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- (71) **Applicant:** IOWA APPROACH INC. [US/US]; 3715 Haven Ave., Menlo Park, CA 94025 (US).
- (72) **Inventor:** MICKELSON, Steven R.; 451 Hawkeye Dr., Iowa City, Iowa 52246 (US).
- (74) **Agents:** TALBOT, C. Scott et al.; Cooley LLP, 1299 Pennsylvania Ave., Suite 700, Washington, District of Columbia 20004 (US).
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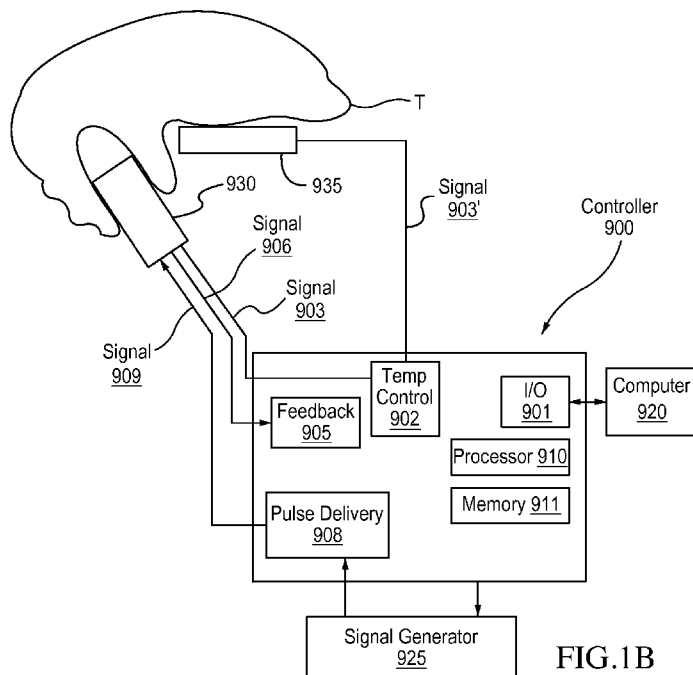


FIG.1B

(57) **Abstract:** Catheter systems, tools and methods are disclosed for the selective and rapid application of DC voltage pulses to drive irreversible electroporation for minimally invasive transurethral prostate ablation. In one embodiment, a switch unit is used to modulate and apply voltage pulses from a cardiac defibrillator, while in another, the system controller can be configured to apply voltages to an independently selected multiplicity or subsets of electrodes. Devices are disclosed for more effective DC voltage application including the infusion of cooled fluid to elevate the irreversible electroporation threshold of urethral wall tissue and to selectively ablate regions of prostate tissue alone.

**METHOD AND APPARATUS FOR RAPID AND SELECTIVE TRANSURETHRAL
TISSUE ABLATION**

Cross-Reference to Related Applications

[1001] This application claims benefit of priority to U.S. Provisional Application Serial No. 61/997,868, entitled “Methods and Apparatus for Rapid and Selective Transurethral Tissue Ablation,” filed June 12, 2014, which is incorporated herein by reference in its entirety.

Background

[1002] The embodiments described herein relate generally to medical devices for therapeutic electrical energy delivery, and more particularly to the surgical specialty of urology. Specifically, systems and methods for delivering electrical energy in the context of ablating tissue rapidly and selectively in minimally invasive transurethral clinical therapies by the application of suitably timed pulsed voltages that generate irreversible electroporation of cell membranes. Such irreversible electroporation can possibly be generated in conjunction with the application of disclosed means of enhancing electroporation efficacy.

[1003] Transurethral resection of the prostate (TURP) remains the gold standard for treating benign prostatic hypertrophy (BPH). Alternatives to surgical resection are ablation of tissues using thermal-based destruction of tissue using multiple forms of energy (laser, microwave, radiofrequency ablation etc.). The most common postoperative complication with known transurethral procedures is urethral stricture, occurring in approximately 4.4% of patients overall. Furthermore known transurethral procedures indiscriminately resect or ablate urethral epithelium in the process of de-bulking the prostate tissues. The urethral injury contributes to the recovery time and morbidity of the acute procedure.

[1004] In the past decade or two the technique of electroporation has advanced from the laboratory to clinical applications, while the effects of brief pulses of high voltages and large electric fields on tissue has been investigated for the past forty years or more. It has been known that the application of brief high DC voltages to tissue, thereby generating locally high electric fields typically in the range of hundreds of Volts/centimeter can disrupt cell membranes by generating pores in the cell membrane. While the precise mechanism of this electrically-driven pore generation or electroporation is not well understood, it is thought that

the application of relatively large electric fields generates instabilities in the lipid bilayers in cell membranes, causing the occurrence of a distribution of local gaps or pores in the membrane. If the applied electric field at the membrane is larger than a threshold value, the electroporation is irreversible and the pores remain open, permitting exchange of material across the membrane and leading to apoptosis or cell death. Subsequently the tissue heals in a natural process.

[1005] Historically, known direct current ablation techniques were pioneered in cardiovascular catheter-based ablation. More recently these techniques have been applied for the treatment of solid tumors with a clinical tool that employed very short impulses. The application of known ablation techniques to solid tumors on other applications, however, has not included selectively targeting tissue for irreversible electroporation ablation. Specifically, tissue susceptibility to irreversible cell injury from strong brief pulses of electricity depends on a number of important variables. Factors include: cell size, geometry, and orientation within the electric field, the constitution of the cell membrane and organelles, and local temperature. While pulsed DC voltages are known to drive electroporation under the right circumstances, the examples of electroporation applications in medicine and delivery methods described in the prior art do not discuss specificity and rapidity of action.

[1006] Thus, there is a need for selective energy delivery for electroporation and its modulation in various tissue types as well as pulses that permit rapid action and completion of therapy delivery. There is also a need for more effective generation of voltage pulses and control methods, as well as appropriate devices or tools addressing a variety of specific clinical applications, particularly in minimally invasive applications. Such more selective and effective electroporation delivery methods can broaden the areas of clinical application of electroporation including therapeutic treatment of a variety of cardiac arrhythmias, tissue ablation, and transurethral applications.

Summary

[1007] The embodiments described herein address the need for tools and methods for rapid and selective application of irreversible electroporation therapy as well as pulse generation and methods in the context of transurethral applications such as in the minimally invasive treatment of benign prostate hyperplasia. In some embodiments [FILL IN]

Brief Description of the Drawings

[1008] FIG. 1A is a schematic illustration of an irreversible electroporation system that includes a DC voltage/signal generator, a controller unit that is configurable to apply voltages to selected subsets of electrodes with independent subset selections for anode and cathode and that is connected to a computer, and one or more medical devices connected to the controller.

[1009] FIG. 1B is a schematic illustration of an irreversible electroporation system that includes a DC voltage/signal generator and a controller according to an embodiment.

[1010] FIG. 2 is a schematic illustration of a waveform generated by the irreversible electroporation system according to an embodiment, showing a balanced square wave.

[1011] FIG. 3 is a schematic illustration of a waveform generated by the irreversible electroporation system according to an embodiment, showing a balanced biphasic square wave.

[1012] FIG. 4 is a schematic illustration of a waveform generated by the irreversible electroporation system according to an embodiment, showing a progressive balanced biphasic square wave.

[1013] FIG. 5 is a schematic illustration of a distal portion of a catheter according to an embodiment, showing two distal electrodes and a lumen for transfer of fluid through the catheter.

[1014] FIG. 6 is a schematic illustration of a distal portion of a catheter according to an embodiment in a tubular anatomy, where two electrodes with the roles of cathode and anode are shown, along with a schematic depiction of the electric field in the region between the electrodes.

[1015] FIG. 7 is a schematic illustration of a distal portion of a catheter according to an embodiment, where multiple electrodes are shown with their various respective roles of anodes or cathodes, along with a schematic depiction of the electric field in the regions between the electrodes.

[1016] FIG. 8 is a schematic illustration of a distal portion of the catheter shown in FIG. 7, where multiple electrodes are shown along with simulation results for isomagnitude contours of electric field lines around the distal portion of the catheter.

[1017] FIG. 9 is an illustration of a catheter according to an embodiment with a series of lateral ablation electrodes, lateral ports for circulation of cooling fluid, and a distal balloon for holding the catheter distal tip firmly in the bladder.

[1018] FIG. 10 is an illustration of a cross section of the shaft of the catheter shown in FIG. 9, with a multiplicity of lumens for circulation of cooling fluid, draining of the bladder, electrode leads, and distal balloon inflation.

