Biodegradation of the Outer Silicone Insulation of Endocardial Leads

Running title: Kołodzińska et al.; Silicone insulation biodegradation

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Abstract:

**Background** - Silicone catheter insulation, larynx prostheses undergo biodegradation. The aim of the study was to verify the conviction that outer silicone lead insulation is biostable, inert and to determine the role of macrophages (M) and *Staphylococcus (S.) aureus* strains in the silicone lead insulation degradation.

**Methods and Results** - Leads removed from 8 patients due to infective and non-infective indications were analyzed with stereomicroscope and classified according to Banacha abrasion classification, additional analysis using scanning electron microscope (SEM) 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, K9328H. Lead fragments were also co-cultured with the bacterial strains and RAW M. In SEM 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 co-cultures presented a further gone level of silicone biodegradation.

**Conclusion** - *S. aureus*, macrophages separately, and *S. aureus* and macrophages co-cultures initiate the biodegradation of silicone insulation. Differences in the level of biodegradation between strains of *S. aureus* were observed, with the most aggressive reaction towards silicone visible in the co-cultures. 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.

**Key words:** Cardiovascular implantable electronic device infection, silicone biodegradation, infective endocarditis, endocardial lead damage, endocardial lead abrasion
Introduction

The development of pacemaker and implantable cardioverter-defibrillator technology improved the quality of life of patients and prolonged their lifespan.\textsuperscript{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. Nowadays silicone, polyether polyurethane, and co-polymers are widely used. Medical grade silicone used as insulation has been improving lead reliability for over 50 years. Its advantages include flexibility, tensile strength, biostability and biocompatibility, it is also considered inert. The most important disadvantages are its low resistance to tearing, low abrasion resistance, and high friction in contact with blood.\textsuperscript{3,4,5}

However in literature scientists indicate that silicone may not be biostable when serving as the insulation or as a component of prostheses.\textsuperscript{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 \textit{Streptococcus sp.}, \textit{Staphylococci}, \textit{Candida albicans}, \textit{Candida tropicalis}. Electron microscopy analysis has revealed degradation of silicone that leads to voice prosthesis deformation and dysfunction due to filamentous and vegetative yeast cell invasion.\textsuperscript{7} Eymann et al. indicated that hydrocephalus silicone shunt catheters cannot be termed “inert” or “biotolerated” and instead should be regarded as “bio-active” implants.\textsuperscript{6}

Insertion of a foreign body, for example an endocardial lead initiates a complicated immunological 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.\textsuperscript{8,9,10} The macrophage has been implicated as a pivotal cell in the physiological healing of...
tissues around implants as well as in the pathogenesis of implant failure.\textsuperscript{11} Macrophages undergo fusion and form foreign 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.\textsuperscript{12,13}

Cardiovascular implantable electronic device (CIED) infection is a rising phenomenon, documented by the 3.1 fold increase in the number of hospitalizations due to CIED infections between 1996 and 2003.\textsuperscript{14} Staphylococcal species cause from the 60\% to 80\% of infections in the largest reported series.\textsuperscript{15} The abrasion of the outer silicone insulation of endocardial leads regardless the level of degradation is strongly associated with infective endocarditis.\textsuperscript{16} Bacterial adhesion to biomaterials initiates biofilm formation.\textsuperscript{17} The presence of a foreign body influences the host’s defense mechanisms by reducing the phagocytic and bactericidal capacity of polymorphonuclear leucocytes. Additively, the intracellular persistence of bacteria inside macrophages may play a pivotal role in the pathogenesis of biomaterial associated infections.\textsuperscript{18} Monocytes, macrophages, 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.\textsuperscript{19,20}

We observed failure of the outer silicone insulation of transcutaneously removed endocardial leads.\textsuperscript{16,21} Scanning electron microscope 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 believed 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 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 due to chronic pocket infection, infective endocarditis, or non-infective indications (Table 1). Leads were analyzed with both optical and scanning electron microscope. The abrasions of the outer insulation were classified according to Banacha classification. Three levels of silicone degradation were distinguished: type 1-3, all in two subtypes a and b.16

