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EDITORIAL COMMENT

Drug-Eluting Stent Endothelium

Presence or Dysfunction*

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The Rosy Prophesy

Drug-eluting stents (DES) have considerably improved the treatment of coronary artery disease since their introduction in 2001 due to the reduction of in-stent restenosis. It seemed for a while that the rosy prophecy made in 2000 was true.

See page 68

First Cracks

In 2004, however, the first report on late stent thrombosis (LST) was published by McFadden et al. (1). More followed, including reports on delayed healing from autopsy (2) and atherectomy specimen (3). Meta-analyses now indicate that, indeed, this therapy is associated with an increased risk of late stent thrombosis in some DES and applications. Daemen et al. (4) report an incidence of 0.6% per year, with a cumulative incidence of 2.4% at 4 years or higher in an all-comers population. With 3 million stents being implanted worldwide each year, the risk of stent thrombosis is becoming a problem of public health proportions.

Delayed Endothelialization

Finn et al. (5) from CVPath Institute Inc. point toward delayed endothelialization as the main cause for late stent thrombosis based on autopsy and pre-clinical studies using denuded rabbit iliac arteries. This observation has not been consistently reproduced by other investigators or in other models (e.g., after direct stenting of swine coronary arteries) (6,7).

In this issue of *JACC: Cardiovascular Interventions*, Nakazawa et al. (8) describe capture of CD34-positive cells via Genous stent (GS) technology (OrbusNeich Medical, Fort Lauderdale, Florida) to enhance early endothelialization of sirolimus-eluting stents (SES) in swine coronary arteries. Scanning electron microscopy was used to assess endothelial presence and confocal microscopy to assess endothelial function and maturity (CD31 expression). Stent endothelialization was studied in single and overlapping GS and SES as well as in GS-modified SES.

They found that overlapping GS and SES increased the percentage stent strut endothelialization at 14 days as compared with SES alone (55% to 79%), but remained lower than GS alone (99%). In other words, SES endothelialization can indeed be enhanced by GS technology, but this endothelium is still sensitive to sirolimus. Indeed, overlapping SES and GS did not improve the number of functional endothelial cells at all as CD31 expression in both SES and GS–SES was the same: 40%. Interestingly, overlapping 2 GS also decreased the number of functional endothelial cells (58% vs. 98%), despite the GS technology.

The direct modification of SES by the GS technology did improve stent strut endothelialization and the number of functional endothelial cells. Each was improved by 30% as compared with SES alone. These numbers, however, remained lower than in the GS alone group, confirming yet again the sensitivity of these cells for sirolimus.

Nakazawa et al. (8) conclude that: "These studies demonstrated that antibody-mediated endothelial progenitor cell capture can enhance endothelial cell coverage and maturation of endothelial cells on DES and may provide a new therapeutic approach."

Endothelial Presence or Endothelial Dysfunction?

What can we learn from this study? The first phase of the study shows that improving endothelial capture is not synonymous to improving endothelial function. It also shows that overlapping a stent causes endothelial dysfunction, even with GS. The second phase of the study shows that in a less injurious setting, GS technology does increase endothelialization in an SES environment and improves the number of functional endothelial cells in terms of CD31 expression. However, the endothelial layer remains incomplete, and endothelial dysfunction is still present. Whether GS technology is able to enhance late endothelialization at a time when the antibody against CD34 is likely covered by a proteinaceous layer (9) is not known.

Chronic Vascular Irritation

Taking into account that not all DES that show delayed healing cause LST (2,3), and that LST occurs at a steady

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rate long after the drugs have eluted from the stent, we have to appreciate that there is more to LST than merely a partial absence of endothelial cells. Chronic vascular or endothelial dysfunction, either stent-, drug-, or coating-induced, may play a more important role than is often suspected (10,11). Indeed, the fact that DES are also associated with endothelial dysfunction of the coronary artery distal to the stent, even after all drug has been released (12–15), indicates the chronic and extensive nature of this phenomenon.

Improving Endothelial Function

While the GS technology enhances endothelialization of SES, endothelial function remains impaired, and its long-term fate remains to be determined. We can expect that improving endothelialization will not be enough to prevent LST as illustrated by the occurrence of LST even with GS (16). The future will lie in improving endothelial function. However, one can only improve that which is present. To that end, enhancing endothelialization by any means is an important first step.

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