Bacterial Colonization and Infection of Electrophysiological Cardiac Devices Detected With Sonication and Swab Culture

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Background—Electrophysiological cardiac devices are increasingly used. The frequency of subclinical infection is unknown. We investigated all explanted devices using sonication, a method for detection of microbial biofilms on foreign bodies.

Methods and Results—Consecutive patients in whom cardiac pacemakers and implantable cardioverter/defibrillators were removed at our institution between October 2007 and December 2008 were prospectively included. Devices (generator and/or leads) were aseptically removed and sonicated, and the resulting sonication fluid was cultured. In parallel, conventional swabs of the generator pouch were performed. A total of 121 removed devices (68 pacemakers, 53 implantable cardioverter/defibrillators) were included. The reasons for removal were insufficient battery charge (n=102), device upgrading (n=9), device dysfunction (n=4), or infection (n=6). In 115 episodes (95%) without clinical evidence of infection, 44 (38%) grew bacteria in sonication fluid, including Propionibacterium acnes (n=27), coagulase-negative staphylococci (n=11), Gram-positive anaerobe cocci (n=3), Gram-positive anaerobe rods (n=1), Gram-negative rods (n=1), and mixed bacteria (n=1). In 21 of 44 sonication-positive episodes, bacterial counts were significant (≥10 colony-forming units/mL of sonication fluid). In 26 sterilized controls, sonication cultures remained negative in 25 cases (96%). In 112 cases without clinical infection, conventional swab cultures were performed: 30 cultures (27%) were positive, and 18 (60%) were concordant with sonication fluid cultures. Six devices and leads were removed because of infection, growing Staphylococcus aureus, Streptococcus mitis, and coagulase-negative staphylococci in 6 sonication fluid cultures and 4 conventional swab cultures.

Conclusions—Bacteria can colonize cardiac electrophysiological devices without clinical signs of infection. (Circulation. 2010;121:1691-1697.)

Key Words: sonication ■ pacemaker, artificial ■ cardioverter-defibrillators, implantable ■ bacteria ■ infection
**Methods**

**Study Population**
We performed a prospective, observational, single-center cohort study in a tertiary care hospital in Luzern, Switzerland. At the beginning of the study, in October 2007, the hospital cared for 1740 patients with implanted cardiac PMs and ICDs. All adult patients in whom the cardiac electrophysiological device was removed for any reason between October 2007 and December 2008 were considered eligible for this study. During this time period, 123 devices in 121 patients were explanted. Two patients, in whom the device was inappropriately stored, were excluded from the study, resulting in a total of 119 participating patients (Figure 1). The following baseline characteristics were assessed: age, sex, diabetes mellitus, heart failure, hypertension, renal failure, chronic liver disease, immunosuppressive therapy, history of infective endocarditis or generator pocket infection, device type (PM/ICD), device position, indwelling time, antibiotic prophylaxis before and operation time during implantation, number of previous device changes, and hematoma after implantation. Patient records were summarized with a standardized case report form to retrieve demographic, clinical, microbiological, and laboratory data. The study protocol was approved by the local ethical committee. All patients signed an informed consent.

Underlying medical conditions were defined as follows: chronic heart failure (New York Heart Association stage II to IV), chronic renal failure (creatinine level >104 μmol/L, >1.18 mg/dL), chronic liver disease (Child classification stage B and C), diabetes mellitus (type I and II), and immunosuppressive therapy (long-term use of corticosteroids >25 mg prednisone-equivalent/d for the past month at least or methotrexate).

Infection was diagnosed as either local infection of the generator pocket (acute inflammation with redness, local warmth, pain, swelling, or purulent drainage intraoperatively or through skin erosion, but without systemic inflammatory symptoms) or PM/ICD-associated infectious endocarditis, defined by the Duke criteria: A definitive diagnosis of endocarditis was made if 2 major criteria, 1 major and 3 minor criteria, or 5 minor criteria were fulfilled. Major criteria include (1) persistently positive blood cultures or (2) transesophageal echocardiographic evidence of endocardial involvement (oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material, dehiscence of prosthetic valve, or new valvular regurgitation). Minor criteria include (1) predisposing heart condition or intravenous drug use, (2) fever (core temperature >38°C), (3) vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions), (4) immunologic phenomena (glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor), (5) positive blood culture but not meeting the major criterion, or (6) echocardiographic findings consistent with infective endocarditis but not meeting the major criterion.