A fresh silicone insulated lead (Synox, Biotronik) was cut into 1 cm 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 microscopy and a scanning electron microscope (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) and cultured with a RAW 264.7 macrophage cell line (American Tissue Culture Collection) at 37°C, 5% CO2 for 9 weeks. Every third day fragments with macrophages were placed in fresh medium (DMEM, 5% FBS, GIBCO; 50U Penicillin, 50μg Streptomycin, GIBCO) with or without lipopolysaccharide (LPS) (1 μg/ml, *E. coli* BO4:111, Sigma).
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. 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.

Co-culturing 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% FBS, GIBCO; 50U Penicillin, 50μg Streptomycin, GIBCO) and incubated for additional 3 weeks.

Results

15 leads were removed transcutaneously from 8 patients, 5 male, 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 (i.e. infective endocarditis-IE, chronic pocket infection-CPI) 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 which 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 appear most
frequently in the intracardiac region, whereas in the pocket they present sparser occurrence (Table 2).

Abrasions classified as type 1a usually occupy from 30-50% of the lead circumference. The type 2b is elongated with a diameter of under 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 cm-3.5 cm, with insulation perforation and metal conductor exposure (the longest diameter of silicone deficiency ranges from 0.5 cm 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 three days). Leads fragments were placed in fresh medium with or without lipopolysaccharide (LPS). 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 paper is innovative because it combines new important information on the role of the immunological 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 other hand 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 co-cultures 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 towards silicone visible in the co-cultures. 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 due to both infective and non-infective indications. At a single location more than one 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 like blood flow, macrophage adhesion, pathogen presence and biofilm formation, the efficiency of the immunological response (decreases e.g. 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 due to recurrent peritonitis. Moreover, the authors observed 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, finally envelopes with a coating layer of exopolysaccharide that prevents the entrance of antibiotics, and allows to acquire resistance to antibiotics over time.\(^1\) \(^7\)

*Staphylococcus aureus* infection determines a poor outcome in patients with infective endocarditis.\(^2\)\(^5\) Sensitivity of *Staphylococcus aureus* to antibiotics such as tetracycline, benzylpenicillin and vancomycin was found to decrease by 2-10-fold when cells were grown adherent to silicone catheters surface.\(^2\)\(^6\) SEM analysis of silicone voice prostheses covered with biofilm revealed degradation of silicone due to filamentous and vegetative yeast cell growth into silicone rubber which allowed for pathogens to avoid detachment.\(^2\)\(^7\),\(^2\)\(^8\),\(^2\)\(^9\) In our experiment all *Staphylococcus aureus* strains participated in silicone insulation biodegradation while presenting different grades of aggression towards 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.\(^3\)\(^0\),\(^3\)\(^1\) 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.\(^1\)\(^8\) The fore mentioned observation may explain the presence of silicone degradation in patients who underwent lead removal due to non-infective 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.\(^1\)\(^8\),\(^3\)\(^2\) Detachment of small silicone fragments may also activate macrophages and foreign body giant cells leading to phagocytosis and “biting out” of silicone debris.
The immunological response of the patient undergoes modification after device implantation. The adhesion of macrophages and foreign body giant cells (FBGCs) 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 (ROI, oxygen free radicals), degradative enzymes, and acid to the privileged zone. On the other hand the adhesion of the macrophages and FBGCs reduce phagocytic capacity, cellular immunity, and bacteriocidal capability.33 Biomaterials may facilitate apoptosis (programmed cell death) and transform macrophages into cells incapable of attacking foreign organisms that may be adherent to the biomaterial.34 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.35 Perry et al. indicated two 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.36 It appears 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 FBGCs.

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.37 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.38,39

Silicone rubber has been widely used as an insulation for more than 50 years, after
undergoing approval during appropriate preclinical material bioqualification tests.\textsuperscript{40} Employing 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.\textsuperscript{40} Purity is another factor that can affect bio-test results.\textsuperscript{40} Our \textit{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 lead. However in the \textit{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.

