21 Hypersensitivity to Cardiovascular Implants: Cardiac Implantable Electronic Devices and Septal Occluders

Golara Honari and Farshad Raissi

21.1 Introduction

Advances in procedural medicine and availability of numerous biomedical devices in various medical and surgical specialties are improving quality-of-life and life expectancy in many patients. However, for a select group of patients, the issue of hypersensitivity to component(s) of medical devices is a concern. Since the early 1970s, allergic reactions to nickel in patients with metallic mitral valves and orthopedic prostheses have been reported [1–4]. Evaluation of putative hypersensitivity reactions to implantable devices requires a comprehensive understanding of the complex surgical, mechanical, environmental, and biologic factors that can affect the outcome of device implantation. Allergic reactions to endoprostheses are rare and unpredictable processes that are not fully understood. Hypersensitivity reactions can potentially be induced by metallic and non-metallic components of a device. Since the focus of this chapter is on the association of metal allergy and medical devices, review of the metal compositions, corrosion, and interaction with the immune system discussed in earlier chapters is highly recommended.

It is of note that there is an increasing trend of metal allergy in younger generations, at least in the United States. In a recent report of patients patch tested by the North American Contact Dermatitis Group, the frequency of positive patch test reactions to nickel was 10% in individuals older than 65 years of age, 17% between 18 and 65 years, and 25.9% in those younger than 18 years [5]. Although these numbers overrepresent the prevalence of nickel allergy in the general population, they can highlight an increasing trend in frequency of metal allergy. Enforcing regulatory measures on the amount of nickel release from consumer products has lowered prevalence of nickel allergy in Europe, but currently there are no similar regulatory measures in the United States [6–9]. Concern about metal sensitivity associated with implantable medical devices has a growing impact on quality-of-life and healthcare costs. There is an expanding interest in the proper evaluation of individuals with suspected metal allergies prior to receiving an implant or postoperatively in patients with localized or systemic hypersensitivity reactions or, at times, with implant malfunctions.

G. Honari (✉)
Stanford University School of Medicine,
Redwood City, CA, USA
e-mail: honari.golara@gmail.com

F. Raissi
Cardiac Electrophysiologist, Sulpizio Cardiovascular Center, Clinical Assistant Professor of Medicine,
University of California San Diego,
9444 Medical Center Dr MC 7411,
La Jolla, CA 92037, USA

J.K. Chen, J.P. Thyssen (eds.), *Metal Allergy*, https://doi.org/10.1007/978-3-319-58503-1_21

21.2 Pacemakers and Implantable Cardioverter Defibrillators

Cardiac arrhythmias are common and important public health concerns. While many patients are managed by medical interventions, a large proportion of them need to be treated via invasive electrophysiology interventions such as ablation therapy and/or cardiac implantable electronic devices (CIED). From the implantation of the first pacemaker in Sweden in 1958, there have been many advances in this field [10]. Device-based antiarrhythmic therapy is a dynamically evolving field of cardiovascular medicine. The main CIED include the pacemaker, implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT) device. It is estimated that more than one million pacemakers and more than 320,000 implantable cardioverter defibrillators are implanted annually worldwide [11]. About a quarter of pacemaker implantations and a third of ICD implantations are replacements for various indications [11]. Putative hypersensitivity is an extremely rare condition that may lead to device replacement.

21.2.1 General Device Characteristics

In general, these devices are made of two implantable components: generator and lead(s). Generators for the most part are covered with a titanium capsule, and leads are attached to the capsule through the pacemaker's header which is composed of two main components: (a) poly-methyl-methacrylate (also used for bulletproof glass and hard contact lenses) and (b) silicone rubber (polydimethylsiloxane). Some headers are fully Silastic (a flexible inert silicone rubber). The sensing/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 one or two defibrillation electrodes (shock coils) for delivering high-energy cardioversion pulses. The majority of shock coils are made of platinum or platinum-iridium, and the remaining are made of tantalum with platinum coating. Leads are most commonly insulated with one of several formulations of polyurethane, silicone rubber, some copolymers of silicone and polyurethane, ethylene tetrafluoroethylene (ETFE) and polytetrafluoroethylene (PTFE), or polychloroparaxylene (parylene). Steroid-eluting electrode tips are available containing about 1.0 mg of dexamethasone with the intent to lower local inflammation, allowing a lower pacing system energy requirement [12–16].

