Biodegradation of the Outer Silicone Insulation of Endocardial Leads

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Background—Silicone catheter insulation, larynx prostheses undergo biodegradation. The aims of the study were to verify the conviction that outer silicone lead insulation is biostable and inert in addition to determining the role of macrophages (M) and Staphylococcus aureus (S aureus) strains in the silicone lead insulation degradation.

Methods and Results—Leads removed from 8 patients because of infective and noninfective indications were analyzed with stereomicroscope and classified according to Banacha abrasion classification, and additional analysis using scanning electron microscope was performed. The examination revealed excavations of different shape and depth in the abraded areas. Fresh silicone-insulated lead was cut into fragments. The fragments were cultured with RAW 264.7 macrophage cell line for 9 weeks. Additional lead fragments were placed with S aureus strains: ATCC 25923, ATCC 29213, and K9328H. Lead fragments were also cocultured with the bacterial strains and RAW M. In scanning electron microscope analysis, diminution in silicone was observed. All S aureus strains provoked insulation damage after 9 weeks. The lowest level of degradation of insulation concerned ATCC 25923. Silicone lead fragments in cocultures presented a further gone level of silicone biodegradation.

Conclusions—S aureus, macrophages separately, and S aureus and macrophages cocultures initiate the biodegradation of silicone insulation. Differences in the level of biodegradation between strains of S aureus were observed, with the most aggressive reaction toward silicone visible in the cocultures. In vivo silicone biodegradation is initiated by tearing among surfaces of the lead insulation, macrophages may be the crucial cells for the process that may be aggravated by pathogen colonization. (Circ Arrhythm Electrophysiol. 2013;6:279-286.)

Key Words: cardiovascular implantable electronic device infection ■ endocardial lead abrasion ■ endocardial lead damage ■ infective endocarditis ■ silicone biodegradation

The development of the pacemaker and implantable cardioverter–defibrillator technology improved the quality of life of patients and prolonged their lifespan.1,2 Since 1958, when the first pacemaker was implanted, a few generations of endocardial leads have been introduced. The most important factor that influences the leads’ reliability is their insulation. Silicone, polyether polyurethane, and copolymers are currently widely used. Medical grade silicone used as insulation has been improving lead reliability for >50 years. Its advantages include flexibility, resistance to tearing, low abrasion resistance, and high friction in contact with blood.3–5

Clinical Perspective on p 286

In the literature, scientists indicate that silicone may not be biostable when serving as the insulation or as a component of prostheses.6,7 Failure of silicone is associated with pathogen colonization and biofilm formation. For instance, the biofilm covering the surface of silicone voice prosthesis is colonized with mixed colonies in 86.6% of cases, comprised mainly of bacteria and yeasts, such as Streptococcus sp., Staphylococci, Candida albicans, and Candida tropicalis. Electron microscopy analysis has revealed degradation of silicone that leads to voice prosthesis deformation and dysfunction because of filamentous and vegetative yeast cell invasion.7 Eymann et al8 indicated that hydrocephalus silicone shunt catheters cannot be termed inert or biotolerated and instead should be regarded as bio-active implants.

Insertion of a foreign body, for example, an endocardial lead initiates a complicated immunologic response. Monocytes are recruited to the site of implant insertion, where they undergo maturation to macrophages and persist at the implant surfaces and in the peri-implant tissue.5–10 The macrophage has been implicated as a pivotal cell in the physiological healing of tissues around implants and in the pathogenesis of implant failure.11 Macrophages undergo fusion and form foreign

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body multinuclear giant cells that are the feature of on-going chronic inflammation in the presence of microorganisms and nonphagocytosable materials under periods of up to 15 years.12,13

