Role of the Preaxillary Flora in Pacemaker Infections
A Prospective Study

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Background—Infection remains a severe complication after pacemaker implantation. The purpose of our prospective study was to evaluate the role of the local bacteriologic flora in its occurrence.

Methods and Results—Specimens were collected at the site of implantation for culture from the skin and the pocket before and after insertion in a consecutive series of patients who underwent elective permanent pacemaker implantation. Microorganisms isolated both at the time of insertion and of any potentially infective complication were compared by using conventional speciation and ribotyping. There were 103 patients (67 men and 36 women) whose age ranged from 16 to 93 years (mean±SD, 67±15). At the time of pacemaker implantation, a total of 267 isolates were identified. The majority (85%) were staphylococci. During a mean follow-up of 16.5 months (range, 1 to 24), infection occurred in four patients (3.9%). In two of them, an isolate of Staphylococcus schleiferi was recognized by molecular method as identical to the one previously found in the pacemaker pocket. In one patient, Staphylococcus aureus, an organism that was absent at the time of pacemaker insertion, was isolated. In another patient, a Staphylococcus epidermidis was identified both at the time of pacemaker insertion and when erosion occurred; however, their antibiotic resistance profiles were different.

Conclusions—This study strongly supports the hypothesis that pacemaker-related infections are mainly due to local contamination during implantation. S schleiferi appears to play an underestimated role in infectious colonization of implanted biomaterials and should be regarded as an important opportunistic pathogen. (Circulation. 1998;97:1791-1795.)

Key Words: pacemakers ■ follow-up studies ■ genes

Despite improvement as the result of better surgical techniques, infection of the pacemaker pocket or lead still remains a potential complication after permanent pacemaker implantation. Rates varying between 0.5% and 5.1% have been reported in retrospective and prospective studies.1-4 Bacteremia and/or endocarditis have also been reported in up to 0.5% of patients.5 When they occur, they carry a high morbidity and mortality.5,6 Infection can involve the pacemaker pocket itself (abscess) or can be disseminated to the blood by the lead that lies within the venous system and impinges on the endocardium (bacteremia/endocarditis). The precise mechanisms involved are incompletely understood. It is currently considered that infections are first due to local bacterial contamination acquired at the time of surgery. Virulent organisms such as Staphylococcus aureus cause infections early after pacemaker implantation,7 whereas coagulase-negative staphylococci (CNS) such as Staphylococcus epidermidis are responsible for delayed infections. Secondary, infection can occur after seeding of the microorganisms through the hematogenous route.8 Alternatively, skin erosion may be the primary mechanism by which local infection occurs. There are very few data available on operative bacteriologic findings and their implications in pacemaker infection.9-12 In a prospective study, we evaluated the role of local bacteriologic flora on pacemaker-related infection and skin erosion. Microorganisms isolated at the time of insertion and of any pertinent clinical event were compared by using phenotypic and molecular methods when consecutive isolates were of the same species.

Methods

Study Patients
From January 1995 through January 1996, specimens were systematically and prospectively collected at the site of implantation for bacteriologic culture in a consecutive series of patients who underwent elective permanent pacemaker implantation. Patients were systematically submitted to shaving and to an antiseptic shower with povidone iodine 10% aqueous solution on the night before the operation. The first specimen was taken preoperatively from the skin at the implantation site over the relevant right or left pectoral region before any skin preparation or desinfection. Antisepsis was performed immediately before surgery; the skin was painted with two solutions, successively: aqueous povidone iodine 10% solution and povidone iodine 7.5% solution. The second specimen was sampled from the pocket as soon as it had been done and the third one from the same pocket after generator insertion immediately before sutur-
ing. Specimens were taken with sterile dry swabs. Infectious risk factors were systematically searched: diabetes mellitus, long-term corticosteroid therapy or anticoagulant agents, postoperative hema
toma, malignancy, and temporary electrodes.

Surgical Technique
Pacemaker implantation was standardized. Operations were performed under local anesthesia. All operators were trained in the technique of pacemaker implantation during the course of the trial. New leads were inserted transvenously through the cephalic vein or alternatively through the subclavian vein. Generators were positioned subcutaneously over the pectoral major muscle. Drains and antibiotics, local or systemic, were never used.

