Cardiac device-related endocarditis: Epidemiology, pathogenesis, diagnosis and treatment – a review

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S Edelstein, M Yahalom. Cardiac device-related endocarditis: Epidemiology, pathogenesis, diagnosis and treatment – a review. Int J Angiol 2009;18(4):167-172.

Cardiac device-related endocarditis (CDE) is a phenomenon for which incidence is on the rise; it presents difficult management problems to the clinician. On one hand, there is the patient who needs the implanted device, and the potential morbidity and mortality associated with its removal. On the other hand, there is the problem of a persistent infection – usually acquired during insertion of an electrical device – that is resistant to many antibiotics, has a high recurrence rate, and necessitates an extensive operation to remove the device if removal is delayed. Most studies recommend device and metal lead replacement if CDE occurs. The aim of the present review is to raise awareness of CDE among clinicians, and to provide an appropriate approach to its management.

Key Words: *Cardiac device; Defibrillator; Endocarditis; Infection; Pacemaker*

Diagnosing problems that require the implantation of cardiac modulators presents a problem to the clinician that is gradually increasing in frequency – specifically, cardiac device-related endocarditis (CDE) (related to pacemakers [PMs] and implantable cardioverter defibrillators). It is not surprising that the insertion of a foreign body into the thorax – along with at least one metal lead passing through a large blood vessel – in direct contact with the heart could lead to an infection related to the presence of foreign bodies.

Such an infection can be acquired during the insertion of the device, as a complication of sepsis and bacteria, or as a result of an infection of the soft tissue surrounding the device.

The infection may include the electrical agent (along with the 'pocket' in which the device is implanted in the subcutaneous tissue), the 'tunnel' in which the electrical lead is positioned before entry into the blood vessel (known as cardiac device infection [CDI]), or the electrode inside the blood vessel (known as CDE). Thus, it is possible for the infection to affect more than one site.

The PM and defibrillator – which is larger than the PM – are located in the subcutaneous tissue (ie, pocket), primarily in the thorax, and are connected to metal leads; afferent leads receive input from the heart, and efferent leads stimulate the heart.

Traditionally, insertion of the device leads was performed by opening the chest wall (thoracotomy) and placing the end of the lead on the epicardial tissue. In recent years, the insertion has been performed using a transverse approach, without opening the chest wall, by inserting the lead into a large main vein leading to the right atrial and ventricular endocardial tissue. The advantages of avoiding a surgical procedure are obvious. However, this new procedure provides microorganisms with a new portal of entry directly to the endocardial tissue and valves, particularly the tricuspid valve, through which the lead enters the right ventricle. The source of microorganisms can be the skin during the implantation of the electrical agent in the subcutaneous tissue, the pocket in which the electrical agent is placed (especially if a local hematoma is formed), the tunnel that forms around the lead before its point of entry into the blood vessel, or bacteria unrelated to the PM, which may be present in the form of a foreign body placed on or in contact with the endocardial tissue, or that applies pressure to the endocardial tissue and tricuspid valve.

EPIDEMIOLOGY AND PREVALENCE

The prevalence range of infection related to cardiac devices is very wide. The prevalence of CDI is between 0.13% and 19.9% (1-6) in patients who underwent implantation of a cardiac device, while the reported prevalence of CDE is between 0.5% and 7% (1-8).

CDE is divided into early- and late-onset categories, and is defined as endocarditis following the insertion of an artificial valve. Although the cut-off definition of endocarditis as it relates to an artificial valve is clear and widely accepted, the cut-off definition concerning early- and late-onset endocarditis as it relates to a cardiac device (ie, CDE) is not uniform, and has been reported to be six weeks (1), three months (9) and one year (6) following insertion of the PM.

