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CLINICAL RESEARCH
Pacing and cardiac resynchronization therapy

Hypersensitivity to material and environmental burden as a possible cause of late complications of cardiac implantable electronic devices

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Aims To evaluate whether patients with late complications of pacemakers or implantable cardioverter-defibrillators have hypersensitivity reactions to some of the materials used in generators or in electrodes, or to environmental metal burden.

Methods and results The cohort consisted of 20 men and 4 women (mean age: 62.3 ± 17.2 years) who had a history of late complications of implanted devices. The control group involved 25 men and 8 women (mean age: 64.6 ± 14.0 years) who had comparable devices, but no history of late complications. Lymphocyte transformation test was used to evaluate hypersensitivity to eight metal pollutants (antimony, manganese, mercury, molybdenum, nickel, platinum, tin, and titanium) selected by results of questionnaires on environmental burden, and by material analysis of generators and electrode surfaces. Exposures to metal pollutants were approximately the same in patients and in controls. Titanium alloy used in generators contained at least 99.32% of titanium and trace levels of other metals; higher levels of tin and platinum were detected in electrode surfaces. Hypersensitivity reactions to mercury and tin were significantly more frequent in patients than in controls (patients and controls: mercury: 68.2 and 31.1%, respectively; $P = 0.022$; tin: 25.0 and 3.2%, respectively; $P = 0.035$). In contrast, hypersensitivity to manganese was significantly more frequent in controls than in patients (patients and controls: 13.6 and 50.0%, respectively; $P = 0.008$).

Conclusion Our findings suggest a possible relation between hypersensitivity to metals used in implantable devices or to environmental metal burden and the occurrence of their late complications.

Keywords Pacemaker • Implantable cardioverter-defibrillator • Late complication • Metal pollutants • Delayed-type hypersensitivity • Lymphocyte transformation test

Introduction

Complications in patients with cardiac implantable electronic devices (CIEDs)—pacemakers or implantable cardioverter-defibrillators (ICD) can be classified as early or late. The prevalence of early complications (i.e. within 6–8 weeks after the procedure) ranges between 5.7 and 12.4%. After this period, the complication rate slightly decreases, being reported in 7.5% of cases at 3 years.[1]

According to a Dutch paper from 2013,[2] the following late complications occurred during a 6-year follow-up in patients who had

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What's new?

- Pacemaker (PM) and implantable cardioverter-defibrillator (ICD) generators contained at least 99.32% of titanium in the alloy, and trace amounts of other metals: antimony, tin, manganese, molybdenum, nickel, and iron. Different types of electrodes contained higher concentrations of tin and/or platinum when compared with other pollutants.
- Patients with late complications of PM and ICD implantations underwent a higher number of implantations than controls without complications (patients and controls: 2.41 and 1.27 implantations on average respectively; $P \leq 0.001$).
- According to lymphocyte transformation test testing, hypersensitivity reactions to mercury and tin were more frequent in patients than in controls (for mercury, 68.2 and 31.1%, respectively, $P = 0.022$; and for tin, 25.0 and 3.2%, respectively, $P = 0.035$). In contrast, hypersensitivity reactions to manganese were significantly more frequent in controls when compared with the patient group (patients and controls: 13.6 and 50.0%, respectively; $P = 0.008$).

undergone a primary implantation of pacemaker: skin erosion (0.53% of patients), a feeling of discomfort in the pocket area (1.71%), pocket infection (0.79%), and infection of the electrode system (0.20%). We assume that hypersensitivity reactions to material can contribute to development of these problems. Delayed-type hypersensitivity to material has not yet been mentioned in the guidelines.[1] So far, this issue has been mostly described in case reports and their reviews.[3] The most frequently reported complication after pacemaker (PM) or ICD implantation is contact dermatitis: the first case report was already described in 1970.[4] Hypersensitivity reactions to various PM or ICD components have been described, including titanium,[5,6] nickel,[7] mercury,[8] silicone,[9] and polyurethane.[10]

Hypersensitivity reactions can lead to systemic complications even without local (cutaneous) manifestations.[11] These reactions are mediated by specific T-lymphocytes; most frequently, they are caused by a chronic exposure to low levels of antigen—hapten,[12] and hereditary predisposition also plays a role.[13] In the general population, hypersensitivity to metals occurs more frequently in women.[14]

Hypersensitivity can be evaluated by lymphocyte transformation test (LTT), which is based on the principle of antigen/allergen-specific induction of cell division in lymphocytes following contact with their respective antigens. A positive reaction in LTT indicates the presence of antigen-specific lymphocytes (memory cells) in the patient's peripheral blood.[15]

Aims

Our work aimed to verify whether patients with late complications of PM or ICD implantation have delayed-type hypersensitivity reactions to some of the materials used in generators or in electrodes, or to most frequent metal pollutants in the environmental burden.

