JACC: CARDIOVASCULAR IMAGING
VOL. 4, NO. 9, 2011

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
DOI:10.1016/j.jcmg.2011.06.012

EDITORIAL COMMENT

Late Loss: Should We Lose It?*

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Soon after the introduction of coronary angioplasty, it became evident that many of the arteries that had been opened would eventually re-narrow, and the therapeutic benefit would be lost. This restenosing of the vessel was caused by a process of elastic recoil after the balloon inflation, accompanied by new tissue growth and constriction of the vessel as part of the healing phase. With the introduction of coronary stents, the elastic recoil and chronic constriction were largely eliminated, and the remaining feature of restenosis was the development of neointimal tissue. The introduction of drug-eluting

See page 1002

stents was aimed at combating this remaining process of restenosis. In an effort to understand the restenosis process, animal models have been created, and among those with physical dimensions matching human arteries, the porcine model has become the most widely studied. The initial angioplasty model involved overstretch with balloons, resulting in disruption of the internal elastic lamina, which uniformly led to a significant neointimal formation over the next 30 days, being most pronounced in the zone of the disrupted internal elastic lamina (1). This severe injury was selected because, in the human procedure in atherosclerotic vessels, the inflated balloon vastly exceeds the preprocedural lumen diameter, and the splitting and disruption of the vessel are well-known mechanisms by which the artery is expanded. With the introduction of stents, the porcine model has continued to be used to identify methods of modifying the healing process in a favorable direction (2). Balloon overstretch prior to stenting disrupts the internal elastic lamina and results in a more effusive healing response than placing a stent without such vascular damage.

The purpose of studying animal models of restenosis and vascular healing is to anticipate like responses in patients. As vascular brachytherapy, and subsequently, drug-eluting stents, were introduced, the porcine model played a major role in establishing that these measures could modify the healing response and likely diminish the incidence of hemodynamically significant re-narrowing of the artery. In order to study various modifications of the healing response, the amount of neointima generated has been used as a continuous variable in order to achieve statistical power with limited numbers of experimental animals. A similar approach has been used in clinical trials where the angiographic late loss of lumen diameter as judged angiographically has been used as a surrogate for important clinical events. Despite the fact that late loss is thought to correlate well with restenosis propensity, how it relates to measures of neointimal formation remains incompletely understood. Although late loss has gained an exalted status in evaluating the effectiveness of drug-eluting stents, the true clinical correlate should be excessive late loss that would create a hemodynamically significant obstruction. With the advent of drug-eluting stents, the formation of neointimal tissue is now viewed as both a negative and a positive feature of the late outcome. While striving for the maximum inhibition of neointimal tissue growth and the least angiographic late loss, it became evident that complete inhibition of neointimal tissue formation would leave stent struts exposed and potentially create a prothrombotic environment. In an effort to balance adequate healing and coverage of stent struts with inhibition of

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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excessive tissue growth, it is appropriate to try to understand the effect of stenting on those outcomes. An important question is how does the angiographic late loss correlate with tissue elaboration and avoidance of exposed stent struts?

The present study by Kim et al. (3) examines both questions: 1) how well angiographic late loss predicts neointimal proliferation after stenting in a porcine model of restenosis; and 2) whether it can also predict stent strut coverage/endothelialization within stents. Kim et al. performed coronary stenting in 49 domestic swine using drug-eluting and bare-metal stents, and followed them for 28 to 90 days for the development of neointimal proliferation and tissue coverage of stent struts. Angiograms were performed, and the late loss was compared with neointimal thickening by optical coherence tomography (OCT) and also by histology. Approximately 7 segments per stent were matched between the 3 assessment methods, resulting in a total of 382 angiographic segments studied.

Late loss and measures of neointimal formation. The mean late loss for all stent implants was 0.60 mm, ranging from −0.46 mm to 2.3 mm. The authors found good correlation between late loss and neointimal thickness when late loss was >0.55 mm but poor correlation when late loss was less than that. The conclusion, therefore, was "angiographic late loss below a threshold value of 0.55 mm correlates poorly with [neointimal thickness] obtained by OCT and histology." Since most commercially available drug-eluting stents have late loss measurements that are <0.55 mm, one implication might be that the amount of neointimal tissue elaborated and the degree of coverage of stents might be imprecisely measured by that late loss finding.

Although it is tempting to make such a conclusion, there are a number of differences between this porcine coronary model and the human condition. In this porcine model, the stent was placed without prior overstretch injury to the vessel, with a stent-to-vessel ratio above 1:1.1, but in most cases, likely not disrupting the internal elastic lamina. The authors point out that the neointimal proliferation was relatively uniform inside the stent circumference (3). Neointimal tissue developing inside stents, especially drug-eluting stents in humans, is often not uniform. Some of the difficulties in correlating measurements obtained by angiography, OCT, and histology should be mentioned. Whereas attempts were made to avoid foreshortening, the angiographic image chosen was a single projection resulting in a 1-dimensional measurement. OCT and histology, on the other hand, measure a 2-dimensional circular structure. The very similar degree of neointimal formation seen by OCT and histology is interesting. The ability to have in vivo measurements obtained by OCT correlate so precisely with postmortem histology is worthwhile. Since this is a stented artery, postmortem shrinkage of the specimens is obviated. OCT appears to be a more precise method to measure the effectiveness of drug-eluting stents in preventing neointimal formation.

Late loss, strut coverage, and OCT. Another important issue relates to whether late loss also can predict neointimal coverage of stent struts, which at least, according to pathological studies, is thought to be a good surrogate for endothelialization. Late loss when it was >0.55 mm did ensure that almost all stent struts were covered by tissue; however, below that level, the correlation between angiographic late loss and neointimal formation was not adequate. When stent strut coverage was considered, the definition used for the OCT measurements was tissue measuring at least 20 μm in thickness overlying the stent struts. The late loss group below 0.55 mm exhibited 22% uncovered stents as judged by this OCT criteria. On the other hand, when stent coverage was measured with histological examination, virtually all stent struts (98.3%) were covered. This finding raises the important question of whether this OCT evaluation of stent coverage is accurate. It has been shown that patients dying from stent thrombosis frequently have uncovered stent struts. On the other hand, many living patients whose stents are not embedded in the arterial wall seem to be free of stent thrombosis even though current invasive measures cannot demonstrate neointimal tissue covering these stent struts. Could part of the paradox be the inability of OCT to accurately reflect very thin neointimal coverage of stent struts? This disparity between OCT measures and histology, although not emphasized in the paper, seems to be one of the more interesting contributions to this investigation. Conversely, the lack of correlation between mild degrees of late loss and the degree of neointimal proliferation in this model is less surprising. In our laboratory, we typically have not performed intravascular ultrasound or OCT imaging prior to terminating the animals. These procedures have been avoided so as not to compromise the histological examination, especially as it relates to stent coverage. However, second-generation OCT or optical frequency domain imaging has

shown great promise in obtaining images reflecting stent coverage and even discriminating between cellular tissue and fibrin coverage (4).

Since the model does not generate the same injury or healing response as is seen in human atherosclerosis, it should be questioned as to how this late loss can predict the degree of neointimal formation in patients. Also, the concentration on late loss as a proper surrogate for predicting clinical events should remain in question. It has never been all about late loss, but rather about excessive late loss, resulting in hemodynamic compromise that correlates with clinical events. Systems of treating obstructive coronary atherosclerosis that result in moderate but stable neointimal tissue with a lumen capable of conducting maximum coronary flow should be the goal of invasive measures of the future.

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Key Words: late loss ■ optical coherence ■ quantitative coronary angiography ■ restenosis ■ stents ■ tomography.