Review Article

Use of Echocardiography in Infectious Endocarditis Associated with Implantable Cardiac Devices

Valor do Ecocardiograma na Endocardite Infecciosa Associada aos Dispositivos Cardíacos Implantáveis

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Abstract

In recent decades, the increase in indications for cardiac implantable electronic devices (CIEDs) has been accompanied by an increased number of complications related to their use, including infectious endocarditis (IE). IE has high morbidity and mortality rates despite advances in diagnostic and therapeutic strategies. The case studies on this topic have significant limitations in terms of diagnostic criteria and methods, which affect decision-making on CIED removal and increase the risk of complications and death. Notwithstanding, echocardiography is critical for diagnosing CIED-associated IE and related potential complications. The limitations and challenges in its diagnosis demand the need for further studies on the topic. The objective of this study was to elucidate the epidemiology, microbiology, risk factors, pathogenesis, diagnosis, and treatment of IE associated with CIEDs to demonstrate the importance of imaging techniques in diagnosis of IE, especially echocardiography.

Introduction

Infectious endocarditis (IE) is a rare disease with an estimated annual incidence of seven to 15 cases per 100,000 individuals, depending on the diagnostic criteria and the study population.[1,2] Despite advances in diagnostic and therapeutic strategies, IE has high morbidity and mortality rates.[1-4]

Bacteria are the primary causative agents of IE, with *Staphylococcus aureus* being the most common causative agent.[2-4] Patients suffering from IE within the past few years have a higher mean age and number of comorbidities, demonstrating changes in the epidemiological profile of the affected population.[1-5] In addition, indications for cardiac implantable electronic devices (CIEDs) have increased with the improved access to health care.[6,7] The use of CIEDs is an effective therapy in cases of heart failure and arrhythmias; however, it often leads to CIED infections. CIED IE is characterized by systemic infection involving endocavitary electrodes.[6-9]

The main risk factors for CIED-associated IE are diabetes mellitus (DM), heart failure with advanced functional class, fever before device implantation, postoperative hematoma, use of temporary pacemaker (PM), and others factors related to the operator and medical center.[6-9]

The diagnosis and treatment of CIED IE are challenging. The accuracy of echocardiography to detect vegetation and sensitivity of blood cultures is low. In addition, treatment of CIED-associated infections requires a complex approach as both intracardiac and extracardiac components might be infected, and their removal often becomes necessary, which increases the risk of complications and death.

The objective of this study was to present the data on the epidemiology, microbiology, risk factors, pathogenesis, diagnosis, and treatment of CIED IE to demonstrate the importance of imaging techniques for its diagnosis, with emphasis on echocardiography, and to discuss the current disease status and diagnostic challenges.

Epidemiology

Similar to valve IE, CIED IE is a rare disease, representing 3.0 to 9.9% of all IE cases.[2,5,6,10] Its incidence is 15 per 1,000 person-years among patients with CIED and higher in patients with implantable cardioverter defibrillator (ICD) compared to those with a PM.[7,9] Although the probability of developing CIED IE increases with the complexity of the device, PM-related infections are the most prevalent because of the relatively higher number of patients implanted with this device.[5,9]

The most affected population is men with advanced age and comorbidities, and the most common comorbidities include DM and chronic kidney disease. The main etiologic agents are *Staphylococcus aureus* (31–35%) and coagulase-negative staphylococci (31.6–44.0%). Vegetations are observed on echocardiogram of approximately 89.8% of CIED IE cases, among which 76.3% patients present with PM leads.[6,9,10]

Palavras-chave

Endocarditis; Pacemaker, Artificial ; Cardiac Resynchronization Therapy; Echocardiography.

