

Hypersensitivity reactions associated with endovascular devices

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Allergic reactions to endoprostheses are uncommon and reported in association with orthopaedic, dental, endovascular and other implanted devices. Hypersensitivity reactions to the biomaterials used in endovascular prostheses are among the infrequent reactions that may lead to local or systemic complications following cardiovascular therapeutic interventions. This article reviews potential immunotoxic effects of commonly used biomaterials. Reports of putative hypersensitivity reactions to endovascular devices, including coronary stents, perforated foramen occluders, pacemakers and implantable cardioverter defibrillators are also reviewed.

Key words: allergic contact dermatitis; Amplatzer; cardioverter defibrillators; endovascular devices; hypersensitivity; implantable; metal allergy; pacemaker; patch test; patent foramen ovale occluder; stent restenosis. © Blackwell Munksgaard, 2008.

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Hypersensitivity to orthopaedic, dental, endovascular and other implanted devices has been reported in case and group studies. However, allergic reactions to endoprostheses are still unpredictable processes that are not fully understood. The strongest chemical allergens associated with biomaterials are often chemically active substances of low molecular weight, often less than 500 Da, such as lipid-soluble organic substances derived from polymer materials or metal ions and metal salts. These are also known as haptens and they only become full allergens after reaction with proteins that may be present in the hosts' antigen-presenting cells (1).

In this article, the potential immunotoxic effects of biomaterials are reviewed as well as the clinical and case studies reported as complications of endovascular devices associated with putative and/or documented hypersensitivity reactions. Coronary stents, perforated foramen occluders, pacemakers and implantable cardioverter defibril-

lators are discussed in more detail and other endovascular devices are briefly mentioned.

General Overview of Immune Responses to Biomaterials

Any adverse effect on the structure or function of the immune system or on other systems as a result of immune system dysfunction is considered an immunotoxic effect.

General types of immunotoxic reactions considered by the United States Food and Drug Administration (FDA) in the Immunotoxicity Testing Guidance include the following (2):

Hypersensitivity

The original Gell and Coombs classification lists 4 types of hypersensitivity reactions (3, 4):

Type I [*immediate* – immunoglobulin (Ig)E mediated] reactions, are the most serious, and

usually associated with complete allergens such as latex proteins. As potential allergens in biomaterials are small molecular haptens, the probability of IgE-related reactions is low, although reported in other settings (5, 6). Type II (*cytotoxic* –IgG/IgM mediated) and type III (*immune complex mediated* – IgG/IgM immune complex) reactions are less likely to occur with medical devices/materials, although cases of aseptic loosening of joint prostheses attributed to immune complex reactions have been reported (7).

Type IV or cell-mediated hypersensitivity reactions are the most common reactions associated with implants.

Chronic inflammation

While acute inflammation is part of the normal wound healing process, chronic inflammation, characterized by infiltration of inflammatory cells that may last months, can lead to granuloma formation, pseudo-capsule formation, loosening of implants affixed to bone or other serious effects (2).

Immunosuppression

Inhibition of the adaptive immune response (i.e. antibody and T-cell responses) may lead to consequent serious infections (2). Some of the drug-eluting coronary stents contain immunosuppressive agents, for example Cypher[®] stents contain sirolimus, but the overall doses of these medications are very low and unlikely to have systemic immunosuppressive effects.

Immunostimulation

This entity has been included separately from hypersensitivity and refers to unintended or inappropriate antigen-specific or non-specific activation of the immune system by biomaterials (e.g. antibody and/or cellular immune response to a foreign protein), adjuvancy and enhancement of the immune response to an antigen. Examples include immunogenicity or adjuvant activity that may not result in adverse signs in relatively short-term animal experiments but are cause for concern with long-term *in vivo* implants that may result in sensitization or autoimmunity. This process may be considered as a possible mechanism in cases of delayed hypersensitivity reactions (8, 9).

Autoimmunity

Molecular mimicry of the host antigens may induce antibodies that cross-react with human proteins and may induce autoimmune disease. A biomaterial (e.g. a gel or oil) may also act as an

adjuvant in inducing an autoimmune response. Although the possible association between silicone breast implants and connective tissue disorders has been raised numerous times, large meta-analyses were unable to establish such an association (10, 11). Whether any putative biotransformed products are capable of inducing autoimmune responses remains a possibility.

Implant devices may also contain low molecular weight chemical stabilizers, cross-linking agents for polymers, and degradation products. These constituents that may be present or produced in trace amounts (e.g. parts per million), should also be evaluated for their potential to produce adverse immunological effects on a case-to-case basis (2).

A decision on whether a material/device is immunotoxic must rely on the available evidence from pre-clinical test results and clinical evaluation as well as prior history of use. Because the available data will often be less than conclusive, good judgment will play an important part in evaluating immunotoxic risk (2).

Concerns for potential complications associated with long-term *in vivo* effects of implants highlight the value of postimplantation surveillance studies.

General Overview of Endovascular Devices

Surgical and medical interventions have played a critical role in life-saving treatment of patients with cardiovascular disorders. While substantial benefits of these interventions are well documented, technical difficulties, device failure and/or tissue–biomaterial interactions may lead to clinically observable complications in some cases (1).

Wide varieties of devices and biomaterials are being used and further introduced in the field of interventional cardiology. While numerous studies evaluate feasibility, safety and clinical outcome of these devices, data on their biocompatibility are rare (12). After implantation, most biomaterials are left in the body for life and local tissue interactions after implantation appear important for their long-term success (12). Hypersensitivity reactions to the biomaterials used in endovascular prostheses are among the infrequent reactions that may lead to local or systemic complications following cardiovascular therapeutic interventions. In the discussion of metal sensitivity and metal-containing implants, two different entities should be considered:

- (1) Symptoms that patients may develop because of localized or systemic hypersensitivity reactions.
- (2) Device malfunction or failure because of the host's increased inflammatory response

such as in-stent restenosis (ISR) potentially associated with metal sensitivity.

