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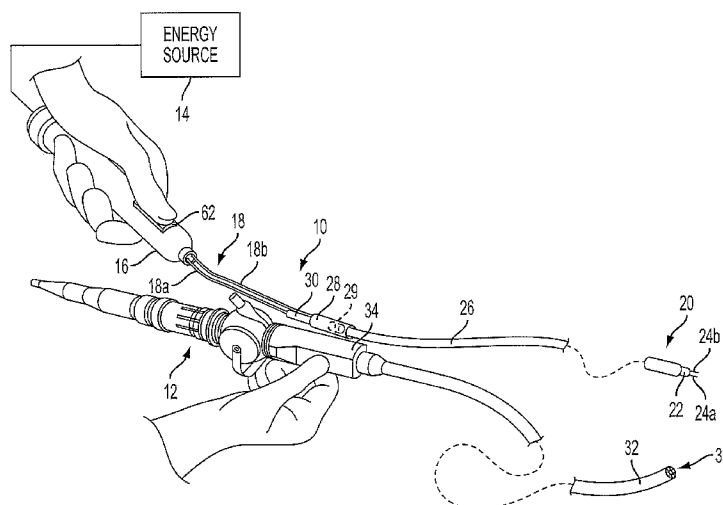


FIG. 1

(57) **Abstract:** An electrical ablation device may generally comprise first and second electrodes coupled to an energy source operative to generate and deliver a first sequence of electrical pulses and a second sequence of electrical pulses to tissue having a necrotic threshold, wherein the first sequence of electrical pulses delivers a first energy dose that is less than the necrotic threshold to induce thermal heating in the tissue and the second sequence of electrical pulses delivers a second energy dose equal to or greater than the necrotic threshold to induce cell necrosis in the tissue by irreversible electroporation. The first sequence of electrical pulses may each be independently characterized by a first amplitude, a first pulse width, and a first frequency. The second sequence of electrical pulses may be characterized by a second amplitude, a second pulse width, and a second frequency.



TITLE**ELECTRICAL ABLATION DEVICES AND METHODS****BACKGROUND**

[0001] Electrical ablation therapy has been used in medicine for the treatment of undesirable tissue, such as, for example, diseased tissue, cancer, malignant and benign tumors, masses, lesions, and other abnormal tissue growths. Apparatuses, systems, and methods for conventional ablation therapies may include electrical ablation therapies, such as, for example, high temperature thermal therapies including, focused ultrasound ablation, radiofrequency (RF) ablation, and interstitial laser coagulation, chemical therapies in which chemical agents are injected into the undesirable tissue to cause ablation, surgical excision, cryotherapy, radiation, photodynamic therapy, Moh's micrographic surgery, topical treatments with 5-fluorouracil, and laser ablation. Conventional electrical ablation therapies may suffer from some of the following limitations: cost, length of recovery, and extraordinary pain inflicted on the patient. In particular, one drawback of conventional electrical ablation therapies may be any permanent damage to healthy tissue surrounding the undesirable tissue due to detrimental thermal effects resulting from exposing the tissue to thermal energy generated by the electrical ablation device. For example, permanent damage to surrounding healthy tissue may occur when using high temperature thermal therapies to expose undesirable tissue to electric potentials sufficient to cause cell necrosis. Accordingly, electrical ablation apparatuses, systems, and methods for the treatment of undesirable tissue having reduced or no detrimental thermal effects to surrounding healthy tissue are desirable.

FIGURES

[0002] The various embodiments of electrical ablation devices and methods thereof described herein may be better understood by considering the following description in conjunction with the accompanying drawings.

[0003] FIG. 1 illustrates an electrical ablation system according to certain embodiments described herein.

[0004] FIG. 2 illustrates a bipolar electrical ablation system according to certain embodiments described herein.

[0005] FIG. 3 illustrates an electrical ablation system including sensors according to certain embodiments described herein.

[0006] FIG. 4 illustrates an electrical ablation system including a temperature sensor according to certain embodiments described herein.

[0007] FIG. 5A is a graphical representation of a series of monopolar electrical pulses that may be applied to undesirable tissue.

[0008] FIG. 5B is a graphical representation of a series of bipolar electrical pulses that may be applied to undesirable tissue.

[0009] FIG. 6A illustrates two electrodes in a monopolar electrical ablation system according to certain embodiments described herein.

[0010] FIG. 6B illustrates two electrodes in a bipolar electrical ablation system according to certain embodiments described herein.

[0011] FIG. 7 is a graphical representation of a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0012] FIGS. 8A-B are graphical representations of a series of electrical pulses that may be applied to undesirable tissue.

[0013] FIG. 9 is a graphical representation of a series of bipolar electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0014] FIGS. 10A-B are graphical representations of a series of bipolar electrical pulses that may be applied to undesirable tissue.

[0015] FIG. 11 is a graphical representation of a series of electrical pulses that may be applied to undesirable tissue.

[0016] FIG. 12 illustrates the use of an electrical ablation system according to certain embodiments described herein.

[0017] FIG. 13 is a photograph of a porcine liver after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0018] FIG. 14 is a graphical representation of electrode temperature during a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0019] FIGS. 15A-D include photographs of porcine liver after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0020] FIG. 16 is a graphical representation of a series of electrical pulses that may be applied to undesirable tissue.

[0021] FIG. 17 is a graph illustrating the area of the necrotic zone of a porcine liver after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0022] FIG. 18A is a graph illustrating the average area of the necrotic zone of a porcine liver after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0023] FIG. 18B includes photographs of porcine livers after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0024] FIG. 19 is a graphical representation of a series of electrical pulses that may be applied to undesirable tissue.

[0025] FIGS. 20A-C include photographs of porcine livers after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0026] FIGS. 21-24 are graphs illustrating the electrode temperature in porcine liver after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0027] FIGS. 25A-C include photographs of porcine livers after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein.

[0028] FIGS. 26A-F are graphical representations of simulated necrotic zones and thermal zones of porcine livers after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein

DESCRIPTION

[0029] Various embodiments are directed to electrical ablation apparatuses, systems, and methods for the treatment of undesirable tissue having reduced or no detrimental thermal effects to surrounding healthy tissue.

[0030] This disclosure describes various elements, features, aspects, and advantages of various embodiments of electrical ablation devices and methods thereof. It is to be understood that certain descriptions of the various embodiments have been simplified to illustrate only those elements, features and aspects that are relevant to a more clear understanding of the disclosed embodiments, while eliminating, for purposes of brevity or clarity, other elements, features and aspects. Any references to “various embodiments,” “some embodiments,” “one embodiment,” or “an embodiment” generally means that a particular element, feature and/or aspect described in the embodiment is included in at least one embodiment. The phrases “in various embodiments,” “in some embodiments,” “in one embodiment,” or “in an embodiment” may not

refer to the same embodiment. Persons having ordinary skill in the art, upon considering the description herein, will recognize that various combinations or sub-combinations of the various embodiments and other elements, features, and aspects may be desirable in particular implementations or applications. However, because such other elements, features, and aspects may be readily ascertained by persons having ordinary skill in the art upon considering the description herein, and are not necessary for a complete understanding of the disclosed embodiments, a description of such elements, features, and aspects may not be provided. As such, it is to be understood that the description set forth herein is merely exemplary and illustrative of the disclosed embodiments and is not intended to limit the scope of the invention as defined solely by the claims.

[0031] All numerical quantities stated herein are approximate unless stated otherwise, meaning that the term “about” may be inferred when not expressly stated. The numerical quantities disclosed herein are to be understood as not being strictly limited to the exact numerical values recited. Instead, unless stated otherwise, each numerical value is intended to mean both the recited value and a functionally equivalent range surrounding that value. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Notwithstanding the approximations of numerical quantities stated herein, the numerical quantities described in specific examples of actual measured values are reported as precisely as possible.

[0032] All numerical ranges stated herein include all sub-ranges subsumed therein. For example, a range of “1 to 10” is intended to include all sub-ranges between and including the recited minimum value of 1 and the recited maximum value of 10. Any maximum numerical limitation recited herein is intended to include all lower numerical limitations. Any minimum numerical limitation recited herein is intended to include all higher numerical limitations.

[0033] As generally used herein, the terms “proximal” and “distal” generally refer to a clinician manipulating one end of an instrument used to treat a patient. The term “proximal” generally refers to the portion of the instrument closest to the clinician. The term “distal” generally refers to the portion located furthest from the clinician. It will be further appreciated that for conciseness and clarity, spatial terms such as “vertical,” “horizontal,” “up,” and “down” may be used herein with respect to the illustrated embodiments. However, surgical instruments may be used in many orientations and positions, and these terms are not intended to be limiting and absolute.

[0034] According to certain embodiments, an ablation apparatus may generally comprise first and second electrodes coupled to an energy source operative to generate and deliver a first sequence of electrical pulses and a second sequence of electrical pulses to tissue having a necrotic threshold, wherein the first sequence of electrical pulses delivers a first energy dose that is less than the necrotic threshold to induce thermal heating in the tissue and the second sequence of electrical pulses delivers a second energy dose equal to or greater than the necrotic threshold to induce cell necrosis in the tissue by irreversible electroporation. The necrotic threshold generally refers the electric field strength that induces cell necrosis by irreversible electroporation. The necrotic threshold may relate to at least the following parameters: cell type, temperature, electrical conductivity, pH and tissue perfusion. Table 1 illustrates the necrotic threshold for several cell types.

Table 1	
Cell Type	Necrotic Threshold
Hepatocyte (healthy porcine)	800 V/cm
Renal cell (healthy porcine)	1000 V/cm

[0035] In certain embodiments, electrical ablation devices may generally comprise one or more electrodes configured to be positioned into or proximal to undesirable tissue in a tissue treatment region (e.g., a target site or a worksite). The tissue treatment region may have evidence of abnormal tissue growth. In general, the electrodes may comprise an electrically

conductive portion (e.g., medical grade stainless steel, gold plated, etc.) and may be configured to electrically couple to an energy source. Once the electrodes are positioned into or proximal to the undesirable tissue, an energizing potential may be applied to the electrodes to create an electric field to which the undesirable tissue is exposed. The energizing potential (and the resulting electric field) may be characterized by various parameters, such as, for example, frequency, amplitude, pulse width (duration of a pulse or pulse length), and/or polarity.

Depending on the diagnostic or therapeutic treatment to be rendered, a particular electrode may be configured either as an anode or a cathode, or a plurality of electrodes may be configured with at least one electrode configured as an anode and at least one other electrode configured as a cathode. Regardless of the initial polarity configuration, the polarity of the electrodes may be reversed by reversing the polarity of the output of the energy source.

[0036] In certain embodiments, a suitable energy source may comprise an electrical waveform generator. The electrical waveform generator may be configured to create an electric field that is suitable to induce thermal heating in the tissue without inducing cell necrosis in the tissue by irreversible electroporation at various electric field amplitudes and durations. The electrical waveform generator may be configured to create an electric field that is suitable to create irreversible electroporation in undesirable tissue at various electric field amplitudes and durations. The energy source may be configured to deliver electrical pulses in the form of direct-current (DC) and/or alternating-current (AC) voltage potentials (e.g., time-varying voltage potentials) to the electrodes. The energy source may also be configured to reverse the potential between the electrodes. The electrical pulses may be characterized by various parameters, such as, for example, frequency, amplitude, pulse width, polarity, total number of pulses, delay between pulses bursts, total number of pulses at a lower voltage, and total number of pulses at high voltage. The undesirable tissue may be heated by exposure to the electric potential difference across the electrodes. The undesirable tissue may be ablated by exposure to the electric potential difference across the electrodes.

[0037] In certain embodiments, the apparatuses, systems, and methods may be configured for minimally invasive ablation treatment of undesirable tissue through the use of irreversible electroporation. Minimally invasive ablation treatment of undesirable tissue may be characterized by the ability to ablate undesirable tissue in a controlled and focused manner having reduced or no thermally damaging effects to the surrounding healthy tissue. The apparatuses, systems, and methods may be configured to ablate undesirable tissue through the use of electroporation or electroporabilization. Electroporation refers to the application of electric pulses to a cell membrane to cause an increase in the permeabilization of the cell membrane. The external electric field (*i.e.*, electric potential/per unit length) applied to the cell may significantly increase the electrical conductivity and permeability of the plasma in the cell membrane.

[0038] More specifically, the apparatuses, systems, and methods may be configured to ablate undesirable tissue through the use of irreversible electroporation. Irreversible electroporation refers to the application of an electric field of a specific magnitude and duration to a cell membrane such that the permeabilization of the cell membrane cannot be reversed. One of the primary parameters affecting the transmembrane potential is the potential difference across the cell membrane. The destabilizing potential may form pores in the cell membrane when the potential across the cell membrane exceeds its dielectric strength causing the cell to die under a process known as apoptosis and/or necrosis. Irreversible electroporation may induce localized heating of the tissue surrounding the electrodes. Irreversible electroporation may lead to cell death without inducing a significant amount of heat in the cell membrane.

[0039] The application of irreversible electroporation pulses to cells may be an effective way for ablating large volumes of undesirable tissue with no or minimal detrimental thermal effects to the surrounding healthy tissue. Without wishing to be bound to any particular theory, it is believed that irreversible electroporation destroys cells with no or minimal heat, and thus, may not destroy the cellular support structure or regional vasculature. A destabilizing irreversible

electroporation pulse, suitable to cause cell death without inducing a significant amount of thermal damage to the surrounding healthy tissue, may have amplitude in the range of several hundred to several thousand volts and may be generally applied across biological membranes over a distance of several millimeters, for example, for a relatively long duration of 1 μ s to 100 ms. Thus, the undesirable tissue may be ablated *in-vivo* through the delivery of destabilizing electric fields by quickly causing cell necrosis.

[0040] The apparatuses, systems, and methods for electrical ablation therapy may be adapted for use in minimally invasive surgical procedures to access the tissue treatment region in various anatomic locations, such as, for example, the brain, lungs, breast, liver, gall bladder, pancreas, prostate gland, and various internal body lumen defined by the esophagus, stomach, intestine, colon, arteries, veins, anus, vagina, cervix, fallopian tubes, and the peritoneal cavity. Minimally invasive electrical ablation devices may be introduced to the tissue treatment region through a small opening formed in the patient's body using a trocar or through a natural body orifice such as the mouth, anus, or vagina using transluminal access techniques known as Natural Orifice Transluminal Endoscopic Surgery (NOTES)[™]. Once the electrical ablation devices (*e.g.*, electrodes) are located into or proximal to the undesirable tissue in the treatment region, electric field potentials may be applied by the energy source to the undesirable tissue. The electrical ablation devices may comprise portions that may be inserted into the tissue treatment region percutaneously (*e.g.*, where access to inner organs or other tissue is done via needle-puncture of the skin). Other portions of the electrical ablation devices may be introduced into the tissue treatment region endoscopically (*e.g.*, laparoscopically and/or thoracoscopically) through trocars or channels of the endoscope, through small incisions, or transcutaneously (*e.g.*, where electric pulses are delivered to the tissue treatment region through the skin). An electrical ablation device is described in commonly owned U.S. Patent Publication No. 20100179530, entitled, "ELECTRICAL ABLATION DEVICES" filed January 12, 2009.

[0041] FIG. 1 illustrates one embodiment of an electrical ablation system 10. The electrical ablation system 10 may be employed to ablate undesirable tissue, such as, for example, diseased tissue, cancer, malignant and benign tumors, masses, lesions, and other abnormal tissue growths in a tissue treatment region using electrical energy. The electrical ablation system 10 may be configured to treat a number of lesions and osteopathologies comprising metastatic lesions, tumors, fractures, infected sites, and inflamed sites in a tissue treatment region using electrical energy. The electrical ablation system 10 may be configured to be positioned within a patient's natural body orifice, *e.g.*, the mouth, anus, and vagina, and/or advanced through internal body lumen or cavities, *e.g.*, the esophagus, stomach, intestines, colon, cervix, and urethra, to reach the tissue treatment region. The electrical ablation system 10 may be configured to be positioned and passed through a small incision or keyhole formed through the patient's skin or abdominal wall using a trocar to reach the tissue treatment region. The tissue treatment region may be located in the patient's brain, lung, breast, liver, gall bladder, pancreas, prostate gland, various internal body lumen defined by the esophagus, stomach, intestine, colon, arteries, veins, anus, vagina, cervix, fallopian tubes, and the peritoneal cavity. The electrical ablation system 10 may be used in conjunction with endoscopic, laparoscopic, thoracoscopic, open surgical procedures via small incisions or keyholes, percutaneous techniques, transcutaneous techniques, and/or external non-invasive techniques, and any combinations thereof.

[0042] Once positioned into or proximate the tissue treatment region, the electrical ablation system 10 may be actuated (*e.g.*, energized) to ablate the undesirable tissue. In one embodiment, the electrical ablation system 10 may be configured to treat diseased tissue in the gastrointestinal tract, esophagus, lung, and/or stomach that may be accessed orally. In another embodiment, the electrical ablation system 10 may be adapted to treat undesirable tissue in the liver or other organs that may be accessible using transluminal access techniques, such as, for example, NOTES™ techniques where the electrical ablation devices may be initially introduced

through a natural body orifice and then advanced to the tissue treatment site by puncturing the walls of internal body lumen. In various embodiments, the electrical ablation system 10 may be adapted to treat undesirable tissue in the brain, lung, breast, liver, gall bladder, pancreas, or prostate gland, using one or more electrodes positioned percutaneously, transcutaneously, translumenally, minimally invasively, and/or through open surgical techniques, or any combination thereof.

[0043] In one embodiment, the electrical ablation system 10 may be employed in conjunction with a flexible endoscope 12, as well as a rigid endoscope, laparoscope, or thoracoscope, such as the GIF-100 model available from Olympus Corporation. In one embodiment, the endoscope 12 may be introduced to the tissue treatment region trans-anally through the colon, trans-orally through the esophagus and stomach, trans-vaginally through the cervix, transcutaneously, or via an external incision or keyhole formed in the abdomen in conjunction with a trocar. The electrical ablation system 10 may be inserted and guided into or proximate the tissue treatment region using the endoscope 12. In other embodiments, the endoscope 12 is not utilized, and instead other techniques, such as, for example, ultrasound or a computerized tomography (CT) scan, may be used to determine proper instrument placement during the procedure.

[0044] In the embodiment illustrated in FIG. 1, the endoscope 12 comprises an endoscope handle 34 and an elongate relatively flexible shaft 32. The distal end of the flexible shaft 32 may comprise a light source and a viewing port. Optionally, the flexible shaft 32 may define one or more channels for receiving various instruments therethrough, such as, for example, electrical ablation devices. Images within the field of view of the viewing port may be received by an optical device, such as, for example, a camera comprising a charge coupled device (CCD) usually located within the endoscope 12, and transmitted to a display monitor (not shown) outside the patient. In one embodiment, the electrical ablation system 10 may comprise a plurality of electrical conductors 18, a handpiece 16 comprising an activation switch 62, and an energy source 14, such as, for example, an electrical waveform generator, electrically

coupled to the activation switch 62 and the electrical ablation device 20. The electrical ablation device 20 may comprise a relatively flexible member or shaft 22 that may be introduced to the tissue treatment region using any of the techniques discussed above, such as, an open incision and a trocar, through one of more of the channels of the endoscope 12, percutaneously, or transcutaneously.

[0045] In one embodiment, one or more electrodes (e.g., needle electrodes, balloon electrodes), such as first and second electrodes 24a,b may extend out from the distal end of the electrical ablation device 20. In one embodiment, the first electrode 24a may be configured as the positive electrode and the second electrode 24b may be configured as the negative electrode. The first electrode 24a may be electrically connected to a first electrical conductor 18a, or similar electrically conductive lead or wire, which may be coupled to the positive terminal of the energy source 14 through the activation switch 62. The second electrode 24b may be electrically connected to a second electrical conductor 18b, or similar electrically conductive lead or wire, which may be coupled to the negative terminal of the energy source 14 through the activation switch 62. The electrical conductors 18a,b may be electrically insulated from each other and surrounding structures, except for the electrical connections to the respective electrodes 24a,b.

[0046] In certain embodiments, the electrical ablation device 20 may be configured to be introduced into or proximate the tissue treatment region using the endoscope 12 (laparoscope or thoracoscope), open surgical procedures, and/or external and non-invasive medical procedures. The electrodes 24a,b may be referred to herein as endoscopic or laparoscopic electrodes, although variations thereof may be inserted transcutaneously or percutaneously. In various embodiments, one or both electrodes 24a,b may be adapted and configured to slideably move in and out of a cannula, lumen, or channel defined within the flexible shaft 22.

[0047] When the electrodes 24a,b are positioned at the desired location into or proximate the tissue treatment region, the electrodes 24a,b may be connected to or disconnected from the

energy source 14 by actuating or de-actuating the activation switch 62 on the handpiece 16. The activation switch 62 may be operated manually or may be mounted on a foot switch (not shown), for example. The electrodes 24a,b may deliver electric field pulses to the undesirable tissue. The electric field pulses may be characterized by various parameters, such as, for example, pulse shape, amplitude, frequency, pulse width, polarity, total number of pulses and duration. The electric field pulses may be sufficient to induce thermal heating in the undesirable tissue without inducing irreversible electroporation in the undesirable tissue. The electric field pulses may be sufficient to induce irreversible electroporation in the undesirable tissue. The induced potential may depend on a variety of conditions, such as, for example, tissue type, cell size, and electrical field pulse parameters. The transmembrane potential of a specific tissue type may primarily depend on the amplitude of the electric field and pulse width.