\textbf{Limitation to the study}

The limitation of this study is the relatively short time of the \textit{in vitro} experiment (weeks) in relation to the \textit{in vivo} silicone damage process that occurred during months after implantation.

\textbf{Acknowledgments:} We are grateful to Andrzej Czubaj PhD, Julita Nowakowska M. Sc, (Laboratory of Electron Microscopy, Faculty of Biology, University of Warsaw) for help with the scanning electron microscope and Anna Ratajska PhD (Department of Pathological Anatomy, Medical University of Warsaw) for making the stereomicroscope accessible to us.

\textbf{Funding Sources:} Internal founds of Medical University of Warsaw

\textbf{Conflicts of Interest Disclosures:} None.
References:


Table 1. Patient characteristics. (M-male, F-female, IE-infective endocarditis, CPI-chronic pocket infection, NI-non-infective indications)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Indication for removal</th>
<th>Number of implanted leads</th>
<th>Pacing mode</th>
<th>Complications during removal</th>
<th>Procedure duration (minutes)</th>
<th>Number of procedures until removal</th>
<th>Time since the last procedure (months)</th>
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<td>VVI</td>
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<td>120</td>
<td>1</td>
<td>84</td>
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Table 2. Lead characteristics and abrasion type according to Banacha Classification. (BP- bipolar, A-active fixation, P-passive fixation, RVA- right ventricular apex, RVOT-right ventricular outflow tract, RAA-right atrium auricle, LVV- left ventricle vein, CS- coronary sinus)

<table>
<thead>
<tr>
<th>Lead</th>
<th>Patient</th>
<th>Tip location</th>
<th>Polarity</th>
<th>Fixation</th>
<th>Dwell time [months]</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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BP- bipolar, A-active fixation, P-passive fixation, RVA- right ventricular apex, RVOT-right ventricular outflow tract, RAA-right atrium auricle, LVV- left ventricle vein, CS- coronary sinus

Figure Legends:

Figure 1. Endocardial lead abrasion in the intracardiac part classified according Banacha classification as mild: A-type 1a with silicone cloudiness, moderate: B- type 2a (resembles a canoe with the ends narrowing and a gradual decrease in the silicone towards the central part of the abrasion), C- type 2b (the longitudinal lesion diameters at most points are the same, and the
depression walls descend vertically), and severe with outer insulation perforation and conductor exposure: D- type 3a. A’- cloudiness of the silicone is the result of diminution in silicone, A” excavation, and hollows in silicone are different shape and deepness hypothetically are the result of macrophages like cells phagocytic abilities. B’, B”, C’, C”, D’ and D” presents diminution in silicone of different shape and in different level of degradation. E, E’, E”- the pocket part of the lead of the youngest patient- silicone fragments are transmitted between parts. The morphology different form observed in A-D hypothetically because of lack of blood flow, and so many phagocytic cells as in the heart chambers that wash out and phagocyte the silicone debris respectively.

**Figure 2.** Macrophage culture on the fresh silicone insulated lead A, A’ and C, C’ without LPS (lipopolysaccharide); B, B’ and D, D’ with LPS. C and D were scraped with syringe needle that provoked macrophage accumulation in the depressions. A’ - D’ characteristic silicone deformation with depressions. The most significant biodegradation shown on B’ and D’. A - D stereomicroscopic view. A’ - D’ SEM (scanning electron microscope) analysis results.

**Figure 3.** A - *Staphylococcus aureus* ATCC 25923 strain biofilm on the fresh silicone insulated lead; A’, A” - macrophages and ATCC 25923 co-culture; B - ATCC 29213 biofilm; B’, B” - ATCC 29213 and macrophages co-culture; C - K9328H biofilm; C’, C”- K9328H and macrophages co-culture. A – C: mild level of silicone degradation; A’ - C’ and A” - C”: moderate silicone biodegradation. B’ and B” show the most severe silicone destruction.
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