Electroacupuncture Improves Survival in Rats with Lethal Endotoxemia via the Autonomic Nervous System

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ABSTRACT

Background: Recent advances have indicated a complex interplay between the autonomic nervous system and the innate immune system. Targeting neural networks for the treatment of sepsis is being developed as a therapeutic strategy. Because electroacupuncture at select acupoints can modulate activities of the autonomic nervous system, we tested the hypothesis that electroacupuncture at specific acupoints could modulate systemic inflammatory responses and improve survival via its impact on the autonomic nervous system in a rat model of sepsis.

Methods: Sprague-Dawley male rats received electroacupuncture for 45 min before and at 1, 2, or 4 h after a lethal dose of intraperitoneal lipopolysaccharide injection (6 mg/kg). Outcomes included survival and systemic cytokine responses. Also, the possible roles of neural circuitry, including the hypothalamic-pituitary-adrenal axis and the autonomic nervous system, were evaluated.

Results: Electroacupuncture pretreatment at the Hegu acupoint significantly attenuate systemic inflammatory responses and improve survival rate from 20% to 80% in rats with lethal endotoxia. Such a site-specific effect requires the activation of muscarinic receptors in the central nervous system, but not increasing central sympathetic tone. In the periphery synergistic, rather than independent, action of the sympathetic and parasympathetic systems is also necessary.

Conclusions: Electroacupuncture pretreatment has a dramatic survival-enhancing effect in rats with lethal endotoxemia, which involves the activation of efferent neural circuits of the autonomic nervous system (e.g., cholinergic antiinflammatory pathway). This approach could be developed as a prophylactic treatment for sepsis or perioperative conditions related to excessive inflammation.

Despite more than 20 yr of extensive research and development, the incidence of sepsis and the number of sepsis-related deaths are rising. Depending upon the standards of medical care, mortality of sepsis could vary between 30% and 70%.1,2 Sepsis is a heterogeneous, dynamic syndrome and involves a complex interplay of different biologic systems, most notably the immune system, the coagulation system, and the autonomic nervous system (ANS).3 Recent advances in the field of neuroimmunology have shown that the ANS is one of the key pathways in the neuroimmune modulating network, and the balance between the two branches of the ANS (e.g., sympathetic and parasympathetic) is important in directing the inflammatory response toward either pro- or antiinflammatory outcomes.4 Consequently,
Acupuncture is a 5,000-plus-year-old practice that is still widely used in many countries today.7 Accumulating evidence has demonstrated that acupuncture at select acupoints can modulate activities of the ANS. For example, electroacupuncture at Neiguan (PC-6; located in the groove caudal to the flexor carpi radialis and cranial to the superficial digital flexor muscles) significantly increases vagal activity, as measured by spectral analysis of heart rate variability.8,9 In contrast, electroacupuncture at Hegu (LI-4; located at the junction of the first and second metacarpal bones) increases sympathetic tone, as evidenced by elevation of blood pressure and increased renal and adrenal nerve activities.10,11 Based on these data, we tested the hypothesis that electroacupuncture at specific acupoints could inhibit systemic inflammatory responses and improve survival via its impact on the ANS in a rat model of sepsis (systemic administration of endotoxin).

Materials and Methods

Animals and Reagents
All studies were conducted in accordance with institutional animal care guidelines and approved by the Animal Care Committee of Shanghai Jiao Tong University (Shanghai, China). Adult male Sprague-Dawley rats (200–300 g), provided by Sino-British SIPPR/BK Lab Animal Ltd. Co. (Shanghai, China), were housed at 22°C on a 12-h light/dark cycle.

Lipopolysaccharide (Escherichia coli 0111:B4), propranolol, phentolamine, clonidine, and mecamylamine were obtained from Sigma (St. Louis, MO). Atropine methyl nitrate was obtained from International Laboratory USA (San Bruno, CA). All test reagents were dissolved in physiologic saline.

Electroacupuncture Technique
The acupuncture points used in this study were Hegu (LI-4), located at the junction of the first and the second metacarpal bones, and Neiguan (PC-6), located in the groove caudal to the flexor carpi radialis and cranial to the superficial digital flexor muscles. A set of nonacupoints located on the ulna side of the metacarpus served as controls. Stainless needles were inserted bilaterally to a depth of 5 mm and then held in place by plastic adhesive tape. Stimulation (current of 4 mA, alternating dense-and-disperse mode, 2 Hz [0.6-ms pulse width] vs. 100 Hz stimulation [0.2-ms pulse width], each lasting for 3 s) was delivered using an electrical stimulation device (HANS LH-202, Huawei Co. Beijing, China) for 45 min.