[0048] In certain embodiments, a protective sleeve or sheath 26 may be slidably disposed over the flexible shaft 22 and within a handle 28. In another embodiment, the sheath 26 may be slidably disposed within the flexible shaft 22 and the handle 28. The sheath 26 may be slideable and may be located over the electrodes 24a,b to protect the trocar and prevent accidental piercing when the electrical ablation device 20 is advanced therethrough. One or both of the electrodes 24a,b may be adapted and configured to slideably move in and out of a cannula, lumen, or channel formed within the flexible shaft 22. One or both of the electrodes 24a,b may be fixed in place. One of the electrodes 24a,b may provide a pivot about which the other electrode may be moved in an arc to other points in the tissue treatment region to treat larger portions of the diseased tissue that cannot be treated by fixing both of the electrodes 24a,b in one location. In one embodiment, one or both of the electrodes 24a,b may be adapted and configured to slideably move in and out of a working channel formed within a flexible shaft 32 of the endoscope 12 or may be located independently of the endoscope 12.

[0049] In one embodiment, the first and second electrical conductors 18a,b may be provided through the handle 28. The first electrode 24a may be slideably moved in and out of the distal

end of the flexible shaft 22 using a slide member 30 to retract and/or advance the first electrode 24a. The second electrode 24b may be slideably moved in and out of the distal end of the flexible shaft 22 using the slide member 30 or a different slide member to retract and/or advance the second electrode 24b. One or both electrodes 24a,b may be coupled to the slide member 30, or additional slide members, to advance and retract the electrodes 24a,b and position the electrodes 24a,b. In this manner, the first and second electrodes 24a,b, which may be slidably movable within the cannula, lumen, or channel defined within the flexible shaft 22, may be advanced and retracted with the slide member 30. As shown in FIG. 1, the first electrical conductor 18a coupled to the first electrode 24a may be coupled to the slide member 30. In this manner, the first electrode 24a, which is slidably movable within the cannula, lumen, or channel within the flexible shaft 22, may be advanced and retracted with the slide member 30. In one embodiment, various slide members, such as the slide member 30, may be rotatable. Thus rotation of the slide member 30 may rotate the corresponding electrode(s) at the distal end of the electrical ablation device 20.

[0050] In various other embodiments, transducers or sensors 29 may be located in the handle 28 (or other suitable location) of the electrical ablation device 20 to sense the force with which the electrodes 24a,b penetrate the tissue in the tissue treatment region. This feedback information may be useful to determine whether one or both of the electrodes 24a,b have been properly inserted in the tissue treatment region. As is particularly well known, cancerous tumor tissue tends to be denser than healthy tissue, and thus greater force may be typically required to insert the electrodes 24a,b therein. The transducers or sensors 29 may provide feedback to the operator, surgeon, or clinician to physically sense when the electrodes 24a,b are placed within the cancerous tumor. The feedback information provided by the transducers or sensors 29 may be processed and displayed by circuits located either internally or externally to the energy source 14. The sensor 29 readings may be employed to determine whether the electrodes 24a,b have been properly located within the cancerous tumor thereby assuring that a

suitable margin of error has been achieved in locating the electrodes 24a,b. The sensor 29 readings may also be employed to determine whether the pulse parameters need to be adjusted to achieve a desired result, such as, for example, reducing the intensity of muscular contractions in the patient.

[0051] Referring to FIG. 2, in one embodiment, the electrical ablation device 20 may comprise a first flexible shaft 22a housing the first electrode 24a and a second flexible shaft 22b housing the second electrode 24b. The electrical ablation device 20 may comprise a first protective sleeve or sheath (not shown) disposed over at least one of the first flexible shaft 22a and second flexible shaft 22b. The electrical ablation device 20 may comprise a first protective sleeve or sheath (not shown) disposed over the first flexible shaft 22a and a second protective sleeve or sheath (not shown) disposed over the second flexible shaft 22b. The length of the first flexible shaft 22a may be different than the length of the second flexible shaft 22b. The length of the first flexible shaft 22a may be greater than or equal to the length of the second flexible shaft 22b. The length of the first protective sleeve or sheath may be different than the length of the second protective sleeve or sheath. The length of the first protective sleeve or sheath may be greater than or equal to the length of the second protective sleeve or sheath. In one embodiment, an electrical ablation device for biphasic pulses may have the first flexible shaft 22a disposed over the first electrode 24a having a positive polarity and the second flexible shaft 22b disposed over the second electrode 24b having a negative polarity, and wherein the length of the first flexible shaft 22a is greater than the length of the second flexible shaft 22b.

[0052] Referring to FIGS. 1 and 3, the electrical ablation device 20 may be configured to measure at least one of the temperature and pressure. The transducers or sensors 29 may comprise at least one of a temperature sensor and a pressure sensor. In certain embodiments, at least one of a temperature sensor and pressure sensor may be located in or proximate the electrical ablation system 10. The temperature sensor and/or pressure sensor may be located within the handle 28. The temperature sensor and/or pressure sensor may be located within the

protective sleeve or sheath 26. The temperature sensor 25 and/or pressure sensor 27 may be located within the flexible shaft 22. The temperature sensor 25 and/or pressure sensor 27 may be located at the distal end of the flexible shaft 22. The protective sleeve or sheath 26 and/or the flexible shaft 22 may comprise one or more vents 31 configured for measuring at least one of the temperature and pressure of the tissue treatment region. The temperature sensor and/or pressure sensor may be located within the electrodes 24a,b. The pressure sensor 27 may be adjacent to at least one of the vents 31. In one embodiment, the pressure sensor 27 may be adjacent at least one of the vents 31 and the temperature sensor 25 may be located at the distal end of the flexible shaft 22. FIG. 4 is a photograph of an electrical ablation device comprising an optical temperature sensor 29 located in the electrode 24a at the distal end of the flexible shaft 22.

[0053] In certain embodiments, the temperature sensor and/or pressure sensor may be separate from the electrical ablation system 10. The electrical ablation device 20 may include the temperature sensor 25 and the pressure sensor may be separate from the electrical ablation system 10. The electrical ablation device 20 may include the pressure sensor 27 and the temperature sensor may be separate from the electrical ablation system 10.

[0054] According to certain embodiments, the temperature sensor may measure the temperature of the tissue treatment region. The temperature sensor may measure the temperature of the undesirable tissue. The temperature sensor may measure the temperature of the tissue surrounding the electrodes. The temperature sensor may measure the temperature before, during, and/or after treatment. The temperature sensor may measure the temperature before the first sequence of electrical pulses is delivered to the tissue. The temperature sensor may measure the temperature after the first sequence of electrical pulses is delivered to the tissue. The temperature sensor may measure the temperature before the second sequence of electrical pulses is delivered to the tissue. The temperature sensor may

measure the temperature after the second sequence of electrical pulses is delivered to the tissue.

[0055] According to certain embodiments, the pressure sensor may measure the pressure of the tissue treatment region. The pressure sensor may measure the pressure of the space between the electrodes. The pressure sensor may measure the pressure surrounding the electrodes. The pressure sensor may measure the pressure before, during, and/or after treatment. The pressure sensor may measure the pressure before the first sequence of electrical pulses is delivered to the tissue. The pressure sensor may measure the pressure after the first sequence of electrical pulses is delivered to the tissue. The pressure sensor may measure the pressure before the second sequence of electrical pulses is delivered to the tissue. The pressure sensor may measure the pressure after the second sequence of electrical pulses is delivered to the tissue.

[0056] The temperature sensor and pressure sensor may provide feedback to the operator, surgeon, or clinician to apply an electric field pulse to the undesirable tissue. The pressure and/or temperature information may be useful to determine whether the undesirable tissue may be treated having reduced or no detrimental thermal effects to surrounding healthy tissue. The feedback information provided by the transducers or sensors 29 may be processed and displayed by circuits located either internally or externally to the energy source 14.

[0057] In one embodiment, the input to the energy source 14 may be connected to a commercial power supply by way of a plug (not shown). The output of the energy source 14 is coupled to the electrodes 24a,b, which may be energized using the activation switch 62 on the handpiece 16, or an activation switch mounted on a foot activated pedal (not shown). The energy source 14 may be configured to produce electrical energy suitable for thermal heating and/or electrical ablation.

[0058] In one embodiment, the electrodes 24a,b may be adapted and configured to electrically couple to the energy source 14 (e.g., generator, waveform generator). Once

electrical energy is coupled to the electrodes 24a,b, an electric field may be formed at a distal end of the electrodes 24a,b. The energy source 14 may be configured to generate electric pulses at a predetermined frequency, amplitude, pulse width, and/or polarity that are suitable to induce thermal heating in the undesirable tissue in the treatment region. The energy source 14 may be configured to generate electric pulses at a predetermined frequency, amplitude, pulse width, and/or polarity that are suitable to induce irreversible electroporation to ablate substantial volumes of undesirable tissue in the treatment region. For example, the energy source 14 may be configured to deliver DC electric pulses having a predetermined frequency, amplitude, pulse width, and/or polarity suitable to induce thermal heating in the undesirable tissue in the treatment region. For example, the energy source 14 may be configured to deliver DC electric pulses having a predetermined frequency, amplitude, pulse width, and/or polarity suitable to induce irreversible electroporation to ablate substantial volumes of undesirable tissue in the treatment region. The DC pulses may be positive or negative relative to a particular reference polarity. The polarity of the DC pulses may be reversed or inverted from positive-to-negative or negative-to-positive a predetermined number of times to induce irreversible electroporation to ablate substantial volumes of undesirable tissue in the treatment region.

[0059] In one embodiment, a timing circuit may be coupled to the output of the energy source 14 to generate electric pulses. The timing circuit may comprise one or more suitable switching elements to produce the electric pulses. For example, the energy source 14 may produce a series of m electric pulses (where m is any positive integer) of sufficient amplitude and duration less than the necrotic threshold to induce thermal heating in the undesirable tissue when the m electric pulses are applied to the electrodes 24a,b and a series of n electric pulses (where n is any positive integer) of sufficient amplitude and duration to induce irreversible electroporation suitable for tissue ablation when the n electric pulses are applied to the electrodes 24a,b. In one embodiment, the electric pulses may have a fixed or variable pulse width, amplitude, and/or frequency.

[0060] The electrical ablation device 20 may be operated either in bipolar mode, *i.e.*, monophasic, or monopolar mode, *i.e.*, biphasic. FIG. 5A is a graphical representation of a series of monopolar electrical pulses having the same polarity in which each pulse has an amplitude of +3,000 VDC. FIG. 6A illustrates two electrodes 24a,b in a monopolar electrical ablation system in which the first electrode 24a has a positive polarity relative to the other electrode 24b. In monopolar mode, a grounding pad may be substituted for one of the electrodes. FIG. 5B is a graphical representation of a series of bipolar electrical pulses having opposite polarity in which the first electrical pulse has an amplitude of +3,000 VDC and the second electrical pulse has an amplitude of -3,000 VDC. FIG. 6B illustrates two electrodes 24a,b in a bipolar electrical ablation system in which the polarity of each electrodes 24a,b alternates. In bipolar mode, the first electrode 24a may be electrically connected to a first polarity and the second electrode 24b may be electrically connected to the opposite polarity. In monopolar mode, the first electrode 24a may be coupled to a prescribed voltage and the second electrode 24b may be set to ground. The energy source 14 may be configured to operate in either the bipolar or monopolar modes with the electrical ablation system 10. In bipolar mode, the first electrode 24a may be electrically connected to a prescribed voltage of one polarity and the second electrode 24b may be electrically connected to a prescribed voltage of the opposite polarity. When more than two electrodes are used, the polarity of the electrodes may be alternated so that any two adjacent electrodes may have either the same or opposite polarities. In bipolar mode, the negative electrode of the energy source 14 may be coupled to an impedance simulation circuit.

[0061] In one embodiment, the energy source 14 may be configured to produce RF waveforms at predetermined frequencies, amplitudes, pulse widths, and/or polarities suitable for thermal heating and/or electrical ablation of cells in the tissue treatment region. One example of a suitable RF energy source may be a commercially available conventional, bipolar/monopolar electrosurgical RF generator, such as Model Number ICC 350, available from Erbe, GmbH. In

one embodiment, the energy source may comprise a microwave energy source configured to produce microwave waveforms at predetermined frequencies, amplitudes, pulse widths, and/or polarities suitable for thermal heating and/or electrical ablation of cells in the tissue treatment region. The microwave power source, such as MicroThermx, available from Boston Scientific Corp., may be coupled to a microwave antenna providing microwave energy in the frequency range from 915 MHz to 2.45 GHz.

[0062] In one embodiment, the energy source 14 may be configured to produce destabilizing electrical potentials (*e.g.*, fields) suitable to induce thermal heating and/or irreversible electroporation. The destabilizing electrical potentials may be in the form of bipolar/monopolar DC electric pulses suitable for inducing thermal heating and/or irreversible electroporation to ablate tissue undesirable tissue with the electrical ablation device 20. A commercially available energy source suitable for generating thermal heating and/or irreversible electroporation electric field pulses in bipolar or monopolar mode is a pulsed DC generator such as Model Number ECM 830, available from BTX Molecular Delivery Systems Boston, MA. In bipolar mode, the first electrode 24a may be electrically coupled to a first polarity and the second electrode 25 may be electrically coupled to a second (*e.g.*, opposite) polarity of the energy source 14. Bipolar/ monopolar DC electric pulses may be generated at a variety of frequencies, amplitudes, pulse widths, and/or polarities. Unlike RF ablation systems, which may require high power and energy levels delivered into the tissue to heat and thermally destroy the tissue, irreversible electroporation may require very little energy applied to the tissue to heat and kill the cells of the undesirable tissue using electric field potentials rather than heat. Accordingly, irreversible electroporation systems may avoid the detrimental thermal effects caused by RF ablation systems.

[0063] In certain embodiments, the energy source may comprise a wireless transmitter to deliver energy to the electrodes using wireless energy transfer techniques via one or more remotely positioned antennas. Those skilled in the art will appreciate that wireless energy

transfer or wireless power transmission refers to the process of transmitting electrical energy from an energy source to an electrical load without interconnecting wires. In one embodiment, the energy source 14 may be coupled to the first and second electrodes 24a,b by a wired or a wireless connection. In a wired connection, the energy source 14 may be coupled to the electrodes 24a,b by way of the electrical conductors 18a,b, as shown. In a wireless connection, the electrical conductors 18a,b may be replaced with a first antenna (not shown) coupled the energy source 14 and a second antenna (not shown) coupled to the electrodes 24a,b, wherein the second antenna may be remotely located from the first antenna. In one embodiment, the energy source may comprise a wireless transmitter to deliver energy to the electrodes using wireless energy transfer techniques via one or more remotely positioned antennas. As previously discussed, wireless energy transfer or wireless power transmission is the process of transmitting electrical energy from the energy source 14 to an electrical load, e.g., the abnormal cells in the tissue treatment region, without using the interconnecting electrical conductors 18a,b. An electrical transformer is the simplest example of wireless energy transfer. The primary and secondary circuits of a transformer may not be directly connected and the transfer of energy may take place by electromagnetic coupling through a process known as mutual induction. Power also may be transferred wirelessly using RF energy.

[0064] In one embodiment, the energy source 14 may be configured to generate DC electric pulses at frequencies in the range of about 1 Hz to about 10,000 Hz, amplitudes in the range of about ± 100 VDC to about $\pm 6,000$ VDC, and pulse width in the range of about 1 μ s to about 100 ms. The polarity of the electric potentials coupled to the electrodes 24a,b may be reversed during thermal heating and/or electrical ablation therapy. For example, initially, the DC electric pulses may have a positive polarity and an amplitude in the range of about +100 VDC to about +6,000 VDC. Subsequently, the polarity of the DC electric pulses may be reversed such that the amplitude is in the range of about -100 VDC to about -6,000 VDC. In one embodiment, the undesirable cells in the tissue treatment region may be electrically ablated with DC pulses

suitable to induce irreversible electroporation at frequencies of about 10 Hz to about 100 Hz, amplitudes in the range of about +700 VDC to about +3,000 VDC, and pulse widths of about 10 μ s to about 50 μ s. In another embodiment, the abnormal cells in the tissue treatment region may be electrically ablated with an electrical waveform having an amplitude of about +500 VDC and pulse duration of about 20 μ s delivered at a pulse period T or repetition rate, frequency $f = 1/T$, of about 10 Hz. Without wishing to be bound to any particular theory, it is believed that an electric field strength of about 800 V/cm to 1,000 V/cm is suitable for destroying living tissue by inducing irreversible electroporation.

[0065] The electrodes 24a,b may have a diameter or radius from 0.5 mm to 1.5 mm, such as, for example, 0.5 mm, 0.75 mm, 1 mm, and 1.5 mm. In various embodiments, the diameter of the first electrode 24a may be different from the diameter of the second electrode 24b. The electrode spacing may be from 0.5 cm to 3 cm. In various embodiments, the distance from the first electrode 24a to the second electrode 24b may be from 0.5 cm to 3 cm, such as, for example, 1 cm, 1.5 cm, 2.0 cm, and 3 cm. In one embodiment, the electrical ablation device 20 may comprise multiple needle electrodes.

[0066] According to certain embodiments, the electrical ablation device 20 may be introduced into the tissue treatment region through a trocar, for example, or inserted to a tissue treatment region transcutaneously, percutaneously, or other suitable techniques. In one embodiment, the cannula, lumen, or channel defined within the flexible shaft 22 may comprise a cutting edge, such as a bevel or other sharp edge, to aid in the puncturing/piercing of tissue.

[0067] According to certain embodiments, a method of treating tissue may generally comprise obtaining an ablation apparatus comprising first and second electrodes coupled to an energy source operative to generate and deliver a first sequence of electrical pulses and a second sequence of electrical pulses to tissue having a necrotic threshold, wherein the first sequence of electrical pulses deliver a first energy dose that is less than the necrotic threshold to induce

thermal heating in the tissue and the second sequence of electrical pulses deliver a second energy dose equal to or greater than the necrotic threshold to induce cell necrosis in the tissue by irreversible electroporation, inserting the first electrode into a mass of tissue having a necrotic threshold, applying a first sequence of electrical pulses to the first electrode less than the necrotic threshold to induce thermal heating, applying a second sequence of electrical pulses to the first electrode to induce cell necrosis by irreversible electroporation, and applying a ground potential to the second electrode, wherein the ablation apparatus is operative to reduce the necrotic threshold of the tissue relative to a corresponding ablation apparatus having an energy source configured to deliver a first sequence of electrical pulses to induce cell necrosis by irreversible electroporation.

[0068] In certain embodiments, the ablation apparatus may reduce the necrotic threshold by 0-500 mV, such as, for example, 50-400 mV, 100-300 mV, and 150-250 mV relative to a corresponding ablation apparatus having an energy source configured to deliver a first sequence of electrical pulses to induce cell necrosis by irreversible electroporation. The ablation apparatus may reduce the necrotic threshold by 0-50%, such as, for example, 10%, 20%, 30%, and 40%, relative to a corresponding ablation apparatus having an energy source configured to deliver a first sequence of electrical pulses to induce cell necrosis by irreversible electroporation.

[0069] According to certain embodiments, a method of treating tissue may generally comprise applying a first sequence of electrical pulses to undesirable tissue to induce thermal heating and applying a second sequence of electrical pulses to undesirable tissue to induce cell necrosis by irreversible electroporation. The first energy dose may be less than the necrotic threshold, less than the critical membrane voltage, less than the threshold for muscle contraction, and/or less than the threshold for ventricular arrhythmia. The first energy dose may reduce the necrotic threshold of the tissue. The first energy dose may reduce the necrotic threshold by 0-500 mV, such as, for example, 50-400 mV, 100-300 mV, and 150-250 mV. The first energy dose may

reduce the necrotic threshold by 0-50%, such as, for example, 10%, 20%, 30%, and 40%. The first energy dose and/or second energy dose may be synchronized with the patient's cardiac cycle to prevent ventricular arrhythmia. According to certain embodiments, the ablation apparatus may reduce the risk of ventricular arrhythmia relative to a similar ablation apparatus comprising a first sequence of electrical pulses to induce cell necrosis in the tissue by irreversible electroporation.

[0070] In certain embodiments, a method of treating tissue may generally comprise inserting the first electrode into a mass of tissue having a membrane potential and a necrotic threshold, applying a first sequence of electrical pulses to the first electrode less than the necrotic threshold to induce thermal heating, applying a second sequence of electrical pulses to the first electrode to induce cell necrosis by irreversible electroporation, and applying a ground potential to the second electrode. In one embodiment, the method may comprise re-applying the sequence of electrical pulses to the first electrode. In one embodiment, the energy source may be operative to generate and deliver a sequence interval between the first sequence and second sequence. The first sequence of electrical pulses may comprise a series of first pulse trains each having a first pulse train amplitude, a first pulse train pulse width, and a first pulse train frequency, and the second sequence of electrical pulses may comprise a series of second pulse trains each comprising a second pulse train amplitude, a second pulse train pulse width, and a second pulse train frequency. The first pulse trains may comprise a plurality of first pulses each having a first amplitude, a first pulse width, and a first frequency, and each of the second pulse trains may comprise a plurality of second pulses each having a second amplitude, a second pulse width, and a second frequency. Each of the first pulses and the second pulses may independently have amplitudes in the range of about ± 100 VDC to about $\pm 10,000$ VDC, pulse widths in the range of about 1 μ s to about 100 ms, and frequencies in the range of about 1 Hz to about 10,000 Hz.

