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Fate of Stent-Related Side Branches After Coronary Intervention in Patients With In-Stent Restenosis

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OBJECTIVES We sought to assess the fate of stent (ST)-related side branches (SB) after coronary intervention in patients with in-ST restenosis.

BACKGROUND In-ST restenosis constitutes a therapeutic challenge. Although the fate of lesion-related SB after conventional angioplasty or initial coronary stenting is well established, the outcome of ST-related SB in patients with in-ST restenosis undergoing repeat intervention is unknown.

METHODS One hundred consecutive patients (age 61 ± 11 years, 22 women) undergoing repeat intervention for in-ST restenosis (101 ST) were prospectively studied. Two hundred and twenty-six SB spanned by the ST were identified. The SB size, type, ostium involvement, location within the ST and take-off angle were evaluated. The SB TIMI (Thrombolysis in Myocardial Infarction trial) flow grade was studied in detail before, during, immediately after the procedure, and at late angiography.

RESULTS Occlusion (TIMI flow grade = 0) was produced in 24 (10%) SB, whereas some degree of flow deterioration (≥1 TIMI flow grade) was observed in 57 SB (25%). The SB occlusion was associated with non–Q wave myocardial infarction in two patients (both had large and diseased SB). Side-branch occlusion at the time of initial stenting (RR [relative risk] 11.1, 95% CI [confidence interval] 3.5–35.5, $p < 0.001$), diabetes (RR 3.5, 95% CI 1.1–10.5, $p = 0.02$), SB ostium involvement (RR 5.0, 95% CI 1.4–17.2, $p = 0.004$), baseline SB TIMI flow grade <3 (RR 5.5, 95% CI 1.7–18.1, $p = 0.005$), and restenosis length (RR 1.05 95% CI 1.01–1.11, $p = 0.03$) were identified as independent predictors of SB occlusion. Late angiography in 19 initially occluded SB revealed that 17 (89%) were patent again. The long-term clinical event-free survival (81% vs. 82% at two years) in patients with and without initial SB occlusion was similar.

CONCLUSIONS Occlusion or flow deterioration of SB spanned by the ST is relatively common during repeat intervention for in-ST restenosis. Several factors (mainly anatomic features) are useful predictors of this event. However, most SB occlusions are clinically silent and frequently reappear at follow-up. (J Am Coll Cardiol 2000;36:1549–56) © 2000 by the American College of Cardiology

Coronary stenting is the most frequently used technique today during coronary interventions (1–5). The implantation of stents (ST) has experienced an exponential increase after some technical and pharmacological refinements have dramatically improved procedural results (3,4). Multiple customized ST designs currently allow the treatment of a wide spectrum of coronary lesions, including those with untoward anatomical features (1–5). However, in-ST restenosis is being increasingly recognized as a challenging clinical problem affecting a growing number of patients (6–13). Different strategies (balloon angioplasty, debulking techniques, brachytherapy and repeat stenting) are currently advocated for the treatment of these patients, yet the procedure of choice remains elusive (6–13). In addition, the outcome of lesion-associated side branches (SB) after conventional angioplasty (14,15) or coronary stenting (16–23) is well established. Nevertheless, the fate of ST-related SB in patients with in-ST restenosis undergoing repeat coronary intervention remains unsettled. Accordingly, the present prospective study was undertaken to assess the incidence, predictive factors and implications of SB occlusion in patients treated for in-ST restenosis.

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METHODS

Patient group. From November 1991 to June 1998, a total of 100 consecutive patients with in-ST restenosis (101 ST) underwent repeat coronary interventions in our hospital. All these patients had angina or objective evidence of ischemia. The characteristics and fate of the 226 SB spanned by these ST were analyzed.

Procedure and protocol. Both the protocol and the technique of coronary stenting in our center have been previously described in detail (5,24). Briefly, balloon catheters and the ST type at the time of initial stenting were selected at the discretion of the primary operator. Since 1994, relatively high pressures (≥12 atm) have been systematically used, and this policy was coincident with the use of both aspirin and ticlopidine on a routine basis. Several types of ST with restenosis were treated: Palmaz-Schatz ST (John-

Abbreviations and Acronyms

ACC/AHA	= American College of Cardiology/American Heart Association
SB	= side branch(es)
ST	= stent(s)
TIMI	= Thrombolysis in Myocardial Infarction

son & Johnson Interventional Systems, Warren, New Jersey) (n = 25); Gianturco-Roubin Flex-ST (Cook, Bloomington, Indiana) (n = 25); NIR ST (Boston Scientific, Maple Grove, Minnesota) (n = 22); Multilink ST (ACS, Guidant, Temecula, California) (n = 10), and other types (n = 19). Patients with in-ST restenosis involving saphenous vein grafts were excluded from the study. Our follow-up protocol in patients undergoing coronary stenting included clinical assessment at one and six months and yearly thereafter, in a specific clinic devoted to patients with percutaneous coronary interventions. In these visits an exercise test (or alternative tests to elicit ischemia) was scheduled.