**Removal of Devices**
Removal of devices was performed in the electrophysiology laboratory or in the operation theater. Routine antibiotic prophylaxis was given immediately before start of operation. Skin was prepared by shaving followed by application of 50% isopropyl alcohol, 1% povidone-iodine solution (Braunoderm) 3 times and by draping with sterile cloths. Before closing, the wound was disinfected again with 7.5% povidone-iodine solution (Braunol). Generators (and leads, if removed) were aseptically removed and placed in solid air-tight containers. NaCl 0.9% was added until coverage of the device in order to prevent drying out.

In case of noninfected devices, the new generator was placed into the same pocket. In case of clinical signs of infection, the new device was placed on the other side of the chest after completion of antibiotic treatment. Patients with no signs of infection did not receive antibiotic treatment, even if bacteria were found.

**Sonication of Removed Devices**
Containers were transported to the microbiology laboratory within 24 hours of removal. The container was vortexed for 30 seconds, sonicated for 1 minute at a frequency $40\pm2$ kHz and power density $0.22\pm0.04$ watts/cm², as determined by a calibrated hydrophone.
Conventional Microbiological Methods

Intraoperative swabs from the generator pocket were collected after removal of the device. Cotton-tipped swabs were placed in Amies agar, then incubated for 48 hours. An additional sheep blood agar plate was incubated for 5 days. Thioglycolate was used for enrichment. Organisms were identified using routine microbiological techniques. No microorganism was isolated.

Outcomes

Microbiological outcome was defined as growth of bacteria in sonication or swab culture. Concordance of the 2 microbiological methods was defined as detection of the same or no microorganism in swab and sonication of a device by standard microbiological methods irrespective of the amount of bacteria. If quantity of microorganism was considered, it is stated in the text.

After device change, patients were routinely seen every 6 to 12 months to control device function and to check for signs of infection. Follow-up lasted until November 15, 2009. Clinical outcomes (death, device infection, removal/change of device for any reason) were assessed at the end of follow-up. If a patient could not be seen, the patient or the doctor providing follow-up care was contacted by phone.

Statistical Analysis

All analyses were performed using STATA software version 9.2 for Windows. For graphical analysis, Origin software (version 8; Origin Laboratory Corp, Northampton, Mass) was used. According to the descriptive nature of the statistical analysis, no significance testing was used. To analyze the occurrence of clinical infection during follow-up in patients with sonication and/or swab positive cultures but no clinical infection at baseline, the incidence (percent) of infection was estimated and exact 95% binomial confidence limits were calculated.

Results

Study Population and Devices

In October 2007, 1740 patients with electrophysiological devices were followed up regularly. Until December 2008, 123 devices had to be removed in 121 patients because of insufficient battery charge (n = 104), device upgrading (n = 9), device dysfunction (n = 4), or infection (n = 6). During 14 months, 6 of 1740 patients developed an infection. This corresponds to an approximate incidence of clinical infection of 0.3%/yr. Two patients with insufficient battery charge of the device were excluded because of inadequate storage of the device. Baseline characteristics of the included 119 patients are summarized in Table 1. Characteristics of the 121 devices, of which 68 (56%) were cardiac PMs and 53 (44%) were ICDs, are shown in Table 2.

Episodes With Infection

Of the 6 cases with infection, generator pocket infection was diagnosed in 4 cases and PM/ICD-associated infective endocarditis in 2 cases (Table 3). All infected devices (3 PMs and 3 ICDs) were completely removed, including the corresponding leads. Antibiotic therapy was started after explantation of the device in the 4 cases of generator pocket infection and 2 weeks before explantation in the 2 cases of PM/ICD-associated infective endocarditis. In both patients with PM/ICD-associated infective endocarditis, transthoracic echocardiography showed vegetation on the lead and blood cultures were positive.

Before removal of the device, serum markers for inflammation were determined. For 4 cases with generator pocket infection, median C-reactive protein was 8.5 mg/L (95% confidence limits, <5 to 50 mg/L) and median procalcitonin was 0.07 µg/L (95% confidence limits, 0.04 to 0.11 µg/L). In cases with infective PM/ICD-associated endocarditis (n=2), C-reactive protein was 131 and 173 mg/L, respectively, and procalcitonin was 1.25 and 31 µg/L, respectively.