[0071] FIG. 7 is a graphical representation of a first sequence of electrical pulses that deliver a first energy dose less than the necrotic threshold to induce thermal heating and a second sequence of electrical pulses that deliver a second energy dose to induce cell necrosis by irreversible electroporation. Time (t) is shown along the horizontal axis and voltage (VDC) is shown along the vertical axis. Initially, the undesirable tissue may be exposed to a series of first pulse trains 70 each having a first pulse train amplitude V_1 , a first pulse train pulse width T_{w1} , and a first pulse train frequency F_1 sufficient to induce thermal heating in the tissue. When the tissue achieves a predetermined temperature and/or pressure, the undesirable tissue 48 may be exposed to a series of second pulse trains 72. The undesirable tissue may be exposed to a series of second pulse trains 72 each having a second pulse train amplitude V_2 , a second pulse train pulse width T_{w2} , and a second pulse train frequency F_2 sufficient to induce thermal necrosis and/or irreversible electroporation in the tissue. The series of first pulse trains 70 may comprise at least one first pulse train and the series of second pulse trains 72 may comprise at least one second pulse train.

[0072] In certain embodiments, at least one of the first pulse train amplitude V_1 , the first pulse train pulse width T_{w1} , and the first pulse train frequency F_1 may be greater than or equal to the second pulse train amplitude V_2 , the second pulse train pulse width T_{w2} , and the second pulse train frequency F_2 . The first pulse train amplitude V_1 may be less than or equal to the second pulse train amplitude V_2 . The first pulse train pulse width T_{w1} may be less than, greater than, or equal to the second pulse train pulse width T_{w2} . The first pulse train frequency F_1 may be greater than or equal to the second pulse train frequency F_2 . The first sequence duration D_1 may be greater than or equal to the second sequence duration D_2 . The total number of first pulse trains may be 70 may be greater than or equal to the total number of second pulse trains 72. In one embodiment, the first pulse train amplitude may be less than the second pulse train amplitude, the first pulse train pulse width may be equal to the second pulse train pulse width, and the first pulse train frequency may be greater than the second pulse train frequency. The

energy source may operative to generate and deliver a sequence interval S_i between the first sequence and second sequence. The sequence interval may be from 0 to 10 seconds, 1 second to 10 seconds, such as, for example, 0.5 seconds, 1 second, and 2 seconds.

[0073] FIGS. 8A-B are graphical representations of a first pulse train 70 and a second pulse train 72, respectively. Time (t) is shown along the horizontal axis and voltage (VDC) is shown along the vertical axis. Each of the first pulse trains 70 may comprise a plurality of first pulses 70a each having a first amplitude v_1 , a first pulse width t_{w1} , and a first frequency f_1 , and each of the second pulse trains 72 may comprise a plurality of second pulses 72a each having a second amplitude v_2 , a second pulse width t_{w2} , and a second frequency f_2 . The first pulses and the second pulses may be each independently characterized by first and second amplitudes in the range of about ± 100 VDC to about $\pm 10,000$ VDC, first and second pulse widths in the range of about 1 μ s to about 100 ms, and first and second frequencies in the range of about 1 Hz to about 10,000 Hz. In one embodiment, the energy source 14 may be configured to generate and deliver DC first pulses and the second pulses at frequencies in the range of 1 Hz to 10,000 Hz, amplitudes in the range of ± 100 VDC to ± 3000 VDC, and pulse width in the range of about 1 μ s to about 100 ms. The first amplitude v_1 may be less than or equal to the second amplitude v_2 . The first pulse width t_{w1} may be less than, greater than, or equal to the second pulse width t_{w2} . The first frequency f_1 may be greater than or equal to the second frequency f_2 . The total number of first pulses may be greater than or equal to the total number of second pulses. In one embodiment, the first amplitude may be less than the second amplitude, the first pulse width may be equal to the second pulse width, and the first frequency may be equal to the second frequency.

[0074] In one embodiment, a first pulse train 70 comprising high-voltage DC electrical pulses having a first pulse train amplitude V_1 of 500 VDC and a first pulse train pulse width T_{w1} of 50 μ s may be applied to the first and second electrodes 24a,b by the energy source 14 to induce thermal heating in the tissue. A second pulse train 72 comprising higher high-voltage DC

electrical pulses having a second pulse train amplitude V_2 of 1000 V and a second pulse train pulse width T_{w2} of 50 μ s may be applied to the first and second electrodes 24a,b by the energy source 14 to induce cell necrosis in the tissue by irreversible electroporation. In one embodiment, the polarity of at least one of the first pulse train 70 and the second pulse train 72 may be inverted or reversed by the energy source 14 during the thermal heating and/or ablation processes.

[0075] In one embodiment, the series of first pulses 70 may comprises a single pulse 70a or multiple pulses having a first amplitude v_1 of 500 VDC, a first pulse width t_{w1} of 10 μ s to 15 μ s, and a period t_1 of about 100 ms ($f_1 = 10$ Hz) sufficient to induce thermal heating in the tissue proximate the electrode-tissue-interface immediately surrounding the respective electrodes 24a,b. In one embodiment, the series of second pulses 72 may comprise 20 to 40 electric pulses 72a having a second amplitude v_2 of 1000 VDC, a second pulse width t_{w2} of 10 μ s to 15 μ s, and a period t_2 of 100 μ s ($f_2 = 10,000$ Hz) sufficient to induce irreversible electroporation. In one embodiment, the series of second pulses 72 may comprise multiple electrical pulses, for example, 20 to 40 electric pulses, having a second amplitude v_2 of 1500 to 3000 VDC, a second pulse width t_{w2} of 10 μ s to 50 μ s, and a period t_2 of 10 μ s. In one embodiment, the undesirable cells in the tissue treatment region may be electrically ablated with DC pulses suitable to induce irreversible electroporation at frequencies of about 10 Hz to about 100 Hz, amplitudes in the range of about +700 VDC to about +1500 VDC, and pulse widths of about 10 μ s to about 50 μ s. In another embodiment, the abnormal cells in the tissue treatment region may be heated with an electrical waveform having an amplitude of about +500 VDC and pulse duration of about 20 ms delivered at a pulse period or repetition rate, frequency $f = 1/T$, of about 10 Hz.

[0076] In certain embodiments, a total dose average power may comprise the average power of the first sequence of electrical pulses, the average power of the second sequence of electrical pulses, and the sequence interval. The first energy dose may have an average power

from 5 Watts to 10 Watts. The second first energy dose may have an average power from 10 Watts to 15 Watts. The total dose average power may be 1 Watt to 5 Watts. In one embodiment, a total dose average power from 5 Watts to 10 Watts may cause thermal coagulation. The first and second sequences of electrical pulses may be configured to reduce or eliminate thermal coagulation at the electrode/tissue interface.

[0077] In certain embodiments, the polarity of the electric potentials coupled to the electrodes 24a,b may be reversed during the electrical ablation therapy. As shown in FIG. 9, the series of first pulse trains 70 may comprise multiple biphasic pulse trains each having a positive first pulse train amplitude $+V_1$ or a negative first pulse train amplitude $-V_1$, a first pulse train pulse width T_{w1} , and a first pulse train frequency F_1 , and the series of second pulse trains 72 may comprise multiple biphasic pulse trains each having a positive second pulse train amplitude $+V_2$ or a negative second pulse train amplitude $-V_2$, a second pulse train pulse width T_{w2} , and a second pulse train frequency F_2 . The first pulses and the second pulses may be each independently characterized by first and second amplitudes in the range of about ± 100 VDC to about $\pm 10,000$ VDC, first and second pulse widths in the range of about 1 μ s to about 100 ms, and first and second frequencies in the range of about 1 Hz to about 10,000 Hz. In one embodiment, the first sequence of electrical pulses and the second sequence of electrical pulses may comprise biphasic pulses. In one embodiment, the first sequence of electrical pulses may comprise biphasic pulses and the second sequence of electrical pulses may not comprise biphasic pulses. In one embodiment, the first sequence of electrical pulses may not comprise biphasic pulses and the second sequence of electrical pulses may comprise biphasic pulses.

[0078] As shown in FIGS. 10A-B, each of the first pulse trains may comprise a plurality of first pulses 70a each having a positive first amplitude $+v_1$ or a negative first amplitude $-v_1$, a first pulse width t_{w1} , and a first frequency f_1 , and each of the second pulse trains comprise a plurality of second pulses 72a each having a positive second amplitude $+v_2$ or a negative second

amplitude $-v_2$, a second pulse width t_{w2} , and a second frequency f_2 . In one embodiment, the first sequence of electrical pulses and the second sequence of electrical pulses may comprise biphasic pulses. In one embodiment, the plurality of first pulses may comprise biphasic pulses and the plurality of second pulses may not comprise biphasic pulses. In one embodiment, the plurality of first pulses may not comprise biphasic pulses and the plurality of second pulses may comprise biphasic pulses.

[0079] In one embodiment, the energy source 14 may be configured to generate and deliver DC first pulses and the second pulses at frequencies in the range of 1 Hz to 10,000 Hz, amplitudes in the range of ± 100 VDC to ± 3000 VDC, and pulse width in the range of about 1 μ s to about 100 ms. In one embodiment, the first pulse trains may comprise a plurality of DC first pulses having a positive polarity and an amplitude in the range of about +100 VDC to about +6000 VDC and a negative polarity and an amplitude in the range of about -100 VDC to about -6000 VDC, the second pulse trains may comprise a plurality of second pulses having a positive polarity and an amplitude in the range of about +100 VDC to about +6000 VDC and a negative polarity and an amplitude in the range of about -100 VDC to about -6000 VDC. In one embodiment, the method may comprise applying a sequence of electrical pulses having a first polarity to induce cell thermal heating and applying a sequence of electrical pulses having an opposite polarity to induce cell necrosis by irreversible electroporation.

[0080] Without wishing to be bound to any particular theory, it is believed that biphasic pulses may reduce the skeletal muscle contractions by reducing or eliminating the action potential caused by a positive monophasic pulse. Biphasic pulses may reduce or eliminate skeletal muscle contractions and cardiac events. A person skilled in the art will understand that poration of the cell membrane occurs when the pulse increases the membrane voltage. A person skilled in the art may expect the poration to be reversed by a negative going pulse. Without wishing to be bound to any particular theory, however, it is believed that hyperpolarization occurs on each side of the cell. For example, the opposite side of the cell membrane may be hyperpolarized

when the electric field switches orientation due to a negative-going pulse. In other words, the polarization of the cell may be dependent on the orientation of the electric field.

[0081] According to certain embodiments, the method of treating tissue may comprise heating the tissue by applying an electric field that is less than the necrotic threshold to lower the necrotic threshold before inducing cell necrosis. The method may comprise lowering the necrotic threshold by heating the tissue by applying an electric field that is less than about 700 V/cm, such as, for example, less than about 500 V/cm and less than about 300 V/cm. The method may comprise lowering the necrotic threshold by 30% by heating the tissue by applying an electric field that is less than about 700 V/cm. The method may comprise heating the tissue by applying an electric field that is less than the necrotic threshold to lower the necrotic threshold and inducing cell necrosis by irreversible electroporation by applying an electric field that is greater than or equal to the necrotic threshold. The method may comprise heating the tissue by applying an electric field that is less than 700 V/cm to lower the necrotic threshold and inducing cell necrosis by irreversible electroporation by applying an electric field that is greater than about 700 V/cm.

[0082] According to certain embodiment, the method of treating tissue may comprise applying a sequence of electrical pulses to increase a membrane potential to less than the necrotic threshold and applying a sequence of electrical pulses to increase a membrane potential to greater than or equal to the necrotic threshold. The method may comprise applying a sequence of electrical pulses to increase a membrane potential from less than zero to greater than zero, applying a sequence of electrical pulses to increase a membrane potential from greater than zero to less than the necrotic threshold, and applying a sequence of electrical pulses to increase a membrane potential from less than the necrotic threshold to the necrotic threshold. The method may comprise applying a sequence of electrical pulses to increase a membrane potential from less than zero to 100 mV, applying a sequence of electrical pulses to increase a

membrane potential from 100 mV to 500 mV, and applying a sequence of electrical pulses to increase a membrane potential from 500 mV to the necrotic threshold.

[0083] In one embodiment, the first sequence of electrical pulses may have a pulse width of 50 μ m or less and subsequent pulses may have higher voltages and pulse widths less than 50 μ m. The pulses may increase the membrane potential from -70 mV to +100 mV, the next sequence of pulses may increase the membrane potential from 100 mV to 500 mV, and the final sequence of pulses may have pulse width of 1 μ s to increase the membrane potential to cause cell necrosis. Without wishing to be bound to any particular theory, it is believed that the synergistic effect of applying the first sequence of pulses to induce thermal heating and applying the second sequence of pulses to induce cell necrosis by irreversible electroporation may decrease the membrane threshold from 1 V to 0.7 V.

[0084] According to certain embodiments, the method may comprise forming a pre-heated zone in the undesirable tissue by applying an electric field that is less than the necrotic threshold. The method may comprise forming a pre-heated zone in the undesirable tissue by applying an electric field that is less than the necrotic threshold and forming a necrotic zone by applying an electric field that is equal to or greater than the necrotic threshold to induce cell necrosis by irreversible electroporation. The method may comprise forming a pre-heated zone by applying an electric field that is less than about 700 V/cm and forming a necrotic zone by applying an electric field that is equal to or greater than about 700 V/cm.

[0085] FIG. 11 is a graphical representation of a series of electrical pulses that may be applied to undesirable tissue. FIG. 11 illustrates the relationship between the pulse parameters and electrode temperature and the size and proportion of the necrotic zone. As shown in FIG. 11, the size and proportion of the necrotic zone may generally increase as the voltage and/or temperature increases. The size and proportion of the necrotic zone and thermal zone may be related to the pulse parameters, such as, for example, energy, peak power, and average power, and electrode spacing. The contribution of voltage and temperature to the size and proportion

of the necrotic zone and thermal zone may be related to the peak pulsed power and average power.

[0086] In one embodiment, a pre-heated thermal zone may be formed in the tissue immediately surrounding the electrodes 24a,b at the tissue-electrode-interface by applying an electric field less than the necrotic threshold. Without wishing to be bound to any particular theory, it is believed that increasing the temperature of the tissue may reduce the electric field necessary to cause cell necrosis in the undesirable tissue 48. Thus, the method of treating tissue may comprise applying a combination of a series of first electrical pulses 70 having substantially lower voltage (in the range of 1000 V to 2000 V) and a series of second electrical pulses 72 having a higher voltage to induce cell necrosis. In one embodiment, a first series of pulses 70 may be applied to create a pre-heated thermal zone to increase the temperature of the tissue and then a second series of pulses 72 to induce cell necrosis at a lower voltage than otherwise would be necessary without the thermal heating of the tissue before inducing irreversible electroporation. In one embodiment, the method of treating tissue may comprise applying a combination of a series of first electrical pulses 70 having substantially lower voltage to increase the size of the pre-heated thermal zone at the same voltage.

[0087] Once positioned by the user, the electrodes may be energized to form a pre-heated zone having a first shape in the tissue treatment region. The shape of the pre-heated zone may be dependent on the position of the first and second electrodes. When the electrodes are re-energized, a necrotic zone having a second shape may be formed in the tissue treatment region. The size of the pre-heated zone may be less than or equal to the size of the necrotic zone. This process may be repeated as often as necessary to create any number of necrotic zones using the electrical ablation apparatus. Various parameters, such as, for example, pressure, temperature, and duration, may be altered or adjusted according to the type of tissue in the tissue treatment region and the desired size of the pre-heated zone and/or necrotic zone. In one embodiment, the ablation apparatus may increase the size of the necrotic zone relative

to a similar ablation apparatus comprising a first sequence of electrical pulses to induce cell necrosis in the tissue by irreversible electroporation. At anytime, the surgeon or clinician may reposition the electrical ablation apparatus within the tissue treatment region and begin the process anew.

[0088] According to certain embodiments, the method of treating tissue may comprise applying a first sequence of electrical pulses to induce thermal heating and applying a second sequence of electrical pulses to induce cell necrosis by irreversible electroporation, wherein the first and second sequences of electrical pulses create a ratio of thermal volume to non-thermal volume of 5 to 1. The thermal volume may comprise the volume of the pre-heated zone. In one embodiment, at least one of the first sequence of electrical pulses, the second sequence of electrical pulses, and sequence interval may be configured to create a ratio of thermal volume to non-thermal volume of 2 to 1. In one embodiment, at least one of the first sequence of electrical pulses, the second sequence of electrical pulses, and sequence interval may be configured to create a ratio of thermal zone volume to necrotic zone volume of 1 to 1.

[0089] According to certain embodiments, the method may comprise measuring at least one of temperature and pressure of the tissue treatment region. The method may comprise measuring at least one of temperature and pressure of the undesirable tissue. The method may comprise measuring at least one of temperature and pressure adjacent at least one of the first and second electrodes. The method may comprise measuring at least one of temperature and pressure adjacent at least one of the first and second electrodes and applying a sequence of electrical pulses when at least one of a predetermined temperature and a predetermined pressure is achieved. The method may comprise measuring at least one of temperature and pressure adjacent at least one of the first and second electrodes and stopping a sequence of electrical pulses when at least one of a predetermined temperature and a predetermined pressure is achieved. The method may comprise measuring at least one of temperature and pressure adjacent at least one of the first and second electrodes and applying a sequence of

electrical pulses to achieve at least one of a predetermined temperature and a predetermined pressure.

[0090] Without wishing to be bound to any particular theory, it is believed that the critical membrane voltage of a cell is inversely proportional to the cell's temperature. In other words, the cell's critical membrane voltage may decrease as the cell's temperature increases. As a result, a lower electric field may be applied to pre-heated undesirable tissue to induce cell necrosis by irreversible electroporation than to the same undesirable tissue without pre-heating. The predetermined temperature may be 40°C to 50°C. For example, an electrical pulse or sequence of electrical pulses may be applied when the temperature of the tissue falls below 50°C. The method may comprise stopping a sequence of electrical pulses when at least one of a predetermined temperature and a predetermined pressure is achieved. For example, an electrical pulse or sequence of electrical pulses may be stopped when the temperature of the tissue reaches 60°C. In one embodiment, the first and second sequences of electrical pulses may be configured to maintain the tissue at a temperature sufficient to induce thermal coagulation. For example, the first and second sequences of electrical pulses may be configured to maintain the tissue at a temperature between 50-60°C. The predetermined pressure may be atmospheric pressure.

[0091] According to certain embodiments, the ablation apparatus may reduce the risk of an electrical arc relative to a similar ablation apparatus comprising a first sequence of electrical pulses to induce cell necrosis in the tissue by irreversible electroporation. Under certain conditions, an arc may form between the two electrodes. For example, high voltage may cause a breakdown in air in the space between the un-insulated conductive portions of the electrodes that are not fully embedded in the tissue. An electrical arc at high voltages (>10k VDC) may occur when the un-insulated conductive portions of the two electrodes are not fully embedded into the tissue or the tissue moves away from the electrode tip and the high voltage causes an electrical breakdown of the gas surrounding the electrode tip. The first and second sequences

of electrical pulses may be configured to reduce or eliminate the creation of an arc. As described in commonly owned U.S. patent application No. 12/651,181, a gel may be continuously supplied to the space to displace the air in the space and prevent an arc from forming. The gel may be any water-based, water-soluble lubricant, such as, for example, KY® Jelly available from Johnson & Johnson.

[0092] FIG. 12 illustrates one embodiment of the electrical ablation system 10 shown in FIG. 1 in use to treat undesirable tissue 48 located on the surface of the liver 50. The undesirable tissue 48 may be representative of diseased tissue, cancer, malignant and benign tumors, masses, lesions, and other abnormal tissue growths. In use, the electrical ablation device 20 may be introduced into or proximate the tissue treatment region through a port 52 of a trocar 54. The trocar 54 may be introduced into the patient via a small incision 59 formed in the skin 56. The endoscope 12 may be introduced into the patient trans-anally through the colon, trans-orally down the esophagus and through the stomach using transluminal techniques, or through a small incision or keyhole formed through the patient's abdominal wall (e.g., the peritoneal wall). The endoscope 12 may be employed to guide and locate the distal end of the electrical ablation device 20 into or proximate the undesirable tissue 48. Prior to introducing the flexible shaft 22 through the trocar 54, the sheath 26 may be slid over the flexible shaft 22 in a direction toward the distal end thereof to cover the electrodes 24a,b until the distal end of the electrical ablation device 20 reaches the undesirable tissue 48.

[0093] Once the electrical ablation device 20 has been suitably introduced into or proximate the undesirable tissue 48, the sheath 26 may be retracted to expose the electrodes 24a,b to treat the undesirable tissue 48. To treat the undesirable tissue 48, the operator initially may locate the first electrode 24a at a first position and the second electrode 24b at a second position using endoscopic visualization and maintaining the undesirable tissue 48 within the field of view of the flexible endoscope 12. The first position may be near a perimeter edge of the undesirable tissue 48. Once the electrodes 24a,b are located into or proximate the undesirable

tissue 48, the electrodes 24a,b may be energized with a first sequence of electrical pulses to deliver a first energy dose that is less than the necrotic threshold to induce thermal heating in the tissue surrounding the electrode/tissue interface. Once the temperature and/or pressure of the undesirable tissue 48 achieves a predetermined threshold, the electrodes 24a,b may be energized with a second sequence of electrical pulses to deliver a second energy dose equal to or greater than the necrotic threshold to induce cell necrosis in the tissue by irreversible electroporation to create a necrotic zone 65. For example, once the first and second electrodes 24a,b are located in the desired positions, the undesirable tissue 48 may be exposed to an electric field generated by energizing the first and second electrodes 24a,b with the energy source 14.

[0094] The electric field created by the first sequence of electrical pulses may have a magnitude, frequency, pulse width suitable to increase the temperature of the undesirable tissue to a predetermined threshold. The electric field created by the second sequence of electrical pulses may have a magnitude, frequency, and pulse width suitable to induce irreversible electroporation in the undesirable tissue 48 within the necrotic zone 65. Without wishing to be bound to any particular theory, it is believed that increasing the temperature of the undesirable tissue to a predetermined threshold may reduce the magnitude, frequency, and/or pulse width of the electric field suitable to induce irreversible electroporation in the undesirable tissue 48. The size of the necrotic zone may be substantially dependent on the size and separation of the electrodes 24a,b. The treatment time may be defined as the time that the electrodes 24a,b are activated or energized to generate the electric pulses suitable for inducing thermal heating and/or irreversible electroporation in the undesirable tissue 48.

