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(54) **ASYMMETRIC BALANCED WAVEFORM FOR AC CARDIAC IRREVERSIBLE ELECTROPORATION**

ASYMMETRISCHE AUSGEGLICHENE WELLENFORM FÜR IRREVERSIBLE WECHSELSTROM-ELEKTROPORATION DES HERZENS

FORME D'ONDE ÉQUILBRÉE ASYMÉTRIQUE POUR ÉLECTROPORATION IRRÉVERSIBLE CARDIAQUE EN COURANT ALTERNATIF

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(72) Inventor: **KONINGS, Maurits K.**
3571 GM Utrecht (NL)

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(74) Representative: **Kramer Barske Schmidtchen Patentanwälte PartG mbB European Patent Attorneys Landsberger Strasse 300 80687 München (DE)**

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(73) Proprietor: **St. Jude Medical, Atrial Fibrillation Division, Inc.**
St. Paul, MN 55117 (US)

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Description

BACKGROUND

5 a. Field

[0001] The instant invention relates generally to a system for electrically isolating cardiac tissue.

10 b. Background Art

[0002] It is generally known that ablation therapy may be used to treat various conditions afflicting the human anatomy. One such condition that ablation therapy finds a particular application is in the treatment of atrial arrhythmias, for example. When tissue is ablated, or at least subjected to ablative energy generated by an ablation generator and delivered by an ablation catheter, lesions form in the tissue. Electrodes mounted on or in ablation catheters are used to create tissue necrosis in cardiac tissue to correct conditions such as atrial arrhythmia (including, but not limited to, ectopic atrial tachycardia, atrial fibrillation, and atrial flutter). Arrhythmia (i.e., irregular heart rhythm) can create a variety of dangerous conditions including loss of synchronous atrioventricular contractions and stasis of blood flow which can lead to a variety of ailments and even death. It is believed that the primary cause of atrial arrhythmia is stray electrical signals within the left or right atrium of the heart. The ablation catheter imparts ablative energy (e.g., radiofrequency energy, cryoablation, lasers, chemicals, high-intensity focused ultrasound, etc.) to cardiac tissue to create a lesion in the cardiac tissue. This lesion disrupts undesirable electrical pathways and thereby limits or prevents stray electrical signals that lead to arrhythmias.

[0003] One candidate for use in therapy of cardiac arrhythmias is electroporation. Electroporation therapy involves electric-field induced pore formation on the cell membrane. The electric field may be induced by applying a direct current (DC) signal delivered as a relatively short duration pulse which may last, for instance, from a nanosecond to several milliseconds. Such a pulse may be repeated to form a pulse train. The electric field may also be induced by applying an alternating current (AC) signal delivered as a relatively short duration pulse which may last, for instance, from a nanosecond to several milliseconds. When such an electric field is applied to tissue in an in vivo setting, the cells in the tissue are subjected to transmembrane potential, which essentially opens up the pores on the cell wall, hence the term electroporation. Electroporation may be reversible (i.e., the temporally-opened pores will reseal) or irreversible (i.e., the pores will remain open). For example, in the field of gene therapy, reversible electroporation (i.e., temporarily open pores) are used to transfect high molecular weight therapeutic vectors into the cells. In other therapeutic applications, a suitably configured pulse train alone may be used to cause cell destruction, for instance by causing irreversible electroporation.

[0004] US 2015/0073401 A1 relates to a method of a tissue destruction using irreversible electroporation.

[0005] US 2010/0023004 A1 relates to cardiac electroporation ablation systems in which pulsed, high voltage energy is delivered to induce electroporation of cells in cardiac tissue followed by cell rupturing.

[0006] US 2012/109122 A1 relates to the field of biomedical engineering and medical treatment of diseases and disorders.

[0007] US 2013/030430 A1 relates to medical systems and methods for use thereof for treating tissue, in particular to the treatment of cardiac tissue using high voltage energy delivery for irreversible electroporation (EP) ablation.

[0008] US 2012/059255 A1 relates to a direction-sensitive electrode assembly for electroporation therapy having an increased selectivity in what tissue is subjected to the electroporation therapy.

[0009] The foregoing discussion is intended only to illustrate the present field and should not be taken as a disavowal of claim scope.

BRIEF SUMMARY

[0010] The present invention concerns an electroporation therapy apparatus according to claim 1.

[0011] Preferred embodiments are defined by the dependent claims.

[0012] Aspects, embodiments and examples of the present disclosure which do not fall under the scope of the appended claims do not form part of the present invention. Methods presented hereinafter are also not part of the present invention.

[0013] The present invention also concerns an electroporation therapy system according to claim 10.

55 BRIEF DESCRIPTION OF THE DRAWINGS

[0014]

FIG. 1 is a schematic and block diagram view of a system for electroporation therapy.

FIG. 2A is a plot of a sinusoidal waveform.

FIG. 2B is a plot of an adapted waveform according to the disclosure.

FIG. 3 is a plot of an asymmetric applied current pattern.

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DETAILED DESCRIPTION OF EMBODIMENTS

[0015] Referring now to the drawings wherein like reference numerals are used to identify identical components in the various views, Figure 1 is a diagrammatic and block diagram view of a system 10 in connection with which electrode assemblies for electroporation therapy may be used. In general, the various embodiments include an electrode assembly disposed at the distal end of a catheter. The electrode assembly can comprise a plurality of individual, electrically-isolated electrode elements. Each electrode element can be individually wired such that it can be selectively paired or combined with any other electrode element to act as a bipolar or a multi-polar electrode for both sensing (more below) and electroporation energization purposes. In the sensing mode, the electrode elements can be electrically scanned to detect or identify which electrode elements (or pairs) have electrical conduction characteristics indicative of contact with the target tissue (e.g., impedance, phase angle, reactance). Once such electrode elements have been identified, an electroporation generator can be controlled to energize the identified electrode elements in accordance with an electroporation energization strategy. The selective energization can improve selectivity of the target tissue, more effectively directing the therapy to just the desired, target tissue.

[0016] Irreversible Electroporation (IRE) of cells is an important technique for producing precisely targeted lesions in, for example, the heart. During application of the high intensity currents to produce such lesions, it is desirable to avoid muscle contractions. If the applied current is a DC (or low frequency) current, then severe muscle contractions can occur because the excitation threshold for excitable tissues (muscle cells and neurons) is much lower than the threshold for electroporation. Therefore, in the case of applied DC current for electroporation, anesthesia may be needed for muscle relaxation. In order to avoid the need for anesthesia and/or muscle relaxants, one can apply a high frequency alternating current. The present disclosure provides manners and solutions for producing sufficient tissue necrosis without the need for anesthesia and muscle relaxants to avoid (skeletal) muscle spasms as result of the applied currents.

[0017] The particular energization strategy chosen will depend on the particular type of electroporation therapy sought to be achieved. Exemplary electroporation therapies include: (1) electroporation-mediated therapy; (2) electroporation-induced primary necrosis therapy; and (3) electric field-induced apoptosis (or secondary necrosis) therapy. Each therapy will be described below.

