Cuban Society of Cardiology
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Original Article

Lead-related infective endocarditis of cardiac stimulation devices

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ABSTRACT

Introduction: Lead-related infective endocarditis of cardiac stimulation devices is an infrequent but with high mortality disease.
Objective: To characterize the lead-related infective endocarditis of cardiac stimulation devices.
Method: Cross-sectional investigation of case series at Hospital "Hermanos Ameijeiras" from January 2007 to January 2011. The sample consisted of 30 patients with a diagnosis of lead-related infective endocarditis of cardiac stimulation devices. For statistical analysis, percentages and hypothesis tests were used with Fisher's exact test.
Results: Males (66%), and the group of 60 years and over (56.7%) predominated. 100% had fever, general symptoms, arthralgia, and 70% respiratory symptoms. 53.3% were admitted with a time of evolution of the symptoms less than 3 months. There was a history of generator (53.3%) or system replacement (46.7%), and pocket infection (30%). Mean number of reinterventions per patient was 2.7. In 70% a staphylococcus was isolated. Vegetations attached to the electrode (96.7%), greater than or equal to 1 cm (80%), and multiple (63.3%) were the most common echocardiographic findings. In 93.3% the electrode was surgically removed. Mortality was 23.3%. Presence of structural heart disease (p=0.04), time of symptoms evolution greater than or equal to 3 months (p=0.002), hemoglobin less than 100 g/L (p= 0.008), and vegetations greater or equal to 1 cm (p=0.004) were associated with higher mortality.
Conclusions: Infective endocarditis should be suspected in all patients with an endocavitary stimulation system with fever of unknown origin associated with general and respiratory symptoms, particularly if there is a history of systemic sepsis or reinterventions. Its high mortality is related to symptoms of long evolution, presence of structural heart disease, anemia and large vegetations.
Key words: Infectious endocarditis, Artificial pacemaker, Implantable cardioverter-defibrillator

Endocarditis infecciosa del electrodo de los dispositivos de estimulación cardíaca

RESUMEN

Introducción: La endocarditis infecciosa del electrodo de los cardioestimuladores es una enfermedad poco frecuente pero con alta mortalidad.
Objetivo: Caracterizar la endocarditis infecciosa del electrodo de los cardioesti-

muladores.

Método: Investigación de corte transversal de serie de casos en el Hospital Hermanos Ameijeiras durante el período enero/2007 − enero/2011. La muestra quedó conformada por 30 pacientes con el diagnóstico de endocarditis infecciosa del electrodo de los cardioestimuladores. En el análisis estadístico se utilizaron porcentajes y pruebas de hipótesis con el test exacto de Fisher.

Resultados: Predominó el sexo masculino (66%) y el grupo de 60 años y más (56,7%). El 100% presentó fiebre, síntomas generales y artralgias; y el 70%, síntomas respiratorios. El 53,3 % fue ingresado con un tiempo de evolución de los síntomas menor de 3 meses. Hubo antecedentes de cambio del generador (53,3%), del sistema (46,7%) y sepsis del bolsillo (30%). El promedio de reintervenciones por paciente fue de 2,7. En el 70% se aisló un estafilococo. Las vegetaciones adheridas al electrodo (96,7%), mayores o iguales a 1 cm (80%), y múltiples (63,3%), fueron los hallazgos ecocardiográficos más comunes. En el 93,3% se empleó tratamiento quirúrgico para remover el electrodo. La mortalidad fue de 23,3%. La presencia de cardiopatía estructural (p=0,04), el tiempo de evolución de los síntomas mayor o igual a 3 meses (p=0,002), la hemoglobina menor de 100 g/L (p=0,008) y las vegetaciones mayores o iguales a 1 cm (p=0,004) se asociaron a una mayor mortalidad.

Conclusiones: La endocarditis infecciosa debe sospecharse en todo paciente con un sistema de estimulación endocavitario, con fiebre de origen desconocido, asociada a síntomas generales y respiratorios, en particular si existe el antecedente de sepsis del sistema o reintervenciones. Su elevada mortalidad se relaciona con síntomas de larga evolución, presencia de cardiopatía estructural, anemia y vegetaciones de gran tamaño.

