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(54) Title: TREATING INFLAMMATORY DISORDERS BY ELECTRICAL VAGUS NERVE STIMULATION

(57) Abstract: A method and an apparatus for treating a patient suffering from, or at risk for, a condition mediated by the inflammatory cytokine cascade, by electrically stimulating vagus nerve activity in an amount sufficient to inhibit the inflammatory cytokine cascade.

TREATING INFLAMMATORY DISORDERS BY ELECTRICAL VAGUS NERVE STIMULATION

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/639,332, filed on December 27, 2004. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Vertebrates achieve internal homeostasis during infection or injury by balancing the activities of proinflammatory and anti-inflammatory pathways. However, in many disease conditions, this internal homeostasis becomes out of balance. For example, endotoxin (lipopolysaccharide, LPS) produced by all Gram-negative bacteria activates macrophages to release cytokines that are potentially lethal (Tracey, K. J. et al., *Science*, 234:470-74 (1986); Dinarello, C. A., *FASEB J.*, 8:1314-25 (1994); Wang, H., et al., *Science*, 285:248-51 (1999); Nathan, C. F., *J. Clin. Invest.*, 79:319-26 (1987)).

Inflammation and other deleterious conditions (such as septic shock caused by endotoxin exposure) are often induced by proinflammatory cytokines, such as tumor necrosis factor (TNF; also known as TNF α or cachectin), interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, IL-18, interferony, platelet-activating factor (PAF), macrophage migration inhibitory factor (MIF), and other compounds. Certain other compounds, for example high mobility group protein 1 (HMG-1), are induced during various conditions such as sepsis and can also serve as proinflammatory cytokines. Proinflammatory cytokines contribute to various disorders, notably sepsis, through their release during an inflammatory cytokine cascade. Inflammatory cytokine cascades contribute to deleterious characteristics, including inflammation and apoptosis, of numerous disorders.

SUMMARY OF THE INVENTION

The present invention is a method and a device for treating cytokine-mediated inflammatory conditions.

The present invention is based, in part, on the discovery that inflammatory disorders can be treated in a subject by electrically stimulating the vagus nerve. Surprisingly, it has also been discovered that the parameters of an electrical signal sufficient to treat inflammatory disorders are significantly milder than the parameters previously used to treat other medical conditions. Thus, it has been discovered that inflammatory disorders can be treated by an electrical signal having its current or voltage significantly smaller than electrical signals previously used to treat other disorders.

In one embodiment, the present invention is a method for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising stimulating the vagus nerve in a subject with an electrical signal, wherein the signal voltage is from 0.01 Volt to 1 Volt, provided that the condition is not ileus, asthma or cystic fibrosis.

In another embodiment, the present invention is a method for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising stimulating the vagus nerve in a subject with an electrical signal, wherein the signal voltage is from 0.01 Volt to 1 Volt, pulse width is from 0.1 ms to 5 ms; signal frequency is from 0.1 Hz to 30 Hz; signal on-time is from 1 second to 120 seconds; and signal off-time is over 2 hours.

In another embodiment, the present invention is an electrical signal generator and use thereof for treating a subject suffering from, or at risk for, an inflammatory disorder. The electrical signal generator comprises an electrode assembly for delivering an electrical signal to the vagus nerve of the subject and a controller controlling the electrical signal by limiting the signal voltage to a range from 0.01 Volt to 1 Volt.

In another embodiment, the present invention is an electrical signal generator and use thereof for treating a subject suffering from, or at risk for, an inflammatory disorder. The signal generator comprises an electrode assembly for delivering an electrical signal to the vagus nerve of the subject and a controller controlling the electrical signal by limiting the signal voltage to a range from 0.01 Volt to 1 Volt,

pulse width to a range from 0.1 ms to 5 ms; signal frequency to a range from 0.1 Hz to 30 Hz; signal on-time to a range from 1 second to 120 seconds; and signal off-time to a range of over 2 hours.

Surprisingly, it has been discovered that electrical vagus nerve stimulation was sufficient for activation of the cholinergic anti-inflammatory pathway, as measured by serum TNF levels in mice, despite the mildness of the conditions of the vagus nerve stimulation (Example 1). The effective half-life of TNF suppression induced by electrical vagus nerve stimulation was between two and three days (Example 2), thus indicating that electrical stimulation is at least as long-lasting as pharmaceutical intervention. Furthermore, electrical vagus nerve stimulation improved severity of collagen-induced arthritis in rats (Example 3).

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a simplified block diagram of an implantable embodiment of an electrical generator suitable for practicing the present invention.

FIG. 2 shows a suitable location of the electric signal generator and electrodes implanted in the patient's body.

FIG. 3 is an illustrative idealized electrical output signal waveform of the signal generator useful for clarifying relevant parameters of the output signal.

FIG. 4 is a bar plot representing the effect of the vagal electrical stimulation on endotoxemia as measured by a percent reduction of serum TNF level.

FIG. 5 is a plot showing the effect of electrical stimulation of VNS by an electrical signal on TNF production in LPS-challenged mice. Vertical axis indicates percent suppression of TNF, horizontal axis indicates hours elapsed between the VNS stimulation and LPS challenge.

FIG. 6 is a plot that shows an arthritis score in rats as a function of a number of days post collagen immunization to induced arthritis (PCID). VNS stimulation started on day 13 and continued till day 20.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, a "subject" is preferably a mammal, more preferably a human patient but can also be a companion animal (e.g., dog or cat), a farm animal

(e.g., horse, cow, or sheep) or a laboratory animal (e.g., rat, mouse, or guinea pig). Preferable, the subject is human.

As used herein, the term "vagus nerve" is used in its broadest sense, and includes any nerves that branch off from the main vagus nerve, as well as ganglions or postganglionic neurons that are connected to the vagus nerve. The vagus nerve is also known in the art as the parasympathetic nervous system and its branches, and the cholinergic nerve. The vagus nerve enervates principal organs including, the pharynx, the larynx, the esophagus, the heart, the lungs, the stomach, the pancreas, the spleen, the kidneys, the adrenal glands, the small and large intestine, the colon, and the liver. Electrical stimulation can be accomplished by direct stimulation of the vagus nerve or an organ served by the vagus nerve.

The disclosed method includes stimulating the entire vagus nerve (i.e., both the afferent and efferent nerves), or by isolating efferent nerves and then stimulating them directly. The latter method can be accomplished by separating the afferent from the efferent fibers in an area of the nerve where both types of fibers are present. Alternatively, the efferent fiber is stimulated where no afferent fibers are present, for example close to the target organ served by the efferent fibers. The efferent fibers can also be activated by stimulating the target organ directly, e.g., electrically, thus stimulating the efferent fibers that serve that organ. In other embodiments, the ganglion or postganglionic neurons of the vagus nerve can be stimulated. The vagus nerve can also be cut and the distal end can be stimulated, thus only stimulating efferent vagus nerve fibers.

The site of stimulation of the vagus nerve may be in the cervical region (in the neck) and a region peripheral and distal of the cervical region including, supra-diaphragmatic or sub-diaphragmatic regions. Peripheral, distal locations including branches of the vagus nerve that innervate the organs, including but not limited to, the spleen, the small intestine and the large intestine. The vagus nerve may also be stimulated using an endotracheal/esophageal nerve stimulator (described, for example, in U.S. Pat. No. 6,735,471, incorporated herein by reference in its entirety), transcutaneous nerve stimulator (as described for example in U.S. Pat. No. 6,721,603, incorporated herein by reference in its entirety) or a percutaneous nerve stimulator. In one embodiment, the vagus nerve is stimulated in

the cervical region. In another embodiment, the vagus nerve is stimulated at a peripheral, distal location. In another embodiment, the vagus nerve is stimulated in the brain by the device.

According to the present invention, the vagus nerve is stimulated by
5 delivering an electrical signal generated by any suitable vagus nerve stimulators. For example, a commercial vagus nerve stimulator such as the Cyberonics NCP™, or an electric probe can be used.