[1019] FIG. 11 is a schematic depiction of electric field lines around the cross section of a catheter according to an embodiment with a series of lateral ablation electrodes.

[1020] FIG. 12 is a schematic illustration of the cross section of a catheter according to an embodiment with a series of lateral ablation electrodes located within a urethra surrounded by prostate tissue, with cooling fluid infused from lateral ports filling an annular space in the urethra.

[1021] FIG. 13 is an illustration of a system for selective prostate tissue electroporation ablation according to an embodiment, including an ablation catheter with ports for cooling fluid infused into the urethra to maintain the urethral tissue lining at a relatively low temperature, and a trans-rectal probe inserted into the rectum and placed in apposition to the prostate and incorporating means for delivery of thermal energy to prostate tissue in order to maintain it at a relatively high temperature.

[1022] FIG. 14 is an illustration of an electroporation ablation catheter according to an embodiment, showing a series of lateral electrodes with ports incorporated for circulation of cooling fluid, and including a distal balloon and a distal tip electrode.

[1023] FIG. 15 is an illustration of an electroporation ablation catheter according to an embodiment, showing a series of ring electrodes, a series of lateral ports, and including a distal balloon and a distal tip electrode.

[1024] FIG. 16 is an illustration of an electroporation ablation catheter according to an embodiment with a series of ring electrodes, lateral ports for cooling fluid circulation and a

distal tip electrode, showing a cut-away cross section view of the catheter shaft, and including a multiplicity of lumens for circulation of cooling fluid, draining of the bladder, electrode leads, and distal balloon inflation.

[1025] FIG. 17 is an illustration of an electroporation ablation catheter according to an embodiment, showing a long flexible electrode, a series of lateral ports, and including a distal balloon and a distal tip electrode.

[1026] FIG. 18 is an illustration of an electroporation ablation catheter according to an embodiment, with a long flexible electrode, lateral ports for cooling fluid circulation and a distal tip electrode, showing a cut-away cross section view of the catheter shaft, and including a multiplicity of lumens for circulation of cooling fluid, draining of the bladder, electrode leads, and distal balloon inflation.

[1027] FIG. 19 is an illustration of left and right lateral views of an electroporation ablation catheter according to an embodiment with a long flexible electrode and a series of lateral ports.

[1028] FIG. 20 is a schematic illustration of a device and electroporation system according to an embodiment for transurethral ablation with a defibrillator voltage input.

[1029] FIG. 21 is a schematic illustration of a device and electroporation system according to an embodiment for transurethral ablation with a defibrillator voltage input and a cooled fluid pump for pumping cold fluid through the device.

Detailed Description

[1030] Systems and methods for electroporation to ablate enlarged prostate tissue in a selective fashion are described herein. The embodiments described herein result in well-controlled and specific delivery of electroporation in an efficacious manner. Specifically, the systems and methods described herein produced the desired results while ensuring at the same time that delicate epithelial tissue in and around the urethral wall is not damaged.

[1031] The embodiments described herein account for the differences in irreversible ablation threshold by creating a local temperature gradient that protects urethral epithelium (cooling it to raise the threshold electric field for ablation) and heating the target prostate

tissue (warming it to make it more susceptible to ablation). In this manner, the targeted prostate tissue can be selectively ablated while leaving the urethra intact and unaffected. As described above, strong exogenous electrical fields can ablate tissue without significantly disrupting the extracellular matrix. The inflammatory response is relatively modest when compared to ablation from thermal injury. The proposed prostate ablation system exploits the tissue-specific susceptibility differences between the transitional epithelial cells of the urethra and the prostate tissue

[1032] In some embodiments, an apparatus includes an electrode controller configured to be operably coupled to a voltage pulse generator and a catheter. The voltage pulse generator is configured to produce a pulsed voltage waveform. The catheter includes a plurality of electrodes. The electrode controller is implemented in at least one of a memory or a processor, and includes a feedback module, a thermal control module and a pulse delivery module. The feedback module is configured to determine a temperature of a target tissue. The thermal control module is configured to produce a signal to control a cooling fluid to the catheter based on the temperature of the target tissue. The pulse delivery module is configured to deliver an output signal associated with the pulsed voltage waveform to the plurality of electrodes, and is further configured to shunt an excess current associated with the pulsed voltage waveform

[1033] In some embodiments, an apparatus includes an electrode controller configured to be operably coupled to a voltage pulse generator, a catheter and a heater. The voltage pulse generator is configured to produce a pulsed voltage waveform. The catheter includes a plurality of electrodes. The electrode controller is implemented in at least one of a memory or a processor, and includes a thermal control module and a pulse delivery module. The thermal control module is configured to produce a first signal to control a cooling fluid to the catheter. The thermal control module is configured to produce a second signal to control a temperature of a heater. The pulse delivery module configured to deliver an output signal associated with the pulsed voltage waveform to the plurality of electrodes. The pulse delivery module is further configured to shunt an excess current associated with the pulsed voltage waveform.

[1034] In some embodiments, a method includes receiving, at a feedback module of an electrode controller, a temperature signal associated with a temperature of a urethral wall against which a medical catheter is disposed. The catheter includes a plurality of

electrodes. A control signal based on the temperature signal is delivered to a cooling unit to produce a flow of cooling fluid to the catheter. An output signal associated with a pulsed voltage waveform is delivered to the plurality of electrodes.

[1035] In some embodiments, a non-transitory processor readable medium storing code representing instructions to be executed by a processor includes code to cause the processor to receive a temperature signal associated with a temperature of a urethral wall against which a medical catheter is disposed. The medical catheter including a plurality of electrodes. The code further includes code to produce a control signal to a cooling unit to produce a flow of cooling fluid to the catheter. The control signal based on the temperature signal. The code further includes code to deliver an output signal associated with the pulsed voltage waveform to the plurality of electrodes when the target tissue is at the target temperature.

[1036] In some embodiments, a system includes a pulse generator unit, a controller unit, a flexible medical device and a fluid pump. The pulse generator unit is configured to produce a pulsed voltage waveform. The controller unit is connected to the pulse generator unit, and is configured to modulate pulses from the generator unit. The controller unit includes shunt circuitry configured to shunt excess current. The controller unit includes a thermal control module. The flexible medical device includes a plurality of electrodes and defines a series of ports through which a cooling fluid can flow. The flexible medical device is configured to be connected to the controller unit such that a voltage signal associated with the pulsed voltage waveform can be conveyed to the plurality of electrodes. The fluid pump is configured to produce the cooling flow in response to a cooling signal produced by the thermal control module of the controller unit. In some embodiments, the system optionally includes a trans-rectal probe including a probe head having a heater. The heater is configured to heat a portion of a prostate tissue in response to a cooling signal produced by the thermal control module of the controller unit.

[1037] In some embodiments, a system or method includes the use of temperature to selectively ablate tissue as the threshold of irreversible electroporation is temperature-dependent, for example with the use of pulses of cold fluid irrigation in the form of saline fluid. In this manner, epithelial tissue in the region of the urethral wall can be left intact, while at the same time the ablation is effectively applied only to deeper tissue structures adjacent to the urethral wall. The delivery of cold fluid can be suitably pulsed in order to ensure that only epithelial tissue is cooled while deeper tissue is not substantively cooled.

Surprisingly, in some embodiments, the pulses of fluid flow can involve periodical infusions of warm fluid in time intervals between voltage pulses. In one embodiment, the control of fluid pulse and temperature parameters is also programmable.

[1038] In some embodiments, the temperature of the transurethral probe can be modulated by other suitable methods such as a closed-loop coolant, thermoelectric transduction, and/or resistive heating coils. A trans-rectal probe could be added to the apparatus to accentuate the delivery of thermal energy (radiant heat, infrared, microwave, ultrasound etc.). Using a two-probe technique the rectal probe could be arranged as a dedicated heating probe and the intra-urethral device as a dedicated cooling source.

[1039] The timing and intensity of thermal delivery are delivered in a manner to optimize the local tissue thermal environment. The goal is to maximally cool the tissues of the urethra and bladder that would be exposed to the ablation impulse while warming the targeted tissues of the prostate. The most direct way to achieve this is to start the cycle with warm irrigation or radiant energy to allow heat transfer into the surrounding prostate tissues followed by a short phase of cooling. The longer first phase would produce a relative steady state increase in the prostate tissue above the normal body temperature but not high enough to cause thermal tissue injury. The second, shorter phase delivers cooling to the local urethra and bladder in such a way as to quickly drop the local tissue temperature below normal body temperature. The ablation impulse would be delivered into tissue with a thermal gradient favoring preservation of the epithelial urethra while increasing susceptibility of the prostate tissues.