Our protocol of repeat angioplasty for patients with in-ST restenosis has also been reported elsewhere (9). All patients signed written, informed consent for the procedure. Balloon size and inflation pressure were left to the discretion of the primary operator after reviewing those used during initial ST implantation. As a general rule, pressures similar to those employed during initial stenting were selected, as was a balloon-to-artery ratio of 1.1:1. In some cases, including some patients with diffuse in-ST restenosis, debulking/facilitating techniques or even repeat stenting procedures were indicated according to the criteria of the primary operator. If repeat stenting was selected, coil designs were avoided whenever possible. Most patients undergoing "elective" repeat stenting were included in a pilot study assessing the results of this strategy (25). Aspirin was the only antiplatelet agent systematically used after the procedure except in patients undergoing repeat stenting, who also received ticlopidine. Serial (every 8 h) enzyme measurements and 12-lead electrocardiograms (ECGs) were obtained during the first 24 h in all patients. A careful clinical follow-up was performed, and telephone contact with the patient or referring physician was attempted for those patients who did not return for follow-up.

In addition, all these patients were asked to return for routine late angiography (six to nine months). Nevertheless, this protocol was made flexible in selected patients (multiple interventions, vascular access difficulties, etc.) when they expressed reluctance to late angiography and they were asymptomatic and ischemia-free at follow-up. During follow-up, clinical events were defined as myocardial infarction, requirement for target vessel revascularization, or death. The diagnosis of myocardial infarction required two of the following: 1) typical, prolonged (>30 min) precordial pain; 2) development of abnormal Q waves; and 3) creatinine kinase increase ≥2 times the upper normal value. All this information was prospectively entered in our dedicated, relational database.

Angiographic analysis. Detailed *qualitative analyses* were performed jointly by two experienced observers who were blinded to the procedure information. Lesion characteristics were established using different projections (24–26). Care was taken in trying to identify, on fluoroscopy, the site of ST deployment in each projection before the injection of contrast material. This was subsequently related to the exact location of the restenosis narrowing and SB location. Vessels with a Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 (27) were classified as occluded. The modified American College of Cardiology/American Heart Association (ACC/AHA) criteria were also used to classify the morphology of the in-ST restenosis lesion (26). In addition, lesions >10 mm in length were considered diffuse restenosis. For the purposes of the present study, special care was taken to identify and classify all ST-related SB (as visualized just before treatment of in-ST restenosis). Any SB that was incorporated within the longitudinal confines of the ST (bridged by the ST) was analyzed.

Side branches were divided into those emerging from within the ST body and those located near (≤3 mm) the ST edges. A take-off angulation <45° or >135° from the parent vessel was considered unfavorable (at risk for occlusion). The SB were further assessed for the presence of ostial narrowing (mild 25% to 50%, moderate 50% to 75%, severe >75%). A previously reported classification of SB (17) was followed. Briefly, SB were classified as type A (≥1 mm in diameter with ostial narrowing), type B (≥1 mm in diameter, without ostial involvement), type C (<1 mm in diameter with ostial narrowing), and type D (<1 mm in diameter without ostium narrowing). The TIMI flow of the ST-related SB was assessed before and after the procedure. When different adjunctive or synergistic devices were used, the exact temporal relation to SB changes was recorded. In addition, SB changes during repeat intervention for in-ST restenosis were correlated to the SB changes that had previously occurred at the time of initial ST implantation. Matching angiographic views were reviewed before intervention, following initial balloon dilation, following specific device (when used), immediately after the procedure and at follow-up.

Quantitative angiographic analysis was carried out off-line by an experienced operator who was blinded to the patient's clinical or procedural characteristics. A commercially available, previously validated, interactive, automatic edge-detection algorithm (ARTREK, Quantim 2000I, QCS, ImageComm Systems) was used (5,17,24). Cine sequences displaying the most severe lumen narrowing, without foreshortening of the selected coronary segment, were selected from among multiple projections. End-diastolic cine frames were selected from a Tagarno 35AX and were digitized with a high-quality cine-video converter. Quantitative analysis was performed in the stented (trunk) parent vessel.

