Restenosis after stenting of matched occluded and non-occluded coronary arteries

Should there be a difference?

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**Aims** It is not known whether the higher restenosis rates reported after balloon angioplasty of occluded as opposed to non-occluded coronary arteries are still found after placement of coronary stents in lesions matched for factors known to affect late angiographic outcome.

**Methods and Results** In a retrospective analysis of 1276 patients who had undergone coronary stent placement and in whom 6-month angiographic follow-up was available, we identified 144 patients with a total coronary occlusion which matched a non-occluded coronary lesion in another 144 patients. Matching lesion pairs were of the same type (de novo or restenotic), were supplied with the same type of stent, had reference vessel diameters identical within 0·3 mm and stented vessel segment lengths identical within 8 mm, and were located in corresponding target vessels. After stenting, statistically identical minimal lumen diameters had been achieved in both groups (occluded: 2·74 ± 0·35 mm, non-occluded: 2·77 ± 0·32 mm, P=0·45). At follow-up, minimal lumen diameters were not different (occluded: 1·65 ± 0·77 mm, non-occluded: 1·76 ± 0·76 mm, P=0·24), reflecting an identical late lumen loss for occlusions (1·09 ± 0·76 mm) and non-occluded lesions (1·01 ± 0·70 mm, P=0·38). Because of the significantly larger acute gain, the loss index was significantly lower for occluded vessels (0·40 ± 0·27 vs 0·51 ± 0·35, P=0·003). Corresponding restenosis rates were 33% (occluded) and 28% (non-occluded; P=0·44). For stented vessel segment lengths >18 mm, restenosis rates were markedly higher (occluded: 42%, non-occluded: 36%) than for stented vessel segment lengths ≤18 mm (occluded: 25%, non-occluded: 22%).

**Conclusions** In occluded and non-occluded coronary lesions matched for factors known to affect the angiographic outcome, no difference between the respective restenosis rates was observed within 6 months of coronary stenting. Thus, either type of coronary lesion appears to exhibit the same propensity for neointimal hyperplasia.

(Eur Heart J 1999; 20: 1175–1181)

**Key Words** Stents, occlusions, coronary disease, restenosis, angiography.

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**Introduction**

Balloon angioplasty of coronary occlusions, as opposed to non-occluded coronary lesions, has been associated with a significantly higher 6-month restenosis rate[1–4]. To explain this discrepancy, several mechanisms are conceivable: an increased propensity in occlusions for thrombus formation at the luminal surface of the lesion, increased elastic recoil, increased vessel remodelling[5], and enhanced neointimal hyperplasia secondary to increased vessel wall injury[6,7]. The placement of coronary stents in non-occluded coronary lesions has been demonstrated to reduce the restenosis rate[8,9]. Also, stenting as opposed to balloon angioplasty of coronary occlusions has recently been shown to lower the restenosis rate[10–13].

It is not known, though, whether stented coronary occlusions ‘behave’ differently during follow-up from stented non-occluded coronary lesions, that is, if their very nature gives rise to a different angiographic outcome. Regardless of whether the target lesion is an occluded or a non-occluded coronary lesion, patient characteristics such as the presence or absence of diabetes, lesion characteristics such as a de novo or a restenotic/reoccluded lesion, angiographic variables such as the baseline reference vessel diameter and the minimal lumen diameter after stenting, and, lastly, procedural
variables such as the type of stent implanted and the length of the stented vessel segment are all known (or suspected) to influence angiographic outcome after stenting\cite{14}. It was therefore the purpose of this study to minimize any influence of these variables by matching and then assessing the restenosis rates after stenting in patients with coronary occlusions vs patients with non-occluded coronary lesions.

**Methods**

**Patients**

Between April 1994 and December 1996, 1928 consecutive patients underwent coronary stent placement at our institution. There were 294 patients who had exclusively non-acute coronary occlusions (age >1 week; thrombolysis in myocardial infarction (TIMI) flow grade 0 or 1; total number, 340) and 1538 patients who had exclusively non-occluded coronary lesions (total number, 2066); the remaining 96 patients had both occluded (total number, 113) and non-occluded coronary lesions (total number, 128). Six-month follow-up angiography data were available from 192 patients (65%) with exclusively occluded coronary lesions (total number, 214), from 1034 patients (67%) with exclusively non-occluded coronary lesions (total number, 1373), and from 50 patients (52%) with both occluded (total number, 60) and non-occluded coronary lesions (total number, 69). This cohort of 1276 patients with a total of 274 occluded and 1442 non-occluded coronary lesions comprised the study group.