[1040] In some embodiments, an irreversible electroporation system is disclosed that includes a DC voltage/signal generator and a controller. Further, the controller is capable of applying control inputs with possibly programmable voltage pulse parameters as well as programmable selection of electrodes as cathodes or anodes. The generator can output waveforms that can be selected to generate a sequence of voltage pulses in either monophasic or biphasic forms and with either constant or progressively changing amplitudes. Methods of control and DC voltage application from a generator capable of selective excitation of sets of electrodes are disclosed.

[1041] In some embodiments, a method includes the treatment of benign prostatic hyperplasia. In one embodiment, a standard defibrillator can be utilized together with a

switch to selectively apply a portion of the voltage pulse generated by the defibrillator unit, while excessive current is shunted away with a suitable shunt circuit.

[1042] The cooling irrigation fluid for any of the devices, systems and methods described herein can be any biocompatible fluid. In some embodiments, the current transfer properties of the fluid are of significant importance, and thus the irrigation fluid is formulated to facilitate the methods described herein. The irrigation used in the cooling phase can have a high electrolyte content (normal saline for example) with the possible inclusion of other biocompatible compounds to facilitate ablation and reduce local injury.

[1043] In some embodiments, the irreversible electroporation system described herein includes a DC voltage/signal generator and a controller unit for applying voltage pulses to electrodes. In one embodiment, the signal generator is capable of being configured to apply voltages to a selected multiplicity or a subset of electrodes on a transurethral minimally invasive catheter device. The controller is additionally capable of being programmable for voltage pulse parameters. In one embodiment where the device through which voltage pulses are applied also carries cooled fluid, the controller unit can also control fluid flow or pulse rate and fluid temperature.

[1044] The DC voltage is applied in brief pulses sufficient to cause irreversible electroporation and can be in the range of 0.5 kV to 10 kV and more preferably in the range 1 kV to 2.5 kV, so that a threshold electric field value in the range of 200 - 1000 Volts/cm is effectively achieved in the prostate tissue to be ablated. In one embodiment, the DC voltage value is selected directly by a user from a suitable dial, slider, touch screen, or any other user interface. The DC voltage pulse also results in a current flowing between the anode and cathode electrodes in the distal region of the catheter device that is inserted into the patient urethra, with the current entering the prostate tissue from the anode(s) and returning back through the cathode electrodes. The forward and return current paths (leads) are both inside the catheter. Areas of prostate tissue where the electric field is sufficiently large for irreversible electroporation are ablated during the DC voltage pulse application.

[1045] As used in this specification, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, the term “a member” is intended to mean a single member or a combination of members, “a material” is intended to mean one or more materials, “a processor” is intended to mean a single processor

or multiple processors; and "memory" is intended to mean one or more memories, or a combination thereof.

[1046] As used herein, the terms "about" and "approximately" generally mean plus or minus 10% of the value stated. For example, about 0.5 would include 0.45 and 0.55, about 10 would include 9 to 11, about 1000 would include 900 to 1100.

[1047] A schematic diagram of the electroporation system according to an embodiment in one embodiment is shown in FIG. 1A. A DC voltage/signal generator 23 is driven by a controller unit 21 that interfaces with a computer device 24 by means of a two-way communication link 29. The controller can perform channel selection and routing functions for applying DC voltages to appropriate electrodes that have been selected by a user or by the computer 24, and apply the voltages via a multiplicity of leads (shown collectively as 26) to a catheter device 22. The catheter device 22, and any of the catheter devices described herein can be similar to the ablation catheters described in PCT Publication No. WO2014/025394, entitled "Catheters, Catheter Systems, and Methods for Puncturing Through a Tissue Structure," filed on March 14, 2013 ("the '394 PCT Application), which is incorporated herein by reference in its entirety.

[1048] Some leads from the controller 21 could also carry control signals to drive pulsatile fluid flow through the device and/or for fluid temperature control (not shown). The catheter device can also possibly send back information such as temperature data from other sensors back to the controller 21 as indicated by the data stream 25, possibly on separate leads. While the DC voltage generator 23 sends a DC voltage to the controller 21 through leads 27, the voltage generator is driven by control and timing inputs 28 from the controller unit 21. Multiple DC voltage pulses can be applied in a pulse train to ensure that sufficient tissue ablation has occurred. Further, the user can repeat the delivery of irreversible electroporation over several distinct pulse trains for further confidence.

[1049] In some embodiments, the electrode controller can include one or more modules and can automatically control the flow of fluid through a catheter (e.g., to produce a pulsed flow or the like), control heating of a particular portion of target tissue (e.g., the prostate), adjust a characteristic of the voltage waveform, or the like. For example, FIG. 1B shows an electroporation system according to an embodiment that includes an electrode controller 900 and a signal generator 925. In some embodiments, the signal generator 925 can be a cardiac

defibrillator device. The electrode controller 900 is coupled to a computer 920 or other input / output device, and is configured to be operably coupled to a medical device 930. The medical device 930 can be one or more of the catheters of the types shown and described herein. Further the medical device 930 can be coupled to, disposed about and/or in contact with a target tissue T. For example, in some embodiments, the medical device can be disposed within a urethra of a patient. In this manner, as described herein, the electroporation system, including the electrode controller 900 and the signal generator 925, can deliver voltage pulses to the target tissue for therapeutic purposes.

[1050] Moreover, in some embodiments, the electrode controller 900 is optionally configured to be operably coupled to a medical device 935 that is distinct from the medical device 930. For example, the electrode controller 900 can optionally be coupled to a trans-rectal probe that includes a mechanism for delivering heat to a portion of the target tissue (e.g., the prostate).

[1051] The controller 900 can include a memory 911, a processor 910, and an input / output module (or interface) 901. The controller 900 can also include a temperature control module 902, a feedback module 905, and a pulse delivery module 908. The electrode controller 900 is coupled to a computer 920 or other input / output device via the input / output module (or interface) 901.

[1052] The processor 910 can be any processor configured to, for example, write data into and read data from the memory 911, and execute the instructions and/or methods stored within the memory 911. Furthermore, the processor 910 can be configured to control operation of the other modules within the controller (e.g., the temperature control module 902, the feedback module 905, and the pulse delivery module 908). Specifically, the processor 910 can receive a signal including user input, temperature data, distance measurements or the like and determine a set of electrodes to which voltage pulses should be applied, the desired timing and sequence of the voltage pulses and the like. In other embodiments, the processor 910 can be, for example, an application-specific integrated circuit (ASIC) or a combination of ASICs, which are designed to perform one or more specific functions. In yet other embodiments, the microprocessor can be an analog or digital circuit, or a combination of multiple circuits.

[1053] The memory device 911 can be any suitable device such as, for example, a read only memory (ROM) component, a random access memory (RAM) component, electronically programmable read only memory (EPROM), erasable electronically programmable read only memory (EEPROM), registers, cache memory, and/or flash memory. Any of the modules (the temperature control module 902, the feedback module 905, and the pulse delivery module 908) can be implemented by the processor 910 and/or stored within the memory 911.

[1054] As shown, the electrode controller 900 operably coupled to the signal generator 925. In some embodiments, the signal generator can be a cardiac defibrillator. The signal generator includes circuitry, components and/or code to produce a series of DC voltage pulses for delivery to electrodes included within the medical device 930. For example, in some embodiments, the signal generator 925 can be configured to produce a biphasic waveform having a pre-polarizing pulse followed by a polarizing pulse. The signal generator 925 can be any suitable signal generator of the types shown and described herein.

[1055] The pulse delivery module 908 of the electrode controller 900 includes circuitry, components and/or code to deliver an output signal associated with the pulsed voltage waveform produced by the signal generator 925. This signal (shown as signal 909) can be any signal of the types shown and described herein, and can be of a type and/or have characteristics to be therapeutically effective. In some embodiments, the pulse delivery module 908 receives input from other portions of the system, and can therefore send the signal 909 to the appropriate subset of electrodes, as described herein.

[1056] The electrode controller 900 includes the temperature control module 902. The temperature control module 902 includes circuitry, components and/or code to produce a control signal (identified as signal 903) that can be delivered to the device 935 and/or a control signal (identified as signal 903') that can be delivered to either a coolant supply (not shown) or to the medical device 930. In this manner, the temperature control module 902 can facilitate heating of a first portion of the tissue (e.g., via the device 935) and/or cooling of a second portion of the tissue T (e.g., the urethral walls).

