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Antibiofilm Activity of Electrical Current in a Catheter Model

Paul Voegele,[a] Jon Badiola,[a] Suzannah M. Schmidt-Malan,[a] Melissa J. Karau,[a] Kerryl E. Greenwood-Quaintance,[a] Jayawant N. Mandrekar,[b] Robin Patel[a,c]

Division of Clinical Microbiology, Department of Laboratory Medicine and Pathology,[a] Division of Biomedical Statistics and Informatics, Department of Health Sciences Research,[b] and Division of Infectious Diseases, Department of Medicine,[c] Mayo Clinic, Rochester, Minnesota, USA

Catheter-associated infections are difficult to treat with available antimicrobial agents because of their biofilm etiology. We examined the effect of low-amperage direct electrical current (DC) exposure on established bacterial and fungal biofilms in a novel experimental *in vitro* catheter model. *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida parapsilosis* biofilms were grown on the inside surfaces of polyvinyl chloride (PVC) catheters, after which 0, 100, 200, or 500 μA of DC was delivered via intraluminally placed platinum electrodes. Catheter biofilms and intraluminal fluid were quantitatively cultured after 24 h and 4 days of DC exposure. Time- and dose-dependent biofilm killing was observed with all amperages and durations of DC administration. Twenty-four hours of 500 μA of DC sterilized the intraluminal fluid for all bacterial species studied; no viable bacteria were detected after treatment of *S. epidermidis* and *S. aureus* biofilms with 500 μA of DC for 4 days.

Catheter-associated infections, including catheter-associated urinary tract infection (CAUTI) and catheter-related bloodstream infection (CRBSI), are associated with morbidity, mortality, and expense, often requiring catheter removal. The pathogenesis of these infections relates to the presence of biofilms on the surface of the catheters.

Compared with planktonic (i.e., free-floating) forms, microorganisms in biofilms exhibit increased resistance to host immunity and antimicrobial therapy (1). Proposed mechanisms underlying biofilm-associated antimicrobial resistance include limited penetration through or neutralization of antimicrobials within biofilms (2, 3); subpopulations of resistant phenotypes, referred to as "persister" cells (4, 5); and dormant stationary-phase zones within biofilms (4, 6, 7). As a result, most conventional systemically administered antimicrobial agents have little ability to cure catheter-associated infections. Catheter removal is necessary in the majority of cases, typically in conjunction with systemic antimicrobial treatment. Strategies to control biofilms, such as coating catheters with silver ions, chlorhexidine or minocycline plus rifampin, have been proposed (8–12), and catheter lock solutions, using conventional antimicrobial agents or antiseptics, have shown activity against catheter-associated biofilms (13–19). However, none of these strategies has solved the clinical challenge of catheter-associated infections, underscoring the need for new approaches.

We previously described an antibiofilm strategy that we termed the electricidal effect. Biofilms of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* on Teflon discs were exposed to 20, 200, or 2,000 μA direct current (DC) for up to 7 days, which resulted in time- and dose-dependent antibiofilm effects, as measured by decreases in numbers of viable cells (20). Subsequent studies confirmed the microbicidal activity of continuously and intermittently applied electrical current against established biofilms of several bacterial and fungal species *in vitro* and in animal models (21–25).

A potential avenue to deliver electrical current is to administer it to the lumen of catheters. This location of biofilm formation in CRBSI and CAUTI provides a site targetable by electrical current. Based on our prior work, we hypothesized that DC delivered via intraluminally placed electrodes would provide an antibiofilm strategy targeting intraluminal biofilms. This approach could limit the use of antibiotics as well as the replacement of infected catheters. In this study, we examined the effect of different amperages and delivery durations of DC on established intraluminal biofilms of four bacterial and one fungal species in a novel *in vitro* catheter model.

