Original Article

Detection of Biofilm-associated Implant Pathogens in Cardiac Device Infections: High Sensitivity of Sonication Fluid Culture Even in the Presence of Antimicrobials

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Abstract

Introduction: Sonication showed more sensitivity than traditional culture in the diagnosis of device infections. Aims of the study were to assess the role of sonication in the microbiological diagnosis and management of cardiac device infections (CDIs), to evaluate the sensitivity of sonication in patients on antimicrobial therapy at the time of device removal, and to analyze biofilm formation of the isolated strains. **Materials and Methods:** A total of 90 devices (31 generators and 59 electrodes) collected from 31 patients with infection underwent sonication before culture. Devices were sonicated for 5 min and centrifuged at 3200 rpm for 15 min. Intraoperative traditional cultures were performed in 26 patients. Microorganisms were identified using conventional methods. Staphylococcal strains were tested for slime production. **Results:** Microbiological diagnosis was achieved in 28 patients (90%). Sonicate fluid was positive in 68/90 (76%) of devices (27/31 [87%] generators and 41/59 [69%] electrodes), whereas intraoperative pocket swabs grew bacteria in 10/26 patients (38%, $P = 0.0007$). Among leads, 37/59 (62.7%) yielded bacteria even in the absence of vegetation. Coagulase-negative Staphylococci accounted for 83.8% (57/68) of the total; *Staphylococcus aureus* and Gram-negative bacilli were found in 4.4% (3/68) and 5.8% (4/68), respectively. Biofilm production was present in 15/22 (69%) staphylococcal strains. Overall, patients on therapy ($n = 23$) had a microbiological diagnosis in 20/23 (86.9%) and 7/22 (30.4%) through sonication and intraoperative cultures, respectively ($P = 0.0002$). **Discussion:** Our data showed the high sensitivity of sonication in the diagnosis of CDIs, even in patients under antimicrobial therapy. **Conclusion:** Sonication represents an essential tool for both diagnosis and management of CDIs.

Keywords: Biofilm, cardiac device infections, sonication technique, staphylococcus, traditional cultures

Introduction

Cardiac implantable electronic device (CIED) infections are life-threatening conditions associated with significant morbidity, mortality and rising global health-care cost.[1]

Their incidence has increased over the time, with an estimated rate of infections between 0.13% and 19.9%.[2,3]

A clear diagnosis of cardiac device infections (CDIs) is of crucial importance to start an appropriate antimicrobial therapy.[4] Traditional pocket swabs and tissue specimens exhibit low sensitivity and specificity for diagnosing CIED infections,[5] whereas blood cultures are generally positive only in case of systemic dissemination[6] and up to 30% of CDIs are culture negative.[7] Moreover, a previous antimicrobial therapy may hamper the diagnostic yield of traditional cultures.[3,4]

CIED infections are characterized by the formation of biofilm, in which bacteria are present in a stationary growth phase and are more resistant to antibiotics than their planktonic counterpart.[8]

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The sonication method, which is based on the application of long-wave ultrasound, has been used to enhance bacterial detection by liberating sessile organisms embedded in biofilms on foreign bodies.[9,10] In the setting of prosthetic joint infections (PJIs), pathogen detection rate was shown to be higher in the sonication fluid than in traditional culture.[9] In a previous study, we were able to demonstrate that sonication fluid culture had higher sensitivity than conventional culture in CDIs.[11] According to these results, in our hospital, the sonication method has been introduced in the routine clinical practice both in PJIs and CDIs.

On the basis of these considerations, the present study was undertaken with the following objectives: (i) to further assess the role of sonication in the microbiological diagnosis of CDIs in the clinical practice; (ii) to identify patients at major risk of developing device-related endocarditis throughout the sonication of different device components; (iii) to evaluate the sensitivity of sonication method in patients on antimicrobial therapy at the moment of device removal; and (iv) to analyze biofilm formation of the staphylococcal strains isolated from culture after sonication.

Materials and Methods

All consecutive patients who underwent explantation of permanent pacemaker (PPM) or implantable cardioverter defibrillator (ICD) because of infection at the Electrophysiology Service at Sapienza University of Rome were included in the study. Patients gave informed written consent, and the study protocol was approved by the local ethics committee.