[1057] In some embodiment, the ablation controller and signal generator can be mounted on a rolling trolley, and the user can control the device using a touchscreen interface that is in the sterile field. The touchscreen can be for example an LCD touchscreen in a plastic

housing mountable to a standard medical rail or post and can be used to select the electrodes for ablation and to ready the device to fire. The interface can for example be covered with a clear sterile plastic drape. In one embodiment, the operator can select the electrodes involved in the voltage pulse delivery. For example, in one embodiment the operator can select electrodes from the touchscreen with appropriate graphical buttons. In one embodiment, the ablation pulse train can be initiated by holding down a hand-held trigger button that is in the sterile field, possibly with the pulse train parameters (such as for example individual pulse parameters, number of pulses in the pulse train) having been programmed. The hand-held trigger button can be illuminated red to indicate that the device is “armed” and ready to ablate. The trigger button can be compatible for use in a sterile field and when attached to the controller can be illuminated a different color, for example white. When the device is firing, the trigger button flashes in sequence with the pulse delivery in a specific color such as red. The waveform of each delivered pulse is displayed on the touchscreen interface. While a touchscreen interface is one embodiment, other user interfaces can be used by a user to control the system such as for example a graphical display on a laptop or monitor display controlled by a standard computer mouse or joystick.

[1058] In some embodiments, the system (generator and controller) according to an embodiment can deliver rectangular-wave pulses with a peak maximum voltage of about 5 kV into a load with an impedance in the range of 30 Ohm to 3000 Ohm for a maximum duration of 200 μ s, with a 100 μ s maximum duration being still more preferred. Pulses can be delivered in a multiplexed and synchronized manner to a multi-electrode catheter inside the body with a duty cycle of up to 50 % (for short bursts). The pulses can generally be delivered in bursts, such as for example a sequence of between 2 and 10 pulses interrupted by pauses of between 1 ms and 1000 ms. The multiplexer controller is capable of running an automated sequence to deliver the impulses/impulse trains (from the DC voltage signal/impulse generator) to the tissue target within the body. The controller system is capable of switching between subsets/nodes of electrodes located on the single use catheter.

[1059] The controllers and generators described herein can output waveforms that can be selected to generate a sequence of voltage pulses in either monophasic or biphasic forms and with either constant or progressively changing amplitudes. FIG. 2 shows a rectangular wave pulse train where the pulses 101 have a uniform height or maximum voltage. FIG. 3 shows an example of a balanced biphasic rectangular pulse train, where each positive voltage pulse

such as 103 is immediately followed by a negative voltage pulse such as 104 of equal amplitude and opposite sign. While in this example the biphasic pulses are balanced with equal amplitudes of the positive and negative voltages, in other embodiments an unbalanced biphasic waveform could also be used as may be convenient for a given application. In some embodiments, generally biphasic voltage pulses are utilized to drive irreversible electroporation ablation in prostate tissue with the device and system of the present disclosure.

[1060] Yet another example of a waveform or pulse shape that can be generated by the system is illustrated in FIG. 4, which shows a progressive balanced rectangular pulse train, where each distinct biphasic pulse has equal-amplitude positive and negative voltages, but each pulse such as 107 is larger in amplitude than its immediate predecessor 106. Other variations such as a progressive unbalanced rectangular pulse train, or indeed a wide variety of other variations of pulse amplitude with respect to time can be conceived and implemented by those skilled in the art based on the teachings herein.

[1061] The time duration of each irreversible electroporation rectangular voltage pulse could lie in the range from 1 nanosecond to 10 milliseconds, with the range 10 microseconds to 1 millisecond being more preferable and the range 50 microseconds to 300 microseconds being still more preferable. The time interval between successive pulses of a pulse train could be in the range of 10 microseconds to 1 millisecond, with the range 50 microseconds to 300 microseconds being more preferable. The number of pulses applied in a single pulse train (with delays between individual pulses lying in the ranges just mentioned) can range from 1 to 100, with the range 1 to 10 being more preferable. As described in the foregoing, a pulse train can be driven by a user-controlled switch or button, in one embodiment preferably mounted on a hand-held joystick-like device. In one mode of operation a pulse train can be generated for every push of such a control button, while in an alternate mode of operation pulse trains can be generated with a pre-determined delay between successive pulse trains, for as long as the user-controlled switch or button is engaged by the user.

[1062] A catheter device for distal ablation with the electroporation system according to an embodiment is shown schematically in FIG. 5. The ablation catheter with shaft 162 has two electrodes disposed in the distal section of the catheter, with a relatively proximally placed electrode 164 of length L_1 exposed on the catheter shaft and a relatively distally placed electrode 163 of length L_2 also exposed on the catheter shaft. The catheter shaft is

made of a material with high dielectric strength such as for example a polymer comprising Teflon. Both electrodes are metallic, and in one embodiment the anode could be poly-metallic in construction, for example comprising regions of Titanium and regions of Platinum. The catheter has a lumen shown as 161 and in one embodiment the distal tip portion 160 could have a diameter that is smaller than that at the relatively proximal shaft section 162, so that the tip is tapered, making for easier insertion into the urethra. In one embodiment the electrode lengths L_1 and L_2 could be different, while in an alternate embodiment they are closely similar in length. The catheter is inserted via the urethra and positioned with its distal portion abutting prostate tissue in the region of which tissue ablation is desired.

[1063] FIG. 6 schematically illustrates a catheter device with shaft 150 and distal electrodes 151 and 152 disposed longitudinally in a urethral vessel in a prostate tissue region, with urethral walls indicated by dashed lines, with inner vessel wall 153 and outer vessel wall 154 respectively. Thus the layer of tissue between lines 153 and 154 is epithelial tissue, while the tissue outside the outer vessel wall is prostate tissue in this schematic depiction. When the electrodes are activated with a voltage applied across them, an electric field is generated in the region around and between the electrodes, depicted schematically by field lines 155 in FIG. 6. In some embodiments, the catheter lumen carries a fluid flow of cooled fluid depicted by arrows 157; the fluid can be for instance a saline fluid which is harmlessly disposed of by the body. The temperature of the saline fluid can be about 55 degrees Fahrenheit or lower.

[1064] In some embodiments, the time for which a cold temperature is maintained at the patient contacting catheter surface is monitored and varied, so that the cooling control is applied in time in a pulse-like format. This is done in order to maintain a surface layer of tissue at a suitably low or cold temperature, while ensuring that deeper regions of tissue undergo no more than marginal cooling. For example, the thermal diffusivity D of skin tissue is known to be in the range of $0.11 \text{ mm}^2/\text{s}$. From standard heat diffusion theory, in a time T the depth x to which a temperature change applied at the surface is propagated is given (in two dimensions) by $x \sim \sqrt{2DT}$. Thus, in 20 seconds of cooling, the depth x would be approximately 2 mm, which is about the thickness of skin tissue. In one mode of operation of the system according to an embodiment, the cooling of the electrodes is performed in discrete time intervals in the range of 10 seconds to 40 seconds, followed by a pulse train application,

the entire duration of the pulse train being in the range of less than about 8 seconds. Thus, the application of cooling could also be performed in pulses.

[1065] The urethral wall tissue in the region between dashed lines 153 and 154 in FIG. 6 is then always at a cold temperature during voltage pulse application. This increases its irreversible electroporation threshold, thereby maintaining its integrity with no ablation occurring in this zone. At the same time prostate tissue beyond the urethral wall, for example in the region denoted 158 in FIG. 6, undergoes irreversible electroporation due to the sufficiently large electric fields in this region. The next ablation in the same tissue region is performed, if necessary, after another cooling pulse is applied over a discrete time interval, and so on. In one method according to an embodiment, a heating pulse could follow a cooling pulse in order to ensure that the temperature in the interior of the tissue does not fall below a threshold value. Suitably cold saline could generally be infused in small quantities in each pulse, for example at a rate in the range of a few milliliters/second or less.

[1066] FIG. 7 schematically depicts one embodiment of the transurethral catheter device according to an embodiment with multiple electrodes in its distal region. In this example, the catheter shaft 175 has four electrodes 170, 171, 172 and 173 disposed in its distal region. With electrode 172 chosen as anode and the other electrodes as cathodes, with an applied voltage the resulting electric field lines are indicated schematically by 176. The resulting electric field intensity would be locally high in the approximate region schematically shown as the region 177 inside the dashed-line ellipse, and this would serve as a selected zone of ablation. It should be clear that by choosing different electrodes or electrode combinations as anodes or cathodes, the desired zone of ablation can be varied. In one embodiment, as before the catheter can have a lumen carrying a pulsed flow of cold fluid in order to increase the electroporation threshold of the urethral wall. In this manner, tissue outside the urethral wall can be selectively ablated while leaving the urethral wall itself unaffected. In one embodiment the catheter device can have at least one temperature sensor such as a thermistor or thermocouple disposed in the distal portion of the device for monitoring temperature.

