Five-Year Angiographic Outcome in Patients Without Restenosis Following Coronary Balloon Angioplasty: A Comparison Between Non Diabetic and Diabetic Lesions

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SUMMARY

Few studies have investigated the long-term angiographic outcome of successful coronary balloon angioplasty (CBA) among diabetic and nondiabetic dilated lesions. The purpose of this study was to evaluate and compare the long-term (>5 years) outcomes of diabetic and nondiabetic CBA lesions which had remained patent 3-12 months after intervention. Twenty-five patients (45 lesions) with diabetes mellitus and 79 patients (138 lesions) without diabetes mellitus were enrolled as subjects. All patients who underwent CBA without restenosis within 3-12 months of the initial CBA based on follow-up angiographic evaluation were included. Quantitative coronary angiograms performed before, immediately after CBA, during the 3-12-month period (mean 4.1±1.0 months), and at or after 5 years (mean 6.4±2.0 years) were compared. There was no significant difference in the reference diameter between nondiabetic and diabetic lesions at any of the four time points studied. The minimum lumen diameter before and immediately after the procedure and at the 3-12-month follow-up did not differ significantly between the two groups. At >5-year follow-up, the minimum lumen diameter was significantly (P=0.005) decreased in diabetic lesions. Total occlusion occurred in 9% (4/45) of the diabetic lesions compared to only 1% (1/138) in the nondiabetic lesions (P=0.007). Diabetic lesions showed significant (P=0.049) narrowing between the 3-12 month period and >5-year follow-up. Fifty-one percent (18/35) of the nondiseased vessels in the diabetic patients at the time of enrollment had new stenosis during the follow-up periods. In conclusion, compared to nondiabetic lesions, patients with diabetic lesions who underwent CBA were more predisposed to have stenotic progression and total occlusion. (Jpn Heart J 2003; 44: 31-39)

Key words: PTCA, Coronary balloon angioplasty, Long-term follow-up, Diabetes mellitus, Restenosis, Total occlusion
SINCE 1979, when Gruentzig, et al1 introduced the technique of percutaneous transluminal coronary angioplasty (PTCA) for the treatment of coronary artery disease (CAD), it has become well known as an effective therapeutic modality. Numerous studies have reported high initial success rates and long-term benefits of PTCA.

Diabetes mellitus is a poor prognostic factor for patients with coronary artery disease.2,3) Atherosclerotic disease in diabetics increases two-fold to three-fold.4) Approximately 10% to 20% of patients currently undergoing PTCA are diabetic. High restenosis rates in diabetics were consistently reported in these patients in several studies.5-9) Likewise, most long-term studies10-13) have shown high incidences of events in diabetics despite PTCA.

Diabetic patients have a metabolic alteration that occurs as a result of hyperglycemia or hyperinsulinemia. Diabetes mellitus results in endothelial dysfunction and accelerated platelet deposition, and several growth factors known to promote the restenotic process are overexpressed in the presence of hyperglycemia14) and have continuously influenced the CBA lesions. Usually restenosis is observed within 6 months after coronary balloon angioplasty (CBA), and most of the follow-up angiographic studies in diabetic patients5,7-9) were conducted less than 1 year following the procedure. However, little is known about the disease progression of the CBA lesions that remained patent 3-12 months after CBA.

The purpose of this study was to evaluate and compare the >5-year angiographic outcomes between diabetic and nondiabetic CBA lesions which did not exhibit restenosis during the 3-12 month post-CBA follow-up period.

PATIENTS AND METHODS

Patient selection: One-hundred and four patients (183 lesions) were retrospectively analyzed. The patients included in this study had:

1. CBA performed between 1987 and 1994 at the Matsue Red Cross Hospital.
2. a postinterventional routine coronary angiogram obtained 3-12 months after the initial CBA. The dilated site had no restenosis (50% >% diameter stenosis (%DS)) on routine 3-12-month angiographic follow-up studies,
3. a second postinterventional coronary angiogram obtained 5 years or more after the initial CBA, and
4. no revascularization at the dilated site performed during the follow-up periods.

Diabetic patients constituted 24% (25/104 patients) of the study population (45 lesions).
Indications for coronary angiogram: The indications for coronary angiograms performed 5 years or more after primary revascularization (mean 6.4±2.0 years) were: evaluation for angina, development of ischemic ECG changes, exercise-provocable ischemia, or redistribution and/or defect in radionuclide ventriculography. If a patient had undergone more than two postinterventional angiograms, the first and the last were considered for analysis.

Definition of diabetes mellitus: Patients were included in the diabetic group if they received active treatment for diabetes mellitus with either an oral hypoglycemic agent or insulin at the time of the initial CBA. Diet-controlled diabetics were included only if documentation of a fasting blood glucose of >140 mg/dL or random blood glucose of >200 mg/dL was available before the initial CBA. All other patients who did not satisfy these criteria were included in the nondiabetic group. All diabetic patients had non-insulin-dependent diabetes mellitus.