[0095] This procedure may be repeated to destroy relatively larger portions of the undesirable tissue 48. At anytime, the surgeon or clinician may reposition the first and second electrodes 24a,b and begin the process anew. In other embodiments, the electrical ablation device may comprise multiple needle electrodes that may be employed to treat the undesirable tissue 48.

Those skilled in the art will appreciate that similar techniques may be employed to ablate any other undesirable tissues that may be accessible trans-anally through the colon, and/or orally through the esophagus and the stomach using transluminal access techniques.

[0096] The embodiments of the electrical ablation devices described herein may be introduced inside a patient using minimally invasive or open surgical techniques. In some instances it may be advantageous to introduce the electrical ablation devices inside the patient using a combination of minimally invasive and open surgical techniques. Minimally invasive techniques may provide more accurate and effective access to the treatment region for diagnostic and treatment procedures. To reach internal treatment regions within the patient, the electrical ablation devices described herein may be inserted through natural openings of the body such as the mouth, anus, and/or vagina, for example. Minimally invasive procedures performed by the introduction of various medical devices into the patient through a natural opening of the patient are known in the art as NOTES™ procedures. Surgical devices, such as an electrical ablation devices, may be introduced to the treatment region through the channels of the endoscope to perform key surgical activities (KSA), including, for example, electrical ablation of tissues using irreversible electroporation energy. Some portions of the electrical ablation devices may be introduced to the tissue treatment region percutaneously or through small – keyhole – incisions.

[0097] Endoscopic minimally invasive surgical and diagnostic medical procedures are used to evaluate and treat internal organs by inserting a small tube into the body. The endoscope may have a rigid or a flexible tube. A flexible endoscope may be introduced either through a natural body opening (e.g., mouth, anus, and/or vagina). A rigid endoscope may be introduced via trocar through a relatively small – keyhole – incision incisions (usually 0.5 cm to 1.5 cm). The endoscope can be used to observe surface conditions of internal organs, including abnormal or diseased tissue such as lesions and other surface conditions and capture images for visual inspection and photography. The endoscope may be adapted and configured with channels for

introducing medical instruments to the treatment region for taking biopsies, retrieving foreign objects, and/or performing surgical procedures.

[0098] Once an electrical ablation device is inserted in the human body internal organs may be reached using trans-organ or transluminal surgical procedures. The electrical ablation device may be advanced to the treatment site using endoscopic transluminal access techniques to perforate a lumen, and then, advance the electrical ablation device and the endoscope into the peritoneal cavity. Transluminal access procedures for perforating a lumen wall, inserting, and advancing an endoscope therethrough, and pneumoperitoneum devices for insufflating the peritoneal cavity and closing or suturing the perforated lumen wall are well known. During a transluminal access procedure, a puncture must be formed in the stomach wall or in the gastrointestinal tract to access the peritoneal cavity. One device often used to form such a puncture is a needle knife which is inserted through the channel of the endoscope, and which utilizes energy to penetrate through the tissue. A guidewire is then feed through the endoscope and is passed through the puncture in the stomach wall and into the peritoneal cavity. The needle knife is removed, leaving the guidewire as a placeholder. A balloon catheter is then passed over the guidewire and through the channel of the endoscope to position the balloon within the opening in the stomach wall. The balloon can then be inflated to increase the size of the opening, thereby enabling the endoscope to push against the rear of the balloon and to be feed through the opening and into the peritoneal cavity. Once the endoscope is positioned within the peritoneal cavity, numerous procedures can be performed through the channel of the endoscope.

[0099] The endoscope may be connected to a video camera (single chip or multiple chips) and may be attached to a fiber-optic cable system connected to a "cold" light source (halogen or xenon), to illuminate the operative field. The video camera provides a direct line-of-sight view of the treatment region. If working in the abdomen, the abdomen may be insufflated with carbon dioxide (CO₂) gas to create a working and viewing space. The abdomen is essentially blown up

like a balloon (insufflated), elevating the abdominal wall above the internal organs like a dome. CO₂ gas is used because it is common to the human body and can be removed by the respiratory system if it is absorbed through tissue.

[0100] Once the electrical ablation devices are located at the target site, the diseased tissue may be electrically ablated or destroyed using the various embodiments of electrodes discussed herein. The placement and location of the electrodes can be important for effective and efficient electrical ablation therapy. For example, the electrodes may be positioned proximal to a treatment region (e.g., target site or worksite) either endoscopically or transcutaneously (percutaneously). In some implementations, it may be necessary to introduce the electrodes inside the patient using a combination of endoscopic, transcutaneous, and/or open techniques. The electrodes may be introduced to the tissue treatment region through a channel of the endoscope, an overtube, or a trocar and, in some implementations, may be introduced through percutaneously or through small – keyhole – incisions.

[0101] Preferably, the various embodiments of the devices described herein will be processed before surgery. First, a new or used instrument is obtained and if necessary cleaned. The instrument can then be sterilized. In one sterilization technique, the instrument is placed in a closed and sealed container, such as a plastic or TYVEK® bag. The container and instrument are then placed in a field of radiation that can penetrate the container, such as gamma radiation, x-rays, or high-energy electrons. The radiation kills bacteria on the instrument and in the container. The sterilized instrument can then be stored in the sterile container. The sealed container keeps the instrument sterile until it is opened in the medical facility.

[0102] It is preferred that the device is sterilized prior to use. This can be done by any number of ways known to those skilled in the art including beta or gamma radiation, ethylene oxide, steam.

[0103] The various embodiments described herein may be better understood when read in conjunction with the following representative examples. The following examples are included for purposes of illustration and not limitation.

[0104] An ablation apparatus comprising two electrodes coupled to a energy source and a temperature sensor according to certain embodiments was used to deliver a series of electrical pulses *ex vivo* to healthy porcine liver to induce irreversible electroporation (Dose 1). In one embodiment, the Dose 1 pulse parameters may include a 3,000 V amplitude, a 10 μ s pulse width, 10 total number of pulses per burst, a frequency of 200 Hz, 6 total number of bursts, and a 3 s delay between each burst. Dose 1 is generally characterized by low energy and high voltage. Dose 1 was not suitable for synchronizing to a patient's cardiac cycle. FIG. 13 is a photograph of the porcine liver after receiving Dose 1. The necrotic zone 100 is generally indicated by the discoloration of the tissue. The temperature was monitored using the temperature sensor illustrated in FIG. 4. FIG. 14 is a graphical representation of temperature during Dose 1. Without wishing to be bound to any particular theory, it is believed that temperature is related to the distance between the electrodes. As shown in FIG. 14, an electrode spacing of 1.5 cm generated a maximum temperature of about 51°C at the positive electrode and an electrode spacing of 1.0 cm generated a maximum temperature of about 59°C at the positive electrode. As shown in FIG. 14, the temperature increases as the distance between the electrodes decreases.

[0105] FIGS. 15A-D include photographs of porcine liver after receiving a series of electrical pulses having an amplitude of 3 kV that may be applied to undesirable tissue to induce irreversible electroporation. FIG. 15A is a photograph of porcine liver after receiving a first sequence of electrical pulses. FIG. 15B is a photograph of the porcine liver after receiving the second sequence of electrical pulses. The temperature of the porcine tissue after the second sequence of electrical pulses was 40°C. FIG. 15C is a photograph of the porcine liver after receiving the third sequence of electrical pulses. The temperature of the porcine tissue after the

third sequence of electrical pulses was 37°C. FIG. 15D is a photograph of the porcine liver after receiving the fourth sequence of electrical pulses. The temperature of the porcine tissue after the fourth sequence of electrical pulses was 45°C. The necrotic zone caused by each sequence of electrical pulses is generally indicated by the discoloration of the tissue. The sequence interval between each series of electrical pulses was 5 seconds. The total dose time was 20 seconds.

[0106] An ablation apparatus comprising two electrodes coupled to a energy source and a temperature sensor according to certain embodiments was used to deliver a series of electrical pulses *ex vivo* to healthy porcine liver to induce irreversible electroporation (Dose 2). In one embodiment, the Dose 2 parameters may include a first series of bursts including a 1000 V amplitude, a 5 μ s pulse width, 500 total number of pulses per burst, a total of 30 first series bursts, a 0.1 s delay between each burst followed by a second series of bursts pulses including a 1500 V amplitude, a 5 μ s pulse width, 500 total number of pulses per burst, a total of 20 second bursts, a 0.1 s delay between each burst followed by a third series of bursts including a 3000 V amplitude, a 10 μ s pulse width, 10 total number of pulses per burst, a total of 10 third series bursts, a 3 s delay between each burst. The frequency may be 200 Hz. Dose 2 is generally characterized by a multi-train dose at a higher energy than Dose 1. Dose 2 was not suitable for synchronizing to a patient's cardiac cycle. As shown in FIG. 16, the first pulse train included 500 pulses per burst at a pulse width of 5 μ s, a frequency of 200 Hz, and an amplitude of 1 kV, the second pulse train included 500 pulses per burst at a pulse width of 5 μ s, a frequency of 200 Hz, and an amplitude of 1.5 kV, and the third pulse train included 10 pulses per burst at a pulse width of 10 μ s, a frequency of 200 Hz, and an amplitude of 3 kV.

[0107] The size and area of the necrotic zone of Dose 1 was compared to the size and area of the necrotic zone of Dose 2. FIG. 17 is a graph illustrating the average area of the necrotic zone for Dose 1 and the average area of the necrotic zone for Dose 2. As shown in FIG. 17,

Dose 1 exhibited a smaller average area of the necrotic zone than Dose 2. FIG. 18A is a graph illustrating the average area of the necrotic zone for Dose 1 and the average area of the necrotic zone for Doses 2a,b. As shown in FIG. 18A, the average necrotic zone dimensions and area for Dose 1 was 1 cm x 2.5 cm and 2.5 cm², respectively. The average necrotic zone dimensions and area for Dose 2 was 2.0 cm x 3.67 cm and 7.34 cm², respectively. FIG. 18B includes photographs of the necrotic zone produced by Doses 1, 2a, and 2b. As shown in FIGS. 17 and 18, the size and area of the necrotic zone generally increases as the energy increases.

[0108] FIG. 19 is a graphical representation of a series of electrical pulses that may be delivered to undesirable tissue to induce irreversible electroporation. The multi-train electrical sequence may be synchronized with a patient's cardiac cycle. As shown in FIG. 19, the pulse train may include up to 180 pulses per burst at a pulse width of 10 μs, a frequency of 200 Hz, and an amplitude of 3 kV. The total burst time of each burst may fit within the latent period, or the period of electrical inactivity of the cardiac cycle. The latent period may also be known as the refractory period. The temperature may be measured between each burst. In one embodiment, the pulse parameters and maximum temperature may be adjusted to achieve a non-thermal zone of cell death ("IRE Dose"). The IRE Dose may include a maximum temperature of 50°C and a typical sequence time of about 1 minute. In one embodiment, for example, the IRE Dose parameters may include a 3,000 V amplitude, a 10 μs pulse width, 15 total number of pulses per burst, frequency of each 10 μs pulse within the bursts of 200 Hz, a 3 s delay between each burst, and 20 total number of bursts. The IRE Dose may be characterized by no or reduced thermal damage to the tissue surrounding the electrode. In one embodiment, the pulse parameters and maximum temperature may be adjusted to slowly increase the temperature of the tissue ("IRE+ Dose"). The IRE+ Dose may increase the temperature of a large volume of tissue by a few degrees, such as, for example, 0-10°C and 1-5°C, over a relatively longer period of time. The IRE+ Dose may include a typical sequence

time of about 8 minutes. For example, the IRE+ Dose parameters may include a 3,000 V amplitude, a 10 μ s pulse width, 20 total number of pulses per burst, frequency of each 10 μ s pulse within the bursts of 200 Hz, a 3 s delay between each burst, and 90 total number of bursts at a maximum temperature of 60°C. The electrode spacing may be 2 cm. The IRE+ Dose may be characterized by a large necrosis zone. In one embodiment, the pulse parameters and maximum temperature may be adjusted to rapidly increase the temperature of the tissue ("IRE+Heat Dose"). The IRE+Heat Dose may increase the temperature of a large volume of tissue by a few degrees, such as, for example, 0-10°C and 1-5°C, over a relatively shorter period of time. The IRE+Heat Dose may include a typical sequence time of about 4 minutes. In one embodiment, for example, the IRE+Heat Dose parameters may include a 3,000 V amplitude, a 10 μ s pulse width, 20 total number of pulses per burst, frequency of each 10 μ s pulse within the bursts of 200 Hz, a 0.1 s delay between each burst, and 90 total number of bursts at a maximum temperature of 60°C. The higher temperature in the tissue surrounding the electrodes may cause thermal coagulation. Without wishing to be bound to any particular theory, it is believed that thermal coagulation may occur at a higher average power and same energy. The IRE+Heat Dose may be characterized by a larger necrotic zone than the IRE Dose and a shorter time than the IRE+ Dose.

[0109] FIGS. 20A-C are photographs of a healthy porcine liver after receiving the IRE Dose, IRE+ Dose, and IRE+Heat Dose, respectively. As shown in the FIG. 20A, the IRE Dose has a necrotic zone having a size of 1.2 cm x 2.3 cm and an area of 2.76 cm². As shown in the FIG. 20B, the IRE+ Dose has a necrotic zone having a size of 2.1 cm x 3.7 cm and an area of 7.77 cm². As shown in the FIG. 20C, the IRE+Heat Dose has a necrotic zone having a size of 1.6 cm x 3.6 cm and an area of 5.76 cm². The IRE+Heat Dose has a thermal zone located within the necrotic zone. The size and area of the thermal zone (lighter area) is smaller than the size and area of the necrotic zone.

[0110] FIG. 21 is a graphical representation of the electrode temperature during the IRE Dose having a maximum temperature limit of 50°C. As shown in FIG. 21, the maximum temperature at the positive electrode was about 47°C at 69 seconds. FIG. 22 is a graphical representation of the temperature during the IRE+ Dose having a maximum temperature limit of 90°C. As shown in FIG. 22, the maximum temperature at the positive electrode was about 62°C at about 430 seconds. FIG. 23 is a graphical representation of the temperature during the IRE+Heat Dose having a maximum temperature limit of 90°C. As shown in FIG. 23, the maximum temperature at the positive electrode was about 88°C at about 220 seconds. FIG. 24 is a graphical representation of the temperature during the IRE+Heat Dose having a maximum temperature limit of 90°C. As shown in FIG. 24, the maximum temperature at the positive electrode was about 96°C at about 259 seconds.

[0111] The size and proportion of the necrosis zone may be also related to electrode spacing. FIGS. 25A-C include photographs of healthy porcine liver after receiving an IRE Dose having an electrode spacing of 1.5 cm, an IRE+ Dose having an electrode spacing of 2.0 cm, an IRE+Heat Dose having an electrode spacing of 2.0 cm. As shown in FIGS. 25A-C, the IRE+ Dose has the largest necrotic zone and the IRE Dose has the smallest necrotic zone. The IRE+Heat Dose has a necrotic zone intermediate the IRE Dose and IRE+ Dose. The IRE+Heat Dose has a thermal zone (lighter area) is smaller than the necrotic zone.

[0112] FIGS. 26A-F are graphical representations of simulated necrotic zones (white) and thermal zones (gray) of porcine livers (black) after receiving a series of electrical pulses that may be applied to undesirable tissue to induce irreversible electroporation according to certain embodiments described herein. FIGS. 26A,B include computer simulation of an IRE Dose having an electrode spacing of 1.5 cm and 2.0 cm, respectively. A necrotic zone of 2.3 cm x 1.02 cm is predicted for an IRE Dose having an electrode spacing of 1.5 cm. A necrotic zone of 2.8 cm wide is predicted for an IRE Dose having an electrode spacing of 2.0 cm. FIGS. 26C,D include computer simulation of an IRE+ Dose having an electrode spacing of 1.5 cm and 2.0

cm, respectively. A necrotic zone of 3.4 cm x 2.09 cm is predicted for an IRE+ Dose having an electrode spacing of 2.0 cm and a 400 V/cm threshold. A necrotic zone of 2.92 cm x 2.04 cm is predicted for an IRE+ Dose having an electrode spacing of 1.5 cm and a 400 V/cm threshold. Without wishing to be bound to any particular theory, it is believed that decreasing the necrotic threshold may increase the size of the necrotic zone. As shown in FIGS. 26A,C, the size of the necrotic zone in FIG. 26A is smaller than the size of the necrotic zone in FIG. 26C. FIGS. 26E,F include computer simulation of an IRE+Heat Dose having an electrode spacing of 2.0 cm and 3.0 cm, respectively. As shown in FIG. 26E, an IRE+Heat Dose having an electrode spacing of 2.0 cm produces a thermal zone (gray region). The width of the necrotic zone of an IRE+Heat Dose having an electrode spacing of 2.0 cm is less than the width of the necrotic zone of an IRE+ Dose having an electrode spacing of 2.0 cm. As shown in FIG. 26F, an IRE+Heat Dose having an electrode spacing of 3.0 cm produces thermal zones around each electrode. The width of the necrotic zone of an IRE+Heat Dose having an electrode spacing of 3.0 cm is less than the width of the necrotic zone of an IRE+Heat Dose having an electrode spacing of 2.0 cm. Without wishing to be bound to any particular theory, it is believed that the ratio of the necrotic zone length and necrotic zone width generally corresponds to the electric field pattern. The electric field pattern generally becomes long and narrow as the electrode spacing increases.

[0113] Although the various embodiments of the devices have been described herein in connection with certain disclosed embodiments, many modifications and variations to those embodiments may be implemented. For example, different types of end effectors may be employed. Also, where materials are disclosed for certain components, other materials may be used. The foregoing description and following claims are intended to cover all such modification and variations.

[0114] Any patent, publication, or other disclosure material, in whole or in part, that is said to be incorporated by reference herein is incorporated herein only to the extent that the incorporated materials does not conflict with existing definitions, statements, or other disclosure

material set forth in this disclosure. As such, and to the extent necessary, the disclosure as explicitly set forth herein supersedes any conflicting material incorporated herein by reference. Any material, or portion thereof, that is said to be incorporated by reference herein, but which conflicts with existing definitions, statements, or other disclosure material set forth herein will only be incorporated to the extent that no conflict arises between that incorporated material and the existing disclosure material.

CLAIMS

What is claimed is:

1. An ablation apparatus, comprising:

first and second electrodes coupled to an energy source operative to generate and deliver a first sequence of electrical pulses and a second sequence of electrical pulses to tissue having a necrotic threshold, wherein the first sequence of electrical pulses delivers a first energy dose that is less than the necrotic threshold to induce thermal heating in the tissue and the second sequence of electrical pulses delivers a second energy dose equal to or greater than the necrotic threshold to induce cell necrosis in the tissue by irreversible electroporation.
2. The ablation apparatus of claim 1, wherein the energy source is operative to generate and deliver a sequence interval between the first sequence and second sequence.
3. The ablation apparatus of claim 1, wherein the first sequence has a first sequence duration and the second sequence has a second sequence duration, and wherein the first sequence duration is greater than the second sequence duration.
4. The ablation apparatus of claim 1, wherein the first sequence has a first sequence total number of pulses and the second sequence has a second sequence total number of pulses, and wherein the first sequence total number of pulses is greater than the second sequence total number of pulses.
5. The ablation apparatus of claim 1, wherein the first sequence comprises a series of first pulse trains each having a first pulse train amplitude, a first pulse train pulse width, and a first pulse train frequency, and the second sequence comprises a series of second pulse trains each

comprising a second pulse train amplitude, a second pulse train pulse width, and a second pulse train frequency.

6. The ablation apparatus of claim 5, wherein the first pulse train amplitude is less than the second pulse train amplitude, the first pulse train pulse width is equal to the second pulse train pulse width, and the first pulse train frequency is greater than the second pulse train frequency.

7. The ablation apparatus of claim 5, wherein each of the first pulse trains comprise a plurality of first pulses each having a first amplitude, a first pulse width, and a first frequency, and each of the second pulse trains comprise a plurality of second pulses each having a second amplitude, a second pulse width, and a second frequency.

8. The ablation apparatus of claim 7, wherein the first pulses and the second pulses are each independently characterized by first and second amplitudes in the range of about ± 100 VDC to about $\pm 10,000$ VDC, first and second pulse widths in the range of about 1 μ s to about 100 ms, and first and second frequencies in the range of about 1 Hz to about 10,000 Hz.

9. The ablation apparatus of claim 7, wherein the first amplitude is less than the second amplitude, the first pulse width is equal to the second pulse width, and the first frequency is equal to the second frequency.

10. The ablation apparatus of claim 7, wherein the plurality of second pulses comprise biphasic pulses.

11. The ablation apparatus of claim 1 comprising at least one of a temperature sensor and a pressure sensor adjacent at least one of the first and second electrodes.

12. The ablation apparatus of claim 1 comprising:
 - a housing for supporting the first and second electrodes; and
 - at least one of a temperature sensor and a pressure sensor located within the housing.
13. The ablation apparatus of claim 1 comprising:
 - a housing having a distal end, a proximal end, and a body extending therebetween for supporting the first and second electrodes;
 - a temperature sensor located within the housing at the distal end; and
 - a pressure sensor located within the housing along the body.
14. The ablation apparatus of claim 1 comprising:
 - a housing having a plurality of vents for supporting the first and second electrodes; and
 - a pressure sensor located adjacent the plurality of vents.
15. The ablation apparatus of claim 1 comprising:
 - a sleeve having a distal end for supporting the first and second electrodes;
 - a first electrode having a positive polarity located at the distal end of the sleeve; and
 - a second electrode having a negative polarity not located at the distal end of the sleeve.
16. The ablation apparatus of claim 1, wherein the energy source is operative to generate and deliver the second sequence when at least one of a predetermined temperature and a predetermined pressure is achieved.