One or both of these phenomena may potentially happen in a given patient.

Coronary Stents for Atherosclerotic Coronary Disease

Percutaneous transluminal coronary angioplasty (PTCA) and stent placement have saved thousands of lives over the past two decades. Mason Sones performed the first diagnostic coronary angiography in 1958 at the Cleveland Clinic, Ohio, and it was not until 1977 that Andreas Gruentzig performed the first coronary angioplasty procedure, at the University Hospital of Zurich (13). Although a revolutionary therapy, about 30–40% of patients were reported to develop restenosis following PTCA (14).

Introduction of the coronary stent, an expandable tube of metallic mesh to prevent vascular recoil and thereby preserve the patency of the vascular lumen, by Jacques Puel in 1986, France (13), was a major step towards reducing the rate of this complication. Although advances in stent technologies and medical therapies have improved the outcome of percutaneous coronary interventions over the past decade, ISR or local reblockage following deployment of bare metal stents usually because of excessive neointimal hyperplasia is reported to be as high as 16–33% (15, 16).

The growing use of stents has stimulated the introduction of a number of different stent designs and biomaterials. Stents can be classified according to their mechanism of expansion (self-expanding or balloon expandable), their composition (stainless steel, cobalt-based alloy, tantalum, nitinol, inert coating, gold coating, active coating, or biodegradable), and their design (mesh structure, coil, slotted tube, ring, multi-design, or custom design).

The JoMed polytetrafluoroethylene (PTFE)-covered stent (JoMed, Rangendingen, Germany) is an example of a covered stent, specifically made

for uncommon applications such as coronary ruptures, aneurysms, and degenerated saphenous vein grafts (17).

One of the latest advancements in stent technology is the introduction of drug-eluting stents, in which the metallic struts of the stent are coated with polymers impregnated with a drug that inhibits local intimal hyperplasia.

Potential allergens in coronary stents

Bare metal stents Metallic ions are the most likely potential allergens in coronary stents. Table 1 demonstrates the composition of some of the commonly used metallic alloys in cardiovascular devices. The susceptibility of the alloys to corrosion and metal ion elution is also an important factor in the study of metal allergies. Intercellular adhesion molecule (ICAM) 1 is known to be involved in the recruitment of inflammatory cells from the bloodstream (18, 19). It has been shown that nickel ions are able to either promote or suppress the expression of ICAM-1 on endothelial cells depending on the concentration and probably the time of exposure.

Messer et al. (20) in an *in vitro* study placed stainless steel, NiTi, CoCrNi, and NiCr alloys in direct contact with primary human microvascular endothelial cells for 72 hr, in an attempt to determine release of metal ions from commonly used vascular stents, and their effect on expression of key cellular adhesion molecules (CAMs) by endothelial cells, as well as cytotoxicity of the alloys by measuring succinate dehydrogenase (SDH) activity and total protein content of the cells. They showed that Ni release was measurable from all alloys and was significantly different for the different alloy types. In their *in vitro* system, metal ion release from the studied stent alloys was not sufficient to activate expression of CAMs on endothelial surfaces, or induce cytotoxicity. However, their supplemental experiments using nickel ions alone confirmed that ICAM-1 was inducible on the endothelial cells by Ni (II) concentrations higher than 100 μmol . Nickel and cobalt chloride

Table 1. Composition of commonly used metallic alloys in cardiovascular devices (94)

Alloy	Nickel (%)	Chromium (%)	Cobalt (%)	Molybdenum (%)	Ferrous (%)	Titanium (%)	Silicon (%)	Manganese (%)	Tungsten (%)
Stainless steel alloy									
Stainless steel L316	10–14	16–18	—	2–3	Balance	—	<1	0.04–2	—
Nitinol alloy									
Nitinol	55	—	—	—	—	45	—	—	—
Cobalt alloys									
L605 cobalt chromium	10	20	50%	—	3	—	—	1.5	15
MP35N	35	20	Balance	9.75	1	1	0.15	0.15	—
Phynox Aka Elgiloy®	14–16	19–21	39–41	6–8	Balance	—	—	—	—

have been linked to enhanced expression of ICAM in other studies as well (21, 22).

Despite its high concentrations of nickel, nitinol had the lowest Ni ion release among the studied alloys. Cobalt alloys contain nickel in equal or higher amounts compared with stainless steel L316 but proportional release of nickel ion from these alloys is less than stainless steel (20, 23).

Nickel is the most frequent allergen found when patch testing patients with allergic contact dermatitis. The latest data from the North American Contact Dermatitis Group showed that nickel sensitivity was present in 16.2% of patients (24). Nickel allergy has been reported in 7–11% of the general population (25).

Cobalt is the second most common metal allergen with a prevalence of 6% in patients with contact dermatitis and 0.9–1.9% in the general population (24, 26). Chromium allergy is reported in 3.4% of patients with contact dermatitis and 0.9–1.1% of the general population (24, 26). Molybdenum and manganese are rare allergens and are not included in standard screening patch test trays.

The coating of stent struts with a biologically inert barrier between the stent surface and circulating blood has been proposed as an option to minimize release of sensitizing metals. The Titan[®] stent is such an example. It is made of stainless steel coated with titanium-nitride-oxide (27).