Table 1. Baseline Clinical and Angiographic Characteristics

Clinical Data	
Age (yrs)	61 ± 11
Female gender	22 (22%)
Hypertension	56 (56%)
Hypercholesterolemia	48 (48%)
Diabetes	23 (23%)
Cigarette smoking	68 (68%)
Reason for coronary angioplasty	
Stable angina	30 (29%)
Unstable angina	50 (50%)
Acute myocardial infarction	1 (1%)
Silent ischemia	19 (19%)
Previous myocardial infarction	51 (51%)
Previous bypass surgery	5 (5%)
Multivessel disease	50 (50%)
≥2 Previous PTCA procedures	31 (31%)
≥2 at the target site	20 (20%)
Angiographic Data	
Left ventricular ejection fraction (%)	67 ± 12
Site of ST restenosis (101 ST)	
Left main	2 (2%)
Left anterior descending	61 (60%)
Right	27 (27%)
Left circumflex	11 (11%)
Total occlusion	6 (6%)
ACC/AHA Classification B2-C	80 (80%)
Diffuse restenosis (>10 mm)	71 (71%)

ACC/AHA = American College of Cardiology/American Heart Association Classification; PTCA = percutaneous transluminal coronary angioplasty; ST = stent.

Statistical analysis. Continuous variables were expressed as mean ±SD and were compared with the two-tailed Student *t* test or the Wilcoxon nonparametric test, as required. Either the chi-square or Fischer exact test was used for discrete variables (absolute values and percentages). Several (18 clinical, 29 procedural and 54 angiographic) variables were studied in relation to the occurrence of SB occlusion and SB flow deterioration. In addition, predictors of SB occlusion or flow deterioration were evaluated with logistic regression analysis. Factors showing a p value <0.15 on univariate analysis were entered into the model. Relative risk (RR) and adjusted RR, with 95% confidence intervals (CI) were calculated. Likelihood ratios were also calculated. Rates of event-free survival were studied with Kaplan-Meier analysis. The Breslow exact test was used to study differences in event-free survival in patients with and without SB occlusion. The SPSS for Windows (version 8.0) statistical software package was used. A p value <0.05 was considered statistically significant.

RESULTS

Procedural results. Baseline demographic characteristics of the 100 study patients are presented in Table 1. Mean age of the group was 61 ± 11 years (range 32 to 82 years) and 22 patients were women. All these patients had angina (mainly unstable angina) or objective evidence of ischemia. Most of these patients had good left ventricular ejection fraction, although a prior history of myocardial infarction was present in half of them (Table 1). The elapsed time from initial stenting to repeat intervention was 194 ± 111 days. Relevant angiographic data are also summarized in Table 1. Most ST were located on the left anterior descending coronary artery, and the restenosis had a relatively complex morphology. Procedural characteristics at the time of initial ST implantation and during the index procedure are displayed in Table 2. Most procedures, 45 (44%) were performed with balloon dilation alone. The "watermelon seed" phenomenon was transitorily observed in six patients. In the remaining patients, including some with diffuse in-ST restenosis, debulking/facilitating techniques (excimer

Table 2. Procedural Data

Complete revascularization*		61 (61%)	
During diagnosis†		34 (34%)	
Emergency‡		8 (8%)	
Type of procedure§			
PTCA alone		45 (44%)	
Adjunctive debulking		19 (19%)	
Repeat stenting		37 (37%)	
Double wire		9 (9%)	
Technical data	Initial ST	Index	p Value
Maximal pressure (atm)	10.9 ± 3.1	11.5 ± 3.0	NS
Balloon diameter (mm)	3.2 ± 0.4	3.2 ± 0.4	NS
Balloon/artery ratio	1.03 ± 0.1	1.07 ± 0.1	NS
Reference vessel (mm)	3.1 ± 0.4	3.0 ± 0.4	NS
Baseline MLD (mm)	0.35 ± 0.3	0.51 ± 0.3	0.01
Post-PTCA MLD (mm)	2.61 ± 0.5	2.37 ± 0.5	0.01
Acute gain (mm)	2.24 ± 0.83	1.75 ± 0.7	0.01
Lesion length (mm)	13.2 ± 9.1	14.8 ± 9.1	NS
ST length (mm)††	22.0 ± 10	21.1 ± 9	NS
ST indication††			
Elective	55 (55%)	29 (78%)	NS
Unplanned	46 (45%)	8 (35%)	NS

PTCA = percutaneous transluminal coronary angioplasty; ST = stent; MLD = miminal lumen diameter. *All major vessels with >70% lumen diameter stenosis. †Ad hoc angioplasty, during the same diagnostic angiographic procedure. ‡Procedures performed on an urgent basis (i.e., not included in the schedule). §At the discretion of the primary operator. ††Index procedure only of the 37 patients undergoing stenting.