17. The ablation apparatus of claim 1, wherein the energy source is operative to not generate and not deliver the second sequence when at least one of a predetermined temperature and a predetermined pressure is achieved.

18. A method of treating tissue, comprising:

obtaining the apparatus of claim 1;

inserting the first electrode into the tissue having a necrotic threshold;

applying a first sequence of electrical pulses to the first electrode less than the necrotic threshold to induce thermal heating;

applying a second sequence of electrical pulses to the first electrode to induce cell necrosis by irreversible electroporation; and

applying a ground potential to the second electrode,

wherein the ablation apparatus is operative to reduce the necrotic threshold relative to a corresponding ablation apparatus having an energy source configured to deliver a first sequence of electrical pulses to induce cell necrosis by irreversible electroporation.

19. A method of treating tissue, comprising:

inserting the first electrode into the tissue having a membrane potential and a necrotic threshold;

applying a first sequence of electrical pulses to the first electrode less than the necrotic threshold to induce thermal heating;

applying a second sequence of electrical pulses to the first electrode to induce cell necrosis by irreversible electroporation; and

applying a ground potential to the second electrode.

20. The method of claim 19 comprising:
forming a pre-heated zone by applying an electric field that is less than about 700 V/cm;
and
forming a necrotic zone by applying an electric field that is greater than about 700 V/cm.
21. The method of claim 19 comprising:
heating the mass of tissue by applying an electric field that is less than about 700V/cm to
lower the necrotic threshold; and
inducing cell necrosis by irreversible electroporation by applying an electric field that is
greater than about 700 V/cm.
22. The method of claim 19 comprising:
applying a first sequence of electrical pulses to the first electrode less than the necrotic
threshold to lower the necrotic threshold;
applying a second sequence of electrical pulses to the first electrode to induce cell
necrosis by irreversible electroporation.
23. The method of claim 19 comprising:
lowering the necrotic threshold by heating the tissue by applying an electric field that is
less than about 700 V/cm.
24. The method of claim 19 comprising:
lowering the necrotic threshold by 30 % by heating the tissue by applying an electric field
that is less than about 700 V/cm.

25. The method of claim 19 comprising:

applying a sequence of electrical pulses to increase a membrane potential from less than zero to 100 mV;

applying a sequence of electrical pulses to increase a membrane potential from 100 mV to 500 mV; and

applying a sequence of electrical pulses to increase a membrane potential from 500 mV to the necrotic threshold.

26. The method of claim 19 comprising:

measuring at least one of temperature and pressure adjacent at least one of the first and second electrodes; and

applying a sequence of electrical pulses when at least one of a predetermined temperature and a predetermined pressure is achieved.

27. The method of claim 19 comprising:

measuring at least one of temperature and pressure adjacent at least one of the first and second electrodes; and

stopping a sequence of electrical pulses when at least one of a predetermined temperature and a predetermined pressure is achieved.

28. The method of claim 19 comprising:

measuring at least one of temperature and pressure adjacent at least one of the first and second electrodes; and

applying a sequence of electrical pulses to achieve at least one of a predetermined temperature and a predetermined pressure.

29. The method of claim 19 comprising:

applying a sequence of electrical pulses to the first electrode, the sequence of electrical pulses having amplitudes in the range of about ± 100 VDC to about $\pm 10,000$ VDC, pulse widths in the range of about 1 μ s to about 100 ms, and frequencies in the range of about 1 Hz to about 10,000 Hz; and

re-applying the sequence of electrical pulses to the first electrode.

30. The method of claim 19 comprising:

applying a sequence of electrical pulses having a first polarity to induce cell necrosis by irreversible electroporation;

applying a sequence of electrical pulses having an opposite polarity to induce cell necrosis by irreversible electroporation.