The timing of endocarditis relative to insertion of the cardiac device is important because removal of the device and its connecting leads is technically easier during the first few months after insertion, when there is minimal scar tissue and

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TABLE 1
Modified Duke criteria for diagnosis of infective endocarditis on pacemaker leads

A. Definitive diagnosis
  1. Pathological criteria
    - Causative agents were found in cultures, or in histological vegetation, emboli or cardiac abscess
    - Causative agents were found in cultures from the electrical lead
  2. Clinical criteria
    - Two major criteria
    - One major and three minor criteria
    - Five minor criteria

B. Possible diagnosis
  - Findings appropriate for CDE that are not definitive or rejected

C. Rejected diagnosis
  - Other solid diagnoses that explain the findings;
  - Disappearance of the CDE syndrome during antibiotic treatment in less than four days; or
  - Lack of pathological proof of CDE during surgery or postmortem, and less than four days of antibiotic treatment

CDE Cardiac device-related endocarditis. Data from reference 1

collagen formation, resulting in fewer mechanical complications during removal (1). The causative agents, course of the disease and prognosis were examined relative to the initial incidence of endocarditis. While there are differences in the aforementioned parameters for endocarditis in an artificial valve, differences between the early- and late-onset CDE groups with respect to causative agents, symptoms, blood tests, echocardiographic investigations and mortality were not found.

RISK FACTORS

Cacoub et al (9) reported on 33 patients who were diagnosed with CDE, and for whom medical histories were collected. There was no difference between these patients and the general population in terms of their medical history (diabetes mellitus, malignancy, immunosuppression, etc), except for hematomas or infections in the device pocket. The prevalence of infection was higher in patients who developed CDE than in patients who had a cardiac device implanted and did not develop CDE. Laguno et al (10) reported risk factors for developing CDI, which included diabetes mellitus, malignancy, treatment with anticoagulants, treatment with corticosteroids, immunosuppression and hematoma in the pocket region following device implantation. Arber et al (7) collected retrospective data on 44 patients and reported a greater incidence (75%) of diabetes mellitus alone than in the general population. Spinler et al (11) reported risk factors for CDI and described nine CDE cases in patients with defibrillator implantation alone. The risk factors included cachexia, malignancy, diabetes mellitus and corticosteroid treatment. Smith et al (12) and Pinski et al (13) reported risk factors for CDI that included implantation by median sternotomy, prolonged operation, replacement of the electrical agent, immunosuppression, diabetes mellitus, advanced age and an additional source of infection, compared with patients who underwent implantation without opening of the chest wall. The latter group of patients was female, overweight and underwent a long procedure for catheter insertion in the operating room versus intervention in the electrophysiology laboratory.

TABLE 2
Definition of terms used in the proposed diagnostic criteria

Major criteria
  1. Positive blood cultures
    - Typical causative agents in two different cultures:
      - Viridans group streptococcus, *Streptococcus bovis*, HACEK group
      - *Staphylococcus aureus*, *Enterococcus* species – in the absence of a primary source
    - Continuous positive blood cultures
      - Positive cultures taken at least 12 h apart
      - Three of three positive cultures, or majority of four or more cultures, when there is at least 1 h between collection of the first and last cultures
  2. Echocardiographical findings
    - Intracardial pendulous mass attached to the lead or in the endocardial structure in contact with the lead
    - Abscess in contact with the lead

Minor criteria
  - Temperature greater than 38°C
  - Vascular findings: Arterial embolus, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, Janeway lesions
  - Immunological findings: Glomerulonephritis, Osler's nodes, Roth's spots
  - Echocardiography: Findings supporting CDE that do not qualify as major criteria
  - Microbiology: Positive blood cultures that do not qualify as major criteria

CDE Cardiac device-related endocarditis; HACEK Haemophilus *species (*Haemophilus parainfluenzae*,* Haemophilus aphrophilus *and* Haemophilus paraphrophilus*),* Actinobacillus actinomycetemcomitans*,* Cardiobacterium hominis*,* Eikenella corrodens *and* Kingella kingae*. Data from reference 1*

DIAGNOSIS

There is a significant delay between disease onset and diagnosis. Cacoub et al (9) reported on 33 patients in whom CDE was diagnosed, and in whom the delay from the onset of symptoms to evidence of the disease was, on average, five months (range one to 27 months). Laguno et al (10) reported an average delay of 17.5 months until the diagnosis in a series of seven patients. Victor et al (8) reported an average delay of 2.6 months (range three days to 15 months) in a series of 23 patients. Overall, based on these studies, the average reported delay in diagnosis was 5.5 months.