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

21.2.2 Associated Hypersensitivities

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 [17, 18]. 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; perhaps the optimum patch test material for titanium is yet to be established. Allergy to other components such as polychloroparaxylene, epoxy resin, triethylenetetramine, an epoxy hardener, nickel, chromium, cobalt, mercury (with undetermined relevance), polyurethane, polysulfone beige, and silicone adhesive has also been reported [19–26]. Reported cases of putative CIED reactions are listed in Table 21.1. It is important to note in many of these cases reported, information is not complete and presence of a true allergic reaction is difficult to prove.

Table 21.1 Reported cases of metal contact sensitivity associated with cardiac implantable devices

Putative allergen	Reference	Reaction type	Patch test results (as reported)	Other diagnostic methods/ comments on management
Titanium	Peters et al. [44]	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. [23]	Localized dermatitis/ vesicular	Titanium + Polyurethane +	Pacemaker was replaced with a customized silicon-coated device, but rash recurred; device was removed and patient managed medically
	Viraben et al. [45]	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. [46]	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. [39]	Localized dermatitis	Titanium metal +	Device was wrapped in a polytetrafluoroethylene (PTFE) sheet, with no recurrence in 3 years
	Freeman [47]	Localized erythema and erosion	Titanium dioxide 50% + Titanium Dioxide 10% +	Pacemaker was replaced by a gold-coated pacemaker with no recurrence
Titanium Nickel Chromium	Dogan et al. [48]	Localized dermatitis over the ICD	Titanium Nickel Chromium	Dermatitis resolved with topical steroids
Chromium Cadmium	Laugier et al. [49]	Localized dermatitis	Cadmium + Chromate +	NA
Nickel Cobalt Chromium	Tilsley and Rotstein [50]	Lichenified plaques on lower extremities	Nickel +++ Cobalt ++ Chromate +	NA
	Landwehr and van Ketel [51]	Pompholyx on both hands	Nickel sulfate 5% in pet. +	
	Moini et al. [52]	Lower extremity dermatitis	Nickel +++ Cobalt +	
Other metals	Brun et al. [25]	Localized dermatitis	Mercury + (undetermined relevance)	
Epoxy	Andersen [22]	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

Table 21.1 (continued)

Putative allergen	Reference	Reaction type	Patch test results (as reported)	Other diagnostic methods/ comments on management
	Romaguera et al. [53]	Generalized pruritus and erythematous plaques on trunk	Epoxy resin +++	NA
	Skoet et al. [21]	Localized dermatitis	Epoxy resin ++	Dermatitis was controlled with topical steroids
Polychloroparaxylene (parylene)	Iguchi et al. [20]	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 [19]	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. [24]	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. [42]	NA	Thiuram mix +	NA
Silicon adhesive	Raque and Goldschmidt [26]	Localized dermatitis	Uncured silicone adhesive—neat +++ Uncured silicone adhesive −10% in pet.: negative	Possible irritant reaction on patch test. Pacemaker was not removed. Dermatitis controlled with topical steroid
Unidentified allergen	Verbov [54]	Localized eczema	Negative (titanium not tested)	Granulomatous reaction on histopathology
	Gimenez [55]	Localized eczema	Negative	NA
	Brun and Hunziker [25]	Localized eczema	Negative to metallic titanium and titanium tetrachloride solution	NA
	Buchet et al. [17]	Generalized pruritus and eosinophilia	Not conclusive due to concomitant dermatitis	Dermatitis resolved in 5 days after device removal
	Weiss [18]	Localized erythema	Negative to titanium plate, polyurethane, and European standard tray	Reactions resolved after replacement with a different device
	Tujita et al. [42]	NA	Negative patch test	NA
	Kono et al. [41]	NA	Negative patch test	NA

21.2.3 Evaluation of Patients with Putative Allergic Reactions to CIEDs

A comprehensive approach to patients with cutaneous or systemic reactions following implantation of pacemaker/ICD is essential. Nonallergic reactions are far more common and include infection, reticulated telangiectatic erythema, circumscribed erythema, pressure dermatitis, middermal elastolysis, and radiation dermatitis [27–36]. Infection is a much more common cause of inflammation associated with CIEDs and should be investigated thoroughly before suspecting allergy. A device pocket tissue culture should be performed, although a negative culture does not always rule out the presence of an infection and may only illustrate the limitations in current bacterial isolation techniques. Chua et al. 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 [30]. The negative cultures in these cases may have been the result of antibiotics administered prior to clinical presentation for surgical treatment [30, 37]. Routine patch testing is not required prior to implantation of a pacemaker or ICD.