Svedman et al. (28) in a trial designed to investigate the frequency of contact allergy to stent materials (gold-plated and stainless steel stents) and common non-metallic allergens, found no significant difference between the prevalence of positive reactions to nickel, cobalt, chromium and palladium and majority of allergens tested in European standard patch test trays. However, they found higher prevalence of positive reaction in patients with gold-plated stents compared with controls

Drug-eluting stents Compositions of materials used in currently available stents are outlined in Table 2. Potential allergens include metals and fragmentation of the coating polymer may expose the metallic strut. Studies on porcine coronary arteries have demonstrated that some biodegradable and nonbiodegradable polymers are capable of inducing a marked inflammatory reaction within the coronary artery with subsequent neointimal thickening (29).

The active drug in Cypher[®] stents is sirolimus, an immune suppressant. The sirolimus content of each stent is between 71 and 314 µg depending on size. Approximately 50% of the total drug is eliminated within the first 10 days of implantation. The drug is 90% removed from the stent by about

Table 2. Composition of materials in the most commonly used drug-eluting stents (95)

Drug-eluting stent trade name	Metallic alloy	Coating polymer	Drug	FDA approval	EC approval
Cypher [®] (96)	316L stainless steel	Composed of two polymers: polyethylene-co-vinyl acetate and poly- <i>n</i> -butyl methacrylate (2:1 ratio respectively)	Sirolimus (immunosuppressant)	April 2003	April 2002 (97)
Taxus [™] (98)	316L stainless steel	Translute [™] : poly (styrene- <i>b</i> -isobutylene- <i>b</i> -styrene)	Paclitaxel (antiproliferative)	March 2004	January 2003 (97)
Endeavor [™] (99)	MP35N	Phosphorylcholine polymer	Zotarolimus (inhibits smooth muscle cell proliferation)	Approved in February	July 2005
Xience [™] V (100)	L605 cobalt chromium	Solef [™] : poly (vinylidene fluoride-co-hexafluoropropene)	Everolimus (immunosuppressant)	Completed phase III clinical trial	January 2006

FDA, Food and Drug Administration; EC, European Commission.

60 days and is completely removed by about 90 days following implantation (30).

The active agent in Taxus™ stents is paclitaxel, an antiproliferative. The paclitaxel content of each stent is between 50 and 209 µg, with burst release in the first 48 hr, slow release over the next 10 days, and none after 30 days (31).

Ethylene oxide (EtO) gas is frequently used in sterilization of medical devices including drug-eluting stents (32) and pacemakers and implantable cardioverter defibrillators (ICDs) (33).

Different types of immune responses have been attributed to EtO, including both immediate and delayed-type hypersensitivity reactions (34–36). Most commonly documented reactions to EtO have been reported in haemodialysis patients, in whom the presence of specific IgE antibodies to EtO by the radioallergosorbent test have been found in as high as 55–63% of symptomatic patients and 6–11% of asymptomatic dialysis patients (34, 37, 38). The presence of IgG antibodies reactive to EtO-exposed human serum albumin as well as type III hypersensitivity reactions and complement activation by EtO have also been reported (36, 39). Standardized patch testing has not been established for EtO, but comparative patch testing with suspected products may confirm the diagnosis of EtO delayed-type hypersensitivity (35).

Hypersensitivity reactions caused by paclitaxel and sirolimus eluting stents seem less likely especially in late cases of putative hypersensitivity.

Reported Complications of Coronary Stents

ISR in bare metal stents associated with metal allergy

It has been hypothesized that contact sensitivity to the metallic components of the stent may increase the endovascular inflammatory responses leading to ISR.

Koster et al. (40) performed a study in which 131 patients, who underwent a clinically driven repeat angiogram, were evaluated for metal sensitivity with patch testing. All patients had received bare stents made of 316L stainless steel within 6.1 months (SD ± 2.7) prior to the repeat angiogram. They found 11 positive patch test results in 10 patients (4 to molybdenum and 7 to nickel); all 10 patients were found to have ISR (lumen loss >50%). While ISR occurred in all patients with positive patch test results, it happened in 69/121 (57%) of patients with negative patch tests. In another study, Hillen et al. (41) investigated the possible role of metal allergy in inducing ISR and did not find a correlation between the presence of positive patch tests and

ISR. The relatively small number of patients (total of 27) limited this study.

Svedman et al. (42) performed a study looking at contact sensitivity to gold in patients with Nir Royal stents (Medinol®; Medinol, Jerusalem, Israel), stainless steel stents coated with gold. Although their data revealed no significant association between the presence of gold allergy and ISR, they identified a higher risk of sensitizing patients to gold with implantation of gold-plated stents. Patients with gold-plated stents have been shown to have higher concentration of blood gold compared with patients who have received stainless steel stent (43).

Norgaz et al. (44) performed patch testing with nickel in 43 patients following deployment of 316L stainless steel stents and 3 of their patients reacted to nickel. Control angiograms 6 months later showed that only 1 of the 3 nickel allergic patients (33%) developed ISR, while the overall rate of ISR in their patients was about 37%. Acknowledging the small number of their patients, these authors concluded that metal allergy should not be considered as a risk factor for developing ISR.