Follow-up
Patients were discharged 3 to 5 days after implantation, and the site was inspected at 3 days, then 3, 6, and 12 months after implantation. In patients with suspected postoperative infections, specimens were taken with swabs or by needle aspiration from the pacemaker pocket. In the presence of potentially infectious complications, blood cultures were systematically sampled by venipuncture. Patients and/or their physicians were systematically called on January 1997. No patient was lost to follow-up.

Bacteriologic Procedures
Bacterial isolates collected at the time of implantation were stored and compared with the isolates cultured at the time of any infection. Bacterial culture and identification were performed according to standard methods by using commercially available reagents. All staphylococcal isolates were identified at the species level by using ID32 STAPH gallery (bioMérieux). When consecutive isolates of the same species were identified from the same patient, their genetic relatedness was evaluated by ribotyping. It consisted of comparing ribosomal DNA (rDNA) restriction fingerprints of the studied isolates. Briefly, whole-cell DNA was restricted by HindIII, sepa
rated by agarose gel electrophoresis, and vacuum transferred to nylon membranes as previously described.13 Plasmid pKK3535 labeled by random priming with digoxigenin-11-dUTP (DIG DNA Labeling Kit, Boehringer Mannheim) was used as a probe specific for genes coding for rRNA.13–15 Hybridization was detected by addition of antidigoxigenin antibodies conjugated to alkaline phos
dphatase, revelation by addition of the chemiluminescent substrate for genes coding for rRNA.13–15 Hybridization was detected by addition of antidigoxigenin antibodies conjugated to alkaline phosphatase, revelation by addition of the chemiluminescent substrate provided by the manufacturer (Boehringer Mannheim), and exposition of the filter to x-ray film.

Statistical Analysis
Results are reported as mean value±SD. We used Kaplan-Meier survival estimates to describe the long-term event-free rate. The analysis was performed with the StatView F-4.5 software (Abacus Concepts Inc).

Results
Population Characteristics
There were 103 patients (67 men and 36 women). Their age ranged from 16 to 93 years (67±15, mean±SD). Implanted pacemakers were dual chamber in 56 and single chamber in 47. Infectious risk factors were found in 28 patients; none of them developed subsequent infection.

Bacteriologic Results at the Time of Implantation
At the time of surgery, a total of 293 samples were collected. Data were missing and nonavailable for 16 samples. Positive culture was obtained in 88.3% of the preoperative skin samples, 48% of the pacemaker pocket samples before insertion, and 37.1% of the pocket samples at the end of surgery (Table 1). A total of 267 isolates were identified. The majority of the isolates were members of the human cutaneous flora, 227 (85%) being staphylococci. S aureus was isolated in nine instances from seven patients, eight of nine times on the preoperative skin. S epidermidis was the most represented species. Staphylococcus schleiferi was isolated in five instances from five patients.

Follow-up
During a mean follow-up of 16.5 months (range, 1 to 24), infection occurred in four patients (3.9%): wound abscess in one, erosion and local infection in one, erosion and bacteremia in one, and bacteremia in one, occurring 10, 1, 16, and 4 months, respectively, after implantation. Infection occurred 7.7±6.7 months after implantation. The 2-year infection rate was 4.6%. S schleiferi was responsible for bacteremia in two patients (patients 1 and 2) and was also isolated over the generator in patient 1 (Table 2). Interestingly, erosion was the initial clinical diagnosis for patient 1 before systematic blood cultures showed evidence of infection. In this patient, two strains of S epidermidis were also cultured from the generator and the skin, respectively. Their antibiotic resistance profiles were significantly different to reject any clonal relatedness between the two strains. In a third patient (patient 3), a strain of S aureus was isolated from a wound abscess and in patient