Methods

Our study involved 24 patients (20 men, 4 women) with the mean age of 62.3 ± 17.2 years who had a history of some of the following late complications of PM or ICD implantation: skin erosion (10 patients, 42%); abscess or infection in the pocket (6 patients, 25%); fluctuation, seroma, or secretion from the pocket (4 patients, 17%); vegetation on the electrode system (3 patients, 12%); and skin fistula (one patient, 4%). Fourteen patients (58.3%) had ICD implants (12 various models from 5 manufacturers), and ten patients (41.7%) had PM implants (9 models from 6 manufacturers).

The control group consisted of 33 individuals (25 men, 8 women) with the mean age of 64.6 ± 14.0 years: 17 of them (51.5%) had ICD implants, 16 of them (48.5%) had PM implants, and none of them had a history of the above-mentioned late complications. The control group had eight various models of ICDs from four manufacturers, and eight various models of PMs from five manufacturers. Generators of all implanted devices were made of titanium alloy. *Tables 1* and *2* provide other characteristics and comorbidities of both groups.

The study protocol complied with the Declaration of Helsinki, and was approved by the Ethics Committee of the University Hospital Brno (Brno, Czech Republic). Written informed consent forms were obtained from all patients and controls before their participation in this project.

Questionnaire of environmental burden

All patients and controls completed a questionnaire of environmental burden aimed at evaluating the types and amounts of materials used in dental fillings, implants (including joint replacements and stents), and other possible sources of environmental burden, such as smoking. All study participants had previously undergone an implantation of PM or ICD containing a generator made of a titanium alloy. The questionnaire survey aimed to identify the subjects' exposure to the most common metal pollutants, and to select the most frequent ones to be tested for hypersensitivity reactions.

Material composition of CIEDs

Before starting any tests on hypersensitivity reactions, it was necessary to establish the exact composition of the implanted devices. Each PM and ICD consists of a generator made of a titanium alloy, a 'transitional part' serving for electrode connection, and the electrode (or electrodes) itself. The transitional part is made of a synthetic resin. As for electrodes used in stimulation systems and defibrillation systems, their surfaces are made of silicon, polyurethane, or their combinations, while their inner parts are made of metal alloys.

Composition analysis of titanium alloys used in generators

A non-invasive method of X-ray fluorescence (XRF) spectrometry was employed to analyse the alloy composition of 38 explanted generators made by 9 different manufacturers: 21 generators for PMs (20 models from 6 manufacturers) and 17 generators for ICDs (17 models from 6 manufacturers). A non-metallic abrasive paste was used to remove the superficial 'corrosion' layer from the analysed part of each device. The analysis was performed with a manual XRF spectrometer Delta Professional manufactured by the Olympus Corporation (Waltham, Massachusetts, USA), which was placed into a Flex Stand in the 'Analytical Plus' settings. The X-ray tube had the following characteristics: the voltage up to 40 kV, the power of 4 W, and the exciting current of 200 μA. The silicon drift detector (SDD) was primarily calibrated on the surface of 3 mm^2, allowing both qualitative and quantitative analysis of the following elements: aluminium, antimony, bismuth, chromium, cobalt, copper, gold, iron, lead, magnesium, manganese, nickel, niobium, phosphorus, silicon, silver, sulphur, tin, titanium, vanadium, zinc, and zirconium. Each sample was measured three times, and mean values were calculated

Table 1 Characteristics of the group of patients with complications and of the control group