The 4 cases of generator pocket infection were caused by CNS in 3 patients and S. aureus in 1 patient. The PM-
Table 2. Characteristics of 121 Electrophysiological Cardiac Devices

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of removed device,* n (%)</td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>68 (56)</td>
</tr>
<tr>
<td>ICD</td>
<td>53 (44)</td>
</tr>
<tr>
<td>Anatomic position of the device, n (%)</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>112 (92)</td>
</tr>
<tr>
<td>Submuscular†</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Reason for device removal, n (%)</td>
<td></td>
</tr>
<tr>
<td>Insufficient generator charge</td>
<td>102 (84)</td>
</tr>
<tr>
<td>Upgrading of the device</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Device dysfunction</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Generator pocket infection</td>
<td>4 (3)</td>
</tr>
<tr>
<td>PM/ICD-associated infective endocarditis</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Indwelling time of the device, y, median (limits)</td>
<td></td>
</tr>
<tr>
<td>Without clinical infection (n=115)</td>
<td>6.4 (2.4–10.2)</td>
</tr>
<tr>
<td>With clinical infection (n=6)</td>
<td>0.7 (0.1–7.0)</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter/defibrillator; PM, pacemaker.

In 11 patients (9%), PM/ICD leads were removed in addition to the generator, which were removed because of dysfunction (n=5), generator pocket infection (n=4), and PM/ICD-associated infective endocarditis (n=2).

†Including pectoral muscle (n=8) and abdominal site (n=1).

associated infective endocarditis was caused by Streptococcus mitis (growth in 6 of 6 blood culture bottles) in 1 patient and S. aureus (growth in 4 of 8 bottles) in the other.

Episodes Without Infection

In 115 episodes, no clinical infection was documented. All patients received a perioperative antibiotic prophylaxis with cefazolin before exchange of the sonicated device. All explanted devices were sonicated, and 112 conventional swab cultures were performed. For episodes without clinical infection, median C-reactive protein at the time of explantation was 9 mg/L (95% confidence limits, <5 to 130 mg/L), and median procalcitonin was 0.08 μg/L (95% confidence limits, 0.06 to 0.35 μg/L). Values were lacking in 23 and 22 episodes, respectively.

Of 115 episodes without clinical infection, sonication fluid grew bacteria in 44 explanted devices (38%), namely in 16 of 65 PMs (25%) and 28 of 50 ICDs (56%). In 21 devices (11 ICDs, 10 PMs), bacterial counts were ≥10 CFU/mL of sonication fluid. Quantitative sonication cultures are shown in Figure 2. Conventional pocket swab cultures grew bacteria in 30 (16 ICDs, 14 PMs) of 112 devices (27%). Bacterial quantity was reported as moderate in 2 cultures (ICDs), few in 20 cultures (12 ICDs, 8 PMs), and after enrichment in 7 cultures (2 ICDs, 5 PMs). In 1 result (PM), quantity was not available. The microorganisms most commonly isolated with either method were Propionibacterium acnes and CNS. Table 4 and Figure 1 show microorganisms and the concordance of sonication and conventional swabs. Overall, concordance of the 2 methods was found in 78 cases (68%). If cultures grown in enrichment medium only were excluded, concordance rose to 83%. In the 6 patients with more than 150 CFU/mL in sonication fluid (4 Propionibacterium acnes, 2 CNS), concordance with conventional swabs was 100%. In the follow-up phase, 2 patients with detection of CNS (both in sonication and swab culture) developed a clinical infection with CNS 3 weeks and 4 months later.

Two of the 56 devices with bacteria detected at the time of removal by sonication or swab developed an infection.