Iijima et al. (45) performed patch tests for metal allergy and follow-up angiography at 6 months in a total of 174 consecutive stented patients. Patients were composed of 2 groups: 109 patients underwent diagnostic angiogram at 6 months following an initial stent deployment, and 65 patients had follow-up angiogram after dilatation for a previous ISR. The prevalence of positive patch tests in the first group was not significantly different between those with or without restenosis (10% versus 9%; $P = \text{NS}$). However, they reported higher prevalence of positive patch tests in the second group (patients who underwent dilatation for recurrence of ISR). The prevalence of positive patch tests in patients with recurrent ISR was 39% versus 12% in cases without the recurrence ($P = 0.02$). A pre-existing metal sensitivity in the second group may have led to a selection bias and should be considered as a potential risk factor for development of prior ISR in these patients. These authors also identified the diffuse pattern of ISR as an independent predictor of recurrent restenosis after treatment of ISR.

Major limitations of the mentioned studies are small cohorts of patients and controversies in choosing the most appropriate metal salts for patch testing as well as evaluation of patch test results. There is little guidance on choosing the appropriate and nonirritating concentrations of metal salts for patch testing, particularly when testing for uncommon allergens such as molybdenum and manganese, which are not

routinely patch tested. An example includes the higher rate of positive patch tests reported with manganese chloride compared with other salts of manganese (Table 3). Metal chlorides are known as potential irritants even at low concentrations and positive reactions on patch testing may not always represent true allergy (46).

Currently available reports of adverse reactions caused by metal-induced delayed-type hypersensitivity involve relatively small numbers of patients and conclusions are not consistent. Particularly in studies of ISR, known risk factors should be considered, including stent length and reference diameter; patient characteristics such as diabetes and behavioural risk factors such as smoking (47). Further studies with larger cohorts of patients are needed before drawing more definite conclusions.

Hypersensitivity reactions associated with drug-eluting stents

Almost 6 months after approval of the Cypher stents, in October 2003, an FDA advisory panel described more than 290 reports of subacute (occurring between 24 hr and 30 days postprocedure) thrombosis and more than 50 reports of possible hypersensitivity reactions associated with Cypher stents.

These cases were reported through The Medical Device Reporting (MDR) system and symptoms included rash, dyspnoea, hives, itching, and fevers (48).

In subsequent updates, FDA announced that in most cases reported to the agency, the putative hypersensitivity reported with the Cypher[®] stent was minor and transient, including skin rashes and itching that resolved within a few days of onset. The majority of these reactions were attributed to peri-procedural concomitant medication(s), although several fatal reactions were also reported that remained unexplained (49, 50).

The recently initiated Research on Adverse Drug Events And Reports (RADAR) project includes a series of investigations lead by a diverse team of experts in North America, who review the reported cases of adverse events on FDA's post-marketing clinical data (51).

In a recent publication, investigators from the RADAR project reviewed the hypersensitivity-like reactions associated with drug eluting stents (DES)s reported to the FDA's Manufacturer and User Device Experience (MAUDE) centre. The postmarketing data showed 251 cases of hypersensitivity-like reaction in the first 18 months after marketing of the Cypher[®] stents and 11 cases in the first 8 months after marketing of the Taxus[™] stents. It is estimated that during this period, over

2 million drug-eluting stents have been deployed worldwide. However, under-reporting is a common phenomenon in data reporting registries (9).

Of the total of 262 cases; 17 distinct cases of putative stent allergy were identified. Four of these cases developed fatal coronary thrombosis that extended into the stent. Histological examination on autopsy of all 4 cases demonstrated intrastent eosinophilic infiltrates and poor intimal healing as late as 18 months after implantation. In 1 of these patients, concomitantly placed bare metal stents (BMS)s were not associated with these hypersensitivity findings (8, 9, 52). Although rare, these data suggest spectrums of hypersensitivity responses to DESs, while no specific allergen has been identified. These reactions vary from excessive inflammation with medial destruction to stent malposition, and aneurysm formation with late in-stent thrombosis. The follow-up of patients with DES to monitor potential late complications along with the development of diagnostic methods to identify potential allergens may help avoid some of the late-term complications with DES and further improve their biocompatibility.

Percutaneous patent foramen ovale occluders

A variety of transcatheter device systems are available for repair of atrial septal defects (ASDs) and patent foramen ovals (PFOs).

Approximately 25% of the general population has a PFO, with no clinical consequence from this anatomical variant in the vast majority of patients. However, in some, the PFO may be the pathway through which thrombotic emboli, air emboli, desaturated blood, and vasoactive substances are shunted and enter the left atrium without traversing the pulmonary circulation. Paradoxical emboli clearly play a role in the development of stroke. The first ASDs were closed percutaneously in 1974 (53), and over the last 2 decades multiple devices have been developed and modified. Currently, the most widely used occluders are the Amplatzer[®] series (AGA Medical Corporation, Golden Valley, MN, USA), and the CardioSEAL/STARflex occluders (NMT Inc., Boston, MA, USA). To date, only the Amplatzer atrial septal occluder (ASO) has been fully approved by the FDA. The CardioSEAL[®] device is available in the United States under a humanitarian device exemption (HDE), but the other devices are still considered investigational.

