Brief report

Scanning Electron Microscopy Analysis of Luminal Inflammation Induced by Different Types of Coronary Stent in an Animal Model

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INTRODUCTION

Coronary drug-eluting stents (DES) have proved effective in reducing restenosis.1,2 However, DES are also associated with delayed endothelialization and persistent inflammatory states which may be due to either the antiproliferative effects of the drugs used or to the polymer used for controlled release.3–6 Both phenomena have been associated with stent thrombosis, the most serious complication of these devices and one which can occur in even very late phases.4 The data used in these studies came from the histological analysis of animal parts and human autopsies. Scanning electron microscopy (SEM), which permits observation of inflammatory cells in a representative area (100 x 100 μm) was quantified at 3 and 7 days. Endothelialization was more complete in bare-metal stents than in drug-eluting stents at both 3 days (P = .016) and 7 days (P = .0001). The degree of inflammation induced by the drug-eluting stents was higher than that induced by the bare-metal stents at both 3 days (11.8 ± 3.5% vs. 4.5 ± 2%; P = .001) and 7 days (26.3 ± 4.4% vs. 1.2 ± 1.5%; P = .0001). In addition, the time sequence was inverted: the inflammatory response increased over time with the drug-eluting stents, while the opposite occurred with the bare-metal stents.

METHODS

The experimental procedures were performed in 12 domestic pigs (25 ± 3 kg), following the general guidelines for the protection of...
RESULTS

Endothelialization was more complete in BMS than DES at both 3 days (82% ± 18% vs. 28% ± 14%, P = .016) and 7 days (97% ± 3% vs. 44% ± 15%, P = .0001) (Fig. 2). No difference in endothelialization was observed between the two DES, between the different arteries (anterior descending, circumflex and right coronary artery) or according to the stent / artery ratio (BMS, 1.17 ± 0.1; DES1, 1.07 ± 0.07; DES2, 1.13 ± 0.16, P = 0.4).

BMS showed a lower density of inflammatory cells than DES at both 3 days (4.5% ± 2% vs 11.8% ± 3.5%; P = .001) and 7 days (1.2% ± 1.5% vs 26.3% ± 4.4%; P = .0001) (Fig. 3). No statistically significant differences were observed between the two DES. The density of inflammatory cells decreased significantly over time with BMS (4.5% ± 2% versus 1.2% ± 1.5%; P = .0001). However, the opposite was true for DES, which showed a significant increase after 7 days (11.8% ± 3.5% vs. 26.3% ± 4.4%; P = .0001).

Inverse correlations were observed between the degree of inflammation and the percentage of endothelialization, with r² values of -0.4 (P < .011) at 3 days and -0.84 (P < .0001) at 7 days (Fig. 4).

DISCUSSION

The recent consensus document on preclinical analysis of DES indicated that semi-quantitative assessment of inflammation induced was one of the most important parameters to take into account. The method described here shows little variability and provides results on a quantitative scale, thereby allowing for more detailed comparison between the responses obtained with different devices.

Differences in long-term response observed in a porcine model between two first-generation DES were published recently. Parameters differentiating between the two stents were in-depth inflammatory response and fibrin deposition. Although the authors acknowledged the difficulty of extrapolating the findings to the clinical field, the fact remains that the findings were undesirable. The analysis of luminal inflammation completes the study of the response to DES via phenomena occurring at the stent-lumen interface, phenomena which are essential to subsequent endothelialization. In fact, we observed a significant inverse correlation between the intensity of the inflammatory response and the percentage of endothelialized stent surface.

A noteworthy finding was the temporal pattern of inflammation, with decreasing inflammatory response being observed in BMS and an increasing response in DES. The release of the drug may play an important part in these results, as it is a short-term analysis. Nevertheless, the persistence of these phenomena over the very long term in other studies seems to confirm the causal role of the polymers used. The possible role of the P5® polymer in
The increase in inflammatory response cannot be determined with the data presented here, but preliminary findings do not provide evidence for such a relationship. The most notable limitation of the study is the difficulty inherent in extrapolating (young and healthy) animal model data to sick humans, although it is recommended by the consensus document. The use of sick (diabetic, hyperlipidemic, or induced genetic deficiency) animal models is being validated but is not yet recommended. The fact that these observations were not correlated with findings using other analytic techniques (histology) can be seen as another limitation. However, we believe that the method described supplements information obtained by other means, rather than replacing it. The role that other antiproliferative drugs may play in inflammatory response remains to be defined.
In conclusion, the vinblastine-eluting stents used in this study produced a greater degree of inflammation than bare-metal stents. In addition, the time sequence was inverted: inflammatory response increased over time with the DES, while the opposite was true for bare-metal stents. There was a significant correlation between observed inflammatory response and coronary stent endothelialization.

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**CONFLICTS OF INTEREST**

None declared.

**APPENDIX. SUPPLEMENTARY MATERIAL**

Supplementary material associated with this article can be found in the online version available at doi:10.1016/j.rec.2010.04.001.

**REFERENCES**