Cardiovascular implantable electronic device infection is a rising phenomenon, documented by the 3.1-fold increase in the number of hospitalizations because of cardiovascular implantable electronic device infections between 1996 and 2003.14 Staphylococcal species cause from the 60% to 80% of infections in the largest reported series.15 The abrasion of the outer silicone insulation of endocardial leads regardless of the level of degradation is strongly associated with infective endocarditis.16 Bacterial adhesion to biomaterials initiates biofilm formation.17 The presence of a foreign body influences the host’s defense mechanisms by reducing the phagocytic and bactericidal capacity of polymorphonuclear leukocytes. The intracellular persistence of bacteria inside macrophages may also play a pivotal role in the pathogenesis of biomaterial-associated infections.18 Monocytes, macrophages, and neutrophils are indicated as crucial cells in the biodegradation of polyurethane outer (environmental stress cracking) and inner insulation (metal ion oxidation) in bipolar pacemaker leads.19,20

We observed failure of the outer silicone insulation of transcutaneously removed endocardial leads.16,21 Scanning electron microscope (SEM) analysis revealed uncharacteristic silicone degradation. In most series, authors concentrate on how material surface chemistry can direct the inflammatory, foreign body, and the wound healing responses. Polyether polyurethane biodegradation is well characterized in the literature, whereas silicone insulation is thought to be inert and biostable. The quantity of implanted silicone-insulated leads is rising, the number of infectious complications is increasing, and a better understanding of the process of silicone biodegradation seems to hold a strategic role for both the silicone’s hosts and the lead designers. The aims of the study were to determine the role of Staphylococcus aureus strains and macrophages in the degradation of the silicone insulation in an in vitro study and to compare the results with in vivo outer silicone insulation damage in the transcutaneously removed leads.

Methods
Silicone-insulated leads were transcutaneously removed from 8 patients hospitalized because of chronic pocket infection, infective endocarditis, or noninfective indications (Table 1). Leads were analyzed with both optical microscope and SEM. The abrasions of the outer insulation were classified according to Banacha classification. Three levels of silicone degradation were distinguished: type 1 to 3, all in 2 subtypes a and b.6 A fresh silicone-insulated lead (Synox, Biotronik, Berlin, Germany) was cut into 1- and 3-cm fragments. The outer insulation was left untouched or scraped by syringe needle. All lead manipulation was conducted without any contact with the lead insulation surface. Leads were handled with forceps placed at both ends of lead fragments. The condition of outer insulation was analyzed with optical microscope and a SEM (LEO 1430 VP, Faculty of Biology, University of Warsaw, Poland).

Macrophages Culturing on Leads
The lead fragments were placed in a 24-well Multiwell Plate (BD Falcon, Franklin Lakes, NJ) and cultured with a RAW 264.7 macrophage cell line (American Tissue Culture Collection, Manassas, VA) at 37°C, 5% CO₂ for 9 weeks. Every third day, fragments with macrophages were placed in fresh DMEM (GIBCO, Grand Island, NY) supplemented with 5% fetal bovine serum, 50 μM penicillin, 50 μg/mL streptomycin (all from GIBCO, Grand Island, NY) with or without lipopolysaccharide (1 μg/mL, E. coli B04:111; Sigma, St. Louis, MO).

Staphylococcus Strains Culturing on Leads
Additional lead fragments were placed with S. aureus strains ATCC 25923, ATCC 29213 (American Tissue Culture Collection), and K9328H. The latter, a methicillin-resistant strain of S. aureus was isolated from the bloodstream of a patient hospitalized in the intensive care unit of our hospital (1a Banacha St, 02-097 Warsaw, Poland). Its identification was performed using traditional phenotype-based methods in combination with antimicrobial susceptibility testing. All strains were cultured in Todd Hewitt broth (Graso) and incubated at 34°C±1°C for 9 weeks.

Coculturing of Macrophages With S aureus on Leads
Lead fragments previously cultured with 3 different strains for 6 weeks were then placed into RAW macrophage cultures with medium (DMEM, 5% fetal bovine serum, GibCO, 50 μg streptomycin, GibCO) and incubated for additional 3 weeks.