The Amplatzer[®] septal occluder was developed in 1997 (54), and consists of 2 self-expandable round discs connected to each other with a 4-mm-wide waist. The device is made up of nitinol wire mesh filled with Dacron fabric (55). The

Table 3. Patch testing in patients with coronary stents: summary of patch test materials and results

Study	Total number of patients	ISR/total number of patients (%)	ISR/number of metal allergic patients (%)	ISR/number of non-metal allergic patients (%)	Metal salts used	Number of positive reactions/total number of patients (number of patients with ISR/number positive reactions)
Koster et al. (40)	131	79/131 (60.3)	10/10 (100)	69/121 (57.0)	Nickel (II) sulfate 2.5% aq. and nickel (II) sulfate 5% pet. Potassium dichromate 0.5% pet. Molybdenum (V) chloride 0.5% pet. Manganese (IV) oxide 10% in pet. 316L stainless steel plates	7/131 (7/7 ISR)
Hillen et al. (41)	27 ^a	9/27 (30)	1/3 (33.3%)	2/8 (25.0)	Nickel sulfate 5.0% pet. Potassium dichromate 0.5% pet. Manganese sulfate 2.0% pet. Ammonium heptamolybdate 1.0% aq.	3/27 (2/3 ISR)
Svedman et al. (42)	22	5/22 (22.7)	3/10 (33.3) ^b	2/12 (16.6) ^b	Gold sodium thiosulfate 2% pet. Palladium chloride 2% pet. European baseline series	10/22 (3/10 ISR)
Norgaz et al. (44)	43	16/43 (37)	1/3 (33.3)	15/40 (37.5)	Nickel sulfate 5.0% pet.	Data not available
Iijima et al. (45)	109 <i>de novo</i> stent	20/109 (18.3)	2/10 (20)	8/99 (8)	Nickel sulfate 5.0% aq.	3/43 (1/3 ISR)
(two study groups)	65 prior ISR	23/65 (35.3)	9/14 (64)	14/49 (28.5)	Potassium dichromate 0.4% aq. Molybdenum 20% in pet. Manganese chloride 2.0% pet. Cobalt chloride 1.0% pet. Titanium 20% in pet. Water as control	12/174 (7/12 ISR) ^c 7/174 (3/7 ISR) 1/174 (1/1 ISR) 14/174 (8/14 ISR) 0/174 0/174 0/174

ISR, in-stent restenosis.

^a34 patients were originally enrolled in this study of which 4 had positive patch tests; but data from 27 patients is reported, 3 of whom had positive patch tests.^bOnly allergy to gold was considered.^cSome patients had positive reaction to more than one allergen.

CardioSEAL[®] occluder is constructed of a cobalt alloy (MP35N) framework to which the polyester fabric is attached (56).

Nickel release from Amplatzer[®] occluder was studied by Ries et al., who measured the serum levels of nickel in 67 patients 24 hr, and 1, 3, and 12 months after occluder implantation. A rise in mean serum levels of nickel was observed, from 0.47 ng/ml before implantation to 1.27 ng/ml 24 hr after implantation to a maximum of 1.50 ng/ml 1 month later, which was statistically significant. Values <2 ng/ml of nickel are considered to be normal (57).

Hypersensitivity associated with PFO occluders

Thrombotic occlusion after implantation of occluders is part of the therapeutic goal as opposed to stents where it represents a major complication after stent deployment (12). Animal studies have shown a positive correlation between nickel release by implants and local tissue inflammation (19). Further studies are warranted to learn more about the interaction between an implant and its surrounding tissue in humans.

Three cases of systemic allergic reactions to PFO occluders without apparent rash, but with positive patch tests are reported to date, and summarized in Table 4. In 1 patient, surgical removal of the device led to uneventful recovery with resolution of symptoms (58). In another case, the patient continued to have systemic symptoms even after the removal of the Amplatzer, but he finally recovered following removal of his stainless steel sternal wires, which contained trace amounts of nickel (59). In the third case, the patient's symptoms were transient and improved with the use of systemic corticosteroids. In fourth case reported by Singh et al. (60), the ASD closure with an Amplatzer[®] septal occluder was aborted because of a history of allergic contact dermatitis to metals. The Amplatzer was subsequently taped to the patient's forearm and caused an erythematous reaction on the skin within 24 hr. The authors used a CardioSEAL[®] occluder for a similar testing and found no skin reaction after 72 hr. The patient's ASD was closed using a CardioSEAL[®] device, but no further follow-up on this patient is available.

Pacemakers and ICDs

Device overview

Device-based anti-arrhythmic therapy is a dynamically evolving field of cardiovascular medicine. The first internally implantable pacemakers were introduced in 1960s and since then have significantly improved. The titanium casing was developed in

Table 4. Reported cases of allergy to PFO occluders

Investigators	Patient	Device	Symptoms	Patch test reactions ^a	Clinical course
Fukahara et al. (58)	37-year-old female	PFO-Star [®] device (nitinol alloy)	2 months postimplantation: fever, dyspnoea, no infectious cause	Positive to nitinol	Uneventful recovery following surgical removal of the PFO occluder; 4 months after implantation
Dasika et al. (59)	11-year-old male	HELEX [®] septal occluder (nitinol alloy)	Reported to be similar to Fukahara's patient	Positive to nickel	Uneventful recovery after surgical removal of PFO occluder and sternal wires
Lai et al. (101)	38-year-old female	Amplatzer [®] (nitinol alloy)	Few days later developed dyspnoea and pericarditis	Positive to nickel	Pericarditis and symptoms improved after 3 weeks on prednisone

PFO, patent foramen ovales.

^aInformation on patch test chemicals used for diagnosis of nickel sensitivity in above cases is limited.

1970s to enclose the battery and circuitry, which replaced the previously used epoxy resin and silicone rubber covers. The titanium shielding also greatly reduces outside electromagnetic interference (61). Implantable cardioverter/defibrillators initially introduced in humans in 1980 and approved by the FDA in 1985, have evolved from a treatment of last resort to a firstline treatment and prophylactic therapy for patients at risk of ventricular tachycardia or ventricular fibrillation (62).

A number of different pacemakers and ICDs are commercially available and the specifics regarding product materials can be obtained from individual vendors (63).

