EDITORIAL COMMENT

Can Stents Damage Coronary Arteries Remote from the Stent?*

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During the past decade, cardiovascular stents and endothelial function have both been the focus of intense research. Because percutaneous coronary interventions tend to be focal or “spot” therapy designed to open a relatively limited vascular segment, the interaction between interventional devices and the endothelium has focused almost exclusively on the site of contact (1–4). Interventionists know well the problems that can occur at the site of stent contact with the endothelium and the rest of the vessel wall in the form of dissection, thrombosis and restenosis. The report by Caramori et al. (5) in this issue of the Journal challenges us to broaden our view of the extent of the interaction between coronary stent and endothelium and raises questions about possible long-term negative effects remote from the stented coronary segment.

This article (5) examines the coronary vasomotion of the left anterior descending coronary artery in 39 patients subclassified into three groups according to the type of percutaneous intervention: Palmaz-Schatz stent, balloon angioplasty or directional atherectomy. No patient had restenosis an average of 19 months after the procedure. Endothelial reactivity was measured at a segment distal to the treated lesion and quantified by the degree of angiographic spasm or dilation induced by intracoronary acetylcholine, which acts directly on the endothelium. The group receiving stents had twice as much distal spasm as the other two groups (22% vs. 9%). Stenting was the only variable associated with this marker of endothelial dysfunction.

Two questions need to be asked. First, are the results real or a function of the limitations of this well-executed original study? Second, why should endothelial dysfunction distal to the stent concern us? As the authors point out, the study’s main limitation is the lack of randomization. But even if the patients had been randomized, the potential for bias remains substantial when trying to control for so many variables that influence endothelial function in three small groups. These factors include smoking, hypertension, lipid status, vitamins C and E, angiotensin-converting enzyme inhibitors, dilated cardiomyopathy and diabetes mellitus (6). These seemed to favor no group, or perhaps the stent group to a small degree. To neutralize the potential bias of these factors that influence endothelial function, the authors used as a control the circumflex artery reactivity, which was equal in all groups. This decreases but does not eliminate the concern about unequal baseline endothelial function in the study groups.

Some questions remain about the methods used for the arterial diameter measurements. A technician blinded to treatment performed measurements. One must assume that the frames used for measurement did not include the stent, which could be visible to the technician. In addition, the criteria used to select the segments for diameter measurement are never discussed. Both of these factors could bias diameter measurements. Two patients in the stent group and one in the balloon angioplasty group required nitroglycerin to reverse intense spasm at the 10⁻⁵ molar dose of acetylcholine. It is unclear how the results from these patients were treated, because the significant difference in the study was evaluated at the 10⁻⁴ molar dose, which was not given to these three patients. Considering the small number of patients in each group, the inclusion or exclusion of the data from these patients might have an important influence on the results. Finally, the small difference between the stent group and the other two groups needs to be viewed cautiously owing to the inherent limitations in quantitative angiography using automated edge detection.

Despite these questions, the findings cannot be dismissed as due to chance or potential limitations in methodology. Every patient in the stent group developed vasoconstriction with high dose acetylcholine, whereas the other two groups had heterogeneous reactions. It now serves as the gold standard until further studies confirm or refute its conclusion.

This study joins growing published data suggesting that stents cause more coronary trauma and endothelial dysfunction than other types of percutaneous interventions (1,7). But this study is novel in suggesting that stents may cause more severe endothelial dysfunction than other types of percutaneous interventions remote from the interventional site. As the authors discuss, stents may adversely affect endothelial function by inhibiting complete endothelial regeneration and promoting excessive inflammatory cell infiltration at the site of injury. The mechanisms by which these local responses might modulate endothelial function downstream remains to be defined.

Because endothelial dysfunction is intimately linked to the initiation and progression of atherosclerotic coronary artery disease (CAD) (8), this study raises the specter that stents may promote CAD in the distal coronary artery. This

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could be a significant limitation for a therapeutic modality that is spot therapy for a diffuse process such as CAD and could threaten to limit the long-term efficacy of the procedure.

The competition between coronary artery bypass grafting surgery (CABG) and percutaneous interventions for the treatment of advanced multivessel CAD has been enjoined for some time. Even with just plain old balloon angioplasty, percutaneous intervention has achieved intermediate-term results similar to CABG with regard to death and major infarction (9), except in certain diabetic patients. There has been a realistic optimism among cardiologists that stents will make percutaneous intervention even more competitive with CABG. Until venous bypass grafts begin to degenerate, spot therapy with any percutaneous intervention has two disadvantages compared with successful CABG. The first is restenosis. The second is the failure to neutralize plaque progression or rupture in the proximal epicardial artery where the majority of these two events occur (10). Therefore, progressive CAD proximal to a graft has little impact on the efficacy of CABG, while significantly limiting the durability of percutaneous interventions. If stents cause significant acceleration of CAD distally, this would create a third obstacle to overcome relative to CABG.

Aside from atherogenesis, endothelial dysfunction can promote coronary thrombosis and reduce coronary flow reserve. There is certainly no reported evidence of stents causing such problems distal to the device. Therefore, the finding of this study needs to be verified and the potential effects of remote stent-induced endothelial dysfunction will have to be investigated. To begin to determine if stents induce distal atherosclerosis, it may be possible to turn to centers with large volumes of long-term follow-up angiograms of patients who have received stents. By matching them with appropriate control subjects, the potential problem of distal progression of CAD could be studied. Doppler technology may also be useful to investigate functional changes.

In the U.S., stents were used in over 50% of all percutaneous interventions in 1997. Although some question this high incidence of stent usage, there are many excellent reasons to support this practice. Stents have performed significantly better than balloon angioplasty in multiple randomized trials in a variety of clinical settings (11–14). Randomized and nonrandomized studies have shown that current techniques for deploying stents have substantially reduced acute complications such as abrupt vessel closure, in-hospital myocardial infarction, emergency CABG, restenosis and target vessel revascularization. The cost-effectiveness of stents versus balloon angioplasty is now becoming apparent as the need for chronic anticoagulation has disappeared and as longer term follow-up has been achieved (15).

Despite the data justifying the high usage of stents, we must continue to monitor for long-term complications unique to either stents in general or a particular stent design. Caramori et al.’s (5) report sounds a warning volley. Whether or not it is a false alarm remains to be determined. However, this theoretical concern will not curb stent usage with its proven benefits until meaningful disadvantages are firmly demonstrated.

REFERENCES