Balloon Angioplasty for the Treatment of Coronary In-Stent Restenosis: Immediate Results and 6-Month Angiographic Recurrent Restenosis Rate

HÉLÈNE ELTCHANINOFF, MD, RENÉ KONING, MD, CHRISTOPHE TRON, MD, VIVEK GUPTA, MD, ALAIN CRIBIER, MD, FACC
Rouen, France

Objectives. The purpose of this prospective study was to evaluate the immediate results and the 6-month angiographic recurrent restenosis rate after balloon angioplasty for in-stent restenosis.

Background. Despite excellent immediate and mid-term results, 20% to 30% of patients with coronary stent implantation will present an angiographic restenosis and may require additional treatment. The optimal treatment for in-stent restenosis is still unclear.

Methods. Quantitative coronary angiography (QCA) analyses were performed before and after stent implantation, before and after balloon angioplasty for in-stent restenosis and on a 6-month systematic coronary angiogram to assess the recurrent angiographic restenosis rate.

Results. Balloon angioplasty was performed in 52 patients presenting in-stent restenosis. In-stent restenosis was either diffuse (≥10 mm) inside the stent (71%) or focal (29%). Mean stent length was 16 ± 7 mm. Balloon diameter of 2.98 ± 0.37 mm and maximal inflation pressure of 10 ± 3 atm were used for balloon angioplasty. Angiographic success rate was 100% without any complication. Acute gain was lower after balloon angioplasty for in-stent restenosis than after stent implantation: 1.19 ± 0.60 mm vs. 1.75 ± 0.68 mm (p = 0.0002). At 6-month follow-up, 60% of patients were asymptomatic and no patient died. Eighteen patients (35%) had repeat target vessel revascularization. Angiographic restenosis rate was 54%. Recurrent restenosis rate was higher when in-stent restenosis was diffuse: 63% vs. 31% when focal, p = 0.046.

Conclusions. Although balloon angioplasty for in-stent restenosis can be safely and successfully performed, it leads to less immediate stenosis improvement than at time of stent implantation and carries a high recurrent angiographic restenosis rate at 6 months, in particular in diffuse in-stent restenosis lesions.

©1998 by the American College of Cardiology

Two large prospective randomized studies (1,2) have demonstrated the superiority of Palmaz–Schatz stents over balloon angioplasty on restenosis rate in patients presenting with stable angina and de novo lesions on arteries larger than 3 mm. With the use of high delivery pressures (3) and antiplatelet regimen (4–6), the incidence of acute stent thrombosis and vascular complications rate has dramatically decreased, explaining the success of stent and its wide utilization across the world.

However, despite excellent immediate results, 20% to 30% of patients may present with an angiographic restenosis and may require additional treatment. Balloon angioplasty for in-stent restenosis has been performed with excellent immediate results (7–16) but angiographic restenosis rate seems to be high. In the few retrospective studies (7–9), which reported incomplete 6-month angiographic follow-up, restenosis rate varied between 30% and 57%. Recently, Bauters et al. (16) reported a 22% angiographic restenosis rate after successful repeat intervention in a series of 103 patients. Rotational atherectomy (17) or laser angioplasty (18,19) could be more effective in treating in-stent restenosis, however no data are yet available on angiographic restenosis rate following these procedures.

The aim of this prospective study was to evaluate the immediate results and 6-month angiographic recurrent restenosis rate after balloon angioplasty for in-stent restenosis by performing a systematic coronary angiography at 6 months in all patients.

Methods

Patient selection. Our study group included 52 consecutive patients and 57 stents presenting with angiographic in-stent restenosis on a coronary angiogram performed between January 1995 and December 1996. Coronary angiogram was performed 6 ± 8 months (2 to 59 months) after stent implantation for recurrence of symptoms and/or positive stress test. Immediate results were assessed and a systematic coronary angiogram was scheduled at 6 months for each patient to assess recurrent restenosis rate, or earlier if clinical suspicion of restenosis.
Definitions. Angina was classified according to the Canadian Cardiac Society angina classification (20). Myocardial infarction was defined by two of the following: chest pain lasting >30 min, new Q waves or ST segment elevation (>1 mV) in at least two contiguous leads on the 12-lead electrocardiogram (ECG), or a more than twofold increase in creatine kinase (CK)-MB above baseline to an abnormal level. Lesion morphology before stent implantation was classified according to the American College of Cardiology/American Heart Association (ACC/AHA) classification (21).