Once other causes are excluded, the management of dermatoses is typically tailored based on clinical findings. Localized dermatitis and mild cases can be treated with topical corticosteroids. In rare cases where allergic reaction is highly suspected, epicutaneous patch testing using relevant allergens customized per device should be performed. If antibiotics are used to irrigate the device pocket prior to insertion, these antibiotics should be added to the patch test panel. In patients with relevant positive reactions to components of a device, replacement of the device with one that is free of the suspected allergen is recommended. An alternative method is wrapping the device generator in a PTFE sheet, which has been successful in preventing recurrence of contact dermatitis [20, 38–43]. Hayes and Loesl reported the case of a patient in whom allergy to polyurethane was documented by patch testing. A specially manufactured device with a Silastic-coated pulse generator and Silastic-insulated leads was substituted and led to resolution of inflammation with no other reactions [19]. Additional reported cases and management options are listed in Table 21.2.

Table 21.2 Evaluation of putative allergic reaction to cardiac implantable devices

(a) Perform a detailed clinical history
(b) Rule out infection; in many cases tissue culture from peri-implant tissue would be most definitive, but this can only be done during the explantation
(c) Consider other diagnosis such as pressure dermatitis and other noninfectious causes such as reticulated telangiectatic erythema
(d) Skin biopsy helps characterize the dermatoses
(e) Consider patch testing only in patients with a significant history of overt contact dermatitis to environmental exposures
(f) Patch testing should be customized toward the components of the implanted device

21.3 Percutaneous Atrial Septal Defect and Patent Foramen Ovale Occluders

A different category of devices reviewed here are devices that are used for closure of holes between the right and left atrium. Two main conditions that cause abnormal flow of blood from the right to left atrium are atrial septal defect (ASD) and patent foramen ovale (PFO). ASD is a congenital heart defect caused by incomplete closure of the atrial septum. It is estimated that each year about

1 in 2000 babies are born with an ASD in the United States [56]. The foramen ovale serves a physiologic purpose in the fetal circulation, helping the flow of oxygenated placental blood from right to left atrium. Soon after birth, this portal will seal; however, in about 25% of healthy individuals, it remains patent. Most patients with PFO are asymptomatic, but several diseases including cryptogenic stroke, transient ischemic attacks (TIA), and migraine headaches with aura have been associated with PFOs. [57–59] A 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 play a role in the development of stroke. That being said, the jury is still out on the clinical benefits of PFO closure for stroke prevention [60].

Percutaneous ASD closure was first performed in 1974 [61]. The first commercially available ASD closure device was developed by Rashkind and Mullins in the early 1980s followed by other devices [62–66]. The first device specifically designed for closure of PFO was designed as a double-umbrella device in 1992 [67]. ASD closure devices can be used to close PFOs as well. The general concept involves approximating the leaflets, closure of the hole between the atria, and subsequent endothelialization of the device. Complete closure of the ASD and PFO is achieved within a few months.

Currently a variety of transcatheter device systems are available for repair of ASDs and PFOs. The US Food and Drug Administration's (FDA) Center for Devices and Radiological Health approved the Amplatzer septal occluder for percutaneous ASD closure and PFO closure [68, 69]. The Amplatzer device is made of two connected circular, self-expanding, nitinol (nickel-titanium alloy) discs that contain thin polyester fabric [69]. Another FDA-approved device is the GORE HELEX septal occluder for percutaneous ASD closure. The implant is made of a circular wire frame made of nitinol and covered with a thin GORE-TEX membrane [70]. Another FDA-approved device to be used only for closure of certain complex ventricular septal defects is the NMT Medical CardioSEAL Septal Occlusion System, which was used off-label for ASD and PFO closure but is currently only used for investigational purposes [71]. The CardioSEAL STARFlex Septal Occlusion System is composed of a metal "double-umbrella" framework made of MP35N alloy and polyester fabrics [71]. The GORE® HELEX® septal occluder is composed of ePTFE patch material supported by a single nitinol wire frame. GORE® CARDIOFORM received FDA preapproval in September 2015 and is made of an ePTFE membrane supported by a platinum-filled nickel-titanium (nitinol) alloy wire frame [72].

The abovementioned devices are all nondegradable with metallic components, but significant advances in this field, including introduction of partially degradable and totally degradable occluders, might change the composition of the applied biomaterials [73].

21.3.1 Hypersensitivity Reactions to ASD and PFO Occluders

Currently, most commonly used occluders contain a metallic frame, and nickel allergy has been identified as the most common cause of surgical device explantation [74].

As mentioned earlier, Amplatzer® and GORE® HELEX® septal occluders have nitinol frames, and the CardioSEAL® occluder is constructed of a cobalt alloy (MP35N) frame.

