Endovascular Brachytherapy and Late Thrombotic Occlusion

To the Editor:

In a recent article, Costa et al. reported a relatively high incidence (6.6%) of sudden thrombotic events occurring 2 to 15 months after percutaneous transluminal coronary angioplasty followed by intracoronary β-radiation. These late thrombosis rates seemed to be higher in patients treated with stents plus radiation (8.8%) than in patients treated with balloons plus radiation (3.2%).

Waksman discussed some evidence that late thrombosis—and not neointimal hyperplasia—is probably the major cause. We can provide further evidence for this mechanism by observations made during a pilot study that we conducted to evaluate the feasibility, safety, and possible efficacy of endovascular brachytherapy (using γ-radiation with an iridium-192 source) for prophylaxis of restenosis after long-segment femoropopliteal percutaneous transluminal angioplasty and stent implantation (Easy-Wallstent) in 33 consecutive patients (23 male, 10 female; mean age, 66 years; mean treated length, 17 cm). A dose of 14 Gy was prescribed at 2 mm beyond the average luminal radius. Long-term pharmacotherapy with aspirin (100 mg/d) was combined with clopidogrel (75 mg/d) for 1 month.

During a mean follow up of 5 months (range, 3 to 10 months), 6 patients (18%) presented with sudden late thrombotic occlusion of the stented segment occurring between 3.5 and 6 months after the intervention. In 5 patients, the occlusion could be successfully treated by local thrombolysis with urokinase in combination with abciximab. The angiograms after successful thrombolysis demonstrated no signs of neointima formation within the stents. One patient had significant stenosis at the proximal stent edge, and 3 had stenosis in the segment proximal or distal to the stent. In one patient, no stenosis could be demonstrated after successful thrombolysis. Three of the 6 patients had poor run-off before the intervention.

We conclude that late thrombosis is not restricted to the use of intracoronary brachytherapy with β-sources. The incidence of late (>3 months) thrombotic occlusion after femoropopliteal stenting followed by endovascular brachytherapy with a γ-source is rather high. The risk is increased in patients with poor run-off and with development or persistence of significant stenosis proximal or distal to the stent. Therefore, we have changed our therapeutic strategy by (1) prolonging therapy with clopidogrel for 6 months, (2) avoiding femoropopliteal stenting plus brachytherapy in patients with poor run-off, and (3) performing early angioplasty after the detection of a recently developed stenosis proximal and/or distal to the stent. In case of thrombotic occlusion, local thrombolysis with urokinase and abciximab seems very effective.

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Response

We read with pleasure the letter from Minar et al. on sudden late thrombosis after intracoronary brachytherapy using γ-sources after femoropopliteal stenting. Although they were dealing with a selected population treated for peripheral artery disease, their findings corroborate our report concerning the clinical impact of this new phenomenon in patients treated with brachytherapy.

Since our article was published, Waksman et al. reported the occurrence of late coronary occlusion in 26 patients (9.1%) receiving either γ- or β-radiation for the treatment of in-stent restenosis, although only 12 patients (3.9% of the total irradiated population) presented with an acute myocardial infarction. This study, which involved a mixed population treated with β- and γ-radiation, may support the hypothesis that late thrombotic vessel occlusion is a frequent phenomenon after intracoronary radiation, regardless of the type of source used (β- or γ-systems).

As we suggested previously, the sudden occlusion of the treated vessel associated with an acute ischemic event seems to be a unique feature of patients treated with intravascular radiation therapy. It is important to distinguish between this thrombotic phenomenon and an angiographic finding of an occluded vessel at follow-up, which may also be due to neointimal proliferation. The incidence of myocardial infarction caused by late (>30 days) coronary occlusion, as documented by angiography, is extremely rare after percutaneous intervention in the general, nonirradiated population. The finding that only 2 of the 854 patients (0.2%) enrolled in the Belgian Netherlands Stent Study (BENESTENT), BENESTENT II pilot phase, and BE-NESTENT II trials had myocardial infarction associated with late target vessel occlusion further supports this concept.

Preliminary data from multicenter prospective trials have now confirmed our findings. In the Beta Radiation in Europe (BRIE) study using the 90Sr/90Y source (Beta-Cath System, Novoste Corporation), 5.3% of the patients had late coronary occlusion documented by angiography.

If delayed endothelialization is the sole mechanism for late thrombosis, the use of prolonged antiplatelet therapy, as proposed by Minar et al., may overcome this problem. In fact, in April 1999, we instituted a prolonged antiplatelet regimen (aspirin plus clopidogrel for 6 months) at our institution, and no cases of late thrombotic occlusion have occurred thus far (>100 cases). However, the efficacy of such prophylaxis must be demonstrated in long-term follow-up studies.

However, if late stent malapposition is implicated in late thrombosis, an alternative solution to avoid the occurrence of this phenomenon should be found. Avoiding stents or the use
of self-expanding stents may be useful in this situation. However, the actual incidence of late stent malapposition in the population treated with catheter-based intracoronary radiation and tubular stent implantation is as-yet undefined and awaits large prospective studies using intravascular ultrasound imaging.

The documentation of the complications of any novel technique is of paramount importance to the scientific community. Such critical analysis should allow us to improve and enhance our knowledge rather than creating pessimism or skepticism. In this regard, the group from Vienna should be congratulated, for our mutual aim is the development of the best treatment for our patients.

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