Chemical Sympathectomy
Rats received a subcutaneous injection of 100 mg/kg guanethidine sulfate (Tokyo Chemical Industry Co. Ltd., Tokyo, Japan), dissolved in 0.9% NaCl, pH adjusted to 7.4, or vehicle of same volume for 2 consecutive days.12

Vagotomy
Under anesthesia and sterile condition, the right cervical vagus nerve of rats was exposed, ligated with a 4-0 silk suture, and transected. In sham-operated animals, the cervical vagus nerve was visualized, but was neither isolated from the surrounding tissues nor transected. Rats were allowed to recover for 4 days before the lipopolysaccharide challenge.

Splenectomy
Under anesthesia and sterile condition, the spleen of rats was identified through a midline laparotomy incision and removed using routine surgical technique. Sham animals received laparotomy without splenectomy. Nine days were allowed for recovery.

Experiment 1: Effect of Electroacupuncture on Survival
Under sodium pentobarbital anesthesia (50 mg/kg, intraperitoneal injection), rats received electroacupuncture 45 min before and at 1, 2, or 4 h after intraperitoneal lipopolysaccharide injection (6 mg/kg) at the following site: Hegu, Neiguan, or nonacupoints. A group of rats that received pentobarbital anesthesia and lipopolysaccharide, but not electroacupuncture, was included as a blank control. The survival rate was observed within the following 7 days. Each group included 20 rats. This experiment demonstrated superior protective efficacy of electroacupuncture at Hegu, relative to Neiguan and nonacupoints, but only before lipopolysaccharide challenge (fig. 1). Thus, electroacupuncture pretreatment at Hegu acupoints was chosen for subsequent experiments.

Experiment 2: Effect of Electroacupuncture on the Systemic Inflammatory Response
Rats received electroacupuncture at Hegu or electrostimulation at nonacupoints before lipopolysaccharide challenge. A
group of rats receiving lipopolysaccharide and anesthesia was included as additional controls. Serum pro-inflammatory cytokines (tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β) and a prototype antiinflammatory cytokine (IL-10) were measured at 2, 4, and 6 h after lipopolysaccharide injection with ELISA (R&D Systems; Minneapolis, MN). At each time point, three groups as mentioned above (n = 6 or 10 per group) were included for obtaining blood samples.

**Experiment 3: The Role of Hypothalamic-Pituitary-Adrenal Axis**

The hypothalamic-pituitary-adrenal axis is one of the major gateways through which the central nervous system modulates the immune function, and provides an important physiologic feedback loop of inflammation through the antiinflammatory effects of corticosteroids. To examine whether activation of hypothalamic-pituitary-adrenal axis is involved in the protective effect of electroacupuncture, serum corticosterone was measured immediately after electroacupuncture pretreatment or electrical-stimulation at nonacupoints and at 2 h after lipopolysaccharide challenge. A group of rats receiving lipopolysaccharide and anesthesia and a group of rats receiving only anesthesia were included as additional controls (n = 10 per group). Corticosterone levels were determined using an immunoassay kit (R&D Systems).

**Experiment 4: The Role of Sympathetic Nervous System**

In this series of experiments, rats were treated with the following agents at 10 min before electroacupuncture at Hegu: centrally acting α2-receptor antagonist clonidine (20 μg/kg, intraperitoneal injection), α-receptor antagonist phenotolamine (1 mg/kg, intraperitoneal injection), β-adrenoceptor antagonist propranolol (5 mg/kg, intraperitoneal injection), or saline (n = 20 per group), and then subjected to lipopolysaccharide challenge. A separate group of rats received chemical sympathectomy before electroacupuncture and lipopolysaccharide challenge. Survival was the primary endpoint. In a separate experiment of the same design, serum TNF-α at 2 h after lipopolysaccharide was examined (n = 6 per group).