Nickel elution in vitro was recently studied by Verma et al. in four devices, the Amplatzer septal occluder (ASO; St. Jude Medical Corporation), GORE HELEX septal occluder (HSO; W.L. Gore & Associates), and a new GORE septal occluder (GSO) in clinical trials, which all have a nitinol frame, and stainless steel sternal wires [75]. They observed higher nickel elution with the Amplatzer septal occluder compared to the other devices, which was significantly higher at 72 h and remained higher up to 90 days [75].

In vivo nickel release from the Amplatzer® occluder was studied by Ries et al., who measured serum levels of nickel in 67 patients at 24 h, and 1, 3, and 12 months after occluder

implantation. A statistically significant rise in mean serum levels of nickel was observed from 0.47 ng/ml before implantation to 1.27 ng/ml 24 h after implantation, to a maximum of 1.50 ng/ml 1 month later. Values <2 ng/ml of nickel are considered to be normal [76]. The presence of nickel allergy is listed as a contraindication for implantation of the Amplatzer®.

Burian et al. in another in vivo study of 24 patients following implantation of the Amplatzer® occluder observed increased serum levels of nickel up to fivefold ($p < 0.01$) versus baseline during the first 6 weeks following the procedure. Although serum nickel levels remained within normal limits (serum values ranged from 0.6 ± 0.2 μg/l), they returned to baseline within 4–6 months [77].

Several cases of systemic allergic reactions to PFO occluders without apparent rash but with positive patch tests have been reported to date [78–84]. A few of these patients developed pericardial effusion and tamponade, which resolved with systemic prednisone without removal of the device [81, 85]. In a few of these patients, surgical removal of the device led to recovery with resolution of symptoms [78, 79, 82–84]. 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 [80]. Considering the thousands of Amplatzer devices implanted over the past decade, the overall incidence of complications associated with metal allergy seems insignificant [86].

On the other hand, no association was found between a positive reaction to nickel on the TRUE test and adverse effects following Amplatzer® implantation in small cohorts [87, 88].

Rigatelli et al. observed a constellation of symptoms in eight out of nine patients who reacted to nickel in the TRUE test, yet decided to proceed with nitinol-based ASD occluders. They referred to these findings as "device syndrome," which consisted of chest discomfort, dyspnea on exertion, asthenia, and mild leukocytosis. The syndrome was treated with prednisone and clopidogrel and in all cases was resolved after 1 week of therapy. In their study ($n = 46$), none of the patients without nickel allergy developed these post-closure symptoms [88].

Despite some conflicting data considering that all these data are from small cohorts and anecdotal reports, it is plausible to obtain at least a clinical history of overt metal allergy as part of the pre-procedural evaluation. Pre-procedural patch testing of patients with suspected metal allergy should be limited to individuals with strong clinical history of metal allergy. Based on available data, presence of nickel allergy is not an absolute contraindication for receiving the occluder devices [88].

Workup for patients with post-procedural complications, including signs of systemic hypersensitivity, eosinophilia, dermatitis, and pericarditis, should include exact details of the procedure including pre- and post-procedural medications and sterilizing methods. Patch testing with metal salts should be considered along with detailed workup to exclude other etiologies.

21.4 General Comments

Long-term prospective data and large-scale cohorts of patients with putative metal allergy to endovascular devices are missing; however, existing data collectively suggests an association between metal allergy and development of localized or systemic hypersensitivity syndromes or neurologic syndromes following implantation of occluder devices in patients who are highly sensitive to metals, most notably to nickel.

The majority of current data regarding putative sensitivity reactions to endovascular devices is based on relatively small cohorts and anecdotal reports. Therefore recommendations listed in Tables 21.2 and 21.3 are mostly based on expert opinion and with limited evidence.

A spectrum of complications, varying from minor localized dermatoses to excessive inflammation, systemic hypersensitivity, and implant failure, are reported in patients with metal allergy. However, as mentioned earlier, only a small portion of individuals with positive patch tests to

Table 21.3 Approach to patients with atrial septal defect or patent foramen ovale occluders