[0018] Electroporation-mediated ablation therapy refers to delivering tissue pre-conditioning effects using electroporation. Pre-conditioning effects would lead to altering the biophysical properties of the tissue which would make the tissue receptive to other ablative therapies such as radio-frequency (RF), ultrasound, and photodynamic therapy. Tissue pre-conditioning may be achieved by delivering electrolytes to the tissue locally using electroporation, thereby changing the biophysical properties of the tissue such as its electrical, acoustical, optical, thermal, and perfusion properties. In this case, the electric field applied to the tissue causes transient and reversible effects of temporarily opening the pores on the cell wall, and the cell remains viable after the application of the electric field. In general, electroporation will involve the application of direct current (DC) or alternating current (AC) to create an electric field sufficient to "tear" the lipid bilayer that forms the cell membrane. There are many voltage level/pulse duration/duty cycle combinations that may be effective. It should be understood that a plurality of factors may affect the particular energization scheme needed to achieve the temporary (*i.e.*, transient and reversible) opening of pores on the cell wall, including species, tissue size, cell size and development stage.

[0019] Electroporation-induced primary necrosis therapy refers to the effects of delivering electrical current in such manner as to directly cause an irreversible loss of plasma membrane (cell wall) integrity leading to its breakdown and cell necrosis. This mechanism of cell death may be viewed as an "outside-in" process, meaning that the disruption of the outside wall of the cell causes detrimental effects to the inside of the cell. Typically, for classical plasma membrane electroporation, electric current is delivered as a pulsed electric field in the form of short-duration direct current (DC) pulses (e.g., 0.1 to 20 ms duration) between closely spaced electrodes capable of delivering a relatively low electric field strength of about 0.1 to 1.0 kV/cm. As discussed herein, an asymmetrical balanced waveform can also be used with AC waveforms as further described below.

[0020] Electric-field-induced apoptosis (or secondary necrosis) therapy refers to the effects of delivering electrical current in such a manner as to cause electromanipulation of the intracellular structures (e.g., such as the nucleus, mitochondria or endoplasmic reticulum) and intracellular functions that precede the disassembly of the cell and irreversible loss of plasma membrane (cell wall). This mechanism of cell death may be viewed as an "inside-out" process, meaning that the disruption of the inside of the cell causes detrimental "secondary" effects to the outside wall of the cell. For electric field-induced apoptosis, electric current is delivered as a pulsed electric field in the form of extremely short-duration DC pulses (e.g., 1 to 300 ns duration) between closely spaced electrodes capable of delivering a relatively high

electric field strength of about 2 to 300 kV/cm. As discussed herein, an asymmetrical balanced waveform can also be used with alternating current to induce electric-field-induced apoptosis.

5 [0021] It should be understood that while the energization strategies for electroporation-mediated ablation therapy, electroporation-induced primary necrosis therapy, electric-field-induced apoptosis (or secondary necrosis) therapy are described as involving DC pulses and AC waveforms other waveforms may be used. For example, exponentially-decaying pulses, exponentially-increasing pulses, monophasic or bi-phasic pulses and combinations of one or more all may be used.

10 [0022] The electroporation embodiments described and depicted herein can involve two different modes of therapy: (1) usage of electroporation therapy to destroy tissue (*i.e.*, cell death) and (2) electroporation-mediated therapy where electroporation mechanism is used to modify a tissue property (*e.g.*, conductivity, reactance, responsiveness/irresponsiveness to photonic energy, responsiveness/irresponsiveness to ultrasonic energy, etc.) for subsequent tissue sensing and/or ablation (*e.g.*, via electrical tissue sensing or electrical energy delivery such as RF energy delivery, via photodynamic-based sensing and/or energy delivery, via ultrasound-based sensing and/or energy delivery, etc.).

15 [0023] As to the first mode of therapy mentioned above (*i.e.*, electroporation alone), it should be understood that electroporation is not substantially energy-dissipative and thus does not substantially thermally alter the target tissue (*i.e.*, does not substantially raise its temperature), thereby avoiding possible thermal effects (*e.g.*, possible pulmonary vein stenosis when using RF energy for a pulmonary vein isolation (PVI) procedure). Even to the extent that RF energy based ablation is used only as a "touch up" after an initial round of electroporation therapy, the thermal effects are reduced due to the corresponding reduction in the application of RF energy. This "cold therapy" thus has desirable characteristics.

20 [0024] As to the second mode mentioned above (*i.e.*, electroporation-mediated therapy), electrochromic dyes may be used for effective monitoring of the progress of and completion of electroporation therapy to condition the target tissue. In the first mode, however, the use of electrochromic dyes do not come into play.

25 [0025] With this background, and now referring again to Figure 1, the system 10 includes a multi-polar or multi-array catheter electrode assembly 12 configured to be used as briefly outlined above and as described in greater detail below. The electrode assembly 12 is incorporated as part of a medical device such as a catheter 14 for electroporation therapy of tissue 16 in a body 17 of a patient. In the illustrative example, the tissue 16 comprises heart or cardiac tissue. It should be understood, however, that implementations may be used to conduct electroporation therapy with respect to a variety of other body tissues.

30 [0026] Figure 1 further shows a plurality of patch electrodes designated 18, 19, 20 and 21, which are diagrammatic of the body connections that may be used by the various sub-systems included in the overall system 10, such as a detector 22, a tissue sensing circuit 24, an energization generator 26 (*e.g.*, electroporation and/or ablation), an EP monitor such as an ECG monitor 28 and a localization and navigation system 30 for visualization, mapping and navigation of internal body structures. It should be understood that the illustration of a single patch electrode is diagrammatic only (for clarity) and that such sub-systems to which these patch electrodes are connected may, and typically will, include more than one patch (body surface) electrode. The system 10 may further include a main computer system 32 (including an electronic control unit 50 and data storage-memory 52), which may be integrated with the system 30 in certain implementations. The system 32 may further include conventional interface components, such as various user input/output mechanisms 34a and a display 34b, among other components.

35 [0027] The detector 22 is coupled to the plurality of electrode elements of the electrode assembly 12 and is configured to identify which elements have characteristics (*e.g.*, if electrical characteristics, then for example, impedance, phase angle, reactance, etc.) indicative of contact of the electrode element with tissue 16. In examples where the electrode elements cover up to 360 degrees (*e.g.*, a distal tip in hemispherical shape or circular catheter with multiple electrodes), it is desirable to energize only those electrode elements that are in contact with tissue, as described above. This may be thought of as a "direction-sensitive" since determining what electrode elements are in contact with tissue also determines the "direction" of the therapy to be delivered to the tissue.

40 [0028] A tissue sensing circuit 24 may be used in connection with the detector 22 for determining an characteristic (*e.g.*, electrical characteristic) to be used in making a "contact" versus "no contact" decision for each electrode element (or pair thereof). The detector 22 may be configured to scan (probe) the electrode elements (or pairs) and record the identification of such in-contact electrode elements. The detector 22, the tissue sensing circuit 24 and the generator 26 are enclosed in a dashed-line box in Figure 1 to indicate the contemplated cooperation necessary to perform the functions described herein. However, it should be understood that no necessary physical integration is implied (*i.e.*, these blocks may be embodied as physically separate components). More particularly, any one of the detector 22, the tissue sensing circuit or the generator 26 may be implemented as a stand-alone component or may be implemented in another portion of system 10 provided such other portion has adequate capabilities to perform the desired function(s).