The criteria for CDE diagnosis are not uniform throughout different studies. Chamis et al (6) defined CDE based on the presence of the following four criteria:

- Presence of a cardiac device;
- No other source of infection;
- A positive culture for typical causative agents from the pocket of the device or its leads; and
- Echocardiographical findings of vegetation on the tricuspid valve or at the end of the electrical lead.

Several studies (7,9) used modified von Reyn criteria (14) to diagnose endocarditis in individuals who had a permanent cardiac device.

In recent studies, it was acceptable to use the modified Duke criteria (15) for endocarditis that is attributed to PM and defibrillator leads (1,6,10,11) (Tables 1 and 2). A definitive diagnosis is possible based on pathological (similar to von Reyn criteria) or clinical criteria.

TABLE 3
Clinical findings, laboratory and scan tests at presentation

Reference	Microscopic hematuria	Anemia*	WBC†	Accelerated ESR	High probability for pulmonary emboli	Peripheral emboli	Splenomegaly	Local pain around generator pocket	Chills	Fever	Patients in study, n
Klug et al (1)	NR	NR	50	93	34	NR	NR	55	NR	93	52
Cacoub et al (9)	NR	NR	NR	NR	41	>5	>5	58	NR	97	33
Arber et al (7)	59	30	66	82	NR	7	11	NR	75	91	44
Victor et al (8)	NR	NR	NR	NR	NR	NR	NR	26	96	100	23

*Data presented as % unless otherwise indicated. *Hemoglobin <110 g/L; †White blood cell (WBC) count >10×10^9/L. ESR Erythrocyte sedimentation rate; NR Not reported*

It is important to mention that it is extremely difficult to cluster the results of the reviewed studies and form conclusions due to the use of different diagnostic criteria (15), and use of other criteria that decreases the sensitivity (true positive) and specificity (true negative).

Besides echocardiography, there are other methods of diagnosing vegetations, most of which are experimental, anecdotal and of very low efficacy (8). Computed tomography for vegetation visualization is an investigative method that has not been studied thus far. Magnetic resonance imaging is contraindicated in individuals who have a PM. There are some anecdotal reports of vegetation visualization using scans of indium-labelled leukocytes.

ECHOCARDIOGRAPHY

It is well known that transesophageal echocardiography (TEE) has a much higher sensitivity and specificity than transthoracic echocardiography (TTE). Klug et al (1) reported sensitivities in visualization of PM endocarditis using TTE and TEE of 30% and 95%, respectively. Cacoub et al (9) reported both a specificity and sensitivity of 96% in identifying PM endocarditis using TEE compared with TTE, which was successful in only 15% of patients. Victor et al (8) reported similar results, in which sensitivity was 96% and specificity was 100% for TEE, and sensitivity was 30% for TTE.

All studies restated the known facts related to the diagnosis of endocarditis – to not rely on TTE for the definitive diagnosis nor to rule out CDE, and TEE should always be performed, provided there are no contraindications (1,3,4,6-10,15).

Most vegetations are shown to attach to the electrical lead, with a small portion attaching to the tricuspid valve. Victor et al (8) reported on 23 patients diagnosed with CDE. Of these, 22 patients had vegetations; 13 (59%) were attached to the lead (77% in the atrium, and 23% in the part touching the right ventricle), seven (32%) were attached to the tricuspid valve and two (9%) were attached to the coronary sinus ostium area. Cacoub et al (9) reported that, of 24 patients diagnosed with CDE, vegetations were found by TEE in 23. The location of vegetations in the study included 20 (87%) in contact with the lead, and only three (13%) on the tricuspid valve.

Victor et al (8) divided the vegetations associated with the electrical lead into three types:

1. Multiple vegetations with delicate sinuses;
2. A single round and elongated vegetation; and
3. A single line or several thick lines of vegetation.

Type 1 and 3 vegetations are associated with a higher incidence of embolic events and difficulty in estimating the vegetation size, which is an important parameter in deciding treatment.

