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inflammatory agent rapamycin. The other components of the stents include the polymer coating and the metal stent itself. The investigators concluded that hypersensitivity to DES is a real entity that causes serious clinical sequelae, and they recommended continuous vigilance and surveillance for any allergic reactions in patients receiving DES.

The Kounis syndrome (3) was described 15 years ago as the concurrence of acute coronary events with allergic or hypersensitivity reactions as well as anaphylactic or anaphylactoid insults. Arachidonic acid metabolites such as leukotrienes and thromboxane; proteolytic enzymes such as chymase and tryptase; histamine and a variety of cytokines and chemokines released during the activation of various interrelated and interacting inflammatory cells such as macrophages, T-lymphocytes, and mast cells have all been incriminated to induce Kounis syndrome. Two variants of Kounis syndrome have been described recently (4). The type I variant, includes patients with normal coronary arteries and represents a manifestation of endothelial dysfunction; the type II variant, includes patients with culprit but quiescent preexisting atheromatus disease. Causes of Kounis syndrome (5) include various conditions, a variety of environmental exposures, and many drugs such as antibiotics, contrast media, intravenous anesthetics, analgesics, skin disinfectants, corticosteroids, thrombolytics, antiinflammatories, and antineoplastics. Antineoplastics capable of inducing acute coronary syndrome (5) are the antimetabolite 5-fluorouracil (Adrucil, UpJohn Pharmaceuticals, Kalamazoo, Michigan), its prodrug capecitabine (Xeloda, Roche Laboratories, Nutley, New Jersey), the alkaloid cisplatin (Platinol, Bristol-Myers Squibb, Princeton, New Jersey), the antimicrotubule paclitaxel (Taxol, Bristol-Myers Squibb), the interleukin-2 agent denileukin difitox (Ontak, Ligand Pharmaceuticals, San Diego, California), the vinca alkaloids, and interferons.

All three components of DES could be responsible for inducing allergic reactions and Kounis syndrome. Polymers, like those in latex and vinyl gloves, have been reported to induce allergic reactions and Kounis syndrome (6). Antineoplastics and antiinflammatory drugs can also induce Kounis syndrome (6). Patients positive for allergic patch-test reactions to stent metal components nickel and molybdenum appear to have increased rates of in-stent thrombosis (7). The inflammatory cells found at autopsy to infiltrate the intima, the media, and the adventitia in one of the patients who died from in-stent thrombosis (8) were the samenamely lymphocytes, plasma cells, macrophages, and eosinophilswith those participating in the process of Kounis syndrome. Indeed, the proportion of 262 cases of allergic reactions in 2 million DES insertions is very low, but it seems likely that some cases might go unreported; thus, it is anticipated that many more cases will be encountered in the coming years.

Responding, therefore, to the appeal of the RADAR (Research on Adverse Drug events And Reports) project and until further studies characterizing the incidence and the course of the reactions and confirming or predicting the DES allergy are undertaken, we recommend, especially in atopic individuals, the following: 1) careful history of adverse drug reactions and allergies in patients receiving DES; 2) intradermal skin tests for every DES component and desensitization strategies; 3) antibody testing including enzyme-linked immunosorbent assay and radioallergosorbent test for every DES component; 4) monitoring the levels of tryptase, histamine, and arachidonic acid products immediately after the allergic reaction appears; and 5) considering the use of corticosteroids and mast-cell stabilizers when the allergic reaction appears. The latter have also abrogated late thrombotic events experimentally (9).

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REFERENCES

- Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug events And Reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81.
- Azarbal B, Currier JW. Allergic reactions after the implantation of drug-eluting stents. J Am Coll Cardiol 2006;47:182–3.
- Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. Br J Clin Pract 1991;45:121–8.
- Nikolaidis LA, Kounis NG, Grandman AH. Allergic angina and allergic myocardial infarction: a new twist on an old syndrome. Can J Cardiol 2002;18:508–11.
- 5. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol 2006;110:7–14.
- Soufras GD, Ginopoulos PV, Papadaki PJ, et al. Penicillin allergy in cancer patients manifesting as Kounis syndrome. Heart Vessels 2005; 20:159-63.
- Kawano H, Koide Y, Baba T, et al. Granulation tissue with eosinophil infiltration in the restenotic lesion after coronary stent implantation. Circ J 2004;68:722–3.
- Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent. Should we be cautious? Circulation 2004;109:701–5.
- Nemmar A, Hoet PHM, Vermylen J, et al. Pharmacological stabilization of mast cells abrogates late thrombotic events induced by diesel exhaust particles in hamsters. Circulation 2004;110:1670–7.