Table 3. Characteristics of 6 Cases With Clinical Infection

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient Age (y)</th>
<th>Site of Infection</th>
<th>Device</th>
<th>Position</th>
<th>Indwelling Time (months)</th>
<th>CRP (mg/mL) Before Start of Treatment</th>
<th>Blood Cultures (Bottles)</th>
<th>Sonicate Fluid From Device (CFU/mL)</th>
<th>Sonicate Fluid From Lead (CFU/mL)</th>
<th>Sonicate Fluid From Pocket (Quantity)</th>
<th>Conventional Swab From Pocket (Quantity)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>Pocket</td>
<td>PM</td>
<td>Subcutaneous</td>
<td>8</td>
<td>Sterile</td>
<td></td>
<td>S. aureus (&gt;1000)</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Sterile</td>
<td>Detection of CNS in sonicate fluid (690 CFU/mL) and swab culture (few) at the time of previous device change</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>Pocket</td>
<td>ICD</td>
<td>Submuscular</td>
<td>4</td>
<td>Sterile</td>
<td></td>
<td>CNS (200)</td>
<td>CNS (&gt;1000)</td>
<td>CNS (few)</td>
<td>CNS (few)</td>
<td>Hematoma cleared out after implantation</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>Pocket</td>
<td>ICD</td>
<td>Subcutaneous</td>
<td>3</td>
<td>Sterile</td>
<td></td>
<td>Sterile</td>
<td>Sterile</td>
<td>CNS (after enrichment)</td>
<td>Sterile</td>
<td>Detection of CNS in sonicate fluid (after enrichment) and swab culture (few) at the time of previous device change</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>Pocket</td>
<td>ICD</td>
<td>Subcutaneous</td>
<td>8</td>
<td>&lt;5</td>
<td></td>
<td>Sterile</td>
<td>Sterile</td>
<td>CNS (after enrichment)</td>
<td>CNS (few)</td>
<td>Forgotten swab tissue during implantation</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>Endocarditis</td>
<td>PM</td>
<td>Subcutaneous</td>
<td>7</td>
<td>&lt;5</td>
<td></td>
<td>Sterile</td>
<td>Sterile</td>
<td>CNS (after enrichment)</td>
<td>Sterile</td>
<td>Exploitation of device and lead after 2 weeks of systemic antibiotic therapy</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>Endocarditis</td>
<td>PM</td>
<td>Subcutaneous</td>
<td>8</td>
<td>Sterile</td>
<td></td>
<td>S. aureus (4/5)</td>
<td>Sterile</td>
<td>CNS (few)</td>
<td>CNS (few)</td>
<td>Exploitation of device and lead after 2 weeks of systemic antibiotic therapy</td>
</tr>
</tbody>
</table>

CFU indicates colony-forming units; CNS, coagulase-negative staphylococci; CRP, C-reactive protein; ICD, implantable cardioverter/defibrillator; and PM, pacemaker.
corresponding to an incidence of 3.6% (95% confidence interval [CI], 0.4% to 12.3%). Considering only the 44 devices growing microorganisms in sonication, the incidence was 4.5% (95% CI, 0.6% to 15.5%), and for sonication-positive devices with quantities >10 CFU/mL, the incidence was 9.5% (95% CI, 1.2% to 30.4%).

**Table 4. Isolated Microorganisms and Concordance of Sonication and Pocket Swab Cultures From Removed Devices Without Clinical Infection (n=115)**

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Sonication Fluid Only</th>
<th>Conventional Swab Only</th>
<th>Sonication and Conventional Swab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes without clinical infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>15</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>7</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gram-positive anaerobic cocci*</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gram-positive anaerobic rods</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gram-negative rods</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mixed bacteria</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative samples</td>
<td>11</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>Not done</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>37</td>
<td>78</td>
</tr>
<tr>
<td>Episodes with clinical infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>1†</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>1‡</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Values represent numbers of devices.
*Include Peptostreptococcus spp., Finegoldia spp., and Micrococcus spp.
†Antiseptic solution in pouch before microbiology, sonication fluid of lead only positive.
‡Microbiology after 2 weeks of systemic antibiotic treatment.

**Negative Controls**
As negative controls, 26 sterile devices (dummies) were sonicated, among which 25 (96%) were negative in sonication cultures; 1 grew 30 CFU/mL CNS.

**Clinical Outcome**
Follow-up lasted 17.9 months (median; range, 10.8 to 24.8 months). Ninety-eight of 115 patients without infection at baseline had no complication, 13 died, 2 developed an infection of the device pocket and devices were removed, and 2 were lost to follow-up. All 6 patients with infection stayed alive and had no further complications. Four of these patients received another device on the other side of the chest after completion of antibiotic treatment; 2 patients did not receive a new device.

**Discussion**
In cardiac devices explanted without clinical signs of infection, bacteria were detected in 38% of sonication fluid and in 27% of conventional generator pocket swab cultures, with a concordance of 68%. Accounting for higher quantities of bacteria (>150 CFU/mL) led to 100% concordance (6 devices). Sonication was more sensitive in detecting bacteria than conventional swabs.