Prior to implantation
(a) A detailed clinical history should be obtained
(b) Only patients with significant history of metal allergy should be considered for patch testing (level III evidence; expert opinion)
(c) Patch testing, if performed, should be conducted with relevant metal salts and device components
(d) Interpretation of positive reactions to metals that are tested as chloride salts such as manganese chlorides in petrolatum should be made with caution due to the high rate of false-positive reactions
(e) Lymphocyte transformation tests should not be performed routinely or as a substitute for patch testing
(f) For individuals with metal allergy, if possible, a device free of the identified allergen or lower elution rate should be considered
(g) Clear discussion with the patient is necessary to inform them that avoiding a potential allergen in the device does not guarantee a desired outcome
Post implantation
(a) Patch testing should only be considered when other causes of failure such as infection, drug eruptions, or other mechanical and surgical etiologies are excluded
(b) In cases of mild cutaneous dermatoses, skin-directed therapies should be optimized to control the symptoms
(c) Decisions regarding surgical explantation are best made though a multidisciplinary approach among treating medical teams

metals will go on to develop complications with their medical devices [89]. Some metal-allergic patients tolerate orthopedic implants containing a metal to which they are allergic, without dermatologic or orthopedic complications [90]. Because methodologies in currently published studies vary widely, special attention is required when interpreting data. Considering the large clinical and economic impact of implanted cardiovascular devices, a multidisciplinary approach is warranted to establish large population-based, multicenter prospective registries and to perform prospective case-control studies, in which methods of sensitivity testing are standardized. In general, patch testing should be tailored toward the specific biomaterials used in a device, in addition to testing with standard screening allergens in select cases.

Most importantly, patients need to be informed that the association between a positive patch test and the outcome of a procedure is still under investigation and, while avoiding a potential allergen in a device should be considered if possible, it does not guarantee a desired outcome.

References

1. Lyell A, Bain WH. Letter: Nickel allergy and valve replacement. Lancet. 1974;1(7854):408–9.
2. Lyell A, Bain WH, Thomson RM. Repeated failure of nickel-containing prosthetic heart valves in a patient allergic to nickel. Lancet. 1978;2(8091):657–9.
3. Elves MW, Wilson JN, Scales JT, Kemp HB. Incidence of metal sensitivity in patients with total joint replacements. Br Med J. 1975;4(5993):376–8.
4. Evans EM, Freeman MA, Miller AJ, Vernon-Roberts B. Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. J Bone Joint Surg Br. 1974;56-B(4):626–42.
5. Warshaw EM, Raju SI, Fowler JF Jr, et al. Positive patch test reactions in older individuals: retrospective analysis from the north american contact dermatitis group, 1994–2008. J Am Acad Dermatol. 2012;66(2):229–40.
6. Thyssen JP. Nickel and cobalt allergy before and after nickel regulation--evaluation of a public health intervention. Contact Dermatitis. 2011;65(Suppl 1):1–68.
7. Caroe C, Andersen KE, Mortz CG. Fluctuations in the prevalence of nickel and cobalt allergy in eczema patients patch tested after implementation of the nickel regulation in denmark. Contact Dermatitis. 2011;64(3):126–31.
8. Teixeira V, Coutinho I, Goncalo M. Allergic contact dermatitis to metals over a 20-year period in the centre of portugal: evaluation of the effects of the european directives. Acta Medica Port. 2014;27(3):295–303.
9. Jacob SE, Goldenberg A, Pelletier JL, Fonacier LS, Usatine R, Silverberg N. Nickel allergy and our children's health: a review of indexed cases and a view of future prevention. Pediatr Dermatol. 2015;32(6):779–85.
10. Senning A. Developments in cardiac surgery in stockholm during the mid and late 1950s. J Thorac Cardiovasc Surg. 1989;98(5 Pt 2):825–32.
11. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009—a world society of arrhythmia's project. Pacing Clin Electrophysiol. 2011;34(8):1013–27.
12. Honari G, Ellis SG, Wilkoff BL, Aronica MA, Svensson LG, Taylor JS. Hypersensitivity reactions associated with endovascular devices. Contact Dermatitis. 2008;59(1):7–22.