Results
Fifteen leads were removed transcutaneously from 8 patients: 5 men, mean patient age was 61.4 years. The mean number of implanted leads per patient was 2.5. The mean number of procedures until removal was 2.3, with the mean time from the last procedure until removal 47 months. Late onset of infective complications (ie, infective endocarditis, chronic pocket infection) was noticed with mean time from last procedure 3.6 years. Patient and lead characteristics are presented in Tables 1 and 2, respectively.

At a single location (intracardiac/venous/pocket), different levels of silicone degradation may be seen. The neighboring surfaces of the outer silicone lead insulation that undergo tearing may present different types of abrasions. Abrasions analyzed with optical microscope, observed in the intracardiac, venous, and pocket part of the lead, are similar and seem most frequently in the intracardiac region, whereas in the pocket they present sparser occurrence (Table 2).

Abrasions classified as type 1a usually occupy from 30% to 50% of the lead circumference. The type 2b is elongated with a diameter of <0.5 cm, a consequence of the lead wreathing/twining itself around another lead. The diameter of the most advanced third level of degradation abrasion type ranges from 1 to 3.5 cm, with insulation perforation and metal conductor exposure (the longest diameter of silicone deficiency ranges from 0.5 to 1 cm) in the center of the abrasion (Figure 1).

In all the leads removed from patients in abraded areas, characteristic silicone degradation of different shape and depression depth was observed in SEM (Figure 1). In cases with the third level of silicone degradation, changes were visible at the margin of the abrasion, in initial changes, for instance in type 1a, the whole abraded surface presented as an excavated area. In the type b, small silicone detachments were observed with less expressed characteristic hollows. SEM abrasion morphology was similar in the intracardiac, venous, and pocket parts of the lead. In the youngest patient in the pocket region of the lead, a type 3a abrasion was present. On the surface of the lead (vis-à-vis), the abrasion fragments transmitted from degradation area were present (Figure 1).
To identify the role of macrophages and *Staphylococcus aureus* strains in silicone biodegradation, an in vitro study was performed. Lead fragments with untouched or scraped by syringe needle outer insulation were covered by macrophages (the presence of macrophages was confirmed every 3 days). Lead fragments were placed in fresh medium with or without lipopolysaccharide. After 9 weeks, all lead fragments remained covered with macrophages, with large clusters of macrophages present in the regions prior damaged with syringe needle. In SEM analysis diminution in silicone was observed (Figure 2). All *S aureus* strains provoked insulation damage after 9 weeks. The lowest level of degradation of outer insulation concerned strain ATCC 25923. Silicone lead fragments cultured with *S aureus* strains, and macrophages presented a further gone level of silicone biodegradation (Figure 3).

**Discussion**

This article is innovative because it combines new important information on the role of the immunologic response to a foreign body with observations of biofilm formation on the outer silicone insulation of the endocardial leads in vivo. The results are confronted with a short-term study on the *Staphylococcus aureus* and macrophage influence on a new silicone-insulated lead in vitro. We indicated macrophages as the crucial cells in silicone degradation. Tearing among surfaces of the outer lead insulation at the cross points initiates the detachment of small fragments of silicone. Activated macrophages may engage in phagocytosis of silicone debris. On the contrary, diminution in silicone induces the accumulation of macrophages at the site of the outer lead insulation excavations/depressions. Under special conditions, such as infection, the described process may be aggravated, which, in turn, leads to stronger silicone biodegradation. Taking into consideration that silicone biodegradation is present only at abraded surfaces, we indicate tearing among outer silicone insulation as the triggering mechanism of silicone biodegradation in vivo. In vitro experiments revealed that *S aureus*, macrophages separately, and *S aureus* and macrophages cocultures initiate the biodegradation of the outer silicone insulation. A difference in the level of biodegradation between strains of *S aureus* was observed, with the most aggressive reaction toward silicone