45 [0029] The tissue sensing circuit 24 as noted above is configured to determine an electrical characteristic associated with an electrode element or pair for purposes of determining whether the electrode element (or pair) is in contact with the tissue 16. The characteristic, when electrical in nature, may be an impedance, a phase angle, a reactance or an electrical coupling index (ECI), as seen by reference to co-pending U.S. Patent Application No. 12/622,488, filed

11/20/2009 entitled "SYSTEM AND METHOD FOR ASSESSING LESIONS IN TISSUE" owned by the common assignee of the present invention. In such an example, multiple skin patch electrodes may be used. Skin (body surface) patch electrodes may be made from flexible, electrically conductive material and are configured for affixation to the body 17 such that the electrodes are in electrical contact with the patient's skin. In one example, the circuit 24 may comprise means, such as a tissue sensing signal source (not shown), for generating an excitation signal used in impedance measurements (e.g., the excitation signal being driven through the subject electrode element) and means, such as a complex impedance sensor (not shown), for determining a complex impedance or for resolving the detected impedance into its component parts. Other patch electrodes (shown only diagrammatically as electrode 19) may preferably be spaced relatively far apart and function as returns for an excitation signal generated by the tissue sensing circuit 24 (as described in U.S. Application No. 12/622,488). As to spacing, tissue sensing patch electrodes (shown only diagrammatically as electrode 19) may be two in number located respectively on the medial aspect of the left leg and the dorsal aspect of the neck or may alternatively be located on the front and back of the torso or in other conventional orientations. Of course, other implementations are possible.

[0030] The detector 22 may receive the measured characteristic from tissue sensing circuit 24 and then determine whether the subject electrode element is in tissue contact based on the value of the determined electrical characteristic, along with predetermined threshold data and decision rules (e.g., if computer-implemented, programmed rules). As shown, the tissue sensing circuit 24 may be coupled through the generator 26 and may use the same conductors to the electrode assembly 12 for excitation purposes as used by the generator 26 for energization purposes. In other examples, the system can determine whether the electrode elements, or other portions of the medical device, are in contact with a tissue or other object within an area of interest through mechanical force sensors, optical force sensors, or other sensors as would be known to one of ordinary skill in the art.

[0031] The electroporation generator 26 is configured to energize the identified electrode elements in accordance with an electroporation energization strategy, which may be predetermined or may be user-selectable. The generator 26 may be configured to communicate with the detector 22 to receive a signal or data set indicative of the electrode elements previously identified during the scanning phase as being in tissue contact. The electroporation energizing strategies (e.g., bi-poles, multi-poles, pulse magnitude, number and duration, etc.) are defined based on their correspondence to a respective one of the electroporation therapies described above, namely: (1) electroporation-mediated therapy; (2) electroporation-induced primary necrosis therapy; and (3) electric field-induced apoptosis (or secondary necrosis) therapy.

[0032] For electroporation-mediated therapy, the generator 26 may be configured to produce an electric current that is delivered via the electrode assembly 12 as a pulsed electric field in the form described above. In another example, the generator 26 may be configured to produce an electric current that is delivered via the electrode assembly 12 as an alternating electric field that comprises an asymmetric balanced waveform as further described below.

[0033] For electroporation-induced primary necrosis therapy, the generator 26 may be configured to produce an electric current that is delivered via the electrode assembly 12 as a pulsed electric field in the form of short-duration direct current (DC) pulses (e.g., 0.1 to 20 ms duration) between closely spaced electrodes capable of delivering a relatively low electric field strength (i.e., at the tissue site) of about 0.1 to 1.0 kV/cm. In another example, the generator 26 may be configured to produce an electric current that is delivered via the electrode assembly 12 as an alternating electric field that comprises an asymmetric balanced waveform as further described below.

[0034] For electric field-induced apoptosis therapy, the generator 26 may be configured to produce an electric current that is delivered via the electrode assembly 12 as a pulsed electric field in the form of extremely short-duration direct current (DC) pulses (e.g., 1 to 300 ns duration) between closely spaced electrodes capable of delivering a relatively high electric field strength (i.e., at the tissue site) of about 2 to 300 kV/cm. In another example, the generator 26 may be configured to produce an electric current that is delivered via the electrode assembly 12 as an alternating electric field that that comprises an asymmetric balanced waveform as further described below.

[0035] In certain other examples (e.g., electroporation-mediated ablation therapy), both electroporation specific energy as well as ablation specific energy can be used in the overall process and in such embodiments, the generator 26 may be further configured to deliver ablation energy as well, or another device may be provided to supply the ablation energy.

[0036] For example, in the case of electroporation-mediated ablation therapy (i.e., electroporation to modify tissue characteristics then followed by RF ablation), the generator 26 may be further configured to generate, deliver and control RF energy output by the electrode assembly 12 of the catheter 14. An ablation energizing power source portion of generator 26 may comprise conventional apparatus and approaches known in the art, such as may be found in commercially available units sold under Ampere™ RF Ablation Generator, available from St. Jude Medical™. In this regard, the ablation functional portion of the generator 26 may be configured to generate a signal at a predetermined frequency in accordance with one or more user specified parameters (e.g., power, time, etc.) and under the control of various feedback sensing and control circuitry as is known in the art. For example, the RF ablation frequency may be about 450 kHz or greater, in certain embodiments. Various parameters associated with the ablation procedure may be monitored including impedance, the temperature at the tip of the catheter, ablation energy and the position of the catheter and

provide feedback to the clinician regarding these parameters. As to ablation therapy, the electrode 18 may function as an RF indifferent/dispersive return for an RF ablation signal.

5 [0037] With continued reference to Figure 1, as noted above, the catheter 14 may comprise functionality for electroporation and in certain examples (*i.e.*, electroporation-mediated ablation therapy) also an ablation function (*e.g.*, RF ablation). It should be understood, however, that variations are possible as to the type of ablation energy provided (*e.g.*, cryoablation, ultrasound, etc.). For example, the example shown in Figure 1 includes a fluid source 36 having a biocompatible fluid such as saline or other electrolyte suitable for the electroporation-mediated therapy chosen, which may be delivered through a pump 38 (which may comprise, for example, a fixed rate roller pump or variable volume syringe pump with a gravity feed supply from the fluid source 36 as shown) for delivery of a suitable electrolyte for electroporation-mediated ablation or saline for irrigation.

10 [0038] In the illustrative example, the catheter 14 includes a cable connector or interface 40, a handle 42, a shaft 44 having a proximal end 46 and a distal 48 end. As used herein, "proximal" refers to a direction toward the end of the catheter near the clinician and "distal" refers to a direction away from the clinician and (generally) inside the body of a patient. The catheter 14 may also include other conventional components not illustrated herein such as a temperature sensor, additional electrodes, and corresponding conductors or leads. The connector 40 provides mechanical, fluid and electrical connection(s) for cables 54, 56 extending from the pump 38 and the generator 24. The connector 40 may comprise conventional components known in the art and as shown may be disposed at the proximal end of the catheter 14.

15 [0039] The handle 42 provides a location for the clinician to hold the catheter 14 and may further provide means for steering or the guiding shaft 44 within the body 17. For example, the handle 42 may include means to change the length of a guidewire extending through the catheter 14 to the distal end 48 of the shaft 44 or means to steer the shaft 44. The handle 42 is also conventional in the art and it will be understood that the construction of the handle 42 may vary. In an alternate example, the catheter 14 may be robotically driven or controlled. Accordingly, rather than a clinician manipulating a handle to advance/retract and/or steer or guide the catheter 14 (and the shaft 44 thereof in particular), a robot is used to manipulate the catheter 14.