13. Medtronic. Sprint quattro®. http://www.medtronic.com/for-healthcare-professionals/products-therapies/cardiac-rhythm/implantable-cardioverter-defibrillators-icds/sprint-quattro/#tab4. Accessed 2 Nov 2016.
14. DiFilippo FP, Brunken RC. Do implanted pacemaker leads and ICD leads cause metal-related artifact in cardiac PET/CT? J Nucl Med. 2005;46(3):436–43.
15. Dionisio P. Advances in the technology of pacing. Rev Port Cardiol. 1999;18(3):289–98.
16. Mirowski M. The automatic implantable cardioverter-defibrillator: an overview. J Am Coll Cardiol. 1985;6(2):461–6.
17. Buchet S, Blanc D, Humbert P, et al. Pacemaker dermatitis. Contact Dermatitis. 1992;26(1):46–7.
18. Weiss R. Pacemaker dermatitis. Contact Dermatitis. 1989;21(5):343–4.
19. Hayes DL, Loesl K. Pacemaker component allergy: case report and review of the literature. J Interv Card Electrophysiol. 2002;6(3):277–8.
20. Iguchi N, Kasanuki H, Matsuda N, Shoda M, Ohnishi S, Hosoda S. Contact sensitivity to polychloroparaxylene-coated cardiac pacemaker. Pacing Clin Electrophysiol. 1997;20(2 Pt 1):372–3.
21. Skoet R, Tollund C, Bloch-Thomsen PE. Epoxy contact dermatitis due to pacemaker compounds. Cardiology. 2003;99(2):112.
22. Andersen KE. Cutaneous reaction to an epoxy-coated pacemaker. Arch Dermatol. 1979;115(1):97–8.
23. Abdallah HI, Balsara RK, O'Riordan AC. Pacemaker contact sensitivity: clinical recognition and management. Ann Thorac Surg. 1994;57(4):1017–8.
24. Dery JP, Gilbert M, O'Hara G, et al. Pacemaker contact sensitivity: case report and review of the literature. Pacing Clin Electrophysiol. 2002;25(5):863–5.
25. Brun R, Hunziker N. Pacemaker dermatitis. Contact Dermatitis. 1980;6(3):212–3.
26. Raque C, Goldschmidt H. Dermatitis associated with an implanted cardiac pacemaker. Arch Dermatol. 1970;102(6):646–9.
27. Wilkerson MG, Jordan WP Jr. Pressure dermatitis from an implanted pacemaker. Dermatol Clin. 1990;8(1):189–92.
28. Beutler BD, Cohen PR. Reticular telangiectatic erythema: case report and literature review. Dermatol Pract Concept. 2015;5(1):71–5.
29. Aneja S, Taylor JS, Billings SD, Honari G, Sood A. Post-implantation erythema in 3 patients and a review of reticular telangiectatic erythema. Contact Dermatitis. 2011;64(5):280–8.
30. Chua JD, Wilkoff BL, Lee I, Juratli N, Longworth DL, Gordon SM. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. Ann Intern Med. 2000;133(8):604–8.
31. Maushagen E, Reichle B, Simon H. Circumscribed erythema after cardiac pacemaker implantation. Z Kardiol. 1994;83(5):340–2.
32. Kreft B, Thomas P, Steinhauser E, Vass A, Summer B, Wohlrab J. Erythema and swelling after im-plantation of a cardioverter defibrillator (ICD). Dtsch Med Wochenschr. 2015;140(19):1462–4.
33. Widmark A, Friberg EG. How 'do's' and 'dont's' can be of significant importance in radiation protection: a case report. Radiat Prot Dosim. 2011;147(1–2):99–101.
34. Rath PC, Purohit BV, Agrawal B, et al. Pacemaker lead endocarditis due to trichosporon species. J Assoc Physicians India. 2015;63(4):66–8.
35. Cutillas E, Ferrando FJ, Marti ME, Mateu A, Rausell N. Reticular variant of mid-dermal elastolysis after insertion of a pacemaker. Clin Exp Dermatol. 2010;35(5):498–500.
36. Kottler D, Lefevre A, Balme B, Martin-Bourret V, Zaharia D, Skowron F. Mid-dermal elastolysis after insertion of a pacemaker. Ann Dermatol Venereol. 2015;142(11):680–4.
37. Dy Chua J, Abdul-Karim A, Mawhorter S, et al. The role of swab and tissue culture in the diagnosis of implantable cardiac device infection. Pacing Clin Electrophysiol. 2005;28(12):1276–81.
38. Taguchi T, Maeba S, Sueda T. Prevention of pacemaker-associated contact dermatitis by polytetrafluoroethylene sheet and conduit coating of the pacemaker system. J Artif Organs. 2014;17(3):285–7.
39. Ishii K, Kodani E, Miyamoto S, et al. Pacemaker contact dermatitis: the effective use of a polytetrafluoroethylene sheet. Pacing Clin Electrophysiol. 2006;29(11):1299–302.
40. Hiranaka T, Nomura F, Kurozumi K. Pacemaker contact dermatitis treated by wrapping with a polytetrafluoroethylene (PTFE) sheet. Pacing Clin Electrophysiol. 1992;8:335–8.
41. Kono K, Hara K, Higashi T, et al. Pacemaker contact dermatitis treated with polytetrafluoroethylene sheet. J Arrhythmia. 2000;16:403–7.
42. Tujita J, Nakamura K, Yasumoto S, Ueno Y. Pacemaker dermatitis: report of two cases. Nishinihon J Dermatol. 1996;58:200–2.
43. Vodiskar J, Schnoring H, Sachweh JS, Muhler E, Vazquez-Jimenez JF. Polytetrafluoroethylene-coated pacemaker leads as surgical management of contact allergy to silicone. Ann Thorac Surg. 2014;97(1):328–9.
44. Peters MS, Schroeter AL, van Hale HM, Broadbent JC. Pacemaker contact sensitivity. Contact Dermatitis. 1984;11(4):214–8.
45. Viraben R, Boulinguez S, Alba C. Granulomatous dermatitis after implantation of a titanium-containing pacemaker. Contact Dermatitis. 1995;33(6):437.
46. Yamauchi R, Morita A, Tsuji T. Pacemaker dermatitis from titanium. Contact Dermatitis. 2000;42(1):52–3.
47. Freeman S. Allergic contact dermatitis to titanium in a pacemaker. Contact Dermatitis. 2006;55(s1):41.
48. Dogan P, Inci S, Kuyumcu MS, Kus O. Contact dermatitis after implantable cardiac defibrillator implantation for ventricular tachycardia. Intractable Rare Dis Res. 2016;5(1):56–7.
49. Laugier P, Hunziger N, Orusco M, Brun B, Reiffers J, Posternak F. Dermite de contact par pacemaker. Dermatologica. 1975;150:219–26.
50. Tilsley DA, Rotstein H. Sensitivity caused by internal exposure to nickel, chrome and cobalt. Contact Dermatitis. 1980;6(3):175–8.

