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CLINICAL REVIEW

Cardiac implantable electronic devices (CIEDs) and allergy

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Abstract

Advances in cardiac implantable electronic devices (CIEDs) have prolonged life expectancy in various medical settings. However, the issue of hypersensitivity to components of CIEDs is still a concern. Since 1970, allergic reactions to metallic and nonmetallic components of CIEDs have been reported. Hypersensitivity reactions to medical devices are rare and not fully understood. In some cases, diagnosis and treatment are difficult. Cardiologists should always keep in mind pacemaker allergy when a patient appears with wound complications and no signs of infection. Patch testing should be tailored toward the specific biomaterials used in a device, in addition to testing with standard screening allergens in select cases.

KEYWORDS
allergic reactions, cardiac implantable electronic devices, hypersensitivity

1 | BACKGROUND

Thousands of implantable pacemakers (PMs) and implantable cardioverter defibrillators, which are referred to as cardiac implantable electronic devices (CIEDs), are implanted in the world each year. PMs provide life-saving therapy for the treatment of bradyarrhythmias; defibrillators also provide treatment for ventricular tachyarrhythmias and sudden arrhythmic death. The prevalence and incidence of PMs implantation are unknown in many countries but there is continued growth due to increased life expectancy and an increasing aging population. However, there is great variability between richer and developing countries. In Europe, there are countries such as France, Italy, and Sweden in which the rate of PMs implantation is >1000 implants per million people, whereas others, such as Azerbaijan, Bosnia and Herzegovina, and Kyrgyzstan, with <25 PM implants per million people. Currently, the estimated number of patients undergoing PM implantation globally is 1 million devices per year.[1]

Regarding the number of ICD implantations, clinical research conducted by the European Heart Rhythm Association in the European Society of Cardiology countries reports that the average number of ICD implantations per million inhabitants in 2015 was 102. The European country with the highest number of implantations was Germany with 358 per million population, followed by San Marino −242- and Italy −238-, whereas the lowest implantation rate was in Ukraine with only one per million population.[2]

1.1 | Implant complications

Device implantation surgery is associated with a risk of complications, especially in the perioperative phase, although a considerable risk remains even in the long term. The most common ones are device infection, lead dislocation and malposition, surgical wound hematoma, and pneumothorax.[1] In the MOST study, complication

rates were 4.8% at 30 days, 5.5% at 90 days, and 7.5% at 3 years after implantation of a dual-chamber PM,[3] but "real-life" data suggest a higher risk.[4,5] In another recent large study with >81 000 patients, major complications occurred in 8.2% within 90 days of device implantation.[6] Complication risks generally increase with the complexity of the procedure such as device upgrading or lead revision. In a Danish study, complications of 9.9% at first implantation and 14.8% at lead upgrade or revision were reported.[1] Of note, among the various complications, delayed-type hypersensitivity to the material has not yet been mentioned in the guidelines.

1.2 | Clinical presentation of CIEDs allergy

Allergies to cardiac devices are rare conditions although known since 1970.[7] The mechanism is unknown but probably results from a delayed-type hypersensitivity reaction[8] to the coating material of the device components. It would be a type IV hypersensitivity reaction according to the classification of Gell and Coombs, mediated by T-cell lymphocytes.[9] In 1997, the incidence was estimated to be about 571 per 1 million[10] and annual incidence of 1–2 per 100 000 patients.[11] In more recent studies, the prevalence of delayed-type hypersensitivity after implantation of CIEDs has been estimated to be approximately 1.5%–2.5%.[12] However, it is not possible to estimate with precision the actual incidence of this rare complication also because, probably, it is underdiagnosed (or underreported) and wrongly interpreted as an infection.

The etiology of this complication is unknown, likely related to genetics or HLA, as sensitivity is usually to multiple encasing materials.