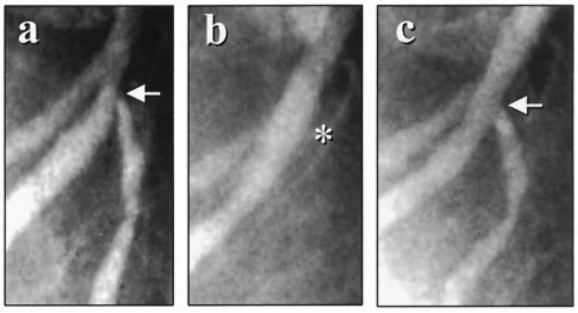

Figure 1. Angiogram in the left anterior oblique projection with cranial angulation showing a restenosed stent in the proximal left anterior descending coronary artery **(a)**. The distal part of the stent spanned a disease-free septal branch (Type B) and a diagonal branch **(arrow)** with ostial involvement (Type A). After treatment **(b)** a good angiographic result was obtained in the left anterior descending coronary artery (parent vessel); the septal branch remained patent but the diagonal branch became occluded **(asterisk)**. This occlusion was clinically silent. The six-month angiogram **(c)** revealed an adequate angiographic result on the left anterior descending coronary artery and patency (reappearance) of the diagonal branch **(arrow)**.

laser = 15; rotablator = 1; cutting balloon = 3) and even repeat stenting (37 patients, 29 [78%] elective, 8 [22%] after failure or suboptimal result with the primary device) were used. The ST used during repeat stenting included: NIR ST (n = 18), Multilink ST (n = 10), Crown ST (n = 4), Gianturco-Roubin ST (n = 3), other types (n = 2).

Angiographic success was obtained in 100 of the 101 (99%) ST. Dilation failure without complications occurred in one patient. Four patients developed a myocardial infarction (only one Q wave). The Q wave infarction was produced after vessel occlusion distal to the treated ST. A non–Q wave infarction was associated with a SB occlusion during ST implantation in a de novo lesion in *another vessel*. Two patients with ST-related SB occlusions (both Type A diagonal branches) had non–Q wave infarctions. In both cases, the SB (not previously protected) was treated after its occlusion (prolonged angina and ST segment changes), eventually with angiographic success. Although these patients were asymptomatic when they left the hemodynamic room, both developed mild (390 and 480 IU of creatinine kinase) enzymatic changes.

Side-branch changes. Of the 226 ST-related SB, 94 (42%) were ≥1 mm, 101 (45%) had associated ostial disease (21 mild, 38 moderate, 42 severe), 80 (35%) had an unfavorable (angulated) takeoff, and 42 (18%) were located near (≤3 mm) the ST margins. Twenty-four SB (10%) became occluded after the intervention (Figs. 1 and 2), and in 57 (25%) a deterioration in anterograde flow (≥1 TIMI flow grade) was documented. In three patients with severe in-ST restenosis, *improvement* in SB flow was seen after intervention. The fate of SB in relation to SB type and classification is presented in Figure 3. Side-branch occlusion was seen in 20 cases (20%) with versus 4 (3%) cases without ostial involvement ($p < 0.001$). Any severity of ostial disease was related to this adverse outcome.

The influence of different clinical, procedural and anatomic variables on SB changes is presented in Figure 4. On logistic regression analysis, SB occlusion at the time of initial stenting, diabetes, SB ostial involvement, SB TIMI flow grade <3, and restenosis length were identified as independent predictors of SB occlusion. The influence of balloon/artery ratio, however, disappeared after adjustment. This model had a sensitivity of 83.3% and a specificity of 79.3% to predict SB occlusion. The probability of SB occlusion within the model was 38.5% when both ostial disease and TIMI flow grade <3 were present (18 SB) and only 2.6% when none of these factors was found (112 SB). When prior SB occlusion at initial stenting was added to the presence of TIMI flow grade <3 and ostium disease (16 SB), the probability of occlusion increased to 65% (vs. only 1% when none of these three factors were present). In addition, although use of device (other than balloon) and adverse SB angulation were associated with SB flow deterioration (Fig. 4, bottom), this was no longer seen after adjustment. Of the 24 SB that became occluded, 10 (41%) also had suffered occlusion (TIMI flow grade 0–1, without enzymatic changes or any clinical sequelae) during initial ST implantation (Table 3). Furthermore, late angiography was available in 19 of the 24 occluded SB, revealing that 17 (89%) were again patent (Figs. 1 and 2).

