New diagnostic pathways urgently needed. Protocol of PET Guidance I pilot study: positron emission tomography in suspected cardiac implantable electronic device-related infection

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A b s t r a c t

Background: Cardiovascular implantable electronic device (CIED) infection is a complication of increasing incidence. We present a protocol of an observational case control clinical trial "Positron Emission Tomography Combined With Computed Tomography (PET CT) in Suspected Cardiac Implantable Electronic Device Infection, a Pilot Study — PET Guidance I" (NCT02196753).

Aim: The aim of this observational clinical trial is to assess and standardise diagnostic algorithms for CIED infections (lead-dependent infective endocarditis, generator pocket infection, fever of unknown origin) with PET CT in Poland.

Methods and results: Study group will consist of 20 patients with initial diagnosis of CIED-related infection paired with a control group of 20 patients with implanted CIEDs, who underwent PET CT due to other non-infectious indications and have no data for infectious process in follow-up. All patients included in the study will undergo standard diagnostic process. Conventional/standard diagnostic and therapeutic process will consist of: medical interview, physical examination, laboratory tests, blood cultures; imaging studies: echocardiography: transthoracic (TTE), and, if there are no contraindications transoesophageal, computed tomography scan for pulmonary embolism if indicated; if there are abnormalities in other systems, decisions concerning further diagnostics will be made at the physician's discretion. As well as standard diagnostic procedures, patients will undergo whole body PET CT scan to localise infection or inflammation. Diagnosis and therapeutic decision will be obtained from the Study Committee. Follow-up will be held within six months with control visits at three and six months. During each follow-up visit, all patients will undergo laboratory tests, two blood cultures collected 1 h apart, and TTE. In case of actual clinical suspicion of infective endocarditis or local generator pocket infection, patients will be referred for further diagnostics. Endpoints for the results assessment — primary endpoints are to standardise PET CT in the diagnostic process: sensitivity, specificity, positive predictive value, and negative predictive value of the diagnosis made by PET CT; secondary endpoints are: assessment of usefulness of PET CT for detection of remote infective complications (metastatic abscesses, infected pulmonary emboli), incidence of particular localisations of infection, influence of PET CT on therapeutic decision: confirmation or change of decision based on PET CT, safety and complications of diagnostic process of CIED-related infections with PET CT.

Conclusions: Evaluation of PET CT use for device-related infections in a case control study may be conclusive and improve diagnostic pathway.

Key words: positron emission computed tomography, cardiac implantable electronic device, infection

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INTRODUCTION

Cardiovascular implantable electronic device (CIED) infection is a complication of increasing incidence. The prevalence of CIED infection is estimated at 2%, with differences between authors ranging from 0.13% to 19.9% [1–4].

According to a European Heart Rhythm Association survey conducted in high-volume centres the prevalence of CIED infections was below 2%. The majority of centres were able to isolate the infectious agent in ≤ 50% of blood cultures, which underscores the difficulty in finding the agent of CIED infection in many cases [5].

Cardiovascular implantable device infections can be categorised into three groups: superficial skin infection, generator pocket infection, and intravascular infection with intact generator pocket. Although local pocket infection is the most common clinical infection, occurring early after implantation, positive blood cultures may be the only sign of late onset intravascular infection [6].

Mortality in CIED-related infective endocarditis treated only with antibiotics reaches 66%, whereas with combined therapy (antibiotics and complete device removal) it is three-fold lower [7].

Prolonged targeted antibiotic therapy (four to six weeks) with complete device removal and revision of indications for re-implantation is recommended in most cases (class I with confirmed diagnosis and IIa with probable diagnosis) [1, 8].

In complicated and uncertain cases additional diagnostic tools are needed, especially if we take into account the load of the patient associated with device removal, prolonged hospitalisation, and re-implantation.

Apart from morbidity and mortality, infections are also associated with significant financial cost for patients and third-party payers. Polish data on this issue are not available yet, but in United States the estimated average cost of combined medical and surgical treatment of CIED-related infection ranges from USD 25,000 for permanent pacemakers to USD 50,000 for implantable cardioverter-defibrillators [9, 10].

Positron emission tomography combined with computed tomography (PET CT) can play an important role in difficult cases of CIED-related infections, but published studies have focused on the outcomes and safety of this procedure, only briefly considering the economic aspects of this diagnostic test [11].

Recent studies show that PET CT scan is an effective and precise tool that can facilitate the diagnostic process and decision making regarding therapy, especially in difficult patients with CIED-related infections. PET CT scan can protect patients from unnecessary device removal or from too late removal. PET CT may also help in diagnosing other sources of infection, embolic complications, neoplasms, autoimmune diseases, and connective tissue diseases [12–15].