Palabras clave: Endocarditis infecciosa, Marcapasos artificial, Cardiodesfibrilador automático

INTRODUCTION

Lead-related infective endocarditis (IE) of cardiac stimulation devices (CSD) is the infection of the intracavitary segment of the lead, which may remain circumscribed to the wire or extend to adjacent structures (tricuspid valve, mural endocardium, and superior vena cava)[1]. Because of the increase in permanent pacemaker (PPM) and cardioverter-defibrillators implants, there has been an increasing number of IE associated with these CSD.

The incidence after the implantation of a stimulation system varies according to the series and ranges from 0.13 to 19%. It is more common in men and there is no particular heart disease that predisposes it. It is subdivided into early (less than 12 months) and late (more than 12 months), according to the time elapsed since the implant or the last surgical manipulation until the onset of symptoms[2-4].

The predisposing factors are collected in approximately one third of patients, among those most involved are: diabetes mellitus, neoplasias, malnutrition, alcoholism, steroid use, chronic renal failure, use of oral anticoagulants, postoperative hematoma, surgical wound and generator-pocket infection, aseptic necrosis, generator exteriorization, use of drains, generator or wire replacement, presence of more than one intracavitary lead, repetitive manipulation, and abandon of wires after an extraction attempt[5,6].

Three pathogenic mechanisms are involved: local contamination during system implantation (more accepted and frequent), generator-pocket infection that extends to the lead, and the hematogenous route[7,8].

Clinical symptoms are poorly evident, and IE should be suspected in all patients with a PPM who present febrile episodes of unexplained cause. The diagnostic confirmation is based on three pillars: microbiological (blood cultures and culture of all prosthetic material), histological (surgery or necropsy) and echocardiographic. However, value of Duke criteria for the definitive diagnosis[9] of this disease is limited.

The sensitivity of transesophageal echocardiography is not 100% profitable and a negative study does not deny an infected lead; if it is clinically suspected, serial exams should be performed[10].

Specificity is not absolute and vegetations must be differentiated from thrombi and fibrin strands attached to the wire[11].

Incidence of negative blood cultures is 60%, higher than that reported in valve IE. In 80% of patients the most frequent microorganism is staphylococcus: *aureus* in acute infection and coagulase-negative in late. Most staphylococci are sensitive to methicillin, suggesting their skin origin[12,13].

It exhibits a high mortality, between 31-66% when the device is not removed, and 18% when the extraction of the electrodes is combined with antimicrobial therapy[6]. Empirical antibiotic therapy consists of the combina-tion of vancomycin and gentamicin and in more severe situations rifampicin may be added[14]. Percu-taneous extraction is the technique of choice for electrodes removal, which can be performed by ma-nual traction or through intravascular devices (pig-tail catheter, intravascular forceps, dilator sheaths, Dotter's basket, fixation devices, and laser sheaths) [15,16]. Surgical extraction, with or without extracorpo-real circulation, is reserved for failures of the per-cutaneous technique and for those involving tricus-pid valve damage or large vegetation[17].

This research aimed to characterize the behavior of lead-related IE of CSD at the *Hermanos Ameijeiras* Hospital and to identify possible variables related to mortality.

METHOD

A cross-sectional study was carried out, in a series of cases, in patients admitted with a diagnosis of lead-related IE of CSD (according to modified Durack criteria)[9], from January 2007 to January 2011. Sample consisted of 30 patients.

Demographic, clinical, laboratory, microbiological, echocardiographic, and therapeutic variables under study were obtained from clinical records. They were expressed in their respective summary measures, absolute and relative frequencies, expres-sed in percentages as they were qualitative varia-bles.

In order to evaluate the association between some variables of interest, Fisher's exact test result was considered when dealing with 2x2 contingency tables, and when there were expected frequencies greater than or equal to 25%. The significance level considered was 0.05.

Table 1. Distribution of patients according to demographic data.

Age Groups	Female		Male		Total	
	Nº	%	Nº	%	Nº	%
< 39	2	20.0	3	15.0	5	16.7
40 – 59	2	20.0	6	30.0	8	26.7
60 and over	6	60.0	11	55.0	17	56.7
Total	10	33.3	20	66.7	30	100

Ethical procedures on the treatment of information sources were fulfilled throughout the research.

RESULTS

Male predominated (66.7%) and the group aged 60 years and over (56.7%) (**Table 1**).

