Cardiac Implantable Electronic Devices Infections

Subjects: Cardiac & Cardiovascular Systems

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The use of increasingly complex cardiac implantable electronic devices (CIEDs) has increased exponentially. One of the most serious complications in terms of mortality, morbidity and financial burden is represented by infections involving these devices. They may affect only the generator pocket or be generalised with lead-related endocarditis. Modifiable and non-modifiable risk factors have been identified and they can be associated with patient or procedure characteristics or with the type of CIED. Pocket and systemic infections require a precise evaluation and a specialised treatment which in most cases involves the removal of all the components of the device and a personalised antimicrobial therapy. CIED retention is usually limited to cases where infection is unlikely or is limited to the skin incision site. Optimal re-implantation timing depends on the type of infection and on the results of microbiological tests. Preventive strategies, in the end, include antibiotic prophylaxis before CIED implantation, the possibility to use antibacterial envelopes and the prevention of hematomas.

cardiac implantable electronic device infection | pocket infection | antimicrobial therapy

1. Introduction

Since the first pacemaker (PM) was implanted by Åke Senning in 1958, cardiac implantable electronic devices (CIEDs) have spread worldwide. More sophisticated systems such as implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy (CRT) devices often represent a lifesaving asset, but device-related infections (DRI), albeit infrequent, still represent a potential life-threatening complication [1]. Their clinical manifestation may be confined to the device pocket or to the leads or extended to the entire system and bloodstream [2].

2. Risk Factors for Cardiac Implantable Electronic Device Infections

The overall incidence of CIED infections ranges from 0.5% to 2.2% of patients according to different populations, type of device and time from implant [2]. CIED infection rate raise has surprisingly exceeded the heightened number of device implantations [3]. In the last 16 years, while the number of implanted electronic devices has almost doubled (95% more), the incidence of CIED infections recorded an increase of more than 200% [4]. This escalation of infections may be caused by the higher complexity of CIED recipients in terms of comorbidities and

ageing (patient-related), as well as by more sophisticated techniques and longer procedural times (procedure-related) [5].

Risk factors for CIED infection have historically been classified into patient-related, procedure-related and additionally sub-classified into non-modifiable and modifiable [6]. According to actual evidence ICDs and CRT devices are more susceptible to infections than PMs (8.9 and 10 vs. 1.8 cases, respectively, per 1000 device/years) [7][8]. The number of implanted leads is critical in terms of risk of infections [9][10]. Whether this finding is related to the mere presence of additional hardware itself or reflects the complexity and duration of the procedure is unclear and still object of debates [11]. The end-stage renal disease brings the highest risk of infection among the non-modifiable patient-related factors, showing a pooled estimate odds ratio (OR) of 8.73 [12]. Other relevant risk factors from the same category are chronic corticosteroid use, history of device infection, chronic obstructive pulmonary disease (COPD), heart failure (HF), malignancy and diabetes mellitus [2]. Although the underlying mechanism is unclear, male gender seems to be associated with an increased risk, while infections in women showed a high mortality rate [13][14]. Surprisingly, there is some evidence indicating that age is inversely related to DRI [15], probably because younger patients may have a weaker immune response against low virulence organisms, and finally they go through many procedures in their lifetime [16]. Procedural time is a sizeable determinant of DRI as longer procedures are indeed independently associated with infectious complications [17]. Device replacement or upgrade, which is a non-modifiable procedure-related risk factor as well, is associated with a 2- to 5-fold risk of DRI compared with de novo implant [2]. Early re-interventions, defined as repeat procedures occurring during a single hospitalisation, are also associated with an 8.8-fold increased risk of CIED infection. Pocket hematoma, temporary pacing wires and unfamiliarity with implant techniques are all independent risk factors for DRI [18]. Modifiable factors leave room to preventive strategies to overcome the increased risk for DRI. Fever in the 24 h before implantation is certainly the most relevant (pooled estimate OR > 4). Improper trichotomy, oral anticoagulants and heparin bridging have a minor impact [6].

Ultimately, an investigation on the WRAP-IT trial population, using a machine learning analysis that considers 81 variables, identified additional non-modifiable risk factors including higher number of CIED procedures, history of atrial arrhythmia, geography (outside North America and Europe), device type (CRT vs. permanent PM/ICD) and lower body mass index. Potentially modifiable risk factors included longer procedure time, implant location (non-left pectoral subcutaneous), peri-operative glycopeptide antibiotic (vancomycin) vs. non-glycopeptide (cefazolin), anticoagulant and/or antiplatelet use and capsulectomy. Chlorhexidine skin preparation and antibiotic pocket wash have been found to be protective from early DRI [19].