20 [0040] The shaft 44 is an elongated, tubular, flexible member configured for movement within the body 17. The shaft 44 is configured to support the electrode assembly 12 as well as contain associated conductors, and possibly additional electronics used for signal processing or conditioning. The shaft 44 may also permit transport, delivery and/or removal of fluids (including irrigation fluids and bodily fluids), medicines, and/or surgical tools or instruments. The shaft 44 may be made from conventional materials such as polyurethane and defines one or more lumens configured to house and/or transport electrical conductors, fluids or surgical tools. The shaft 44 may be introduced into a blood vessel or other structure within the body 17 through a conventional introducer. The shaft 44 may then be advanced/retracted and/or steered or guided through the body 17 to a desired location such as the site of the tissue 16, including through the use of guidewires or other means known in the art.

25 [0041] The localization and navigation system 30 may be provided for visualization, mapping and navigation of internal body structures. The system 30 may comprise conventional apparatus known generally in the art (*e.g.*, an EnSite™ NavX™ Navigation and Visualization System, commercially available from St. Jude Medical, Inc. and as generally shown with reference to commonly assigned U.S. Patent No. 7,263,397 titled "Method and Apparatus for Catheter Navigation and Location and Mapping in the Heart,". It should be understood, however, that this system is exemplary only and not limiting in nature. Other technologies for locating/navigating a catheter in space (and for visualization) are known, including for example, the CARTO navigation and location system of Biosense Webster, Inc., the AURORA® system of Northern Digital Inc., commonly available fluoroscopy systems, or a magnetic location system such as the gMPS system from St. Jude Medical, Inc. In this regard, some of the localization, navigation and/or visualization system would involve a sensor be provided for producing signals indicative of catheter location information, and may include, for example one or more electrodes in the case of an impedance-based localization system, or alternatively, one or more coils (*i.e.*, wire windings) configured to detect one or more characteristics of a magnetic field, for example in the case of a magnetic-field based localization system. Further discussion regarding other examples of systems and medical devices that can be used in an electroporation system can be found in U.S. Patent No. 9,289,606, filed 2 September 2010.

30 [0042] When using an AC waveform, the present disclosure provides, among other things, an asymmetric balanced waveform designed in such a way that electroporation is enhanced in a non-linear way, and at the same time, no net low frequency components are produced. This asymmetric balanced waveform is able to cause electroporation in the tissues of the heart, without producing unwanted side-effects such as (skeletal) muscle contraction.

35 [0043] It is possible to produce irreversible electroporation with a high frequency asymmetrical, balanced electromagnetic current without muscle contraction in view of different time constants that are associated with the various processes involved, in combination with the non-linear character of the electroporation as a function of the strength of the current density that is imposed on the membranes of the tissue.

40 [0044] There are two possibilities for cells to undergo irreversible electroporation. One mechanism for a cell to undergo irreversible electroporation comprises rupture of a portion of the cell membrane. This essentially creates permanent hole within the membrane. The second mechanism for a cell to undergo irreversible electroporation comprises lysis as

a consequence of chemical imbalances caused by molecular transport through transient pores. This can also be known as a secondary process to electroporation. Rupture is believed to be prompt and can occur within 100 microseconds after a large applied pulse. However, it has also been shown that rupture is a stochastic process. At lower intensities of the applied electric field, the second mechanism dominates.

[0045] Within the framework of finding an optimal waveform for the applied current in order to achieve local cardiac electroporation without significant muscle contraction, the following five key concepts are of specific interest. The first key concept comprises the stages of the cell membrane while undergoing electroporation. Electroporation comprises three stages. These three stages comprise, charging of the cell membrane, creation of pores, and evolution of larger pore radii. Charging of the cell membrane can occur between 0- 0.5 μ s, creation of pores can occur between 0.5- 1.4 μ s, and evolution of larger pore radii can occur between 1.4 μ s to 1 ms.

[0046] The second concept comprises the proportionality of the new pore creation to the voltage over the membrane. The creation of new pores is proportional to $e^{(\Phi_m)^2}$, in which Φ_m is the voltage over the membrane. As a result, if N is

the number of pores, then $\frac{d}{dt}N = \alpha e^{\beta(\Phi_m)^2} \left(1 - \frac{N}{N_{FINAL}}\right)$, in which α and β are constants, and N_{FINAL} denotes a theoretical final equilibrium number of pores (for t goes to infinity).

[0047] As seen in the above equation, the Φ_m appears in the form of the square $(\Phi_m)^2$ in the exponent, and therefore, on basis of this non-linearity, the production rate of new pores would be enhanced if the time duration of the transmembrane voltage Φ_m would be reduced by a factor 2 and amplitude of Φ_m would be multiplied by a factor 2. As a result, in order to enhance pore formation, it is better to have a higher value of Φ_m during a shorter period of time that a lower value of Φ_m that is spread out over a longer period of time. This steep non-linearity corresponds to the "threshold value" of Φ_m , $\text{thres} \approx 1$ V as proposed in earlier models of pore formation.

[0048] The third concept comprises building up the voltage over the membrane. The voltage Φ_m over the membrane is built up during the first stage ("charging of the cell membrane") mentioned above. As a result, substantial formation of pores in the membranes commences only after 0.5 μ s.

[0049] The fourth concept comprises having the highest values of the applied field always point in the same direction. Formation of aqueous pores can follow a certain scheme, where the formation of the actual aqueous pores is preceded by more subtle stages of alterations in the membrane and initial formation of aqueous pockets that start to penetrate the membrane. It is favorable for early pore formation to have all of the highest values of the applied field over the membrane $E_m = \nabla \Phi_m$ always point in the same direction. In one embodiment, this direction can be from the outside to the inside. In another example, the direction can be from the inside to the outside. Utilizing this concept allows the repetitive series of high values of Φ_m "work in the same direction." This allows the penetrating effect of initial dimples enhance each other.

[0050] If $\Phi_m(t)$ would be a purely sinusoidal function of time, then such a "constructive series of maximal field strengths" would not take place. This type of sinusoidal function is illustrated in FIG. 2A. FIG. 2A comprises a first positive phase 201, a second positive phase 203, a first negative phase 205, and a second negative phase 207. As the first positive phase and the first negative phase are similar in all ways except direction, a constructive series of maximal field strengths is not achieved. In the alternative, FIG. 2B illustrates an adapted waveform. FIG. 2B comprises a first positive phase 211, a second positive phase 213, a first negative phase 215, and a second negative phase 217. In contrast to FIG. 2A, the first negative phase 215 and the second negative phase 217 of the adapted waveform of FIG. 2B have been flattened and lengthened in time. As a result of this change to the waveform the penetrating effect of initial dimples would enhance each other.

[0051] The fifth concept comprises adding a latency period between each positive and negative phase. A short latency period, during which the applied current is zero, can be inserted between each positive and negative phase in figure 2 in order to avoid damage to the circuit (e.g., MOSFET) components of the current generator system.