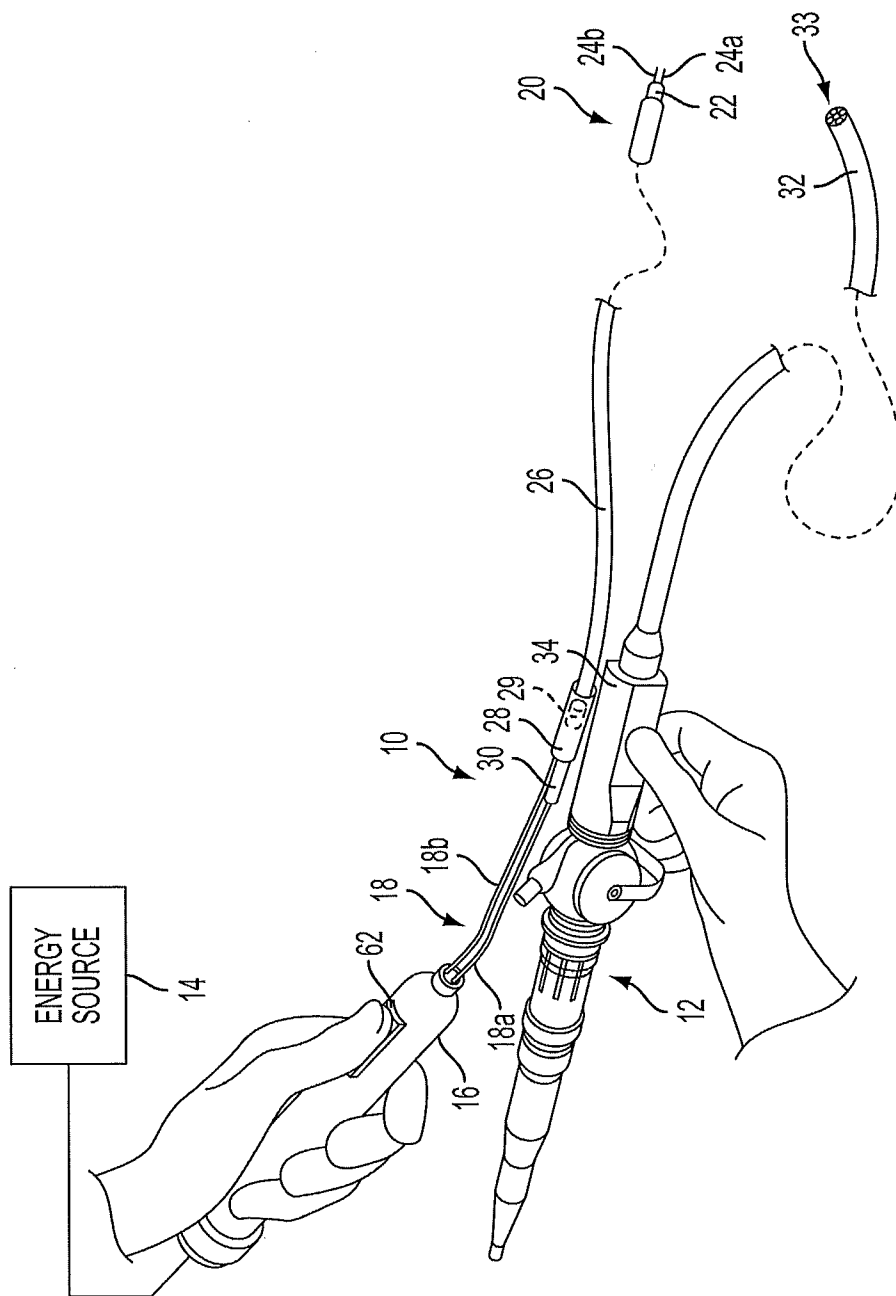


FIG. 1

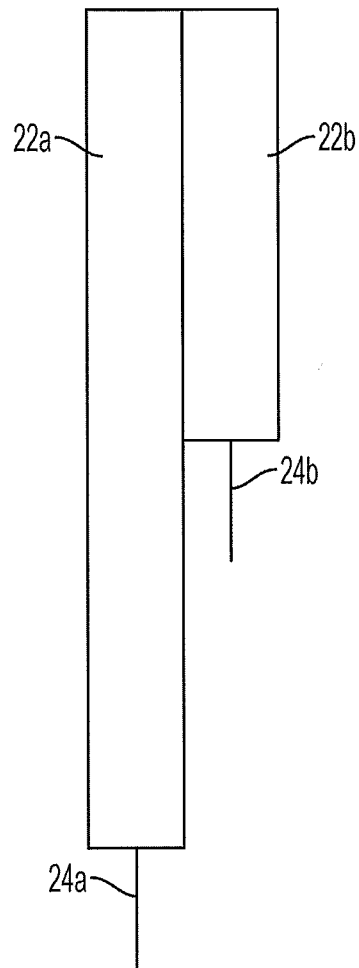


FIG. 2

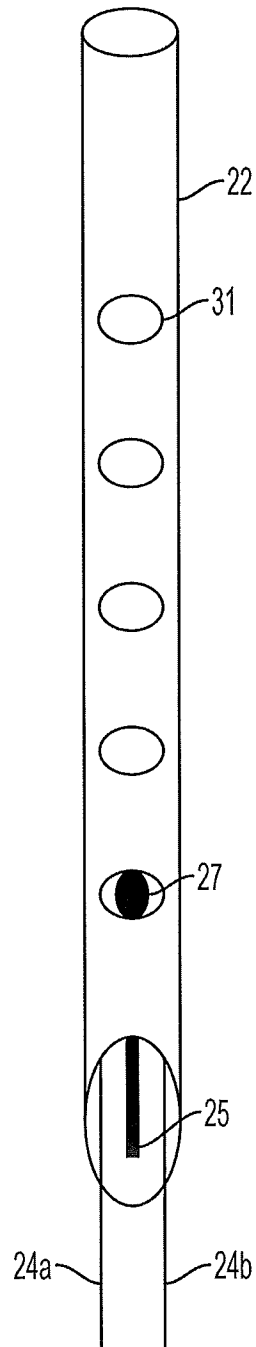


FIG. 3

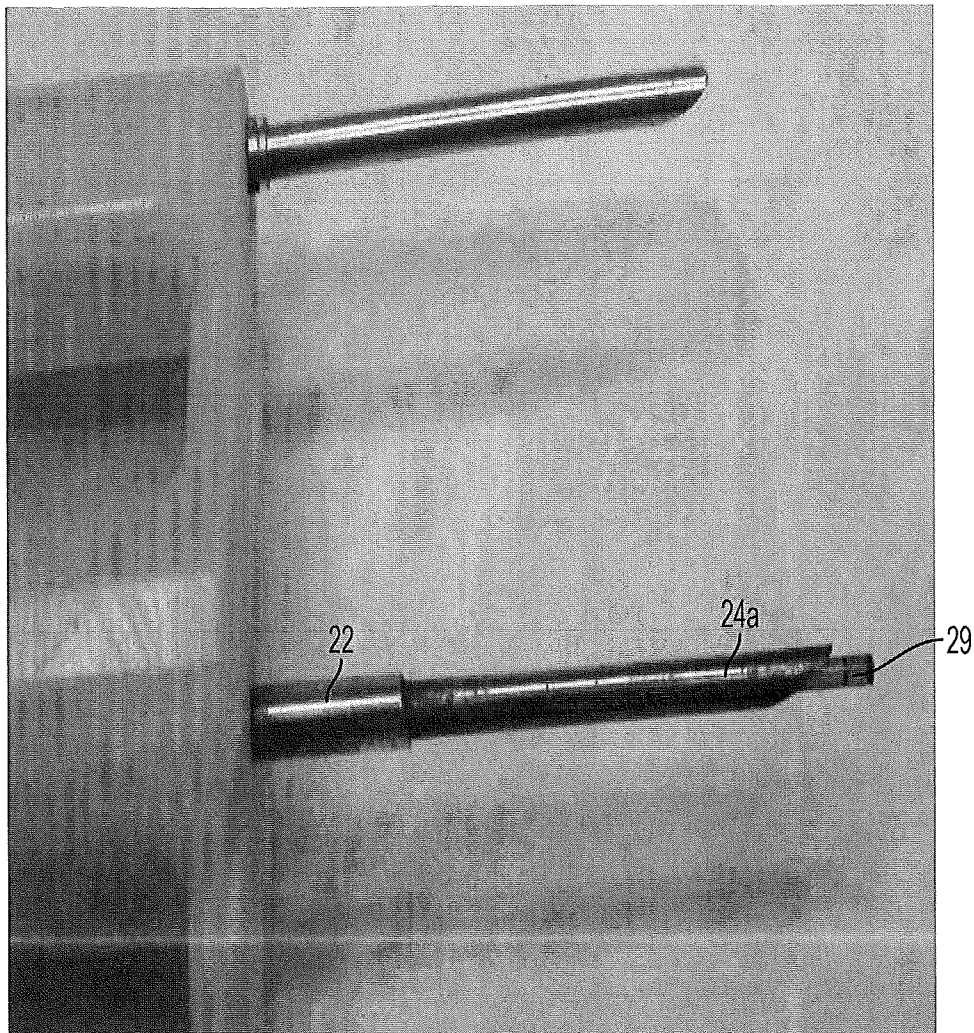


FIG. 4

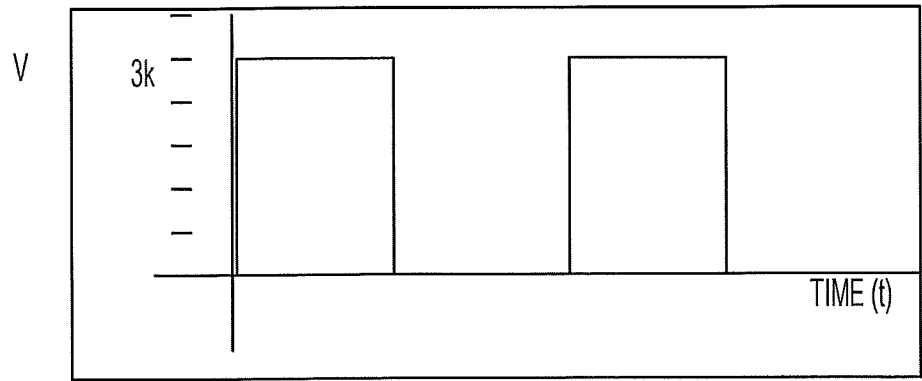


FIG. 5A

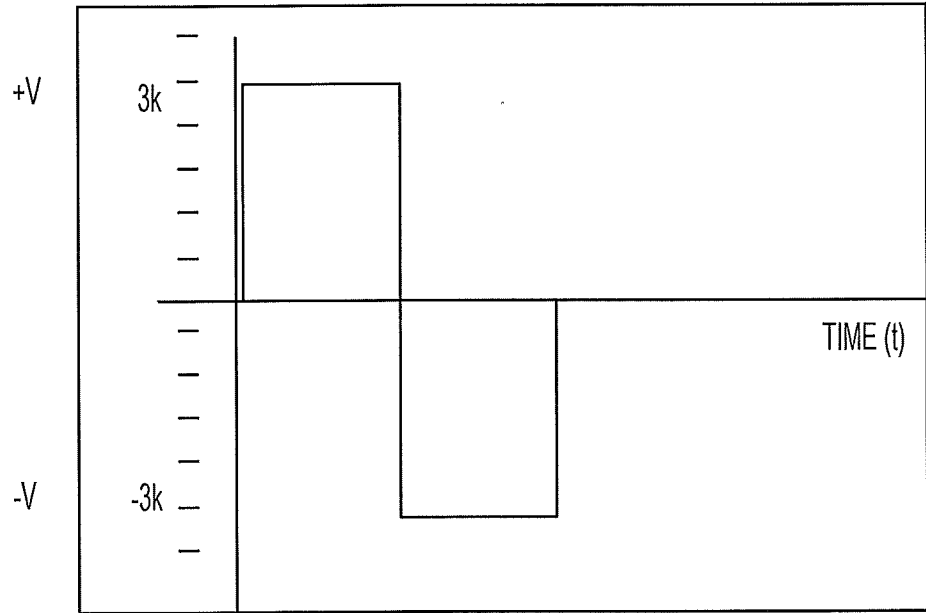


FIG. 5B

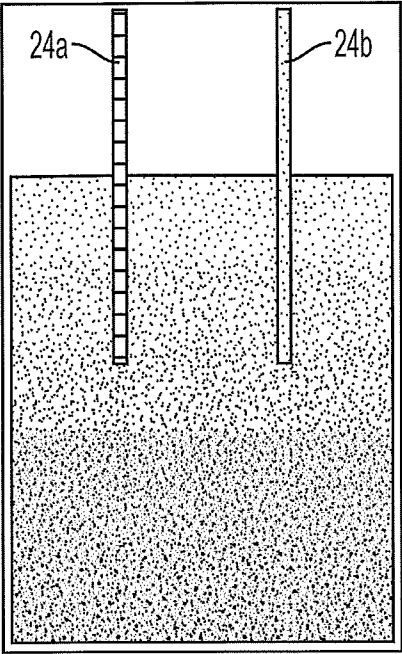


FIG. 6A

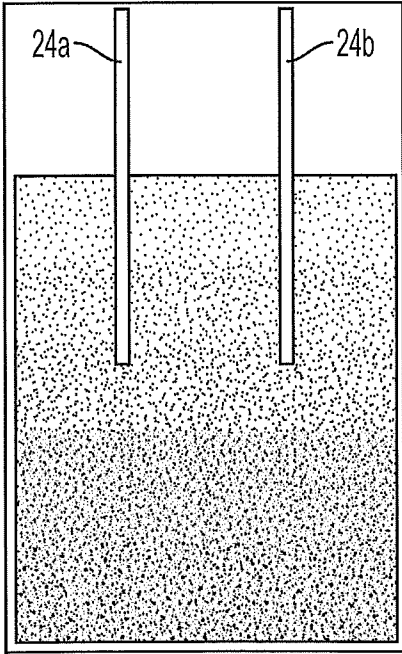


FIG. 6B

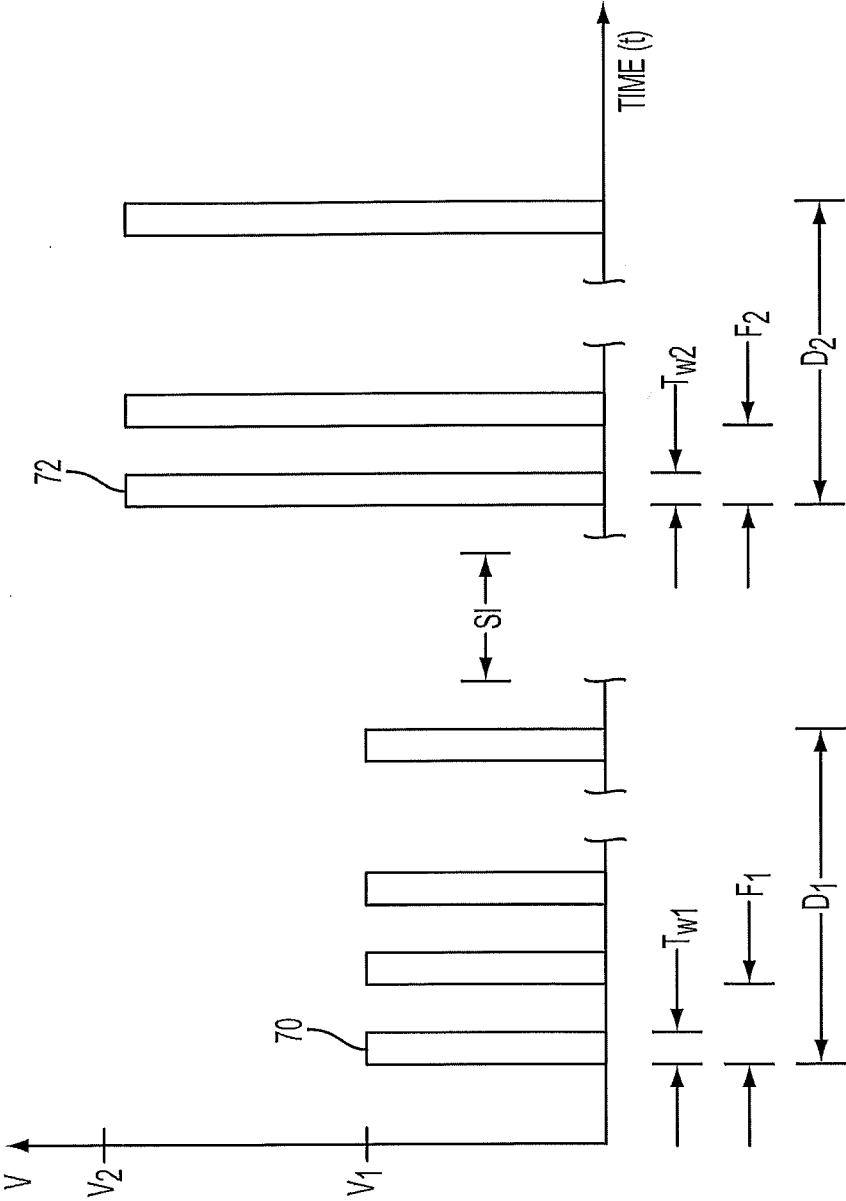


FIG. 7

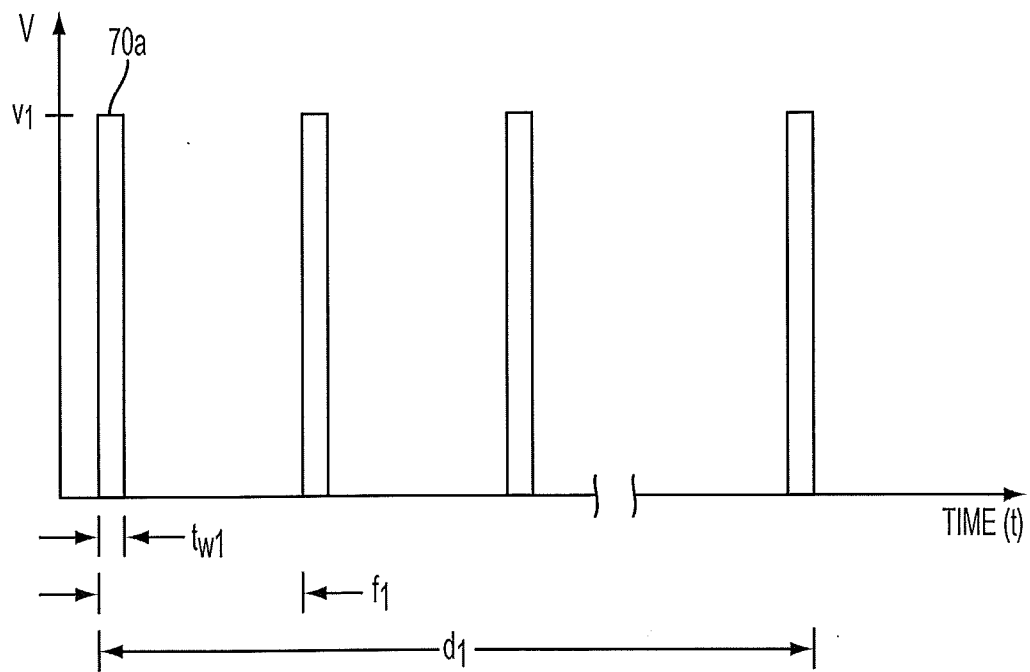


FIG. 8A

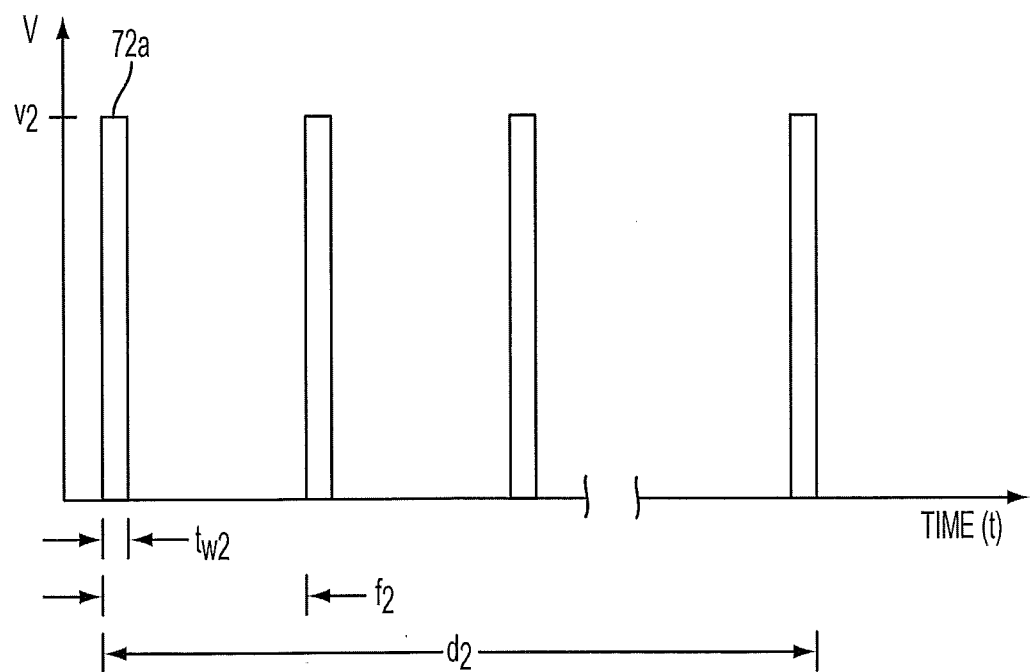


FIG. 8B

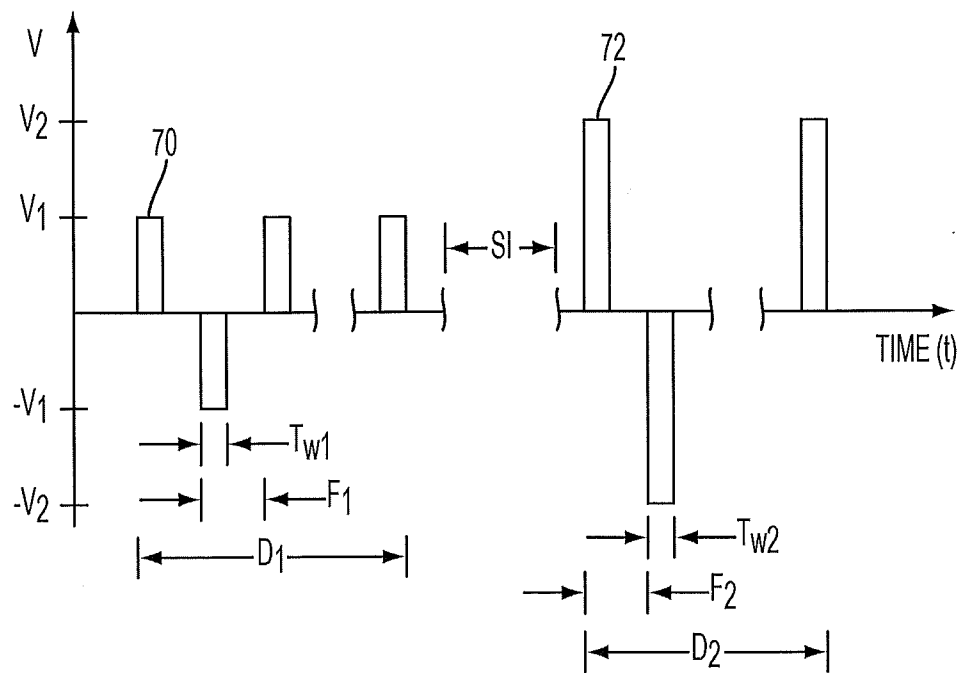


FIG. 9

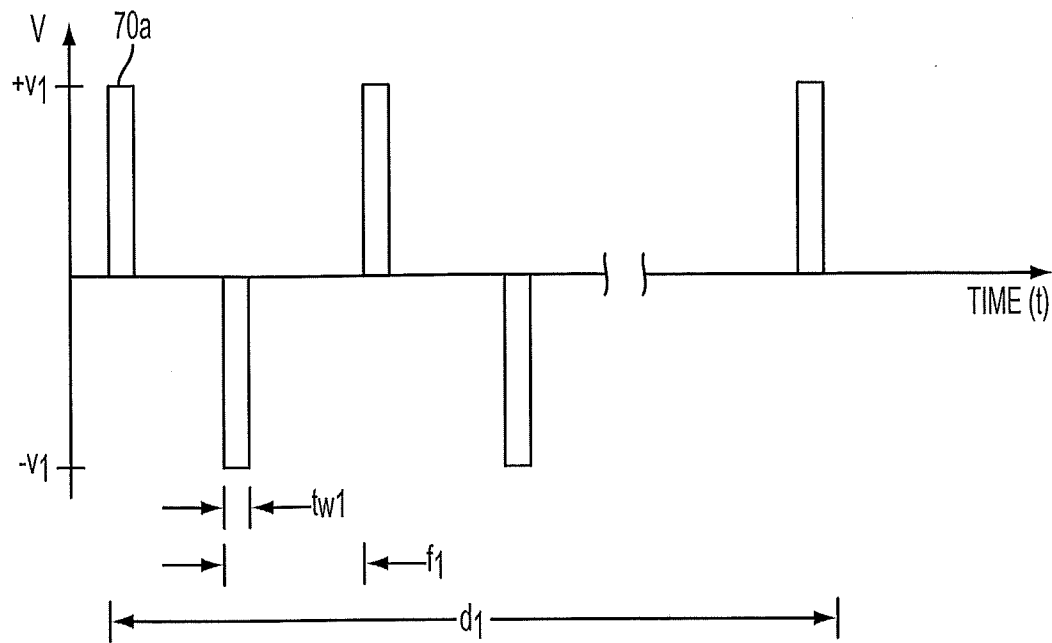


FIG. 10A

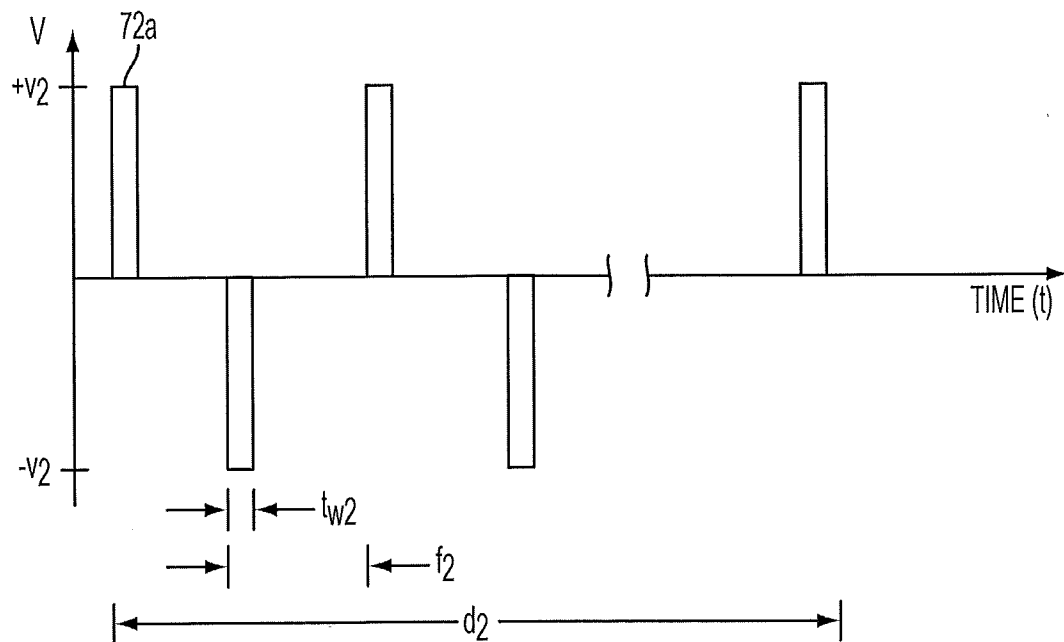


FIG. 10B

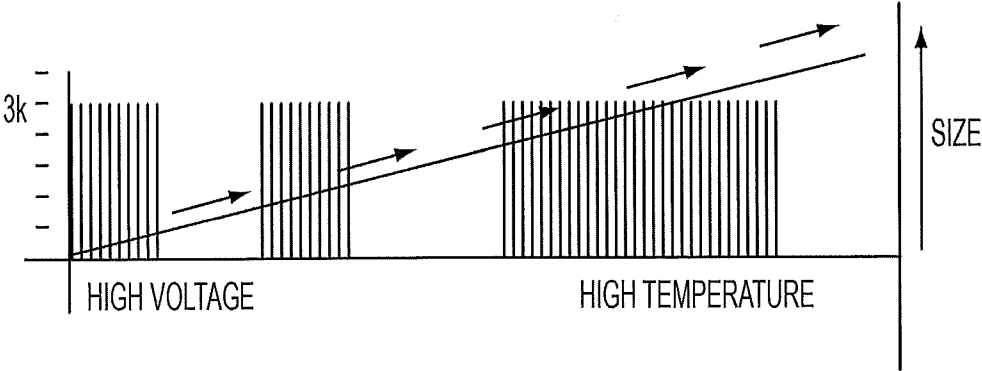


FIG. 11

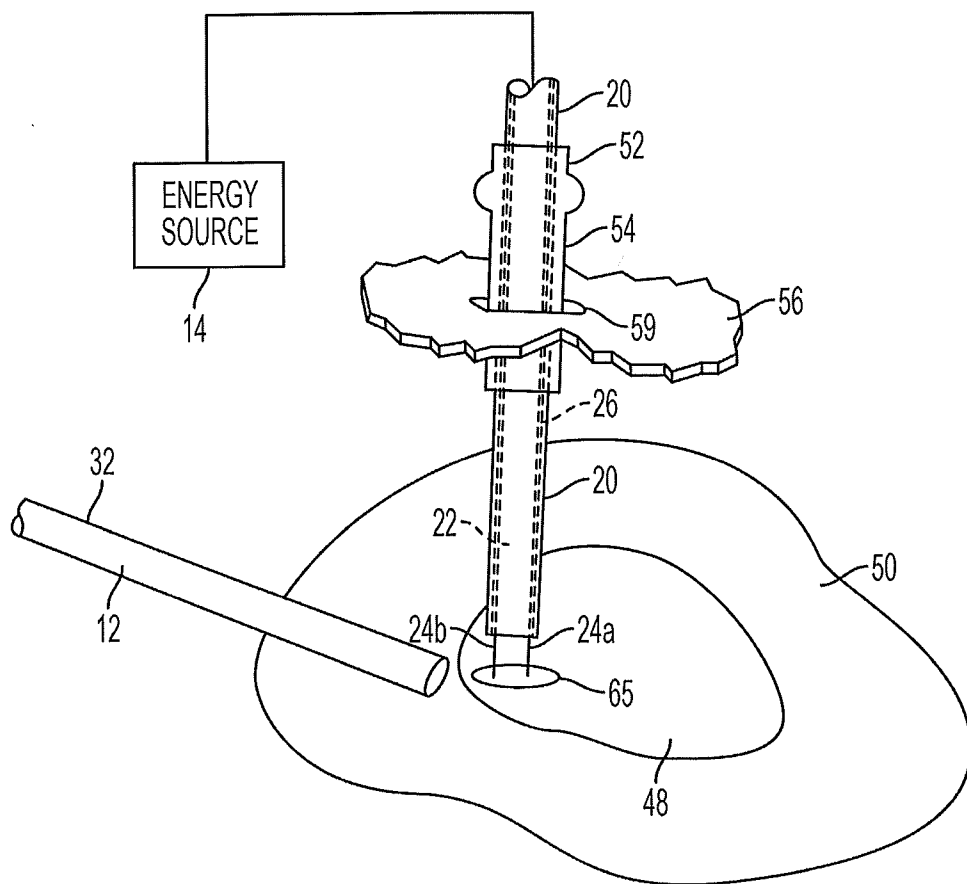


FIG. 12

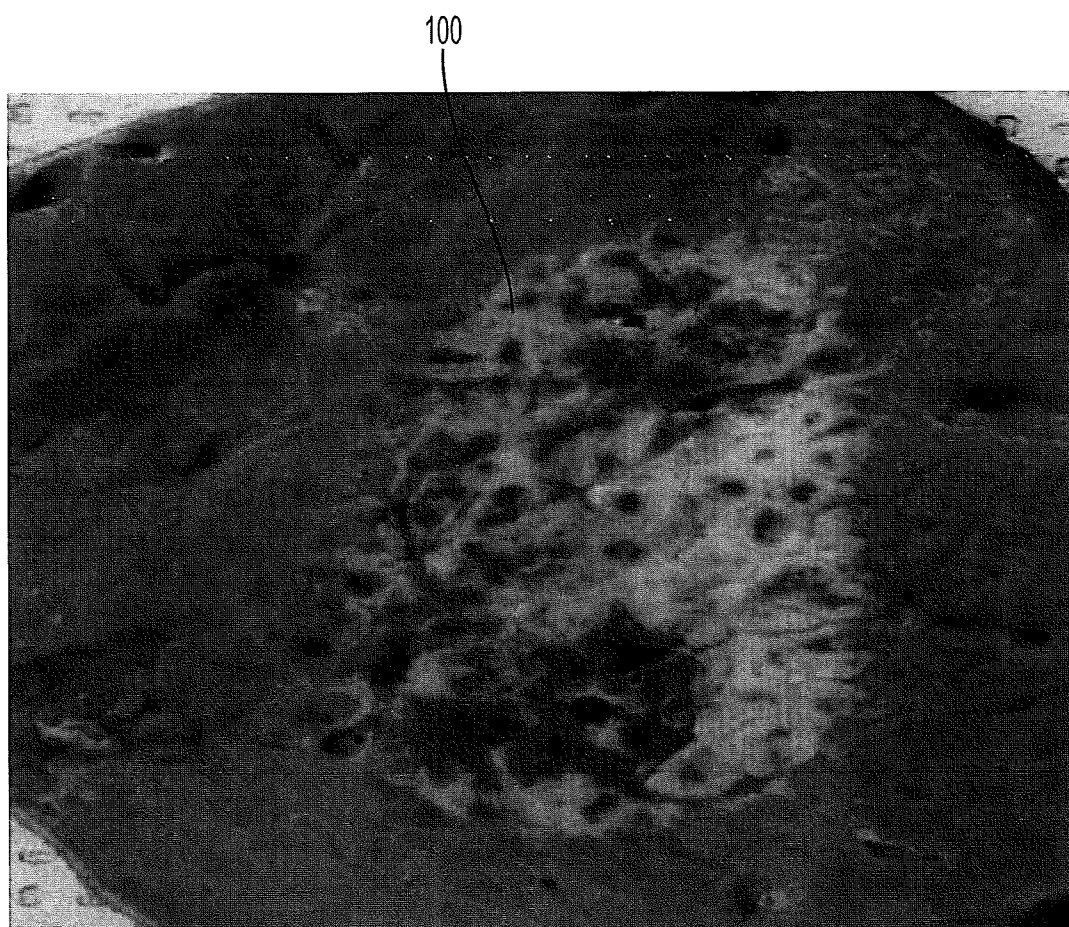


FIG. 13

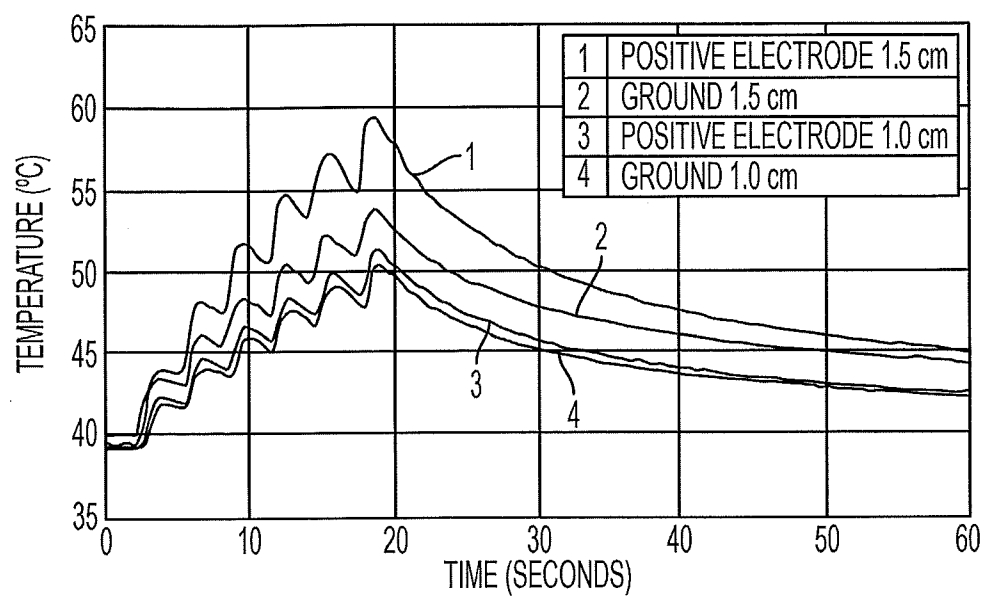


FIG. 14

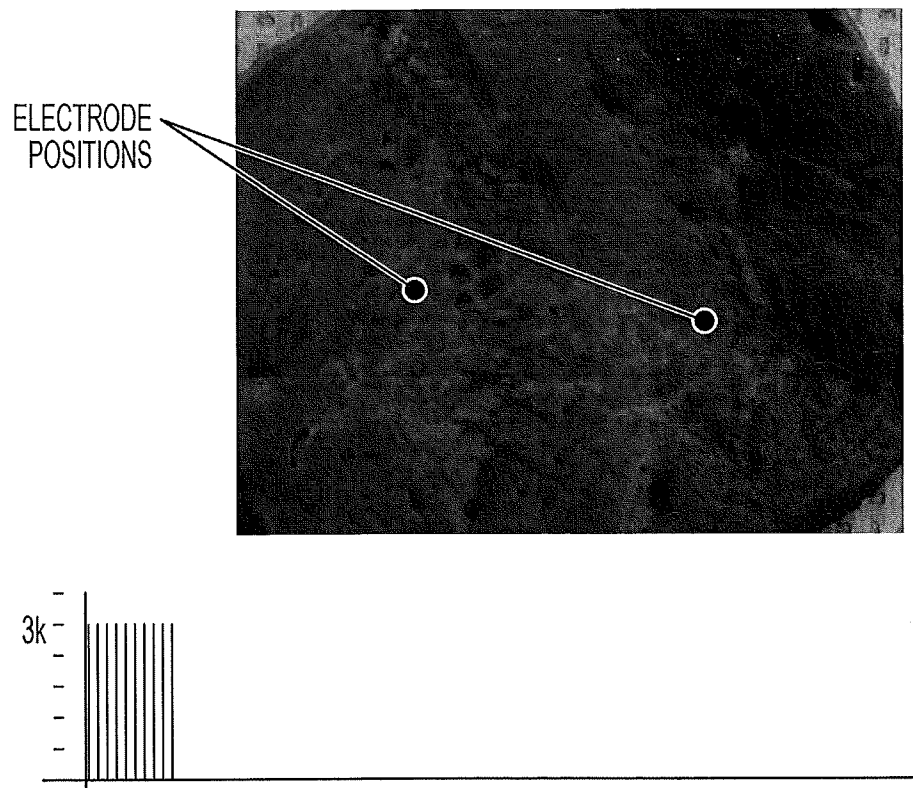


FIG. 15A

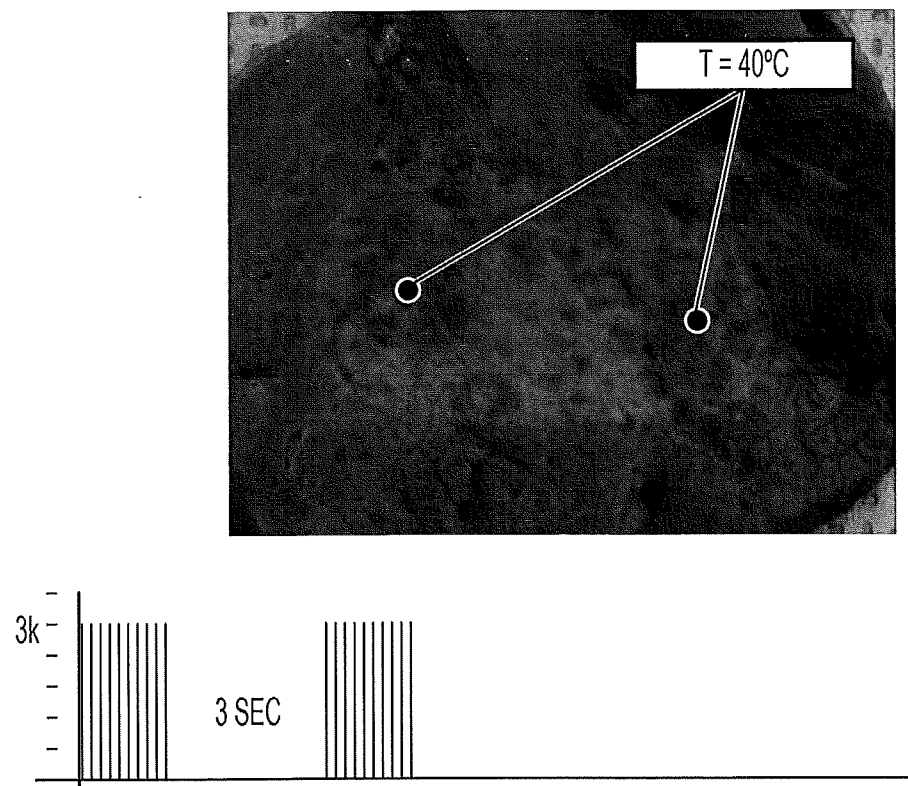


FIG. 15B

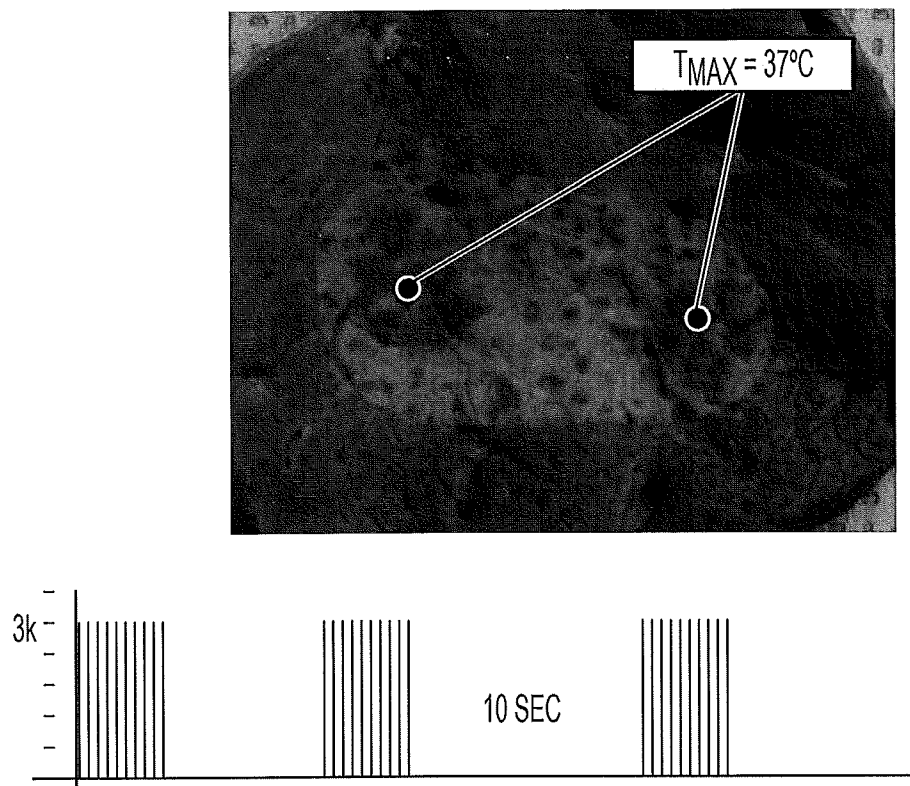


FIG. 15C

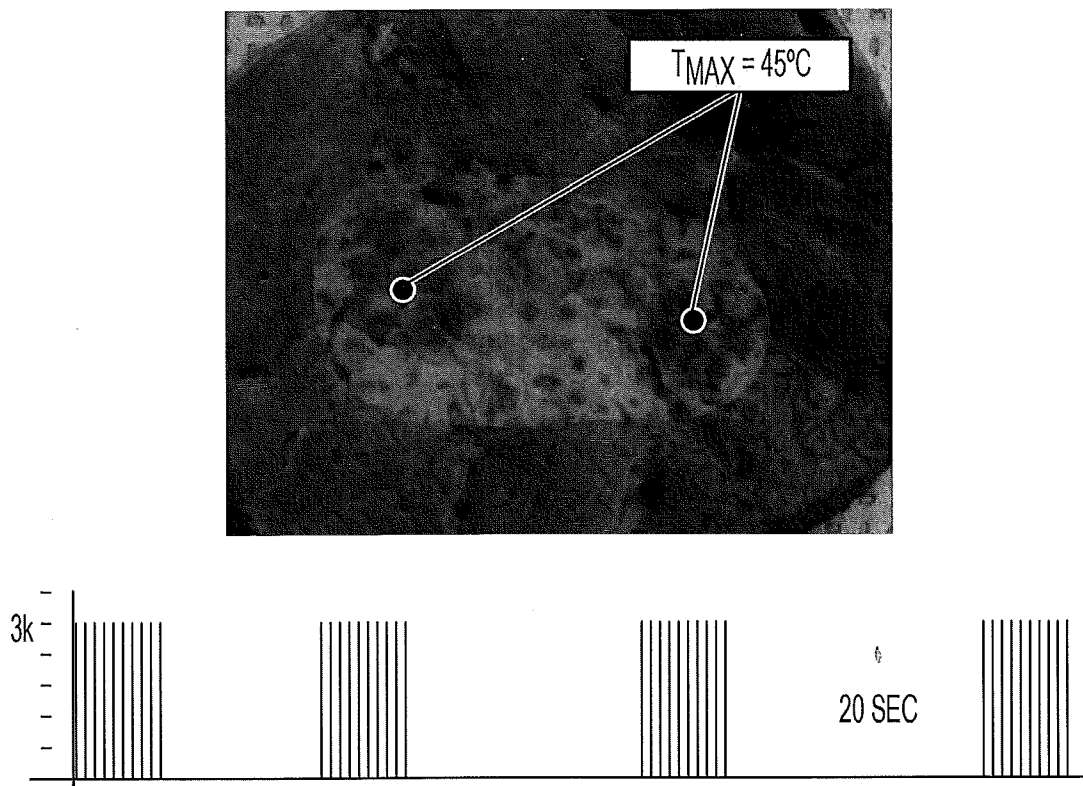


FIG. 15D

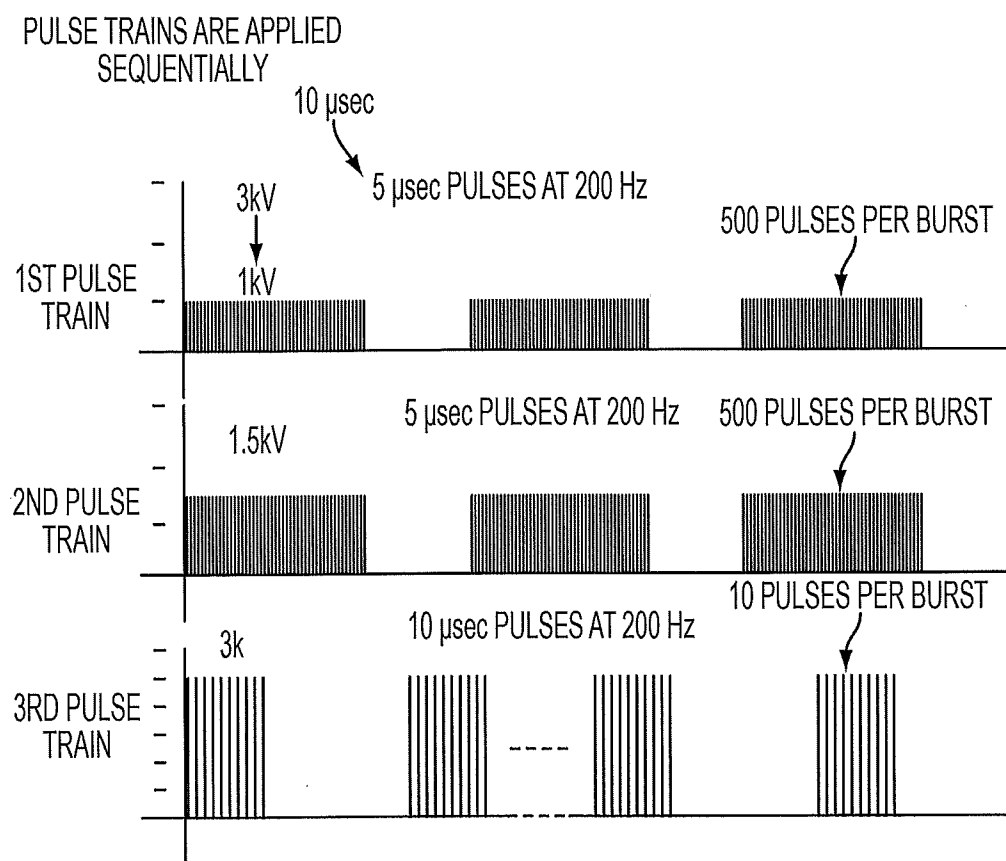


FIG. 16

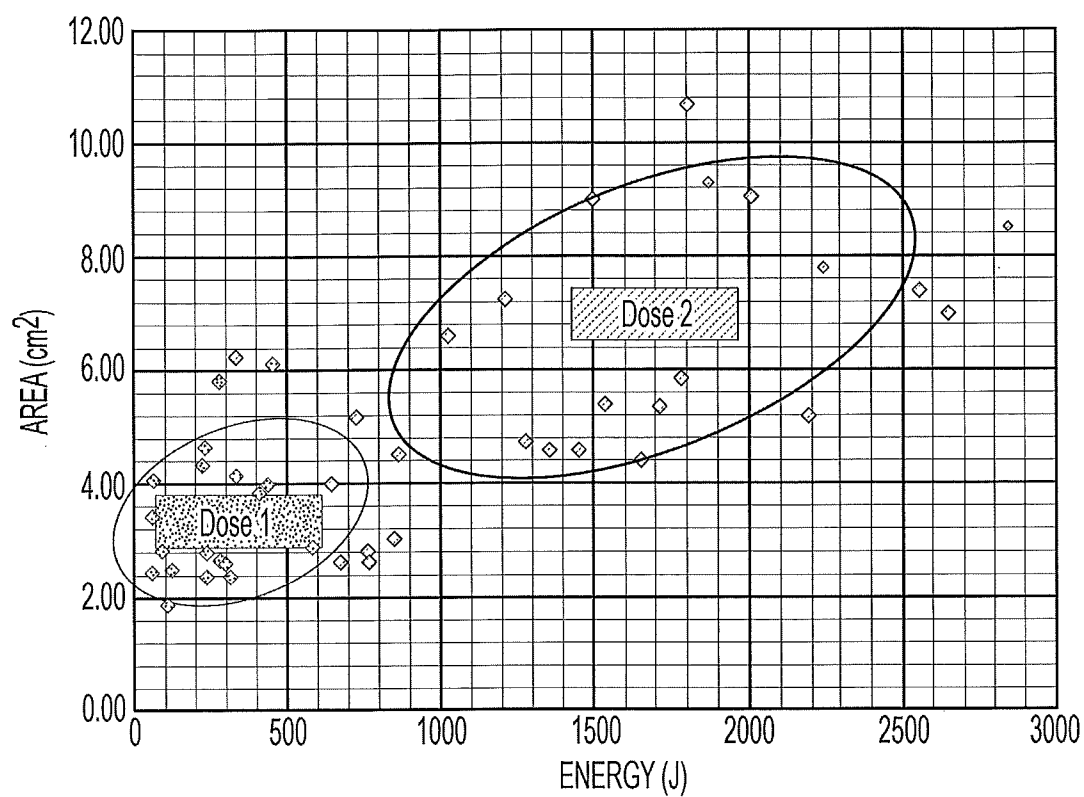


FIG. 17

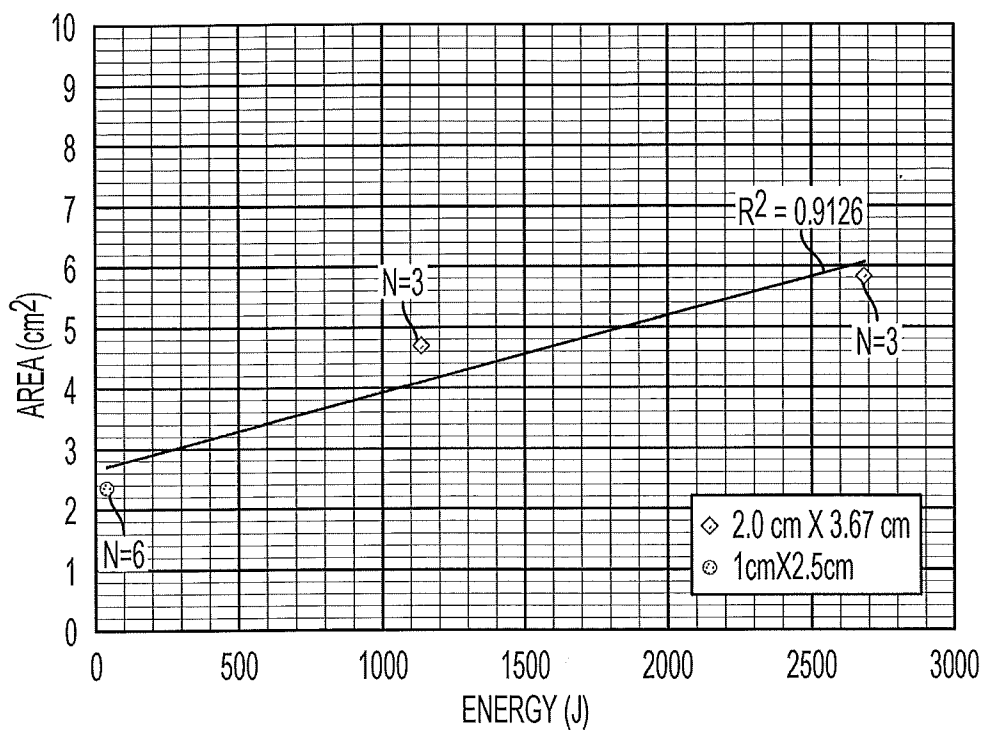


FIG. 18A