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Clinical characteristics

The clinical presentation in patients with CIED IE is similar to that of patients with other infections, including fever (80%) and chills (51%). Based on the data of three case series, the clinical, epidemiological, and microbiological characteristics of patients affected by CIED IE are summarized in Table 1.[6,9]

Vegetations were observed on echocardiography in approximately 90% of the cases, among which 76% patients exhibited lead vegetations. With respect to the microbiological profile, approximately 84% of blood cultures were positive, with a predominance of *S. aureus* and coagulase-negative staphylococci.[6,9,10]

The main sources of infection were the sites for inserction of CIEDs and intravascular catheters. The most common complications of such infection included acute renal failure, heart failure, and, less frequently, rheumatic diseases, septic shock, and pulmonary thromboembolism.[6,9,10] Concomitant valve IE was observed in 37.2% of patients and was associated with increased in-hospital mortality.[6] The most common comorbidities were persistent bacteremia, heart failure, and pulmonary thromboembolism.

Risk factors

The main risk factors for CIED IE are shown in Chart 1. We observed a significantly higher incidence of CIED IE in male patients. Another relevant characteristic was the presence of comorbidities, especially those that decreased immunity, such as DM and acute renal failure. The probability of infection increased with rise in the New York Heart Association (NYHA) functional class. Another risk group included patients undergoing treatment with a vitamin K antagonist, possibly because of the increased probability of hematoma formation in the PM pocket, which increased the risk of infection. Other risk factors included hypertrophic cardiomyopathy, chronic anemia (hemoglobin below 9 g/dL for more than one year), and chronic obstructive pulmonary disease.

Chart 1 – Modifiable and non-modifiable risk factors for infective endocarditis associated with cardiac implantable electronic devices.

Modifiable risk factors	Unmodifiable risk factors
Number of manipulations of CIED	Age
Better management of patients with comorbidities	Gender
Chronic corticosteroid therapy	Comorbidities
Surgeon's experience	Upgrade from ICD to CRT
Buried electrodes	More than two electrodes
Anticoagulation therapy	Recent manipulation of CIED
Low hemoglobin	
Hematoma in the pacemaker pocket	
Time elapsed after surgery	

Source: adapted from Palraj.[10] CIED, cardiac implantable electronic device; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

Table 1 – Clinical, epidemiological, and microbiological characteristics of patients with infective endocarditis associated with cardiac implantable electronic devices.

Reference	Athan et al.[6]	Ortiz-Bautista et al.[9]	Kim DH et al.[10]
Study design	Prospective cohort study on patients with definitive IE from 61 centers in 28 countries	Retrospective cohort study on patients with definitive IE from three tertiary centers	Retrospective cohort study on patients with definitive IE from a single center
Study period	2000-2006	1995-2014	2006-2011
Total IE cases (cases associated with CIED)	2,760 (177)	1,182 (100)	80 (80)
Male patients	131 (74)	75 (75)	58 (73)
Mean age (years)	71,2	67 ± 14	67
Fever > 38 °C	143 (80,7)	79 (81)	53 (66)
Comorbidities			
Diabetes mellitus	48 (27,1)	46 (46)	30 (38)
Cancer	19 (10,7)	9 (9)	
Hemodialysis	11 (6,2)	3 (3)	5 (6)
Chronic renal disease	ND	14(14)	ND
CIED			
Pacemaker	152 (87,9)	84 (84)	45 (56)
ICD	21 (12,1)	16 (16)	35 (44)
Microbiological analysis			
Positive blood culture	149 (84,2)	67 (73)	69 (86)
Positive blood cultures in pacemaker leads or valvular vegetations	93 (52,5)	ND	ND
Staphylococcus aureus	62 (35)	31 (31)	37 (46,3)
Methicillin-resistant *Staphylococcus* aureus	26 (14,7)	9 (29)	29 (36)
Coagulase-negative *staphylococci*	56 (31,6)	44 (44)	-
Enterococcus	9 (5,1)	3 (3)	-

IE, infective endocarditis; CIED, cardiac implantable electronic device; NA, not available; ICD, implantable cardioverter defibrillator. The results are expressed as absolute values and either percentages or means in parentheses.

Inexperience of surgeon, use of temporary MP, early re-intervention due to hematoma in the PM pocket, number of lead revisions, lead replacement, upgrade from ICD to CRT, device complexity, and longer surgery duration increased the chances of CIED IE.