[0052] The non-linear character of electroporation when using a high frequency asymmetrical, balanced electromagnetic current can be exploited through several different mechanisms. One mechanism for exploiting the non-linear character of electroporation is using a high frequency. The high frequency can be utilized by applying an AC waveform that contains a fast sequence of alternating "positive" phases and "negative" phases. The strength and the length of each alternating positive and negative phase can be used to further exploit the non-linear characteristic of electroporation. This mechanism can be referred to as an asymmetric waveform. The asymmetric waveform can be achieved by letting the strength of the applied current that flows in one direction (the "positive" direction) be much higher than the strength of the applied current that flows in the opposite direction (the "negative" direction). Another mechanism that can be used to exploit the non-linear characteristic of electroporation is balancing the current imparted to a target tissue during a treatment. This balancing can be achieved by making the "negative" phases last longer than the "positive" phases to compensate for the higher amplitude of the positive phases. The length of the phases can be controlled in such a way that the net current imparted to a target tissue during a treatment, integrated over time, is near or at zero.

[0053] FIG. 3 illustrates a high frequency asymmetrical, balanced electromagnetic current pattern as incorporating the mechanisms discussed above. The illustrated high frequency asymmetrical, balanced electromagnetic current pattern 301 depicts a suitable applied current function $I(t)$ as discussed throughout the disclosure. The high frequency asymmetrical, balanced electromagnetic current pattern 301 can comprise a first positive phase 303, a second positive phase 305, a third positive phase 307, a first negative phase 311, a second negative phase 313, a third negative phase 315, and an applied voltage line 319. The first positive phase 303 comprises a first current and a first time. By integrating the first current and the first time, a first net current can be determined. The first negative phase 311 comprises a second current and a second time. By integrating the second current and the second time, a second net current can be determined. The first positive phase 303 and the first negative phase 311 can comprise a cycle. The illustrated pattern further shows a second positive phase 305 that comprises a third current and a third time, a second negative phase 313 that comprises a fourth current and a fourth time, a third positive phase 307 that comprises a fifth current and a fifth time, and a third negative phase 315 that comprises a sixth current and a sixth time. By integrating the current and the time for each of the phases present in FIG. 3, a net current for each phase can be determined. Each of the pairs of positive phases and negative phases can comprise a separate cycle. While each phase comprises a net current, when the net current of a positive phase and the net current of a paired negative phase (a cycle) are combined, the resulting net current is near or at zero. The applied voltage line 319 illustrates the value of $I(t)$ that produces a voltage of 0.5 Volt over the membrane.

[0054] Although the net current, integrated over time, amounts to around or at zero, the net electroporation effect (the "pushing effect of the applied current density on the molecules in the membrane that ultimately leads to a breach (electroporation hole)") does NOT amount to zero. The electroporation effect is the "pushing effect of the applied current density on the molecules in the membrane that ultimately leads to a breach or an electroporation hole. The electroporation effect can be achieved if the amplitude of the positive phase equals α times the amplitude of the negative phase. This results in the "pushing effect on the molecules in the membrane" of the positive phase being much larger than α times the "pushing effect on the molecules in the membrane" of the negative phase.

[0055] As a result, even if the duration of the negative phase is α times the duration of the positive phase (such that the net current, integrated over time, is near or at zero), there is still a "build-up" effect of the pushing on the molecules in the membrane in the "positive" direction.

[0056] It is possible to produce irreversible electroporation with a high frequency asymmetrical, balanced electromagnetic current without muscle contraction at least because the different time constants that are associated with the various processes involved, in combination with the non-linear character of the electroporation strength as function of the strength of the applied current density field.

[0057] As stated previously, muscle contraction during electroporation of a target tissue can be a concern. When looking for the possibility of irreversible electroporation without muscle contraction, it is important to note that the minimum strength of the applied currents needed for activation of excitable tissues (neurons and muscle cells) is much lower than the minimum strength needed for electroporation. Therefore, in order to avoid unwanted muscle contractions, it is important to consider the various time constants τ_{chron} (chronaxie time) associated with activation of various excitable tissues.

[0058] The chronaxie time associated with neurostimulation ranges from about 130 microseconds for thick myelinated fibers (which are present in e.g. the spinal cord), and about 500 microseconds for non-myelinated cells. The threshold for excitation of excitable tissue depends on the frequency of the applied electric field. To determine the threshold for

excitation of excitable tissue the following equation can be used.

$$E_{\text{threshold}} = E_{\text{rheobase}} \left(1 + \frac{\tau_{\text{chron}}}{T} \right),$$

in which $T = 1 / f$, and f is the frequency of the applied electric field, and in which E_{rheobase} is about 5.4 V/m for thick myelinated fibers, and up to 20 V/m for other cells. The values of E_{rheobase} can be determined by one of ordinary skill in the art. The structure of the last equation can be attributed to an "integrating" effect within time intervals that are shorter than the chronaxie time τ_{chron} :

[0059] Further, no neurostimulation takes place under other conditions. To determine whether neurostimulation occurs the following equation can be used.

$\forall t \in [0, \tau_{\text{chron}}]: \int_0^t E_m d\tau = \int_0^t \frac{1}{a_m} \Phi_m d\tau < S_{\text{threshold}}$, in which a_m is the thickness of the membrane and $S_{\text{threshold}}$ is a fixed value related to E_{rheobase} .

[0060] This equation implies that even at high frequencies, neurostimulation can be provoked if the applied electric field is very large and causes the integral to exceed the threshold within the interval $[0, \tau_{\text{chron}}]$ viz. within a single positive (or negative) phase (i.e., within $0.5 / f$) of the applied electric field. This underscores the importance of keeping the intensity of the applied AC waveform as low as possible, even at high frequencies f .

[0061] As a result of the above information, a sixth key concept can be added to the five concepts discussed above. The sixth concept comprises obtaining a maximum electroporation while minimizing excitation. To achieve this a max-

imum electroporation needs to be obtained within minimum $\int_0^t E d\tau$.

[0062] As discussed above, there are now six key concepts that can be utilized to provide a framework of finding an optimal waveform for the applied current in order to achieve local cardiac electroporation without significant muscle contraction.

[0063] First, electroporation consists of three stages: charging of the cell membrane (0 - 0.5 μ_s), creation of pores (0.5 - 1.4 μ_s), and evolution of larger pore radii (1.4 μ_s to 1 ms). Therefore, maximization of the creation of pores should take place within time intervals of around 1 microsecond.

[0064] Second, the creation rate of new pores is proportional to $e^{(\Phi_m)^2}$. Therefore: the $\Phi_{m(t)}$ should contain relatively high but short peaks.

[0065] Third, the repetitive series of high peaks of Φ_m should "work in the same direction." Therefore: the waveform should be asymmetric, i.e.: the positive (or negative) peaks should be substantially larger in amplitude than the negative (or positive) peaks.

[0066] Fourth, a short latency period, during which the applied current is zero, should be inserted between each positive and negative phase in FIG. 3 in order to avoid damage to the MOSFET components of the current generator system.

[0067] Fifth, the repair mechanisms within the cells that aim at repairing the electroporation holes, need more than 0.5 seconds to be effective. Therefore, in order to frustrate and counteract these repair mechanisms, the time interval between any two bursts of applied asymmetrical AC waveforms should not exceed 0.5 seconds.

[0068] Sixth, maximum electroporation needs to be obtained with minimum $\int_0^t E_m d\tau$. Therefore, the integral over

time of each single entire period of the periodic function $\Phi_{m(t)}$ should amount up to near or at zero, i.e.: $\int_0^T \Phi_m d\tau = 0$.