Hypertensive and ischemic heart disease were the most common structural heart defects in our series, 16.7% and 13.3% respectively (**Table 2**). The history of diabetes mellitus was recorded in 20% of the patients. Atrioventricular block (53.3%), was the most frequent electrical diagnosis that led to device implantation.

Table 2. Distribution of patients according to structural heart disease, comorbidity and electrocardiographic diagnosis for device implantation (n=30).

Variables	Nº	%
Structural heart disease		
Ischemic	4	13.3
Dilated	3	10.0
Hypertrophic	1	3.3
Hypertensive	5	16.7
Congenital	2	6.7
Comorbidities		
Diabetes mellitus	6	20.0
Neoplasms	2	6.7
Device implant electrical diagnosis		
AV block	16	53.3
SND	8	26.7
HOCM	1	3.3
VF /VT	5	16.7

AV: atrioventricular. SND: sinus node disease. VF: ventricular fibrillation. HOCM: hypertrophic obstructive cardiomyopathy. VT: ventricular tachycardia.

Table 3. Distribution of patients according to clinical picture and clinical laboratory results (n=30).

Variables		Nº	%
Fever		30	100
General symptoms		30	100
Respiratory symptoms		21	70
Arthralgia		30	100
Pulmonary Embolism		2	6.7
Time of onset of symptoms	< de 3 months	16	53.3
	≥ de 3 months	14	46.7
Hemoglobin	≥ de 10 gr/l	18	60.0
	< de 10 gr/l	12	40.0
Erythrocyte sedimentation	≥ de 60 mm/h	10	33.0
	< de 60 mm/h	20	66.6
Leukogram (leucocytes)	≥ 10 x 10^9/L	20	66.6
	< de 10 x 10^9/L	10	33.3

Table 4. Distribution of patients according to characteristics inherent to the stimulation system, and microbiological results (n=30).

Variables		Nº	%
PPM	Single chamber	14	46.7
	Dual chamber	11	36.7
ICD	Single chamber	5	16.6
Number of leads	≥ 2	23	76.7
	< 2	7	23.3
Infection	SW	1	3.3
	Pocket	9	30.0
Pocket expansion		4	13.3
Generator replacement due to exhaustion		16	53.3
System replacement		14	46.7
Reinterventions average		2.7	
Hemocultures	Positives	27	90.0
	Negatives	3	10.0
Pathogenic microorganisms isolated in blood cultures	SA coagulase positive	8	26.7
	SA coagulase negative	13	43.3
	Enterobacteriaceae	4	13.3
	Escherichia Coli	2	6.7
Antibiotic prior to blood culture	Yes	12	40.0
	No	18	60.0

ICD: implantable cardioverter-defibrillator. SA: Staphylococcus aureus. SW: surgical wound. PPM: permanent pacemaker.

100% of the patients in this series had fever, general symptoms, and arthralgia (**Table 3**). 70% reported respiratory symptoms, but pulmonary embolism was demonstrated in only 6.7%. 66.6% of the patients presented leukocytosis, expression of a serious systemic infection; however, patients with hemoglobin ≥ 100 g/L (60%) and erythrocyte sedimentation < 60 mm/h (66%) predominated. The 53.3% of the total was admitted to the institution with a time of evolution of the symptoms less than 3 months.

IE predominated in single chamber systems (46.7%). The antecedent of the generator replacement, system replacement, and generator pocket infection were collected in 53.3%, 46.7% and 30% of the sample, respectively (**Table 4**). 76.7% of the patients had more than 2 endocavitary leads and the mean number of reinterventions per patient was 2.7. 90% of those affected had positive blood cultures, and in 70% of the total the isolated germ was staphylococcus coagulated positive (26.7%) and coagulase negative (43.3%). Sixty percent of the patients had not received antibiotic treatment prior to taking the blood sample.

The positivity of transthoracic echocardiography was 56.7% and transesophageal echocardiography was 100% (**Table 5**). The most common echocardiographic findings were vegetations attached to the lead (96.7%), greater than or equal to 1 cm (80%) and multiple (63.3%).

In 60% of the patients, standard antibiotic therapy was used for each germ, and multitherapy in the remaining 40% (**Table 5**). In only one patient, antibiotic treatment was used as the only therapeutic option, justified by the impossibility of percutaneous extraction and high surgical risk. In 93.3%, lead was surgically removed, always under extracorporeal circulation, and 33.3% of cases required anoxic arrest. In one patient the lead was removed by manual traction.