Clinical and angiographic follow-up. Late clinical follow-up (mean 21 ± 18 months, range 3 to 102 months) was obtained in all (100%) patients. During this time three patients died (all noncardiac causes), none suffered a myocardial infarction, and 24 patients required revascularization (20 coronary angioplasty [14 target site, 6 other site] and 4 coronary surgery). The event-free survival at two years was similar for patients with and without SB occlusion (81% vs. 82%; NS). In addition, recurrent restenosis rate (with a 74% rate of late angiography in eligible patients) was documented in 33/70 (47%) patients; again, this was not influenced by the previous occurrence of SB occlusion.

DISCUSSION

Interventional catheter-based therapy has been revolutionized by the widespread use of coronary ST (1–5). Consequently, in-ST restenosis has become a major clinical problem affecting an increasing number of patients (6–17). Histopathologic studies have demonstrated that in-ST restenosis results from smooth muscle cell hyperplasia (28), whereas intravascular ultrasound has confirmed that in-ST restenosis is caused by soft tissue growth within the ST, without significant changes of the metallic struts (29,30). Conventional balloon angioplasty has been used for many years in patients presenting with ST restenosis (6–9). This technique is readily performed and is associated with good initial clinical and angiographic results (6–9). Additional ST expansion and tissue extrusion out of the ST struts contribute to the lumen enlargement obtained with balloon dilation (29). However, some of these patients, in particular those with diffuse in-ST restenosis, have relatively high

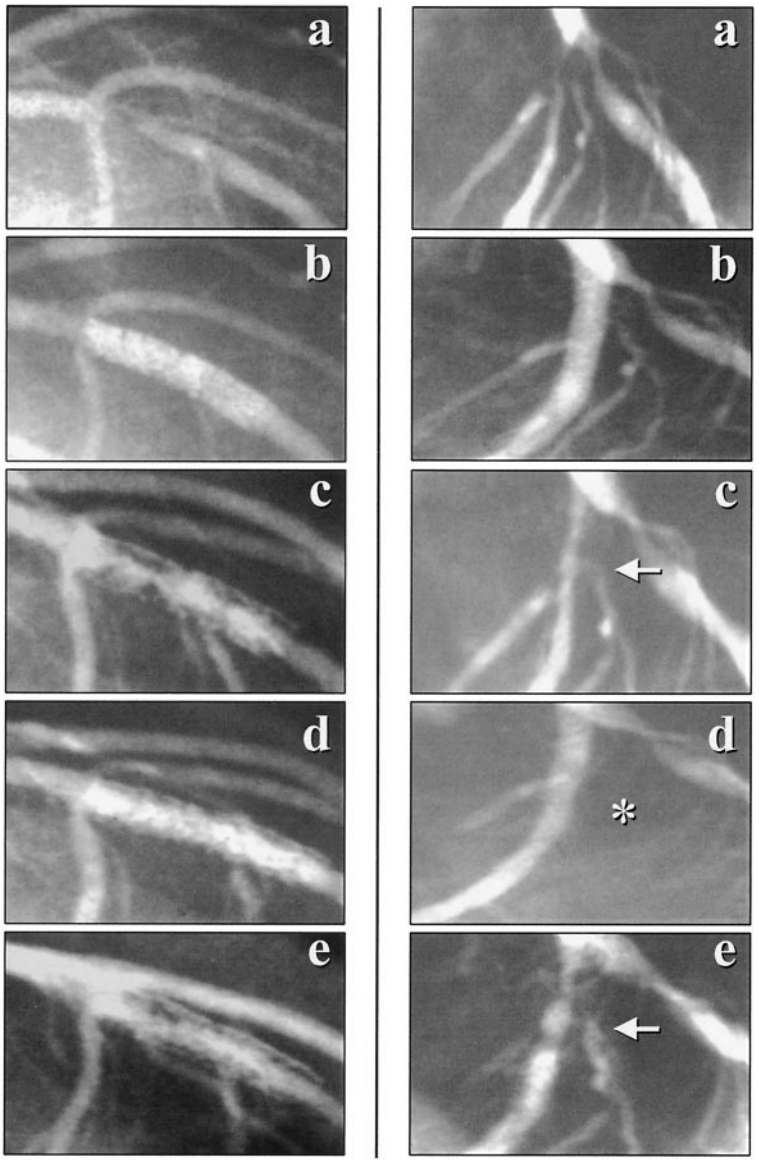

Figure 2. Left panel. Angiogram in the right anterior oblique projection revealing a severe stenosis in the mid-left anterior descending coronary artery. **(a)** De novo lesion. **(b)** After initial stenting. **(c)** Stent restenosis (before treatment). **(d)** Immediately after treatment of in-stent restenosis (index procedure). **(e)** At six-month follow-up. A large diagonal branch and two small septal perforator side branches are always visualized. **Right panel.** Angiogram in the left anterior oblique projection with cranial angulation in a patient with a tight lesion in the proximal left anterior descending coronary artery (**a** to **e**, timing same as above). A diagonal branch—with severe ostium involvement—remained patent after initial stenting, occluded (without clinical sequelae) during treatment of in-stent restenosis **(asterisk)** and reappeared at follow-up **(arrow)**.