, in which T is the duration of one single entire period of the periodic function $\Phi_{m(t)}$. Furthermore, in combination with the fourth concept, this implies that the shallow negative phases in figure 2b should be broadened in time to let

$$\int_0^T \Phi_m d\tau = 0$$

[0069] Hereinafter a method of applying electroporation to a target tissue as discussed throughout the disclosure is disclosed. This method does not form part of the present invention. The method can comprise sending an asymmetric balanced waveform from an electroporation generator to a medical device. The asymmetric balanced waveform can comprise a first positive phase and a first negative phase. The first positive phase comprises a first current and a first time and the first negative phase comprises a second current and a second time. The first current is greater than the second current and the second time is greater than the first time. The asymmetric balanced waveform is configured to irreversibly electroporate a target tissue

[0070] It is intended that all matter contained in the above description or shown in the accompanying drawings shall be interpreted as illustrative only and not limiting. Those of ordinary skill in the art will understand that the embodiments described and illustrated herein are nonlimiting examples, and thus it can be appreciated that the specific structural and functional details disclosed herein may be representative and do not necessarily limit the scope of the present invention which is defined solely by the appended claims.

Claims

1. An electroporation therapy apparatus, comprising:

an electroporation generator (26), wherein the electroporation generator (26) is configured to output an asymmetric balanced waveform to a medical device (14) comprising an electrode assembly comprising a circular catheter having a plurality of electrode elements disposed on the circular catheter,

wherein the asymmetric balanced waveform comprises a first positive phase (303) and a first negative phase (311), wherein the first positive phase (303) comprises a first current and a first time and wherein the first negative phase (311) comprises a second current and a second time,

wherein the first current is greater than the second current and wherein the second time is greater than the first time,

wherein the first time is between 0,5 μ_s and 130 μ_s ,

wherein there is a latency period, during which an applied current is zero, between the first positive phase (303) and first negative phase (311),

wherein the electroporation generator (26) is further configured to receive a signal for identifying which pairs of the plurality of electrode elements have electrical characteristics indicative of contact with a target tissue when the target tissue is energized with an excitation signal, wherein the electroporation generator is configured to use an electroporation energization strategy to energize at least one of the pairs of the plurality of electrode elements identified as having contact with the target tissue with the asymmetric balanced waveform configured to irreversibly electroporate the target tissue; and wherein the electroporation generator (26) is configured to determine whether neurostimulation will occur using

the equation $\forall t \in [0, \tau_{\text{chron}}]: \int_0^t E_m d\tau = \int_0^t \frac{1}{a_m} \Phi_m d\tau < E_{\text{threshold}}$, wherein τ_{chron} is the chronaxie

time, a_m is the thickness of the membrane, $E_{\text{threshold}} = E_{\text{rheobase}} \left(1 + \frac{\tau_{\text{chron}}}{T}\right)$, E_{rheobase} is between 5,4 V/m and 20 V/m, $T=1/f$, f is the frequency of the applied electric field, Φ_m is the applied voltage over the membrane, and E_m is the applied electrical field.

2. The electroporation therapy apparatus of claim 1, wherein the first positive phase (303) and the first negative phase (311) comprises a cycle and wherein the electroporation generator (26) is configured to output a plurality of cycles to the target tissue.
3. The electroporation therapy apparatus of claim 2, wherein the electroporation generator (26) is configured to insert a latency between each of the plurality of cycles.
4. The electroporation therapy apparatus of claim 3, wherein the electroporation generator (26) further comprises a MOSFET and wherein the latency period is configured to avoid damage to the MOSFET.
5. The electroporation therapy apparatus of claim 3 or 4, wherein the latency period between each of the plurality of cycles is less than 0.5 seconds.
6. The electroporation therapy apparatus of any one of claims 2 to 5, wherein an area of each positive phase and each negative phase in each of the plurality of cycles corresponds to a net current for each phase, wherein, when the net current of a positive phase and the net current of a paired negative phase in a cycle are combined, the resulting net current is near zero.
7. The electroporation therapy apparatus of any one of claims 2 to 6, wherein the plurality of cycles is configured to apply an applied current function to the target tissue.
8. The electroporation therapy apparatus of claim 7, wherein the applied current function comprises a value of 0.5 Volts.
9. The electroporation therapy apparatus of any one of the preceding claims, wherein the medical device (14) comprises a circular catheter.
10. An electroporation therapy system, comprising:
 - a medical device (14) comprising a circular catheter having a plurality of electrodes disposed on the circular catheter; and
 - an electroporation therapy apparatus according to any of claims 1-9.

Patentansprüche

1. Elektroporationstherapiegerät, mit:

einem Elektroporationsgenerator (26), wobei der Elektroporationsgenerator (26) konfiguriert ist zum Ausgeben einer asymmetrisch ausgeglichenen Wellenform an eine medizinische Vorrichtung (14), die eine Elektrodenanordnung aufweist, die einen kreisförmigen Katheter mit einer Mehrzahl von Elektrodenelementen hat, die auf dem kreisförmigen Katheter angeordnet sind, wobei die asymmetrisch ausgeglichene Wellenform eine erste positive Phase (303) und eine erste negative

Phase (311) aufweist, wobei die erste positive Phase (303) einen ersten Strom und eine erste Zeit aufweist, und wobei die erste negative Phase (311) einen zweiten Strom und eine zweite Zeit aufweist, wobei der erste Strom größer als der zweite Strom ist, und wobei die zweite Zeit größer als die erste Zeit ist, wobei die erste Zeit zwischen 0,5 μ s und 130 μ s liegt,

wobei zwischen der ersten positiven Phase (303) und der ersten negativen Phase (311) eine Latenzzeitperiode vorliegt, während der ein angelegter Strom gleich null ist,

wobei der Elektroporationsgenerator (26) ferner konfiguriert ist zum Empfangen eines Signals zum Identifizieren der Paare von der Mehrzahl von Elektrodenelementen, die elektrische Charakteristiken haben, die kennzeichnend sind für einen Kontakt mit einem Zielgewebe, wenn das Zielgewebe mit einem Erregungssignal energetisiert wird, wobei

der Elektroporationsgenerator konfiguriert ist zur Verwendung einer Elektroporationsenergetisierungsstrategie, um mindestens eines von den Paaren von der Mehrzahl von Elektrodenelementen zu energetisieren, die als einen Kontakt mit dem Zielgewebe habend identifiziert worden sind, mit der asymmetrisch ausgeglichenen Wellenform, die konfiguriert ist für irreversible Elektroporation des Zielgewebes; wobei

der Elektroporationsgenerator (26) konfiguriert ist zum Bestimmen, ob eine Neurostimulation auftritt unter Ver-

wendung der Gleichung $\forall t \in [0, \tau_{\text{chron}}]: \int_0^t E_m d\tau = \int_0^t \frac{1}{a_m} \Phi_m d\tau < E_{\text{threshold}}$, wobei τ_{chron} die

Chronaxiezeit ist, a_m die Dicke der Membran ist, $E_{\text{threshold}} = E_{\text{rheobase}} \left(1 + \frac{\tau_{\text{chron}}}{T} \right)$, E_{rheobase} zwischen 5,4 V/m und 20 V/m liegt, $T=1/f$, f die Frequenz des angelegten elektrischen Felds ist, Φ_m die über der Membran angelegte Spannung ist, und E_m das angelegte elektrische Feld ist.