However, there are some issues concerning low sensitivity connected with elevated marker uptake in myocardium and in the case of small vegetations, especially lead-related [14, 15].

In most studies assessing PET CT in the diagnostic process of CIED-related infections standard oncologic protocols were used. Those protocols may not be optimal to assess fludeoxyglucose (FDG) uptake by inflammatory cells. Leccisotti et al. [16] showed that delayed image acquisition (3 h vs. 1 h) significantly improved sensibility and specificity in cases of intravascular infection.

Most available data comes from retrospective analyses, case reports, or from studies with small sample sizes. A properly planned prospective case-control study evaluating the role of 18F-FDG PET CT in comparison with standard diagnostic workup (echocardiography and blood cultures) is yet to be conducted [17].

The aim of this observational non-experimental clinical trial is to assess and standardise diagnostic algorithms for CIED infections (lead-dependent infective endocarditis, generator pocket infection, fever of unknown origin) with PET CT in Poland.

METHODS AND RESULTS

Observational single-centre non-experimental case-control clinical trial.

Study group and eligibility

Twenty patients with implanted CIED and suspected or diagnosed CIED-related infection or fever of unknown origin. Control group consisting of 20 patients with implanted CIEDs, who have undergone PET CT due to non-infectious indications and have no data for infectious process in follow-up.

Age eligible for the study is 18 years and older; gender eligible for study: both.

Inclusion and exclusion

Inclusion and exclusion criteria are shown in Table 1.

Trial conduction

All patients included in the study will undergo a standard diagnostic process. The conventional/standard diagnostic and therapeutic process will consist of: medical interview, physical examination, laboratory tests, blood cultures (three sets, 1 h apart, repeated after 24 h and — if applicable — with fever peak above 38°C); imaging studies (echocardiography: transthoracic, and if there are no contraindications transoesophageal, in case of negative or equivocal result repeated after 7–10 days, or in series if necessary, computed tomography scan for pulmonary embolism if indicated); if there are abnormalities in other systems, decisions concerning further diagnostics will be made by the physician in charge.

As well as the standard diagnostic procedures patients will undergo whole-body PET CT scan to localise infection or inflammation.

Then the investigating team will make a decision concerning further treatment (antibiotics and complete device removal vs. conservative treatment). The team will consist

Table 1. Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Age: 18 years and older	1. Lack of written informed consent
2. Written informed consent for participating in the study and written standard version of informed consent for PET CT scan	2. Pregnancy or breast feeding
3. Suspected or diagnosed generator pocket infection	3. Inability to stay supine for the time of PET CT scan
4. Suspected or diagnosed CIED-related infective endocarditis	4. Unstable cardio-pulmonary state
5. Fever of unknown origin in patient with CIED	5. Glucose level above 200 mg/dL

CIED — cardiovascular implantable electronic device; PET CT — positron emission computed tomography

of: two cardiologists with experience in implantable devices, one echocardiographer, one radiologist, and a specialist in nuclear medicine experienced in PET CT.

Infective endocarditis will be diagnosed on the basis of modified Duke criteria and positive cultures or vegetations on an explanted device (generator and/or leads).

Women of childbearing age will be given a pregnancy test prior to radiological examinations.

In all groups in all uncertain cases decisions concerning diagnostics and treatment will be made by the Investigation Committee.

PET CT methods

Before PET CT scan a patient should drink still water, abstain from drinks containing caffeine and tannin. Six to fifteen hours before the scan after a meal low in carbohydrates and high in fat (30% cream, 150 mL) a patient should be fasting until PET CT scan. For 24 h prior to the scan a patient should follow a low-carbohydrate diet.

After the scan patients are a source of radiation for about 6 h, so he or she should avoid contact with children and pregnant women during that period.

All patients will be examined by a physician before PET CT and if there are no contraindications they will be given the isotope intravenously. Then they will stay in a warm waiting room. Most studies will be performed with 18F-FDG because the disintegration time of Fluorine-18 (109 min) enables its transport from the cyclotron. The dose of 18F-FDG depends on the patient's weight and varies from 270 to 420 MBq. Isotope uptake time is about 45–180 min. After that time the patient will be asked to empty his or her bladder and go to the examination room. First CT scan lasting 2 min will be performed followed by the PET scan lasting about 20 min. Usually the area from mid thigh to eye level will be scanned.