recurrent restenosis rate (11,12). In this setting, removal of the intra-ST proliferative material with debulking techniques has been advocated to optimize final results and reduce the restenosis rate (10–12). More recently, great enthusiasm has been generated by the use of brachytherapy to prevent recurrent restenosis (13). Nevertheless, despite the large interest focused on clinical research in patients with in-ST restenosis, no information is yet available concerning the incidence, predictive factors and clinical implications of SB occlusion in this cohort of patients.

Outcome of side branches after balloon angioplasty and initial stenting. Side-branch occlusion during conventional coronary angioplasty is a well-described phenomenon occurring in up to 10% of patients (14,15). Potential mechanisms include displacement of atheromatous plaque to the ostium of the SB, embolization of atheromatous debris, thrombus formation, spasm and vessel dissection. The SB with proximal disease are particularly prone to experience occlusion after balloon dilation, being the clinical consequence directly related to SB vessel diameter (14,15).

Stent implantation may further jeopardize SB patency. Side-branch occlusion after ST implantation is also relatively frequent and a benign event (16–20). In many of these patients, SB occlusions occur during balloon predilation but also may be seen either during ST deployment or after high-pressure optimization. In addition to the above-

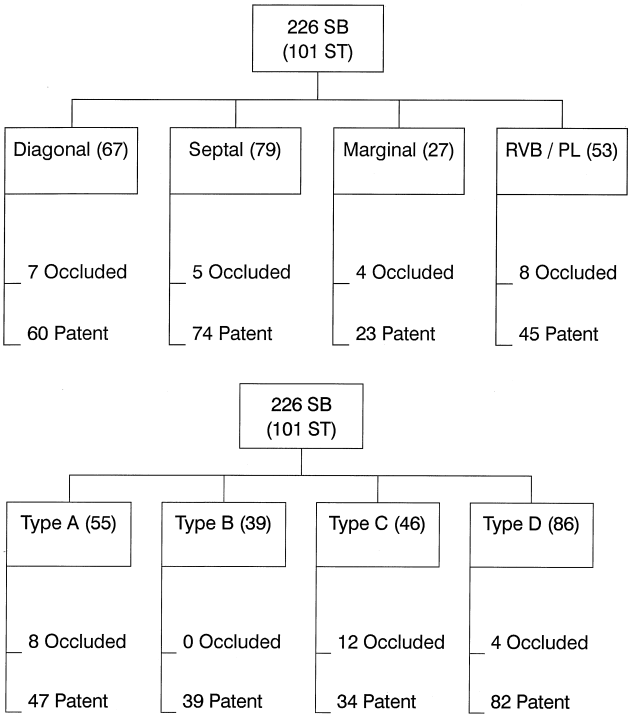

Figure 3. Flow diagram illustrating the occurrence of side-branch (SB) occlusion in relation to location **(top)** and SB classification **(bottom)**. RVB = right ventricular branch; PL = posterolateral branch; ST = stent.