Characteristics	Patients (*N* = 24)	Controls (*N* = 33)	*P*-value*
Sex—men	20 (83%)	25 (76%)	0.533
Age (years)	62.3 ± 17.2	64.6 ± 14.0	0.872
BMI (kg/m^2)	27.7 ± 3.5	27.7 ± 4.8	0.619
Number of ICD	14 (58.3%)	17 (51.5%)	0.788
Of which primary prevention	4 (29%)	7 (41%)	0.707
CRT function	10 (42%)	6 (18%)	0.078
Number of electrodes			
1	8 (33.3%)	12 (36.4%)	0.058
2	7 (29.2%)	17 (51.5%)	
3	9 (37.5%)	4 (12.1%)	
Age at the time of primary implantation (years)	54.0 ± 18.1	59.9 ± 12.0	0.378
Age at the time of complication (years)	59.8 ± 17.4	–	–
Time from primary implantation to complication (years)	5.9 ± 4.7	–	–
1–2 years	10 (42%)		
3–5 years	3 (12%)		
6–10 years	5 (21%)		
11–15 years	5 (21%)		
>15 years	1 (4%)		
Time from primary implantation to testing (years)	7.9 ± 5.1	4.8 ± 4.1	0.016
Time from complication to testing (years)	2.5 ± 2.3	–	–
Number of implantations before testing	2.4 ± 1.1	1.3 ± 0.5	<0.001
Positive cultivation at the time of complication	9 (37.5%)	–	–
Coagulase-negative staphylococci (CoNS)	4 (16.7%)		
Staphylococcus aureus	2 (8.3%)		
Staphylococcus epidermidis	2 (8.3%)		
Enterococcus faecalis	1 (4.2%)		
Addressing the complication		–	–
Subpectoral reimplantation	11 (45.8%)		
Contralateral reimplantation	2 (8.3%)		
Epicardial reimplantation	2 (8.3%)		
Reimplantation after 6 months	2 (8.3%)		
Explantation of the entire system	2 (8.3%)		
Explantation of the device	2 (8.3%)		
Conservative treatment	3 (12.5%)		

Categorical variables are described by absolute and relative frequencies; continuous variables are described by means and standard deviations.
*P-value of the Fisher's exact test is provided for categorical variables; *P*-value of the Mann–Whitney *U* test is provided for continuous variables.

from the measured values. Metal concentrations in the alloys were expressed in percentage (%). The aim of the analysis was to select metals to be tested for hypersensitivity reactions.

Trace analysis of electrode surfaces

Electrodes of stimulation systems and of defibrillation systems are covered with silicon, polyurethane, or a combination of both. Hypersensitivity reactions to either silicon or polyurethane cannot be evaluated by the commercially available LTT. We have therefore decided to use trace analysis in order to determine the concentrations of elements/metals in electrode surfaces, and to test hypersensitivity reactions to these elements/metals. Concentrations of metal pollutants in the surfaces of six new (i.e. unused) electrodes from five manufacturers were analysed.

The samples were mineralised in a microwave digestion system (MWS 3+ Berghof, Germany) with the use of nitric acid, and concentrations of most elements contained in electrode surfaces were subsequently determined by inductively coupled plasma mass spectrometry (Agilent 7700x ICP-MS, Japan). Concentrations of lead in the samples were determined by the AMA254 analyser (Altec Ltd, Czech Republic) directly in solid samples. Other parts of the devices were not analysed.

Evaluation of hypersensitivity reactions by lymphocyte transformation test

Overall, 50 mL of venous blood were collected from each patient into tubes containing anti-coagulant and into two serum tubes. Blood samples were well isolated against cold and sent by overnight delivery for LTT testing. Tested metals were selected according to information on the material composition of devices and on metal exposure provided in patients' questionnaires. Finally, the following eight metals were tested: antimony (Sb), inorganic mercury (Hg), manganese (Mn), molybdenum (Mo), nickel (Ni), platinum (Pt), tin (Sn), and titanium (Ti)—as titanium dioxide (TiO_2) and titanium sulphate ($TiSO_4$).