Angiographic analyses: Serial quantitative coronary analyses were performed before and immediately after CBA, during the 3-12 month follow-up period, and 5 years or more after CBA. Quantitative computer-assisted angiographic measurements were taken on end-diastolic frames using a cardiac image analysis system (CMS version 3.0, MEDIS). Restenosis was defined as >50% follow-up diameter stenosis. Stenotic progression/regression was defined as an increase/decrease in diameter stenosis >10% when comparing >5 year angiographic data to 3-12 months. The 10% cut-off (2.5 times the standard deviation of the degree of stenosis (3.2%) between repeated measurements) was used to ensure that the difference in the measured stenosis severity did not reflect an inaccuracy in the method of measurement. 15,16) Lesions were classified according to the American College of Cardiology/American Heart Association classification. 17) A nondiseased vessel was defined as a vessel without >50% diameter stenosis at the first CBA. Analyses of angiographic characteristics and disease progression were conducted on the left anterior descending artery, left circumflex artery, and right coronary artery. The left main trunk was excluded from the analysis.

Statistical analyses: Data were analyzed using Stat View 4.01 software. Continuous data are presented as mean±SD. Comparisons between groups were performed using the chi-square test to analyze the differences in categorical variables. The Student t test was used for continuous variables. A value of P<0.05 was considered to indicate statistical significance.

RESULTS

Baseline characteristics: The baseline characteristics of the study population are detailed in Table I. Seventy-seven percent (80/104) of the patients were men. Mean age was 64±8 years. CBA was performed for stable angina pectoris in 44%
prior myocardial infarction (MI) in 25% (26/104), acute MI in 27% (28/104) and unstable angina pectoris in 4% (4/104) of the patients. There were no statistically significant differences in the baseline characteristics between the diabetic and nondiabetic patients. The angiographic characteristics of the lesions before and immediately after CBA and during the 3-12 month follow-up are summarized in Table II. There were no statistically significant differences in the baseline angiographic characteristics between the diabetic and nondiabetic lesions.

Changes in lumen diameter: The changes in lumen diameter at the dilated sites are shown in Table II and the Figure. There were no significant differences in reference diameter between the nondiabetic and diabetic lesions at any of the four time points studied (before the procedure, immediately after the procedure, at the 3-12-month follow-up, and after 5 years). The minimum lumen diameter (MLD) before and immediately after the procedure and at the 3-12-month follow-up did not differ significantly between the two groups. However, at the >5-year follow-up, the MLD was significantly ($P=0.005$) lower in the diabetic lesions than in the nondiabetic lesions (1.54±0.68 mm vs. 1.84±0.58 mm).

More than five-year outcomes: As shown in Table III, the overall >5-year restenosis rate was 8.2% (6.5% in the nondiabetic group vs. 13.3% in the diabetic group, $P=NS$). Total occlusion at >5-year follow-up occurred in 0.7% of the nondiabetic lesions and 8.9% of the diabetic lesions ($P=0.007$). Compared to the nondiabetic lesions, the diabetic lesions showed significant narrowing between the 3-12-month follow-up and the >5-year follow-up (3.5±30.6% in the diabetic group vs. 5.0±19.7% in the nondiabetic group, $P=0.049$).

Table I. Baseline Characteristics of the Study Population*

<table>
<thead>
<tr>
<th></th>
<th>All n=104</th>
<th>Non-DM n=79</th>
<th>DM n=25</th>
</tr>
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<tbody>
<tr>
<td>Age, years</td>
<td>64±8</td>
<td>64±8</td>
<td>65±8</td>
</tr>
<tr>
<td>Males (%)</td>
<td>80 (77)</td>
<td>60 (76)</td>
<td>20 (80)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>25 (100)</td>
<td>NA</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75 (72)</td>
<td>59 (75)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>52 (50)</td>
<td>43 (54)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>22 (21)</td>
<td>14 (18)</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Stable AP (%)</td>
<td>46 (44)</td>
<td>39 (49)</td>
<td>7 (28)</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>26 (25)</td>
<td>17 (22)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>Acute MI (%)</td>
<td>28 (27)</td>
<td>20 (25)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>Unstable AP (%)</td>
<td>4 (4)</td>
<td>3 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>No. of diseased vessels (%)</td>
<td>1 62 (60)</td>
<td>49 (62)</td>
<td>13 (52)</td>
</tr>
</tbody>
</table>

* $p$: NS for all values; DM=diasbetes mellitus; AP=angina pectoris; MI=myocardial infarction.
Table II. Angiographic Characteristics of the Lesions