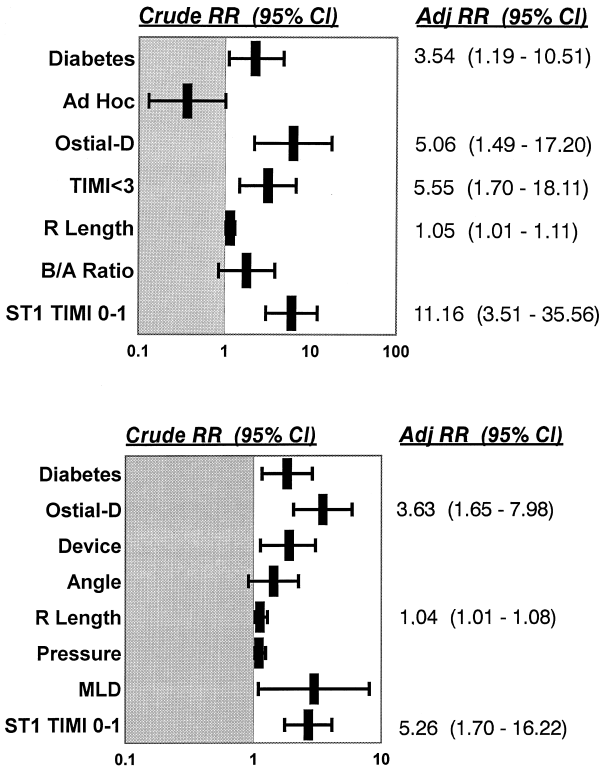

Figure 4. Clinical, procedural, and angiographic predictors of side-branch (SB) occlusion **(top)** and of SB flow deterioration **(bottom)**. Crude (unadjusted) relative risks (RR) and confidence intervals (CI) are displayed in a logarithmic scale. Adj RR = adjusted relative risks; Ad Hoc = procedures performed during the diagnostic coronary angiogram; Ostial-D = ostial disease in the SB; R Length = restenosis length (studied per 1 mm of increment); B/A Ratio = balloon/artery ratio using quantitative angiography (>1.13, upper tertile); Device = use of any device different from balloon angioplasty; angle = adverse takeoff angulation of the SB; MLD = minimal lumen diameter of the parent vessel after intervention (per 1 mm of increment); ST1 = during initial stenting.

described mechanisms occurring during balloon dilation, SB occlusion may result from partial or complete blockage of the SB by the ST struts (16,17). Finally, longitudinal redistribution of atherosclerotic plaque during high-pressure ST deployment in the parent vessel may contribute to the classic "snowplow" effect (20). In any case, the more aggressive dilation of the vessel during stenting is likely implicated.

Many factors appear to enhance the likelihood of SB occlusion during stenting. First, ostium involvement of the SB has been identified in most previous studies as a reliable predictor of SB occlusion (16–20). Second, it has been suggested that ST indication may also play a role because ST implanted to seal major vessel dissections are associated with a higher incidence of SB occlusion. In particular, SB arising within the dissecting plane are prone to occlusion (18). Finally, some investigators have suggested that some ST designs may offer particular advantages in patients with major SB who are to undergo ST implantation (18). The ratio of metal to free spaced area in the fully deployed ST can be also an important factor (16–18).

Most series have suggested that SB occlusion after stenting is a benign event. Spontaneous recanalization of the initially occluded SB may explain, at least in part, the low rate of adverse events. However, of particular concern is that ST placement across the SB results in the "stent jail" phenomenon, which may be clinically relevant when large SB require treatment. However, the inaccessibility to angioplasty catheters is only relative. Although "stent jail" limits interventional access to the compromised branch and the procedure is technically demanding, it appears to be safe and effective in up to 84% of patients (20). The ST-related SB may be easily dilated when they emerge from coil stents, but dilation through the ST diamonds in slotted-tube designs may be more challenging. Special care should be taken before dilation to know ST-diamond perimeter in order to select appropriate balloon diameters and avoid balloon rupture or entrapment. Moreover, during SB treatment one should always bear in mind the importance of the parent vessel, and every effort should be made to prevent any deterioration in its lumen.

Present findings. The following are the major findings of the present study: 1) repeat intervention in patients with in-ST restenosis has a 10% risk of acute SB occlusion; 2) most of these iatrogenic SB occlusions are clinically silent, and this phenomenon does not appear to have acute or long-term clinical implications; 3) although SB occlusion remains a largely unpredictable event, special care should be taken in patients with large SB that already became occluded during initial stenting and those SB with ostium compromise or a deteriorated flow; patients with diabetes

Table 3. Side-Branch Occlusion: Initial Stenting versus Treatment of In-Stent Restenosis. SB Occlusion (TIMI flow grade 0) During Intervention for In-ST Restenosis (n = 24)*

	Sensitivity	Specificity	+LR (95% CI)	−LR (95% CI)
TIMI flow grade 0 ST1 (n = 16)	17%	94%	2.81 (1.00–8.01)	0.89 (0.74–1.06)
TIMI flow grade 0–1 ST1 (n = 24)	42%	93%	6.01 (3.00–12.02)	0.63 (0.45–0.88)

SB = side branch; TIMI = Thrombolysis in Myocardial Infarction coronary flow grade; LR = likelihood ratio; ST = stent; ST1 = initial stent implantation; CI = confidence intervals.

*Of the 24 SB with TIMI flow grade 0 during the index procedure, 10 had previously experienced occlusion during initial stenting (4 TIMI flow grade 0 and 6 TIMI flow grade 1).

and those with diffuse restenosis are also at higher risk; and 4) most SB experiencing acute occlusion are patent at late follow-up.