**Experiment 5: The Role of Parasympathetic Nervous System**

In this series of experiments, rats were treated with the following agents before electroacupuncture at Hegu: muscarinic receptor antagonist atropine methyl nitrate (5 μg/kg in 5 μl; intracerebroventricular injection under anesthesia; coordinates: 0.8 mm posterior to bregma, 1.5 mm lateral to midline, and 4.0 mm below the skull surface); nicotinic receptor antagonist mecamylamine (1 mg/kg; intraperitoneal injection); atropine methyl nitrate (1 mg/kg; intraperitoneal injection); or saline (intracerebroventricular injection as a control for atropine methyl nitrate; intraperitoneal injection as a control for mecamylamine or atropine methyl nitrate; n = 20 per group), and then subjected to lipopolysaccharide challenge. Of note, mecamylamine, at the dose 1 mg/kg used in this study, predominantly antagonizes peripheral and nonspecific nicotinic receptors, and atropine methyl nitrate is unable to penetrate the blood-brain barrier. Separation of groups of rats receiving vagotomy, splenectomy, or sham surgery before the electroacupuncture pretreatment and lipopolysaccharide challenge were also included in the experiments (n = 20 per group). Survival was the primary endpoint. In a separate experiment of the same design, serum TNF-α was examined at 2 h after lipopolysaccharide challenge (n = 6 per group).

**Statistical Analysis**

Data are expressed as mean ± SD. In Experiments 2 and 3, comparison of serum inflammatory cytokines and corticosterone levels in the different treatment groups and different time points was carried out by using two-way ANOVA with the Tukey test. In Experiments 4 and 5, the differences of serum TNF-α at 2 h after lipopolysaccharide exposure among different treatment groups were analyzed using one-way ANOVA followed by post hoc Bonferroni correction for multiple comparisons. For survival analysis, Kaplan–Meier analysis was used followed by a log-rank test. P value <0.05 was considered statistically significant (two-tailed). All statistical analyses were performed by SPSS 16.0 for Windows (SPSS Inc., Chicago, IL).

**Results**

**Electroacupuncture Pretreatment at Hegu Improved Survival in Rats with Lethal Endotoxemia**

Three out of 20 rats receiving electroacupuncture treatment at nonacupoints before lipopolysaccharide challenge survived the endotoxemia (fig. 1). Electroacupuncture at Hegu before lipopolysaccharide challenge conferred dramatic protection: 16 of 20 rats survived the endotoxemia (P < 0.0001 vs. 4/20 in the blank control). No further dropouts within an observation period of 7 days indicates that electroacupuncture pretreatment conferred a lasting protection and did not merely delay the onset of death. Less protective effects were observed in rats receiving electroacupuncture at Neiguan before lipopolysaccharide challenge (survival rate: 10/20; P = 0.049 vs. Hegu). When delivered after lipopolysaccharide challenge, electroacupuncture treatment did not affect the survival rate at either Hegu or Neiguan.

**Electroacupuncture Pretreatment Attenuated the Systemic Inflammatory Response to Lipopolysaccharide**

Figure 2A displays that serum TNF-α was approximately 900 pg/ml at 2 h after the lipopolysaccharide challenge, and decreased to a level less than 60 pg/ml at 4 and 6 h. Such a temporal profile is consistent with previous reports. Electroacupuncture pretreatment at Hegu (but not electro-stimulation at nonacupoints) significantly decreased serum...
TNF-α level at 2 h after lipopolysaccharide challenge (P < 0.0001). TNF-α level at 4 (P = 0.23) and 6 h was not affected (P = 0.11). Figure 2B displays that serum IL-1β was approximately 1,000 pg/ml at 2 h after the lipopolysaccharide challenge, and reached a plateau at 4 h after lipopolysaccharide challenge. Electroacupuncture pretreatment at Hegu significantly decreased IL-1β throughout the entire observation period (P < 0.0001). Figure 2C displays that serum IL-6 was approximately 6,500 pg/ml at 2 h after the lipopolysaccharide challenge, and reached a plateau at 4 h after lipopolysaccharide challenge. Electroacupuncture pretreatment at Hegu significantly decreased IL-6 throughout the entire observation period (P < 0.0001). Figure 2D displays that the prototype antiinflammatory cytokine IL-10 was not affected by electroacupuncture pretreatment (P = 0.76, 0.45, and 0.63, respectively).

**The Protective Effect of Electroacupuncture Pretreatment Could Not Be Attributed to the Activation of Hypothalamic-Pituitary-Adrenal Axis**

Serum corticosteroid in rats receiving lipopolysaccharide challenge was significantly decreased, rather than increased, by electroacupuncture pretreatment at Hegu as well as at nonacupoints (P < 0.0001 for both; fig. 3). Electroacupuncture at Hegu or nonacupoints alone also significantly decreased serum corticosteroid levels in rats not exposed to lipopolysaccharide (P < 0.0001 for both; fig. 3). Thus, the beneficial effect of electroacupuncture is not associated with increasing corticosteroid levels.

