

## Bacterial Inhibition by Electrical Stimulation

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**Significance:** Much evidence shows that electrical stimulation (ES) promotes the wound healing process. The inhibitory effect of ES on bacterial growth has been proposed as a mechanism to explain the useful effects of ES on wound healing. Bacterial burden has been associated with chronic wounds. The extensive use of antibiotics can lead to the spread of multiple drug resistant bacteria. Whether biophysical energies, such as ES, can be used as a treatment modality against pathogenic microorganisms remains an open question.

**Recent Advances:** The research literature provides evidence for useful effects of ES in terms of inhibition of bacterial growth. The type of ES, its polarity, and the intensity of the current play a major role in establishment of antibacterial effects. Both direct current (DC) and high voltage pulse current are more effective at inhibiting bacterial growth than are other types of ES. The exact mechanism underlying the antibacterial effects of ES is not clear.

**Critical Issues:** Available evidence indicates that microampere DC ( $\mu$ ADC) is better than other ES types for inhibition of bacterial growth. The results of most studies also support the application of cathodal current for bacterial growth inhibition. The current intensity of ES would appear to be tolerable by humans if used clinically for treatment of infected wounds.

**Future Directions:** The cathodal  $\mu$ ADC appears to be more effective for inhibition of microorganism growth. Further research, especially *in vivo*, is necessary to clarify the inhibitory effects of ES on wound bacterial infections.



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### SCOPE AND SIGNIFICANCE

SUBSTANTIAL EVIDENCE NOW supports the use of electrical stimulation (ES) for promoting wound healing.<sup>1-5</sup> Numerous mechanisms have been suggested to explain the phenomenon of wound healing by ES, including increased angiogenesis due to release of angiogenic factors (vascular endothelial growth factor, fibroblast growth factor-2),<sup>6-9</sup> increased circulation<sup>10,11</sup> and direct antibacterial effect of ES.<sup>12</sup>

Over 30 years ago, Rowley was the first to report a bacteriostatic effect of ES.<sup>13</sup> Since then, bacteriostatic and bactericidal effects of ES have been extensively documented.<sup>12-15</sup> This review focuses on the *in vitro* and

*in vivo* evidence that supports a role for ES in the inhibition of bacterial growth during wound healing.

### TRANSLATIONAL RELEVANCE

The research literature provides evidence for useful effects of ES in terms of inhibition of bacterial growth.<sup>12-15</sup> The type of ES and its different parameters may be important in establishment of antibacterial effects. ES is suggested to affect bacterial growth via direct and indirect effect but, the exact mechanism underlying this effect is still poorly understood. The examination of ES antibacterial effect based on *in vitro* and *in vivo* available evidence can indicate the potential of ES for

#### Abbreviations and Acronyms

- AC = alternating current
- DC = direct current
- ES = electrical stimulation
- HVPC = high-voltage pulsed current
- LIDC = low intensity direct current
- LVBPC = low-voltage biphasic pulsed current
- LVMPC = low-voltage monophasic pulsed current
- $\mu$ ADC = microampere direct current

bacteriostatic and bactericidal effect on microorganism growth that is very important for the wound healing process.