Diagnosis of CDI was made according to the international definitions of pocket infection and device-related endocarditis.[12,13]

Device removal was performed under aseptic condition in the cardiac electrophysiology laboratory by interventional electrophysiologists who have been specialized in CIED implantation and extraction. Lead extraction was performed manually with or without the assistance of traction devices including stylets, locking stylets (Lead Locking Device 1, 2, and EZ LLDTM, Spectranetics®, Colorado Springs, CO, USA), snares, laser, or radiofrequency.[14,15]

A complete device removal including generators, atrial and/or ventricular leads was performed, and the collected devices, placed in different sterile containers, were submitted to culture after sonication. Blood cultures (n = 3 for each patient) and intraoperative pocket swabs were performed in 24 (77.4%) and 26 (83.8%) patients, respectively.

All samples reached the microbiology laboratory within 3 h from the collection.

The sonication process was performed as previously described.[16,17] Briefly, after collection, devices were covered with sterile NaCl 0.9% or Ringer's solution then vortexed for 30 s, sonicated for 5 min at a frequency 40 ± 2 kHz and power density 0.22 ± 0.04 W/cm^2, vortexed again for 30 s, and centrifuged at 3200 rpm for 15 min. The BactoSonic (BANDELIN electronic GmbH & Co. KG) was used for sonication. Anaerobic and aerobic sheep blood agar plates were incubated at 37°C for up to 10 days, and the microorganisms were identified using conventional methods. The VITEK-2 (Bio-Merieux, Marcy l'Etoile, France) system was used to perform the antimicrobial susceptibility testing. Given that daptomycin MIC was not performed by VITEK-2 system, we evaluated daptomycin MICs 50/90 by macrobroth dilution method with a final bacterial inoculum of ≈5 × 10^5 CFU/mL.

Staphylococcal strains were tested for slime production by a modification of the Christensen method.[18] Briefly, 10 ml volume of tryptic soy broth (TSB) in plastic test tubes was inoculated with single colonies and incubated statically for 48 h at 37°C, after which the contents were decanted, and 1 ml volume of a 0.4% aqueous solution of trypan blue (Sigma Chemical Co, St Louis, Missouri, USA) was added. Each tube was then gently rotated to ensure uniform staining of any adherent material on the inner surface and the contents decanted. The tubes were then placed upside down to drain. A positive result was indicated by the presence of an adherent layer of stained material on the inner surface of the tube. The presence of stained material at the liquid–air interface alone was not regarded as indicative of slime production. Tubes filled with TSB only were considered as negative controls. The amount of slime production was classified as absent (0) and present (1).

All experiments were run in triplicate.

Statistical analyses were performed using GraphPad Prism version 7 (GraphPad Software MacKiev). Categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate. Continuous data were analyzed with Student's t-test or the nonparametric Mann–Whitney in case of values not normally distributed. $P < 0.05$ was considered statistically significant.

Results

Characteristics of population

A total of 31 patients (21 M, 10 F, mean age 74.5 ± 11.2 years) underwent device removal throughout transvenous lead extraction because of infection: 29 had pocket infection and 2 had device-related endocarditis. The collected devices were 90, distributed as follows: 31 generators (28 PPM and 3 ICD) and 59 electrodes [Figure 1]. In addition, in 26 patients, pocket swab was performed. Twenty-two out of 31 patients (70%) had a previous pocket revision before the onset of the infection with a median duration of device placement of 623 days (range: 41–2950). Fever was present only in 37.9% of the patients (11/31), whereas signs of pocket infection were predominant (decubitus in 19/31, pocket tenderness in 21/31, and fistula in 10/31). Median time from device explantation to re-implantation was 5.65 days (range: 0–29).

General characteristics of population are summarized in Table 1.

Microbiological analysis

Blood cultures were positive for bacterial growth in 5 out of 24 patients (20%): *Staphylococcus epidermidis* and *Corynebacterium striatum* (>3 blood cultures each) in the patients with device-related endocarditis and coagulase-negative Staphylococci (CoNS) in 3 patients with pocket infection (1 blood culture each).

Culture after sonication of the device led to a definite microbiological diagnosis in 28 patients (90%).