MATERIALS AND METHODS

Microorganisms. *Staphylococcus epidermidis* Xen43, *Staphylococcus aureus* Xen30, *Pseudomonas aeruginosa* Xen5, *Escherichia coli* IDRL-7029, and *Candida parapsilosis* IDRL-7250 were studied. The Xen strains were generous gifts of PerkinElmer Caliper Life Sciences (formerly Xenogen Corporation), Waltham, MA, and the IDRL isolates were clinical isolates collected at Mayo Clinic, Rochester, MN.

Catheters. Six-millimeter-inner-diameter 28 French (Fr) polyvinyl chloride (PVC) thoracic catheters (Atrium Medical Corporation, Hudson, NH) were cut to a length of 45 mm and sterilized by using ethylene oxide. Polyoxymethylene plastic caps were used to seal the catheter bottoms and tops; platinum electrodes (50 mm in length and 1.6 mm in diameter) were inserted through and held in place by the latter (Fig. 1).

Biofilms. Microorganisms were subcultured from frozen aliquots onto BBL Trypticase soy agar with 5% sheep blood plates (TSA II; Becton Dickinson, Franklin Lakes, NJ) and incubated at 37°C overnight. One to three colonies were added to 2.5 ml of Trypticase soy broth (TSB) and grown for 1 to 3 h at 37°C on an orbital shaker to reach a 0.5 McFarland standard. One hundred microliters of the 0.5 McFarland standard solutions was added to 0.9 ml TSB in sterile PVC catheters capped at one end, placed into a sterile glass box, and incubated on an orbital shaker at 37°C

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Address correspondence to Robin Patel, patel.robin@mayo.edu.

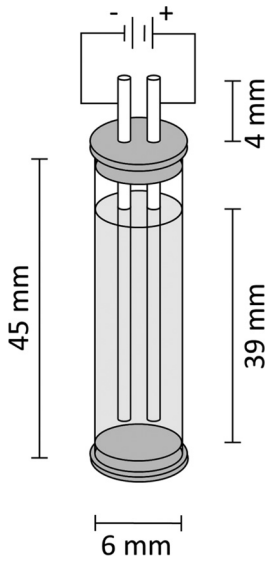

FIG 1 Catheter biofilm model. PVC catheters (inner diameter of 6 mm) were cut to a length of 45 mm, and polyoxymethylene plastic caps were used to seal the bottom of the catheters and were placed into catheter tops to hold platinum electrodes (50 mm in length and 1.6 mm in diameter) in place.

for 24 h. TSB was then removed by using a pipette and replaced with 1.1 ml phosphate buffer.

Phosphate buffer. Phosphate buffer (1×) was prepared with 426 mg Na_2HPO_4, 205 mg KH_2PO_4, 640 mg glucose, and 1 liter distilled water; filter sterilized; and stored at 4°C. The stock phosphate buffer was diluted to 3% in sterile water for each experiment.

Electrical treatment. Electrical current was applied by using an 8-channel computer-controlled current generator designed by the Mayo Clinic Division of Engineering (Rochester, MN) via anode and cathode electrical hooks connected to the electrodes. Catheters were treated with 0, 100, 200, or 500 μA DC current for either 24 h or 4 days, with testing being performed in triplicate.

Biofilm and planktonic cell densities. Biofilm and planktonic cell densities were determined by quantitative culture. Intraluminal phosphate buffer was quantitatively cultured to obtain planktonic cell densities. To obtain biofilm densities, caps were aseptically removed from the catheters, which were gently rinsed in sterile saline and placed into test tubes containing 5 ml of sterile saline. Biofilms were removed by vortexing for 30 s, sonication for 5 min, and vortexing again for 30 s; the resultant fluid was quantitatively cultured. CFU were counted after 24 to 48 h. Biofilm reduction was expressed by subtracting the mean $\log_{10}$ CFU per square centimeter of exposed catheters from that of nonexposed catheters.