**Table 1.** Patient Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Indication for Removal</th>
<th>No. of Implanted Leads</th>
<th>Pacing Mode</th>
<th>Complications During Removal</th>
<th>Procedure Duration, min</th>
<th>No. of Procedures Until Removal</th>
<th>Time Since the Last Procedure, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>68</td>
<td>IE</td>
<td>2</td>
<td>ICD-DR</td>
<td>None</td>
<td>100</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>55</td>
<td>IE</td>
<td>3</td>
<td>BiA-V</td>
<td>None</td>
<td>110</td>
<td>3</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>46</td>
<td>IE</td>
<td>3</td>
<td>DDD</td>
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<td>7</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>80</td>
<td>CPI</td>
<td>3</td>
<td>A-BiV</td>
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<td>80</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>65</td>
<td>CPI</td>
<td>2</td>
<td>BiA</td>
<td>None</td>
<td>80</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>85</td>
<td>Ni</td>
<td>4</td>
<td>BiA-BiV</td>
<td>None</td>
<td>60</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>79</td>
<td>Ni</td>
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<td>BiA</td>
<td>None</td>
<td>130</td>
<td>1</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
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<td>Ni</td>
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<td>None</td>
<td>None</td>
<td>120</td>
<td>1</td>
<td>84</td>
</tr>
</tbody>
</table>

A-BiV indicates atrial and biventricular pacing; BiA, biatrial pacing; BiA-V, biatrial and ventricular pacing; BiV, biventricular pacing; CPI, chronic pocket infection; ICD-DR, dual chamber rate adaptive implantable cardioverter defibrillator; IE, infective endocarditis; F, female; M, male; and Ni, noninfective indications.

**Table 2.** Lead Characteristics and Abrasion Type According to Banacha Classification

<table>
<thead>
<tr>
<th>Lead</th>
<th>Patient</th>
<th>Tip Location</th>
<th>Polarity</th>
<th>Fixation</th>
<th>Dwell Time, mo</th>
<th>Abrasion in the Intracardiac Part</th>
<th>Abrasion in the Venous Part</th>
<th>Abrasion in the Pocket</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>RAA</td>
<td>BP</td>
<td>A</td>
<td>42</td>
<td>3a</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>RVA</td>
<td>BP</td>
<td>A</td>
<td>42</td>
<td>2b</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>RAA</td>
<td>BP</td>
<td>P</td>
<td>125</td>
<td>1a, 1b</td>
<td>1a</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>CS</td>
<td>BP</td>
<td>P</td>
<td>125</td>
<td>1b, 3a</td>
<td>1a, 1b</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>RVOT</td>
<td>BP</td>
<td>A</td>
<td>85</td>
<td>1a</td>
<td>1a, 1b</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>RAA</td>
<td>BP</td>
<td>P</td>
<td>155</td>
<td>1b, 2b</td>
<td>1b, 2b</td>
<td>1b</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>RVA</td>
<td>BP</td>
<td>P</td>
<td>155</td>
<td>2a, 1b</td>
<td>1b, 2b</td>
<td>1b</td>
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<tr>
<td>8</td>
<td>4</td>
<td>RAA</td>
<td>BP</td>
<td>A</td>
<td>44</td>
<td>1a, 1b</td>
<td>2b</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>RVA</td>
<td>BP</td>
<td>A</td>
<td>44</td>
<td>3a</td>
<td>1b</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>RVOT</td>
<td>BP</td>
<td>A</td>
<td>44</td>
<td>3a</td>
<td>1b</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>RAA</td>
<td>BP</td>
<td>P</td>
<td>78</td>
<td>1a, 1b</td>
<td>1a, 1b</td>
<td>1b, 3a</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>CS</td>
<td>BP</td>
<td>A</td>
<td>78</td>
<td>1a, 1b, 3a</td>
<td>1a, 1b</td>
<td>1a, 1b, 3a</td>
</tr>
<tr>
<td>13</td>
<td>6</td>
<td>LVV</td>
<td>BP</td>
<td>P</td>
<td>72</td>
<td>2a</td>
<td>1a, 1b, 2b</td>
<td>1a, 1b</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
<td>RAA</td>
<td>BP</td>
<td>A</td>
<td>48</td>
<td>1a, 1b</td>
<td>1b</td>
<td>2a, 2b</td>
</tr>
<tr>
<td>15</td>
<td>8</td>
<td>RVA</td>
<td>BP</td>
<td>P</td>
<td>84</td>
<td>0</td>
<td>0</td>
<td>2b, 3a</td>
</tr>
</tbody>
</table>

A indicates active fixation; BP, bipolar; CS, coronary sinus; LVV, left ventricle vein; P, passive fixation; RAA, right atrium auricle; RVA, right ventricular apex; and RVOT, right ventricular outflow tract.
visible in the cocultures. The limitation of this study is the relatively short time of the in vitro experiment (weeks) in relation to the in vivo silicone damage process that occurred during months after implantation.