3. Pathogenesis and Microbiology of Cardiac Implantable Electronic Device Infections

There are two key classes of clinical manifestations, device pocket infections and leads-related endocarditis. The most common source of contamination is the air or the hands of the operators and pocket infection is the prevalent expression of this pathway [6]. Direct lead seeding during bloodstream infections is the mechanism of late lead vegetation formation. The pathways for germs penetration are usually skin, mouth, gastrointestinal or urinary tract

infections [20]. A retrograde progression of infection from the bloodstream to the pocket has been described, and device infection could represent the first clinical expression of a subclinical bacteraemia. It is commonly accepted, although controversial, that infections occurring within 1 year are probably due to contamination at the time of surgery, while those occurring later may be caused by blood-bared germs [5]. ICD infections generally occur earlier after the implant compared with PM infections (125 vs. 415 days, respectively) [7]. This finding is probably related to procedural time and higher susceptibility of ICD leads to shelter micro-organisms seeding. Data suggest that more than a half of DRI is related to procedural contamination. In 55% of patients indeed, a DRI is detected before 12 months after last procedure [21]. Similarly, it has been detected that 25% of CIED infections occur in the first month (0–28 days after device placement), 33% later (29 days to 1 year after device placement), and 42% of total DRI are delayed (>1 year after device placement), implying that only 4 out of 10 infections are not primarily related to peri-procedural contamination [22]. A study including only patients with lead-associated endocarditis, showed that more than two-thirds of individuals developed the disease at least 1 year after the procedure, supporting the theory that late infections are mainly lead-related and secondary to bacteraemia [23]. As expected, risk factors for DRI within 6 months of implantation are different from those related to later infections. The presence of epicardial leads or immediate peri-procedural wound complications seem to be associated with early infections, while the hospitalisation span, the presence of COPD and other comorbidities are mostly associated with delayed infections. Therefore, different pathogenetic mechanisms are associated with distinct clinical presentations, both in terms of time (early versus late) and of clinical manifestation (pocket infection versus lead/systemic infection), which in turn are burdened with different prognosis. In fact, some studies have found higher mortality in lead-related CIEDs or bloodstream infections (29%) compared with isolated pocket infection (5%) [24]. The microorganisms by far most frequently involved in DRI are Gram-positive bacteria (70–90%), especially normally non-pathogenic germs such as coagulase-negative Staphylococci (CoNS, 37.6%) that usually are skin saprophytes [25]. The second most common pathogen, namely Staphylococcus aureus (StA) (30.8%), is the most lethal. It is the most common cause of bacteraemia and early pocket infections and the one that is much prone to adhere to non-biological material creating the biofilm. The biofilm is a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface, which prevents the effective action of host defences and the penetration of antibiotics [26]. Gram-negative bacilli and other Gram-positive cocci are rarely isolated in CIED infections. Finally, a common and critical situation, ranging from 12% to 49% of situations, is that of clinical infections with negative cultures [27].

4. Cardiac Device-Related Infective Endocarditis and Bacteriemia

Bloodstream infection usually refers to a CDRIE which is defined as the presence of lead or valvular vegetations in combination with positive blood cultures [28]. Nevertheless, the clinical spectrum of systemic CIED infection includes two other conditions:

- A left-sided endocarditis in a CIED carrier: the therapeutic approach follows the current guidelines for valve endocarditis [29]. If surgery is required for left-sided endocarditis, an open-heart removal of the CIED is

recommended regardless of the presence of acknowledged device involvement. If there is no indication for valve surgery, complete hardware extraction should be considered even if there is no evidence of associated device infection.

- An occult bacteraemia in a CIED carrier: in this case, there is not an alternative source of infection which resolves only after CIED extraction [30].