Examples of suitable vagus nerve stimulators are described, for example, in
U.S. Pat. Nos. 4,702,254; 5,154,172; 5,231,988; 5,330,507; 6,473,644; 6,721,603;
10 6,735,471; and U.S. Pat. App. Pub. 2004/0193231. The teachings of all of these publications are incorporated herein by reference in their entirety.

The vagus nerve can be stimulated by means of either an implanted device or a device worn external to the patient's body, such as Cyberonics NCP™ device described in U.S. Pat. No. 5,231,988 or a Medtronic™ device described in U.S. Pat
15 No. 5,330,507. Both patents describe apparatus for stimulating the right or left vagus nerve with continuous and/or phasic electrical signal.

A schematic diagram of a typical electrical signal generator device suitable for practicing the present invention is shown in FIG. 1. Referring to FIG. 1, a
20 typical signal generator 10 includes a battery (or set of batteries) 12, which may be of any type conventionally employed for powering medical electronic devices. Battery 12 is connected to a voltage regulator 14. Regulator 14 smoothes the battery output to produce steady output voltage as well as provides voltage multiplication or division if necessary.

Regulator 13 supplies power to signal controller 16. Signal controller 16 can
25 include a microprocessor. Signal controller 16 controls functions of the device such as output signal current or voltage, output signal frequency, output signal pulse width, output signal on-time, output signal off-time. Controller 16 can be programmed to control daily times for continuous or periodic modulation of vagal activity as well as output signal start delay time. Such programmability allows the
30 output signal to be adjusted for the treatment regimen.

When device 10 is implanted, a built-in antenna (not shown) can be used to enables communication between device 10 and external programming or monitoring devices (not shown).

Signal controller 16 controls driver 18 which generates the desired electrical
5 signal. The output signal is applied to the patient's body via electrodes 20a and 20b.

Analyzer 22 can be provided to process any relevant physiological parameters of a patient such as heart rate or blood pressure detected by detector 24.

As mentioned above, device 10 can be worn external to the patient's body or can be implanted. FIG. 2 illustrates one embodiment of the present invention where
10 signal generator 10 is implanted in the patient's chest in a pocket formed by the surgeon just below the skin. One suitable location for the generator is in the patient's chest, as a pacemaker pulse generator would be implanted, with the electrodes 20a and 20b imlanted in the patient's neck.

Electrodes 20a and 20b can be bipolar stimulating electrodes of the type
15 described in U.S. Pat. No. 4,573,481, incorporated herein by reference in its entirety. In this embodiment, electrodes form an assembly which is surgically implanted on the vagus nerve in the patient's neck. The two electrodes are wrapped around the vagus nerve, and the assembly is secured to the nerve by a spiral anchoring tether as disclosed in U.S. Pat. No. 4,979,511, incorporated herein by reference in its entirety.

20 Structurally, the electrode assembly can comprise two ribbons of platinum which are individually bonded to each of the two spiral loops wrapped around the vagus nerve. Each loop further includes silicone rubber. An additional helical loop that includes silicon rubber is provided to tether the electrode assembly to the vagus nerve. The inner diameter of the helical bipolar electrodes may typically be about
25 two millimeters (mm), and an individual spiral is about seven mm long (measured along the axis of the nerve).

Instead of implanting the electrode assembly in the patient's neck, the assembly may be implanted on the vagus nerve as it enervated any of the organs listed above. The implantation of electrodes 20a and 20b is accomplished in
30 substantially the same manner as was described for the neck location.

The operation of signal generator 10 to control and treat inflammatory disorders will be described by reference to the signal waveform and parameters

shown in FIG. 3. The latter is an idealized representation of the output signal delivered by driver 18. FIG. 3 serves to clarify terminology used to refer to the parameters of an electrical signal. Such parameters include signal on-time, signal off-time, signal frequency, signal pulse width, signal current, and signal voltage.

5 Treatment of inflammatory disorders can be accomplished by applying voltage to electrodes 20a and 20b as well as by driving a current between electrodes 20a and 20b. While the pulses shown in FIG. 3 have positive voltage or current output, electrical signals having negative outputs can also be used.

Signal controller 16 controls the output signal by limiting the output to a
10 suitable range of parameters specified above with reference to FIG. 3. A range of each parameter can be chosen independently from any other parameter. Alternatively, a combination of ranges for any number of parameters can be chosen. Preferred examples of specific values for the parameters and combinations of parameters as provided below with respect to the controller are also applicable to the
15 disclosed methods of treatment.

Signal controller can limit signal voltage to a range from about 0.01 Volt to about 1 Volt, preferably to a range from about 0.01 Volt to about 0.1 Volt, more preferably, to a range from about 0.01 Volt to about 0.05 Volt.

Signal controller can limit signal current to a range from about 1 mA to
20 about 100 mA, preferably to a range from about 1 mA to about 10 mA, more preferably to a range from about 1 mA to about 5 mA.

In some embodiments, both signal voltage and signal current are controlled.

In other embodiments, either in addition to or independently from controlling signal voltage, signal current or both, signal controller can further control one or
25 more parameters selected from pulse width, on-time and frequency. Signal controller can limit the pulse width to a range from about 0.1 ms to about 5 ms, preferably to a range from about 0.1 ms to about 1ms, more preferably to a range from about 0.1 ms to about 0.5 ms. Signal controller can limit signal on-time from
30 seconds to about 60 seconds, more preferably, to a range from about 20 seconds to about 40 seconds. Signal controller can limit signal frequency to a range from about

0.1 Hz to about 30 Hz, preferably, to a range from about 1 Hz to about 30 Hz, more preferably, to a range from about 10 Hz to about 30 Hz.

In other embodiments, either in addition to or independently from controlling signal voltage and/or signal current, as well as signal width, signal frequency and/or signal on-time, signal controller can further control signal off-time. In one
5 embodiment, a subject can be treated with one pulse. In another embodiment, signal controller can limit signal off-time to a range of over 5 minutes, preferably, over 2 hours, more preferably, over 4 hours, even more preferably, over 8 hours, still more preferably, over 12 hours. In another embodiment, signal controller can limit signal
10 off-time to a range of from about 2 hours to about 48 hours, preferably to a range from about 4 hours to about 36 hours, more preferably, to a range from about 6 hours to about 36 hours. In other preferred embodiments, signal controller can limit signal off-time to a range selected from: from about 6 to about 36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours and from about 20 to about 28
15 hours. Alternatively, signal off-time can be undefined as one skilled in the art will readily determine the desired time interval between two consecutive signals.

As mentioned above, various parameters can be limited to the specified ranges alone or in combination. In one example, signal controller can limit a combination of parameters as follows: signal voltage to a range from about 0.01
20 Volt to about 1 Volt; pulse width to a range from about 0.1 ms to about 5 ms; signal frequency to a range from about 0.1 Hz to about 30 Hz; signal on-time from about 1 second to about 120 seconds. Signal off-time can be undefined. Alternatively, signal off-time can be limited to a range over about 5 minutes. In other preferred embodiments, signal controller can limit signal off-time to a range selected from:
25 from about 6 to about 36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours and from about 20 to about 28 hours.

In another example, signal controller can limit a combination of parameters as follows: signal current to a range from about 1 mA to about 100 mA; pulse width to a range from about 0.1 ms to about 5 ms; signal frequency to a range from about
30 0.1 Hz to about 30 Hz; signal on-time from about 1 second to about 120 seconds. Signal off-time can be undefined. Alternatively, signal off-time can be limited to a range over about 5 minutes. In other preferred embodiments, signal controller can

limit signal off-time to a range selected from: from about 6 to about 36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours and from about 20 to about 28 hours.

In a preferred embodiment, signal controller can limit a combination of
5 parameters as follows: signal voltage to a range from about 0.01 Volt to about 0.1 Volt; pulse width to a range from about 0.1 ms to about 1ms; signal frequency to a range from about 1 Hz to about 30 Hz; signal on-time to a range of from about 10 seconds to about 60 seconds; signal off-time to a range of over 2 hours.