In general, these devices are made of 2 implantable components: generator and lead(s). Generators for the most part are covered with a titanium capsule; leads are attached to the capsule through the pacemaker's header. Most headers are composed of 2 main components: (a) poly-methylmethacrylate (also used for bullet-proof glass and hard contact lenses) and silicone rubber (polydimethylsiloxane). Some headers are fully silastic (a flexible inert silicone rubber). The pacing leads are flexible insulated wires, which are connected to the pulse generator header on one side and carry the impulses to the heart, stimulating the heart through the pacing electrodes. Leads also carry information from the heart back to the pulse generator, which the physician accesses via a special programmer. The conductor wires consist of MP35N (an alloy of Ni, Co, Cr, and Mo) or MP35N with a silver core for high-current applications (mainly defibrillation). The pacing electrodes are commonly made of platinum alloyed with 10–20% iridium. ICD leads also have similar pacing electrodes at the tip but additionally have 1 or 2 defibrillation electrodes (shock coils) for delivering high-energy cardioversion pulses. The shock coils are usually 5–10 cm long and are most commonly located in the right ventricle and the superior vena cava. The majority (approximately 70%) of shock coils are made of platinum or platinum-iridium, whereas the remaining (approximately 30%) are made of tantalum with platinum coating. A few older defibrillation lead models have titanium shock coils, but these are not common (64).

Leads are most commonly insulated with one of several formulations of polyurethane, silicone rubber, some copolymers of silicone and polyurethane, expanded PTFE or polychloroparaxylylene (parylene) (65, 66).

Reported cases of allergy and other reactions associated with pacemakers and ICDs are primarily reports of localized pain and/or dermatitis syndromes occurring within 2 days to 24 months after implantation and a few cases of generalized

pruritus or dermatitis that resolved after pacemaker removal (67, 68). Some of the identified or putative allergens in pacemaker-induced reactions are listed in Table 5.

Titanium generally has excellent biocompatibility, although it has rarely been associated with cell-mediated hypersensitivity. Diagnosis of titanium allergy based on patch testing is uncommon. Alternative methods of investigating titanium allergy such as lymphocyte proliferation tests, intradermal testing with serum incubated with titanium and X-ray energy dispersive spectroscopy (EDAX) on the skin biopsy of involved skin have been described (Table 5). Allergy to other components such as polychloroparaxylylene (69, 70), epoxy resin (71), triethylenetetramine, an epoxy hardener (72), nickel (73), chromium, cobalt, mercury (74) and polyurethane (75) has also been reported.

Management of pacemaker/ICD reactions typically includes control of local dermatitis with topical corticosteroids in mild cases or replacement of the device with one that is free of the suspected allergen. An alternative method is wrapping the device in a PTFE sheet, as reported by investigators from Japan, which has been successful in preventing recurrence of contact dermatitis during the reported follow-up periods of up to 3 years (69, 76–79). Replacement with customized silicone or gold-coated pacemakers has also been reported to cause resolution of such sensitivity reactions (70, 75, 80, 81).

Hayes and Loesl (70) reported the case of a patient in whom allergy to polyurethane was documented by patch testing and replacing the device with a specially manufactured device with a silastic-coated pulse generator and silastic-insulated leads, led to resolution of inflammation with no other reactions.

Device malfunction because of hypersensitivity has been noted by Abdallah et al., who reported a patient in whom allergic reactions lead to accumulation of serous fluid in the pacemaker pocket. The device failure was attributed to 'fluid creating an excessive drain on the power source' (75).

Non-allergic cutaneous findings associated with pacemaker implantation have also been described such as telangiectatic erythematous cutaneous reaction (82), circumscribed erythema (83), pressure dermatitis (84), and should be considered in the differential diagnosis of dermatoses associated with pacemakers.

Clearly, infection is a much more common cause of inflammation associated with implantable electrophysiological devices and should be investigated thoroughly before suspecting an allergy. The device pocket tissue culture should be performed, although a negative culture does

Table 5. Reported cases of contact sensitivity associated with pacemakers

Putative allergen	References	Reaction type	Patch test results	Other diagnostic methods/Comments on management
Titanium	Peters et al. (102)	Localized dermatitis	Titanium plate ++; nickel sulfate 2.5% +	Patient developed localized dermatitis 2 months after placement of parylene coating – no other information available
	Abdallah et al. (75)	Localized dermatitis/vesicular	Titanium +; polyurethane +	Pacemaker was replaced with a customized silicon coated device but rash recurred and device was removed and patient managed medically.
	Viraben et al. (103)	Granulomatous local dermatitis	Negative	Electron probe microanalysis (EDAX) was performed on the skin biopsy, detecting titanium restricted to the granuloma area. Rash cleared with topical steroid
	Yamauchi et al. (104)	Local erythema	Patch test negative to standard trays and pacemaker components	Intracutaneous test with the serum incubated with titanium was positive after 2 days. No information on management available.
	Ishii et al. (76)	Localized dermatitis	Titanium metal +	Device was wrapped in a polytetrafluoroethylene (PTFE) sheet, with no recurrence in 3 years
	Freeman (81)	Localized erythema and erosion	Titanium dioxide 50% +; titanium dioxide 10% +	Pacemaker was replaced by a gold-coated pacemaker with no recurrence
Nickel, Cobalt, chromium	Laugier et al. (105)	Localized dermatitis	Cadmium +; chromate +	NA
	Tilsley and Roitstein (106)	Lichenified plaques on lower extremities	Nickel +++; cobalt ++; chromate +	NA
	Landwehr and van Ketel (73)	Pompholyx on both hands	Nickel sulfate 5% in pet. +	NA
	Moimi et al. (107)	Lower extremity dermatitis	Nickel +++; cobalt +	NA
Mercury	Brun et al. (74)	Localized dermatitis	Mercury +	NA
	Hiranaka et al. (77) ^a	NA	Mercury + ^b	NA
Epoxy	Andersen et al. (72)	Localized desquamation and discoloration	Epoxy resin 1% in pet. +; Epoxy resin hardener: ++; (Triethylenetetramine 0.5% in pet.)	Pacemaker was replaced by a device in a titanium capsule
	Romaguera et al. (108)	Generalized pruritus and erythematous plaques on trunk	Epoxy resin +++	NA
Polychloroparaxylene (parylene)	Skoet et al. (71)	Localized dermatitis	Epoxy resin ++	Dermatitis was controlled with topical steroids
	Iguchi et al. (69)	Localized erythema dermatitis	Positive patch test to the Polychloroparaxylene (parylene) coating	Parylene coating was stripped off a pacemaker and the device was wrapped in polytetrafluoroethylene (PTFE) sheet with no recurrence in 2 year follow-up
Polyurethane and parylene	Hayes and Loesl. (70)	Lead dislodgment and drainage at the implant site	Polychloroparaxylene (parylene) +; Polyurethane +	Pacemaker was replaced with specially manufactured device with a Silastic-coated pulse generator and Silastic-insulated leads, and had no other reactions
Polysulfone beige and polyurethane	Dery et al. (80)	Localized dermatitis and pain over the pacemaker	Polysulfone beige and polyurethane 75D, components from the pacemaker lead connector	Pacemaker was replaced with a customized silicon coated device with no recurrence in 18 months
Thiuram mix	Tujita et al. (79) ^a	NA	Thiuram mix + ^b	NA

