Overview of Restenosis in Peripheral Arterial Interventions

Restenosis continues to complicate percutaneous procedures, but new treatments hold promise.

BY ROBERT S. DIETER, MD, RVT, AND JOHN R. LAIRD, JR, MD

Noncoronary atherosclerotic vascular disease affects more than 10 million people in the US. Up to half of these patients have symptomatic lower-extremity peripheral arterial disease (PAD). Furthermore, carotid artery disease contributes to significant morbidity and mortality rates in these patients. Approximately 5% of the hypertensive patients have renal artery stenosis.

The endovascular management of vascular disease began nearly 40 years ago when Charles Dotter, MD, introduced percutaneous transluminal angioplasty (PTA). Angioplasty and stenting achieve a greater lumen diameter by intimal and medial dissections and the compression and shifting of the atherosclerotic plaque. Unfortunately, angioplasty and stenting may lead to late vessel remodeling and restenosis (Figure 1). This article highlights the pathophysiology of restenosis and overviews the restenosis in various peripheral arterial beds.

VASCULAR BIOLOGY OF RESTENOSIS

The vascular biology of restenosis can be divided into three phases. Immediately after PTA, the vessel can undergo acute vessel recoil (stents effectively treat this acute recoil). The second phase of restenosis involves the late negative remodeling of the vessel. After injury, the myofibroblasts found in the adventitia may be stimulated to produce a collagen-rich, extracellular matrix. Furthermore, endothelial injury induced by PTA and stenting results in the exposure of collagen in the subintimal space, von Willebrand factor, and the lipid core. This injury results in the activation of platelets with subsequent release of growth factors and other mediators of inflammation. This inflammation stimulates the third phase of restenosis—the activation and migration of vascular smooth muscle cells and fibroblasts into the area of injury. The histology of late vessel restenosis is of limited cellularity. Restenotic lesions are composed primarily of smooth muscle cells, proteoglycans, collagen, and extracellular material.

RISK FACTORS FOR RESTENOSIS

Patient and Lesion Specificity

Risk factors for the development of restenosis have been identified. These factors can be broadly classified as patient specific and lesion specific. Patients with diabetes are at particularly high risk for restenosis. Diabetic patients characteristically have increased endothelial dysfunction associated with increased platelet activity and a more aggressive cellular response to injury. Most studies have shown female gender to be a predictor of restenosis. Furthermore, systemic inflammation (as measured with C-
reactive protein, lipoprotein (a), postprocedural von Willebrand factor, and plasminogen activator inhibitor-1 antigen correlate with unfavorable outcomes.1

Muscular arteries (distributing), which have a high vascular smooth muscle content in their media in general, have a higher restenosis rate than elastic (conductance) arteries. Other lesion-specific factors associated with restenosis include vessel diameter, lesion length, plaque burden, and the status of the distal (run-off) vessels. One of the most powerful predictors of restenosis is the vessel diameter—smaller vessels (and those with a smaller lumen diameter after PTA/stenting) are at greater risk of restenosis. Furthermore, lesions with a greater plaque burden and those with a poor distal run-off are more susceptible to developing significant restenosis.

Restenosis Based on Anatomic Bed

Table 1 summarizes the rates of restenosis for various vascular beds.

Carotid arteries. Carotid artery PTA and stenting is rapidly emerging as an efficacious modality for treating symptomatic and asymptomatic carotid artery disease. Data are emerging regarding the midterm restenosis rate after carotid artery stenting. As an elastic (conductance) artery, the restenosis rate is expected to be low. Indeed, the restenosis rate has ranged from 5% to 8% after carotid PTA/stenting.2 Risk factors identified for restenosis after carotid artery stenting include female gender, advancing age (in contrast to carotid endarterectomy, in which younger age predicts restenosis), and variably the number of stents implanted. Restenosis lesions after carotid endarterectomy are at higher risk of in-stent restenosis.3 Interestingly, residual stenosis after the carotid artery stenting procedure, but not vessel size after the procedure per se, has been found by some to be a predictor of restenosis.2

Renal arteries. The treatment of choice for renal artery stenosis is generally percutaneous. The vast majority of lesions require stenting because of the aorto-ostial location of atherosclerotic renal artery stenosis. Many studies have shown that the rate of restenosis for PTA/stenting of renal arteries is between 15% and 25%. In the GREAT trial, the restenosis rate in the bare metal stent arm was 14.3%. Smokers have been demonstrated to have a higher restenosis rate than nonsmokers.4 Vessels <4 mm in diameter have a higher rate of restenosis.4 Furthermore, the longer the follow-up duration is, the greater the detection of restenosis will be, suggesting that unlike coronary arteries in which the majority of restenosis occurs in the first 6 months after intervention, there is a late attrition rate.4

Iliac arteries. The restenosis rate after percutaneous treatment of iliac artery stenosis has been extensively studied. The iliac arteries are conductance vessels (elastic) with a high elastin content in their media. Consequently, the rate of restenosis is expected to be relatively low. The 1-year patency rate after PTA of iliac stenoses averages 78% (67%-92%), whereas for iliac occlusions, it averages 68% (59%-94%).5 The 1-year patency rate for stenting of iliac stenoses averages 90% (78%-97%), and for iliac occlusions it averages 72% (68%-94%). In the Dutch Iliac Stent Trial, clinical success was similar at 2 years for claudicants who underwent PTA or stenting of iliac disease.6 The angiographic restenosis rate after stenting in the Palmaz multicenter Registry was 8% at 9 months, and in the Wallstent Registry, it was 12% at 6 months. In the more recent CRISP trial, the 12-month primary patency rate for the SMART stent was 94.7% (as determined by duplex and ankle-brachial index). Although there remains some controversy regarding whether stenting is superior to PTA for iliac stenoses, most operators favor a low threshold for provisional stenting.