### CLINICAL RELEVANCE

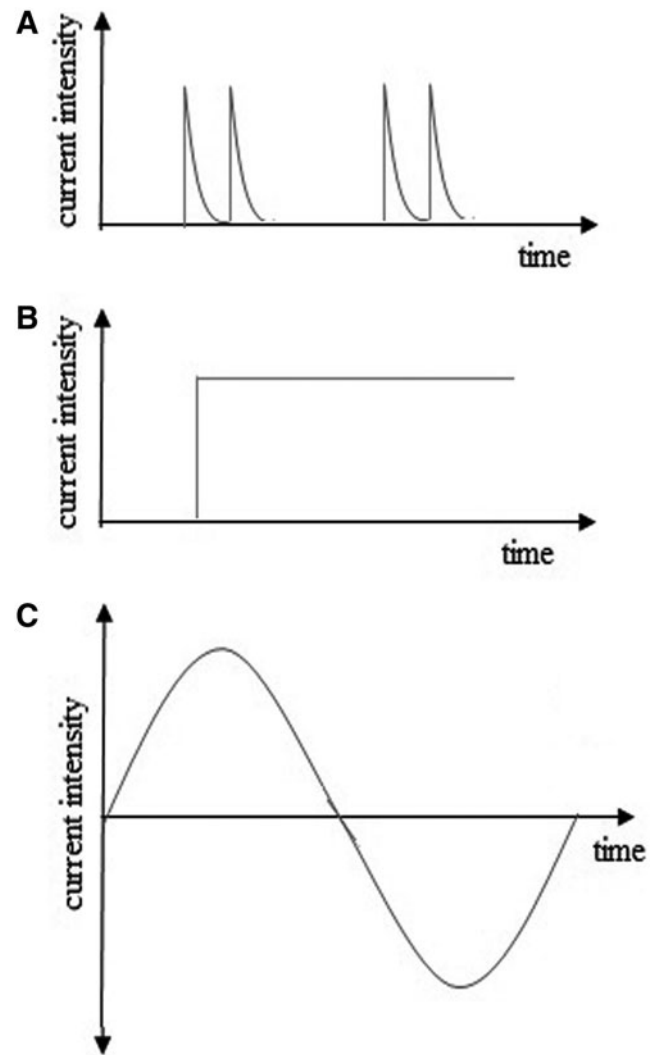
Bacterial invasion is one of the factors that delay the wound healing process.<sup>12</sup> Bacteria rupture viable cell membranes and maintain chronic inflammation that prevents wound healing.<sup>16</sup> However, the extensive use of antibiotics for the treatment of bacterial infection has led to the spread of multiple drug resistant bacteria. Recent studies have therefore, focused on the potential use of ES as a treatment modality against pathogenic microorganisms.<sup>12–15</sup> If the antibacterial effects of ES can be induced in human infected wounds, ES may prove to be a superior antimicrobial agent that would overcome some of the issues currently raised by antibiotic resistance.

### DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

#### Parameters of ES for antibacterial effects in research

The available research that has examined the capacity for ES to inhibit or destroy pathogens indicates that various parameters of ES (*e.g.*, current type, current density, polarity, *etc.*) have been employed in the past. Various types of ES have been used in this research, including low-intensity direct current (LIDC), alternating current (AC), and high-voltage pulsed current (HVPC) with diverse parameters (Fig. 1). In an early study, Rowley<sup>13</sup> focused on the *in vitro* antibacterial effects of AC (milliampere level) and cathodal direct current (DC). They reported that the growth rate of *Escherichia coli* was affected very little or not at all by AC, while a bacteriostatic effect occurred with cathodal DC. Later, Rowley *et al.*<sup>12</sup> demonstrated that cathodal DC had a bacteriostatic effect on the *in vivo* growth of *Pseudomonas aeruginosa* when applied to rabbit skin wounds at an amplitude of 1 mA for 72 h.

Barranco *et al.*<sup>15</sup> applied DC stimulation with stainless steel, platinum, gold, and silver electrodes at amplitudes of 0.4, 4, 40, and 400  $\mu\text{A}$  for 48 h on *Staphylococcus aureus* in an *in vitro* model. The authors observed that the silver anode electrode had a bactericidal effect on *S. aureus* at 0.4 and 4  $\mu\text{A}$ , while other electrodes induced growth inhibition only at 400  $\mu\text{A}$ . Spadaro *et al.*<sup>17</sup> applied DC current with silver, platinum, stainless steel, gold, and copper electrodes on four bacterial species *in vitro*. They found that, at a high current range (400  $\mu\text{A}$ ),



**Figure 1.** Various waveforms of electrical stimulation (ES) are available in research, including (A) high-voltage pulsed current, (B) direct current, and (C) alternating current.