Pocket swab yielded bacteria in 10 out of 26 (38%) patients, whereas sonicate fluid was positive in 68/90 (76%) of devices ($P = 0.0007$). Considering the different components of the devices, 27/31 (87%) generators and 41/59 (69%) electrodes (atrial and/or ventricular) grew bacteria in the sonication fluid ($P = 0.07$). In one case, generator culture was sterile and microbiological diagnosis was only possible after the culture of electrodes. Cultures from generators and electrodes yielded the same microorganism in the totality of cases. With the exception of 4 electrodes collected from the 2 patients with device-related endocarditis, 37 out of 59 leads (62.7%) yielded bacteria even in the absence of vegetations at echocardiography.

CoNS accounted for 83.8% (57/68) of the total whereas *Staphylococcus aureus* and Gram-negative bacilli including *Pseudomonas aeruginosa* and *Klebsiella spp.* were found in 4.4% (3/68) and 5.8% (4/68) of the total, respectively. As expected, *S. epidermidis* was the predominant microorganism causing CDI (48/68, 70.5%) followed by *Staphylococcus hominis* (7/68, 10.3%). *Staphylococcus haemolyticus* and *Staphylococcus capitis* accounted each for 1.4% of the total. A multidrug-resistant *C. striatum* causing device-related endocarditis was found in 3 out of 68 samples (4.4%) [Table 2].

Among CoNS, resistance to oxacillin was found in 41 out of 57 (72%). Daptomycin was *in vitro* effective against all the *Staphylococcus spp.* strains, with a MIC 50/90 of 0.25 µg/ml.

Microbial biofilm production

Biofilm production was evaluated in 22 staphylococcal strains: 15 (69%) strains were biofilm producers. When considering the bacterial species, 73% of *S. epidermidis*, 67% of *S. aureus*, and *S. hominis* produced biofilm. No statistical differences among staphylococcal species were observed in biofilm production ($P = 0.9$).

Antimicrobial therapy and sensitivity of sonication fluid culture

Among the patients with CDI ($n = 31$), 23 out of 28 patients (82.1%) were on therapy at the moment of device removal. Overall, bacterial growth was shown in 20/23 (86.9%) and 7/22 (30.4%) patients on therapy through sonication and intraoperative cultures, respectively ($P = 0.0002$) [Table 2].

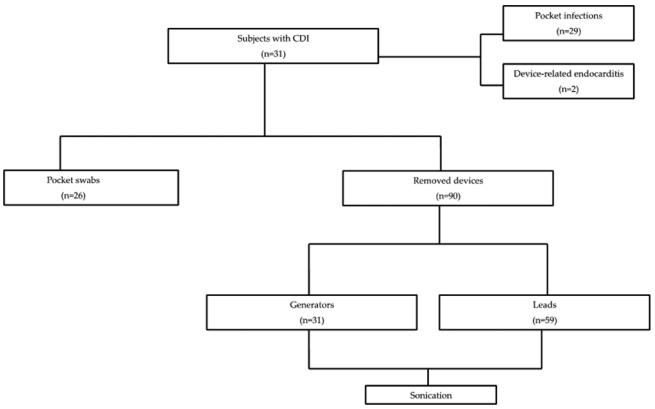

Figure 1: Diagnostic flowchart. A total of 90 device components (31 generators and 59 leads) collected from 31 patients (29 with pocket infection, 2 with device related endocarditis) were included in the study. Intra-operatory pocket swabs were performed in 26 patients. Leads included atrial and/or ventricular leads

Table 1: General characteristics of study population (*n*=31)

Characteristics	Subjects with CDI, *n* (%)
Mean age, year	74.5±11.2
Males, *n* (%)	21 (67.7)
Females, *n* (%)	10 (32.3)
Type of implanted device *n* (%)	
PPM	28 (90.3)
ICD	3 (9.7)
Reason for Device implantation, *n* (%)	
Sick sinus syndrome	4 (12.9)
Atrioventricular block type III	9 (29)
Chronic atrial fibrillation	7 (22.5)
Secundary prevention	2 (6.4)
Other	9 (29)
Median (range) duration of device placement, days	623 (41-2950)
Previous pocket revision, *n* (%)	22 (70)
Anticoagulant therapy, *n* (%)	14 (45)
Symptoms	
Fever	11 (37.9)
Fistula	10 (41.6)
Pocket tenderness	21 (72.4)
Decubitus	19 (65.5)
Median (range) duration of symptoms, days	47.14 (3-234)
Median (range) time from device explantation to re-implantation, days outcome	5.65 (0-29)
Survival	29 (93.5)
Complication	1 (3.2)
Death	1 (3.2)