Alternatively, signal off-time can be undefined. In other preferred embodiments,
10 signal controller can limit signal off-time to a range selected from: from about 6 to about 36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours and from about 20 to about 28 hours.

Alternatively, signal controller can limit a combination of parameters as
follows: signal current to a range from about 1 mA to about 10 mA; pulse width to a
15 range from about 0.1 ms to about 1ms; signal frequency to a range from about 1 Hz to about 30 Hz; signal on-time to a range of from about 10 seconds to about 60 seconds; signal off-time to a range of over 2 hours. Alternatively, signal off-time can be undefined. In other preferred embodiments, signal controller can limit signal
20 off-time to a range selected from: from about 6 to about 36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours and from about 20 to about 28 hours.

More preferably, signal controller can limit a combination of parameters as
follows: signal voltage to a range from about 0.01 Volt to about 0.05 Volt; pulse
width to a range from about 0.1 ms to about 0.5 ms; signal to a range from about 10
25 Hz to about 30 Hz; signal on-time to a range from about 20 seconds to about 40 seconds; signal off-time to a range of from about 2 hours to about 24 hours.

Alternatively, signal off-time can be undefined. In other preferred embodiments,
signal controller can limit signal off-time to a range selected from: from about 6 to
about 36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours
30 and from about 20 to about 28 hours. In other preferred embodiments, signal controller can limit signal off-time to a range selected from: from about 6 to about

36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours and from about 20 to about 28 hours.

Alternatively, signal controller can limit a combination of parameters as follows: signal current to a range from about 1 mA to about 5 mA; pulse width to a range from about 0.1 ms to about 0.5 ms; signal to a range from about 10 Hz to about 30 Hz; signal on-time to a range from about 20 seconds to about 40 seconds; signal off-time to a range of from about 2 hours to about 24 hours. Alternatively, signal off-time can be undefined. In other preferred embodiments, signal controller can limit signal off-time to a range selected from: from about 6 to about 36 hours, from about 12 to about 36 hours, from about 16 to about 30 hours and from about 20 to about 28 hours.

As used herein, "treatment" includes prophylactic and therapeutic treatment. "Prophylactic treatment" refers to treatment before onset of an inflammatory condition to prevent, inhibit or reduce its occurrence. Therapeutic treatment is treatment of a subject who is already experiencing an inflammatory disorder.

"Inflammatory disorders" are usually mediated by an inflammatory cytokine cascade, defined herein as an *in vivo* release from cells of at least one proinflammatory cytokine in a subject, wherein the cytokine release affects a physiological condition of the subject. Nonlimiting examples of cells that produce proinflammatory cytokines are monocytes, macrophages, neutrophils, epithelial cells, osteoblasts, fibroblasts, smooth muscle cells, and neurons.

As used herein, a "cytokine" is a soluble protein or peptide which is naturally produced by mammalian cells and which act *in vivo* as humoral regulators at micro- to picomolar concentrations. Cytokines can, either under normal or pathological conditions, modulate the functional activities of individual cells and tissues. A proinflammatory cytokine is a cytokine that is capable of causing any of the following physiological reactions associated with inflammation: vasodilation, hyperemia, increased permeability of vessels with associated edema, accumulation of granulocytes and mononuclear phagocytes, or deposition of fibrin. In some cases, the proinflammatory cytokine can also cause apoptosis, such as in chronic heart failure, where TNF has been shown to stimulate cardiomyocyte apoptosis. Nonlimiting examples of proinflammatory cytokines are tumor necrosis factor

(TNF), interleukin (IL)-1 α , IL-1.beta., IL-6, IL-8, IL-18, interferon.gamma., HMG-1, platelet-activating factor (PAF), and macrophage migration inhibitory factor (MIF). In preferred embodiments of the invention, the proinflammatory cytokine that is inhibited by cholinergic agonist treatment is TNF, an IL-1, IL-6 or IL-18, 5 because these cytokines are produced by macrophages and mediate deleterious conditions for many important disorders, for example endotoxic shock, asthma, rheumatoid arthritis, inflammatory bile disease, heart failure, and allograft rejection. In most preferred embodiments, the proinflammatory cytokine is TNF.

Proinflammatory cytokines are to be distinguished from anti-inflammatory 10 cytokines, such as IL-4, IL-10, and IL-13, which are not mediators of inflammation. In preferred embodiments, release of anti-inflammatory cytokines is not inhibited by cholinergic agonists.

When referring to the effect of the vagus nerve stimulation on an inflammatory disorder, the use of the terms "treatment", "inhibition", "decrease" or 15 "attenuation" encompasses at least a small but measurable reduction in the symptoms associated with the disorder being treated.

The present invention is directed to the treatment of inflammatory disorders or conditions mediated by an inflammatory cytokine cascade. In one aspect, the disorder is not ileus, asthma or cystic fibrosis.

20 In another aspect, the invention is the use of any of the devices described above in the manufacture of a therapeutic article for treating inflammatory disorders in a subject, wherein the device, in operation directly, stimulates the vagus nerve to treat inflammatory disorders. The term "in operation" is intended to mean the device during use or application of the device on, to, or near the subject to directly 25 stimulate the vagus nerve to treat inflammatory disorders.

In a further aspect, the invention relates to the use of a device in the manufacture of a therapeutic article for treating inflammatory disorders in a subject, wherein the device is used solely to stimulate the vagus nerve for the purpose of treating inflammatory disorders. The term "solely" includes the use of the device to 30 selectively treat inflammatory disorders where other diseases or conditions could potentially be treated by stimulation of the vagus nerve.

It is preferred that no medical condition other than an inflammatory disorder is treatable by the direct stimulation of the vagus nerve by the device. In one embodiment, the device may be adapted specifically to treat only inflammatory disorders by direct stimulation of the vagus nerve.

5 The condition can be one where the inflammatory cytokine cascade causes a systemic reaction, such as with septic shock. Alternatively, the condition can be mediated by a localized inflammatory cytokine cascade, as in rheumatoid arthritis.

 Nonlimiting examples of conditions which can be usefully treated using the present invention include appendicitis, peptic ulcer, gastric ulcer, duodenal ulcer,
10 peritonitis, pancreatitis, ulcerative colitis, pseudomembranous colitis, acute colitis, ischemic colitis, diverticulitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Crohn's disease, enteritis, Whipple's disease, allergy, anaphylactic shock, immune complex disease, organ ischemia, reperfusion injury, organ necrosis, hay
15 fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, pneumonitis,
 pneumoultramicroscopic silicovolcanoconiosis, alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, herpes virus infection
20 disseminated bacteremia, Dengue fever, candidiasis, malaria, filariasis, amebiasis, hydatid cysts, burns, dermatitis, dermatomyositis, sunburn, urticaria, warts, wheals, vasculitis, angitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, myocardial ischemia, periarteritis nodosa, rheumatic fever, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory
25 distress syndrome, meningitis, encephalitis, multiple sclerosis, cerebral infarction, cerebral embolism, Guillame-Barre syndrome, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia gravis, thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, Behcet's
30 syndrome, allograft rejection, graft-versus-host disease, Type I diabetes, ankylosing spondylitis, Berger's disease, Reiter's syndrome and Hodgkin's disease.

In more preferred embodiments, the condition is appendicitis, peptic, gastric or duodenal ulcers, peritonitis, pancreatitis, ulcerative, pseudomembranous, acute or ischemic colitis, hepatitis, Crohn's disease, asthma, allergy, anaphylactic shock, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, septic abortion, disseminated bacteremia, burns, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory distress syndrome, cerebral infarction, cerebral embolism, spinal cord injury, paralysis, allograft rejection or graft-versus-host disease. In the most preferred embodiments, the condition is endotoxic shock.

10 In another preferred embodiment, the conditions are sepsis, endotoxic shock, allograft rejection, rheumatoid arthritis, adult respiratory distress syndrome, asthma, systemic lupus erythematosus, pancreatitis, peritonitis, burns, myocardial ischemia, allograft rejection, graft-versus-host disease, congestive heart failure, organ ischemia, reperfusion injury, cachexia and cystic fibrosis.