[1067] Isomagnitude contours for electric field lines corresponding to the catheter described in the previous paragraph and depicted in FIG. 7 are illustrated in FIG. 8. As before, the catheter shaft 175 has four electrodes 170, 171, 172 and 173 disposed in its distal region. Given a set of electrode polarities and tissue/material properties, Maxwell's equations can be solved for the electric field in the region surrounding the catheter. Results

from such a computational simulation are illustrated in FIG. 8, where corresponding contours of equal electric field magnitude or isomagnitude contours were generated and are shown as contours 181 and 182 in FIG. 8. It is evident that the contours bulge outward preferentially near the source electrode 172. In this manner the treatment zone may be suitably tailored or customized as desired for the procedure at hand.

[1068] FIG. 9 is an illustration of an embodiment of an electroporation ablation catheter with a series of lateral ablation electrodes and a distal balloon. As shown in FIG. 9, the catheter has a through lumen 17 and a distal balloon 1 that is inflated from a port 4 through which for example a saline fluid is infused to expand the balloon. The catheter has a series of electrodes such as 3 arrayed in lateral pairs as shown in the top and bottom representations (rotated by 90 degrees about the catheter axis relative to each other) in FIG. 9, as well as a series of lateral ports 2 adjacent to respective electrodes. Electrodes leads 7 and 8 of opposite polarities are used to apply voltages of opposing polarities respectively on each electrode of a laterally opposing electrode pair. Proximal port 4 is used to infuse or withdraw saline or other fluid to expand or contract the distal balloon 1, while ports 5 and 6 are used for the circulation of cooling fluid (forward and backward flows). In use, the catheter is positioned in the urethra with the distal tip in the bladder; subsequently, the distal balloon is inflated, thereby holding the catheter in place within the urethra, with the region of catheter shaft with electrodes abutting prostate tissue. The through lumen 17 is used to drain the bladder as needed in the procedure. The series of electrodes on the device would be spaced with a separation between closest edges in the approximate range 1 mm to 7 mm. The catheter diameter would be approximately in the range of 2 mm; the small separation (approximately the catheter diameter) between opposing electrodes in a laterally opposed pair implies that a reduced voltage can be used to drive electroporation. The catheter shaft is constructed of flexible material such as Teflon that also has a suitably high dielectric strength.

[1069] As shown in FIG. 10, the cross section of the shaft of the catheter with lateral electrodes and lateral ports has a multiplicity of lumens. The central lumen 17 drains the bladder, while the electrode leads (of opposing polarities) pass through lumens 10 and 11. Lumen 16 carries saline or other fluid to inflate or deflate the distal balloon. Lumens 12 and 13 carry cooling fluid in one direction (forward, for example), while lumens 14 and 15 carry cooling fluid in an opposite direction (backward, for example), thereby in effect circulating cooling fluid through the lateral ports and maintaining a circulating saline pool in the urethra

around the electrodes. The cooling fluid can be for example saline fluid at a temperature in the range between approximately 50 degrees Fahrenheit and 75 degrees Fahrenheit, so that it is significantly colder than normal body temperature. The cooling fluid reduces the temperature of the epithelial tissue of the urethral wall, correspondingly increasing the threshold electric field for irreversible electroporation. In this situation, the electric field generated between the lateral electrodes leaves the urethral wall tissue unaffected, while the electric field in the region of prostate tissue can drive irreversible electroporation there.

[1070] FIG. 11 provides a schematic depiction of electric field lines around the cross section of a catheter with a series of lateral ablation electrodes. In FIG. 11, laterally opposing electrodes 3 are shown on the left and right sides of the catheter shaft cross section, and when a voltage is applied across the lateral electrode pair, corresponding electric field lines 20 are schematically shown in the illustration.

[1071] The geometry of the catheter disposed in the urethra is illustrated schematically in cross section in FIG. 12. The urethra has a urethral wall 32 and the ablation catheter 30 according to an embodiment is disposed within the urethral cross section. Cooling fluid 31 circulated through the catheter's lateral ports as described above serves to lower the temperature of the urethral wall 32 and generally forms an annular space around the catheter. The cooling fluid is delivered in brief pulses no more than approximately between 10 seconds and 40 seconds in duration, as described earlier. In this manner, while the urethral wall is rapidly cooled due to proximity with the cooling fluid during the application of electroporation voltage pulses, the prostate tissue 33 external to the urethra and just adjacent to it is not cooled very much, and is thus susceptible to irreversible electroporation by the electric field generated between the catheter electrodes. The delivery of electroporation voltage pulses is arranged to occur while the cooling fluid is in circulation to cool the urethral wall, with the delivery of cooling fluid itself occurring in flow pulses that are of a longer duration than the electroporation voltage pulses as described in the foregoing.

[1072] In some embodiments, the prostate ablation system can further include a trans-rectal probe inserted into the rectum and placed in apposition to the prostate, with the trans-rectal probe incorporating a means of thermal energy delivery for example in the form of focused ultrasound, radiant heat source, infrared source, thermoelectric heating source, or microwave source or other such means of thermal energy delivery that are known in the art. As shown in FIG. 13, the trans-rectal probe 508 is inserted into the rectum 507, and the probe

has a probe head 510 incorporating means for thermal energy delivery. The prostate 504 and the bladder 505 are indicated in FIG. 13, and the trans-urethral ablation catheter 501 is inserted into the urethra 503 by access through the penis 502. The ablation catheter has a distal balloon 506 that when inflated, as shown in FIG. 13, serves to lodge the distal portion of the catheter firmly within the bladder and thus the catheter itself firmly within the urethra with the ablation electrodes indicated as dots 511 positioned adjacent to the prostate.

[1073] The rectal probe 508 heats the prostate tissue by a relatively modest amount to stay within a safe range, generating a temperature increase preferably in the range of 3 to 10 degrees Fahrenheit. This thermal energy delivery could itself be pulsed, for example in pulses lasting between approximately 10 seconds and 60 seconds, depending on the mode of thermal energy delivery and the associated specific details of heat transfer to tissue. For example, in the case where the thermal energy is delivered by focused ultrasound by means of incorporating one or more ultrasound transducers and possibly ultrasound reflectors as well thereby generating a focal spot or focal zone for ultrasound within the prostate tissue, the local tissue temperature in the focal zone can be increased quite rapidly. The local tissue heating has the effect of decreasing the irreversible electroporation threshold electric field, thus making it possible to successfully ablate prostate tissue with generated electric fields that are not too large. In this case electric field values in the range of a few hundred Volts/cm would suffice to drive irreversible electroporation in the desired treatment zone in prostate tissue, while at the same time the cooled urethral wall (cooled with cooling fluid circulated through the ablation catheter) is left intact without being ablated.

[1074] Several variations of ablation catheter design or embodiment can be constructed as may be convenient from a manufacturing standpoint or for procedural ease of use. In one variation illustrated in FIG. 14, two views of an ablation catheter with fluid ports co-located with electrodes are shown in the top and bottom sketches (the two views differ by a 90 degree rotation about the catheter long axis). In this construction, the ablation catheter has a distal electrode 1 and a distal balloon 65, as well as a series of laterally opposed pairs of distal electrodes 3 incorporating fluid ports 2. The series of electrodes on the device would be spaced with a separation between closest edges in the approximate range 1 mm to 7 mm. Electrode leads 63 and 64 connect to electrodes on opposite lateral sides respectively. Fluid track or tube 60 carries fluid (for example, saline) to inflate or deflate the distal balloon 65, while fluid tubes 61 and 62 can support cooling fluid circulation flow in opposite directions

(for example, forward and backward respectively). The lateral fluid ports permit the circulation of cooling fluid; thus cooling fluid exits the ports on one side of the catheter (for example, the left side of the catheter as seen looking down from the distal end) and enters the ports on the opposite side of the catheter (for example, the right side of the catheter as seen looking down from the distal end). In this manner the annular space between the catheter and the inner wall of the urethra is filled with cooling fluid along the portion of the catheter shaft with the electrodes and fluid ports. Furthermore, the catheter can possibly incorporate a through lumen for evacuation or draining of the bladder.