The diagnosis of CIED systemic infection is very challenging and it should always be suspected in case of history of fever positively responding to antibiotic therapy and relapsing after its discontinuation [31]. However, several studies have found that 20–50% of patients with CDRIE may present without systemic signs of infection, such as fever, chills, malaise or anorexia and it should spur clinicians to increase their attentiveness to CIED infections [10][22][32][33]. The most frequent complication of CDRIE is the presence of a tricuspid valve vegetation, which occurs in about one-third of the cases [34]. Tricuspid involvement can present with valve alterations (stenosis or regurgitation), pulmonary emboli or pneumonia [35][36]. Tricuspid regurgitation, which is the most prevalent, when severe may require surgical correction coupled with open-heart lead extraction. In case of small tricuspid vegetations, with mild or moderate valve insufficiency, percutaneous extraction can be performed and medical treatment continued for valve endocarditis [30]. Septic thrombophlebitis of the axillary-subclavian axis, even though it is a rare condition, can occur when multiple leads are placed through the same vessel (e.g., CRT or abandoned leads). This complication is at very high risk of pulmonary embolism and an aggressive antithrombotic therapy is recommended before the explant of the whole device [37]. The diagnosis of CDRIE is still based on the modified Duke criteria, but many studies have highlighted some criticism about their predictive value in this setting [29][38]. In order to increase the sensitivity for CIED infection diagnosis, the European Heart Rhythm Association developed the International CIED Infection Criteria in 2020; unfortunately, many limitations are still present [6]. Caution should be maintained in cases of incidental masses on leads without clinical signs of infection because they may be of thrombotic origin [39]. In this situation, four sets of blood cultures and inflammatory markers should be obtained over 2–4 days. If they are all negative, clinical and echocardiographic follow-up is warranted and anticoagulant treatment should be considered, keeping in mind that a mass on right heart CIED leads without signs of infection may also represent a malignancy [40]. Not all patients with a CIED and positive blood cultures have an underlying CIED lead infection. Individuals with positive blood cultures, but no evidence of localised CIED infection constitute a group of difficult management. The risk of underlying CIED lead infection in presence of bacteraemia depends on several factors including duration and source of bacteraemia, type of device, the number of device-related procedures and especially the type of microorganism isolated in blood cultures [41]. Gram-positive organisms remain the predominant pathogens associated with CIED: CoNS and StA are more prone to adhere to non-biological materials [42][43]. Moreover, StA is the most common cause of bacteraemia and early pocket infections. For this reason, many studies tried to identify the clinical predictors of underlying CDRIE in patients presenting with StA bacteraemia, but no signs of pocket infection. Uslan et al. identified different independent predictors of CIED infection such as: relapsing bacteraemia after an appropriate period of antibiotic therapy (when no other source of bacteraemia has been identified), persisting bacteraemia for more than 24 h, implanted ICD, prosthetic cardiac valve and bacteraemia within 3 months of device implantation [44].

5. Diagnosis of CDRIE

CDRIE is defined, according to European guidelines, as an infection extending to the electrode leads, cardiac valve leaflets or endocardial surface; however, local device infection and CDRIE are difficult to be differentiated. Clinical manifestations are the same of other forms of endocarditis, with some differences: fever is less prevalent especially in the elderly, while respiratory and rheumatological symptoms as well as local signs of infection are predominant [29]. The diagnosis should start from blood cultures, no less than two sets; three or more are recommended [45]. Suspected CIED infection with negative cultural findings should consider fungal/mycobacterial blood cultures to exclude an unrecognised causative pathogen [41]. Swab samples from the device and generator pocket tissue for culture and susceptibility testing are valuable instruments [41]. Tissue cultures acquired during the surgical exploration are more sensitive than swab cultures [45]. The use of biomarkers was investigated by Lennerz et al. concluding that pro-calcitonin and high sensitivity C-reactive protein could aid in the diagnosis [46]. Recent studies have suggested that leads and generator sonification after removal may help the microbiology testing [47].

Trans-thoracic (TTE) and trans-oesophageal echocardiography (TOE) are the first essential instruments of the diagnostic workup as they help sizing and follow-up of the vegetations identifying possible valvular involvement and dysfunction. TTE can detect pericardial effusion, ventricular dysfunction and pulmonary artery pressure better than TOE, while the latter would be more accurate for the diagnosis of lead-related endocarditis and peri-valvular extension of the infection. TTE and TOE must be performed both when CDRIE is presumed and intracardiac echocardiography may be considered in case both tests are negative [29].

When the echocardiographic investigations are negative or doubtful and the clinical suspicion is quite reasonable, Fluorine-18-fludeoxyglucose (18F-FDG) positron emission tomography/computerised tomography (PET/CT) scanning and radiolabelled leucocyte scintigraphy have been described as a complementary tool not only in the diagnosis of CDRIE, but also in the search for complications including pulmonary septic embolism [29].

99mTc-labeled hexa-methyl-propylene-amine-oxime (HMPAO) white blood cell (WBC) scintigraphy with single-photon-emission computed tomography–computed tomography (SPECT-CT) detects and localises metabolically active cells involved in inflammation and infection. In the study by Erba et al. 99mTc-HMPAO WBC scintigraphy was 94% sensitive for both detection and localisation of CIED infection and associated complications, with a 95% negative predictive value to exclude device-associated infection during a febrile episode and sepsis [48]. 18F-FDG-PET/CT, conversely, performs better for pocket infections than for lead infections: for pocket infections, pooled sensitivity and specificity were 93% and 98%, respectively, while for lead infections sensitivity was 65% although specificity was still high (88%) [49]. Aside from that, delayed image acquisition could increase 18F-FDG-PET/CT diagnostic accuracy in suspected CDRIE [50]. Previous antibiotic therapy may yield false-negative PET/CT imaging despite CDRIE being present [51].

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