We found that patients that had experienced SB occlusion during initial stent deployment had a 11-fold risk increase for subsequent occlusion of the same SB during repeat intervention for in-ST restenosis. In fact, this was the strongest independent predictor for SB occlusion. We also found a five-fold risk increase in SB with either preexisting ostial disease or abnormal flow. All these findings, suggesting a key role for anatomical factors, are in accordance with results obtained after balloon dilation or initial stenting (14–18). The presence of diffuse in-ST restenosis would in turn enhance the likelihood of SB occlusion.

Finally, diabetes mellitus also emerges as an important clinical risk factor, even after adjustment for other adverse baseline characteristics frequently found in these patients, such as vessel size. The influence of technical or procedural factors, however, appears to be less dramatic. We were unable to detect any protective effect of debulking techniques on ST-related SB outcome. On the contrary, in our series the use of devices other than balloons was associated with a higher risk of flow deterioration in the SB spanned by the ST, but this association disappeared after adjustment. Therefore, this may reflect a selection bias, in that such devices were more frequently used in complex cases. In fact, careful observations regarding the exact timing of SB occlusion during the procedure revealed that only a minority of SB occlusions could be directly attributable to debulking or repeat stenting itself. Furthermore, in our series some technical data associated with a more aggressive intervention (i.e., balloon/artery ratio, inflation pressures and final lumen diameters) were related to SB flow changes on univariate analysis. However, their influence on SB occlusion disappears after adjustment.

We can only speculate as to the mechanism of SB occlusion. However, potential mechanisms implicated in SB occlusion in this setting appear to be largely the same as those previously reported during dilation or ST implantation in de novo lesions. These include thrombus formation, dissection, plaque embolization (debris), ostial compromise by displaced ST struts and spasm at the ostium. However, this latter circumstance appears unlikely because intracoronary nitroglycerin was systematically given in our patients. Intimal disruption involving the ostium of the SB may be operative. Nevertheless, a special form of "snowplow effect" manifested by both plaque remodeling and material sifting along the cleavage plane provided by the underlying ST appears as an attractive explanation, unique to this pathologic setting.

On the other hand, it is also important to keep in mind the dynamic nature of the anatomopathologic changes induced by balloon dilation of a restenosed ST. Extrusion of neointimal material out of the ST struts may be facilitated throughout a nearby SB, promoting its occlusion. However, as recently demonstrated (30), significant acute lumen loss occurs immediately after coronary interventions in patients with in-ST restenosis. Neointimal tissue reintrusion back into the ST seems to explain this early loss of lumen area (30). These dynamic changes may be related to the flow changes observed in the SB spanned by the ST and, more importantly, could also explain its reappearance at follow-up. Dissolution of thrombus, relief of spasm, or plaque remodeling are alternative explanations.

Another important finding of the present study is that the loss of a SB during repeat intervention for in-ST restenosis was rarely associated with significant ischemic manifestations. Therefore, in-ST restenosis with small-to-moderate size related SB should not preclude coronary intervention in these patients. From a pragmatic point of view our findings suggest that small (<1 mm) SB arising from a restenosed ST may be disregarded when repeat intervention is being planed. They are not associated with adverse events, and they are not appropriate for revascularization. Conversely, in selected patients with large SB at risk it may be wise to use a double-wire technique. Should SB occlusion occur with or without concomitant ischemic manifestations, dilation of the occluded, ST-jailed SB could be readily attempted.

Study limitations. Our study group represents a series of consecutive patients undergoing repeat coronary intervention for in-ST restenosis. However, the number of major SB spanned by the ST was relatively low, probably reflecting a selection at the time of initial ST implantation. Nevertheless, this represents current clinical practice during coronary stenting. In addition, the most appropriate technique to prevent SB occlusion and the strategy best suited to dilated SB jailed by the ST cannot be determined from our data and are beyond the scope of this study. The same applies to the management of in-ST restenosis after radical or complete ST reconstruction of true bifurcated lesions (23).

Conclusions. Side-branch occlusion and flow deterioration are relatively frequent during coronary intervention for in-ST restenosis, but neither one is associated with an adverse clinical outcome. Identification of threatened SB

morphology is challenging, but prior occlusion during initial stenting, ostial disease, and compromised SB flow constitute useful markers of vessels at jeopardy. The risk is also higher in patients with diabetes and those with diffuse in-ST restenosis. Therefore, it may be justifiable to take special precautions in the management of large SB in patients with these risk factors. Nevertheless, ST-related SB should not preclude repeat percutaneous interventions in these patients.

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