INVITED COMMENTARY

Can Molecular Imaging Predict In-Stent Restenosis?

Ever since the pioneering work by Grüntzig more than 20 y ago (*1*), acute vessel closure and restenosis in the first 6 mo have remained the main limitations of percutaneous transluminal coronary angioplasty. The simultaneous publication of the BENESTENT (*2*) and the STRESS (*3*) studies, the 2 landmark trials demonstrating a significant reduction in the rate of angiographic restenosis with stents, has resulted in a sharp increase in the use of stents for treatment of intracoronary stenoses. Most percutaneous coronary interventions performed in the United States and Western Europe currently use stents because of their success, in comparison with balloon angioplasty, in enlarging the vessel lumen, reducing restenosis rates, covering dissections, and reducing early complications. Nevertheless, 16%–42% of selected patients receiving optimal therapy within the early clinical trials experienced in-stent restenosis within 6 mo after the procedure, demanding target vessel revascularization in 9%–15% of patients (*4*). Concurrent with the widespread use of stents, treatment has shifted to more complex lesions and higher-risk patient groups, resulting in an increased in-stent restenosis rate that not only represents a significant clinical problem but also results in a huge economic burden (*4*).

Restenosis after balloon angioplasty is caused predominantly by local negative remodeling of the vessel wall (*5*). Stents achieve a greater initial lumen diameter and prevent negative remodeling. However, stent implantation provokes an enhanced intimal hyperplastic reaction, resulting in a relatively greater late loss in comparison with balloon angioplasty (*6*). Neointimal hyperplasia can be described in 4 stages. During the first stage instantaneous thrombosis occurs, whereas the second stage consists of an inflammatory reaction. In the third (proliferative) stage, smooth muscle cells (SMC) replicate, migrate, and produce the extracellular matrix molecules. The fourth stage is characterized by remodeling of the neointima and vascular wall (*7*). Although diabetes mellitus, small vessel size, lesion lengths > 20 mm, and small final lumen diameter have been identified as risk factors, it remains difficult to accurately predict in-stent restenosis (*8,9*).

Ideally, a simple noninvasive test should be available to predict restenosis, but at present, noninvasive imaging has been used only to detect restenosis after stent implantation. Various studies have been published on the use of myocardial perfusion imaging to evaluate patients after stent placement. Three recent studies used ^{99m}Tc-labeled agents to detect ischemia (*10–12*). Galassi et al. (*10*) studied 97 patients after coronary stent placement (128 ± 41 d after the intervention) and demonstrated a sensitivity of 100% and a specificity of 86%. The authors also showed that angina and electrocardiography changes during the exercise test were less accurate, with a significantly lower sensitivity. Milavetz et al. (*11*) reported data from the Mayo Clinic nuclear cardiology database showing a similar sensitivity (95%) and a slightly lower specificity (73%). However, detection of restenosis is not the ultimate goal; prediction of restenosis at an early stage to allow optimal management of these patients would be preferred.

In this issue of *The Journal of Nuclear Medicine,* Johnson et al. describe the use of nuclear molecular imaging to detect proliferating SMC early after stent placement in an animal model (*13*). The authors studied 14 pigs undergoing stent implantation of one or more of the major epicardial coronary arteries. Within 1 wk after the procedure, SPECT with ^{111}In-labeled Z2D3 F(ab′)2 was performed. Z2D3 is a mouse and chimeric antibody that binds an antigen expressed by proliferating SMC in human atheroma (*14*). In their study, Johnson et al. used this approach to detect, at a very early stage, the presence of proliferative SMC after coronary stent placement. After the animals were sacrificed, the hearts were excised and the coronary arteries processed to compare the SPECT results with histopathologic results. Sixteen (62%) of the stented vessels were positive on SPECT imaging, which correlated with a higher neointimal proliferation index in comparison with SPECT-negative vessels (42 ± 11 vs. 11 ± 11, $P < 0.001$). There was no difference in the percentage of luminal narrowing in the SPECT-positive and -negative vessels. These results indicate that imaging with ^{111}In Z2D3 F(ab′)2 can detect early proliferative activity of SMC. These results may lead toward a better understanding, on a molecular basis, of the clinical problem of in-stent restenosis. More important, if clinically applicable, this would be one of the first areas in which molecular findings translate into a clinical application. However, additional questions remain. First, it is not clear whether restenosis will actually develop in all vessels with active prolif-

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eration; this was not demonstrated in the study. The pathophysiology of in-stent restenosis, as described above, not only involves proliferation but also requires a phenotypic change of contractile, dormant SMC to cells that are capable of migration and secretion of matrix proteins, which comprise the major part of the neointima in restenotic stents. Furthermore, some patients have been shown to have neointimal hyperplasia after stent placement without clinical restenosis and late regression of the neointima (*15*). Therefore, the presence of proliferation does not necessarily indicate imminent clinical in-stent restenosis. Nonetheless, the described method may have a significant impact on the evaluation and understanding of the effects of drugs aimed at inhibition of SMC proliferation after stent placement. Because drug-eluting stents, which have demonstrated a strong beneficial effect on in-stent restenosis, are currently a major focus in interventional cardiology, the described method may be of significant clinical value.

Finally, as the authors indicate, the resolution of SPECT is suboptimal, and PET may be preferred. Shields et al. (*16*) reported on the use of PET imaging with ^{18}F-FDG–labeled agents to image cell proliferation. Considering the rapid development of noninvasive angiography with multislice CT (*17*), and the option of combined PET/CT, integration of molecular imaging with PET and noninvasive coronary angiography with CT may add substantially to translate the molecular findings into clinically useful information.

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