Clinical presentation can mimic a PM infection and, therefore, can lead to multiple device replacements and repositions and to unnecessary prolonged antibiotic therapy.[10,13,14]

Hypersensitivity reaction to a component of device usually manifests as a local contact dermatitis but occasionally may be generalized, especially if the allergy is to a component of the catheters.[10,15] Therefore, it can be manifested with pruritus, pain, cutaneous eruption, erythema, and swelling at the site of PM insertion (Figure 1). Severe erythroderma and anogenital dermatitis, however, have also been described[10,16,17] as well as the eruption of lichenified plaques on the forearms, thighs, and legs[18] (Table 1). However, a PM infection, a relatively more common and serious complication, should be excluded before considering PM allergy. Unlike infection, the clinical presentation of a hypersensitivity reaction does not present with fever and neutrophilic leukocytosis, whereas it often manifests with eosinophilia and negative cultures from blood, eventually removed leads, and pocket materials. The onset of the reaction may be early or delayed and range from weeks to even years.[16]

1.3 | The components that cause reaction

Implantable pulse generators contain similar components, although not always the same, and information from the manufacturer's website may be too vague to be helpful. In addition to metals, urethanes,

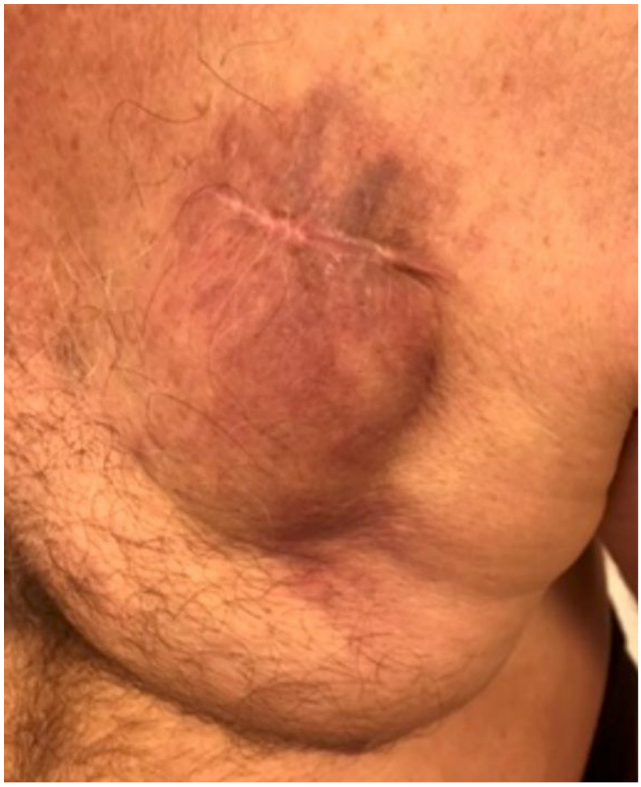

FIGURE 1 A patient with a pacemaker referred to erythema and swelling at the site of CIED insertion after replacement with a new device covered with parylene. The patient also complained of pruritus and pain in the device wound.

TABLE 1 Allergic reaction to CIEDs.

Cutaneous reaction	Time after implant	Occurrence
Pompholyx on hands	2 days	Rare
Local eczema/ erythema	2 weeks–21 months	Frequent
Lower limbs eczema	2 weeks	Infrequent
Local swelling	3 weeks–17 months	Frequent
Generalized erythema	2 months	Infrequent
Granulomatous erythema	3 months	Infrequent
Vesicular lesions	3– 8 months	Rare
Generalized eczema	18 months	Infrequent
Disseminated plaques	2 years	Rare

and epoxies, these may also use silicones, polyether ether ketone (PEEK), polyethylene terephthalates, polysulfone, and parylene, which are not reported to cause allergic reactions and to which there are no commercially available extracts.

Each cardiac device has a generator usually made of a titanium alloy, the electrodes (made of platinum/iridium) that lodge distally in the cardiac chambers and a transition part, made of a synthetic resin (bisphenol A epoxy resin, epichlorohydrin, o-cresyl glycidyl ether, bisphenol F, and ethylenediamine dihydrochloride), that serves to connect the electrodes with the generator (Figure 2). As for the electrodes used in pacing and defibrillation systems, their surfaces are