CDI: Cardiac device infection; PPM: Permanent pacemaker; ICD: Implantable cardioverter defibrillator

On the other hand, all the patients who were not on therapy at the moment of device removal had a positive culture

Table 2: Microbiology of cardiac device infections

	Subjects with CDI (*n*=31), *n* (%)	Subjects on therapy (*n*=23), *n* (%)	Devices (*n*=90), *n* (%)	Generators (*n*=31), *n* (%)	Electrodesa[a] (*n*=59), *n* (%)	Microorganisms (*n*)
Sonication (positive cultures)	28/31 (90)	20/23 (86.9)	68 (76)	27 (87)	41 (69)	*S. epidermidis* (48); *S. hominis* (7); *S. aureus* (3); Gram-negative bacilli (4); *S. haemolyticus* (1); *S. capitis* (1); *C. striatum* (3); *C. amycolatum* (1)
Intraoperative pocket swab (positive cultures)[b]	10/26b (38.4)*	7/22 (30.4)**	NA	NA	NA	Coagulase-negative Staphylococci (9); *S. aureus* (1)
Blood cultures (positive cultures)	5/24 (20)	5/23 (21.7)	NA	NA	NA	*S. epidermidis* (1); *C. striatum* (1); Coagulase-negative *Staphylococci* (3)

*P=0.0007; **P=0.0002, [a]Include atrial and/or ventricular electrodes. [b]Intraoperative pocket swab were performed on 26 subjects.
S. epidermidis: *Staphylococcus epidermidis, S. Hominis*: *Staphylococcus hominis*, *S. Haemolyticus*: *Staphylococcus haemolyticus*, *S. capitis*: *Staphylococcus capitis*, *C. striatum*: *Corynebacterium striatum*, *C. amycolatum*: *Corynebacterium amycolatum*, *S. Aureus*: *Staphylococcus aureus*, CDI: Cardiac device infection, NA: Not available

(5/5, 100%) after sonication treatment, compared with 3/4 (75%) through intraoperative cultures (P = 0.44).

According to the duration of antimicrobial therapy before the explantation (> or <14 days), we found that 15/18 (83.3%) patients who were on therapy >14 days had a positive culture whereas all the patients who were on therapy <14 days had a positive culture (5/5, 100%, P = 0.13).

Discussion

The incidence of CDIs has increased over the time independently of the growing relative proportion of implantable cardiovascular devices implants.[2] Due to the wide variety of presenting symptoms,[19] identifying the causative microorganism of CDIs is essential to institute appropriate antimicrobial therapy. Sonication before culture showed higher sensitivity in bacterial detection than conventional cultures[10,11] due to the fact that bacteria, which are adherent to the device and embedded in the biofilm, can be efficiently dislodged from foreign body throughout this technique.[20-22]

However, the usefulness of sonication might rely not only on the microbiological diagnosis but also on understanding the pathogenesis of CDI. In this setting, it is important to collect and analyze both generators and electrodes to establish how and when electrodes are colonized or infected by bacteria. In fact, knowing which type of patient is at major risk of developing endocarditis compared to those who only develop pocket infection might have important clinical and therapeutic implications. Although several studies had been focused on the pathophysiology of CDIs, there is still a lack of certain data about the source of device infection, with local perioperative wound contamination and hematogenous seeding being the two involved mechanisms.[4,19,23] In our study, generators yielded bacteria in 87% (28/31) whereas electrodes showed bacterial growth in 69% (41/59). Among leads, 37/59 (62.7%) yielded bacteria even in the absence of vegetations at echocardiography. This finding is consistent with the hypothesis that bacteria first infect generators and then lead tips and that patients who present with signs and symptoms of pocket infection usually have involvement of the intravascular components of the system.[21]

Our data confirmed the high sensitivity of sonicate culture (90%) in the diagnosis of CDI; thus, sonication should always be performed in the microbiology laboratory to provide information regarding the causative agents and the best therapeutic approach in CDIs. However, still, a percentage of infection had no bacterial isolation, especially in patients on therapy >14 days before device removal.[5] In this setting of patients, the use of additional techniques such as molecular methods, which are less hampered by a previous antimicrobial therapy, might improve the bacterial detection rate.[24]