electrodes inhibited bacterial growth at both negative and positive poles, while at lower current levels (0.4 and 4  $\mu\text{A}$ ), only the silver electrode had a bacteriostatic effect when used as the anode. Bolton *et al.*<sup>18</sup> investigated the effect of DC stimulation on microorganisms in intact human skin. Current was delivered through carbon-filled electrodes for 4 or 24 h with 10, 25, 50, 75, and 100  $\mu\text{A}$ . Bactericidal effects were seen at 4 and 24 h beneath the positive electrode. The authors suggested that the bactericidal effect of the electric current was dependent on the current density and on the acid pH that was generated at the positive electrode. The *in vitro* study by Karba *et al.*<sup>19</sup> examined the effect of LIDC (0.2–1 mA) on *Candida albicans*. The authors found that DC for all amplitudes and application times (2, 10, and 18 h) inhibit the *C. albicans* growth.

However, the inhibitory action of DC was dose-dependent and time-dependent with respect to the electric current. In an *in vivo* study, Wolcott *et al.*<sup>14</sup> used LIDC for treatment of chronic skin ulcer initially colonized with *Pseudomonas* and *proteus* organisms. In this study, the cathodal DC (microampere level) was initially applied to the ulcers. The authors observed that the treated ulcers became free of pathogens within a few days. Another *in vitro* study by Liu *et al.*<sup>20</sup> showed antimicrobial activity of low amperage DC (10  $\mu$ A) around the cathode when current was applied to *S.aureus* and *Staphylococcus epidermidis* for 16h. Del Pozo *et al.*<sup>21</sup> demonstrated marked reduction of *S. epidermidis*, *S. aureus*, and *P. aeruginosa* biofilm by prolonged exposure to DC stimulation. Current was delivered via stainless steel or graphite electrodes with 20, 200 or 2,000 microamperes for 1–7 days. These authors observed that a higher electrical current intensity resulted in a greater decrease in viable bacteria at all time points studied. Subsequent to these reports, numerous other studies established that application of weak DC (0.1–10  $\mu$ A) through a silver ion electrode increased the antimicrobial action of silver by increasing the rate of silver release.<sup>22–24</sup> Spadaro *et al.*,<sup>17</sup> in an *in vitro* study, demonstrated that silver, when used as an anode, is extremely bacteriostatic, even at the lowest current, whereas the penetration of the silver ion applied topically is limited. The addition of LIDC to metallic silver increased the penetration depth of silver into the wound site.<sup>25</sup>

The use of HVPC for inhibition of bacterial growth was initially based on the results of studies using LIDC. Unlike DC, scant research has examined the antibacterial effects of HVPC *in vitro* and *in vivo*. Kincaid and Lavoie<sup>26</sup> reported that growth of *S.aureus*, *E. coli*, and *P. aeruginosa* (bacterial species that are commonly found in open wounds) was inhibited *in vitro* at both the anode and cathode after exposure to HVPC for 2 h at 250 V. Similarly, Szuminsky *et al.*<sup>27</sup> evaluated the antibacterial effect of HVPC on four bacterial species (*S. aureus*, *E. coli*, *Klebsiella*, and *P. aeruginosa*) in an *in vitro* study. The authors suggested that HVPC at both the positive and negative electrode exerted antimicrobial effects when applied at 500 V for 30 min. Conversely, Guffey and Asmusen<sup>28</sup> compared the inhibitory effect of HVPC and DC in an *in vitro* study and showed that DC stimulation showed antibacterial effects, but HVPC did not, when current was applied for 30 min at < 160 V. Daeschlein *et al.*<sup>29</sup> showed that low voltage pulsed current had an antibacterial effect on Gram-positive and Gram-negative bacteria *in vitro* and they ob-

served this antibacterial effect at both positive and negative polarity.