**Peripheral Sympathetic Nervous System and Particularly β-adrenoceptors, but Not Increased Central Sympathetic Tone, Are Necessary for the Protective Action of Electroacupuncture**

Consistent with a previous study of sympathectomy with 6-hydroxydopamine in an animal model of thermal injury with sepsis, ablation of the sympathetic nervous system with guanethidine before lipopolysaccharide challenge significantly increased survival rate (10/20 vs. 3/20 in the control rats; P = 0.025) and attenuated serum TNF level (P < 0.0001). However, electroacupuncture pretreatment at the Hegu did not confer further protection in sympathectomized rats (survival rate: 8/20 vs. 10/20 in sympathectomized rats without electroacupuncture; P = 0.66; fig. 4A). Also, serum TNF level did not differ between sympathectomized rats with or without electroacupuncture pretreatment (P = 0.49; fig. 4B). Pretreatment with the β-antagonist propranolol (survival rate: 3/20; P < 0.0001; TNF-α: P < 0.0001), but not the α-antagonist phentolamine (survival rate: 16/20; P = 0.67; TNF-α: P = 0.55; figs. 4C and D) completely abolished the effects of electroacupuncture on survival and serum TNF. Somewhat surprisingly, pretreatment with clonidine, a centrally acting α₂-agonist that decreases central sympathetic tone, did not block the effects of electroacupuncture (survival rate: 18/20 vs. 16/20; P = 0.44; TNF-α: P = 0.68; figs. 4E and F).

**Central Muscarinic Receptor, Vagus Nerve, Peripheral Nicotinic Receptor, and Spleen Are Required for the Protective Action of Electroacupuncture**

The vagus nerve has recently been identified as a major pathway through which immune function is regulated by the

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**Fig. 2.** Pretreatment of electroacupuncture at Hegu decreases the serum pro-inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-6, interleukin-1β), but does not affect the antinflamatory cytokine IL-10 in rats receiving lipopolysaccharide. After receiving electroacupuncture at Hegu or nonacupoints (sham), rats were injected with lipopolysaccharide (6 mg/kg, intraperitoneal injection); blood was collected 2, 4, and 6 h afterward. Serum tumor necrosis factor-α (A), interleukin-1β (B), interleukin-6 (C), and interleukin-10 (D) were measured using commercially available ELISA kits. Data are mean ± SD. For the time point of 2 h, n = 10 per group; for 4 and 6 h, n = 6 per group. * P < 0.001 versus LPS alone. EA = electroacupuncture; IL-1β = interleukin-1β; IL-6 = interleukin-6; IL-10 = interleukin-10; LPS = lipopolysaccharide; TNF-α = tumor necrosis factor-α.
central nervous system, which is termed the "cholinergic anti-inflammatory pathway." Our results indicated that unilateral (right-sided) cervical vagotomy before lipopolysaccharide challenge significantly attenuated the protective effects of electroacupuncture (survival rate: 7/20 vs. 16/20 in sham-operated rats; \( P < 0.005 \); TNF-\( \alpha \): \( P < 0.0001 \); figs. 5A and B). Systemic treatment with the nicotinic antagonist mecamylamine (survival rate: 4/20; \( P < 0.001 \); TNF-\( \alpha \): \( P < 0.001 \)), but not the muscarinic antagonist atropine methyl nitrate (survival rate: 19/20; \( P = 0.32 \); TNF-\( \alpha \): \( P = 0.65 \); figs. 5C and D), completely blocked the protective effects of electroacupuncture. Atropine methyl nitrate delivered directly into the brain completely blocked the protective effects of electroacupuncture (survival rate of 6/20 vs. 15/20 in vehicle controls; \( P = 0.007 \); TNF-\( \alpha \): \( P < 0.0001 \); figs. 5E and F). These results are consistent with an