15 In another preferred embodiment, the conditions are appendicitis, ulcerative colitis, Crohn's disease, allergy, reperfusion injury, systemic lupus erythematosus, hepatitis, Behcet's syndrome, multiple sclerosis and atherosclerosis.

In another preferred embodiment, the conditions are endotoxic shock and sepsis.

20

The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

25 *EXAMPLE 1 Electrical Vagus Nerve Stimulation Using Decreased Stimulation Intensities and Durations are Sufficient for Activation of the Cholinergic Anti-Inflammatory Pathway.*

To determine whether decreased stimulation parameters could achieve anti-inflammatory effects, intact vagus nerves were electrically stimulated at progressively lower stimulation intensities and durations in the setting of lethal endotoxemia. Male 8- to 12-week-old BALB/c mice (25-30 g; Taconic) were housed at 25°C on a 12 hour light/dark cycle. Animals were allowed to acclimate to the

facility for at least 7 days prior to experimental manipulation. Standard mouse chow and water were freely available. All animal experiments were performed in accordance with the National Institutes of Health (NIH) Guidelines under protocols approved by the Institutional Animal Care and Use Committee of the North Shore-
5 Long Island Jewish Research Institute.

Mice were anesthetized with isoflurane (1.5- 2.0%) and placed supine on the operating table. A ventral cervical midline incision was used to expose and isolate the left cervical vagus nerve. For electrical stimulation, the intact vagus nerve was placed across bipolar platinum electrodes (Plastics One) connected to a stimulation
10 module (STM100C, Biopac Systems) and controlled by an acquisition system (MP150, Biopac Systems). Electrical stimulation parameters were programmed using AcqKnowledge software (Biopac Systems). Stimulation parameters included (100mA, 2ms, 5Hz) for 20 min (10 min before LPS administration and 10 min after), (100mA, 2ms, 5Hz) for 2 min (1 min before LPS administration and 1 min
15 after), (100mA, 2ms, 5Hz) for 30 sec (5 min after LPS administration), and (1mA, 0.5ms, 30Hz) for 30 sec (5 min after LPS administration). Sham operated electrical VNS mice underwent cervical incision followed by dissection of the underlying submandibular salivary glands only. The vagus nerve was neither exposed nor isolated.

20 Mice were injected with endotoxin (*Escherichia coli* LPS 0111:B4; Sigma) that was dissolved in sterile, pyrogen-free saline at stock concentrations of 1 mg/ml. LPS solutions were sonicated for 30 min immediately before use for each experiment. Mice received an LD₅₀ dose of LPS (7.5 mg/kg, i.p.). Blood was collected 2 h after LPS administration, allowed to clot for 2 h at room temperature,
25 and then centrifuged for 15 min at 2,000 x g. Serum samples were stored at -20°C before analysis. TNF concentrations in mouse serum were measured by ELISA (R & D Systems).

As shown in FIG. 5, all four stimulation parameters were sufficient for TNF suppression. The control mice group who received LPS followed by sham VNS had
30 a mean serum TNF level of 2755 ± 424 pg/ml. Serum TNF levels in the electrical VNS groups were as follows; 20 min (712 ± 128 pg/ml, 25.8% of control, p= 0.02), 2 min (688 ± 114 pg/ml, 25.0% of control, p= 0.02), 30 sec at 100mA (821 ± 378

pg/ml, 29.8% of control, $p=0.46$), and 30 sec at 1mA (767 ± 144 pg/ml, 27.8% of control, $p=0.03$). The 30 sec 1mA group corresponds to a clinically approved stimulation protocol (REF).

5 These results indicate that cholinergic anti-inflammatory pathway activation is responsive to physiologic, clinically well-tolerated electrical stimulation parameters. Additionally, the application of supraphysiologic current doses or prolonged stimulation durations does not provide any additional benefits in terms of reduced pro-inflammatory cytokine production.

10 *EXAMPLE 2 The Effective Half-Life of Electrical Vagus Nerve Stimulation-Mediated TNF Suppression is Between Two and Three Days.*

To determine how long the anti-inflammatory effects of vagus nerve stimulation last after the completion of stimulation, mice underwent electrical stimulation for 30 sec (1mA, 0.5ms, 30Hz), and were allowed to recover for defined time periods prior to LPS administration. Control mice underwent sham surgery at time 0 and were challenged with LPS at the identical time periods as stimulated mice. Results for the four experimental groups are depicted in FIG. 5. Waiting for two hours between VNS and subsequent lipopolysaccharide (LPS) administration resulted in a 71% suppression of TNF (control= 1606 ± 326 pg/ml vs. VNS= 474 ± 157 pg/ml, $p=0.01$). Waiting for one day between VNS and LPS administration resulted in a 72% suppression of TNF (control= 2813 ± 503 pg/ml vs. VNS= 783 ± 87 pg/ml, $p=0.004$). Waiting two days between VNS and LPS resulted in a 44% suppression of TNF (control= 1590 ± 351 pg/ml vs. VNS= 892 ± 85 pg/ml, $p=0.09$). Finally, waiting for three days resulted in no TNF suppression (control= 1253 ± 202 pg/ml vs. VNS= 1393 ± 263 pg/ml, $p=0.7$). Animals were euthanized two hours after LPS administration.

25 These results indicate that the cholinergic anti-inflammatory pathway's effects are very long lasting, persisting for at least two days after stimulation. Furthermore, there was no significant difference in the anti-inflammatory effects between the two hour delay as opposed to a one day delay prior to LPS challenge. Finally, the data indicate that the anti-inflammatory effects of vagus nerve stimulation are abolished three days after stimulation.

EXAMPLE 3 Electrical vagus nerve stimulation improves severity of arthritis in a rat model of collagen-induced arthritis

To determine if vagus nerve stimulation could ameliorate the severity of
5 arthritis in a rat collagen-induced arthritis model, rats received repeated vagus nerve stimulation via implanted electrodes for several days after collagen immunization and were scored for arthritis severity.

Purified Rat Type II Collagen (CII) (Chondrex, Redmond, WA, USA) was dissolved in 0.01M acetic acid. Equal volumes of collagen solution and incomplete
10 Freund's adjuvant (IFA; Difco Laboratories, Detroit, MI) were emulsified at 4°C so that 200 ul of emulsion contains 150ug of rat CII (Åkerlund et al, Clinical & Experimental Immunology 1999 115: 32-41; Kokkola R et al., Arthritis Rheum. 2003 48:2052-8.). Rats were immunized intradermally at the base of the tail with a volume of 200ul per animal. A chronic, destructive arthritis developed with a mean
15 onset of 14 days after immunization.

A previously described arthritis clinical scoring system was utilized (Kokkola R et al., Arthritis Rheum 2003. 48(7): 2052-2058). This scoring system has proven reliable and highly discriminative for therapeutic studies (Åkerlund et al, Clin Exp Immunol 1999, 115:32-41). Rats were observed daily for clinical signs of
20 arthritis, including erythema and swelling of the joints. The interphalangeal joints of the digits, the metacarpophalangeal joint and wrist in the forepaw, and the metatarsophalangeal joint and ankle joint in the hind paw are each considered as one category of joint. Each paw was scored on a scale of 0-4 as follows: 0= unaffected, 1= 1 type of joint affected, 2= 2 types of joints affected, 3= 3 types of joints
25 affected, 4= 3 types of joints affected and maximal erythema and swelling. An arthritis index was calculated for each rat and expressed as the cumulative score for all paws, with a maximum possible score of 16. Two independent observers performed all arthritis evaluations. The observers were additionally blinded to the identity of the animals.