Table 2 Comparison of some comorbidities and selected therapies in both groups

Comorbidity, therapy	Patients ($N = 24$)	Controls ($N = 33$)	P-value*
LVEF (%)	43.6 ± 17.2	47.1 ± 16.4	0.525
LVEF ≤ 40%	13 (54.2%)	18 (60.0%)	0.784
Dilated cardiomyopathy	11 (45.8%)	8 (24.2%)	0.099
CAD/MI	10 (41.6%)	16 (48.5%)	0.788
Atrial fibrillation	8 (33%)	15 (45.4%)	0.420
Hypertension	15 (62.5%)	23 (69.7%)	0.584
Dyslipidaemia	14 (58.3%)	19 (57.6%)	0.999
Diabetes mellitus	5 (20.8%)	10 (30.3%)	0.547
Lower extremity PAD	4 (16.7%)	2 (6.1%)	0.227
CKD	7 (29.1%)	5 (15.1%)	0.324
COPD/bronchial asthma	5 (20.8%)	2 (6.1%)	0.119
Thyroid disease	4 (16.7%)	6 (18.2%)	0.119
Cancer	2 (8.3%)	4 (12.1%)	0.999
Allergy	9 (37.5%)	12 (36.3%)	0.999
Smoker or ex-smoker	13 (54%)	20 (60%)	0.388
Anticoagulant therapy	8 (33.3%)	13 (39.4%)	0.782
Antiplatelet therapy	11 (45.8%)	10 (30.3%)	0.274

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease.
Categorical variables are described by absolute and relative frequencies.
*P-value of the Fisher's exact test is provided for categorical variables; P-value of the Mann–Whitney U test is provided for continuous variables.

Table 3 Comparison of selected environmental burden with metal pollutants based on questionnaires completed by patients and controls

Metal	Patients ($N = 24$)	Controls ($N = 33$)	P-value*
Ag	24 (100%)	33 (100%)	0.999
Al	3 (12.5%)	2 (6%)	0.640
Au	6 (25%)	9 (27%)	0.999
Cd	13 (54%)	20 (60%)	0.786
Cr	20 (83.3%)	24 (72.7%)	0.524
Cu	24 (100%)	33 (100%)	0.999
Hg	24 (100%)	33 (100%)	0.999
Ni	20 (83.3%)	24 (72.7%)	0.524
Pb	13 (54%)	20 (60%)	0.786
Sn	24 (100%)	33 (100%)	0.999
Ti	24 (100%)	33 (100%)	0.999

*P-value of the Fisher's exact test is provided.

Lymphocyte transformation tests were performed according to a previously described methodology.[15] The stimulation index (SI) was used to evaluate the lymphocyte proliferative response. For each patient were determined two values of SI of reactivity of tested metals. The resulting SI was determined as the arithmetic mean of these two values. Stimulation index (SI) ≥ 2 was considered as a positive response in our evaluation. The laboratory worker who evaluated LTT method did not know which samples were taken from patients with late complications of CIEDs or from controls.

The statistical analysis

Categorical variables were described by absolute and relative frequencies; continuous variables were described by means and standard deviations. Values of SI of hypersensitivity reactions were described by minimum, median and maximum values, and by values of the 25th and 75th percentiles. The Mann–Whitney U test was used to compare the statistical significance of continuous variables between patients and controls. The statistical significance of categorical variables was compared by the Fisher's exact test.

Results

Late complications occurred most frequently between the 10th and 24th month after the implantation of an CIED (10 patients, i.e. 42%). Microbiological agents were proved in nine patients (37.5%) who developed a late complication (smear from the wound surface or cultivation of the wound contents was positive in six patients, and blood culture was positive in three patients). According to *Table 1*, the two groups were significantly different in two parameters: patients with complications had a significantly longer time from the primary implantation to LTT testing than controls (7.87 vs. 4.75 years, $P = 0.016$), and also a higher number of implantations performed before testing (2.41 vs. 1.27 implantations on average, $P \leq 0.001$). Differences in other characteristics and comorbidities between the two groups were not significant.

Questionnaire of environmental burden

Table 3 shows results of the questionnaire survey. Exposures to metal pollutants are not significantly different between the cohort of patients with late complications and the control group. The obtained data was used to select metal pollutants (tin, nickel, lead, titanium) to which hypersensitivity reaction tests would be subsequently performed.

Material composition of cardiac implantable electronic devices

Composition analysis of titanium alloys of cardiac implantable electronic device bodies

Table 4 shows the results of composition analysis of metal concentrations in titanium alloys used in bodies of 38 explanted CIEDs: 17 ICDs (17 models from 6 manufacturers) and 21 PMs (20 models from 6 manufacturers); the analysis was performed by XRF spectrometry, and its results are blinded: only the type and number of a given CIED are provided.

In each device, the titanium alloy contained at least 99.32 ± 0.10% of titanium; 9 devices (23.7%) contained 100% of titanium. Other metals were present in trace amounts: iron in 19 devices (50%), nickel in 15 devices (39.4%), tin in 7 devices (18.4%), antimony in 5 devices (13.1%), molybdenum and manganese in 2 devices (5.3%). The obtained results were used to select metals to which hypersensitivity reaction tests would be subsequently performed.