CLINICAL SIGNS

Signs of CDE are similar to signs of typical endocarditis, with a few exceptions. Fever is the most common sign, and in most cases, has a long duration and is accompanied by chills. Some patients were admitted to hospital for investigation of fever of unknown origin. This syndrome in a patient with a cardiac device should arouse suspicion given the typical delay in diagnosis of CDE. In approximately one-half of patients, there is tenderness or there are signs of inflammation in the area surrounding the implanted cardiac device; this is most likely a manifestation of the portal of entry of microorganisms. Splenomegaly and peripheral findings as a manifestation of emboli are rare in CDE compared with endocarditis unrelated to a cardiac device. An elevated erythrocyte sedimentation rate is not common in most patients, but the prevalence of leukocytosis (50%), anemia (30%) and microscopic hematuria (59%) is lower than in typical valvular endocarditis.

Pulmonary embolus, the manifestation of a 'peripheral' embolus in right heart endocarditis, is common – both at the time of presentation and as an iatrogenic embolic event after removing the electrical lead. Approximately one-third to one-half of patients experience at least one occurrence of pulmonary embolus, and in approximately 40% of these patients, the embolus is asymptomatic.

An elaboration of the findings in several large studies is presented in Table 3.

CAUSATIVE AGENTS AND SITES OF ISOLATION

The percentage of positive blood cultures in CDE is significantly lower than in endocarditis unrelated to cardiac devices (Table 4). On the other hand, a large percentage of positive cultures were found to be from the electrical lead, which explains the inclusion of this fact as pathological criteria for a definitive diagnosis (Table 1). For a patient with suspected CDE, the recommendation at the time of evaluation is to take cultures from as many sites as possible. These cultures should include blood cultures, localized cultures from the region of the pocket in which the device was placed (if there are signs of infection) and a culture from the end of the electrical lead if it was removed. Cultures grown from samples taken from these three locations increase the probability of finding a causative agent and providing the best treatment. The most commonly isolated microorganisms are *Staphylococcus* species (70% to 100% of the positive cultures). Cacoub et al (9) reported that

TABLE 4
Categorization of causative agents by isolation site and type

Reference	GNB isolate*, %	Multiple organism isolates*, %	Amount of MRSE (%) in all STE isolates, n	Amount of MRSA (%) in all STA isolates, n	Positive culture from generator wire†, %	Positive culture from local skin‡, %	Positive blood cultures§, %	Isolates from all sites, %	Patients in study, n
Klug et al (1)	11	0	75 (25)	14 (0)	81	33	63	94	52
Cacoub et al (9)	9	18	52 (6)	21 (NR)	91	NR	82	NR	33
Arber et al (7)	25	0	25 (54)	50 (18)	NR	NR	NR	NR	44
Victor et al (8)	22	4	61 (NR)	13 (NR)	NR	NR	NR	NR	23
Spinler et al (11)	12	0	38 (NR)	50 (0)	0	88	12	89	9

**Percentage of all isolates; †Percentage of all wire samples; ‡Percentage of all local skin samples; §Percentage of all samples. GNB Gram-negative bacillus; MRSA Methicillin-resistant* Staphylococcus aureus (*STA); MRSE Methicillin-resistant* Staphylococcus epidermidis (*STE); NR Not reported*

18% of all isolates were a mixture of at least two causative agents – a fact not mentioned in other studies.

Almost all of the staphylococcal isolates contain *Staphylococcus aureus* and *Staphylococcus epidermidis*. The rest of the causative agents – Gram-negative rods, streptococci and others – are relatively small in number, particularly when compared with endocarditis unrelated to a cardiac device.

Analysis by Arber et al (7) of data from 44 patients diagnosed with CDE relating to isolation of *Staphylococcus* species found that the ratio of *S aureus* isolate to *S epidermidis* isolate is 1.1:1 for patients who are not diabetic, and 11:1 for diabetic patients (P=0.02).

An additional significant difference between CDE and valvular endocarditis unrelated to a cardiac device was that a small percentage of CDE cases were resistant to methicillin in *Staphylococcus* species in general, and *S epidermidis* in particular (Table 4). It is acceptable to assume all *S epidermidis* infections and most *S aureus* infections in the cardiac device and artificial valve were acquired in the hospital, where the percentage of methicillin-resistant bacteria is high; methicillin-resistant bacteria are associated with artificial valve endocarditis. A small percentage of resistant cases may be explained by infection acquired in the community, and not at a hospital (community-acquired infections are not associated with artificial valve endocarditis).