30 Electrical vagus nerve stimulation was started on the 13th day post collagen immunization day (PCID). VNS rats were stimulated for 10 min once a day (5 V, 1-2 mA; 0.5 msec pulse; 30 Hz; 10 min on-time of alternating 30 seconds "on" and

300 seconds “off”) through day 20 (day 16 was skipped). These stimuli were generated using the STMISOC stimulation adapter, STM100C stimulator module, and MP150 Data Acquisition System, all from Biopac Systems, Inc. Where indicated, all animals were anesthetized using isoflurane inhalation gas (2-4%).

5 During surgical procedures, animals were placed on a maintenance anesthesia dose via a mask delivery system. Following isoflurane anesthesia induction, animal were placed in supine position, and a 2 cm ventral midline cervical incision was made between the mandible and sternum. The subcutaneous tissue was dissected and retracted laterally. The mandibular salivary glands were bluntly separated and
10 retracted laterally. The left vagus nerve was isolated between the sternomastoid and sternohyoid muscles, dissected free from the neighboring carotid artery, and controlled with a 4-0 silk suture. A Teflon-coated silver electrode 0.003 inch in diameter was secured to the vagus nerve by multiple 360 degree circular wrappings around the nerve. The Teflon only was stripped from the ends of the wire to
15 minimize electrical stimulation of the surrounding cervical muscles. The silver wire ends then were tunneled subcutaneously around the left neck to the dorsal cervical midline. At this point, they were exited through the skin and be attached to stimulating wires traveling through the tether apparatus.

As shown in FIG. 6, repeated electrical stimulation of the vagus nerve
20 resulted in decreased clinical signs of arthritis (as measured by erythema and swelling of the joints) as compared with control and sham animals (stimulated rats: N=4; sham: N=5; control: N=3.) On day 16, the arthritis score in rats receiving vagus nerve stimulation was significantly less than that in control and sham animals ($p<0.05$). On day 19, the arthritis score in rats receiving vagus nerve stimulation
25 was significantly less than that in sham treated animals ($p<0.05$). These results indicate that repeated vagus nerve stimulation is effective at lessening arthritis severity in collagen-induced arthritis.

While this invention has been particularly shown and described with
30 references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising stimulating the vagus nerve in a subject with an electrical signal, wherein the signal voltage is from 0.01 Volt to 1 Volt, provided that the condition is not ileus, asthma or cystic fibrosis.
2. The method of Claim 1 wherein the signal voltage is from 0.01 Volt to 0.05 Volt.
3. The method of Claim 1 wherein pulse width is from 0.1 ms to 5 ms; signal frequency is from 0.1 Hz to 30 Hz; and signal on-time is from 1 second to 120 seconds.
4. The method of Claim 1 wherein signal voltage is from 0.01 Volt to 0.05 Volt; pulse width is from 0.1 ms to 0.5 ms; signal frequency is from 10 Hz to 30 Hz; and signal on-time is from 20 seconds to 40 seconds.
5. The method of Claim 1 wherein the inflammatory disorder is selected from the group consisting of appendicitis, peptic ulcer, gastric ulcer, duodenal ulcer, peritonitis, pancreatitis, ulcerative colitis, pseudomembranous colitis, acute colitis, ischemic colitis, diverticulitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Crohn's disease, enteritis, Whipple's disease, allergy, anaphylactic shock, immune complex disease, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, pneumonitis, pneumotransmicroscopicsilicovolcanoconiosis, alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria,

- 5 filariasis, amebiasis, hydatid cysts, burns, dermatitis, dermatomyositis, sunburn, urticaria, warts, wheals, vasculitis, angiitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, myocardial ischemia, periarteritis nodosa, rheumatic fever, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory distress syndrome, meningitis, encephalitis, multiple sclerosis, cerebral infarction, cerebral embolism, Guillame-Barre syndrome, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia
- 10 gravis, thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, Behcet's syndrome, allograft rejection, graft-versus-host disease, Type I diabetes, ankylosing spondylitis, Berger's disease, Reiter's syndrome and Hodgkin's disease.
- 15 6. The method of Claim 5 wherein the condition is selected from sepsis, endotoxic shock, allograft rejection, rheumatoid arthritis, adult respiratory distress syndrome, asthma, systemic lupus erythematosus, pancreatitis, peritonitis, burns, myocardial ischemia, allograft rejection, graft-versus-host disease, congestive heart failure, organ ischemia, reperfusion injury, cachexia and cystic fibrosis.
- 20
7. The method of Claim 5 wherein the condition is selected from appendicitis, ulcerative colitis, Crohn's disease, allergy, reperfusion injury, systemic lupus erythematosus, hepatitis, Behcet's syndrome, multiple sclerosis and
- 25 atherosclerosis.
8. The method of Claim 5 wherein the condition is endotoxic shock.
9. The method of Claim 5 wherein the condition is sepsis.
- 30
10. The method of Claim 5, wherein the condition is appendicitis.

11. The method of Claim 5, wherein the condition is ulcerative colitis.
12. The method of claim 5, wherein the condition is Crohn's disease.
- 5 13. The method of claim 5, wherein the condition is allergy.
14. The method of claim 5, wherein the condition is organ ischemia.
15. The method of claim 5, wherein the condition is reperfusion injury.
- 10 16. The method of claim 5, wherein the condition is allograft rejection.
17. The method of claim 5, wherein the condition is graft-versus-host disease.
- 15 18. The method of claim 5, wherein the condition is rheumatoid arthritis.
19. The method of claim 5, wherein the condition is systemic lupus erythematosus.
- 20 20. The method of claim 5, wherein the condition is pancreatitis.
21. The method of claim 5, wherein the condition is peritonitis.
22. The method of claim 5, wherein the condition is burns.
- 25 23. The method of claim 5, wherein the condition is Behcet's disease.
24. The method of claim 5, wherein the condition is multiple sclerosis.
- 30 25. The method of claim 5, wherein the condition is cachexia.
26. The method of claim 5, wherein the condition is hepatitis.

27. The method of claim 5, wherein the condition is atherosclerosis.
28. The method of Claim 5 wherein the subject is a human.
- 5 29. The method of claim 5 wherein said vagus nerve activity is stimulated at a peripheral distal location.
- 10 30. The method of claim 5 wherein said vagus nerve activity is stimulated in the cervical region.
31. The method of claim 5 wherein ganglions or post-ganglionic neurons are stimulated.
- 15 32. The method of Claim 5 wherein the vagus nerve is stimulated in the brain.
33. The method of Claim 5 wherein the efferent vagus nerve is stimulated.
34. The method of Claim 5 wherein the afferent vagus nerve is stimulated.
- 20 35. A method for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising stimulating the vagus nerve in a subject with an electrical signal, wherein the signal voltage is from 0.01 Volt to 1 Volt, pulse width is from 0.1 ms to 5 ms; signal frequency is from 0.1 Hz to 25 30 Hz; signal on-time is from 1 second to 120 seconds; and signal off-time is over 2 hours.
36. The method of Claim 35 wherein the signal off-time is from 2 hours to 24 hours.
- 30 37. An electrical signal generator for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising:

an electrode assembly for delivering an electrical signal to the vagus nerve of the subject; and

a controller controlling the electrical signal by limiting the signal voltage to a range from 0.01 Volt to 1 Volt.

5

38. The signal generator of Claim 37 wherein the signal voltage is limited to a range from 0.01 Volt to 0.05 Volt.

39. The signal generator of Claim 37, the controller limiting pulse width to a range from 0.1 ms to 5 ms; signal frequency to a range from 0.1 Hz to 30 Hz; and signal on-time to a range from 1 second to 120 seconds.

40. The signal generator of Claim 37, the controller limiting signal voltage to a range from 0.01 Volt to 0.05 Volt; pulse width to a range from 0.1 ms to 0.5 ms; signal frequency to a range from 10 Hz to 30 Hz; and signal on-time to a range from 20 seconds to 40 seconds.

41. An electrical signal generator for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising:
an electrode assembly for delivering an electrical signal to the vagus nerve of the subject; and
a controller controlling the electrical signal by limiting the signal voltage to a range from 0.01 Volt to 1 Volt, pulse width to a range from 0.1 ms to 5 ms; signal frequency to a range from 0.1 Hz to 30 Hz; signal on-time to a range from 1 second to 120 seconds; and signal off-time to a range of over 2 hours.