Table 4 XRF spectrometry—results of composition analysis of titanium alloys used in bodies of 38 explanted devices (blinded)

Device	Ti (%)	Fe (%)	Ni (%)	Sn (%)	Sb (%)	Mo (%)	Mn (%)
ICD 1	100.00 ± 0.00						
ICD 2	99.959 ± 0.009	0.041 ± 0.009					
ICD 3	99.974 ± 0.008	0.026 ± 0.008					
ICD 4	99.922 ± 0.006		0.014 ± 0.004	0.064 ± 0.003			
ICD 5	100.00 ± 0.00						
ICD 6	99.962 ± 0.008	0.023 ± 0.007	0.015 ± 0.004				
ICD 7	99.925			0.75 ± 0.02			
ICD 8	99.912	0.024 ± 0.007		0.064 ± 0.003			
ICD 9	100.00 ± 0.00						
ICD 10	99.966 ± 0.005		0.017 ± 0.004			0.017 ± 0.001	
ICD 11	100.00 ± 0.00						
ICD 12	99.86 ± 0.01	0.025 ± 0.007	0.020 ± 0.005	0.042 ± 0.006	0.051 ± 0.007		
ICD 13	99.943 ± 0.007				0.057 ± 0.007		
ICD 14	99.939 ± 0.009	0.040 ± 0.008	0.021 ± 0.005				
ICD 15	99.93 ± 0.01	0.050 ± 0.009	0.018 ± 0.005				
ICD 16	100.00 ± 0.00						
ICD 17	100.00 ± 0.00						
PM 1	99.963 ± 0.009	0.039 ± 0.009					
PM 2	99.970 ± 0.008	0.030 ± 0.008					
PM 3	99.802 ± 0.009		0.017 ± 0.004	0.180 ± 0.007			
PM 4	100.00 ± 0.00						
PM 5	99.983		0.017 ± 0.004				
PM 6	99.93 ± 0.01	0.047 ± 0.009	0.022 ± 0.005				
PM 7	99.94 ± 0.01		0.016 ± 0.004				0.04 ± 0.01
PM 8	99.959 ± 0.009	0.027 ± 0.008	0.013 ± 0.004				
PM 9	99.885 ± 0.004			0.115 ± 0.002			
PM 10	99.55 ± 0.01	0.041 ± 0.009		0.347 ± 0.009	0.063 ± 0.006		
PM 11	99.966 ± 0.008	0.034 ± 0.008					
PM 12	99.977 ± 0.007	0.023 ± 0.007					
PM 13	99.966 ± 0.008	0.027 ± 0.008				0.0066 ± 0.0009	
PM 14	99.32 ± 0.10		0.017 ± 0.005				0.61 ± 0.01
PM 15	99.946 ± 0.010	0.039 ± 0.009	0.012 ± 0.004				
PM 16	99.940 ± 0.010	0.041 ± 0.009	0.019 ± 0.004				
PM 17	99.80 ± 0.01	0.052 ± 0.007			0.175 ± 0.008		
PM 18	99.917 ± 0.007				0.083 ± 0.007		
PM 19	100.00 ± 0.00						
PM 20	100.00 ± 0.00						
PM 21	99.961 ± 0.003	0.025 ± 0.007	0.015 ± 0.005				

Trace analysis of metal concentrations in electrode surfaces

Electrode surfaces are made of silicon, polyurethane, or their combinations. Trace analysis was used to determine the concentrations of 19 selected metal pollutants in the surfaces of 6 new (i.e. unused) electrodes from 5 manufacturers. The results are shown in *Tables 5* and *6*.

Significant differences in concentrations of tin and platinum were found in various types of electrode surfaces. Polyurethane surfaces contained markedly higher concentrations of tin, whereas silicon surfaces contained markedly higher concentrations of platinum; combined silicon-polyurethane surfaces contained higher concentrations of both metals. Concentrations of other metals detected in electrode surfaces were not markedly different.

Testing hypersensitivity reactions by lymphocyte transformation test

Table 7 shows values of SI for hypersensitivity reactions to eight selected metals, with the cut-off value for SI ≥ 2 (i.e. weakly positive).