(Continued)

Table 5. Continued

Putative allergen	References	Reaction type	Patch test results	Other diagnostic methods/Comments on management
Silicon adhesive	Raque and Goldschmidt (109)	Localized dermatitis	Un cured silicone adhesive; neat: +++ 10% in pet.: negative	Possible irritant reaction on patch test. Pacemaker was not removed. Dermatitis controlled with topical steroid
Unidentified allergen	Verbov (110)	Localized eczema	Negative (titanium not tested)	Granulomatous reaction on histopathology
	Gimenez (111)	Localized eczema	Negative	NA
	Brun and Hunziker (74)	Localized eczema	Negative to metallic titanium and titanium tetrachloride solution	NA
	Buchet et al. (68)	Generalized pruritus and eosinophilia	Not conclusive due to concomitant dermatitis	Dermatitis resolved in 5 days after device removal
	Weiss (67)	Localized erythema	Negative to titanium plate, polyurethane and European standard tray	Reactions resolved after replacement with a different device
	Tujita et al. (79) ^a	NA	Negative patch test	NA
	Kono et al. (78) ^a	NA	Negative patch test	NA

NA, no information available.

^aAs referenced by Ishii et al. (76).

^bReaction strength not specified.

not rule out the presence of an infection and may only illustrate the limitations in current isolation techniques. Chua et al. (85) have showed that 32% of patients with clinical signs and symptoms of ICD infection had negative tissue and swab cultures, and yet they responded well to treatment with total device and hardware removal and antibiotics. The negative cultures in these cases may have been the result of antibiotics administered prior to clinical presentation for surgical treatment (85, 86).

Miscellaneous Reports of Reactions to other Endovascular Devices

Anecdotal reports of allergic reactions to other endovascular devices are rare and beyond the scope of this review, but 2 are briefly described.

Lyell et al. (87) reported a case of a nickel allergic patient who developed life-threatening periprosthetic incompetence with 2 successive nickel-containing mitral valve prostheses. The patient subsequently received a nickel-free prosthesis, which lead to satisfactory results in 22 months follow-up (88).

Gimenez-Arnau et al. (89) reported a patient who developed generalized eczematous dermatitis 3 weeks after receiving an endoluminal repair for an abdominal aortic aneurysm with a straight Vanguard[®] endograft made of a self-expanding nitinol alloy. Patch testing was positive to nickel sulfate and cobalt chloride. The patient's symptoms were attributed to nickel allergy, and symptoms were controlled with systemic antihistamine and topical corticosteroid therapy.

Conclusion

The majority of current data regarding putative sensitivity reactions to endovascular and other cardiovascular biomaterials is based either on anecdotal case reports or data gathered from small cohorts.

A spectrum of responses, varying from benign reactions to excessive inflammation and systemic hypersensitivity reactions are reported. These reactions should be considered relative to the context of their application. For example, a local and possibly allergic inflammatory reaction in a coronary stent may increase the risk of ISR, whereas a similar process after implantation of a PFO occluder could be considered part of the therapeutic goal.

Minor allergic reactions caused by medical devices may lead to minor, transient symptoms or may have no clinical consequences at all. No definitive dermatological syndrome has been reported in association with medical devices,

although multiple cases of systemic hypersensitivity reactions have been attributed to drug-eluting stents and Amplatzer[®] PFO occluders (9, 58, 59).

While there is little doubt that these medical devices, in rare instances, can induce allergic reactions, whether or not these reactions can cause device malfunction still needs further study.

Multiple investigators have studied the causal role of allergic reactions in failed joint implants. Review of a number of published reports on metal sensitivity in patients with joint implants shows that the prevalence of metal sensitivity in patients with a failed or failing prosthetic joint is approximately 6 times that of the general population and approximately 2 to 3 times that of all patients with a metal implant (90). However, this association does not prove a causal effect. It is still not known whether these patients are metal sensitive as a result of device failure, or whether the device failure occurred because of a pre-existing metal sensitivity, or because of alternate mechanisms (90). The same concept may apply to other implants including endovascular devices.