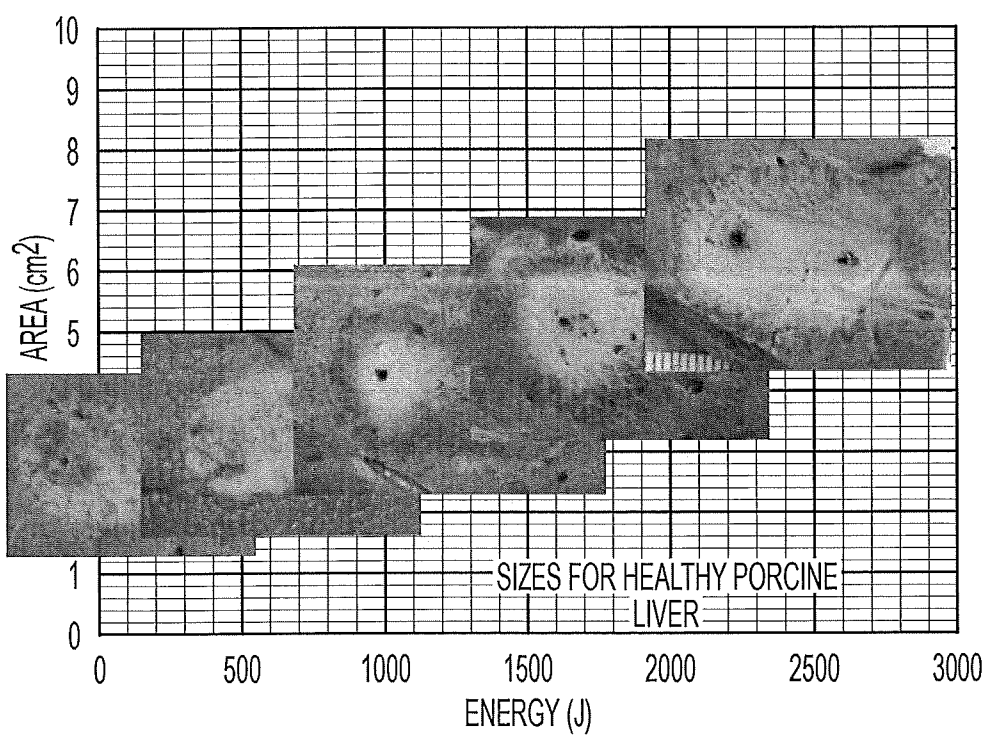


FIG. 18B

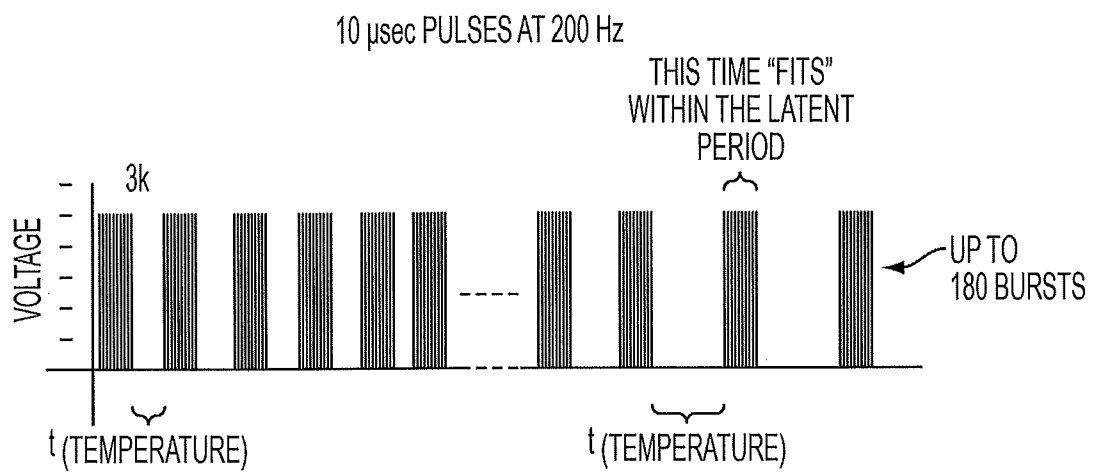


FIG. 19

IRE DOSE
SIZE OF NECROTIC ZONE
1.2 cm x 2.3 cm
AREA OF NECROTIC ZONE
2.76 cm²

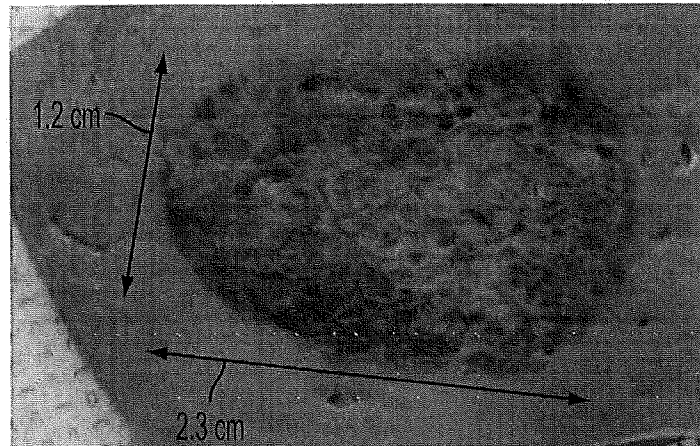


FIG. 20A

IRE+ DOSE
SIZE OF NECROTIC ZONE
2.1 cm x 3.7 cm
AREA OF NECROTIC ZONE
7.77 cm²



FIG. 20B

IRE+HEAT DOSE
SIZE OF NECROTIC ZONE
1.6 cm x 3.6 cm
AREA OF NECROTIC ZONE
5.76 cm²

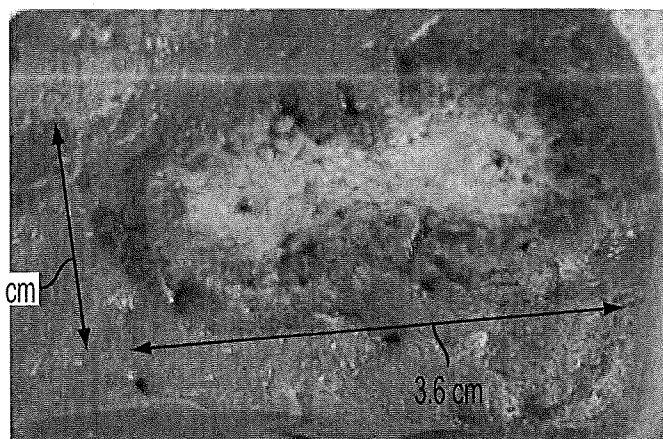


FIG. 20C

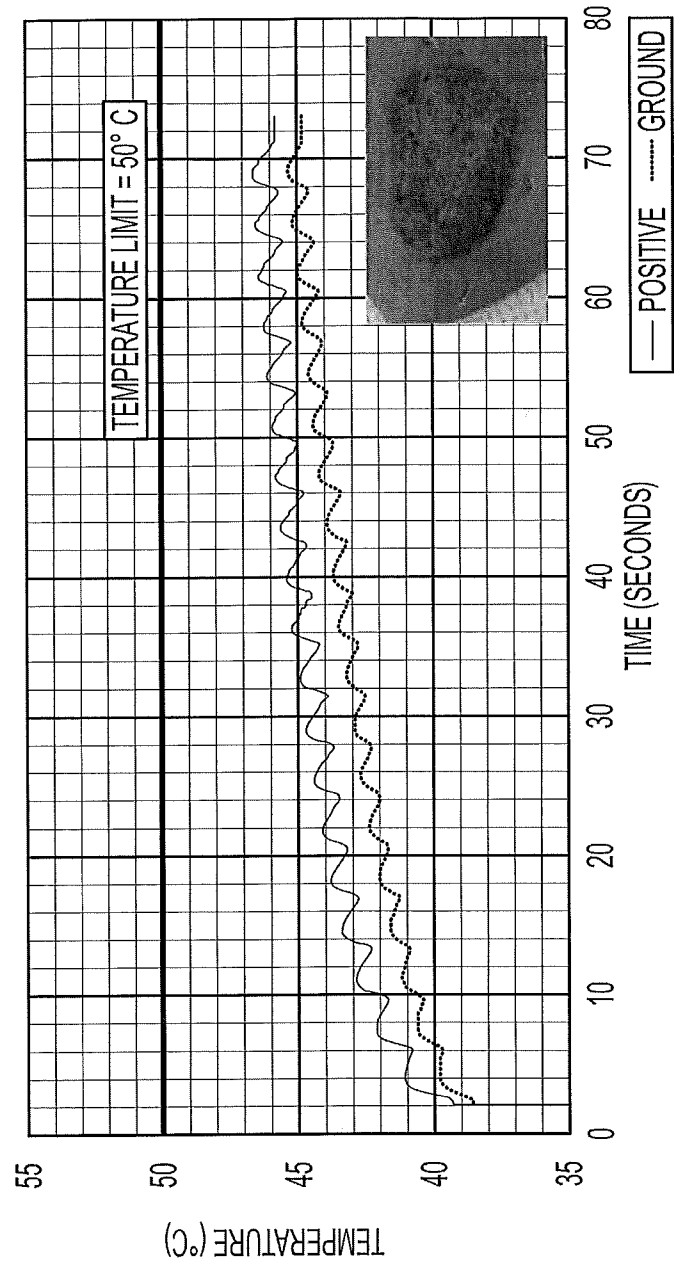


FIG. 21

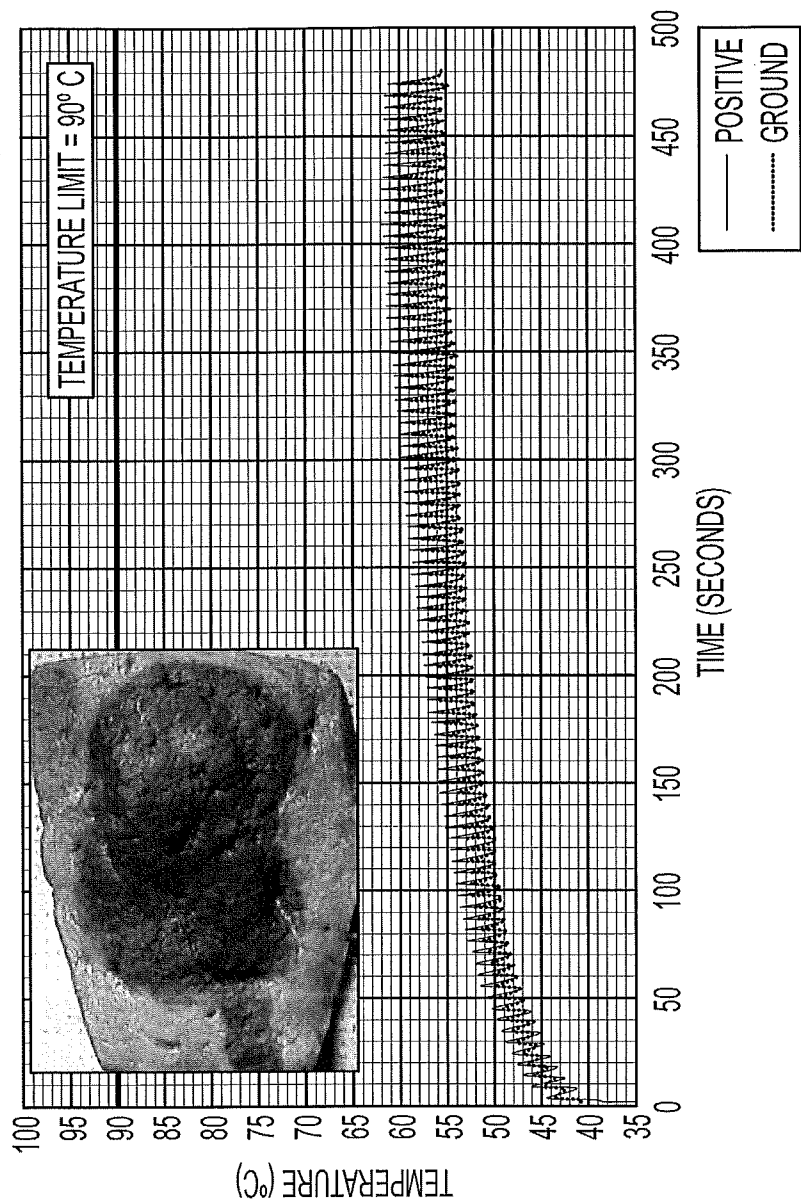


FIG. 22

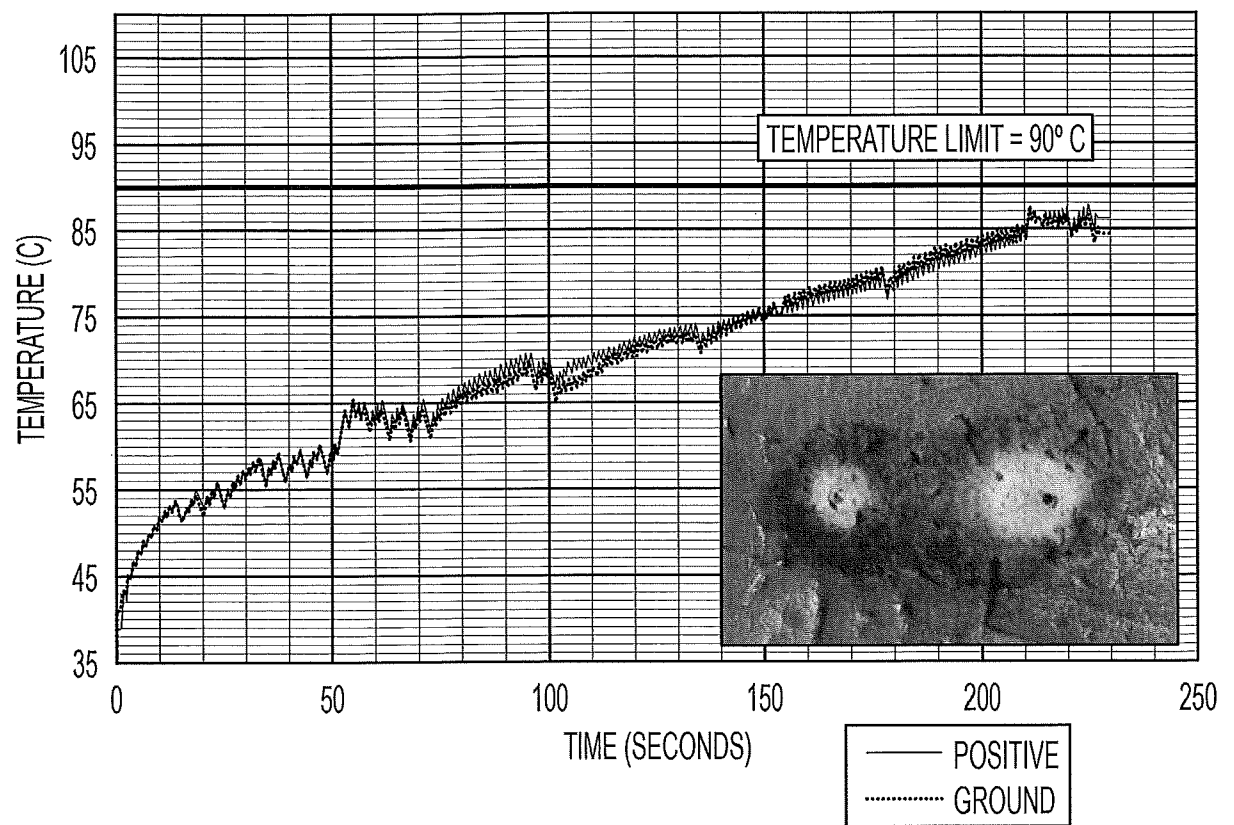


FIG. 23

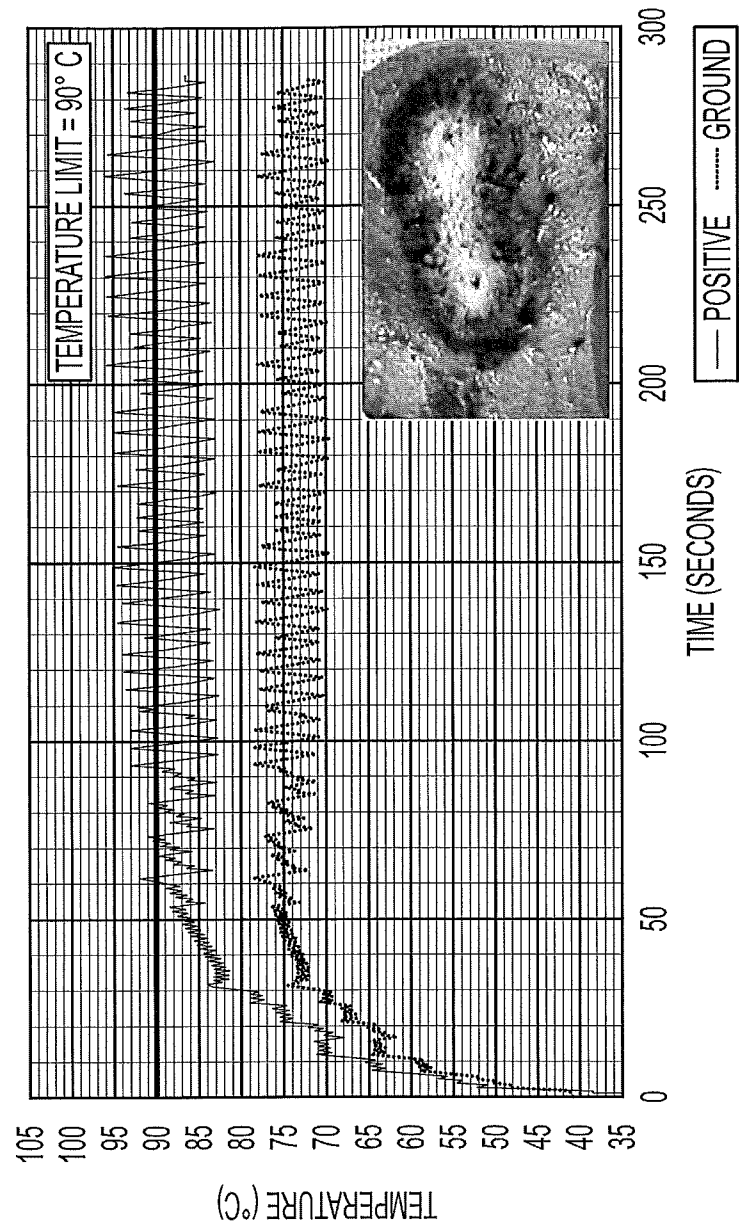


FIG. 24

IRE DOSE
ELECTRODE SPACING
1.5 cm

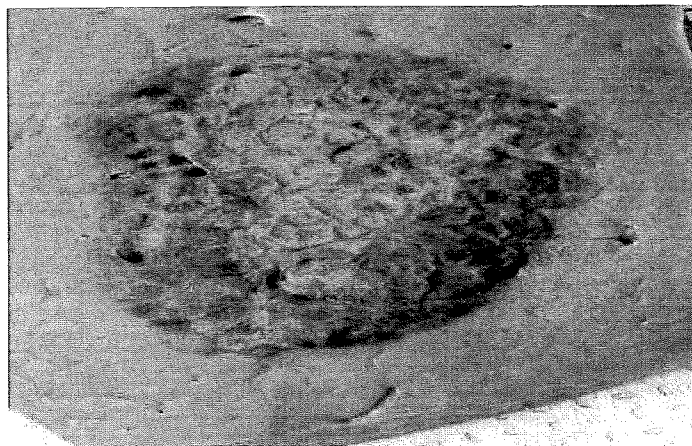


FIG. 25A

IRE+ DOSE
ELECTRODE SPACING
2.0 cm

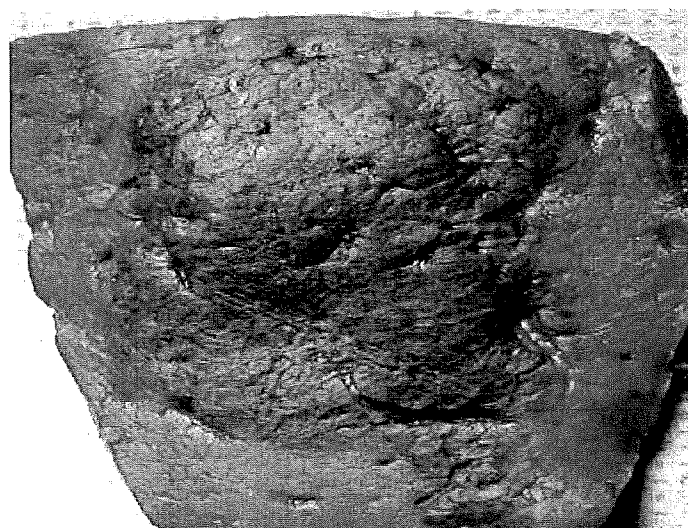


FIG. 25B

IRE+HEAT DOSE
ELECTRODE SPACING
2.0 cm

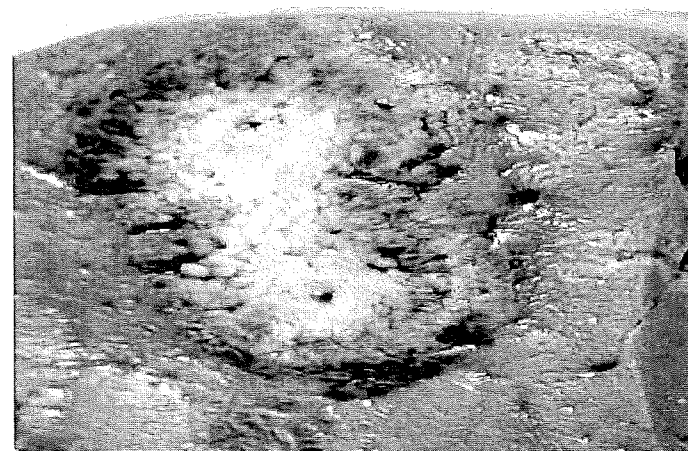


FIG. 25C

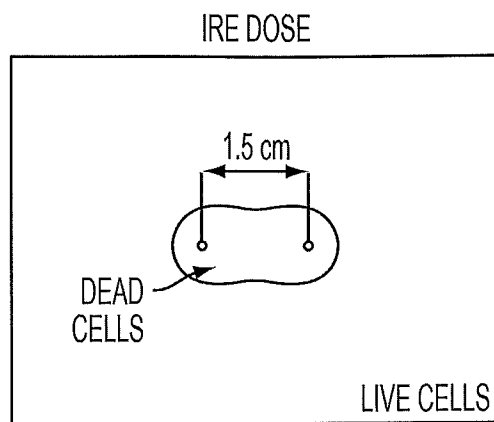


FIG. 26A

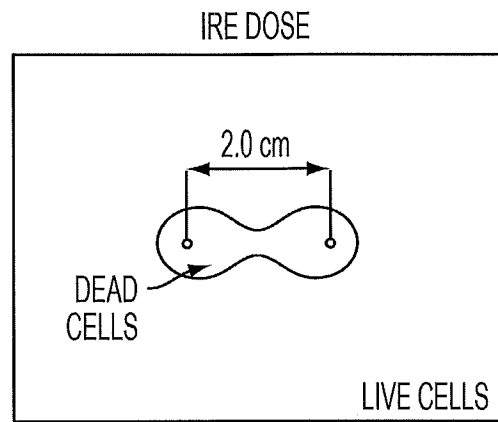


FIG. 26B

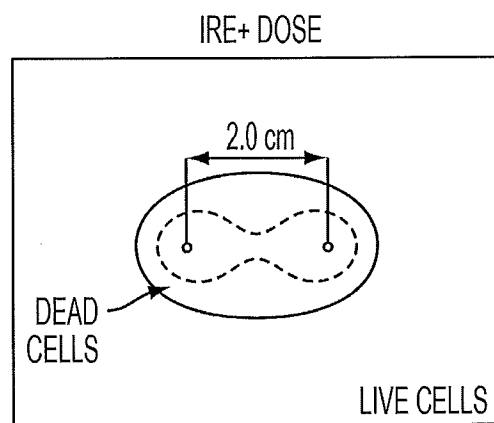


FIG. 26C

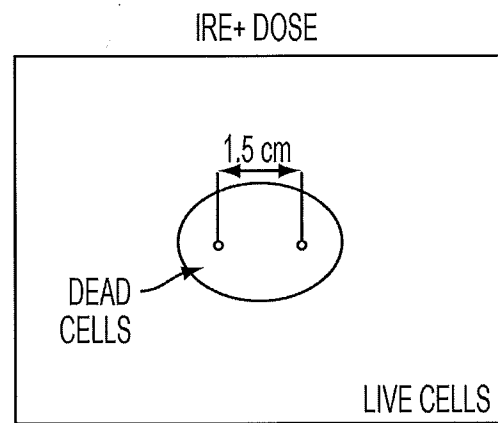


FIG. 26D

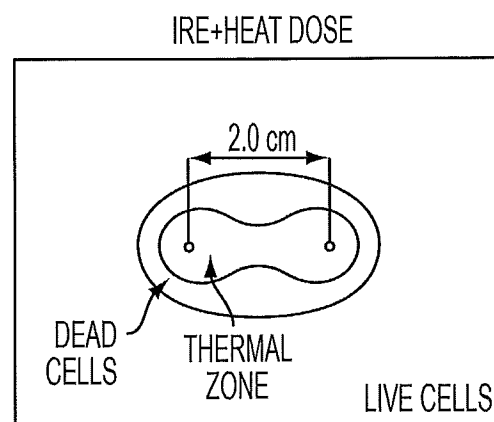


FIG. 26E

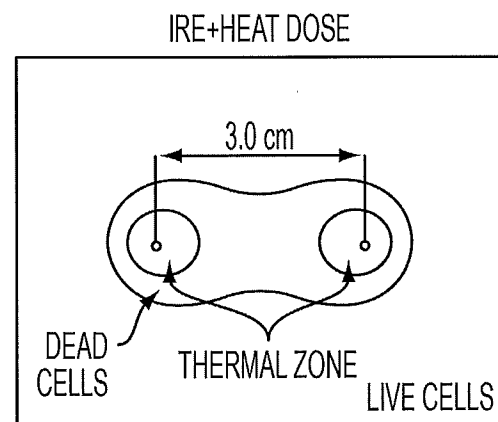


FIG. 26F

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/026049