[1075] In another alternate embodiment of the ablation catheter according to an embodiment, as shown in FIG. 15, the catheter can have a distal tip electrode and a distal balloon, as well as a series of ring electrodes 3 and lateral fluid ports 2 disposed along a distal portion of the catheter shaft. The lateral fluid ports are used for circulation of cooling fluid, as described in the foregoing, while the ring electrodes and the tip electrode are used to generate an electric field for ablation with suitable voltage pulses, as described above. The series of electrodes on the device would be spaced with a separation between closest edges in the approximate range 1 mm to 7 mm. FIG. 16 shows a cut-away view of such a catheter where fluid ports 5 are visible from the inside of the shaft, while the cross-section view provided illustrates a set or multiplicity of lumens. A central lumen 41 serves to drain the bladder, while lumens 43 and 46 are cooling fluid irrigation lumens carrying fluid flow in opposite directions (for example, forward and backward respectively). Lumen 44 carries fluid to inflate or deflate the distal balloon, while lumens 42 and 45 act as passages for electrode leads of opposite polarities respectively and possibly also for cooling fluid irrigation/circulation.

[1076] In yet another alternate embodiment, the ablation catheter can have, as illustrated in FIG. 17, a distal tip electrode, a distal balloon, a long flexible electrode 3 (for example, in the form of a long helical winding of metallic composition) and a set of lateral ports 2 on either side of the catheter for circulation of cooling fluid. The series of lateral ports on the device would be spaced with a separation between closest edges in the approximate range 1 mm to 7 mm. As shown in the cut-away view of such a catheter in FIG. 18, fluid ports 3 are visible from the inside of the shaft, while the cross-section view provided illustrates a set or multiplicity of lumens. A central lumen 50 serves to drain the bladder, while lumens 52 and 54 are cooling fluid irrigation lumens carrying fluid flow in opposite directions (for example,

forward and backward respectively). Lumen 55 carries fluid to inflate or deflate the distal balloon, while lumens 51 and 53 act as passages for electrode leads of opposite polarities respectively and possibly also for cooling fluid irrigation/circulation.

[1077] In still another alternate embodiment of ablation catheter shown in FIG. 19, left and right views of a catheter with proximal end 71 and distal end 72 are both shown for clarity (left and right views are marked L and R respectively), the catheter having a long flexible electrode 80 and lateral ports 6 for cooling fluid irrigation through the irrigation shaft 75 with lumen 77 for fluid irrigation as well as electrode leads. The distal electrode is not marked.

[1078] In the embodiments with a distal electrode, while the distal electrode can generally be either an anode or a cathode, in some embodiments it is a cathode, since this can reduce the likelihood of flash arcing. The various embodiments of ablation catheters described above can be used in Trans-Urethral Rectoscopy Procedures (TURP), where the tissue resection is performed by irreversible electroporation ablation. In such an application, as shown in FIG. 20, an ablation catheter device 401 with multiple electrodes is shown (two electrodes 402 and 403 marked in its distal portion are shown for schematic illustration purposes). The catheter in this embodiment can be connected to a pulse generator 409 in the form of a defibrillator unit, which could possibly be a standard commercial unit such as a Booker Box. The catheter can incorporate an IGBT switch, possibly disposed in the catheter handle 405. In some embodiments, the switch can even be mounted in a disposable unit or box 407 that connects to the catheter handle and interfaces with the defibrillator unit. In an alternate embodiment, the switch can be incorporated in the catheter handle. The switch unit is designed to operate in pulsed fashion so that for example only a discrete time interval of pulse, for example 700 microseconds of defibrillator output, is passed through the catheter in a set of discrete pulses. The switch unit also is capable of accepting a variety of DC voltage sources, and has an in-built shunt circuit to shed or shunt away excess current. In this manner, even a standard defibrillator could be used with the ablation catheter device described herein to generate irreversible electroporation. In particular, the ablation catheter device can be very beneficial in Trans-Urethral clinical applications such as TURP.

[1079] As shown in FIG. 21, in some embodiments the catheter handle 405 can further be connected to a fluid pump 413 capable of pumping cooled fluid such as cooled saline through the catheter. Preferably the pump is capable of delivering and controlling pulsatile fluid flow

wherein the fluid is delivered in pulses. In one embodiment the saline pump can deliver either cooled or heated or warmed fluid, while in another embodiment the saline pump can deliver cooled fluid while a trans-rectal probe with a means of inducing heating of prostate tissue is also used in the procedure. As indicated by the dashed lines between switch unit 407 and fluid pump 413, the switch unit can also drive control signals to the pump for setting fluid pulse control parameters such as fluid temperature and flow. Furthermore, when the ablation catheter is used in conjunction with a trans-rectal probe, the switch unit is capable of suitably timing or coordinating the delivery of cooling fluid through the catheter and thermal energy delivery via the rectal probe. In some embodiments the thermal energy delivery from the rectal probe is also performed in pulsed fashion.

[1080] In an alternate embodiment, instead of a defibrillator unit, the signal generator box 409 could comprise a programmable pulse generator of the types previously described herein. In a further alternate embodiment, such programmability (for example, of electrode selection) can be made from the switch unit 407, possibly through connection to a computer or other user interface. Further, in one embodiment sensed temperature data from the distal portion of the medical device (from a thermistor or thermocouple, for example) can be used to adjust the temperature of the saline fluid flow.

[1081] While various specific examples and embodiments of systems and tools for selective tissue ablation with irreversible electroporation were described in the foregoing for illustrative and exemplary purposes, it should be clear that a wide variety of variations and alternate embodiments could be conceived or constructed by those skilled in the art based on the teachings according to an embodiment. While specific methods of control and DC voltage application from a generator capable of selective excitation of sets of electrodes were disclosed, persons skilled in the art would recognize that any of a wide variety of other control or user input methods and methods of electrode subset selection etc. can be implemented without departing from the scope according to an embodiment. Likewise, while the foregoing described a range of specific tools or devices for more effective and selective DC voltage application for irreversible electroporation through fluid irrigation and catheter devices, other device constructions or variations could be implemented by one skilled in the art by employing the principles and teachings disclosed herein without departing from the scope according to an embodiment in a variety of medical applications.

[1082] Furthermore, while the present disclosure describes specific embodiments and tools involving irrigation with saline fluids and the use of temperature to selectively ablate tissue by taking advantage of the temperature-dependence of the threshold of irreversible electroporation, it should be clear to one skilled in the art that a variety of methods and devices for steady or pulsed fluid delivery, or for tissue or electrode cooling, or thermal energy delivery via a trans-rectal probe, could be implemented utilizing the methods and principles taught herein without departing from the scope according to an embodiment.

[1083] Accordingly, while many variations of methods and tools disclosed here can be constructed, the scope according to an embodiment is limited only by the appended claims.

Claims

1. An apparatus, comprising:
an electrode controller configured to be operably coupled to a voltage pulse generator configured to produce a pulsed voltage waveform and a catheter including a plurality of electrodes, the electrode controller implemented in at least one of a memory or a processor, the electrode controller including a feedback module, a thermal control module and a pulse delivery module, the feedback module configured to determine a temperature of a target tissue, the thermal control module configured to produce a signal to control a cooling fluid to the catheter based on the temperature of the target tissue, the pulse delivery module configured to deliver an output signal associated with the pulsed voltage waveform to the plurality of electrodes, the pulse delivery module further configured to shunt an excess current associated with the pulsed voltage waveform.
2. The apparatus of claim 1, wherein the voltage pulse generator unit is a cardiac defibrillator.
3. The apparatus of claim 1, wherein the pulse delivery module is configured to select at least a first electrode from the plurality of electrodes and a second electrode from the plurality of electrodes and deliver the output signal associated with the pulsed voltage waveform to the first electrode and the second electrode.
4. The apparatus of claim 1, wherein the pulse delivery module is configured to modulate a characteristic of the output signal, the characteristic including at least one of an amplitude of the output signal, a period of the output signal, or duration of the output signal.
5. The apparatus of claim 1, wherein the pulse delivery module is configured produce the output signal by incorporating intervals with zero voltage into voltage pulses from the voltage pulse generator.
6. The apparatus of claim 1, wherein the electrode controller is configured to interface with an external device to program at least one of an amplitude of the output signal, a period of the output signal, or a duration of the output signal.