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**Fig. 4.** Peripheral sympathectomy or \( \beta \)-adrenoceptor blockade, but not a central sympatholytic, abrogates the protective effect of electroacupuncture. Data are survival rate (n = 20 per group) and serum tumor necrosis factor-\( \alpha \) level (n = 6 per group). (A, B) SD rats received guanethidine (100 mg/kg, subcutaneous injection, for 2 consecutive days) or vehicle. On the morning of the third day, rats were pretreated with electroacupuncture, and then received lipopolysaccharide (6 mg/kg, intraperitoneal injection). * \( P < 0.01 \) versus vehicle alone; # \( P < 0.05 \) versus electroacupuncture plus vehicle. (C, D) Propranolol (5 mg/kg, intraperitoneal injection), but not phentolamine (1 mg/kg, intraperitoneal injection), abolished the protective effect of electroacupuncture. * \( P < 0.0001 \) versus electroacupuncture plus vehicle control. (E, F) Intraperitoneal injection of clonidine, a centrally acting \( \alpha_2 \)-adrenoceptor agonist (20 \( \mu \)g/kg, dissolved in saline), does not affect the protective effect of electroacupuncture. * \( P < 0.01 \) versus electroacupuncture plus vehicle control.

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Fig. 5. Central muscarinic receptor, vagus nerve, peripheral nicotinic receptor, and spleen are required for the protective action of electroacupuncture at Hegu. Data are survival rate (n = 20 per group) and serum tumor necrosis factor-α level (n = 6 per group). (A, B) Cervical vagotomy versus sham surgery, at 4 days before lipopolysaccharide injection (6 mg/kg, intraperitoneal injection). *P < 0.01 versus electroacupuncture plus sham surgery. (C, D) Pretreatment with the nicotinic receptor antagonist mecamylamine (1 mg/kg, intraperitoneal injection) versus the muscarinic receptor antagonist atropine methyl nitrate (1 mg/kg, intraperitoneal injection). *P < 0.001 versus electroacupuncture plus vehicle control. (E, F) Atropine methyl nitrate (5 μg/kg), delivered via the intracerebroventricular route at 15 min before electroacupuncture pretreatment. *P < 0.001 versus electroacupuncture plus vehicle control. (G, H) Surgical ablation of the spleen *P < 0.001 versus sham surgery. AMN = atropine methyl nitrate; EA = electroacupuncture; i.c.v. = intracerebroventricular; TNF-α = tumor necrosis factor-α level.
important role of the central muscarinic receptors in modulating peripheral cytokine production. Recent work on the anatomical basis of the cholinergic antiinflammatory pathway indicates that the spleen is required for vagus control of inflammation, although the splenic nerve is classified as cat-echolaminergic. In our study, although splenectomy per se significantly reduced serum TNF-α level compared with sham surgery group (P < 0.0001; fig. 5H), which is consistent with a previous study, it did not improve the survival rate of rats challenged with a lethal dose of lipopolysaccharide (P = 0.77; fig. 5G). When electroacupuncture was applied to splenectomized animals, its survival-enhancing effect disappeared (survival rate of 6/20 vs. 17/20 in sham surgery controls; P < 0.0001; fig. 5G). Also, electroacupuncture failed to inhibit serum TNF-α level in splenectomized animals, unlike in intact animals (P = 0.50; fig. 5H).

Discussion

The current study for the first time demonstrated that electroacupuncture pretreatment at the Hegu acupoints can dramatically improve survival in rats with lethal endotoxemia. The production of proinflammatory cytokines (TNF-α, IL-6 and IL-1β) was also significantly attenuated, but anti-inflammatory cytokine serum IL-10 was not affected. Our study also demonstrated selectivity of the acupuncture: electroacupuncture at Hegu acupoints produced more powerful protection than electroacupuncture at Neiguan acupoints; electrostimulation at nonacupoints was not effective at all. To our knowledge, the site-specific effects of acupuncture, i.e., “true” treatment acupoints with selective physiologic effects, have not been fully validated or accepted. A few influential clinical trials of migraine headache failed to show significant difference between acupuncture at select acupoints versus sham acupuncture. In the current study, the use of anesthesia during electroacupuncture excluded some likely nonspecific physiologic effects caused by electrostimulation procedure, such as pain and immobilization stress, and thus provided more solid evidence for the existence of site-specific effects.

The timing of electroacupuncture treatment seems critical for the “rescue” effect in our study, because electroacupuncture must be delivered before lipopolysaccharide injection to produce a protective action. We speculate that the explicit requirement for pretreatment may be specific to the lipopolysaccharide model used in this study: immune pathology of endotoxemia models using bolus injection is characterized by a very rapid and overwhelming innate immune response that is very difficult to stop once it is in motion. Although bacterial infection models do not recapitulate many important features of human sepsis, they can provide important insights into mechanisms of the host response to pathogens.