The most significant risk factors were higher NYHA status, higher number of PM pulse generator substitutions, higher number of lead revisions, and upgrade from ICD to CRT. It is important to highlight that ICD usually demands a higher frequency of revisions than PMs, and, unlike lead revisions, surgeries for pulse generator replacements are elective.[6,8-10]

Diagnosis

Echocardiography

Imaging methods, particularly echocardiography, play a fundamental role in the diagnosis, management, and monitoring of IE.[12,13] Echocardiography is the technique of choice for diagnosing IE; it is also useful for assessing prognosis and risk of embolism and for peri- and postoperative therapeutic monitoring.[14] In patients with CIED IE, echocardiography is critical for the diagnosis of valvular vegetations and tricuspid valve involvement, quantification of tricuspid regurgitation, determination of the size of vegetations, and follow-up after pacemaker lead extraction (Figure 1).

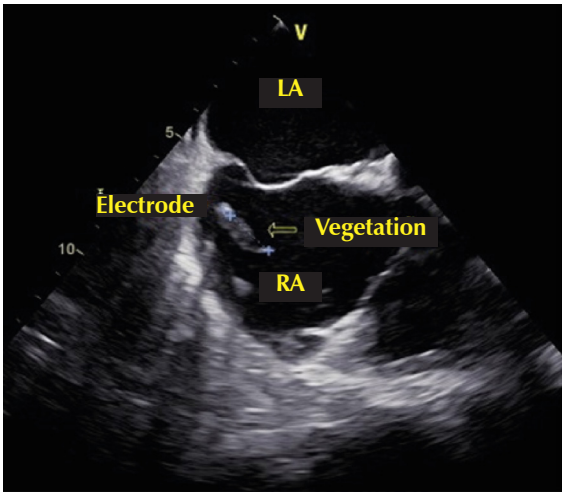
Transthoracic echocardiography (TTE) facilitates better detection of several prognostic factors, including the presence of pericardial effusion, ventricular dysfunction, and elevated pulmonary arterial pressure. Transesophageal echocardiography (TEE) has higher sensitivity and specificity than transthoracic echocardiogram (TTE) for detection of PM endocarditis.[15-19] TEE allows visualization of the ventricular electrode in atypical locations, such as the proximal superior vena cava and other regions, which are difficult to be visualized on TTE. In addition, the sensitivity of TEE for assessing the involvement of the left side of the heart and perivalvular extension of the infection is higher than that of TTE. However, both TTE and TEE can produce false negative results in the presence of PM infections and absence of detectable vegetations (Figure 2).

The diagnosis of CIED IE is challenging even when using TEE. However, diagnosis is crucial before and during the surgery (intraoperative echocardiography). In addition, intracardiac echocardiography is viable and effective in patients with CIED,[20] and its sensitivity of detection of vegetation is higher in these cases.[20-22]

Real-time three-dimensional (3D) TEE allows analysis of cardiac structure volumes in any plane. A recent study has shown that conventional TEE underestimates the size of cardiac vegetations, whereas 3D TEE is better for analyzing the morphology and size of vegetations, consequently overcoming the limitations of conventional TEE in predicting the risk of embolism more efficiently in IE patients.[23] Furthermore, 3D TEE is useful for determining the extent of perivalvular infection, dehiscence of valve prosthesis, and valve perforation.[24] Although 3D TEE is being increasingly performed in clinical practice together with conventional TEE at many medical centers, the former should complement standard echocardiography in most cases.

The modified Duke criteria, which are widely used for IE detection, are difficult to be applied to CIED IE because of its low sensitivity.[25] Modified Duke criteria have been proposed for identification of CIED IE,[17,26] including the presence of local signs of infection and pulmonary embolism as major criteria.[16]

Normal echocardiography results do not exclude CIED-related infections. In difficult cases, other types of imaging techniques, including positron emission computed tomography (PET-CT) with fluorine-18 fluorodeoxyglucose (18F-FDG)[27,28] and scintigraphy with radiolabeled leukocytes,[29] are employed for detection of CIED IE and associated complications, including septic pulmonary embolism.