**Coronary intervention**

The patients were informed about the coronary interventional procedure and gave their written consent. During the procedure, a total of 10 000 to 15 000 units of heparin were given as a bolus injection. Balloon angioplasty utilized the monorail system after passage of the lesions with a guide wire. Adjunctive stent implantation was routinely performed after recanalization of a total occlusion and in non-occluded lesions if the following criteria were met: (1) suboptimal result of balloon angioplasty (residual stenosis >20% or major dissection) or (2) bailout situation.

High-pressure stent implantation was angiographically guided using non-compliant balloons. The aim was to achieve a visually estimated residual diameter stenosis of 0%. Patients were discharged on a 4 to 12 weeks prescription combination of 100 mg. day\(^{-1}\) of acetylsalicylic acid and 500 mg. day\(^{-1}\) of ticlopidine. A repeat angiogram was scheduled after 6 months.

**Quantitative coronary angiography**

Angiographic variables obtained for every patient included the reference vessel diameters proximal and distal to the lesion and the minimal lumen diameter. Measurements were taken in identical ‘worst view’ projections using a hand-held digital caliper with optically magnified images. The proximal and distal reference vessel diameters were averaged to obtain a mean reference vessel diameter. The primary end-point of the study was restenosis at follow-up, defined as a diameter stenosis of \(\geq 50\%\).

**Definitions of derived angiographic variables**

Acute gain=minimal lumen diameter post-stenting minus minimal lumen diameter at baseline; late lumen loss=minimal lumen diameter post-stenting minus minimal lumen diameter at follow-up; loss index=late lumen loss divided by acute gain.

**Matching**

A computerized algorithm was used to find pairs of occluded and non-occluded lesions which matched with respect to the patient’s gender and history of diabetes, the target vessel, the type of lesion (de novo or restenotic), and the type of stent used. The reference vessel diameter and stented vessel segment length had to be identical within 0.3 mm and 8 mm, respectively. The matching algorithm was programmed such that the 274 occluded lesions were consecutively called up, and for each, the set of non-occluded lesions was scanned for a stenosis meeting the matching criteria. In case of a successful matching, neither lesion nor patient could be matched again.

**Statistics**

Continuous variables are presented as mean \(\pm\) standard deviation, where appropriate. In case of a non-Gaussian distribution, median and range are given. Group differences among continuous variables were assessed with the Mann–Whitney U-test. Nominal data were analysed with the chi-square test. Statistical significance was assumed at the 5% level.

**Results**

**Lesions**

The 274 total occlusions were supplied with stents of a median total length of 24 mm, whereas in the 1442 non-occluded lesions the median length of the stented vessel segment amounted to only 15 mm (\(P<0.001\)). A statistically significant difference between both sets of lesions was also found for the restenosis rates (occlusions: 38% vs non-occluded lesions: 27%, \(P<0.001\)).

**Matched patients**

The matching process yielded 144 lesion pairs in 288 patients. Pertinent characteristics for these patients are
summarized in Table 1. There were no statistically significant differences between patients with total occlusions and patients with non-occluded lesions (except for the prevalence of hypertension).

**Indication for repeat angiography**

Repeat angiography in the 288 matched patients was performed electively in 102 patients with total occlusions (71%) and in 97 patients with non-occluded coronary lesions (67%), on the grounds of recurrent symptoms in 42 patients with total occlusions (29%) and in 47 patients with non-occluded coronary lesions (33%,

**Angiographic analysis of matched lesions**

Table 2 summarizes the angiographic and procedural variables for matched lesions. The cumulative frequency distributions for minimal lumen diameter at baseline, after stenting and at follow-up are shown in Fig. 1. Despite the significantly different baseline, the minimal lumen diameter achieved acutely after stenting was not different for occluded vs non-occluded lesions. The slight difference between minimal lumen diameters at follow-up did not reach statistical significance; this fact is also reflected in a similar late lumen loss in both groups (Fig. 2). The loss index, however, was significantly lower for occlusions (0.40 ± 0.27 vs 0.51 ± 0.35, P=0.003; Fig. 3). In contrast to the whole cohort of occluded and non-occluded lesions, the restenosis rate for matched occlusions was statistically not different from that of non-occluded lesions (33% and 28%, respectively).

The restenosis rates for matched occluded and non-occluded lesions were also determined relative to baseline reference diameter, minimal lumen diameter post-stenting, and length of the stented vessel segment. Lesions for which either of the former two variables exceeded 2.75 mm tended to be associated with lower restenosis rates. For stented vessel segment lengths ≤18 mm, a significantly lower restenosis rate was found than for stented vessel segment lengths >18 mm (24% vs 39%, respectively, P=0.006). The restenosis rates for both occluded and non-occluded lesions were lower for stented vessel segment lengths ≤18 mm (25% and 22%, respectively) than for stented vessel segment lengths >18 mm (42% and 36%, respectively; P=0.045 between occlusions, P=0.073 between non-occluded lesions; Fig. 4). Within either range of stented vessel segment lengths, no statistically significant difference was found between occluded and non-occluded lesions.