We have previously presented the abrasion of outer silicone insulation leads in the intracardiac part and indicated its important role in infective endocarditis development. In the present study, we characterize the phenomenon using the example of 8 patients who underwent lead removal because of both infective and noninfective indications. At a single location >1 type of silicone degradation was observed, and neighboring outer insulation of implanted leads presented different abrasion types depending on contact surface tearing and time. Disparity may be the consequence of specific conditions, such as blood flow, macrophage adhesion, pathogen presence and biofilm formation, the efficiency of the immunologic response (decreases, eg, with age) to foreign body and to pathogens.

Microbial infections of medical implants increase patient morbidity, mortality, patient cost, and recovery time. For example, Giangrande et al demonstrated that ultrastructural analysis of a chronic Tenckhoff peritoneal catheter revealed external surface structural defects and small linear tears that were frequent in catheters used for a longer time and removed because of recurrent peritonitis. Moreover, the authors observed that structural defects facilitated microbial adhesion and colonization that predisposed the patients to the recurrence of peritonitis. We have previously presented the Banacha classification of the outer silicone insulation abrasion of the endocardial leads related to the friction among implanted leads, strengthened by the tricuspid valve, cardiac pressure generated during systole and diastole, and blood flow. The abrasions of the outer insulation in the intracardiac part of the leads regardless of their level of progression were associated with infective endocarditis. Tears favored pathogen adhesion, colonization and validated vegetation formation. Silicone approved for medical use especially for catheters and insulation seems to be subjected to the universal mechanism of degradation in the human body.

Elek and Conen in 1957 showed that susceptibility to bacterial infection was significantly increased by the presence of foreign body material. Biofilm formation occurs when free-floating bacterium adheres to a foreign surface,
undergoes genetic transformation, proliferates into bacterial microcolonies, and finally envelops with a coating layer of exopolysaccharide that prevents the entrance of antibiotics, and allows resistance to antibiotics over time. Staphylococcus aureus infection determines a poor outcome in patients with infective endocarditis. Sensitivity of Staphylococcus aureus to antibiotics, such as tetracycline, benzylpenicillin, and vancomycin, was found to decrease by 2- to 10-fold when cells were grown adherent to silicone catheters surface. SEM analysis of silicone voice prostheses covered with biofilm revealed degradation of silicone because of filamentous and vegetative yeast cell growth into silicone rubber, which allowed for pathogens to avoid detachment. In our experiment, all Staphylococcus aureus strains participated in silicone insulation biodegradation, while presenting different grades of aggression toward it. We hypothesize that in vivo abrasions of silicone create a safe location for pathogen accumulation and make washing off by blood flow difficult while further aggravating silicone destruction. Pichlmaier et al and Dy Chua et al reported asymptomatic bacterial colonization of pacemakers. Moreover, Boelens et al showed intracellular persistence of bacteria inside macrophages in the pericatheter tissue without signs of inflammation and indicated this as the possible cause of biomaterial-associated infections. The above-mentioned observation may explain the presence of silicone degradation in patients who underwent lead removal because of noninfective indications. Clinical signs may develop when certain physical conditions of the patients disturb the balance between bacteria and the host response in favor of the bacterium. Detachment of small silicone fragments may also activate macrophages and foreign body giant cells leading to phagocytosis and biting out of silicone debris.