Statistical methods. Comparison among 4 current levels (0, 100, 200, and 500 μA) was first performed by using the Kruskal-Wallis test. If the results were significant, further comparisons were performed in a pairwise manner (0 versus 100 μA, 0 versus 200 μA, 0 versus 500 μA, 100 versus 200 μA, 100 versus 500 μA, and 200 versus 500 μA) by using the Wilcoxon rank sum test. No adjustment was performed for multiple comparisons due to small sample sizes. All tests were two sided; P values of <0.05 were considered statistically significant. Analyses were performed by using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Results are shown in Fig. 2. We detected statistically significant differences between no electrical current exposure and electrical current exposure of 200 μA and higher for all microorganisms studied ($P \leq 0.02$). Higher amperage yielded greater reductions of biofilm viability at all times studied. Time-dependent reductions in numbers of viable biofilm cells were observed, with lower viable-cell counts when electrical current was applied for longer periods of time. No viable cells were detected when *S. aureus* or *S. epidermidis* biofilms were exposed to 500 μA DC for 4 days. Reductions of 5.2 to 5.5 $\log_{10}$ CFU/cm^2 were observed when *P. aeruginosa* and *E. coli* biofilms were exposed to 500 μA DC for 4 days ($P < 0.02$). *C. parapsilosis* biofilms were more resistant, with a maximum reduction of 3.2 $\log_{10}$ CFU/cm^2 being achieved after 4 days of treatment with 500 μA DC (P value of 0.01). Significant biofilm reductions were also observed for treatment with 200 μA for 24 h, ranging from 1.4 to 2.1 $\log_{10}$ CFU/cm^2 ($P < 0.02$). Application of 100 μA DC for 24 h (and 4 days) reduced *E. coli* biofilm densities and the number of planktonic cells ($P \leq 0.02$); 100 μA applied for 4 days reduced the *S. epidermidis* biofilm density (P value of 0.01). A greater biofilm effect was measured with 500 μA than with 200 μA DC ($P < 0.05$) for all organisms and durations, except for *C. parapsilosis* after 24 h and *S. epidermidis* and *P. aeruginosa* after 4 days, possibly due to the small sample size. Likewise, 500 μA showed greater reductions than did 100 μA DC for biofilms and planktonic cells with 24 h and 4 days of application ($P \leq 0.05$), except for *S. aureus* and *S. epidermidis* planktonic cells with 4 days of exposure. Comparison between treatments with 100 and 200 μA DC showed less marked differential reductions of biofilm densities and numbers of planktonic cells; however, a significant difference in effect was measured for 200 μA compared to 100 μA DC for both planktonic cells and biofilms at 24 h and 4 days for *P. aeruginosa* ($P \leq 0.05$).

Generally, greater reductions were observed for planktonic cells than for biofilms. No viable planktonic cells were observed after exposure to 500 μA DC at any time point for all bacterial species studied. However, viable planktonic *C. parapsilosis* cells were found after 24 h of exposure to 500 μA DC (reduction of 2.4 $\log_{10}$ CFU/ml; P value of 0.01). Exposure to 200 μA achieved reductions ranging from 1.7 to 6.2 $\log_{10}$ CFU/ml ($P < 0.02$) after 24 h and from 3.6 to 7.0 $\log_{10}$ CFU/ml ($P < 0.02$) after 4 days for all bacterial species. Reductions in numbers of planktonic cells ranging from 1.1 to 4.4 $\log_{10}$ CFU/ml were measured after 4 days of exposure to 100 μA for the bacterial species. Again, *C. parapsilosis* was more resistant, with a reduction of just 0.7 $\log_{10}$ CFU/ml after 4 days of exposure to 100 μA DC ($P = 0.16$).