<table>
<thead>
<tr>
<th></th>
<th>All n=183</th>
<th>Non-DM n=138</th>
<th>DM n=45</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LADn (%)</td>
<td>50 (27)</td>
<td>38 (28)</td>
<td>12 (27)</td>
<td></td>
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<tr>
<td>LCXn (%)</td>
<td>80 (44)</td>
<td>64 (46)</td>
<td>16 (36)</td>
<td></td>
</tr>
<tr>
<td>RCA n (%)</td>
<td>48 (26)</td>
<td>32 (23)</td>
<td>16 (36)</td>
<td></td>
</tr>
<tr>
<td>LMTn (%)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Vein graftn (%)</td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous PTCA at same site (%)</td>
<td>41 (22)</td>
<td>31 (22)</td>
<td>10 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>AHA/ACC (%)</td>
<td>A 87 (48)</td>
<td>66 (48)</td>
<td>21 (47)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B1 79 (43)</td>
<td>59 (43)</td>
<td>20 (44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B2 11 (6)</td>
<td>9 (6)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 6 (3)</td>
<td>4 (3)</td>
<td>2 (4)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Preprocedure
- Reference diameter (mm)
- Minimum lumen diameter (mm)
- Stenosis (%)

Postprocedure
- Minimum lumen diameter (mm)
- Stenosis (%)

At 3-12-month follow-up
- Reference diameter (mm)
- Minimum lumen diameter (mm)
- Stenosis (%)

At > 5-year follow-up
- Reference diameter (mm)
- Minimum lumen diameter (mm)
- Stenosis (%)
- %DS (> 5-years) - %DS (3-12-month) (%)

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery; LMT = left main trunk; PTCA = percutaneous transluminal coronary angioplasty; %DS = % diameter stenosis.

Figure. Serial changes in the MLD during the follow-up periods.
Incidence of new lesions in nondilated vessels: Forty two % of 154 nondiseased vessels at the time of enrollment had new stenotic lesions (%DS>50%) during the follow-up period. New lesions were evident in 51% (18/35) and 40% (47/119) of the nondiseased vessels among the diabetic and nondiabetic patients, respectively.

**DISCUSSION**

The major findings of the present study are the following: (1) MLD was significantly decreased in the diabetic lesions, (2) the rate of total occlusion and degree of narrowing were higher in the diabetic lesions, and (3) about 40% of the patients in both groups had new atherosclerotic lesions.

This study evaluated the long-term angiographic outcomes of patients who underwent CBA and had no restenosis at 3-12 months following the initial intervention. Restenosis is a time-related phenomenon, having a peak incidence 2-3 months after the procedure with no further increase in the restenosis rate thereafter. Most long-term studies have described the mortality and morbidity outcomes in this group of patients, while there is a paucity of angiographic outcome studies in the literature. This study is important because it describes the long-term angiographic results of diabetic lesions.

Recent experimental and clinical studies have demonstrated that the contribution of neointimal hyperplasia to short-term restenosis after CBA is mostly related to vessel remodeling (ie, chronic sclerosis with vessel construction). Nobuyoshi, et al showed pathologically that, after two years, intimal proliferation at the dilated sites become difficult to identify as evidence of antemortem balloon angioplasty and that the change in smooth muscle from a synthetic phenotype to a contractile phenotype contributes to regression at the dilated sites. In our study, about 40% of the dilated sites in both groups, had stenotic regression, while 24% of the dilated sites in the diabetic group and 17%...
in the nondiabetic group had stenotic progression. In addition, restenosis of the diabetic lesions at the dilated sites was noted to occur between the 3-12-month follow-up and the >5-year follow-up period. These findings suggest that the CBA patients may experience late (>5 years) restenosis.

Inoue, et al.\(^28\) have shown that once a given target lesion was safely treated with PTCA and has surpassed the 6-month vascular repair period without restenosis, the atheromatous segment was converted to a vascular scar virtually incapable of future plaque rupture by atherosclerosis for several years after CBA. In our study, total occlusion at >5-year follow-up occurred in 8.9% of the diabetic lesions. Aronson, et al.\(^14\) reported that the metabolic alterations associated with diabetes mellitus can promote restenosis through the unique alterations in local growth factor production and action, which in turn induce proliferation of smooth muscle cells and extracellular matrix synthesis. They suggested that the dilated sites of the diabetic lesions received continuous stimulation by growth factors that were not present in nondiabetic patients and that some of the lesions had eventual plaque rupture.

Nobuyoshi, et al.\(^21\) showed that new atherosclerotic lesions occurred in 15% of their PTCA patients within 1 year, and in 47% between 1 to 10 years after the procedure. In our study, about 40% of the patients in both groups had new lesions, which supports their results.

**Study limitations:** This study was a retrospective analysis, and therefore the conclusions and results are subject to the limitations inherent in the study design. Data from the literature showed that the >1-year restenosis rate was very low.\(^5,27\) However, since >1-year follow-up catheterization is not usually routinely done, the follow-up rate in this study might be lower than that in other long-term follow-up studies. However, few studies\(^21,29\) have described angiographic findings after balloon angioplasty.

The present study has demonstrated that dilated diabetic lesions can continue to progress, and that some had plaque rupture and total occlusion several years after CBA. Based on the results of this study, it is concluded that diabetic patients who have undergone CBA may require careful angiographic follow-up.

**ACKNOWLEDGEMENT**

We wish to thank Masaki Aoto for his continued and invaluable assistance, and Yasukazu Notsu for his excellent technical assistance.
REFERENCES