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**Table 1  Demographic patient data**

<table>
<thead>
<tr>
<th></th>
<th>Occlusions</th>
<th>Non-occluded lesions</th>
<th>P</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>144</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>125 (87%)</td>
<td>125 (87%) (M)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 ± 9</td>
<td>59 ± 9</td>
<td>0.52</td>
</tr>
<tr>
<td>Angina class (CCS)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (5%)</td>
<td>13 (9%)</td>
<td>0.54</td>
</tr>
<tr>
<td>1</td>
<td>13 (9%)</td>
<td>13 (9%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62 (43%)</td>
<td>59 (41%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>53 (37%)</td>
<td>46 (32%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9 (6%)</td>
<td>13 (9%)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>19 (13%)</td>
<td>18 (13%) (M)</td>
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<tr>
<td>Diabetes</td>
<td>11 (8%)</td>
<td>11 (8%) (M)</td>
<td></td>
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<tr>
<td>Hyperlipidaemia</td>
<td>101 (70%)</td>
<td>106 (74%) (M)</td>
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<tr>
<td>Hypertension</td>
<td>70 (44%)</td>
<td>88 (56%)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>never</td>
<td>51 (35%)</td>
<td>62 (43%)</td>
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<tr>
<td>current</td>
<td>47 (33%)</td>
<td>32 (22%)</td>
<td></td>
</tr>
<tr>
<td>ex</td>
<td>46 (32%)</td>
<td>50 (35%)</td>
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<tr>
<td>Coronary artery disease</td>
<td></td>
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<tr>
<td>1 vessel</td>
<td>67 (47%)</td>
<td>52 (36%)</td>
<td></td>
</tr>
<tr>
<td>2 vessels</td>
<td>57 (40%)</td>
<td>68 (47%)</td>
<td></td>
</tr>
<tr>
<td>3 vessels</td>
<td>20 (14%)</td>
<td>24 (17%)</td>
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<tr>
<td>Prior CABG</td>
<td>2 (1%)</td>
<td>6 (4%)</td>
<td>0.28</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>69 (48%)</td>
<td>53 (37%)</td>
<td>0.07</td>
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<td>Target vessel distribution</td>
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<td>(M)</td>
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<tr>
<td>LAD</td>
<td>59 (41%)</td>
<td>59 (41%)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>33 (23%)</td>
<td>33 (23%)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>52 (36%)</td>
<td>52 (36%)</td>
<td></td>
</tr>
</tbody>
</table>

CABG=coronary artery bypass grafting; CCS=Canadian Cardiovascular Society; LAD=left anterior descending coronary artery; LCx=left circumflex coronary artery; RCA=right coronary artery; (M)=variable included in matching algorithm.
Collaterals

Clearly discernible collaterals were present in 103 occluded (72%) and 16 non-occluded lesions (11%). Restenosis rates in occluded lesions corrected for the presence or absence of collaterals, were 34% and 29%, respectively \((P=0.728)\); in non-occluded lesions, the corresponding restenosis rates were 13% and 30%, respectively \((P=0.250)\).

Matched versus unmatched lesions

Mean baseline reference diameter \((2.92 \pm 0.54 \text{ mm})\) and mean minimal lumen diameter post-stenting \((2.78 \pm 0.43 \text{ mm})\) for the 130 unmatched occlusions were statistically not different from the corresponding values (cf. Table 2) for the 144 matched occlusions. In the unmatched set of lesions, though, the median length of the stented vessel segment was at 30 mm (range, 6–156 mm) significantly longer than in the matched set of lesions \((P<0.001)\). However, this difference did not result in statistically significant differences in minimal lumen diameter at follow-up \((1.49 \pm 0.92 \text{ mm}, \ P=0.12\) vs matched occlusions) and restenosis rate \((43\%, \ P=0.098\) vs matched occlusions) and restenosis rate \((43\%, \ P=0.098\) vs matched occlusions).

In the 1298 unmatched non-occluded lesions, the median stented vessel segment length was at 15 mm (range, 4–99 mm) shorter by 1 mm \((P<0.001)\) than in the 144 matched non-occluded lesions. No statistically significant differences were found between the two sets of lesions as regards baseline reference diameter \((2.90 \pm 0.45 \text{ mm})\), minimal lumen diameter post-stenting \((2.82 \pm 0.38 \text{ mm})\) and at follow-up \((1.81 \pm 0.81 \text{ mm})\), and restenosis rate (27%).