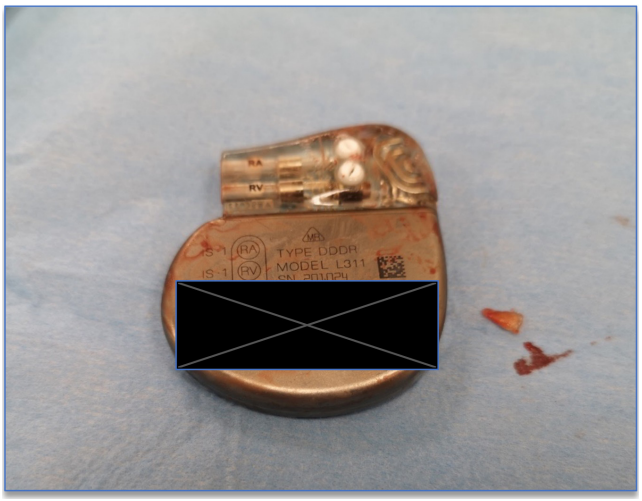

FIGURE 2 A dual-chamber pacemaker has a titanium alloy. The transition part serves to connect the electrodes with the generator and it is made of a synthetic resin (bisphenol A epoxy resin, epichlorohydrin, o-cresyl glycidyl ether, bisphenol F, and ethylenediamine dihydrochloride). The electrodes used in pacing and defibrillation systems are made of polyurethane, silicone, or their combinations, whereas their internal parts are made of metal alloys (nickel, cobalt, chromium, and molybdenum) but are not in contact with human tissue or blood.

made of polyurethane, silicone, or their combinations, whereas their internal parts are made of metal alloys (nickel, cobalt, chromium, molybdenum) but are not in contact with human tissue or blood.

In a small and monocentric study conducted by Manousek et al,[19] they investigated the exact composition of implantable devices made by different manufacturers. They found that CIED generators contain at least 99.32% of titanium and other metals (tin, nickel, antimony molybdenum, iron, and manganese) were present only in trace. Even 23.7% of the generator was made of 100% titanium. Instead, the electrode surface is made of silicon, polyurethane, or a combination of the two.

However, different brands of CIEDs are available and the specifics regarding product materials can be obtained from individual manufacturers.

There are several cases of allergies to PM components described in the literature in which multiple allergens have been identified as culprits, such as nickel,[18,20] cobalt,[18] polyurethane,[21] titanium,[22,23] and silicone.[7,22] Identification of the specific agent, though the reliability of this test for certain metallic agents may be unreliable, especially in the case of titanium.[24]

1.4 | Diagnosis

Time to symptoms widely varies, ranging from days to years. However, most reactions occur between several weeks to a few months after implantation. Complete blood cell count is usually normal, but eosinophilia can be seen. Identifying the specific material to which the patient is allergic is very important because this helps the clinician identify which material should be avoided in any future implantation and/or which device component should be isolated.

Diagnosis can be made with skin patch testing. Therefore, it is necessary to obtain all materials contained in the device that are in contact with human tissue and blood from the manufacturer, and every component must be tested. In fact, allergies to multiple PM components have been reported.[25]

Specimens from all the PM and lead components should be applied on the patient skin for at least 72 h (and sometimes up to 120 h) since traditional patch testing (48 h) maybe insufficient for the diagnosis of CIED allergies. Cutaneous reaction around nickel should be interpreted with caution since up to 20% of the population is positive. And on the contrary, a negative result does not exclude PM contact sensitivity, especially with titanium, whereas a negative skin patch does not exclude hypersensitivity reaction.[23,26–28] Therefore, there are other methods of allergy evaluation, particularly for titanium allergy, that have been reported: the most used test is the lymphocyte transformation test (LTT), but intradermal testing with serum incubated for titanium, and energy dispersive X-ray spectroscopy (EDAX) on skin biopsy of the affected area can also be used.[13,25]

Cases have been reported in which the patch test with titanium gave negative results but LTT for the same metal showed increased proliferation in vitro. Once the cause of the allergy is removed, it is also possible that LTT will show no more hyper-reactivity to the metal that was previously observed.[16,29]

Proposed clinical criteria for diagnosis of hypersensitivity reaction to CIEDs may be summarized in five major points: (1) appearance of Eruption (erythema or eczema) over the device pocket, (2) absence of systemic or local infection (cultures of blood, pocket tissue, and device material should be negative); (3) positive patch test reaction to a metal used in the implant; (4) early exteriorization of the device (within the first 6 months postimplantation) or recurrent exteriorization of the device (>2 occasions); (5) absence of recurrences of exteriorization after implantation of a device covered with gold or PTFE Minor diagnostic criteria for postimplantation metal hypersensitivity reactions can be considered: (i) dermatitis resistant to therapy, (ii) systemic allergic dermatitis reaction, (iii) histology consistent with allergic contact dermatitis (presence of multinucleated giant cells in the pocket tissue biopsy), (iiii) positive in vitro test to metals, for example, the LTT (Table 2).[30]