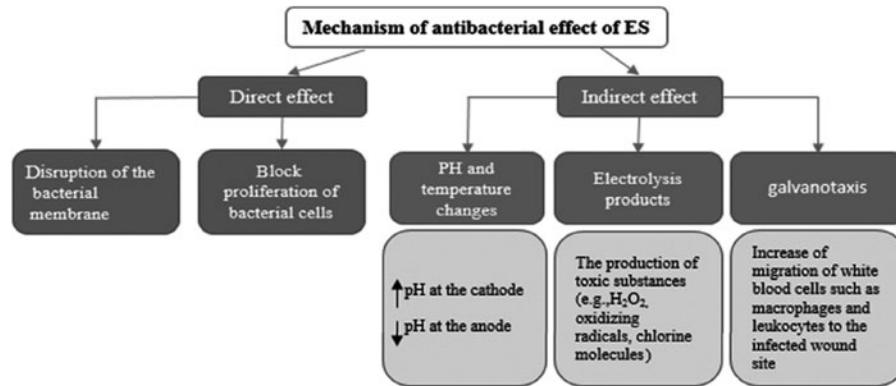
The efficacy of DC and AC at exerting antibacterial effects has only been investigated in one *in vitro* study to date, and this showed positive effects of AC. Petrofsky *et al.*<sup>30</sup> exposed three types of bacteria (*S. aureus*, *E. coli*, and *P. aeruginosa*) to either biphasic sine wave, 5 or 20 mA, or DC stimulation, at 100  $\mu$ A, for 30 min *in vitro*. The authors reported that DC stimulation had no bacteriostatic effects for any of the bacteria, whereas AC stimulation (both 5 and 20 mA) significantly reduced the growth of *P. aeruginosa*, but had little effect on *S. aureus* or *E. coli*. Another investigation that compared the antibacterial effects of AC and DC stimulation *in vitro* showed that AC had no inhibitory effect on growth of *P. aeruginosa*, whereas both the cathodal and anodal DC stimulation inhibited growth of this organism.<sup>31</sup>

In a comparable study, Merriman *et al.*<sup>32</sup> evaluated the effects of four types of ES—microampere direct current ( $\mu$ ADC), HVPC, low voltage monophasic pulsed current (LVMPC), and low voltage biphasic pulsed current (LVBPC)—on bacterial growth *in vitro*. They demonstrated an inhibitory effect for  $\mu$ ADC and HVPC at both negative and positive polarity whereas LVMPC and LVBPC had no inhibitory effect at any polarity.

The research literature provides evidence to indicate a useful effect of ES for inhibition of bacterial growth. Review of these results suggests that the type of ES plays a major role in establishment of antibacterial effects. Both DC and HVPC appear to be effective at inhibiting bacterial growth. Although the efficacy of the antibacterial effect of HVPC has been shown, the voltages used in several studies (250 to 500 V) are too high to be tolerated by humans and also may be damaging to the formation of collagen.<sup>33</sup> Therefore,  $\mu$ ADC would appear to be more effective than other ES types for inhibition of bacterial growth. This also supports the thought that the antibacterial effect may be contributing to the promotion of wound healing that is observed with LIDC.<sup>2</sup>

When compared with AC and biphasic (charge balanced) current which have no pH effects, DC creates strong pH effects, while HVPC has little to no polar effects, indicating that pH plays a role in establishment of antibacterial effects by ES. Although some studies have indicated antibacterial effects at both the anode and cathode,<sup>17,26,27,29,31,32</sup> most research supports the application of cathodal current for bacterial inhibition.<sup>12–14,20</sup>

The evidence also indicates that different current intensities might affect the antibacterial



**Figure 2.** A diagram of direct and indirect effects of ES on microorganism growth. It is suggested that plasma transmembrane potential is related to the cell cycle processes. Low transmembrane potential facilitates cell proliferation, while high potential tends to inhibit it. Transmembrane potential of microbes differs from other cells, such as fibroblasts. Thus, different characteristics of the membrane of microbes might be responsible for inhibition of microbe proliferation by ES.<sup>19</sup>

effects of ES. Overall, the inhibitory effect of ES is proportional to the amplitude and application time of electric current. Thus, higher current intensities create more inhibitory effects than do lower intensities.<sup>15,17,19</sup> Collectively, the amplitude of the electric current would appear to be tolerable if used on an infected wound in human tissues. However, further *in vivo* or clinical wound research is needed to confirm the antibacterial effects observed in *in vitro* studies.