LA, left atrium; RA, right atrium.

Figure 1 – *Transesophageal echocardiogram showing vegetation attached to an implantable cardioverter defibrillator.*

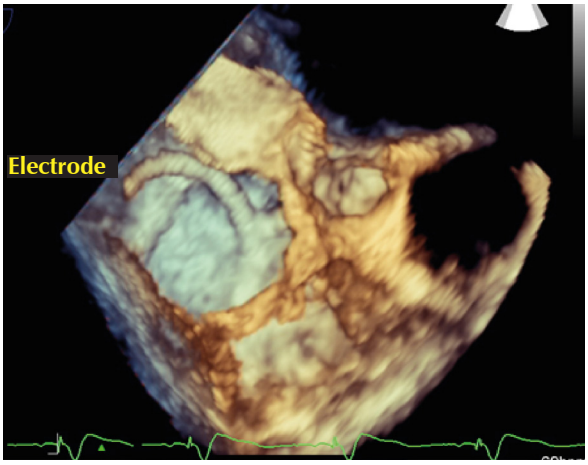


Figure 2 – *Three-dimensional transesophageal echocardiogram showing an implantable cardioverter defibrillator in the right atrium. The image belongs to a Chagas heart disease patient with high fever and positive blood cultures for Staphylococcus aureus without detectable cardiac vegetations.*

Other imaging techniques

Nuclear imaging

Several studies have shown promising results of PET-CT with 18F-FDG and scintigraphy with radiolabeled leukocytes in IE patients. These techniques are crucial because they reduce the rate of misdiagnosed cases classified in the category "possible IE" using Duke's criteria and detect peripheral embolism and metastatic infections.[30]

The results of PET-CT with 18F-FDG should be carefully interpreted in patients who recently underwent cardiac surgery because the inflammatory response might result in non-specific uptake of 18F-FDG in the postoperative period. In addition, several pathological conditions can mimic the manifestations of increased focal uptake of 18F-FDG, including active thrombi, soft atherosclerotic plaques, vasculitis, primary cardiac tumors, metastatic cardiac tumors, postoperative inflammation, and foreign body reaction.[29] Another limitation of PET-CT with 18F-FDG is the location of septic emboli in the brain due to the high uptake of this marker in the cerebral cortex.

Furthermore, PET-CT with 18F-FDG is a promising technique employed in patients with established IE, in whom this examination can help monitor the response to antimicrobial treatment. However, not enough data is available to make general recommendations. (Figure 3)

Multislice computed tomography

Multislice computed tomography (MSCT) is useful for detection of abscesses and pseudoaneurysms with diagnostic accuracy similar to or higher than that of TEE to evaluate complications of the perivalvular extension of infection, pseudoaneurysms, abscesses, and fistulas.[31]

In aortic IE, MSCT is useful to define the size, structure, and occurrence of calcification of the aortic valve, aortic root, and ascending aorta, which are relevant criteria for surgery. In right-chamber IE, CT may reveal concomitant lung disease, including abscesses and infarctions.

Compared to CT, magnetic resonance imaging (MRI) presents with a higher sensitivity for detection of brain injuries, which has been confirmed in IE patients. However, CT is more feasible and practical for critically ill patients and could be used as a viable alternative when MRI is not available.

Contrast MSCT has high sensitivity and specificity for detection of splenic and other abscesses. Nonetheless, differential diagnosis from infarction is difficult.