The immunologic response of the patient undergoes modification after device implantation. The adhesion of macrophages and foreign body giant cells to the biomaterial surface creates a microenvironment between the cell membrane and the biomaterial. In the process of frustrated phagocytosis, above-mentioned cells may release mediators of degradation, such as
reactive oxygen intermediates (oxygen free radicals), degradative enzymes, and acid to the privileged zone. On the other contrary, the adhesion of the macrophages and foreign body giant cells reduce phagocytic capacity, cellular immunity, and bactericidal capability. Biomaterials may facilitate apoptosis (programmed cell death) and transform macrophages into cells incapable of attacking foreign organisms that may be adherent to the biomaterial. In 1994, Guo et al showed active transport of rubber fragments containing silicon from the peritoneal cavity to the spleen by adherent macrophages in rats with 100% silicon rubber drain fragments implanted intraperitoneally. Perry et al indicated 2 problems concerning activated macrophages trying to phagocytose particles of silicone from the lead insulation, namely lead insulation damage with implant malfunction and continued tissue inflammation, precluding complete healing. It seems that macrophages adherent to the silicone surface poorly respond to bacterial colonization, pathogens present a stronger capacity for insulation biodegradation, which aggravates macrophages and the influence of foreign body giant cells.

There have been reports of macrophages adhered and spread out on the titanium-alloy surface throughout a culture period with an unchanged phenotype visible in scanning electron microscopy. In our study, macrophages were also spread out on the silicone surface evenly with the exception of surfaces scraped with syringe needle where in the tears clusters of macrophages accumulated. Macrophages have been proved to accumulate on rough surfaces in vitro.

Silicone rubber has been widely used as an insulation for >50 years, after undergoing approval during appropriate preclinical material bioqualification tests. Using their own technology, manufactures prepare silicone elastomers through a process of cross-linking and use different elastomer fillers which act to reinforce the cross-linked matrix. Purity is another factor that can affect bio-test results. Our in vitro experiment revealed that under the proposed conditions pathogens and macrophages may take part in the biodegradation of the outer silicone insulation of Biotronik Synox (Berlin, Germany) lead. However in the in vivo study, the symptoms of biodegradation were only present in the abrasion area. We indicate that under special conditions in the human body silicone insulation of the endocardial leads may not be inert or biostable. Tearing influences the insulation condition and facilitates macrophage and pathogen accumulation. Mechanical forces strengthened by the biological factors decrease the durability of insulation. The outer insulation damage may play a part in infective endocarditis...
development and may also prompt lead dysfunction. Insulation defects may be asymptomatic and in the case of severe abrasion with perforation may, for example, result in oversensing or undersensing. Future studies are needed to single out the population in danger of lead-dependent complications.

Limitation

The study limitation includes the relatively short time of the in vitro experiment (weeks) in relation to the in vivo silicone damage process that occurred during months after implantation.

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Disclosures

None.

References


CLINICAL PERSPECTIVE
Cardiovascular implantable electronic device infection is a rising phenomenon. Outer silicone insulation abrasion is a risk factor of lead-dependent infective endocarditis. Heretofore, scientists focused their research efforts on understanding how material surface chemistry can direct the inflammatory, foreign body, and the wound healing responses. In our article, we present the consequences of interaction among human host, pathogen, and silicone insulation of the endocardial leads. *S aureus*, macrophages separately, and *S aureus* and macrophages cocultures initiate the biodegradation of silicone insulation. Differences in the level of biodegradation between strains of *S aureus* were observed, with the most aggressive reaction toward silicone visible in the cocultures. In vivo silicone biodegradation is initiated by tearing among surfaces of the lead insulation, macrophages may be the crucial cells for the process, which may be aggravated by pathogen colonization. Our observations may influence the treatment of infective endocarditis (eg, initial therapy should involve antibiotics highly active against biofilm, may indicate a direction for new antibiotics design), explain why total hardware removal is currently essential for good results in infective endocarditis treatment, elucidate the possibility of late lead-dependent complications, such as pulmonary hypertension, and indicate the need to isolate the population of patients in danger of late lead-dependent infective endocarditis. Moreover, our remarks may help in lead insulation design.
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