Hypersensitivity reactions (SI ≥ 2) to at least one of the tested metals were reported in 21 patients (87.5%) and 26 controls (78%). Hypersensitivity reactions to mercury and tin were statistically significantly more frequent in patients with late complications of CIEDs

Table 5 Concentrations of metal pollutants in the surfaces of new electrodes (blinded)

Surface/material	Al μg/g	As μg/g	Ba μg/g	Be μg/g	Cd μg/g	Co μg/g	Cr μg/g	Cu μg/g	Hg μg/g	Mo μg/g
Polyurethane 1	0.32	<0.004	<0.05	<0.01	0.0002	0.0265	0.11	0.12	0.0038	<0.007
Polyurethane 2	0.77	<0.004	<0.05	<0.01	<0.0002	0.0523	<0.03	0.15	0.0006	<0.007
Silicon 1	0.49	<0.006	0.064	<0.01	0.0071	0.134	0.21	<0.4	0.0023	<0.05
Silicon 2	1.01	<0.006	0.231	<0.01	0.0007	0.489	0.63	<0.4	0.0083	<0.05
Silicon 3	0.73	0.007	0.123	<0.01	<0.0005	0.162	0.27	<0.4	0.0007	<0.05
Silicon-polyurethane	0.68	<0.003	0.23	<0.007	<0.0001	0.006	0.38	0.12	0.0018	<0.004

Table 6 Concentrations of metal pollutants in the surfaces of new electrodes (blinded)—continued

Surface/material	Ni μg/g	Pb μg/g	Pt μg/g	Sb μg/g	Sn μg/g	Sr μg/g	Ti μg/g	V μg/g	Zn μg/g
Polyurethane 1	0.059	<0.02	0.009	<0.005	4.68	0.011	<0.009	0.005	<1.8
Polyurethane 2	0.467	<0.02	0.02	<0.005	7.33	<0.01	<0.009	<0.002	<1.8
Silicon 1	0.214	<0.02	4	<0.008	<0.04	<0.09	0.107	<0.001	<1.1
Silicon 2	0.588	<0.02	5	<0.008	0.05	0.10	0.124	0.002	1.4
Silicon 3	1.19	<0.02	6	<0.008	<0.04	<0.09	0.129	<0.001	<1.1
Silicon-polyurethane	0.086	<0.01	2	<0.003	3.40	0.008	0.036	0.003	<1.1

when compared with the control group (patients and controls: for mercury, 68.2 and 31.1%, respectively; $P = 0.022$; and for tin, 25.0 and 3.2%, respectively; $P = 0.035$). In contrast, hypersensitivity reactions to manganese were significantly more frequent in controls when compared with the patient group (patients and controls: 13.6 and 50.0%, respectively; $P = 0.008$).

Discussion

Our work aimed to prove a possible link between late complications in patients with PM and ICD implantations and their hypersensitivity reactions to some of the materials used in generators or in electrodes, and to the most common metal pollutants in the environmental burden. Delayed-type hypersensitivity to material might contribute to some late complications of CIED implantations, the prevalence of which is estimated at approximately 1.5–2.5%.[2]

According to basic epidemiological and clinical data, the time from primary implantation to testing was statistically significantly longer in our patients with late complications of CIED implantations when compared with the control group (patients and controls: 7.9 ± 5.1 and 4.8 ± 4.1, respectively; $P = 0.016$), and the number of implantations before testing was higher (patients and controls: 2.4 ± 1.1 and 1.3 ± 0.5, respectively; $P < 0.001$). Late complications occurred most frequently between the 10th and 24th month after the primary implantation (10 patients, 42%). The literature distinguishes infectious complications (with a proven etiologic agent) from potential hypersensitivity reactions.[1] At the time of complication, cultivation of agents from the wound or from the blood culture was positive in nine (37.5%) of our patients: smear from the wound or cultivation of the wound contents was positive in six patients (25%), and blood culture was positive in three patients (12.5%). However, cultivations of macroscopically obviously purulent content of wounds were repeatedly negative. Each of these nine patients had a hypersensitivity reaction to at least one of the tested metals. During a hypersensitivity reaction, CD4+ T cell subpopulations produce cytokines and chemokines, leading to an inflammatory infiltration of the affected tissue by neutrophils, which gives a purulent character to the effusion, for example.[12] Hypersensitive reactivity to tested metals was present in patients without positive cultivation (62.5% of our patients). Clinical presentation of late complications in wound of our patients with CIED is the same as described in case reports. Therefore, we suppose, that primary aetiology of described complications is hypersensitivity to CIED materials. But, we cannot exclude, that hypersensitivity reaction and infection as running simultaneously.

