Letter to the Editor

The Kounis Syndrome in Everolimus-Eluting Stents and Paclitaxel-Eluting Stents

TO THE EDITOR

The 2-year results from the SPIRIT III randomized trial published in *Catheterization Cardiovascular Interventions* [1] showed that patients undergoing stenting of target lesions with jailed side branches with the thin strut everolimus eluting stent had lower rates of myocardial infarction and target lesion revascularization compared with the thiker strut paclitaxel eluting stent (2.9% vs. 10.3% and 3.9% vs. 10.3%, respectively) with comparable rates of cardiac death (1.9% vs. 1.7%). Although the causes of these disparities were characterized as uncertain, potential explanations were given as thicknes of strut, differences in the polymer coatings and physical flow obstruction, and/or thrombogenicity near or within the jailed side branch. Similarly, the SPIRIT IV trial [2] showed 75% reduction in stent thrombosis favoring everolimus when compared with paclitaxel stents but only in nondiabetics. In the latter, neither percentage of diabetic women nor possible causes were given. This point is crucial because about 24.6% of population are sensitized to nickel, whereas only 10.2% to cobalt and 8.7% to chromium with female prevalence [3]. Paclitaxel-eluting and other first generation stents use a 316L stainless strut containing nickel, chromium, manganese, titanium, and molybdenum, whereas the second-generation everolimus-eluting stents release less than 2% nickel ions and use a cobalt-chromium strut.

Pathology and thrombus aspiration findings point toward hypersensitivity inflammation with infiltration of eosinophils, macrophages, T-lymphocytes, and mast cells [4]. Platelet activation leads to stent thrombosis. Human platelets bring and are activated through receptors for multiple agonists mainly thromboxane, ADP, thrombin, and glycoprotein IIb/IIIa. However, a subset of platelets contains FCεRI and FCεRII IgE receptors, which are activated by antigens [5]. Hypersensitivity reactions are associated with stent implantation, and acute coronary events associated with hypersensitivity reactions constitute the Kounis syndrome [6], which has been implicated in the development of acute early and late stent thrombosis. Stent thrombosis seems to correspond temporally with early, late, and chronic hypersensitivity inflammation after persistent, repetitive, or continuous allergen exposure [7].

Stent components such as metals, polymer, and first-generation eluted drugs are all potential antigens ready to ''join forces'' and react with platelets to induce Kounis syndrome [8]. It is known that simultaneous exposure to several antigens can trigger mediator release, and the corresponding IgE antibodies, despite their different specificities, can have additive effects [9]. Experimentally induced platelet activation in human plasma by thrombin or ADP can be inhibited by antihistames [10].

Avoiding persistent, prolonged, and chronic multiple antigen exposure may prevent platelet activation and minimize intrastent thrombosis.

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REFERENCES

1. Applegate R, Hermiller J, Williams J, et al. Evaluation of the effects of everolimus-eluting and paclitaxel-eluting stents on target lesions with jailed side branches: 2-Year results from the SPIRIT III randomized trial. Catheter Cardiovasc Interv 2010; DOI: 10.1002/ccd.22606.

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2. Stone GW, Rizvi A, Newman W, Mastali K, Wang JC, Caputo R, Doostzadeh J, Cao S, Simonton CA, Sudhir K, Lansky AJ, Cutlip DE, Kereiakes DJ; SPIRIT IV Investigators. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663–1674.
3. Rui F, Bonenzi M, Prodi A, et al. Nickel, cobalt and chromate sensitization and occupation. Contact Dermatitis 2010;62:225–231.
4. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391–399.
5. Hasegawa S, Pawankar R, Suzuki K, Nakahata T, Furukawa S, Okumura K, et al. Functional expression of the high affinity receptor for IgE (FcepsilonRI) in human platelets and its intracellular expression in human megakaryocytes. Blood 1999;93: 2543–2551.
6. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): A natural paradigm? Int J Cardiol 2006; 110:7–17
7. Galli SJ, Tsai M, Piliponski AM. The development of allergic inflammation. Nature 2008;454:445–454.
8. Kounis NG. Drug-eluting stent thrombosis: the Kounis hypersensitivity-associated acute coronary syndrome revisited. JACC Cardiovasc Interv 2009;2:583–593
9. Nopp A, Johansson SGO, Lundberg M, Oman H. Simultaneous exposure of several allergens has an additive eff ecton multisensitized basophils. Allergy 2006:61:1366–1368.
10. Petrikova M, Jancinova V, Nosal R, Majekova M, Holomanova D. H1-antihistamines and activated blood platelets. Inflamm Res 2006;55 (suppl):S51–S52.