DISCUSSION

In this study, we demonstrated that DC reduces staphylococcal, *E. coli*, *P. aeruginosa*, and *C. parapsilosis* biofilms on the intraluminal surface of catheters in a time- and dose-dependent manner. The most dramatic effects (i.e., no detectable viable cells) were observed when *S. epidermidis* and *S. aureus* biofilms were exposed to 500 μA DC for 4 days, although large reductions ($\geq$5.0 $\log_{10}$ CFU/cm^2) were also observed when *P. aeruginosa* and *E. coli* biofilms were exposed to 500 μA DC for 4 days. Reductions of $>$1.0 $\log_{10}$ CFU/cm^2 were observed with *C. parapsilosis* exposed to 200 or 500 μA DC; however, the degree of reduction was lower than that observed with the other organisms studied. Exposure to 100 μA DC yielded biofilm reductions for *S. epidermidis* (after 4 days) as well as for *E. coli* and *P. aeruginosa* (after 24 h). Overall, these results show that electrical current, applied via intraluminal electrodes, has a marked effect on microbial biofilms on catheter surfaces.

The underlying mechanism of the effect observed is not fully

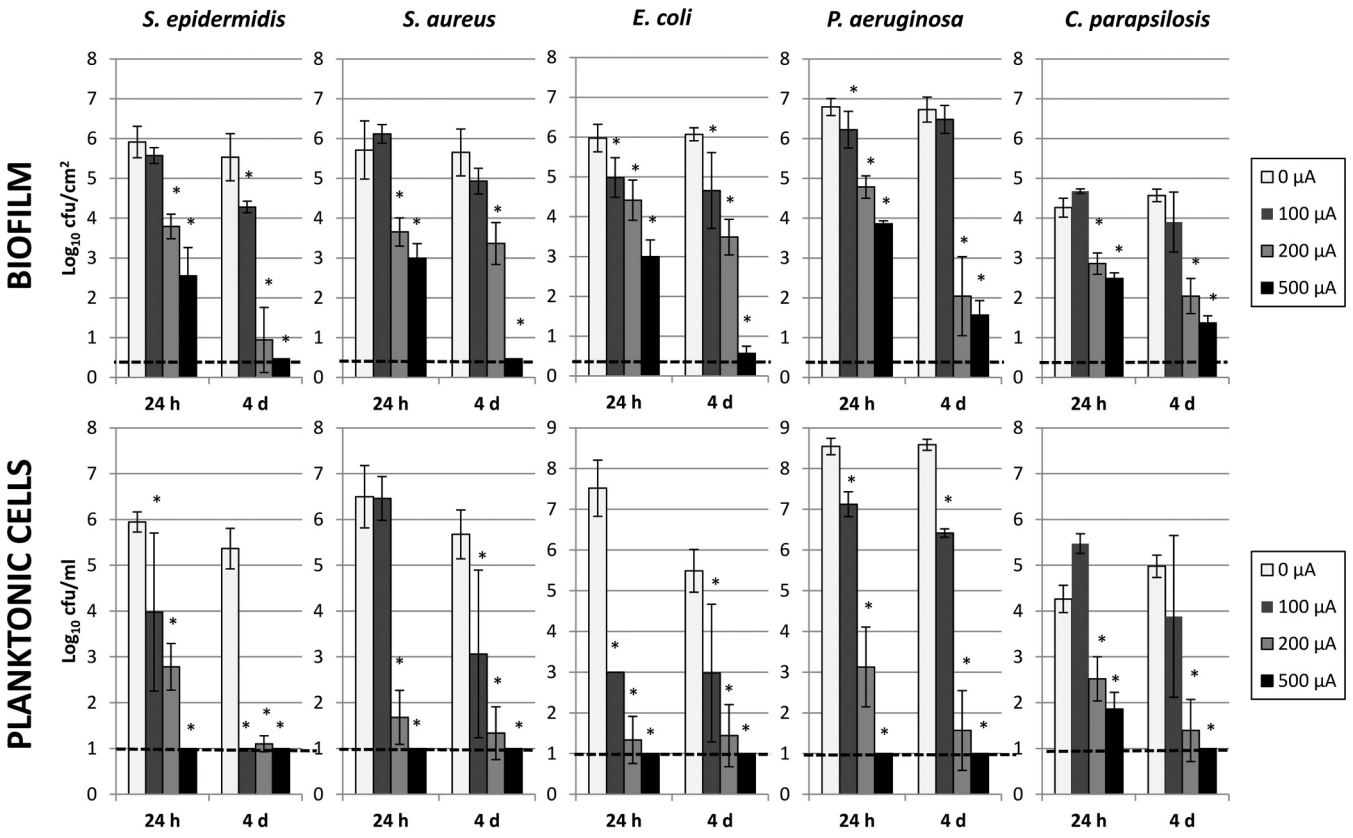

FIG 2 Results for quantitative cultures of *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida parapsilosis* biofilms on PVC catheters and planktonic cells in the study buffer after exposure to 0, 100, 200, and 500 μA DC for 24 h and 4 days. The *x* axis represents hours (h) and days (d) of DC exposure. The *y* axis shows results for quantitative cultures as $\log_{10}$ CFU per square centimeter for biofilm and $\log_{10}$ CFU per milliliter for planktonic cultures. Error bars indicate standard deviations. The dashed line indicates the limit of detection. *, statistical significance ($P < 0.05$) compared to 0 μA.

understood. Oxidative stress (26–30), damage to the cell walls (31, 32), changes in pH (33, 34), and the formation of hypochlorous acid by electrolysis (33) have been proposed. The results generated here support an electrochemical mechanism. Detachment promoted by enhanced repulsive forces between microorganisms and surface materials may also play a role (31, 35–38).

Although our results are consistent with previously reported data showing a bactericidal effect of DC on sessile and planktonic cells, previous studies either used different electrode positioning, focusing on biofilms grown on discs placed between two electrodes (22, 25, 39), or investigated the effects of custom-fabricated, electrically conductive catheters on bacterial colonization in agar plates (40). In this study, electrodes were simply placed into the lumen of commercially available catheters on which biofilms had been grown. Theoretically, this could be adapted to clinical settings by introducing electrodes into infected catheters, without the need for expensive changes to the design of available catheters.