According to data from the questionnaires, the environmental exposure to metal pollutants was comparable in both groups (*Table 3*). Metal pollutants such as mercury, tin (part of dental amalgam alloy, among others), titanium and other elements can be present in patients' bodies long before CIED implantation. This fact can be linked to the development of hypersensitivity reactions to the above-mentioned metals.[16,17]

Determination of the exact material composition of CIEDs was essential: in this respect, we focused on device bodies (generators) and electrode surfaces. Based on the XRF spectrometry, we found that the titanium alloy of used (explanted) devices contains at least 99.32% of titanium. Other metals were present in trace amounts: antimony, iron, manganese, molybdenum, nickel, and tin (*Table 4*).

Table 7 Comparison of hypersensitivity reactions to eight selected metals in both groups, with the cut-off value for SI ≥ 2

	Patients ($N = 24$)		Controls ($N = 33$)		P*
Metal	**<2**	**≥2**	**<2**	**≥2**	
Hg	7 (31.8%)	15 (68.2%)	19 (67.9%)	9 (32.1%)	0.022
Mn	19 (86.4%)	3 (13.6%)	14 (50.0%)	14 (50.0%)	0.008
Mo	20 (87.0%)	3 (13.0%)	27 (84.4%)	5 (15.6%)	0.999
Ni	13 (54.2%)	11 (45.8%)	19 (57.6%)	14 (42.4%)	0.999
Pt	17 (100%)	0 (0.0%)	24 (88.9%)	3 (11.1%)	0.272
Sb	16 (84.2%)	3 (15.8%)	22 (73.3%)	8 (26.7%)	0.492
Sn	18 (75.0%)	6 (25.0%)	30 (96.8%)	1 (3.2%)	0.035
TiO_2	16 (72.7%)	6 (27.3%)	26 (89.7%)	3 (10.3%)	0.150
$TiSO_4$	16 (76.2%)	5 (23.8%)	27 (93.1%)	2 (6.9%)	0.115
At least one metal with SI ≥ 2		21 (87.5%)		26 (78.8%)	0.494
At least two metals with SI ≥ 2		13 (54.2%)		19 (57.6%)	0.999

*P-value of the Fisher's exact test is provided.

These metals—apart from iron—were included in the list of metals tested for hypersensitivity. Another mechanism of action is assumed in the case of iron, namely via the oxidative stress during the so-called Fenton reaction.[18] Ideal would be to test patients with different devices separately. However, this is practically impossible. We are not able to find enough patient with late complications with the same type of device. On the other hand, according to analysis of the composition of CIED body, the differences between manufactures are small.

Electrode surfaces are coated with polyurethane, silicon, or their combinations. Hypersensitivity reactions to these materials cannot be evaluated by the commercially available LTT test. We have therefore performed a trace analysis in order to determine the concentrations of metals in these components (*Tables 5* and *6*), which revealed marked differences in tin and platinum concentrations in electrode surfaces, unlike other metals. We have therefore selected tin and platinum from the analysed metals to be tested for hypersensitivity reactions.

Some studies mentioned reactivity to silicon or polyurethane that were documented by patch test results.[3] According to our analysis of electrode surfaces, it cannot be excluded that patients react to metal pollutants present in these materials. Composition of internal metal parts of the leads is known, but it has no relationship to the metal pollutants in silicone or polyurethane surfaces. Therefore, we do not provide such analysis. Small fixation parts of leads we did not analysed.

Finally, hypersensitivity was tested for eight selected metals: antimony, manganese, mercury, molybdenum, nickel, platinum, tin, and titanium (tested as titanium dioxide, TiO_2, and titanium sulphate, $TiSO_4$; reactivity to titanium in these two substances might be different).

Hypersensitivity reactions (SI ≥ 2) to at least one of the tested metals were established in 21 patients, i.e. 85% of persons in the cohort with late complications of CIED implantation; in the control group, these reactions were reported in 26 persons (78%; $P = 0.494$). Reactivity to mercury (16 patients, 69.5%) and to nickel (12 patients, 50%) occurred most frequently. According to literature, hypersensitivity to nickel is the most common type of metal hypersensitivity in the general (unselected) population.[14] Hypersensitivity to titanium, which is generally considered to be a highly biocompatible material, was established in 11 patients (46%) in our cohort.

