

## Small Is Beautiful A Miniature Stent Model

Mark J. Post, Johannes Waltenberger

Recent successes by drug eluting stents in the battle against restenosis have boosted the volume of stent related research. The goal of this research is to further reduce restenosis rates by improving stent and polymer design and by testing and modifying drugs from various classes. The novel mouse model described by Ali et al,<sup>1</sup> offers new opportunities to study fundamental and perhaps applied aspects of vascular biology related to stent implantation. In the absence of in vitro models of vascular healing that eventually may replace animal experiments, small animal models are especially welcome. The first mouse model of vascular healing was developed by Lindner and coworkers more than 10 years ago.<sup>2</sup> They injured the carotid artery with a guide wire and observed the same sequence of apoptosis, invasion of leukocytes, smooth muscle cell migration, and proliferation and reendothelialization as found in rabbits, pigs, and humans. Animal models of diseases and related therapies serve two purposes: to increase the understanding of pathobiology and to evaluate new therapies down to the histopathologic level. Models are simplifications of reality, and animal models are no exception. The predictive value of a model depends on a largely empirical framework that links animal behavior with clinical experience. Fortunately, animal models of vascular healing in various species and arterial beds have already provided a solid reference for this novel stent model. Most of these models, however, especially in rats, lack preexistent pathology such as atherosclerosis, which may explain some of the false-positive results with pharmacological inhibition of intimal hyperplasia. The various models of atherosclerosis that are currently available in mice may provide a more realistic response to vascular injury.

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The presented mouse stent model appears to be technically demanding and the investigators should be commended for this achievement. Specific features of the model are associated with limitations as well as opportunities that deserve further attention.

First, a cuff was used to bridge the gap between the small calibre carotid artery and the larger aorta while at the same time facilitating the connection by avoiding sutures. The cuff,

however, inflicts by itself an injury to the artery that leads to apoptosis of medial smooth muscle cell,<sup>3</sup> adventitial inflammation,<sup>4</sup> and subsequent intimal hyperplasia. In the setting of hypercholesterolemia, the cuff injury induces accelerated atherosclerosis. The mechanism of the injury is not completely understood, but is likely related to an inflammatory response in the adventitia.<sup>4</sup> In larger arteries, the endothelium seems to remain intact. Using the most elegant technique of OCT in the mouse stent model, no intimal thickening was observed in the cuffed area. In hypercholesterolemic animals, however, lesions are likely to form and potentially disturb flow patterns down stream in the stent area.

Second, the stented aorta is heterotopically transplanted into the carotid position of a recipient mouse and is in effect similar to an ex situ arterial interposition graft such as the radial artery graft in coronary bypass surgery. The performance of these grafts is usually quite good in spite of disruption of adventitial connections through vasa vasorum and nerves. However, graft intimal hyperplasia does occur in these bypasses, possibly as a result of transient ischemia during the procedure.<sup>5</sup> In the mouse model, the syngeneic nature of the transplant and presumed immunologic responses may further stimulate neointima formation. If neointima grows in the nonstented segment of the aorta graft it can easily be mistaken for the candy wrapper effect observed in some endovascular therapies, most notably ionising radiation but occasionally also in the vicinity of drug eluting stents.<sup>6</sup>

As a transplant mouse model, the stented aorta also offers exciting opportunities. Issues such as the involvement of circulating versus local cells can easily be studied. Genetic and biochemical requisites of local and circulating cells can further be identified by using aortas from transgenic donors and/or place them in transgenic recipients. For instance, the novel model offers the potential to study the effect of individual genes on intimal hyperplasia, when crossing transgenic mice in the ApoE<sup>-/-</sup> background.

Third, the high incidence of thrombosis reported in this study is likely a result of the transplant procedure and the unusual anastomosis. If thrombosis really turns out to be related to the stent injury however, the model might serve as a worse case scenario to study interventions that aim to reduce the risk of thrombosis.

Finally, the stent and the recipient aorta are less than 1 mm in diameter. Stenting of small calibre arteries is associated with a higher frequency and degree of restenosis. In several trials artery size was an independent predictor of restenosis with arteries smaller than 2.75 mm in diameter being especially at risk. This phenomenon has been attributed to a higher metal-to-artery ratio resulting in more vascular injury,<sup>7</sup> hence more intimal hyperplasia. On the other hand the

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From the Departments of Physiology (M.J.P.) and Cardiology (J.W.), CARIM, Maastricht University, and the Department of Biomedical Engineering (M.J.P.), Technical University Eindhoven, The Netherlands.

Correspondence to Mark J. Post, MD, PhD, Department of Physiology, Maastricht University, PO Box 626, 6200 MD, Maastricht, The Netherlands. E-mail m.post@fys.unimaas.nl

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favorable high shear stress conditions in the mouse aorta and carotid may balance the growth of neointima. Although the influence of shear stress on intimal hyperplasia in stented arteries remains controversial, the relationship seems to be inverse in animal models, ie, increase in shear stress reduces intimal hyperplasia.<sup>8</sup> Allometric studies indicate that shear stresses in the mouse may be up to a factor 40 higher than in humans,<sup>9</sup> suggesting a favorable condition for stent patency.

In summary, this novel stent model is a most welcome addition to many test tools available in vascular biology.

### Disclosures

None.

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