51. Landwehr AJ, van Ketel WG. Pompholyx after implantation of a nickel-containing pacemaker in a nickel-allergic patient. Contact Dermatitis. 1983;9(2):147.
52. Moini C, d'Alteroche A, Cosnay P, et al. Contact dermatitis following cardiac pacemaker implantation. Arch Mal Coeur Vaiss. 1996;89(2):253–6.
53. Romaguera C, Grimalt F. Pacemaker dermatitis. Contact Dermatitis. 1981;7(6):333.
54. Verbov J. Pacemaker contact sensitivity. Contact Dermatitis. 1985;12(3):173.
55. Gimenez CJ. Dermites au pacemaker. Acta Dermatol. 1985;8:117–9.
56. Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the united states, 2004–2006. Birth Defects Res A Clin Mol Teratol. 2010;88(12):1008–16.
57. Snijder RJ, Luermans JG, de Heij AH, et al. Patent foramen ovale with atrial septal aneurysm is strongly associated with migraine with aura: a large observational study. J Am Heart Assoc. 2016;5(12):e003771.
58. Zier LS, Sievert H, Mahadevan VS. To close or not to close: contemporary indications for patent foramen ovale closure. Expert Rev Cardiovasc Ther. 2016;14:1235–44.
59. Sun YP, Homma S. Patent foramen ovale and stroke. Circ J. 2016;80(8):1665–73.
60. Dalen JE, Alpert JS. Cryptogenic strokes and patent foramen ovales: What's the right treatment? Am J Med. 2016;129(11):1159–62.
61. Mills NL, King TD. Nonoperative closure of left-to-right shunts. J Thorac Cardiovasc Surg. 1976;72(3):371–8.
62. Rashkind WJ. Transcatheter treatment of congenital heart disease. Circulation. 1983;67(4):711–6.
63. Rome JJ, Keane JF, Perry SB, Spevak PJ, Lock JE. Double-umbrella closure of atrial defects. Initial clinical applications. Circulation. 1990;82(3):751–8.
64. Babic UU, Grujicic S, Popovic Z, Djurisic Z, Vucinic M, Pejcic P. Double-umbrella device for transvenous closure of patent ductus arteriosus and atrial septal defect: first experience. J Interv Cardiol. 1991;4(4):283–94.
65. Das GS, Voss G, Jarvis G, Wyche K, Gunther R, Wilson RF. Experimental atrial septal defect closure with a new, transcatheter, self-centering device. Circulation. 1993;88(4 Pt 1):1754–64.
66. Sharafuddin MJ, Gu X, Titus JL, Urness M, Cervera-Ceballos JJ, Amplatz K. Transvenous closure of secundum atrial septal defects: preliminary results with a new self-expanding nitinol prosthesis in a swine model. Circulation. 1997;95(8):2162–8.
67. Bridges ND, Hellenbrand W, Latson L, Filiano J, Newburger JW, Lock JE. Transcatheter closure of patent foramen ovale after presumed paradoxical embolism. Circulation. 1992;86(6):1902–8.
68. Schwetz BA. From the food and drug administration. JAMA. 2002;287(5):578.
69. FDA. AMPLATZER PFO occluder. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm526921.htm. Accessed 1 Nov 2016.
70. FDA. HELEX septal occluder. http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm077730.htm. Accessed 1 Nov 2016.
71. FDA Document. CardioSEALÒ septal occlusion system; summary of safety and effectiveness data. http://www.accessdata.fda.gov/cdrh_docs/pdf/H990004b.pdf. Updated 2001. Accessed 2 Oct 20016.
72. FDA. Premarket approval (PMA). http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/nncfm?start_search=1&applicant=&tradename=&productcode=&pmanumber=p050006&supplementnumber=&advisorycommittee=&docketnumber=&supplementtype=&expeditedreview=&ivdproducts=off&combinationproducts=off&decisiondatefrom=&decisiondateto=&noticedatefrom=&noticedateto=&PAGENUM=25. Accessed 20 Feb 2016.
73. Tang B, Su F, Sun X, Wu Q, Xing Q, Li S. Recent development of transcatheter closure of atrial septal defect and patent foramen ovale with occluders. J Biomed Mater Res B Appl Biomater. 2016; doi:10.1002/jbm.b.33831.
74. Verma SK, Tobis JM. Explantation of patent foramen ovale closure devices: a multicenter survey. JACC Cardiovasc Interv. 2011;4(5):579–85.
75. Verma DR, Khan MF, Tandar A, et al. Nickel elution properties of contemporary interatrial shunt closure devices. J Invasive Cardiol. 2015;27(2):99–104.
76. Ries MW, Kampmann C, Rupprecht HJ, Hintereder G, Hafner G, Meyer J. Nickel release after implantation of the amplatzer occluder. Am Heart J. 2003;145(4):737–41.
77. Burian M, Neumann T, Weber M, et al. Nickel release, a possible indicator for the duration of antiplatelet treatment, from a nickel cardiac device in vivo: a study in patients with atrial septal defects implanted with an amplatzer occluder. Int J Clin Pharmacol Ther. 2006;44(3):107–12.
78. Uguz E, Erdogan K, Sener E. Explantation of an atrial septal occluder device in a patient with nickel hypersensitivity. Anadolu Kardiyol Derg. 2014;14(4):402–3.
79. Fukahara K, Minami K, Reiss N, Fassbender D, Koerfer R. Systemic allergic reaction to the percutaneous patent foramen ovale occluder. J Thorac Cardiovasc Surg. 2003;125(1):213–4.
80. Dasika UK, Kanter KR, Vincent R. Nickel allergy to the percutaneous patent foramen ovale occluder and subsequent systemic nickel allergy. J Thorac Cardiovasc Surg. 2003;126(6):2112.
81. Lai DW, Saver JL, Araujo JA, Reidl M, Tobis J. Pericarditis associated with nickel hypersensitivity to the amplatzer occluder device: a case report. Catheter Cardiovasc Interv. 2005;66(3):424–6.