Discussion

Major findings

This study is based on the retrospective analysis of 1276 consecutive patients who had undergone high-pressure stent placement in a total of 274 non-acute coronary occlusions and 1442 non-occluded coronary lesions and in whom repeat angiography had been performed electively in about 70% of patients and on the grounds of recurrent symptoms in the remainder. The restenosis
rate in the group of occlusions was at 38% significantly higher than in the group of non-occluded lesions where it was only 27%. However, the median length of the stented vessel segment — a variable known to affect restenosis — was found to be significantly higher in the group of occlusions than in the group of non-occluded lesions (namely, 24 mm vs 15 mm). Therefore, it is possible that the longer stented vessel segment length was responsible for the higher restenosis rate in occlusions. To minimize the influence of such confounding factors on the restenosis rate, and possibly to determine an effect solely related to the nature of the lesion (i.e., occluded or non-occluded), matching of the lesions for known confounding variables was performed.

The matching process identified 144 lesion pairs. In these, the acute result of the intervention (in terms of minimal lumen diameter and residual diameter stenosis) was the same for both lesion groups. At follow-up,
minimal lumen diameter and percent diameter stenosis were also not different between groups, indicative of an identical late lumen loss for occluded and non-occluded lesions. Interestingly, the loss index, i.e. the late lumen loss normalized by the acute lumen gain, was lower for occlusions. This indicates that, in occlusions, the significantly higher degree of lumen enlargement required to achieve an acute angiographic result identical to that of non-occluded lesions is not compensated for by an increased late lumen loss. The restenosis rates in the matched lesion subsets (33% for occluded and 28% for non-occluded lesions) were statistically not different, and neither were the reocclusion rates (5% and 3%, respectively).

Collaterals

The presence of angiographically visible collateral flow has been shown to be a predictor of restenosis after balloon angioplasty\textsuperscript{[17]}. In our study, no statistically significant difference in restenosis rates was found between lesions subtended by collaterals and lesions for which no collaterals were visible, either for occluded or for non-occluded lesions. The absence after coronary stenting of a negative remodelling enhanced by collateral flow might explain this finding.

Lesion matching

Since the matching algorithm attempted to assign a non-occluded lesion to every occlusion under the conditions presented, no corresponding non-occluded lesion could be found for 130 occlusions (47%). These turned out to have a significantly longer median stented vessel segment length (i.e. 30 mm) than the matched occlusions, indicative of the fact that occlusions tended to be longer than non-occluded lesions. Nevertheless, stented vessel segment lengths up to 64 mm were included among the matched sets of lesions. Thus, we feel that the findings of this study hold true for an acceptably wide range of lesion lengths encountered in clinical practice.

Possible differences in mechanisms of restenosis between occluded and non-occluded lesions

An occlusion per se is considered to be a risk factor for a poor late outcome after balloon angioplasty\textsuperscript{[1,2,4]} and also after stenting\textsuperscript{[14]}. In this study, the late lumen loss was not different between occluded and non-occluded lesions, when matched for factors known to affect the
restenosis rate. This indicates that neither a greater amount of thrombotic material present before stenting \[13,18,19\] nor deeper vessel wall injury, nor increased wall stress induced by stenting \[6,7\] appear to affect late angiographic outcome in occlusions other than in non-occluded lesions.

**Length of stented vessel segment**

The length of the stented vessel segment is known to be a major determinant of late outcome in non-occluded \[14-16\] as well as occluded lesions \[5,13\]. In the present study, the restenosis rate was significantly higher for stented vessel segment lengths \(>18 \text{ mm}\) than for shorter stented vessel segment lengths \((\geq 18 \text{ mm})\). This was true for both occluded and non-occluded lesions. However, within either range of stented vessel segment lengths no difference was found between the restenosis rates of the matched cohorts of occluded and non-occluded lesions.

**Limitations of the study**

This study had a retrospective design. Our findings therefore need to be validated in a prospective study. Overly long occlusions were under-represented because no corresponding non-occluded lesions could be assigned under the matching conditions. Computerized quantitative coronary angiography was not available. However, it has been shown that quantitative coronary angiography using a hand-held digital caliper compares favourably with the computerized technique \[20\].

**Conclusions**

Stenting of occluded as opposed to non-occluded coronary artery lesions is not associated with different restenosis rates when the lesions are matched for factors known to affect the angiographic outcome, specifically, when the length of the stented vessel segment is not different between these types of lesion. Since neointimal hyperplasia remains a major factor in late luminal narrowing after stenting, the propensity for neointima formation is apparently not different in occluded and non-occluded coronary lesions.

**References**