We will use following parameters of CT: configuration of 64 detectors, voltage 140 kV, current intensity automatically adjusted to patient size 10–120 mA, slice thickness 1.25 cm, ratio of table feed during one lamp spin to slice thickness 1.375:1, collimation 20 mm.

In PET we will use an iterative reconstruction method (number of subsets 28, number of iterations 2), time of ac-

quisition in one position of the table — 2 min. The following parameters will be analysed: standardised uptake value (SUV) in the CIED area (pocket, leads), SUV of vascular background — pulmonary trunk, SUV of a liver, SUV max. in other potential changed areas, volume with increased SUV > 40% of the background. Myocardial 18F-FDG uptake will be assessed with qualitative visual scale: 0 — homogeneously minimal; 1 — mostly minimal or mild uptake; 2 — mostly intense or moderate uptake; and 3 — homogeneously intense.

Echocardiography

All participants will undergo transthoracic echocardiography at least three times during the study. Evaluated parameters will be as follows: diameters, contractility, ejection fraction, presence of valvular abnormalities, presence of abnormalities suggesting endocarditis (vegetations, abscesses, perforations, fistulae, pseudoaneurysms, valve aneurysms, dehiscence of prosthetic valves), and presence of vegetation on leads.

All participants will undergo transoesophageal echocardiography at least once during the study, unless there are contraindications. During the transoesophageal echocardiography the following parameters will be evaluated: presence of valvular abnormalities, presence of abnormalities suggesting endocarditis (vegetations, abscesses, perforations, fistulae, pseudoaneurysms, valve aneurysms, dehiscence of prosthetic valves), and presence of vegetations on leads.

Follow-up

Follow-up will be held within six months, with control visits at three and six months.

During each follow-up visit, all patients will undergo laboratory tests (complete blood count, erythrocyte sedimentation rate, C-reactive protein, two blood cultures 1 h apart) and transthoracic echocardiography. In case of clinical suspicion of infective endocarditis or local generator pocket infection, patients will be referred for further diagnostics in our clinic.

Statistical analysis

Initial analysis will consist of validation of appropriateness of randomisation (comparison of baseline characteristics, Wald-Wolfowitz test) verification of distribution of continuous

Table 2. Primary and secondary endpoints of the study

Primary endpoints
• Standardisation of PET CT in diagnostic process of local infections and lead-dependent endocarditis in clinical practice.
• Sensitivity, specificity, and positive and negative predictive values of the diagnosis held by PET CT
Secondary endpoints
• Assessment of usefulness of PET CT for detection of remote infective complications (metastatic abscesses, infected pulmonary emboli)
• Incidence of particular localisations of infection
• Influence of PET CT on therapeutic decision: confirmation or change of decision based on PET CT (percentage)
• Safety and complications of diagnostic process of CIED-related infections with PET CT

PET CT — positron emission computed tomography

data with Shapiro-Wilk test. Baseline demographic characteristics and clinical variables will be summarised for each arm of the study. Continuous data will be presented as arithmetic means and standard deviation for normally distributed variables or as medians and inter-quartile ranges (25–75th) for abnormally distributed variables. Normality will be tested by Shapiro-Wilk test.

Comparison of two groups will be based on parametric Student's two-sample t-test, Cochran-Cox test, or non-parametric Mann-Whitney test as appropriate. Student's paired t-test or Wilcoxon's test will be used to compare continuous variable differences between baseline and the end of observation period.

Categorical data will be given as absolute and relative frequencies (percentages). The differences in proportions between them will be examined using the χ^2 test with Yates correction or Fisher's exact test as appropriate.

A logistic regression model will be used to identify independent factors influencing sensitivity and specificity of the tested diagnostic tool. For the longitudinal analysis curves of cumulative probability of events will be constructed according to the Kaplan-Meier method, and the cumulative event rates will be compared by the log-rank test. A Cox proportional hazards regression analysis will be performed to assess any potential influence of covariates. The assumptions of the Cox proportional hazards model will be checked by visual inspection of the log-log survival function by time curve.

The outcomes of the analysis will be shown as hazard ratios and 95% confidence intervals. Prior to essential statistical analysis all gathered data will be formally and logically checked.

All null hypothesis will be two-tailed with a 0.05 type I error rate.

Data and study safety management
During the study the investigators will regularly fill in case report forms. Database management and quality control for the study will be performed by a statistician. Information entered into the database will be systematically checked and evident errors will be corrected. All of the omissions and/or questions concerning the data will be discussed with the investigator in order to maintain the completeness of the database.

Patients' medical data available in an electronic hospital database system (CliniNet) will be used in the analyses.