Balloon angioplasty procedure for in-stent restenosis. Balloon size used for balloon angioplasty was determined to obtain a reference artery diameter: balloon diameter ratio close to 1. During the procedure, patients received an intracoronary bolus injection of heparin (5,000 to 7,500 U). The arterial sheath was removed 4 h after the end of the procedure. Patients were receiving aspirin (250 mg daily). No ticlopidin or reopro were administered to the patients.

Angiographic analysis. Quantitative coronary angiographic analyses were performed: 1) before and after balloon angioplasty for in-stent restenosis; 2) at 6-month follow-up to assess recurrent restenosis rate. They were compared with the angiographic analyses performed before and after stent implantation. At least two angiographic projections (orthogonal if possible) were recorded in such a way that they were suitable for quantitative analysis by the Philips DCI automated QCA system. The absolute stenosis minimal lumen diameter (MLD) and reference diameter were measured on-line by the computer using the known contrast-empty guiding catheter as a scaling device after intracoronary injection of 150 μg of nitroglycerin. Acute gain was defined as the difference between the MLD immediately after the procedure (sten implantation or balloon angioplasty) and the MLD before the procedure. Angiographically visible dissections were defined according to the modified National Heart, Lung and Blood Institute criteria (22). Angiographic success was defined as a residual diameter stenosis ≥50% in the absence of severe coronary artery dissection (type D1 or greater). Clinical success was defined as an angiographic success in the absence of major complications such as death, myocardial infarction and bypass surgery (23). Angiographic restenosis was defined by a diameter stenosis ≥50%.

Follow-up. In-hospital, ECG was performed immediately and 12 h after balloon angioplasty. Creatine kinase measurements were performed on the following day after angioplasty. Complications and clinical events were noted, including death, need for coronary bypass surgery or repeat coronary angioplasty, myocardial infarction and vascular complications. All patients were asked to return for a 6-month follow-up angiogram, regardless of symptomatic status; angiography was performed earlier if there was a clinical indication. The following information was obtained: Canadian class angina, need for rehospitalization, cardiac events such as myocardial infarction, coronary artery bypass surgery or death. If the patient did not return for 6-month angiogram, clinical information was obtained by phone.

Statistical analysis. For the five patients who had more than one stent presenting in-stent restenosis, we selected one stent from each patient using a random unit generator and deleted the other stent from the formal analyses. Thus, all formal analyses were performed on 52 patients. Data were reported as mean ± SD values. Comparisons were made using Student’s t-test for continuous variables and chi-square test for qualitative clinical variables; p < 0.05 was considered significant.

Results

Study group. The clinical characteristics of our population are presented in Table 1. Baseline angiographic characteristics obtained before stent implantation are shown in Table 2. Mean ejection fraction was 64% ± 10%. Mean lesion length was 14 ± 5 mm.

Stent implantation. Maximal balloon pressure used for stent deployment was 11 ± 3 atm and maximal balloon diameter was 3.05 ± 0.28 mm. The indications for stent implantation were: suboptimal result in 7, de novo lesion in 23,
occlusive or nonocclusive dissection in 16, restenosis in 6. In 63% of cases, Palmaz–Schatz stents were implanted, Freedom stents in 17% and Advanced Vascular Engineering (AVE) in 13%. The remaining 7% were stents of various designs. Mean stent length was 16 ± 7 mm (6 to 40 mm).

**In-stent restenosis characteristics.** In-stent restenosis was either diffuse (≥10 mm; 71%) or focal (29%). When focal, in-stent restenosis was located either inside the stent (n = 11; 21%) or at one of the extremities of the stent (n = 4; 8%). Mean in-stent restenosis length was 16 ± 8 mm (5.5 to 38 mm).