Hypersensitivity to mercury (*Figure 1*) and tin was significantly more frequent in patients with late complications of CIED implantations when compared with the control group (patients and controls: for mercury, 68.2 and 31.1%, respectively; $P = 0.022$; and for tin, 25.0 and 3.2%, respectively; $P = 0.035$). Both of these metals are contained in dental amalgam alloys, which had been present in patients' bodies before the first implantation of CIED.

In contrast, hypersensitivity reactions to manganese were significantly more frequent in controls when compared with the patient group (patients and controls: 13.6 and 50.0%, respectively; $P = 0.008$). This can be explained by the absence of manganese in implanted devices. Trace amounts of manganese were established by XRF spectrometry only in two of the 38 analysed CIEDs. However, the presence of manganese was objectively proved in the whole blood of patients and controls (see Supplementary material online, *Table A.1* in the Appendices), which might have led to hypersensitivity. Hypersensitivity reactions, accompanied by the production of pro-inflammatory cytokines and by increased levels of oxidative stress, contribute to changes of biological properties of tissues (skin, hypodermis, microcirculation), and can thus contribute to development of the above-mentioned complications.[12]

Limitations

Our work has several limitations. First, many of our patients with late complications underwent LTT testing for hypersensitivity reactions a long time after their complications occurred, ranging from 2 months to 8 years. Eleven patients (45.8%) were tested 0–2 years after the complication occurred, eight patients (30%) within one year after the complications. It is anticipated that reactivity to metals does not change significantly, unless the environmental burden changes significantly.[19] However, such changes were not reported, according to data from the questionnaires. Second, our study was monocentric, and involved a relatively small number of patients and controls. Despite this limitation, it is obvious that hypersensitivity reactions to metals are frequent in these individuals. Ideally, the best way will be

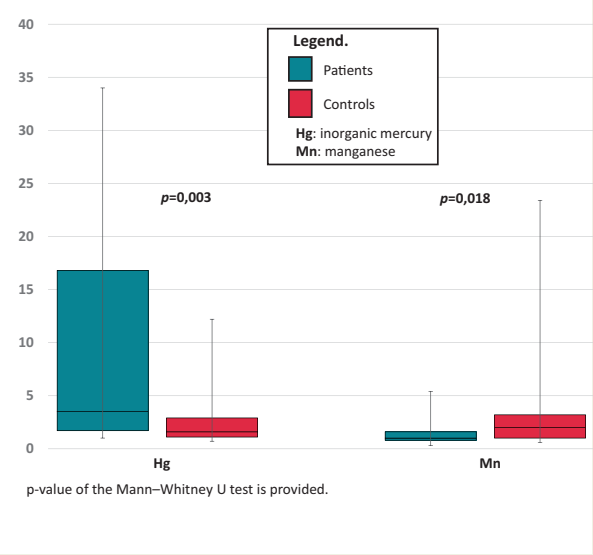

Figure 1 Stimulation indices (SI) for Hg and Mn in both groups. *P*-value of the Mann–Whitney *U* test is provided.

to test patients with only one type of CIED with uniform composition of the same generator and lead. Unfortunately, this is in real world impossible. Third, both groups were only tested for hypersensitivity reactions to eight metals, selected according to data from questionnaires and to material composition of the devices. It cannot be ruled out that patients or controls could have had hypersensitivity reactions to other metals, which were not tested.

Conclusion

Our patients with late complications of CIED implantations underwent a higher number of implantations (including re-implantations) than the control group, and also had more frequent hypersensitivity reactions to mercury and to tin. As much as 87.5% of these patients had hypersensitivity reactions to at least one tested metal. It seems that patients with late complications of CIED implantations react not only to metals present in device materials, but also to those present in the environmental burden. Hypersensitivity reactions, accompanied by the production of cytokines and by increased levels of oxidative stress, contribute to changes of biological properties of tissues, and can thus contribute to development of late complications.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: Vera Stejskal is owner of the *MELISA®* trademark and receives royalties from *LTT-MELISA®* tests. Other authors have declared no conflict of interest related to this study.

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