Author’s Reply

Reply to Letter Regarding Article, “Sirolimus-Eluting Stents Suppress Neointimal Formation Irrespective of Metallic Allergy”

We appreciate Dr Kounis and colleagues’ interest in our article “Sirolimus-eluting stent suppress neointimal formation irrespective of metallic allergy”. As they pointed out, sensitization to drug-eluting stents (DES) would be not determined by exposure to a single component such as metal because DES have 2 other major components: drug and polymer. In fact, it has been reported that polymers are the likely cause of localized hypersensitivity reaction to DES! Also, there is no evidence that sirolimus does not play a role in hypersensitivity or other reactions. Therefore, detection of an activated response to DES should be performed using multiple components. However, the present study was intended to explore the impact of metallic allergy on angiographic outcomes, which was already reported for bare metal stents9 rather than detection of the cause of the hypersensitivity reaction or sensitization to DES. We hypothesize that sirolimus-eluting stents suppress neointimal formation, irrespective of metallic allergy, because of the immunosuppressive effect of the drug. Although we demonstrated that there was no relationship between metallic allergy and neointimal formation, irrespective of metallic allergy detected in our study may have activated response to DES in these patients.

It has been reported that DES induce delayed arterial healing characterized by inhibition of neointimal formation, incomplete endothelialization, and persistent fibrin deposition, which is considered to be the main substrate of late stent thrombosis (LST).4 On the other hand, endothelial dysfunction may also play a role in the occurrence of LST or other adverse events, because recent clinical reports suggest that DES may impair endothelial responses to acetylcholine and exercise-mediated vasodilation in humans, the so-called paradoxical vasoconstriction.5,6 It is assumed that sirolimus or paclitaxel directly affects endothelial function, as in vitro data have shown an effect of sirolimus and of paclitaxel on endothelial cells, demonstrating an increase in tissue factor and PAI-1 mRNA and protein, which are important factors for the induction of thrombosis.7,8 These are the most probable explanations at present of the endothelial dysfunction that occurs following DES placement; however, vascular biology in the stent-implanted coronary artery is undoubtedly complicated and not fully understood. As Kounis et al suggested, these findings may be associated with inflammatory and/or hypersensitivity reactions, because DES components can provoke allergic reactions.9 Unfortunately, blood tests to monitor inflammatory mediators, macrophages, and T-cell activation were not performed in our study, although no overt systemic reaction was observed. The patients with metallic allergy detected in our study may have had activation of a local hypersensitivity reaction, which is not necessarily detected by angiography alone. In fact, these reactions are more prominently seen in the adventitial area than in the neointima, which may eventually cause malapposition secondary to positive remodeling! These inflammatory cells secrete various inflammatory mediators that could induce paradoxical vasoconstriction or prothrombotic condition. Previous pathologic studies have shown that inflammatory reaction is not the only substrate of LST, but certainly plays an important role in selected cases! Therefore, long-term follow-up with careful observation for these patients is of paramount importance, which may give us insight to the vascular response following DES implantation.

References

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