Limitations of this study relate to the methodology employed and the ability to extrapolate our findings. The phosphate buffer did not resemble physiological body fluids such as blood or urine. Chlorine, which is abundantly present in body fluids and which might enhance the effect by formation of hypochlorous acid (33), was not added to the study buffer (but might have been present in small quantities as a result of having grown biofilms in TSB). Catheter materials like silicone or latex, which are widely used in urinary or venous catheters, might behave differently with regard to biofilm growth and/or reduction achieved by electrical current than the PVC catheters used in this study. It also has to be considered that in this model, electrodes were placed intraluminally, not affecting the outer catheter surface. *In vivo* biofilms may grow on the outer and inner surfaces of infected catheters (41, 42). Interestingly, studies using electrified catheters with comparable electrode positioning showed reduced encrustation by *Proteus mirabilis* biofilms at the catheter eyelet region *in vitro* (43) and reduced microbial populations associated with catheter-associated urinary tract infections *in vivo* (44, 45). Finally, safety issues need to be addressed to use this strategy in a clinical setting. The use of low-dose electrical current within the urinary tract appears to be safe; a study of electrified catheters in sheep reported no physical or chemical changes of urine or the tissues of the urinary tract with an amperage of 400 μA (44). Similarly, an electrified urinary catheter trial in humans did not show adverse effects or evidence of catheter damage (45). Possible adverse reactions to electrical current delivered into intravascular catheters, including cardiac arrhythmias, hemolysis, and thrombus formation, require further investigation.

In conclusion, our results demonstrate that biofilms in catheters can be reduced by using low-dose DC. Although further *in*

vitro and *in vivo* studies are needed, this strategy might be useful to combat clinically challenging catheter-associated infections.

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