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61N1/32 A61B18/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/035537 A2 (ARDIAN INC [US]; DEMARAIS DENISE [US]; ZADNO NICOLAS [US]) 29 March 2007 (2007-03-29)	1-10
Y	abstract; claims 73, 89; figures 18-27 paragraph [0109]	11-17
Y	----- US 2008/300571 A1 (LEPIVERT PATRICK [US]) 4 December 2008 (2008-12-04) abstract paragraph [0135]	11-17
A	----- WO 2008/101086 A2 (ETHICON ENDO SURGERY INC [US]; LONG GARY L [US]) 21 August 2008 (2008-08-21) the whole document -----	1-17



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

13 June 2012

Date of mailing of the international search report

21/06/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Wetzig, Thomas

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/026049

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-30
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/026049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007035537	A2	29-03-2007	NONE

US 2008300571	A1	04-12-2008	EP 2195070 A1 16-06-2010
			US 2008300571 A1 04-12-2008
			WO 2008150871 A1 11-12-2008

WO 2008101086	A2	21-08-2008	EP 2120758 A2 25-11-2009
			US 2008200912 A1 21-08-2008
			US 2010087813 A1 08-04-2010
			US 2010130975 A1 27-05-2010
			US 2011306971 A1 15-12-2011
			WO 2008101086 A2 21-08-2008