<table>
<thead>
<tr>
<th>Species</th>
<th>Skin</th>
<th>Pacemaker Pocket</th>
<th>Generator</th>
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<tbody>
<tr>
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<tr>
<td>simulans</td>
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<td>2</td>
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<tr>
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<td>5</td>
<td>2</td>
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<tr>
<td>capitis</td>
<td>2</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
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</tr>
<tr>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>caprae</td>
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<td>2</td>
<td>0</td>
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<tr>
<td>aureus meti S</td>
<td>7</td>
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<tr>
<td>aureus meti R</td>
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<tr>
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<tr>
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<tr>
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<td>102</td>
<td>97</td>
</tr>
<tr>
<td>Total positive samples</td>
<td>83 (88.3%)</td>
<td>49 (48.0%)</td>
<td>36 (37.1%)</td>
</tr>
</tbody>
</table>
4, a strain of \( S\) epidermidis \( \) was identified at the site of skin erosion. No organism could be cultured in an additional patient (patient 5) at the site of erosion although a strain of \( S\) haemolyticus had been isolated on the preoperative skin 9 months earlier. Hence this patient was not considered as infected.

**Epidemiological Analysis of Bacterial Strains**

The organisms collected at the time of infection were compared with those collected at the time of pacemaker implantation. No strain of \( S\) aureus was recovered at the time of pacemaker implantation for patient 3, although a strain of \( S\) epidermidis was isolated on the preoperative skin and a strain of \( S\) schleiferi from the pacemaker pocket. A strain of \( S\) epidermidis was isolated at the time of pacemaker insertion in patient 4; however, this strain was different from the one isolated at the time of skin erosion on the basis of different antibiotic resistance profiles. In patients 1 and 2, \( S\) schleiferi was isolated over the generator (patient 1) or on the preoperative skin (patient 2), together with other microorganisms that were not cultured afterward (Table 2). Antibiotic resistance and biochemical profiles of the different isolates of \( S\) schleiferi were identical, and ribotypes of the consecutive isolates of each patient were identical (Figure). However, the ribotypes of strains isolated from patients 1 and 2 were unrelated (Figure). Ribotype of the strain of \( S\) schleiferi isolated on the preoperative skin of patient 3 was not determined.

**Discussion**

Infection is a serious, potentially life-threatening complication after pacemaker surgery; morbidity and mortality are reported to be high.\(^6\) Its prevention would greatly benefit from a better knowledge of mechanisms involved. Several mechanisms have been advocated,\(^7\) although none has been fully validated. Local perioperative wound contamination is usually described as the major mechanism predisposing to local or systemic pacemaker infection.\(^7\) The presence of a superficial foreign body can predispose to skin erosion or necrosis and also cause infection. Besides, microorganisms can colonize foreign bodies such as pacemaker leads by the hematogenous route. The predictive values of preoperative and operative local bacteriologic flora have not been fully explored; conclusions drawn from small series are elusive.\(^8\)–\(^12\)

In this prospective study, 4 patients out of 103 (3.9%) developed infection. Two of them developed bacteremia shown by positive blood cultures (patients 1 and 2), one developed a wound abscess (patient 3), and one a local infection (patient 4). \( S\) schleiferi was associated with two of these four cases of infection and was also isolated at the time of pacemaker implantation (Table 2). The frequency of association of \( S\) schleiferi with infections in this series is surprising compared with its low frequency of isolation in the prospective samples (5 out of 267 isolates). Four other cases of pacemaker infection caused by \( S\) schleiferi have been reported previously.\(^16\) When analyzing these six cases (two from the present study plus four from the previous study\(^16\)), the interval between pacemaker implantation and infection...
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varied between 6 weeks and 16 months, with a median of 10 to 12 months. In the present study we have demonstrated by a molecular method that the strain associated with pacemaker infection and present in blood cultures was already present in the operative sample at the time of pacemaker insertion. This supports a previous hypothesis that delayed infections caused by CNS are due to local bacterial contamination acquired at the time of surgery. This also strongly suggests that infection is likely to begin at the pacemaker pocket and extend down the lead. Furthermore, strains of S schleiferi isolated from our two patients displayed different ribotypes (Figure) assessing the lack of pathogenic link between them and allowing exclusion of a specific operator contamination. Besides pacemaker infections, S schleiferi has been associated with other human conditions such as infections of wounds, hip prostheses or vascular devices, brain empyema, and bacteremia, but the frequency of these infections is extremely low compared with those caused by other species of staphylococci such as S aureus or S epidermidis. However, S schleiferi may be misidentified as S aureus because both species express a fibrinogen affinity factor (clumping factor), a characteristic frequently used to identify S aureus. Hence the actual responsibility of S schleiferi in human infections especially on biomaterials may have been underestimated as coagulase-negative staphylococci from infected materials are not systematically identified at the species level senso stricto by all laboratories. Moreover, bacteriologic cultures from pacemaker skin erosion are not currently done if signs of infection are not patent. The peculiar association of S schleiferi with pacemaker infection may reflect the expression by this species of specific virulence factors such as surface receptors that are presently unknown.