**Balloon angioplasty procedure for in-stent restenosis.** Balloon angioplasty was performed at a mean of 5.9 ± 8.2 months after stent implantation (2 to 59). Indications for repeat intervention were the presence of angina or stress test ischemia, or both in all the patients. Maximal balloon diameter used for balloon angioplasty was 2.98 ± 0.37 mm, and maximal balloon inflation pressure was 10 ± 3 atm, two parameters not statistically different from those used for stent implantation. After balloon angioplasty, there was no angiographic evidence of dissection or thrombus. Angiographic success rate was 100%.

**Immediate and in-hospital clinical outcome.** No patient died, developed myocardial infarction or required emergency coronary artery bypass graft surgery. There was no case of abrupt vessel closure after dilatation. Bleeding and vascular complications were not observed.

**Clinical follow-up at 6 months.** Clinical follow-up was obtained in all patients at a mean of 5.3 ± 3.5 months. A majority of patients (60%) was asymptomatic. There was no death and no patient developed myocardial infarction. Target vessel revascularization was performed in 18 (35%) patients: coronary bypass surgery in nine and repeat balloon angioplasty in nine patients with stent implantation inside the first one in five cases. All these procedures were uneventful.

**Angiographic follow-up.** Follow-up coronary angiogram was obtained in 48 patients (i.e., in 92% of patients and stents suitable for follow-up). Mean follow-up period was 5.7 ± 3.6 months. Indications for repeat angiogram were: clinical and/or stress test suspicion of restenosis in 19 patients and systematic control in 29 patients. Recurrent restenosis was observed in 26 of 48 stents, which was a 54% angiographic restenosis rate. Four patients did not return for control angiogram: all of them were asymptomatic at 6 months.

**Quantitative angiographic analysis.** All the measurements obtained at the time of stent implantation, at the time of balloon angioplasty for in-stent restenosis and at 6-month follow-up angiogram were compared and are shown on Table 3. Acute gain was less after balloon angioplasty for in-stent restenosis than after stent implantation: 1.19 ± 0.60 mm vs. 1.75 ± 0.68 mm (p = 0.0002).

**Angiographic pattern of in-stent restenosis and its relation with recurrent restenosis.** Diffuse pattern was far more frequent than focal pattern: 71% vs. 29%. Using univariate analysis, the diffuse pattern of in-stent restenosis was the only predictor of recurrent restenosis after balloon angioplasty for in-stent restenosis (p = 0.046). Recurrent restenosis rate was 63% vs. 31% when in-stent restenosis was focal (p = 0.046). Similarly, target vessel revascularization was required more often when in-stent restenosis was diffuse: 49% vs. 8%, p = 0.009. Interestingly, the morphology of the recurrent restenotic lesion at 6 months was comparable to that observed initially at the time of in-stent restenosis in 76% of cases.

**Discussion**

During the past few years there has been a dramatic explosion in coronary stent utilization. There is a general recognition that stents address many of the major limitations of conventional balloon angioplasty, offering a solution for abrupt or threatened closure, a safer and more effective therapy for patients with saphenous vein graft disease and a partial solution to the problem of restenosis (1,2). Furthermore, stent implantation techniques have been revised (3) and pharmacologic regimens (4 – 6) have been improved, both leading to a decrease in the frequency of stent thrombosis with fewer bleeding/vascular complications and a shorter hospital stay. However, 20% to 30% of patients will present restenosis (1,2) and may require further management. Few data are yet available on the best choice of revascularization treatment in these patients. Balloon angioplasty for in-stent restenosis has been evaluated in few retrospective studies (7–15) with excellent immediate results. Macander et al. (9) reported a high success rate of 97% in 75 restenotic Cook (Gianturco–Roubin) stents. Success rate was 100% and 97.6% respectively in two recent series of balloon angioplasty for in-stent restenosis (13,14). Clinical follow-up obtained in several series (14,15)

---

**Table 3. Angiographic Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Stent Implantation</th>
<th>BA for ISR</th>
<th>6-month Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Mean reference diameter (mm)</td>
<td>2.95 ± 0.47†</td>
<td>3.24 ± 0.45†</td>
<td>2.91 ± 0.55*</td>
</tr>
<tr>
<td>Minimal lumen diameter (mm)</td>
<td>0.89 ± 0.51</td>
<td>2.65 ± 0.44</td>
<td>1.02 ± 0.47</td>
</tr>
<tr>
<td>Diameter stenosis (%)</td>
<td>73 ± 15</td>
<td>18 ± 10</td>
<td>66 ± 11</td>
</tr>
</tbody>
</table>

