EDITORIAL COMMENT

A Cutting Edge Technology, or Is It?*

Spencer B. King, III, MD, MACC
Atlanta, Georgia

Since the first days of angioplasty, restenosis has been the major limitation. Over the brief history of percutaneous interventions, therapies to prevent restenosis have come and gone with a frequency that rivals treatments for rheumatoid arthritis over the last hundred years. We have also learned to be skeptical regarding any claim of benefit from a therapy for established restenosis. In the recently published American Heart Association and the American College of Cardiology Guidelines on Percutaneous Coronary Interventions (1), there are no recommendations for any therapy for restenotic lesions that are not stented.

However, since stenting has become the predominant percutaneous coronary artery intervention, the most common form of restenosis is currently in-stent restenosis. There is now an approved treatment for this condition—endovascular brachytherapy. Three randomized trials, two using beta radiation (START, INHIBIT) and one using gamma radiation (GAMMA-1), have shown significant reduction in re-restenosis of treated in-stent lesions that receive radiation therapy. Before brachytherapy can be delivered, mechanical removal or displacement of the obstructing lesion must be done. Also pertinent is the fact that only a minority of patients with in-stent restenosis are currently being treated in centers in which brachytherapy is available. Therefore, identification of lesion removal or displacement methods that show an advantage would be beneficial with and without radiation. In a large series of in-stent restenosis lesions treated with balloon angioplasty, rotary ablation, laser therapy or restenting, no method was found to be superior and all lead to approximately the same re-restenosis rates (2). Although the cutting balloon was developed more than 10 years ago, it has only recently become available in the U.S. Among other uses, it has been suggested for in-stent restenosis.

Most claims for decreasing restenosis have been made on clinical and angiographic grounds without exploration of the mechanisms whereby these therapies may be effective. The current report from Adamian et al. (3) is no exception to this generalization. Nevertheless, a great deal of what is done in interventional cardiology is based on results obtained by experienced and trusted colleagues who try new devices in the early stage of their development.

The current observations reported by Adamian et al. (3) in this issue of the Journal involve four selected therapies for in-stent restenosis: balloon angioplasty, rotational ablation, stent placement and cutting balloon angioplasty. These therapies were not randomized, and the authors state that selection was based on operator preference without major consideration for baseline differences. It is also pointed out that the cutting balloon became popular during the latter part of the experience reported herein and, therefore, there was temporal inhomogeneity of the therapies delivered. In addition, the authors sought to reduce clinical and angiographic variables by a matching process that reduced the total number of in-stent restenosis cases from 648 to 258 following the matching. Four relatively equal-sized groups were created without major defined differences in baseline demographic characteristics. Angiographic follow-up was planned around the six-month mark and clinical follow-up averaged 11 months. The authors found no difference in the restenosis rate or the target vessel revascularization for balloon angioplasty, restenting or rotary ablation therapies but found a significant improvement in the restenosis rate among those lesions treated with the cutting balloon. Concerning these results, there are reasons to be skeptical and there are reasons to be hopeful.

The authors point out the obvious limitations of a small, nonrandomized registry; however, causes for these results other than chance occurrence should be explored. Although not mentioned in this communication, totally occluded stents have been reported to have the highest re-restenosis risk. The numbers are small, and it is not emphasized but the baseline presence of a totally occluded stent was 10.8% and 8.9% in the percutaneous transluminal coronary angioplasty (PTCA) and stent groups, respectively, whereas it was only 1.8% in the cutting balloon group. In addition, if a bias in favor of the effectiveness of the cutting balloon occurred during the process of this study, then the enthusiasm for reintervention in the cutting balloon group may have been less than for other therapies. This potential “placebo effect” can even influence randomized trials but one would assume that the angiographic assessment of the lesion severity at follow-up would not be influenced by the prior therapy given. The results of this series are better than some other observations of cutting balloon angioplasty. This may have resulted from a different method of applying the technology. In some prior observations, cutting balloon was utilized with low inflation pressures which could have produced less vessel expansion. This was not the case in the present study where the average maximum inflation pressure was 10.7 barr compared to 13.1 barr in the PTCA group. Also, the balloon to vessel ratio was the same for all groups.