Data on microbiological analysis of electrophysiological devices are scarce. A study by Dy Chua et al.24 compared pocket tissue with swab culture in 36 patients without and 35 patients with clinical infection of PMs/ICDs. They found concordant positive results in only 8% of noninfected devices, whereas in infected devices, concordance was 31%; they conclude that culture in noninfected devices is nonspecific. In fact, whether the detection of bacteria on devices corresponds to true colonization/subclinical infection or contamination is difficult to determine, as is the risk for future infection. We nevertheless believe that the high proportion of bacteria found is relevant because of the following reasons:

Sonication of explanted prosthetic material has shown to be more sensitive than conventional microbiological culture in the diagnosis of foreign body infection, especially in orthopedic prosthesis and breast implants.22,25,26 In our study, using sonication, bacteria grew in 38% of noninfected de-
services, whereas in conventional culture, bacteria grew in 27%. In the 6 infected devices, sonication was positive in all 6 cases; swab culture was positive in 4 cases. The higher proportion of positive sonication results in infected devices is well explained by the fact that these patients were treated with antibiotics before removal, hampering conventional culture.

Improved sensitivity of sonication compared with conventional culture in such situations is helpful in establishing the microbiological diagnosis.

In the noninfected devices, interpretation is more difficult, because no clinical correlate exists. Quantification of bacteria could help in distinguishing between colonization and contamination. In hip and knee prostheses, a cutoff of 10 CFU/mL bacteria in sonication fluid predicted infection. In our study, when including all results irrespective of quantity, discordance between swab and sonication was found in 32%. If cases with very small quantities of growth (after enrichment only) were excluded, discordant results were found in 17% only. Using a high cutoff of >150 CFU/mL for sonication and minimum few growth in swab culture, concordance was 100%. Thus a correlation between sonication and growth in swab culture may be postulated.

To rule out contamination of devices, we used 26 dummies undergoing a similar procedure as real devices. Only in 1 dummy was bacterial growth detected by sonication (30 CFU/mL CNS). Because all controls but 1 (dummies) were negative, contamination is not likely to have occurred during transport of the device or during sonication procedure, but if so, rather during explantation. However, a concordance up to 100% when using a high cutoff for sonication speaks for the existence of real bacterial colonization in noninfected devices.

P. acnes and CNS were by far the most frequently cultivated bacteria in sonication fluid and in conventional swabs. Both bacteria species are part of the normal skin flora and known to survive in biofilms on foreign bodies, eventually causing low-grade infections associated with different prosthetic materials, including cardiac devices. This fact underlines the plausibility of the relevance of these findings and exerts practical implications relative to prophylaxis during implantation of cardiac devices.

During follow-up, 2 of 115 devices explanted for battery change or dysfunction became clinically infected with CNS, which were documented also at the time of device exchange. Even if molecular studies were not performed to prove clonality, infection with the same microorganism as detected before is probable, underlining the significance of the presence of bacteria. Considering sonication-positive devices with significant numbers of bacteria (>10 CFU/mL), the incidence of infection was estimated at 9.5% (95% CI, 1.2% to 30.4%), which is clinically relevant. As follow-up was relatively short (mean, 17.9 months), the number of patients developing infection might even be higher during longer observation periods.

To our knowledge, bacterial colonization of cardiac devices is not known yet. Although the ratio of later infection in our cohort was low, we consider the issue relevant regarding the increasing number of patients with implanted devices. Possibly, the proportion of clinical infection is lower due to the fact that cardiac devices are under little mechanical stress compared with prosthetic devices such as prosthetic joints.

Strengths of this study are the large number of clinically noninfected cardiac devices examined with detailed clinical and microbiological data. However, there were several important limitations in our study, including the lack of a gold standard for subclinical infections of cardiac devices. Another limitation was the nonblinded collection of controls. Also, the explanteur (cardiologist or surgeon) was another person than the collector of the controls. Another drawback is the short follow-up, when taking into account that infections in this series occurred up to 7 years after implantation. For future studies, it would be important to include histology to analyze inflammatory reaction.

In conclusion, we showed by sonication and conventional culture that microorganisms colonize electrophysiological devices. Sonication of the device before culture could represent a more sensitive technique to detect microorganisms in device-related infections. However, the role of bacteria detected in asymptomatic cardiac devices needs to be elucidated by further studies to discuss adequate preemptive antibiotic therapy.

Disclosures

None.

References

Sonication of Electrophysiological Cardiac Devices


15. Mandrekar JN, Cockerill FR, Steckelberg JM, Greenleaf JF, Patel R. Sonication of removed infected devices might be more sensitive in isolating bacteria, especially when patients are already receiving antibiotic treatment.


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