*p = 0.012 reference diameter pre-BA vs. reference diameter poststent; **p = 0.02 reference diameter post-BA vs. reference diameter poststent; ***p = 0.0001 MLD post-BA vs. MLD poststent; †p < 0.0001 reference diameter pre-BA vs. reference diameter poststent. Data presented are mean value ± SD. BA = balloon angioplasty; ISR = in-stent restenosis; MLD = minimal lumen diameter.
appears satisfactory with a 18% to 36% need for repeat target vessel revascularization. Recently, Reimers et al. (15) reported complete clinical follow-up on 124 patients with a target vessel revascularization rate of 11%. However, angiographic mid-term results appear less encouraging, with high restenosis rate reaching 57% in the few retrospective studies (7–9) reporting incomplete angiographic follow-up on less than 50% of patients.

Thus, the aim of our prospective study was to evaluate the immediate results and the angiographic recurrent restenosis rate observed after balloon angioplasty for in-stent restenosis by performing a systematic coronary angiogram at 6 months. In our series, angiographic follow-up was obtained in 93% of patients.

Results of our series. In our prospective series of 52 patients presenting with in-stent restenosis and treated by balloon angioplasty, immediate results were excellent with a 100% clinical and angiographic success rate. There was no major complication. These optimal results are in agreement with those reported in previous series (13,14,16), reporting excellent immediate results and the absence of major complications. This common observation may result from the mechanism of balloon angioplasty which is somewhat different. Applying pressure in a stented wall does not create disruption as compared to the frequency of dissections observed in a diseased wall. Despite a 100% procedural success rate, the lumen dimensions after balloon angioplasty in the current study were consistently and significantly smaller than after stent implantation, with less final MLD and less acute gain. This observation has already been confirmed by an intravascular ultrasound study (11) which suggests that the relatively high residual stenosis is partly as a result of remaining in-stent neointimal tissue which cannot be totally extruded through the struts of the stent. The deeper arterial structures surrounding the stent may also limit the effectiveness of balloon angioplasty. We could observe that the reference diameter before balloon angioplasty for in-stent restenosis was significantly less than after stent implantation, suggesting that neointimal hyperplasia might also affect the initial reference segment.

In our study, angiographic recurrent restenosis rate of the overall population was very high (54%). Our results suggest that balloon angioplasty for in-stent restenosis may not be the ideal treatment, especially for diffuse lesions, because of the high restenosis rate. Our results differ from those published by Bauters et al. (16) who reported a 22% angiographic restenosis rate only. However, the population was different in our two series with a majority of diffuse lesions in our series (71%) in comparison to 28% only in the series of Bauters et al. In their series, diffuse lesions were also associated with a high recurrent restenosis rate. Similarly, in our series the need for target revascularization (8%) was very low at follow-up when restenosis was focal. The high angiographic restenosis rate presented in our series, especially in diffuse lesions, could be accounted for by the nonaggressive approach to repeat balloon angioplasty with a mean inflation pressure of 10 atm and a 2.98-mm balloon diameter. However, in our series, maximal inflation pressure and maximal balloon diameter were not found to be predictors of restenosis. Few data are available on alternative treatments proposed to these patients and not yet evaluated at long term. Rotational atherectomy and laser angioplasty offer the potential advantages of debulking the lesion in addition to the effects of balloon angioplasty, which is systematically performed after debulking. In the only series (17) reporting the preliminary results of rotational atherectomy in 100 cases, procedural success was 100% with no major complications. Clinical follow-up was obtained for 67% of patients at a mean of 7 ± 2 months: clinical restenosis rate was 27% but no angiographic follow-up was reported. Laser angioplasty (18,19) could offer another alternative treatment and has been evaluated in two recent series. Procedural success was achieved in 93% and 98%, respectively. Complications were rare among the 151 restenosed stents in the LARS Study (18): minor perforations (1.5%), dissections (8.5%) and non Q-wave myocardial infarction (2.3%). In the other study (19), angiographic follow-up was not performed and subsequent target vessel revascularization rate was 21%. Directional atherectomy has not been recommended for in-stent restenosis. Bowerman et al. (24) reported one case of in-stent restenosis (Gianturco–Roubin) treated by directional atherectomy. The procedure was complicated by disruption of the stent which was snared by the atherectomy cutter. Finally, implantation of a second stent inside the first one could be another alternative and should require further investigation. The best therapeutic option should be assessed with the results of randomized studies comparing different interventional techniques.