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From the Fuqua Heart Center, Atlanta, Georgia.
at 1:1.2. Finally, the overall in-stent restenosis rate during the time frame of this study (1997 to 1999) was 38%. Given the earlier reports from the same group, many will find this surprising. The authors have pointed out that the potential reason for this finding is the changing character of the lesions treated. Stented lesions have indeed become longer and vessel diameters have become smaller. The characteristics of in-stent restenosis lesions also may have changed leading to an overall high re-restenosis rate with most of the therapies tried. Stent underdeployment has been emphasized by many, including this group, as a cause of failure when treating in-stent restenosis. However, since there is no intravascular ultrasound control in this study, the influence of completeness of stent deployment on the outcomes must remain speculative.

Despite these concerns, there are clear reasons to be hopeful for this technology. One of the major concerns about treating diffuse in-stent restenosis with balloon angioplasty is the appearance of the segment after treatment. Since avoiding additional stenting is now often a priority, methods of assuring an adequate post-treatment lumen are desirable. Improvement in postprocedure minimal lumen diameter (MLD) was very little and not significant; however, the late loss advantage for the cutting balloon in this series is quite striking. Late loss of 0.63 mm occurred in the cutting balloon group, whereas late loss was well over 1 mm for the other groups. Since the final MLD after the procedure was similar for the three nonstented groups, this reduced late loss was the important difference in the study.

Are there mechanistic explanations for the finding of a reduced amount of proliferative tissue in the cutting balloon group? The authors speculate that the mechanism for lumen enlargement with the cutting balloon is plaque extrusion through the stent struts. However, this is also the likely explanation for lumen enlargement with balloon angioplasty as well as rotary ablation and restenting procedures. If disrupting the restenotic tissue prior to extruding it through the stent struts is helpful, one would expect rotary ablation to be effective. The rotablator not only disrupts the tissue, but also removes some of it so that less is available for extrusion through the struts. However, the ARTIST Trial comparing direct rotary ablation with balloon angioplasty for in-stent restenosis failed to show superiority for the ablative approach (4). It remains attractive, however, to speculate as to whether reduction in the amount of proliferative tissue extruded into the vessel wall outside the stent could result in a decreased stimulus for cytokine release and subsequent proliferation and migration. Since in-stent restenotic lesions have been found to be composed in large measure by proteoglycans and are frequently fairly echolucent, they have a high water content. Could the process of incising these lesions and then squeezing them result in desiccating the material with loss of liquid components into the vessel lumen? If this occurs, then less volume of neointimal tissue would be available for trans-stent extrusion.

The preceding is pure speculation, but this hypothesis should be tested in experimental studies. Regardless of the cause of the benefit shown by Adamian et al. (3) the standard recommendation is that there should now be a well-controlled clinical trial of the cutting balloon versus plain old balloon angioplasty. A modest-sized randomized trial comparing balloon angioplasty to cutting balloon therapy for in-stent restenotic lesions is nearing completion in Europe. This trial, led by Dr. Colombo, will be of great interest as it should remove undetected baseline differences that could have influenced this observational study. However, the problem is that since endovascular brachytherapy has demonstrated efficacy for in-stent restenosis, that therapy is increasingly applied. Controlled trials of brachytherapy comparing balloon angioplasty to cutting balloon would be a logical next step. As the authors point out, the cutting balloon may be helpful for its tendency not to slip during inflation in in-stent restenotic lesions regardless of its effect on restenosis rates. This may be of particular advantage for patients undergoing brachytherapy since it would avoid injury to the distal or proximal artery which is an important component of the “edge effect” restenotic lesions sometimes seen with brachytherapy. On the down side, it is less maneuverable and is limited in length.

The current observation raises many questions. Whether this technology remains one that is favored for in-stent restenosis by certain enthusiasts or becomes a documented superior approach depends on the willingness to mount definitive randomized trials.

**Reprint requests and correspondence:** Dr. Spencer B. King, III, 95 Collier Road NW, Suite 2075, Atlanta, Georgia 30309. E-mail: sking@acri.com.

**REFERENCES**