82. Prestipino F, Pragliola C, Lusini M, Chello M. Nickel allergy induced systemic reaction to an intracardiac amplatzer device. J Card Surg. 2014;29(3):349–50.
83. Belohlavek J, Belohlavkova S, Hlubocky J, Mrazek V, Linhart A, Podzimek S. Severe allergic dermatitis after closure of foramen ovale with amplatzer occluder. Ann Thorac Surg. 2013;96(3):e57–9.
84. Rabkin DG, Whitehead KJ, Michaels AD, Powell DL, Karwande SV. Unusual presentation of nickel allergy requiring explantation of an amplatzer atrial septal occluder device. Clin Cardiol. 2009;32(8):E55–7.
85. Jain M, Singh S, Cadeiras M. A case of nitinol allergy causing pericardial tamponade. J Invasive Cardiol. 2013;25(9):E180–2.
86. Meier B. Nickel allergy and device closure of the patent foramen ovale, now that we were told should we care? Catheter Cardiovasc Interv. 2009;74(4):652.
87. Kim HJ, Shin JU, Lee J, et al. Positive reactions to nickel on a patch test do not predict clinical outcome of nickel alloy-based atrial septal defect occluder implantation. Dermatology. 2015;230(2):184–8.
88. Rigatelli G, Cardaioli P, Giordan M, et al. Nickel allergy in interatrial shunt device-based closure patients. Congenit Heart Dis. 2007;2(6):416–20.
89. Niki Y, Matsumoto H, Otani T, et al. Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials. 2005;26(9):1019–26.
90. Carlsson A, Moller H. Implantation of orthopaedic devices in patients with metal allergy. Acta Derm Venereol. 1989;69(1):62–6.