls. MLD, minimal luminal diameter. Solid lines represent twice the variability (0.60 mm) for repeated measurements of MLD of the same lesion during two separate angiographic studies.
al16 found a significant decrease in minimal luminal diameter in 185 patients from immediately after PTCA to day 1, whereas one other study reported no significant difference at the same interval in 16 patients. Coronary arterial dimensions appeared to be stable during the first 24 hours after Palmaz-Schatz stent placement.18,36

The vascular recoil of 14% found in this study is similar to that of 15% reported after stent placement in 167 patients37 and higher than that of 3% found by de Jaegere et al38 in 50 patients who received the Wiktor stent. The difference, however, is not explained by different scaffolding properties of the stents that were used. The more plausible explanation is the different method used for the calculation of elastic recoil. de Jaegere et al38 used the mean diameter of the stented segment that is obviously greater than minimal luminal diameter used by us. If the same method is applied for their data, the difference between the diameter of the inflated balloon and the minimal luminal diameter is 0.53 mm, similar to that observed in the present study. The vascular recoil for the same Wiktor stent was 9% when implanted in the normal coronary arteries of Yorkshire pigs.39 We cannot exclude that for stent implantation, other mechanisms than for PTCA may be responsible for the immediate loss in lumen diameter after deflation of the balloon–stent assembly. Angioscopy has shown that stenotic segments bulge into the lumen of human coronary arteries at the articulation site of Palmaz-Schatz stents.40 This mechanism may have been even more operative in our patients who had important vessel wall disruption secondary to large dissections. Nevertheless, Palmaz-Schatz stenting in the present study was associated with a much lower loss of the theoretically achievable lumen diameter than that of 32% reported for PTCA.41

Quantitative Angiographic Follow-up

Restenosis after PTCA is regarded as a local vascular wall response to the injury caused by balloon dilation.14 A new potentially relevant factor related to the presence of the stent wires in the vessel wall is added after coronary stenting.22 This factor may constitute a continuous stimulus for intimal hyperplasia affecting both its rate and its duration.23 The vessel wall response to stent placement has been characterized by variable degree of inflammatory reaction, as well.21,23,42 Animal studies have shown that the thickness of the intimal layer covering the stented vessel segments peaks at 4–8 weeks after stent deployment.20,39,43 Whereas luminal changes had already ceased 2 weeks after balloon injury, they continued to show progression even after 3 months from stent implantation.23

Clinical studies have demonstrated that restenosis occurs in 20–56% of the patients managed with intracoronary stent placement.19,44–49 The incidence of this event appears to be influenced by the indication for stenting.19,49 The restenosis rate in the present study is similar to that of 33% found by Haude et al48 and lower than that of 41% and 56% reported by Roubin et al46 and Fajadet et al,49 respectively, in patients who received stents in circumstances similar to ours. Patient characteristics may have played a role in this difference. The proportion of patients with multiple stents and of those with the stent placed in the left anterior descend-
Conclusions

The results of this study suggest that both the overall incidence and the time course of restenosis after emergency coronary stenting resemble those seen after conventional PTCA. Stent implantation appeared to prevent most of the elastic recoil occurring after PTCA alone without succeeding in its complete elimination. After a peak at 3 months, the luminal changes were gradually attenuated and the coronary lumen remained almost stable in the period after the first 6 months. If not otherwise indicated, a 6-month angiographic control would reveal the vast majority of changes expected to occur after coronary stent placement.

Acknowledgments

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References

32. Lesperance J, Hudon G, White CW, Laurier J, Waters D: Comparison by quantitative angiographic assessment of coronary stenoses of one view showing the severest narrowing to two orthogonal views. Am J Cardiol 1989;64:462-465
Time course of restenosis during the first year after emergency coronary stenting.
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