42. The signal generator of Claim 41, the controller limiting the signal off-time to a range from 2 hours to 24 hours.

30

43. Use of an electrical signal generator for construction of a medical device for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising:
- 5 an electrode assembly for delivering an electrical signal to the vagus nerve of the subject; and
- a controller controlling the electrical signal by limiting the signal voltage to a range from 0.01 Volt to 1 Volt, provided that the condition is not ileus, asthma or cystic fibrosis.
- 10 44. The use of a signal generator of Claim 43, the controller limiting the signal voltage to a range from 0.01 Volt to 0.05 Volt.
45. The use of a signal generator of Claim 43, the controller limiting pulse width to a range from 0.1 ms to 5 ms; signal frequency to a range from 0.1 Hz to 30
- 15 Hz; and signal on-time to a range from 1 second to 120 seconds.
46. The use of a signal generator of Claim 43, the controller limiting signal voltage to a range from 0.01 Volt to 0.05 Volt; pulse width to a range from 0.1 ms to 0.5 ms; signal frequency to a range from 10 Hz to 30 Hz; and
- 20 signal on-time to a range from 20 seconds to 40 seconds.
47. The use of the electrical signal generator of Claim 43, wherein the condition mediated by the inflammatory cytokine cascade is selected from the group consisting of appendicitis, peptic ulcer, gastric ulcer, duodenal ulcer,
- 25 peritonitis, pancreatitis, ulcerative colitis, pseudomembranous colitis, acute colitis, ischemic colitis, diverticulitis, epiglottitis, achalasia, cholangitis, cholecystitis, hepatitis, Crohn's disease, enteritis, Whipple's disease, allergy, anaphylactic shock, immune complex disease, organ ischemia, reperfusion injury, organ necrosis, hay fever, sepsis, septicemia, endotoxic
- 30 shock, cachexia, hyperpyrexia, eosinophilic granuloma, granulomatosis, sarcoidosis, septic abortion, epididymitis, vaginitis, prostatitis, urethritis, bronchitis, emphysema, rhinitis, pneumonitis,

- 5 pneumotransmicroscopicsilicovolcanoconiosis, alveolitis, bronchiolitis, pharyngitis, pleurisy, sinusitis, influenza, respiratory syncytial virus infection, HIV infection, hepatitis B virus infection, hepatitis C virus infection, disseminated bacteremia, Dengue fever, candidiasis, malaria,
- 10 filariasis, amebiasis, hydatid cysts, burns, dermatitis, dermatomyositis, sunburn, urticaria, warts, wheals, vasculitis, angiitis, endocarditis, arteritis, atherosclerosis, thrombophlebitis, pericarditis, myocarditis, myocardial ischemia, periarteritis nodosa, rheumatic fever, Alzheimer's disease, coeliac disease, congestive heart failure, adult respiratory distress syndrome,
- 15 meningitis, encephalitis, multiple sclerosis, cerebral infarction, cerebral embolism, Guillame-Barre syndrome, neuritis, neuralgia, spinal cord injury, paralysis, uveitis, arthritides, arthralgias, osteomyelitis, fasciitis, Paget's disease, gout, periodontal disease, rheumatoid arthritis, synovitis, myasthenia gravis, thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome,
- 20 Behcet's syndrome, allograft rejection, graft-versus-host disease, Type I diabetes, ankylosing spondylitis, Berger's disease, Reiter's syndrome and Hodgkin's disease.
- 25
48. The use of the electrical signal generator of Claim 43 wherein the condition is selected from sepsis, endotoxic shock, allograft rejection, rheumatoid arthritis, adult respiratory distress syndrome, asthma, systemic lupus erythematosus, pancreatitis, peritonitis, burns, myocardial ischemia, allograft rejection, graft-versus-host disease, congestive heart failure, organ ischemia, reperfusion injury, cachexia and cystic fibrosis.
- 30
49. The use of the electrical signal generator of Claim 43 wherein the condition is selected from appendicitis, ulcerative colitis, Crohn's disease, allergy, reperfusion injury, systemic lupus erythematosus, hepatitis, Behcet's syndrome, multiple sclerosis and atherosclerosis.
50. The use of the electrical signal generator of Claim 43 wherein the condition is endotoxic shock.

51. The use of the electrical signal generator of Claim 43 wherein the condition is sepsis.
- 5 52. The use of the electrical signal generator of Claim 43 wherein the condition is appendicitis.
53. The use of the electrical signal generator of Claim 43 wherein the condition is ulcerative colitis.
- 10 54. The use of the electrical signal generator of Claim 43 wherein the condition is Crohn's disease.
55. The use of the electrical signal generator of Claim 43 wherein the condition is allergy.
- 15 56. The use of the electrical signal generator of Claim 43 wherein the condition is organ ischemia.
- 20 57. The use of the electrical signal generator of Claim 43 wherein the condition is reperfusion injury.
58. The use of the electrical signal generator of Claim 43 wherein the condition is allograft rejection.
- 25 59. The use of the electrical signal generator of Claim 43 wherein the condition is graft-versus-host disease.
60. The use of the electrical signal generator of Claim 43 wherein the condition is rheumatoid arthritis.
- 30

61. The use of the electrical signal generator of Claim 43 wherein the condition is systemic lupus erythematosus.
- 5 62. The use of the electrical signal generator of Claim 43 wherein the condition is pancreatitis.
63. The use of the electrical signal generator of Claim 43 wherein the condition is peritonitis.
- 10 64. The use of the electrical signal generator of Claim 43 wherein the condition is burns.
65. The use of the electrical signal generator of Claim 43 wherein the condition is Behcet's disease.
- 15 66. The use of the electrical signal generator of Claim 43 wherein the condition is multiple sclerosis.
- 20 67. The use of the electrical signal generator of Claim 43 wherein the condition is cachexia.
68. The use of the electrical signal generator of Claim 43 wherein the condition is hepatitis.
- 25 69. The use of the electrical signal generator of Claim 43 wherein the condition is atherosclerosis.
70. The use of the electrical signal generator of Claim 43 wherein the subject is a human.
- 30

71. The use of the electrical signal generator of Claim 43 wherein said vagus nerve activity is stimulated at a peripheral distal location.
72. The use of the electrical signal generator of Claim 43 wherein said vagus nerve activity is stimulated in the cervical region.
73. The use of the electrical signal generator of Claim 43 wherein ganglions or post-ganglionic neurons are stimulated.
74. The use of the electrical signal generator of Claim 43 wherein the vagus nerve is stimulated in the brain.
75. The use of the electrical signal generator of Claim 43 wherein the efferent vagus nerve is stimulated.
76. The use of the electrical signal generator of Claim 43 wherein the afferent vagus nerve is stimulated.
77. The use of an electrical signal generator of Claim 43 in the manufacture of a therapeutic article for treating an inflammatory disorder in a subject, wherein the device, in operation, directly stimulates the vagus nerve to treat the inflammatory disorder.
78. The use of an electrical signal generator of Claim 43 in the manufacture of a therapeutic article for treating an inflammatory condition in a subject, wherein the device is used solely to stimulate the vagus nerve for the purpose of treating an inflammatory disorder.
79. Use of an electrical signal generator for construction of a medical device for treating a subject suffering from, or at risk for, an inflammatory disorder, comprising:

5 a controller controlling the electrical signal by limiting the signal voltage to a range from 0.01 Volt to 1 Volt, pulse width to a range from 0.1 ms to 5 ms; signal frequency to a range from 0.1 Hz to 30 Hz; signal on-time to a range from 1 second to 120 seconds; and signal off-time to a range over 2 hours.

