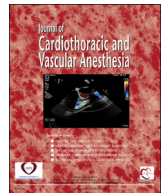


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Editorial

Anaphylaxis During Intracardiac and Endovascular Implantations: A Multifactorial Problem Involving Kounis Syndrome

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IN TODAY'S MEDICAL PRACTICE, several artificial life-saving devices commonly are used for assisting cardiac function, facilitating therapy, closing cardiac defects, and treating medical disorders. Such devices include artificial cardiac valves, pacemakers, defibrillators, coronary stents, left ventricular assist devices, aortic grafts, and stents for femoral arteries. Despite the fact that all have proved to be extremely useful therapeutic inventions, they can induce foreign body reactions and hypersensitivity reactions due to their metal, polymer, and eluting drug ingredients:

- Cobalt, chromium, nickel, and wolfram alloy are metal components of artificial cardiac valves,¹ although nickel-free artificial cardiac valves also are available today.²
- Nitinol, a nickel and titanium alloy, is used in devices for closure of patent foramen ovale and atrial septal defects, peripheral arteries, and aortic grafts.³
- Stainless steel, containing nickel, chromium, titanium, manganese, and molybdenum, is used in coronary stent struts.⁴
- Cardiac pacemakers and defibrillators have generators, which are covered with titanium; have conductor wires consisting of an alloy of nickel, cobalt, chromium, and

molybdenum; and have pacing electrodes, which are made of platinum alloyed with 10% to 20% iridium.⁵

- Titanium and ruby bearings are used in left ventricular assist devices.⁶

All these metal ingredients alone or combined with other sensitizing substances can induce mild or severe hypersensitivity reactions that pose problems for both anesthesiologists and surgeons. Apart from nickel, chromium, and cobalt, which are known for inducing skin hypersensitivity, other metals such as aluminum, beryllium, copper, gold, iridium, mercury, palladium, platinum, rhodium, and titanium are emerging human body sensitizers. Although the latter is considered an excellent biocompatible metal with good corrosion behavior, hypersensitivity reactions to titanium already have been reported.⁷ Titanium alloy can induce hypersensitivity and immune dysfunctions, rendering titanium no longer biologically inert.⁸

With the increasing number of endovascular procedures being performed for peripheral and aortic vascular disease, the use of devices containing nitinol in the femoral artery and aorta has increased proportionately. Nickel allergy is one of the most common allergies worldwide, and medical history often suggests contact with metal jewelry or occupational exposure. In the United States,⁹ nickel, chromium, and cobalt induce allergic skin reactions in about 14%, 4%, and 9%, respectively; in Europe,¹⁰ they induce reactions in about 20%, 4%, and 7%, respectively.

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The nickel–titanium alloy nitinol is composed of 55% nickel and 45% titanium and has induced a “hypersensitivity device syndrome”⁴ resembling Kounis hypersensitivity-associated acute coronary syndrome.¹¹ The latter can manifest as coronary spasm, acute myocardial infarction, and even stent thrombosis. It is caused by the specific antigenicity of metal ions that can be induced by histamine and tryptase release from degranulated mast cells and by activating platelets via FCγRI, FCγRII, FCεRI, and FCεRII receptors.

The nitinol-induced device syndrome has appeared in 9 patients who had documented symptomatic allergies to nickel, which had been evidenced by cutaneous patch skin tests; these patients experienced symptoms resulting from interatrial shunts.¹² These patients preferred to be implanted with the full-nitinol Amplatzer septal occluder (Golden Valley, MN) device and low-nitinol Premere closure system (Frederica, DE). The patients previously had been informed about the possibility of experiencing some symptomatology after the implantation and were free to choose alternative therapeutic options. However, 8 out of 9 patients experienced a short bout of symptoms that included chest discomfort, exertional dyspnea, asthenia, palpitations, worsening of migraine headache, and mild leukocytosis between the second and third post-operative days. Two patients with negative skin patch testing, but with occluder system implantation, developed atrial fibrillation that resolved with antiarrhythmic treatment. Treatment with prednisone and clopidogrel alleviated these symptoms, which finally resolved within 1 week of therapy.

Recent reports have shown that the self-expandable nitinol stents used in peripheral vascular disease, and especially for occlusion of superficial femoral artery disease, have induced intractable and persistent allergic reactions that on some occasions necessitated surgical extraction of the stent.^{13,14}

Furthermore, the recently developed Ovation Abdominal Stent Graft 73 (Trivascular Inc, Santa Rosa, CA), which consists of the aortic body and comprises a proximal stent for suprarenal fixation, polytetrafluoroethylene (teflon) graft material, and a self-expanding nitinol stent cage, has induced hypersensitivity reactions. Indeed, the iliac limbs and iliac extensions comprise a nitinol stent encapsulated in polytetrafluoroethylene. Proximal seal and support are achieved by inflatable rings filled with low-viscosity radioopaque polyethylene glycol that solidifies during deployment.¹⁵ Polyethylene glycol and nitinol can act as antigens, especially in susceptible patients. Polyethylene glycol is a strong sensitizer and has induced anaphylactic shock on several occasions.¹⁶

A 78-year-old male patient with hypertension, diabetes mellitus, coronary artery disease with previous angioplasty, and abdominal aortic aneurysm experienced acute back pain, tachycardia, hypotension, and rapid loss of consciousness during polymer infusion of the inflatable rings of the 26-mm Ovation Abdominal Stent Graft 73, which was implanted for endovascular aneurysm repair.¹⁷ The patient was resuscitated successfully with immediate discontinuation of polymer infusion, laryngeal mask, massive fluid therapy with colloid solution, and standard therapy for anaphylactic reaction. In another similar report,¹⁸ an 82-year-old man with a 5.3-cm

asymptomatic abdominal aortic aneurysm who underwent endovascular repair using an Ovation stent graft developed a severe anaphylactic reaction, resulting in cardiopulmonary arrest. The patient was resuscitated successfully, but the procedure was abandoned and the patient refused any further treatment. The anaphylactic reaction was attributed to polymer infusion into the inflatable rings of the aortic body under continuous angiography, but the rings were not filled, even though the entire amount of the polymer was administered, indicating that the polymer inadvertently went into the bloodstream.

All of these reports raised important questions concerning the device component involvement, the pathophysiology of these reactions, and the future prevention of such reactions. In these reports, the patients had been exposed to various drugs, materials, and substances. The diagnosis and treatment of anaphylactic reaction were based only on clinical criteria, and no other specific tests were carried out, such as immunoglobulin E (IgE), specific IgE, tryptase measurements, or skin tests. Furthermore, the kind of angiographic substances and the type of local anesthetics used during the procedure have not been described. However, several angiographic materials and local anesthetics have induced serious allergic reactions.^{19,20}

Mast cells, which are the main cells involved in anaphylactic reactions and can be activated by nonallergic triggers, often without degranulation, but with selective release of potent and vasoactive compounds, are able to induce anaphylactic shock.²¹ Furthermore, IgE antibodies with different specificities can have additive effects, and small, even sub-threshold, numbers of them can join forces and trigger mast cells to release their mediators.²² On the other hand, clinical studies indicated that susceptible individuals simultaneously exposed to several allergens, as occurs during implantation of the above devices, have more symptoms than monosensitized individuals.²³

Therefore, careful history of adverse drug reactions with monitoring of inflammatory mediators, along with lymphocyte transformation studies to detect material allergy, must be undertaken before implantation of such sophisticated medical devices when this is appropriate. The previously issued warnings by the Food and Drug administration on indications and contraindications for implantation of such devices²⁴ should be applied strictly.

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