Drug-Eluting Stent Implantation May Not Affect Vasomotor Function in Early Phase

The study by O bata et al. (1) demonstrates that drug-eluting stents (DES) adversely affect endothelium-dependent vasomotor function with a reduction in vascular endothelial growth factor (VEGF). This report addressed a very important issue because it has been reported that endothelialization and its function are impaired following DES implantation (2,3). However, we are not convinced by the findings in the present study that DES affect vasomotor function 2 weeks after implantation. As we have previously reported (4), there is no histologic difference between DES and bare-metal stents (BMS) within 2 weeks following implantation. Moreover, vascular healing of the stented segment in acute myocardial infarction generally takes a much longer time to complete than stable plaques do in the case of both DES and BMS because these lesions generally contain large necrotic cores. Therefore, it is surprising that the authors report differences in response to intracoronary acetylcholine because the extent and functionality of endothelium for lesions stented with either DES or BMS lesions is not different 2 weeks after implantation. Furthermore, angiography cannot detect the underlying atherosclerotic disease in the distal segments where vasomotor function was assessed, and it is possible that the differences observed were due to differences in atherosclerotic burden between the 2 groups because endothelial function has been shown to be heavily influenced by the presence of underlying atherosclerotic disease.

The authors also speculate that lack of VEGF in DES might be responsible for impaired endothelialization or its function. As the authors mentioned in the introduction, a compensatory up-regulation of VEGF is usually observed when endothelium is denuded, whereas VEGF is down-regulated upon complete re-endothelialization (5). We do agree that high blood concentrations of sirolimus at an early time point could impair endothelial cells in the portion distal to the stent and be responsible for vasomotor dysfunction. However, the sirolimus concentration in the anterior interventricular vein is far below its IC[50] (1.0 to 1.5 nmol/l) even at 3 days (0.5 nmol/l) and even further below at 2 weeks (0.2 nmol/l) following implantation. Even if sirolimus had a detrimental effect on endothelial cells in the distal vessel, the VEGF level should be higher in the presence of active ongoing arterial repair. In fact, our in vitro and in vivo data clearly showed VEGF up-regulation after endothelial injury. In our own assays, human umbilical vein endothelial cells are grown until confluence and VEGF expression is measured using cytokine array (RayBiotech Inc., Norcross, Georgia) in the presence and absence of scratching or treatment with everolimus (2 nmol/l) for 16 h. The VEGF level was greater in the scratched and everolimus group (1.7 ± 0.4- and 1.8 ± 0.6-fold increase, respectively) as compared with the nonscratched control group. Similarly, we have observed up-regulation of VEGF messenger ribonucleic acid in the bare-metal stented rabbit iliac arteries as compared with nonstented iliac arteries at 7 days (1.4 ± 0.2-fold increase). Thus, VEGF is up-regulated in the lesions where endothelialization is incomplete. It is hard to reconcile these findings with those of O bata et al. (1). The vascular biology of DES implantation is just being understood and larger clinical studies as well as preclinical studies are needed to deepen our understanding.

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REFERENCES

1. O bata JE, Kitta Y, Takano H, et al. Sirolimus-eluting stent implantation aggravates endothelial vasomotor dysfunction in the infarct-related...

Reply

We appreciate the opportunity to reply to questions raised by Dr. Nakazawa and colleagues. Please note that the coronary arteries distal to the stented segment but not the stented lesion were examined for the endothelial vasomotor function in our study (1). As described in our study (1), myocardial ischemia-reperfusion induces endothelial injury in the coronary trees for their entirety distal to the occluded segment in the infarct-related coronary artery. Thus, the healing process of the coronary arteries distal to the stented segment but not the stented lesion affected our data. Our previous reports (2–5) agreed that the atherosclerotic burden strongly affects coronary endothelial vasomotor functions. However, our study (1) showed that the frequencies of the atherosclerotic risk factors were comparable between the drug-eluting stent (DES) and bare-metal stent (BMS) groups. In addition, the 2 groups had no difference in cardiac medications, lesion, and procedural variables of percutaneous coronary intervention except for stent selection, and acute myocardial infarction (AMI)-related variables that potentially influence the coronary endothelial vasomotor function, as described in our study (1). Thus, the implanted stents were only the discriminate factor for the difference in the coronary endothelial vasomotor responses to acetylcholine between the patients treated with BMS and DES.

A number of previous reports (6,7) demonstrated that the vascular endothelial growth factor (VEGF) expression is increased in cardiomyocytes as well as vascular endothelial cells in ischemic or injured hearts and that sirolimus is capable of inhibiting VEGF production and the VEGF-mediated cellular signaling pathway in various types of cells. Our study (1) also showed that VEGF levels in the anterior interventricular vein (AIV), reflecting VEGF levels released from the ischemic myocardium, were increased in AMI patients treated with BMS compared with control subjects. As we described in our study (1), sirolimus levels in AIV in our study were 10- to 500-fold lower than the levels to exert its biological effects in vitro experiments (8,9). Considering the fact that sirolimus is eluted into coronary circulation over a period of 4 weeks, these exposure times were much longer as compared with the in vitro experiments. Moreover, the chronic exposure to the circulating sirolimus might cause a local accumulation of considerable amounts of this drug in the myocardium and the entire vascular bed distal to sirolimus-eluting stent (SES) in the infarct-related coronary artery. Thus, there is a possibility that SES could induce a decrease in VEGF release from myocardium and endothelium of large and resistance vessels, which may play a possible role in the mechanisms for endothelial vasomotor dysfunction in the infarct-related coronary arteries treated with SES.

REFERENCE


Early Detection of Rheumatic Heart Disease and Prevention of Heart Failure in Sub-Saharan Africa

In a recent issue of the Journal, Damasceno et al. (1) highlighted the need for action to reduce the prevalence of heart failure in sub-Saharan Africa, where this pathology is an important cause of mortality as well as a serious economic burden. Rheumatic heart disease is the most frequent cause of heart failure in this region of the world and is responsible for at least one-third of cases. In this context, the authors are prudent to insist on the need for a strategy of prevention with regards to risk factors for heart failure. Nevertheless, we would like to underline important new findings that should be considered when attempting to reduce the incidence of this life-threatening pathology.