7. The apparatus of claim 1, further comprising:
the catheter, a proximal end of the catheter including a handle, at least a portion of the electrode controller disposed within the handle.
8. The apparatus of claim 1, wherein the thermal control module is configured to produce the signal to control at least one of a flow of the cooling fluid or a temperature of the cooling fluid.
9. The apparatus of claim 1, wherein the thermal control module is configured to produce the signal to produce a pulsed flow of the cooling fluid.
10. The apparatus of claim 1, wherein:
the signal is a first signal;
the target tissue is a portion of a urethra; and
the thermal control module is configured to produce a second signal to control a temperature of a heater, the heater configured to heat a portion of a prostate tissue.
11. An apparatus, comprising:
an electrode controller configured to be operably coupled to a voltage pulse generator, a catheter and a heater, the voltage pulse generator configured to produce a pulsed voltage waveform, the catheter including a plurality of electrodes, the electrode controller implemented in at least one of a memory or a processor, the electrode controller including a thermal control module and a pulse delivery module, the thermal control module configured to produce a first signal to control a cooling fluid to the catheter, the thermal control module configured to produce a second signal to control a temperature of a heater, the pulse delivery module configured to deliver an output signal associated with the pulsed voltage waveform to the plurality of electrodes, the pulse delivery module further configured to shunt an excess current associated with the pulsed voltage waveform.
12. The apparatus of claim 11, wherein:
the catheter is configured to be disposed within a urethra such that the plurality of electrodes can supply voltage to a prostate; and
the heater is included in a trans-rectal probe.

13. The apparatus of claim 11, wherein the heater is an ultrasound heater, the second signal is configured to control a characteristic of ultrasound energy produced by the ultrasound heater.
14. The apparatus of claim 11, wherein the heater is an infrared heater, the second signal is configured to control a characteristic of infrared energy produced by the infrared heater.
15. The apparatus of claim 11, further comprising:
an inflation controller configured to be operably coupled to the catheter, the catheter including an expandable member, the inflation controller implemented in at least one of a memory or a processor, the inflation controller configured to produce an inflation signal to control an inflation fluid to the expandable member.
16. A method, comprising:
receiving, at a feedback module of an electrode controller, a temperature signal associated with a temperature of a urethral wall against which a medical a catheter is disposed, the catheter including a plurality of electrodes;
delivering a control signal to a cooling unit to produce a flow of cooling fluid to the catheter, the control signal based on the temperature signal; and
delivering an output signal associated with a pulsed voltage waveform to the plurality of electrodes.
17. The method of claim 16, wherein the delivering the output signal is performed when a temperature of the urethral wall is maintained below a body temperature.
18. The method of claim 16, wherein the control signal is associated with at least one of a flow of the cooling fluid or a temperature of the cooling fluid.
19. The method of claim 16, wherein the output signal is in a range between about 200 Volts and about 4000 Volts.
20. The method of claim 16, wherein the control signal is a first control signal, the method further comprising:
delivering a second control signal to a heater to heat a portion of a prostate tissue.

21. A non-transitory processor readable medium storing code representing instructions to be executed by a processor, the code comprising code to cause the processor to:

receive a temperature signal associated with a temperature of a urethral wall against which a medical catheter is disposed, the medical catheter including a plurality of electrodes;

produce a control signal to a cooling unit to produce a flow of cooling fluid to the catheter, the control signal based on the temperature signal; and

deliver an output signal associated with a pulsed voltage waveform to the plurality of electrodes when the target tissue is at the target temperature.

22. A system, comprising:

a pulse generator unit configured to produce a pulsed voltage waveform;

a controller unit connected to the pulse generator unit, the controller unit configured to modulate pulses from the generator unit, the controller unit including shunt circuitry configured to shunt excess current; the controller unit including a thermal control module;

a flexible medical device including a plurality of electrodes, the flexible medical device defining a plurality of ports through which a cooling fluid can flow, the flexible medical device configured to be connected to the controller unit such that a voltage signal associated with the pulsed voltage waveform can be conveyed to the plurality of electrodes;

a fluid pump configured to produce the cooling flow in response to a cooling signal produced by the thermal control module of the controller unit; and

a trans-rectal probe including a probe head having a heater, the heater configured to heat a portion of a prostate tissue in response to a cooling signal produced by the thermal control module of the controller unit.

23. The system of claim 22, wherein the heater is configured to produce a focused ultrasound energy pulse to heat the portion of the prostate tissue.

24. The system of claim 22, wherein the heater is configured to produce an infrared energy pulse to heat the portion of the prostate tissue.

25. The system of claim 22, wherein the catheter includes an expandable member configured to limit movement of catheter within the urethra.

26. An apparatus, comprising:
a catheter shaft defining a flow passage;
a plurality of electrodes coupled to a distal end portion of the catheter shaft;
a controller coupled to a proximal end portion of the catheter shaft, the controller configured to receive a voltage input from a pulse generator and produce a timed pulsed voltage waveform based on the voltage input to the plurality of electrodes, the controller configured to control a flow of fluid through the flow passage.
27. The apparatus of claim 26, wherein the pulse generator is a cardiac defibrillator.
28. The apparatus of claim 26, wherein the controller is disposable.
29. A method of producing irreversible electroporation, comprising:
positioning a catheter within a urethra such that each of a plurality of electrodes coupled to the catheter is in operable communication with a target tissue;
flowing a coolant flow through the catheter such that a temperature of a urethral wall is maintained at a target temperature;
heating, via a trans-rectal probe, a portion of a prostate tissue; and
applying at least one voltage pulse to the plurality of electrodes to generate an electric field for irreversible electroporation ablation in the region of the target tissue.