MRI

MRI is more sensitive than CT for detection of IE involvement of the brain. Studies involving systematic brain MRI during acute IE found lesions in 60–80% of patients.[32] Regardless of neurological symptoms, the most common abnormalities are ischemic injuries (50–80% of patients), and small ischemic injuries are more frequent than large territorial infarctions.[33] Other lesions were observed in 10% of patients, including parenchymal or subarachnoid hemorrhages, abscesses, and mycotic aneurysms.[32-35]

The systematic use of brain MRI affects the diagnosis of IE when adding a minor Duke[36] criterion in patients with brain injuries without neurological symptoms. A study has shown that brain MRI findings improve the diagnosis of IE in 25% of patients with undefined IE, leading to earlier diagnosis.[34]

In most cases, cerebral MRI is abnormal in patients with IE and neurological symptoms and,[37] therefore, does not improve the diagnosis of IE because these patients already have a minor Duke criterion. In contrast, MRI reveals brain damage in patients without neurological symptoms in most cases and ischemic damage in at least 50% of the cases.[38]

In summary, cerebral MRI improves the characterization of the lesions in patients with IE and neurological symptoms, and it is a crucial technique that can facilitate diagnosis of IE in patients with undefined IE without neurological symptoms.

Treatment

The treatment of CIED infections varies depending on the involvement of electrodes and/or endocardium and a patient clinical status. Complete or partial removal of the device, and conservative treatment along with maintenance of the device in situ and suppression antibiotic therapy or some treatment options (Chart 2).

Conservative treatment with blood culture and early reevaluation is recommended in cases that involve inflammation of the pacemaker pocket in less than 30 days postoperatively without signs or symptoms of infection. The CIED can be retained in cases with negative blood cultures and improvement in local inflammation. In such cases, treatment with an oral antibiotic for seven to ten days is recommended. The complete removal of CIED and antibiotic therapy is indicated if blood cultures are positive or, at the time of reevaluation, the patient shows signs of infection in the pacemaker pocket or signs/symptoms of systemic infection. In cases with signs of infection in the pacemaker pocket (fluctuation, purulent secretion, and suture dehiscence) during initial evaluation, the recommended procedures are blood culture, echocardiography, empirical antibiotic therapy, and referral for the early and complete removal of the CIED (less than two weeks after diagnosis). Antibiotic therapy should be maintained for ten to 14 days and guided by blood culture results whenever possible. Treatment should be extended to four weeks in cases of infection of the PM and/or valve (confirmed by echocardiography or microbiological analysis) and six weeks in cases of extracardiac infection.[39]

The complete removal of the pulse generator and the

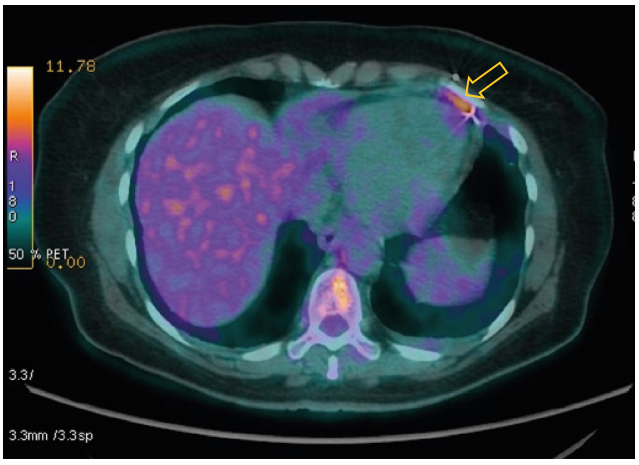


Figure 3 – *Positron emission tomography showing mild glycolytic hypermetabolism in the left ventricular electrode (arrow) of a patient with an epicardial pacemaker lead infection.*

Chart 2 - Empirical antibiotic therapy for infections due to cardiac implantable electronic devices.