TREATMENT

The possible approaches to the treatment of CDE are antibiotic treatment only (medical treatment [MT]) or a combination of antibiotic treatment and removal of the electrical leads with or without the device itself (surgical/medical treatment [SMT]). There are no prospective studies that compare MT with SMT. There are some reports of MT alone, which on occasion was curative, but in most patients there was an exacerbation of CDE-related bacteremia, and severe complications such as pericarditis, bronchopleural fistulas or uncontrollable sepsis.

Removal of the electrical lead can be performed in one of two ways – by opening the chest wall or by pulling the lead (external traction). External traction is problematic in three aspects. First, a blood clot will usually develop in the cardiac space and attach to the lead. Pulling the lead could result in releasing the clot and causing an embolus. Second, pulling the lead through the tricuspid valve is occasionally accompanied by mechanical damage to the endocardial wall or, more frequently, to the tricuspid valve, on occasion creating a hemipericardium and tamponade, and fatal arrhythmia such as ventricular tachycardia or ventricular fibrillation. Third, six to eight weeks after the insertion of the lead, neoepithelization takes place and fibrocollagen tissue affixes to the surrounding tissue along the lead, which makes pulling the lead by external traction very difficult if it is performed after this process has started (10,16).

Klug et al (1) reported their attempt at MT, quoted another source (2) and recommended the immediate removal of the entire PM system in CDE patients. According to the authors, replacement of the PM system should be considered in every CDI case. As for the method of removal of the leads, one study designed a flowchart based on studies by Mugge et al (17) and Robbins et al (18). With the presence of large vegetations (10 mm or more), the PM system should be removed by opening the chest wall. In patients with small vegetations (less than 10 mm), the lead is only removed by external traction. There were no embolic complications at the time of external traction, and the authors questioned the safety of pulling the lead, even with the presence of larger vegetations. Based on a review of the literature, it appears that the recommendation to avoid external traction of the leads in the presence of large vegetations is simply a 'gut feeling' and not a decision based on fact (evidence-based medicine). There are few reported cases of external traction of the leads in the presence of huge vegetations (40 mm) with morbidity and mortality. The authors themselves opposed vegetation size as a restriction at the time of this prospective study. Laguno et al (10) described seven patients suffering from CDE. One patient underwent immediate removal of the lead along with antibiotic treatment and recovered, while in the other six patients, there was an initial attempt to treat with antibiotics (MT). In all six patients, MT failed and lead removal was required. One patient died during the antibiotic treatment due to intracranial hemorrhage. In three patients, eradication of the causative agents failed or the endocarditis syndrome did not disappear, necessitating urgent removal of the lead (two by external traction and one by opening the chest wall). Two patients responded to treatment, but there was a recurrence 15 months following the conclusion of a six-week treatment period, which necessitated the removal of the most recently inserted leads by external traction.

Victor et al (8) presented 23 CDE patients treated with a combination of antibiotic therapy and external traction of the leads. Follow-up was between two and 70 months, with one patient not completing the follow-up. Only one patient died of persistent candidemia (*Candida glabrata*) two months after the

TABLE 5
Therapeutic approaches, complications and mortality. Summary of 184 patients

Reference, year	Mortality associated with PM, %		Mortality, %		Total events ending with wire removal, %	Complications		SMT		SMT as IT	MT failure	MT as IT	Patients, n
	SMT	MT	SMT	MT		ET*	TO*	With ET	With TO				
(20) 1981	0	–	0	–	100	NR	NR	NR	NR	NR	NR	NR	44
(19) 1988	0	–	0	–	100	NR	NR	NR	NR	NR	NR	NR	9
(7) 1994	NR	NR	25	46	57	NR	NR	NR	NR	NR	NR	NR	44
(11) 1998	22	–	22	–	100	–	3 (33)	0	9 (100)	6 (67)	3 (100)	3 (33)	9
(10) 1998	0	100	0	100	100	2 (40)	0	5 (83)	1 (17)	1 (14)	6 (100)	6 (86)	7
(9) 1998	NR	–	24	–	100	NR	NR	NR	NR	NR	NR	NR	33
(8) 1999	4	–	17	–	100	0	0	18 (78)	5 (22)	23 (100)	–	0	23
(6) 2001	17	100	17	67	100	NR	NR	NR	NR	12 (80)	2 (67)	3 (20)	15
Total	NC	100	14	46–100	~100	NC	NC	NC	NC	(90)	(90)	NC	184