Most manufacturers advise against use of a medical device in allergic patients. However, it has been shown that metal allergic patients can tolerate orthopaedic prostheses containing the allergenic metals (91). At this point, there is no strong data to support routine preprocedural evaluation of patients for allergy to device components. Occasionally, the issue of metal allergy is raised by some patients and/or physicians based on a prior history of metal contact sensitivity. Clinical history of metal sensitivity is present in about 80% of patients with a positive patch test to nickel (92).

Obviously there is no role for such evaluation in case of an emergency. In elective cases, patch testing may be considered. Patch testing should be tailored towards the specific biomaterials used in a device, in addition to testing with standard screening allergens. For patients with a clinical history of dermatitis, we generally test with the expanded North American Standard Screening Tray (65 allergens), and for patients without a history of dermatitis, we use an abbreviated North American Standard Screening Tray (first 20 allergen) as well as the prosthesis tray (93). The standard tray contains the most common allergenic metals, nickel, chrome, and cobalt salts along with rubber accelerators, and selected topical medications. Bacitracin or a related antibiotic may be used as an irrigation solution for some procedures. Patch testing is also performed with individual chemicals used in the device, metal salts relevant to the specific alloy, and pieces of the device if available and in appropriate form (thin

and flat with smooth surfaces and edges). Some vendors provide patch test kits that contain solid pieces of the devices; for example Medtronic Inc., (Minneapolis, MN, USA) provides patch test kits for pacemakers and nerve stimulators. When testing solid pieces, false-positive reactions from pressure effects and false-negative reactions from inadequate chemical release may occur. Patch

Table 6. Recommendations for evaluation of patients with putative stent/cardiac device allergy

Detailed history including

History of contact sensitivity or putative reactions to metals, rubber, latex, adhesives, acrylics, sutures, topical antibiotics and implanted devices or during the perioperative period of prior procedures. Exact details of procedure including pre- and postprocedural medication and sterilizing products. Exact device information including complete listing of biomaterials and sterilizing methods of the device.

Patch testing with baseline series:

North American Contact Dermatitis Group (NACDG) Screening Series (65 allergens), European Baseline Series (EBS) or T.R.U.E. test (TT) with additional screening or aimed allergens as indicated for patients with clinical history of dermatitis or Abbreviated Screening Series (first 20 NACDG allergens, EBS or TT for patients without a history of dermatitis). Focused patch testing with modified prosthesis tray (93):

- Ammonium molybdate 1% aq.
- Titanium powder 1% pet.
- Titanium dioxide 10% in pet.
- Palladium chloride 1% pet.
- Manganese chloride 2% aq.
- Chlorhexidine gluconate 0.5% aq.
- Tantalum powder 1% pet.
- Iridium chloride 1% aq.
- Indium sulfate 10% aq.
- Cobalt chloride 1% pet.
- Bacitracin 20% pet.^a
- Methyl methacrylate 2% pet.^a
- Polydimethylsiloxane 10% pet.
- Colophonium 20% pet.^a
- Neomycin sulfate 20% pet.^b
- Formaldehyde 1% aq.^c
- Nickel sulfate 2.5% pet.^b
- Potassium dichromate 0.25% pet.^b
- Gold sodium thiosulfate 0.5% pet.
- Patch testing kit if provided by the manufacturer^c

Other testing as indicated

- Latex RAST
- Ethylene oxide RAST
- Complete blood count with differential
- Serum IgE level

Reporting of putative adverse reactions

Suspected cases should be reported to the manufacturer and to the competent authorities of the relevant country. The Medical Device Reporting system in the United States is available on <http://www.fda.gov/cdrh/mdr/>. A list of contact points for the Medical Device Vigilance System in the European Economic Area can be accessed at http://ec.europa.eu/enterprise/medical_devices/ca/ca_vig.htm

T.R.U.E., thin-layer rapid use epicutaneous test; RAST, radioallergosorbent test.

^aOn NACDG Screening Series.

^bOn NACDG, EBS and TT Baseline Series.

^cBeware of potential false-positive reactions from pressure or false-negative reactions from inadequate metal release.

testing with metal salts is preferable to testing with solid components of the devices.

The role of lymphocyte proliferation tests and intradermal testing is not well defined. To our knowledge, there are no data regarding EtO-related allergies in endovascular devices. Patch testing for this gas-sterilizing agent is not standardized. EtO-specific IgE and IgG measurements could be considered as an option in this case, as well as patch testing with actual EtO-sterilized device components.

Continuing improvements in immunological testing methods will likely improve future assessment of patients susceptible to hypersensitivity responses. Another important factor in further defining the underlying mechanisms of biomaterial incompatibility is pathological examination of peri-implant tissues in explanted devices. Until additional prospective, longitudinal studies are conducted and the role of hypersensitivity reactions in patients receiving endovascular devices is better defined, the risk of such events may be considered minimal. However, in the event of temporally related cutaneous or systemic signs and symptoms of allergic reactions, proper evaluation of such patients for potential allergy to the implanted device(s) should be considered. In such patients, careful review of the concomitant medications used prior to, during and after the procedure as well as other exposures and potential allergies are essential. Suspected cases should be reported to the manufacturer and to the competent authorities of the relevant country. The MDR system in the United States is available on <http://www.fda.gov/cdrh/mdr/>. A list of contact points for the Medical Device Vigilance System in the European Economic Area can be accessed at http://ec.europa.eu/enterprise/medical_devices/ca/ca_vig.htm

Our recommendations for evaluation of a patient with putative stent or other cardiac device allergies are summarized in Table 6.

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