Superficial femoral, popliteal, and tibial arteries. Because they are muscular (distributing) arteries, the femoropopliteal and tibial vessels have high rates of restenosis after percutaneous interventions. The primary patency rates for PTA of femoropopliteal lesions averages 61% at 1 year (47%-86%).5 The patency rate depends on the type of lesion (stenosis vs occlusion) and the indication (claudication versus critical limb ischemia).7 Three-year patency rates range from 61% for claudicants with stenoses to 30% in patients with critical limb ischemia and occlusions.7 Femoropopliteal lesions that have been stented have 3-year patency rates of 58% to 66%.7 In a meta-analysis of stenting for femoropopliteal occlusive disease, the rates of in-stent restenosis were independent

<table>
<thead>
<tr>
<th>Artery</th>
<th>Average Restenosis at 1 Year</th>
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<tbody>
<tr>
<td>Carotid</td>
<td>5%-8%</td>
</tr>
<tr>
<td>Renal</td>
<td>15%-25%</td>
</tr>
<tr>
<td>Iliac</td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>6%-41%</td>
</tr>
<tr>
<td>Stent</td>
<td>3%-32%</td>
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<tr>
<td>SFA, Popliteal, Tibioperoneal</td>
<td>14%-53%</td>
</tr>
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TABLE 1. AVERAGE RESTENOSIS RATES AFTER PERCUTANEOUS INTERVENTIONS
TREATING RESTENOSIS

THHERAPIES DIRECTED AT PREVENTING OR TREATING RESTENOSIS
Brachytherapy

Brachytherapy has been evaluated for de novo lesions in the femoropopliteal segments, as well as in-stent restenosis in renal arteries and femoropopliteal segments. The Vienna-2 trial evaluated gamma irradiation for the treatment of recurrent femoropopliteal lesions after PTA. At 1 year, the restenosis was reduced from 54% in the PTA-only group to 28% in the PTA/brachytherapy group. The randomized PARIS (Peripheral Arterial Radiation Investigational Study) failed to demonstrate a significant reduction in restenosis after PTA of femoropopliteal lesions, although it was hampered by follow-up angiography in less than half the patients and a lower-than-expected rate of restenosis (28%) in the control group. Caution should be used in implanting stents after brachytherapy because there is an unacceptably high rate of late thrombotic occlusions in these patients, likely a direct result of the significantly delayed endothelialization (Figure 1). The role of vascular brachytherapy is discussed in more detail in the article by Ron Waksman, MD, FACC, on page 43 of this issue.

Drug-eluting Stents

After the success of drug-eluting stents (DES) for the treatment of coronary artery disease, there has been an interest in the use of DES for the treatment of PAD. Ongoing trials, such as SIROCCO in the SFA and the GREAT trial in the renal arteries, will help answer the questions of the clinical efficacy of DES for the treatment of PAD. Although several molecules have been tested, sirolimus and paclitaxel currently are the most promising candidate molecules for the peripheral use of DES. Sirolimus is a weak antibiotic but a powerful immunosuppressant. It blocks the cell cycle from progressing from G1 to the S phase. This phase transition is normally stimulated by cytokines (eg, IL-2). Sirolimus achieves this inhibition by targeting 56 protein kinase p70, eIF-F4, p27, pRB, and other regulatory components of the cell cycle. The SIROCCO I and II trials have evaluated sirolimus-coated SM-ART stents for the treatment of SFA lesions. Six-month results showed a significant reduction in in-stent stenosis (0% vs 7.7%). However, 24-month data from the SIROCCO I trial demonstrated restenosis rates of 40% (slow-release), 44.1% (fast-release), and 47.1% (placebo). This phenomenon of late restenosis, which has also been seen in the renal artery, represents additional challenges to developing efficacious sirolimus-coated stents for the periphery.

Paclitaxel (a derivative of the Pacific yew tree) holds promise for DES treatment of PAD. Paclitaxel binds to the beta subunit of tubulin, leading to the inhibition of microtubule disassembly. By blocking microtubule disassembly, paclitaxel prevents cell progression from G2 to M, interferes with the mitotic spindle apparatus, inhibits smooth muscle cell migration, and signal transduction. Paclitaxel produces a significant reduction in coronary in-stent restenosis and will likely be tested for the periphery.

FUTURE DIRECTIONS

Restenosis is the Achilles’ heel of percutaneous intervention. The pathophysiological mechanisms of restenosis are complex. Potential therapies to prevent or treat restenosis include vascular brachytherapy and drug-eluting stents. Newer modalities such as laser debulking, the use of cutting balloons, plaque excision, or cryoplasty may demonstrate improved success rates. Trials are needed to determine if the existing or emerging modalities will produce clinically relevant results.

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