*Data presented as n (%) unless otherwise indicated. *Except death. ~ Approximately; ET External traction; IT Initial treatment; MT Medical treatment; NC Not conclusive; NR Not reported; PM Pacemaker; SMT Surgical/medical treatment, TO Thoracotomy*

insertion of the PM, and three patients died nine, 20 and 24 months following PM implantation, respectively – all due to causes unrelated to the PM. Studies of treatment, complications and mortality are summarized in Table 5. In analyzing the table, the small total number of subjects should be noted; the number of patients in each study was small, the criteria for diagnosis of CDE were not identical in the different studies (refer to the Diagnosis section) and the treatment details were incomplete. A great deal of information is lacking in the body of the studies (designated in the table as 'not reported' [NR]), and a large portion of the information may have been incorrectly interpreted due to the lack of a full report. For example, in the report on mortality in patients treated with MT, only a partial number is reported because patients whose treatment failed (eg, persistent bacteremia in spite of treatment) were required to undergo external removal of the leads. Thus, the results of this group were transferred to the combination treatment group (SMT), and the mortality (even if it occurred following failure of two weeks of MT and one day following the removal of the leads) was recorded as mortality in the SMT group, even though the mortality should have been attributed to the failure of MT and the delay in removal of the lead.

In spite of the mentioned limitations, and with the absence of prospective studies that compare MT and SMT, it is unclear why the recommended treatment is controversial. Approximately 90% of patients received SMT as the initial treatment, and almost all eventually underwent removal of the electrical lead, either as the initial treatment or treatment following failure of MT. Even with the small number of cases, it is possible to say that most lead removal procedures were performed by external traction and only a minority were performed by thoracotomy. The rate of complication associated with lead removal was low (although the numbers are too small for quantitative analysis) regardless of whether they were performed by external traction or thoracotomy. The mortality associated with MT alone is high (46% to 100%), which is difficult to quantify due to the small number of cases, compared with the mortality associated with SMT (14%). The large percentage of patients who underwent lead removal, along with low complication and mortality rates in patients who underwent lead removal compared with those treated with antibiotics alone, make SMT the treatment of choice in every patient with CDE. MT alone is not recommended and should be reserved only for those patients who refuse lead removal, or for those in whom lead removal would result in grave complications.

SUMMARY

CDE is a phenomenon for which incidence is on the rise as a result of diagnostic and technological advances. The prevalence of CDI ranges between 0.13% and 19.9%, and the prevalence of CDE ranges between 0.5% and 7%.

The definition of early and late CDE is not uniform, as it is with infective endocarditis of the artificial valve. There is a significant delay in diagnosing CDE – an average of 5.5 months from clinical onset – that the clinician should be aware of any time a clinical sign or symptom (eg, fever, redness, tenderness, hematoma, etc) develops in a patient who previously underwent cardiac device insertion.

The percentage of positive blood cultures among all blood cultures in CDE is relatively low compared with infective endocarditis of the native or artificial valve. The clinician must insist on taking cultures from any suspected site of infection related to the catheter, lines or device before antibiotic initiation.

The definition of CDE is based on the modified Duke criteria: a significantly low prevalence of accompanying classical symptoms and signs compared with classical infective endocarditis. The most common pathogens are *Staphylococcus* species (*S aureus* and *S epidermidis* – one-half each). Typically, the prevalence of methicillin-resistant cocci in CDE is low compared with prevalence in infective endocarditis of an artificial valve.

The recommended treatment approach is a combination of wire removal (surgically or by traction) along with antibiotic therapy. An MT approach is not recommended due to the high rate of failure and recurrent exacerbation of the infective endocarditis.

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