80. The use of Claim 79, the controller limiting the signal off-time to a range from 2 hours to 24 hours.
- 10 81. The use of an electrical signal generator of Claim 79 in the manufacture of a therapeutic article for treating an inflammatory disorder in a subject, wherein the device, in operation, directly stimulates the vagus nerve to treat the inflammatory disorder.
- 15 82. The use of an electrical signal generator of Claim 79 in the manufacture of a therapeutic article for treating an inflammatory condition in a subject, wherein the device is used solely to stimulate the vagus nerve for the purpose of treating an inflammatory disorder.

20

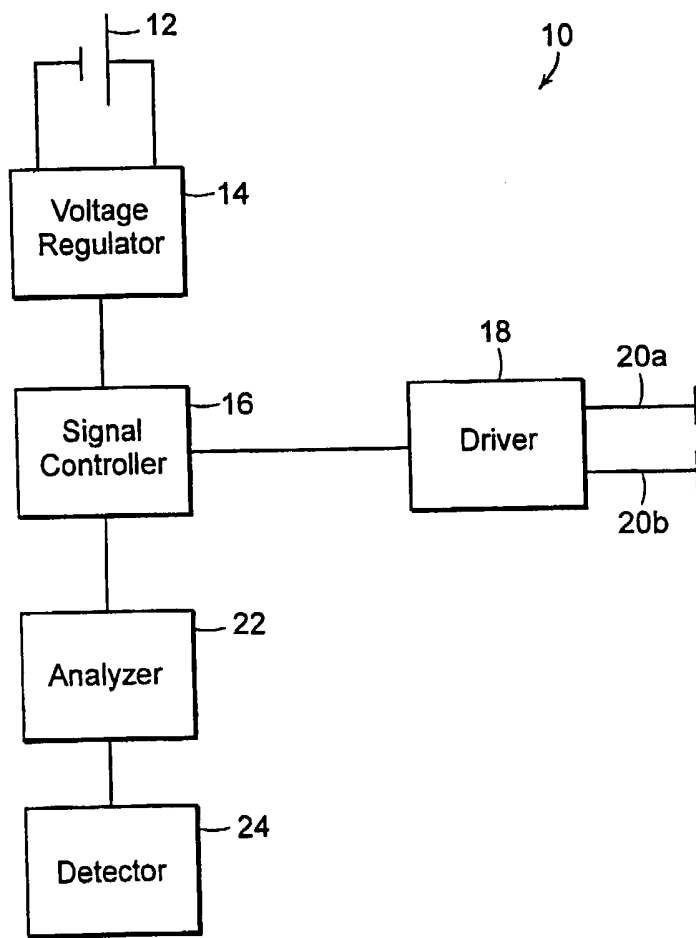


FIG. 1

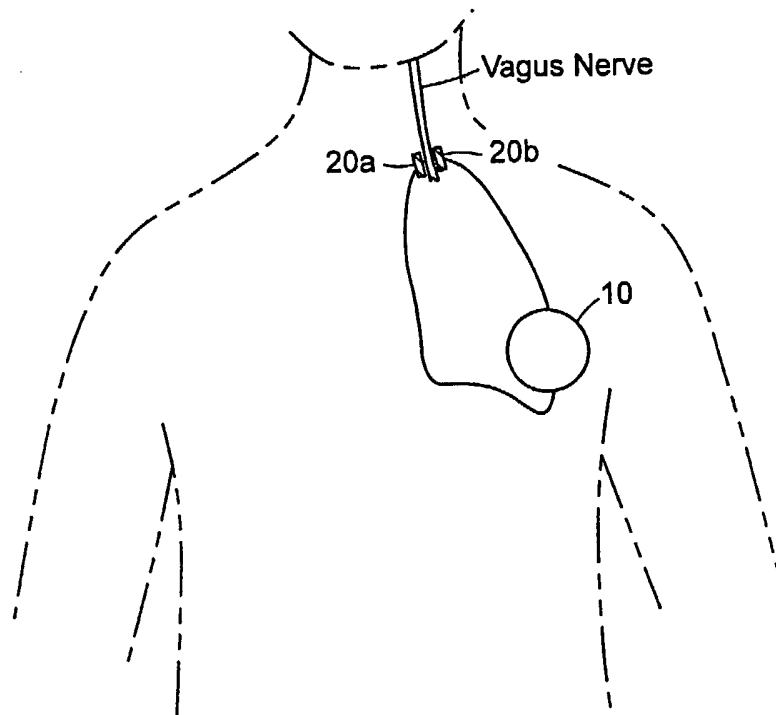


FIG. 2

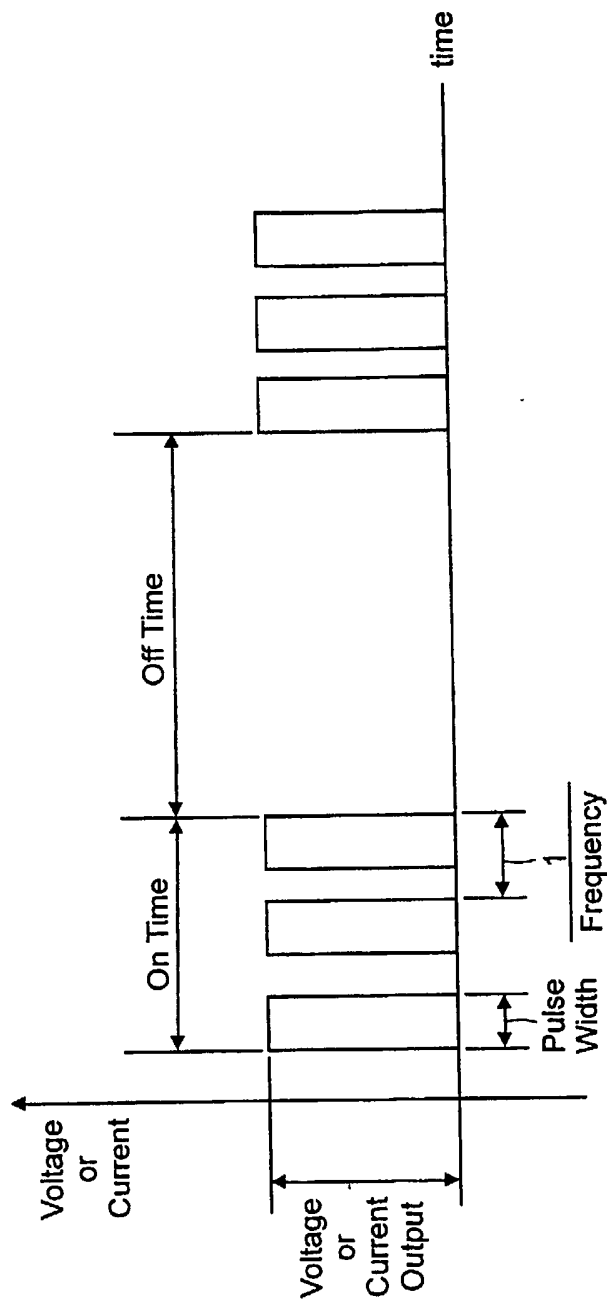


FIG. 3

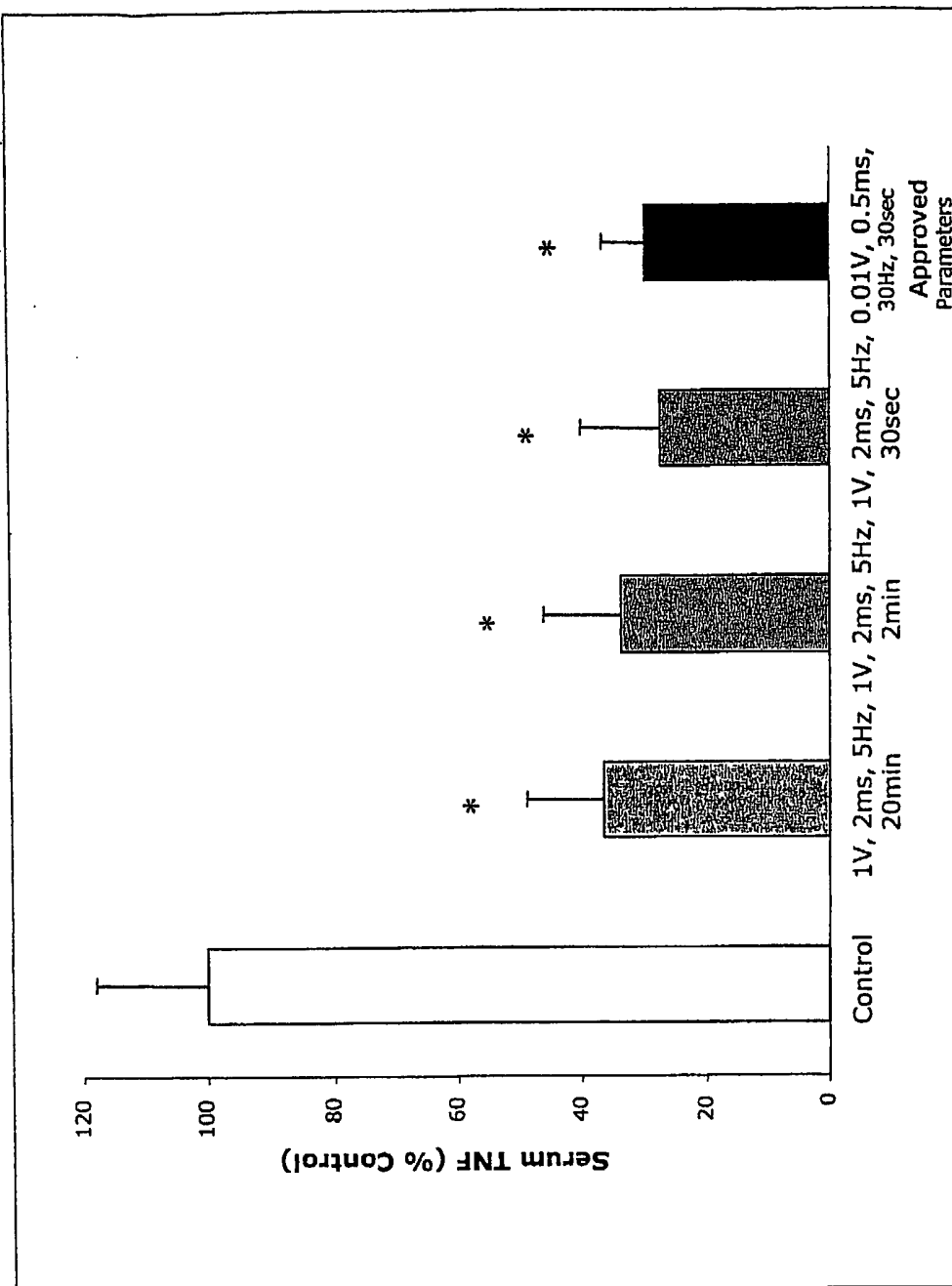


FIG. 4

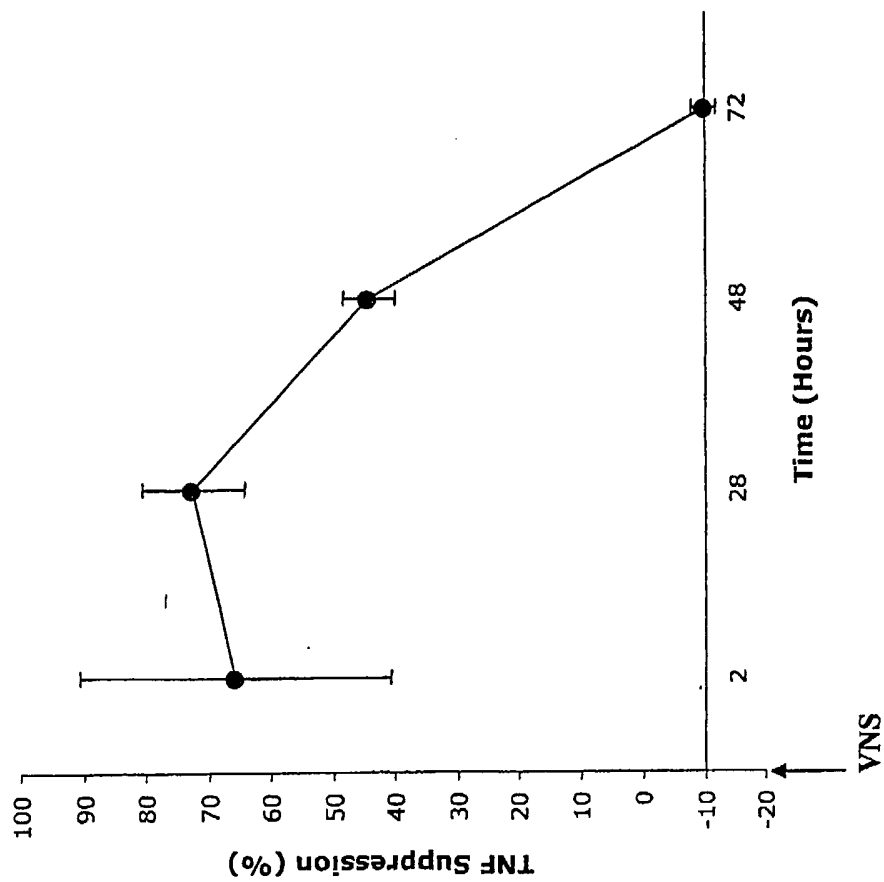


FIG. 5

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ARTHRITIS SCORE - ALL FOUR LIMBS - EXPERIMENT "C"

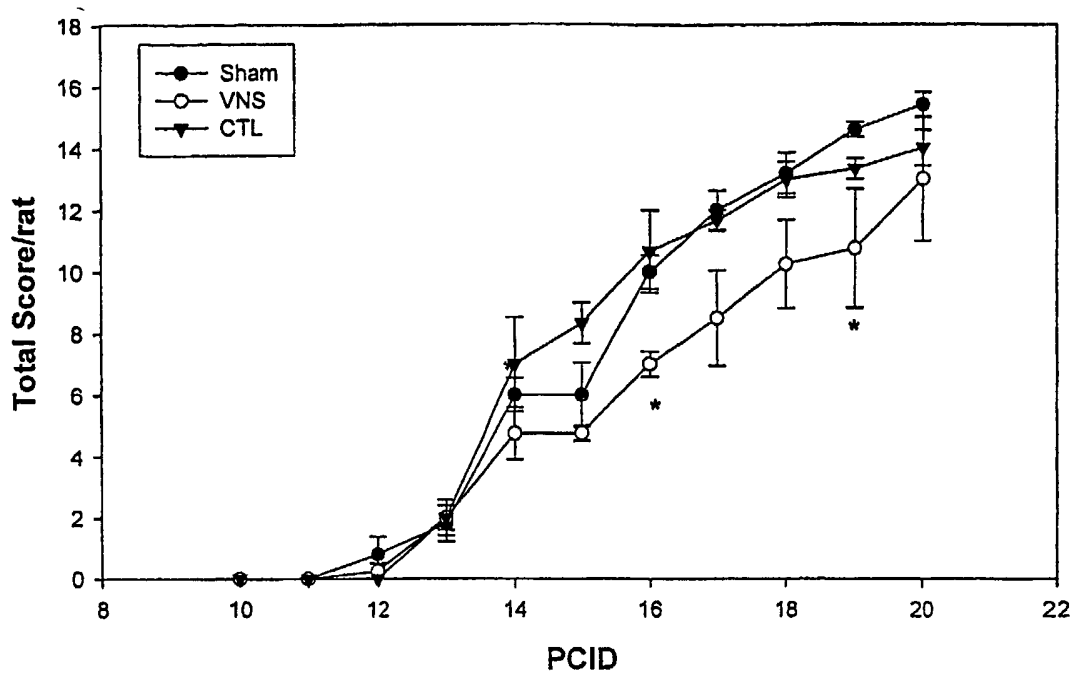


FIG. 6