2. Elektroporationstherapiegerät nach Anspruch 1, bei dem die erste positive Phase (303) und die erste negative Phase (311) einen Zyklus aufweisen, und wobei der Elektroporationsgenerator (26) konfiguriert ist zum Ausgeben einer Mehrzahl von Zyklen an das Zielgewebe.

3. Elektroporationstherapiegerät nach Anspruch 2, bei dem der Elektroporationsgenerator (26) konfiguriert ist zur Einfügung einer Latenz zwischen jedem von der Mehrzahl von Zyklen.

4. Elektroporationstherapiegerät nach Anspruch 3, bei dem der Elektroporationsgenerator (26) ferner ein MOSFET aufweist, und wobei die Latenzzeitperiode konfiguriert ist zur Vermeidung einer Beschädigung des MOSFETs.

5. Elektroporationstherapiegerät nach Anspruch 3 oder 4, bei dem die Latenzzeitperiode zwischen jedem von der Mehrzahl von Zyklen kleiner als 0,5 Sekunden ist.

6. Elektroporationstherapiegerät nach einem der Ansprüche 2 bis 5, bei dem ein Bereich jeder positiven Phase und jeder negativen Phase in jedem von der Mehrzahl von Zyklen einem Nettostrom für jede Phase entspricht, wobei, wenn der Nettostrom einer positiven Phase und der Nettostrom einer gepaarten negativen Phase in einem Zyklus kombiniert werden, der resultierende Nettostrom nahe null ist.

7. Elektroporationstherapiegerät nach einem der Ansprüche 2 bis 6, bei dem die Mehrzahl von Zyklen konfiguriert ist zum Anlegen einer verwendeten Stromfunktion an das Zielgewebe.

8. Elektroporationstherapiegerät nach Anspruch 7, bei dem die verwendete Stromfunktion einen Wert von 0,5 Volt aufweist.

9. Elektroporationstherapiegerät nach einem der vorangegangenen Ansprüche, bei dem die medizinische Vorrichtung (14) einen kreisförmigen Katheter aufweist.

10. Elektroporationstherapiesystem, mit:

einer medizinischen Vorrichtung (14), die einen kreisförmigen Katheter mit einer Mehrzahl von Elektroden aufweist, die auf dem kreisförmigen Katheter vorgesehen sind; und einem Elektroporationstherapiegerät nach einem der Ansprüche 1 bis 9.

Revendications

1. Appareil de thérapie par électroporation, comprenant :

un générateur d'électroporation (26), dans lequel le générateur d'électroporation (26) est configuré pour sortir une forme d'onde équilibrée asymétrique vers un dispositif médical (14) comprenant un ensemble d'électrodes comprenant un cathéter circulaire ayant une pluralité d'éléments d'électrode disposés sur le cathéter circulaire, dans lequel la forme d'onde équilibrée asymétrique comprend une première phase positive (303) et une première phase négative (311), dans lequel la première phase positive (303) comprend un premier courant et un premier temps et dans lequel la première phase négative (311) comprend un second courant et un second temps, dans lequel le premier courant est supérieur au second courant et dans lequel le second temps est supérieur au premier temps, dans lequel le premier temps est compris entre 0,5 μ s et 130 μ s, dans lequel il existe une période de latence, pendant lequel un courant appliqué est nul, entre la première phase positive (303) et la première phase négative (311), dans lequel le générateur d'électroporation (26) est en outre configuré pour recevoir un signal pour identifier quelles paires de la pluralité d'éléments d'électrode ont des caractéristiques électriques indiquant un contact avec un tissu cible lorsque le tissu cible est excité avec un signal d'excitation, dans lequel le générateur d'électroporation est configuré pour utiliser une stratégie d'excitation d'électroporation pour exciter au moins une des paires de la pluralité d'éléments d'électrode identifiés comme ayant un contact avec le tissu cible avec la forme d'onde équilibrée asymétrique configurée pour induire de manière irréversible une électroporation dans un le tissu cible ; et dans lequel le générateur d'électroporation (26) est configuré pour déterminer si une neurostimulation va se

produire en utilisant l'équation $\forall t \in [0, \tau_{\text{chron}}]: \int_0^t E_m d\tau = \int_0^t \frac{1}{a_m} \Phi_m d\tau < E_{\text{threshold}}$ où τ_{chron} est le temps de

chronaxie, a_m est l'épaisseur de la membrane, $E_{\text{threshold}} = E_{\text{rheobase}} \left(1 + \frac{\tau_{\text{chron}}}{T}\right)$, E_{rheobase} est entre 5,4 V/m et 20 V/m, $T=1/f$, f est la fréquence du champ électrique appliqué, Φ_m est la tension appliquée sur la membrane, et E_m est le champ électrique appliqué.

2. Appareil de thérapie par électroporation selon la revendication 1, dans lequel la première phase positive (303) et la première phase négative (311) comprennent un cycle et dans lequel le générateur d'électroporation (26) est configuré pour délivrer une pluralité de cycles au tissu cible.

3. Appareil de thérapie par électroporation selon la revendication 2, dans lequel le générateur d'électroporation (26) est configuré pour insérer une latence entre chacun de la pluralité de cycles.

4. Appareil de thérapie par électroporation selon la revendication 3, dans lequel le générateur d'électroporation (26) comprend en outre un MOSFET et dans lequel la période de latence est configurée pour éviter d'endommager le MOSFET.

5. Appareil de thérapie par électroporation selon la revendication 3 ou 4, dans lequel la période de latence entre chacun de la pluralité de cycles est inférieure à 0,5 seconde.

6. Appareil de thérapie par électroporation selon l'une quelconque des revendications 2 à 5, dans lequel une zone de chaque phase positive et de chaque phase négative dans chacun de la pluralité de cycles correspond à un courant net pour chaque phase, dans lequel, lorsque le courant net d'une phase positive et le courant net d'une phase négative appariée dans un cycle sont combinés, le courant net résultant est proche de zéro.

7. Appareil de thérapie par électroporation selon l'une quelconque des revendications 2 à 6, dans lequel la pluralité de cycles est configurée pour appliquer une fonction de courant appliqué au tissu cible.

8. Appareil de thérapie par électroporation selon la revendication 7, dans lequel la fonction de courant appliqué comprend une valeur de 0,5 volt.

9. Appareil de thérapie par électroporation selon l'une quelconque des revendications précédentes, dans lequel le

dispositif médical (14) comprend un cathéter circulaire.

10. Système de thérapie par électroporation, comprenant :

5 un dispositif médical (14) comprenant un cathéter circulaire ayant une pluralité d'électrodes disposées sur le cathéter circulaire ; et
un appareil de thérapie par électroporation selon l'une quelconque des revendications 1 à 9.