For biofilm detection, we performed the Christensen method in plastic tubes, which has been shown to correlate well with other methods such as scanning electron microscopy.[25] We classified the amount of slime production as absent or present, and we showed that 69% of staphylococcal strains were biofilm producers. However, this percentage might have been underestimated due to the difficulty in discriminating between weak and biofilm-negative isolates throughout the tube method.[25]

Although frequently regarded as contaminants, CoNS became of clinical relevance in the setting of device infections.[26] In fact, we found that the majority of CDIs were caused by *Staphylococcus* species (60/68, 88.2%), supporting the concept that wound contamination at the time of implantation or during the device procedure is crucial in the development of subsequent infection.

Furthermore, the finding that the majority of staphylococcal strains were biofilm producers suggests that biofilm formation is a key factor in the development of CDIs, representing a survival strategy through which microorganisms can attach to foreign bodies and better resist antibiotics and host defense system. In biofilm, microorganisms can be up to 1000-fold more resistant to antimicrobials than their planktonic counterparts.[8] Therefore, infections in the presence of an implant are persistent and difficult to eradicate, and removal of all foreign-body material is needed.

In our study, 72% of Staphylococcal strains were resistant to methicillin: this finding may be explained by the fact that a

previous pocket revision was frequent in our population (70%). Since antimicrobial susceptibility pattern is relevant for the selection of empirical treatment and considering that most of CoNS and *S. aureus* causing CDIs are nowadays methicillin resistant, clinicians who treat these infections should be aware that beta-lactams might be ineffective and that first choices should include vancomycin or daptomycin.[4] Daptomycin has more advantages than vancomycin: first, it is active against biofilm bacteria; then, it is more rapidly bactericidal toward staphylococcal strains; and finally, daptomycin has fewer side effects, especially regarding renal toxicity.[27,28] Thus, in the setting of CDIs, daptomycin might be considered as the best antimicrobial acting against staphylococcal biofilm. In the present study, all the tested staphylococcal strains were sensitive to daptomycin, highlighting the increasing role of this drug in the setting of biofilm-associated infections.

In our study, Gram-negative bacteria were detected in only 5.8% (4/68) of devices, showing a lower percentage than other published evidence,[5] which found Gram-negative bacilli as the causative organisms in 27.4% of CDIs. This finding might have important therapeutic implications in our institution, where empirical treatment usually does not cover Gram-negative bacilli.

As expected, the more the patient is on therapy before device explantation, the more is the possibility to have a negative culture. This is especially true for traditional culture, which is hampered by a previous or concomitant antimicrobial therapy. Conversely, the sonication technique, which acts by dislodging bacteria embedded in the biofilm, has been shown to retain its value in the microbiological diagnosis of prosthetic joint infections, even in the presence of antimicrobials.[9] In fact, planktonic bacteria are more sensitive to the inhibitory effect of anti-infective agents than are biofilm bacteria.[9] In the present study, sonication culture confirmed its high sensitivity even in those patients who were on antimicrobial therapy at the time of device removal, especially when compared with traditional intraoperative cultures ($P = 0.0002$).

Furthermore, among patients on antimicrobial therapy, 83.3% of patients who were on therapy >14 days and 100% of patients who were on therapy <14 days showed bacterial growth, thus highlighting the usefulness of sonication method even in the setting of previous antimicrobial use. This finding is of particular relevance because it is not uncommon that patients with CDI are given antimicrobial therapy before the complete removal of the device. Moreover, patients with a definite or suspected diagnosis of device-related endocarditis surely receive preoperative antimicrobial therapy; in this specific setting, the sonication of the explanted device might represent a pivotal add-on to reach the microbiological diagnosis of the infection and to establish the most appropriate therapy.

Conclusion

Our data confirmed the high sensitivity of sonication before culture in the diagnosis of CDIs, even in patients on antimicrobial therapy. In addition, sonication might give physicians' important information regarding the pathogenesis of these infections by early detecting patients who are at major risk of developing device-related endocarditis.

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Conflicts of interest

There are no conflicts of interest.

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