Total mortality was 23.3% (7/30). The existence of structural heart disease (p=0.04), the time of evolution of symptoms greater than or equal to 3 months (p=0.002), hemoglobin less than 100 g/L (p=0.008), and vegetations greater or equal to 1 cm (p=0.004) were significantly associated with higher mortality (**Table 6**). No relationship was found between

mortality and the remaining variables under study.

Table 5. Distribution of patients according to echocardiographic and therapeutic characteristics (n=30).

Variables		Nº	%
TTE	Positive	17	56.7
	Negative	13	43.3
TEE	Positive	30	**100**
	Negative	0	0.0
Lead vegetation		29	**96.7**
Valve vegetation		3	10.0
Mural vegetation		2	6.7
Tricuspid insufficiency		2	6.7
Multiple vegetation		19	**63.3**
Vegetation size	≥ 1 cm	24	**80.0**
	< 1 cm	6	20.0
Antibiotic treatment	Standard	18	**60.0**
	Multi therapy	12	40.0
Lead extraction	Surgical	28	**93.3**
	Manual extraction	1	3.3
ECC		28	**93.3**
AA		10	33.4

ECC: extracorporeal circulation, AA: anoxic arrest, TEE: transesophageal echocardiography, TTE: transthoracic echocardiography

DISCUSSION

The prevalence of males had a similar behavior to that found in the reviewed literature, since there is a greater frequency of PPM implantation in this subpopulation. Same occurs with the subgroup of 60 years and older patients, justified by a higher CSD implantation rate in the elderly (14.5 x 100000 inhabitants)[18].

The increase in hypertensive and ischemic heart disease with aging, together with the predominance of the 60 years and over subgroup, justify the higher prevalence of these heart diseases in our series.

Diabetic patients are more prone to local infection after catheter placement and other devices than the general population. It is therefore likely that diabetics are at increased risk of acquiring this disease[19].

The most common symptoms of lead-related IE of CSD are: fever, general symptoms, arthralgia, respiratory symptoms and pulmonary embolism[3], similar to the behavior in our research. According to other authors[11], more than 50% of the patients present clinical or radiological lung disease, secondary to septic embolism. These complications are interpreted as primary pulmonary infection and confuse the diagnosis. The physician recognizes and treats only the consequence, but the underlying cause continues until becoming more evident.

The leukocytosis found expresses the severity of the systemic infection; however hemoglobin and erythrocyte sedimentation showed erratic behavior.

Despite the predominance of patients with a diagnosis of the disease in the first 3 months from the onset of symptoms, it is striking that a high percentage of patients are still diagnosed late. Significant delay for diagnosis and therefore for treatment justifies the still gloomy outcome of the lead-related IE of CSD.

The most recognized pathogenic mechanism in IE on CSD is local contamination during system implantation[7]. A number of local factors are mentioned in relation to the procedure, which may favor infection, among which are: surgical wound and generator pocket infection, pocket expansion, and generator and system replacements, the first one due to depletion. The number of reinterventions and the permanence of more than 2 endocavitary leads are the predisposing factors most frequently cited by the different series[5,16,19]. Results similar to our research.

Studies have indicated a greater frequency of IE in patients with dual chamber systems, justified by a longer surgical time, a greater quantity of prosthetic material, and the greater difficulty in total extraction of the system when local complications occur[5,7]. However, in this investigation, patients with single chamber PPM predominated; a result that is justified by the predominance of single chamber cardiac stimulation in the country.

The positivity of blood cultures in the IE by leads oscillates between 70-77%. Previous administration of antibiotics, intermittent bacteremia and low virulence of the causative agents, justify their low positivity[20]. The superiority of positive results of the blood cultures in our study, compared to what was reported by other authors is related to the fact that 60% of the patients had not received antibiotic treatment prior to sampling.

Table 6. Relationship between mortality and clinical-epidemiological. microbiological. clinical laboratory and echocardiographic variables.