### Antibacterial mechanisms of ES

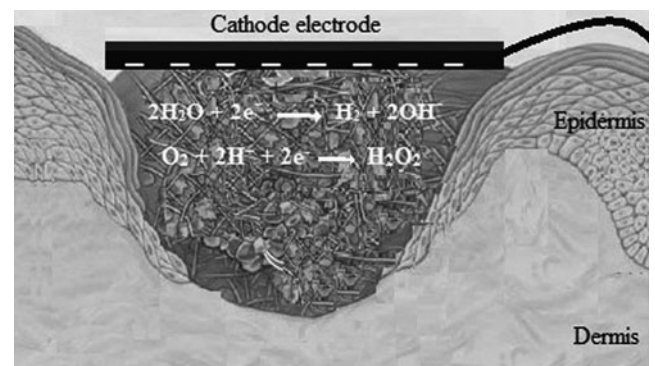
The exact mechanisms by which ES inhibits the growth of microorganisms are unknown and are also controversial. However, two mechanisms are currently proposed to explain the antibacterial effects of ES: a direct effect and an indirect effect (Fig. 2). The direct effect proposes that electric current directly results in bacterial death by disruption of the integrity of the bacterial membrane or electrolysis of molecules on the bacterial cell surface.<sup>19,20,24</sup> Evidence has been presented to support a blockage of proliferation of bacterial cells by DC<sup>19</sup> but further *in vitro* and *in vivo* research is needed to understand the underlying mechanism of these direct antibacterial effects.

Two factors—temperature and pH—were suggested as possible mechanisms to explain the indirect effect of ES. However, according to available evidence, temperature changes are minimal during the application of electric current.<sup>27</sup> Thus, temperature changes would not appear to contribute to the antibacterial effects of ES.

The investigations of application of DC and HVPC indicate that the pH at the cathode tends to be alkaline<sup>18,19,21,26,27,32,34</sup> and, conversely, acidic at the

anode (Figs. 3 and 4, respectively).<sup>18,19,27,32,34</sup> The pH changes are significantly more marked with DC than with HVPC.<sup>32</sup> Due to the waveform of HVPC (it has a low average current), alterations of pH under the electrodes will be very slight.<sup>27</sup> Because the pH changes beneath the electrodes are transient, most investigators believe that these changes are also not the primary cause of the antibacterial effects of ES.<sup>12,27,34</sup> However, when combined with the direct effect of electric current, they may contribute to inhibition of bacterial growth.

The production of toxic substances (*e.g.*, H<sub>2</sub>O<sub>2</sub>, oxidizing radicals, chlorine molecules, *etc.*) as a result of electrolysis has been suggested as another mechanism to explain the indirect antibacterial effects of ES.<sup>18,20,24</sup> Liu *et al.*<sup>20</sup> revealed that a lower level of DC (10  $\mu$ A) produced the antibacterial substances, H<sub>2</sub>O<sub>2</sub> and chlorine, at the cathode and anode, respectively (Figs. 3 and 4, respectively). It is likely that the other antibacterial substances,

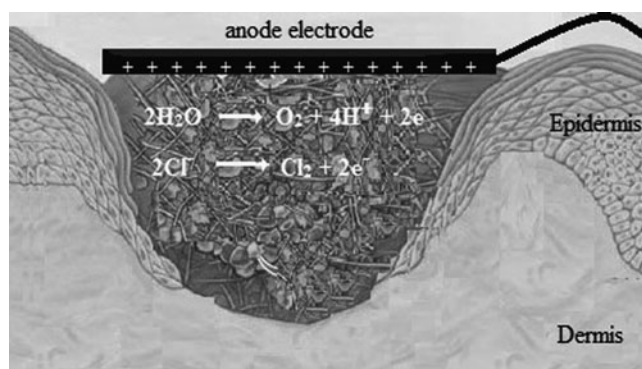


**Figure 3.** This scheme shows that pH at the cathode (negative pole) tends toward alkaline and H<sub>2</sub>O<sub>2</sub>, as an antibacterial substance, produced at the cathode.

such as  $\text{H}_2\text{O}_2$ , ozone, and hypochlorite are also produced if a higher level of electrical current is applied.<sup>20</sup> However, Del Pozo *et al.*<sup>21</sup> did not observe the generation of chlorine or  $\text{H}_2\text{O}_2$  when LIDC was applied for 7 days.