REPLY

We appreciate the letter by Dr. Kounis and colleagues that expands upon our discussion of the literature on stent-associated hypersensitivity (1). In conjunction with the RADAR (Research on Adverse Drug events And Reports) project (2), we have started a protocol that incorporates some of the suggestions of Dr. Kounis and colleagues. This protocol includes skin tests to stent components and laboratory tests. It also features a methodical approach to dechallenge and rechallenge (3) for concomitant medication while maintaining antiplatelet coverage. To refer patients, please contact Dr. Marc Feldman, Associate Professor, Department of medicine, University of Texas, San Antonio (E-mail: feldmanm@uthscsa.edu).

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REFERENCES

- Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug events And Reports (RADAR) project. J Am Coll Cardiol 2006;47:175–81.
- Bennett CL, Nebeker JR, Lyons EA, et al. The Research on Adverse Drug events And Reports (RADAR) project. JAMA 2005;293: 2131-40.
- 3. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med 2004;140:795–801.

Real-Time Intracardiac Echocardiographic Imaging of the Posterior Left Atrial Wall Contiguous to Anterior Wall of the Esophagus

In a recent issue of the Journal, Good et al. (1) reported that esophageal location and movement during left atrial ablation can be detected using a barium ingestion-digital cine-fluoroscopic imaging technique. The disadvantages of the barium ingestioncine-fluoroscopic imaging technique, which they used in the report, include; 1) no real-time imaging during energy delivery of the left atrial posterior wall contiguous to the anterior esophageal wall, which is the most important/only region to be imaged and protected; 2) gaps in barium contrast of the entire esophageal mucosa border that may provide misleading information of the extent of contact along the contiguous posterior left atrial wall; 3) an active effect of barium ingestion on esophageal luminal diameter and movement; and 4) risk of aspiration. In addition, Figures 1A and 1B in the report (1) compare differing anteroposterior projections, creating the illusion of movement that should have been confirmed with the same angled projection.

Intracardiac echocardiography (ICE) can provide real-time imaging of the left atrial posterior wall contiguous to the anterior esophageal wall during energy delivery for left atrial ablation (2). Our ICE studies of esophageal imaging in more than 235 patients showed that the left atrial posterior wall contiguous to the anterior esophageal wall can be imaged in each case. This imaging technique can provide real-time anatomic imaging of this region (3). In addition to anatomic imaging of this region, the ablation catheter tip location and creation of echogenic lesions can also be evaluated during real-time ICE imaging (4). The ICE imaging can guide changes in the energy-delivery strategy to protect the esophagus from damage during ablation in this region and allow for safe lesion delivery in closer proximity to the esophagus than can be safely recommended with the barium ingestion–cine-fluoroscopic imaging technique.

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Please note: Drs. Ren and Callans are the faculty members of AcuNav peer training courses and have received honorarium for the training courses.

REFERENCES

- 1. Good E, Oral H, Lemola K, et al. Movement of the esophagus during left atrial catheter ablation for atrial fibrillation. J Am Coll Cardiol 2005;46:2107–10.
- Ren JF, Marchlinski FE, Callans DJ. Esophageal imaging characteristics structural measurement during left atrial ablation for atrial fibrillation: an intracardiac echocardiographic study (abstr). J Am Coll Cardiol 2005;45 Suppl A:114A.
- Ren JF, Marchlinski FE, Callans DJ, Schwartzman D. Practical Intracardiac Echocardiography in Electrophysiology. Oxford, UK: Blackwell Futura, 2005:194–203.
- Ren JF, Callans DJ, Marchlinski FE, Nayak H, Lin D, Gerstenfeld EP. Avoiding esophageal injury with power titration during left atrial ablation for atrial fibrillation: an intracardiac echocardiographic imaging study (abstr). J Am Coll Cardiol 2005;45 Suppl A:114A.

REPLY

Our study (1) describes a simple, practical, and inexpensive method to visualize the position of the esophagus in relation to the left atrium during left atrial catheter ablation in *real-time*. We have the following responses to the points raised by Dr. Ren and colleagues:

- Because the barium paste typically remains in the esophagus for >45 to 60 min, fluoroscopic imaging of the esophagus after a barium swallow is indeed real-time, and the anterior part of the esophagus is easily visualized.
- 2. Although there may be gaps in the continuity of mucosal staining after barium is swallowed, one can usually simply extrapolate from the more proximal to distal segments of the esophagus.
- 3. Although it is possible that barium swallow may facilitate esophageal peristalsis, patients swallow their own saliva during procedures performed under conscious sedation. Furthermore, as already discussed in our study (1) there was no correlation between the prevalence and extent of esophageal peristalsis and the amount of barium swallowed.
- Aspiration has not occurred during or after barium swallow in over 500 patients who underwent left atrial catheter ablation under conscious sedation in our electrophysiology laboratory.
- Figures 1A and 1B (1) are identical anteroposterior projections randomly chosen from many examples of esophageal migration. As seen in Figure 1 (1), there is marked migration of the esophagus. This clearly is not an *illusion*.

Finally, we do not dispute that intracardiac echocardiography also may be used for real-time monitoring of the esophagus. However, we find the barium swallow to be much simpler and practical than intracardiac echocardiography.

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