During the past decade, the immunomodulatory efficacy of acupuncture has been supported by increasing number of randomized controlled clinical trials for a number of immune- or inflammatory-related diseases, such as allergic asthma, childhood persistent allergic rhinitis, and rheumatoid arthritis. Animal studies have also indicated that acupuncture pretreatment has protective effects against endotoxin-induced acute lung and kidney injuries. However, little is known about its biologic basis.

In this study, we found that electroacupuncture at Hegu does not enhance the release of glucocorticoids or antiinflammatory cytokines (e.g., IL-10), suggesting that humoral pathways are not responsible for the immunomodulatory efficacy of electroacupuncture. Instead, such an effect requires the participation of muscarinic receptors in the central nervous system, but not increasing central sympathetic tone. Synergistic, rather than independent, action of peripheral sympathetic and parasympathetic systems is also necessary. At the first glance, these results seem difficult to explain or discriminate the roles of sympathetic and parasympathetic components. However, newly identified cholinergic antiinflammatory pathway suggests that the long-standing attempt to separate the neural circuitry that controls immune responses into discrete sympathetic and parasympathetic components is imprecise. On the contrary, at least in the periphery, the involvements of sympathetic versus parasympathetic systems are not independent, either anatomically or functionally. From a systematic perspective, our data strongly support this important conceptual advance. We now put forward the following framework mainly based on the cholinergic antiinflammatory pathway to explain our findings: electroacupuncture at Hegu activates a brain muscarinic receptor-mediated network possibly through somatoautonomic reflexes and subsequently increases vagus nerve activity. The vagus nerve terminates in synaptic-like structures around principal cells of the celiac-superior mesenteric plexus ganglia, a site where cholinergic antiinflammatory spleen fibers originate. Via two serially connected neurons in these ganglia, vagus nerve modulates the activities of splenic nerve through nicotinic acetylcholine receptor. Increased norepinephrine released by the splenic nerve then acts on β-adrenergic receptors expressed on B and T cells of the spleen to produce acetylcholine. Enhanced acetylcholine levels in the spleen then activates nicotinic receptor expressed on macrophages to inhibit proinflammatory cytokine release.

In addition, since it has been suggested that lipopolysaccharide-induced hemodynamic instability contributes to mortality, a paradoxical hypertensive response mediated by stimulation at Hegu acupoints might explain electroacupuncture’s survival-enhancing effect. However, both previous studies and our preliminary data indicated that the pressor response elicited by electroacupuncture at Hegu acupoints lasts for only 2 or 3 min after cessation of the stimulation. Also, if the protective effect is mediated by pressor effect, electroacupuncture delivered after lipopolysaccharide injection should have been more effective; however, it’s...
clearly not the case in this study. Thus, hemodynamic effect produced by electroacupuncture cannot account for its survival-enhancing effect.

In conclusion, electroacupuncture pretreatment at the Hegu acupoints inhibited systemic inflammatory responses and enhanced survival in rats with lethal endotoxemia. The underlying mechanism involves the activation of efferent neural circuits of the ANS, e.g., the cholinergic antiinflammatory pathway. These findings encourage the development of electroacupuncture as a prophylactic treatment for sepsis or other perioperative conditions related to excessive inflammation.

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ANESTHESIOLOGY REFLECTIONS

The Ethereal Peter Parker, M.D., D.D.

“Peter Parker” is regarded as the alter ego of the fictional character Spiderman by many younger physicians; however, older professionals may recognize “Peter Parker” as the name of the Presbyterian medical missionary who introduced surgical anesthesia to China. Indeed, Rev. Dr. Parker (1814–1888) was etherizing Chinese patients for surgery as early as the summer of 1847 and was chloroforming others by the following year. In later years, Parker’s likeness (left) was captured by engraver A. H. Ritchie. In 1896 a Yale professor named Rev. George B. Stevens, M.D., published (right) a 356-page biography, The Life, Letters, and Journals of the Rev. and Hon. Peter Parker, M.D., Missionary, Physician, and Diplomatist: The Founder of Medical Missions and Founder of the Ophthalmic Hospital in Canton. Biographer Stevens’ reference to Parker as “diplomatist” reminds readers that the missionary also served on diplomatic missions as an interpreter on behalf of U.S. Presidents Tyler and then Pierce in negotiating America’s first treaty with China. (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the Anesthesiology Reflections online collection available at www.anesthesiology.org.)

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