Gas formation at the cathode and corrosion and discoloration at the anode were observed for both HVPC and DC.<sup>15,26,32</sup> These by products can also affect the growth of microorganisms. However, in the *in vivo* condition, the antibacterial effects of ES are unlikely to result from electrolysis products. In addition, the human wound environment is much more complex and it may constantly receive a new supply of highly buffered fluids that can remove electrolysis products rapidly from the wound environment.<sup>32</sup>

One suggested mechanism for indirect antibacterial effects of ES has been that the antibacterial effect of electric current may be the result of galvanotaxis (directional migration of cells to the anode or cathode).<sup>35</sup> Research has demonstrated that lymphocytes, neutrophils, and macrophages migrate toward negative polarity,<sup>1,36</sup> although some researchers have reported that fibroblast cells and macrophages migrated toward positive polarity.<sup>1</sup> Application of ES to a wound can also induce the release of prostaglandins and the other cytokines,<sup>37,38</sup> which would attract macrophages to the wound site.<sup>28</sup> Thus, the indirect antibacterial effects of ES may be the result of galvanotactic attraction of white blood cells, such as macrophages



**Figure 4.** This scheme shows that pH at the anode (positive pole) tends toward acidic and chlorine molecules, as an antibacterial substance, produced at the anode.

## TAKE-HOME MESSAGES

### Basic science advances

- *In vitro* studies have demonstrated antibacterial effects of ES.
- The type of ES plays a major role in establishment of antibacterial effects. Both DC and HVPC are more effective in inhibition of bacterial growth than are other ES types.
- Although an antibacterial effect of ES is shown at both the anode and cathode, most of the evidence supports the application of a cathodal current.
- The bacterial inhibitory action of ES is proportional to the amplitude and application time of the electric current.
- The electric current directly results in bacterial death by disruption of the integrity of the bacterial membrane or by electrolysis of molecules on the cell surface.
- Changes in pH were suggested as a possible mechanism for the indirect effects of ES (especially DC) on inhibition of bacterial growth.
- The production of toxic substances (*e.g.*,  $\text{H}_2\text{O}_2$ , oxidizing radicals, chlorine molecules) and galvanotoxic effects of ES might be other mechanisms for indirect antibacterial effects of ES.

### Clinical science advances

- ES has a potential for bacteriostatic and bactericidal effects on *in vivo* microorganism growth.
- Cathodal microampere DC and HVPC might provide a treatment modality for promoting the healing of chronic wounds with bacterial burdens.
- Further experimental studies, especially *in vivo*, are necessary to clarify the direct and indirect inhibitory effects of ES on wound bacterial infections.

and leukocytes to the infected wound rather than a direct response to electrolysis products or pH changes.

In general, the direct bacterial inhibitory effects of ES appear to be more important than indirect effects, although both contribute to the overall antibacterial response. However, further studies, especially *in vivo*, must be done to elucidate the exact mechanism that gives rise to the observed antibacterial effects of ES.

## CONCLUSION

The available evidence indicates that ES inhibits the growth of microorganisms. Cathodal  $\mu\text{ADC}$  appears to be more effective than other types of ES. The exact mechanisms that result in antibacterial effects of ES are unknown, but direct effects of ES on the bacteria appear to be more important than indirect effects. The number of studies on this topic is limited and further research, especially *in vivo*, is necessary to clarify the mechanisms underlying the antibacterial effects of ES in infected wounds.

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## AUTHOR DISCLOSURE AND GHOSTWRITING

The authors have no competing interests. No ghostwriters were used to write this article.

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