The Study Committee will supervise the protocol, study progress, and publications. The Study Safety Committee will be responsible for supervision of propriety of study progress and patient safety.

All study data in paper case report forms will be kept in the Ischaemic Heart Disease Second Department, Institute of Cardiology, Warsaw. The electronic database will be kept in two copies. Synchronisation of data will be conducted on a monthly basis.

The estimated study time for the recruitment of patients and data analysis is planned at two years.

Registration and ethics aspects
The trial is registered as "Positron Emission Tomography Combined With Computed Tomography (PET CT) in Suspected Cardiac Implantable Electronic Device Infection, a Pilot Study — PET Guidance I" on ClinicalTrials.gov; Identifier: NCT02196753 and has obtained Local Ethics Committee approval IK-NP-0021-31/1424/15.

Endpoints to calculate the results
Primary and secondary endpoints are listed in Table 2.

CONCLUSIONS AND CLINICAL IMPLICATIONS
Local and systemic infections associated with CIED are an increasing clinical problem of late complications due to absolute growth in the number of treated subjects. In numerous cases diagnosis slips away from typical criteria used for infective endocarditis and radical curative treatment, i.e. system removal with concomitant antibiotics is usually delayed. PET offers diagnostic support in infectious diseases that are becoming more and more established in practice guidelines. Validation of PET use for device-related infections in a case control study may be conclusive and improve the diagnostic pathway.

Conflict of interest: none declared

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Nowe schematy diagnostyczne. Protokół badania pilotażowego PET Guidance I: pozytonowa tomografia emisyjna u chorych z podejrzeniem infekcji związanej z wszczepialnym urządzeniem do elektroterapii serca

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S t r e s z c z e n i e

Wstęp: Infekcje związane z wszczepialnymi urządzeniami do elektroterapii serca (CIED) są narastającym problemem klinicznym. W artykule przedstawiono, stworzony przez autorów niniejszej pracy, protokół badania obserwacyjnego "Positron Emission Tomography Combined With Computed Tomography (PET CT) in Suspected Cardiac Implantable Electronic Device Infection, a Pilot Study — PET Guidance I" (NCT02196753).

Cel: Celem pracy była ocena przydatności i standaryzacja procesu diagnostycznego infekcji związanych z CIED z użyciem pozytonowej tomografii emisyjnej (PET CT).

Metody i wyniki: Badana grupa będzie składać się z 20 chorych z CIED, u których ustalono wstępne rozpoznanie infekcji związanej z CIED. Grupę kontrolną będzie stanowić 20 pacjentów z CIED, u których wykonano PET CT z innych, pozainfekcyjnych wskazań i u których w wywiadzie nie stwierdzono rozwoju objawów infekcji. Wszyscy chorzy włączeni do badania będą poddani standardowej diagnostyce z wykorzystaniem rutynowych badań laboratoryjnych (w tym co najmniej 2 posiewy z krwi), echokardiografii przezklatkowej (TTE) i opcjonalnie przezprzełykowej oraz klasycznej tomografii komputerowej. Diagnostyka może zostać rozszerzona przez zespół leczący w przypadku zaistnienia dodatkowych wskazań. U wszystkich chorych zostanie wykonane badanie PET CT całego ciała. Komitet Badania na podstawie zebranych danych klinicznych postawi diagnozę i ustali sposób postępowania. Wizyty kontrolne odbędą się po 3 i 6 miesiącach; wykonane będą badania laboratoryjne (w tym 2 razy posiewy z krwi) i TTE. W przypadku utrzymującego się/nowego podejrzenia infekcji związanej z CIED podjęta będzie standardowa diagnostyka. Punkty końcowe badania obejmują — pierwszorzędowe punkty końcowe (standaryzacja zastosowania PET CT): czułość, specyficzność, pozytywna i negatywna wartość prognostyczna PET CT; drugorzędowe punkty końcowe: przydatność PET CT w ocenie powikłań infekcyjnych (obecność ropni, zakażonej zatorowości), typowe miejsca lokalizowania się infekcji, wpływ PET CT na decyzje terapeutyczne; potwierdzenie lub modyfikacja decyzji na podstawie PET CT, bezpieczeństwo i powikłania związane z wykorzystaniem PET CT w diagnostyce stanów infekcyjnych związanych z CIED.

Wnioski: Oczekuje się, że zastosowanie PET CT w stanach infekcyjnych związanych z CIED może mieć korzystny wpływ na ich diagnostykę.

Słowa kluczowe: pozytonowa tomografia emisyjna, wszczepialne urządzenia do elektroterapii serca, infekcja

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