Although a local antisepsis was applied, several organisms (mostly staphylococci) were cultured in the pocket and over the generator before suturing. This phenomenon plays an important role, suggesting a local contamination with the staphylococci present within the skin appendages (including hairs, sebaceous glands, and sweat glands), which might contaminate the wound margins during surgical procedure, probably during the pocket achievement. The present study also showed that S epidermidis, although representing the majority of strains isolated at the time of implantation, was very rarely responsible for subsequent infection. In a previous study, Ramsdale et al. took preoperative microbiologic specimens in more than 470 patients, but the results of preoperative culture were not found to be predictive of subsequent infection. In their series, six patients had pathogens over the skin before surgery (among which five were S aureus), but none of the six patients developed infection. No data are available concerning bacteriologic findings in the pacemaker pocket and wound margins in their study. Bacteriologic examinations were also performed by Bluhm et al. Samples were obtained from tissue fluid of the pacemaker pocket 1 day after surgery. Out of 34 patients not receiving an antibiotic prophylaxis regimen, cultures were positive in 10 but none developed subsequent infection. Another study from the same authors led to the same conclusions. Only one study was made to predict the causative organism in postoperative infection. Specimens for culture were taken from the nose, the throat, and from the wound margins at the end of the operation. A needle aspiration was performed from the pacemaker pocket in each patient with suspected infection. Identity of a strain of S aureus isolated from the nose before surgery to that collected at the time of infection from a wound culture was demonstrated by phage typing, with no molecular marker being available in 1983. For the other seven patients in their series, no definitive conclusion could be drawn by analysis of the preoperative and postoperative microbiologic flora. In contrast, our prospective study evidenced the pathogenic role of the preaxillary flora, notably that of S schleiferi, in early and late pacemaker infections.

Another important finding deals with pacemaker erosion. Our results support the hypothesis that apparently clinical pacemaker erosion without obvious local infection may be primarily caused by infection (two of three patients in our series); systematic local sampling and blood cultures should be recommended in this setting. Indeed, specific microorganisms such as S schleiferi or S epidermidis can be responsible for nosocomial infections, especially in the presence of foreign bodies.

Conclusions

Our study shows that numerous strains of organisms are present in the pacemaker pocket at the time of implantation despite careful preoperative preparation of the skin, suggesting their subcutaneous origin. They are very rarely responsible for subsequent infection. Among these organisms, S schleiferi appears to play a particular and so far underestimated role in infectious colonization of implanted biomaterials and should be regarded as an important opportunistic pathogen. This study gives new insights into the pathogenesis of infections secondary to pacemaker infections and strongly supports the hypothesis that pacemaker-related infections are mainly due to local contamination during implantation. These data equally support the hypothesis that pacemaker erosion can be caused by primary infection. Our findings further raise the question of a likely benefit of antibiotic prophylaxis in this setting to prevent subsequent major infections.

Addendum

Since submission of this paper, an additional patient was admitted for pacemaker erosion 29 months after implantation. A strain of S schleiferi was cultured from the pacemaker pocket, skin sample and pacemaker itself at the time of complication, while a strain of S schleiferi has also been isolated from the pocket at the time of implantation. Molecular analysis confirmed the genetic relationship between the two strains. Hence, 4 patients out of 5 in whom a strain of S schleiferi had been isolated at the time of implantation presented an infective complication: 3 were associated with S schleiferi and 1 with S aureus.

References

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