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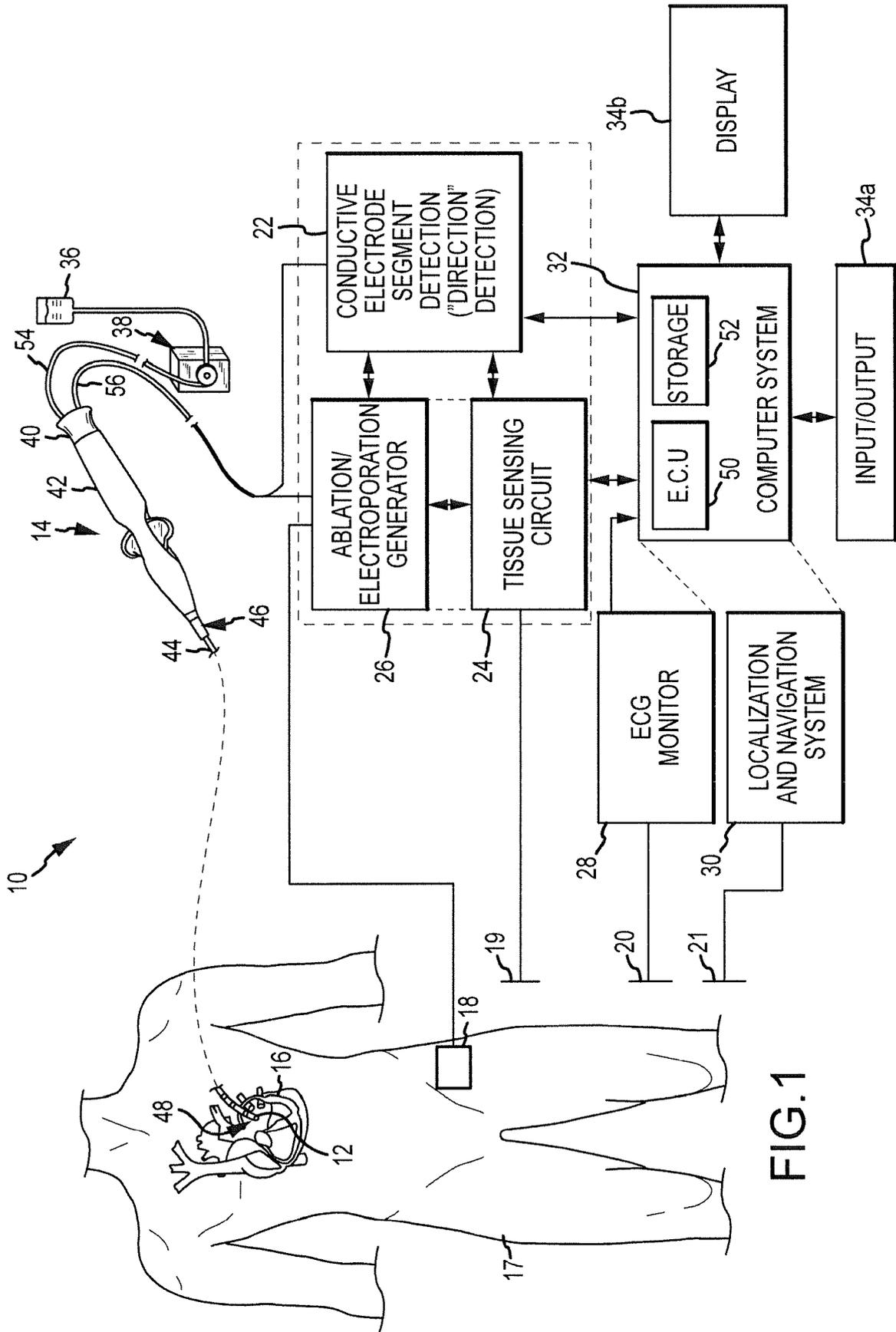


FIG.1

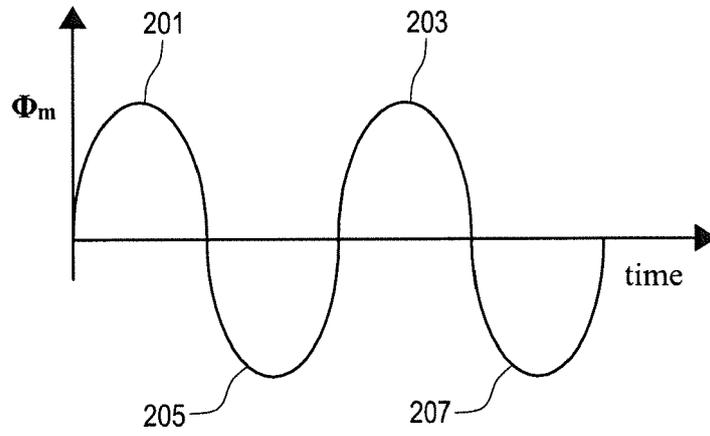


FIG. 2A

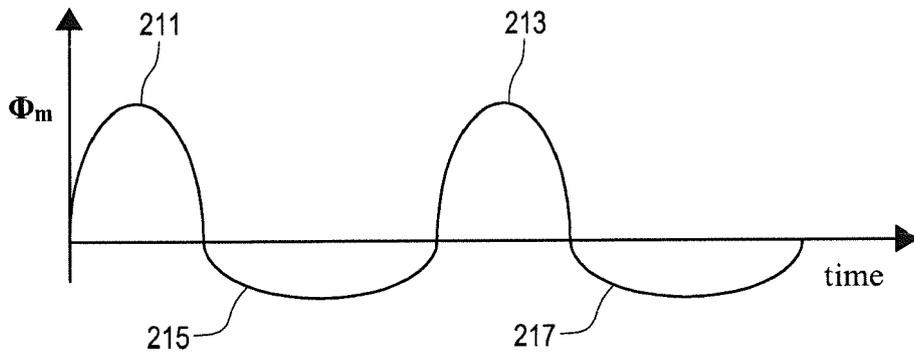


FIG. 2B

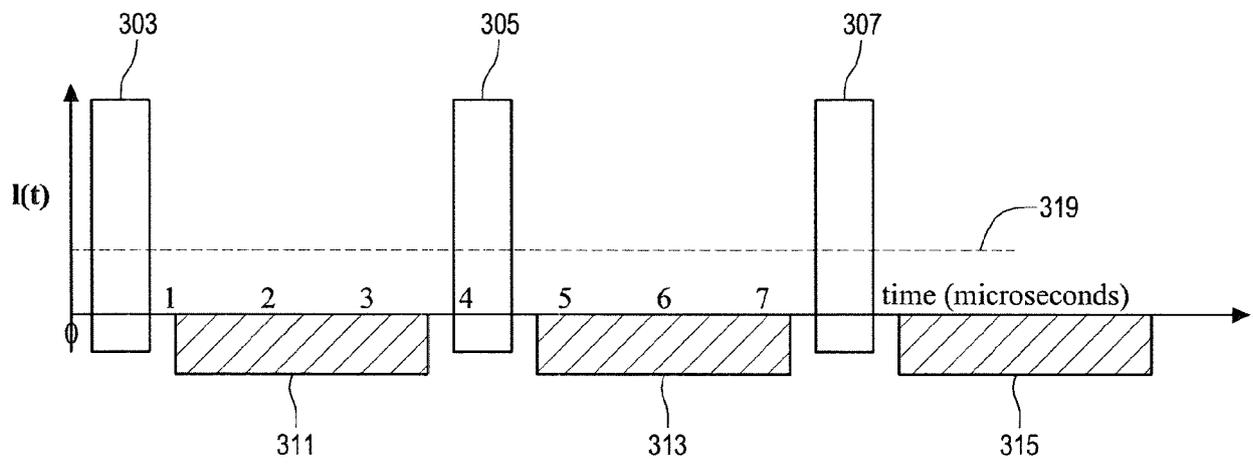


FIG. 3

REFERENCES CITED IN THE DESCRIPTION

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