Mechanisms of in-stent restenosis and balloon angioplasty for in-stent restenosis. The understanding of the mechanisms of in-stent restenosis and of balloon angioplasty and other interventional techniques should help in the best choice of treatment for in-stent restenosis. In an intravascular ultrasound study, Hoffman et al. (10) evaluated the mechanisms of balloon angioplasty for in-stent restenosis and showed that 1) chronic stent recoil was minimal within Palmaz–Schatz stents, 2) late lumen loss and in-stent restenosis were the result of neointimal tissue proliferation, 3) neointimal tissue proliferation was uniformly distributed over the length of the stent except for a tendency for exaggerated neointimal tissue accumulation at the central articulation of the Palmaz–Schatz stent and 4) stents appeared to affect the adjacent vessel segments, causing a combination of arterial remodeling and tissue proliferation. Mechanisms of balloon angioplasty for in-stent restenosis have also been evaluated by intravascular ultrasound. Mehran et al. (11) showed that lumen enlargement obtained by balloon angioplasty resulted from a combination of additional stent expansion (accounting for 56% of lumen enlargement), tissue extrusion out of the stent and neointimal redistribution within the stent (accounting for 44%). Furthermore, that study showed that angiographic residual stenosis after balloon angioplasty for in-stent restenosis was relatively higher in comparison to that observed after stent implantation. These ultrasound observations are in disagreement with those of Gordon et al. (7) who, in an angiographic study, concluded
that lumen enlargement after balloon angioplasty was entirely due to neointimal tissue compression or extrusion out of the stent rather than to additional stent expansion. Because the metallic stainless-steel stent struts are relatively radiolucent (but intensively echorellective), intravascular ultrasound appears more accurate than angiography in providing information regarding stent dimensions.

Angiographic pattern of in-stent restenosis and its relation with recurrent restenosis. In our study, diffuse in-stent restenosis pattern was far more common than focal pattern and was associated with a significantly higher angiographic recurrent restenosis rate on follow-up in comparison to the focal pattern: 63% vs. 31%. These findings are comparable to those observed by Sharma et al. (25) who observed diffuse pattern of in-stent restenosis in 78% of cases. In that same study, clinical recurrent restenosis rate was higher when in-stent restenosis was diffuse vs. focal: 42% vs. 18% (p = 0.03). These observations might lead to more aggressive strategies such as laser or rotational atherectomy for diffuse in-stent restenosis.

Limitations of the study. Several types of stents were included in our series. This resulted from the prospective design of the study started in 1995, at the time when several types of stents were available to accommodate different types of lesions. However, when subdividing our population according to the presence of a coil or a tubular stent, 6-month recurrent restenosis rate was comparable, in favor of similar mechanisms for restenosis after balloon angioplasty for in-stent restenosis. The number of patients is limited but statistically significant to address the problem of restenosis rate after balloon angioplasty for in-stent restenosis. We are aware of the superiority of ultrasound over QCA for assessment of the coronary diameters. However, ultrasound was not available in this study.

Conclusion. Balloon angioplasty for in-stent restenosis is associated with excellent immediate results but a high incidence of angiographic recurrent restenosis. The higher recurrent restenosis rate observed in diffuse vs. focal lesions suggests that the treatment of diffuse in-stent restenosis may require more aggressive debulking strategies. Rotational atherectomy, laser angioplasty and stenting should be evaluated as alternatives to balloon angioplasty in prospective randomized studies to determine the best therapeutic option in this indication. The problem of in-stent restenosis should require careful attention with the increasing rate of stent implantation all over the world and the uniform persistence of a restenosis rate of 20% to 30% after stent implantation.

References