Diagnosis	Antibiotic	Dose/length of treatment
Early inflammation of the pacemaker pocket	Flucloxacillin	0.5–1.0 g every 6 hours orally for 7–10 days
Uncomplicated infection of the pacemaker pocket	Vancomycin	1 g every 12 hours IV for 10–14 days
	OR	
	Daptomycin	4 mg/kg every 24 hours IV for 10–14 days
	OR	
	Teicoplanin	6 mg/kg at 0, 12, and 24 h, and then every 24 hours for 10–14 days
Cardiac implantable electronic device-related infective endocarditis with pending blood culture results (e.g., patients with sepsis)	Vancomycin	1 g every 12 hours IV for 4–6 weeks
	AND	
	Meropenem	1 g every 8 hours IV for 4–6 weeks
	OR	
	Daptomycin	9–10 mg/kg every 24 hours IV for 4–6 weeks
	AND	
	Meropenem	1 g every 8 hours IV for 4–6 weeks
Cardiac implantable electronic device-associated infective endocarditis with negative blood cultures	Vancomycin	1 g every 12 hours IV for 4–6 weeks
	AND	
	Gentamycin	1 mg/kg every 12 hours for 4–6 weeks
	OR	
	Daptomycin	9-10 mg/kg every 24 hours IV for 4–6 weeks
	AND	
	Gentamycin	1 mg/kg every 12 hours for 4–6 weeks

Source: adapted from Sandoe et al.[39] IE, infective endocarditis; CIED, cardiac implantable electronic device; IV, intravenously.

percutaneous extraction of endocardial leads should be preferred whenever possible. The failure rate of the procedure varies according to the time elapsed since CIED implantation and corresponds to 5% after three years and 20% after 12 years.[40] The most common minor complication is pulmonary embolization, which affects the patients with large vegetations, although it is not clinically relevant in most cases.[39,41] Major complications are rare, and in-hospital mortality due to sepsis can reach 2.7%.[40] Concomitant involvement of valves (native or prosthesis) is not a contraindication for percutaneous lead extraction. However, surgical removal should be considered in cases in which vegetations are large (>20 mm) or valve replacement is indicated for other reasons.[37,42]

Antibiotic treatment against Gram-positive bacteria with vancomycin, daptomycin, or teicoplanin is sufficient in cases of uncomplicated infections of the PM pocket. In cases of PM infection or associated valve involvement, for whom blood cultures results are either not available or are negative, the antimicrobial spectrum should be expanded to cover Gram-negative bacteria with meropenem or gentamicin.[39]

It is noteworthy that some of the patients have no clinical conditions to be submitted complete removal of CIED, and some patients refuse to undergo the procedure. For such cases, the pulse generator should be removed whenever possible, leaving the PM leads *in situ*; in addition, intravenous antibiotic therapy, followed by long-term oral suppression antibiotic therapy, is recommended.[39] Nonetheless, preserving the PM leads considerably increases the risk of infection recurrence, that might become higher than 50%,[43,44,45] 30-day mortality (Hazard Ratio [HR], 6.9; Confidence interval 95% - CI95% 1,36-35,6)[46] and in one-year.[6]

The optimal time to re-implant the CIED depends on the indication of its use. Whenever possible, re-implantation should be avoided until the signs and symptoms of local and systemic infection are resolved.

Limitations

This study had some limitations. First, CIED IE is a rare disease and difficult to diagnose. Therefore, different studies described different diagnostic criteria for definitive IE and used different inclusion and exclusion criteria, which decreased the accuracy of reviews and analyses. For instance, only a few studies included patients with concomitant valve IE. Second, complementary imaging techniques, including nuclear medicine examination, were not employed in some studies. Third, the studies on CIED IE used different experimental designs. For instance, some studies included hospitalized patients with IE sequentially, and only the subgroup with ICED was evaluated, whereas other studies were conducted in medical centers for implantation of electronic cardiac devices, and patients were followed-up for potential complications, including IE. For this reason, data from different studies should be used with caution.

Conclusions

CIED IE has high morbidity and mortality rates, and its diagnosis is difficult and usually inaccurate. Removing the cardiac device increases the risk of complications and death. The rate of this type of infection is increasing because of the increasing number of referrals and implantations of cardiac devices, which are usually the best therapeutic approach for heart failure and arrhythmias. Future studies must focus on development of adequate diagnostic tools, including imaging examinations.

Conflict of interest

The authors have declared that they have no conflict of interest.

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