Variables		Not deceased (n=23)		Deceased (n=7)		p
		Nº	%	Nº	%	
Age groups	≤ 39	4	17.4	1	14.3	
	40 − 59	7	30.4	1	14.3	*
	60 and older	12	52.2	5	71	
Diabetes mellitus		4	17.4	2	28.5	0.433[a]
Structural heart disease		9	39.1	6	85.0	**0.040**[a]
Time of onset of symptoms	< 3 months	16	69.5	0	0	**0.002**[a]
	≥ 3 months	7	30.4	7	100	
Blood culture	Positive	20	87	7	100	0.436[a]
	Negative	3	13.0	0	0.0	
Pathogenic microorganisms isolated in blood cultures	Staphylococcus	14	60.8	7	100	*
	Enterobacteriaceae	4	17.4	0	0.0	
	Escherichia coli	2	8.7	0	0.0	
Hemoglobin	≥ 10 g/L	17	73.9	1	14.3	**0.009**[a]
	< 10 g/L	6	26.1	6	85.0	
Erythrocyte sedimentation	≥ 60 mm/hr	6	26.1	4	57.1	0.143[a]
	< 60 mm/hr	17	73.9	3	42.8	
Leukogram	≥ 10 x 10^9/L	15	65.2	5	71.4	0.571
	< 10 x 10^9/L	8	34.8	2	28.5	
Vegetation (number)	Multiple	15	65.2	4	57.1	0.515[a]
Vegetation (size)	≥ 1 cm	5	21.7	6	85.0	**0.005**[a]

* It is not calculated because there are 66.7% of expected frequencies lower than 5
[a] Fisher exact test

The predominance of staphylococci as a causal agent is due to its greater capacity for binding to the protein matrix that is formed in the catheter (biofilm), as well as its skin origin[13].

The echocardiography is a cornerstone diagnostic tool in the IE; it also allows evaluating its evolution, prognosis and hemodynamic situation. The high diagnostic positivity of this tool found in our study is related to the technological and professional quality of the laboratory, as well as to the high incidence of multiple and large vegetation, which facilitates their visualization.

In spite of the positivity of the transthoracic echocardiogram, it was decided to perform transesophageal to every patient under study, due to their greater sensitivity and specificity; in addition to providing a better visualization of the right atrium and the superior vena cava, a more precise description of the vegetation and its relation with neighboring structures. The common finding of large and multiple vegetations could be the justification for the high incidence of respiratory symptoms, as an expression of pulmonary embolism, found in our patients.

The treatment of lead-related IE requires a complete system removal for its eradication, isolated antibiotic therapy is not sufficient. Manual traction is the most commonly used technique for newly implanted wires and, in the case of chronic leads, specific extraction systems are required. If vegetation is larger than 1 cm, surgical extraction with extracorporeal circulation is recommended, given

the potential risk of pulmonary embolization[15].

The low use of percutaneous removal of leads in our series is explained by the lack of specific means of traction for this route, the high percentage of vegetations larger than 1 cm and because the leads were implanted many years ago. Their low use kept us from establishing the relationship with mortality.

Extracorporeal circulation was used in all patients, due to the possibility of working in a stationary and «dry» myocardium, and with better vegetation visualization, despite the greater operative risk.

The existence of structural heart disease was associated with higher mortality. The deterioration of the cardiovascular state implies an increased operative risk, with a high incidence of transoperative complications.

Late diagnosis of IE involves a delay in the start of specific therapy. Severe uncontrolled systemic infection leads to deterioration of the general condition of the patient, with a greater cardiovascular and systemic involvement, which leads to undergo surgery having an unfavorable clinical condition.

In the course of an infectious illness, anemia is an expression of more serious infections, longer evolution, more virulent germs, and greater deterioration of the patient's general condition. The existence of hemoglobin less than 100 g/L was associated with a higher mortality.

Large vegetations have a potential and increased risk of pulmonary embolization; that when recurrent, with or without septic pulmonary infarction, is a serious complication and implies an elevation of the surgical risk in patients with IE. In the investigation, the echocardiographic finding of vegetations greater than or equal to 1 cm was related to a higher mortality.

CONCLUSIONS

Lead-related infective endocarditis of cardiac stimulation devices should be suspected in every patient with a stimulation system that presents fever of unknown origin associated with general and respiratory symptoms, in particular if there is a history of sepsis on the system or multiple reinterventions. The positivity of blood cultures was high and staphylococcus was the most common etiologic agent. Transesophageal echocardiography was positive in the whole sample; multiple and large lead vegetations were the most common findings. Antibiotic therapy together with leads removal under extracor-poreal circulation surgery was the most widely used therapeutic option.

Mortality is high and was related to symptoms of long evolution, presence of structural heart disease, anemia and large vegetations.

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