1.5 | Treatment: Some examples from the literature

Once a diagnosis of allergy to a component of CIEDs has been made, especially if severe, it is ideal to remove and replace the offending component or coat them completely. Of note, there are no clear indications and guidelines to follow and there are cases reported in the literature that have been treated in completely different manners. Topical corticosteroids drug therapy with a duration of 2 weeks[26] or 6 months[31] can permanently resolve the skin reaction but often upon discontinuation of the drug, there is a recurrence.[32] A study conducted by Yang Bai et al.[33] investigated the possibility of treating

TABLE 2 Diagnostic criteria for allergic reaction to CIEDs.

Diagnostic criteria for allergic reaction to CIEDs
Major
Erythema/Eczema over the CIED pocket
Early/Recurrent Exteriorization of the device
Absence of systemic or local infection
Positive patch test reaction to a metal used in the implant
No exteriorization after replacement with a generator covered with Gold or PTFE
Minor
Dermatitis resistant to therapy
Systemic allergic dermatitis reaction
Histology consistent with allergic contact dermatitis
Positive in vitro test to metals

Abbreviations: CIEDs, cardiac implantable electronic devices; PTFE, Polytetrafluoroethylene.

TABLE 3 Suggested allergy checklist for CIEDs.

	Pre-op allergy checklist
☐ Yes ☐ No	Chronic systemic allergic dermatitis
☐ Yes ☐ No	Cutaneous reaction to metals (excluding nickel)
☐ Yes ☐ No	Previous history of erythema/eczema after surgical procedures
☐ Yes ☐ No	Previous history of erythema/eczema after dental procedures
	In case of an affirmative answer consider specific patch testing before implantation only in patients with a significant history of overt contact dermatitis to environmental exposures

TABLE 4 Suggested patch test panels for CIEDs.

Suggested patch test panels for CIEDs	
Nickel	**Manganese**
Chromium	Cobalt
Platinum	Iridium
Molybdenum	Epichlorohydrin
TDI (toluene diisocyanate)	MDI (methylene diphenyl diisocyanate)
Bisphenol A epoxy resin	Bisphenol F
Ethylenediamine dihydrochloride	o-Cresyl glycidyl ether

Abbreviation: CIED, cardiac implantable electronic device.

pocket effusion or hematoma caused by an allergic reaction with an antihistamine: in nine patients promethazine 25 mg/day was administered intramuscularly for 6 days with clinical benefit.

In cases where a hypersensitivity reaction to a generator component is suspected, there have been reports describing the resolution of symptoms with the use of a gold-coated PM in place of titanium.[31,34] In another case, however, the allergy was effectively treated with a coating with antibiotic-coated envelopes.[10]

Other methods described include wrapping the generator or cables in a sheet of polytetrafluoroethylene.[35] In another case, they decided to switch to an epicardial pacing system keeping the same components.[24]

What can be done to prevent an allergic reaction to CIEDs? Obviously in real life, it is impossible to perform a skin patch test or other tests on all patients who are candidates for device implantation. Nevertheless, we recommend in selected subjects, for example, those with a known history of allergic eczema, to perform an allergy screening (Tables 3 and 4) and to use one of the methods in the literature to decrease the risk of a hypersensitivity reaction.[36] Future studies are needed to investigate the benefits of screening for CIEDs hypersensitivity before or after a procedure, and consequently, novel strategies must be applied to screen for CIEDs hypersensitivity.

2 | CONCLUSIONS

Device allergy is a rare clinical condition, probably underreported. Diagnosis and treatment can be difficult because there are no clear indications or guidelines. However, clinical suspicion should always keep in mind when a patient appears with wound complications, especially with multiple recurrences and when no signs or proof of infection can be found. More extensive and controlled trials need to be carried out to clarify the exact relationship between hypersensitivity reactions and CIEDs before specific guidelines will help us to prevent or manage CIEDs hypersensitivity reactions.

CONFLICT OF INTEREST

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