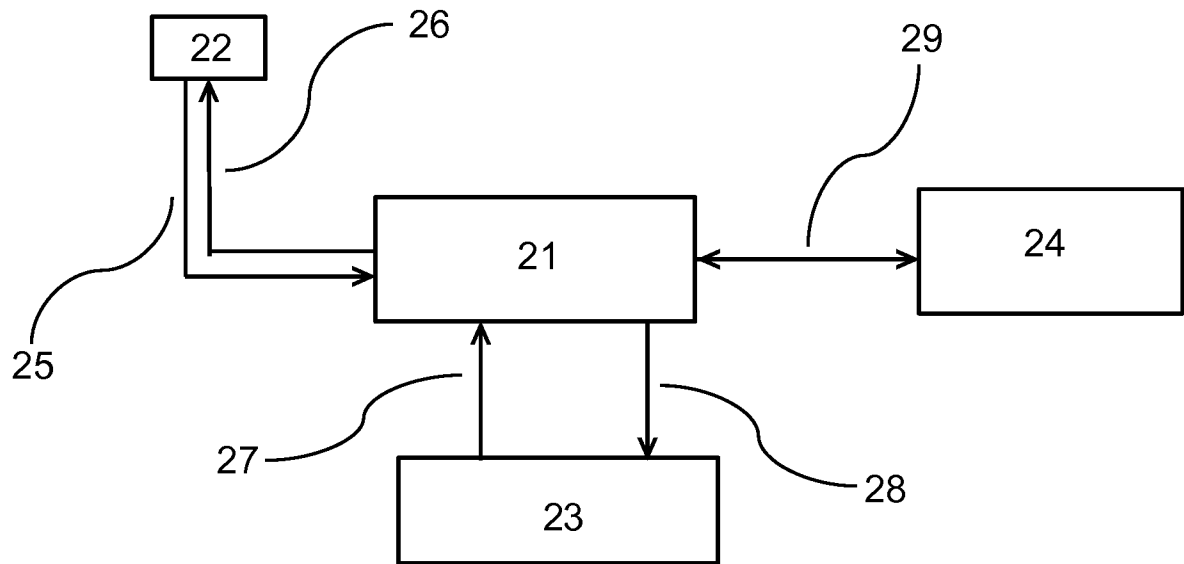


FIG. 1A

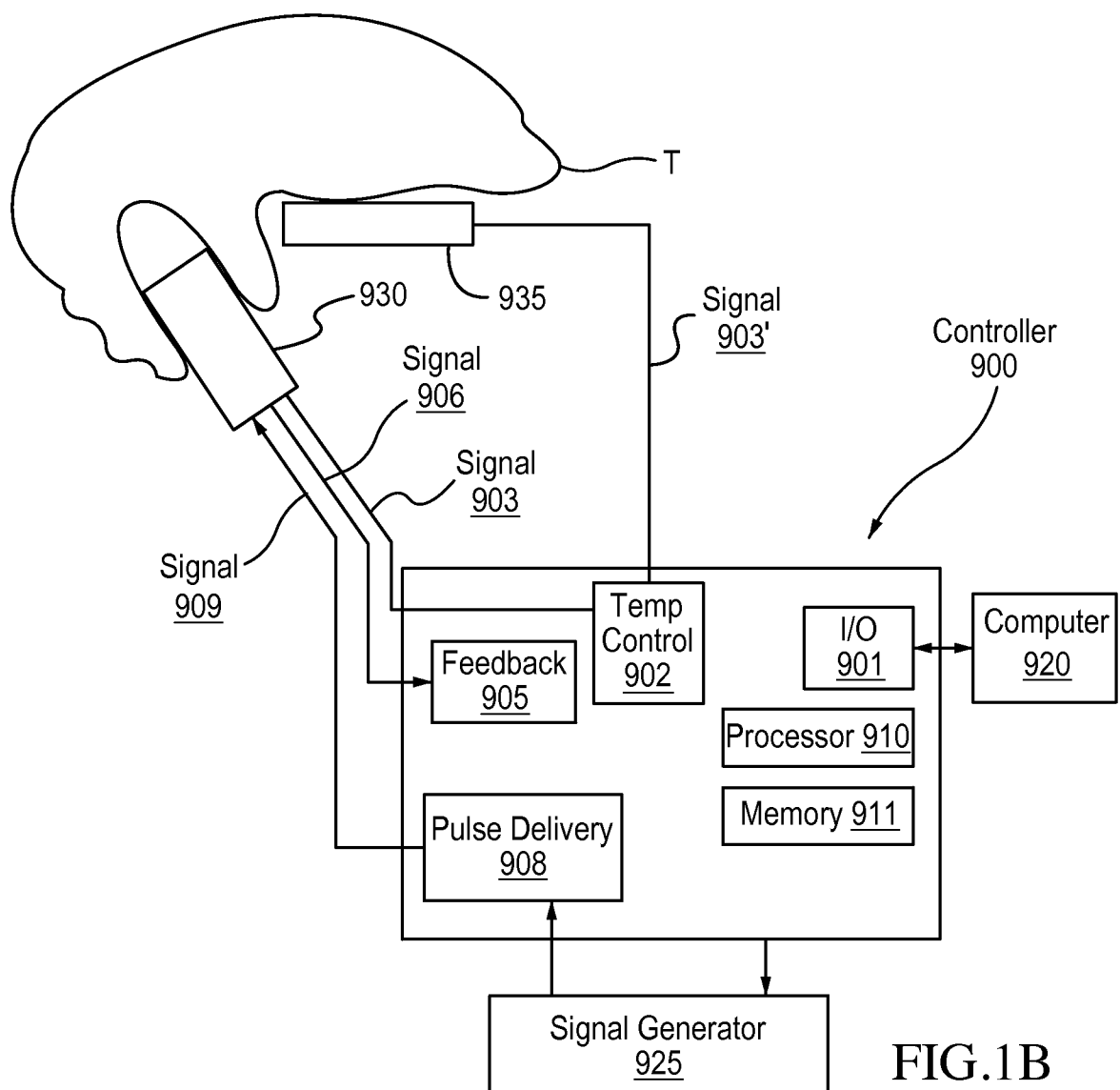


FIG. 1B

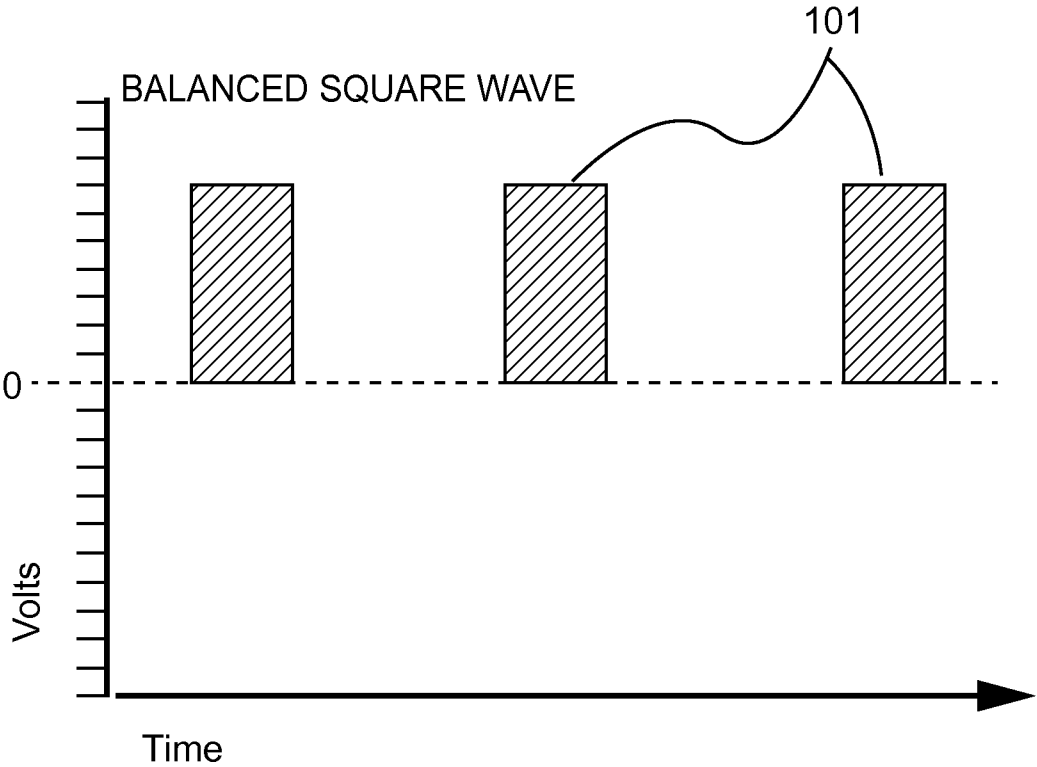


FIG. 2

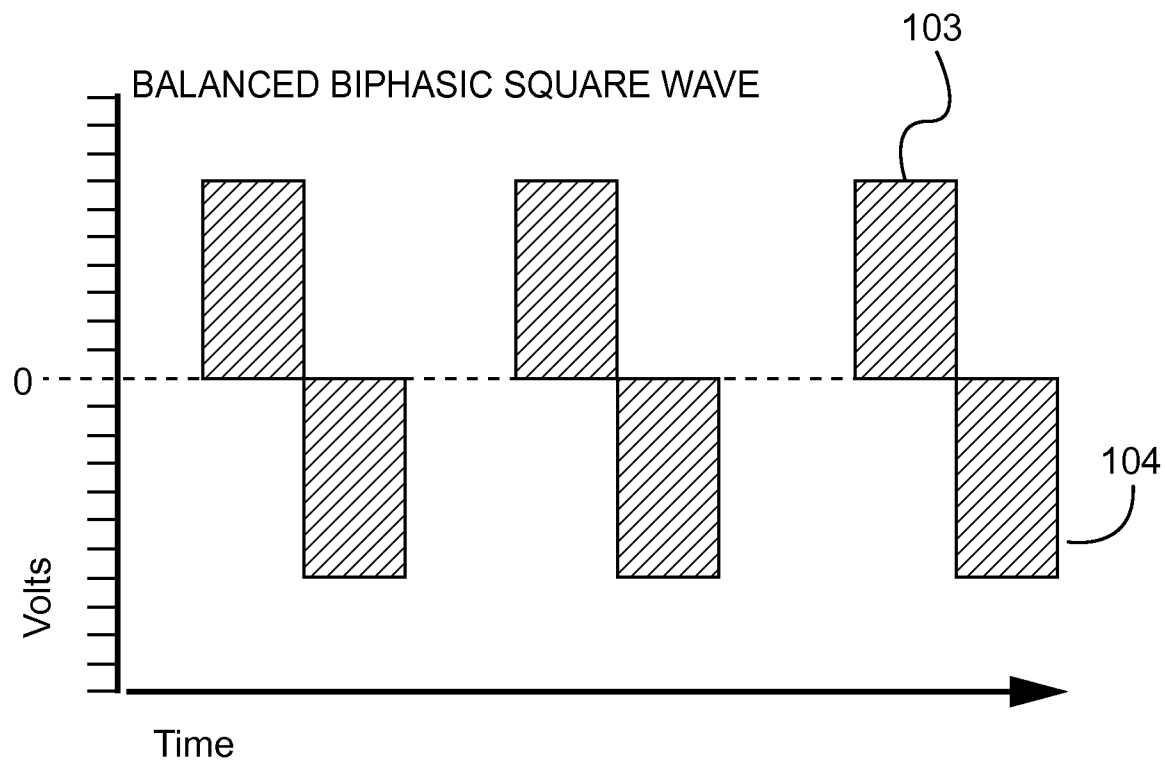


FIG. 3

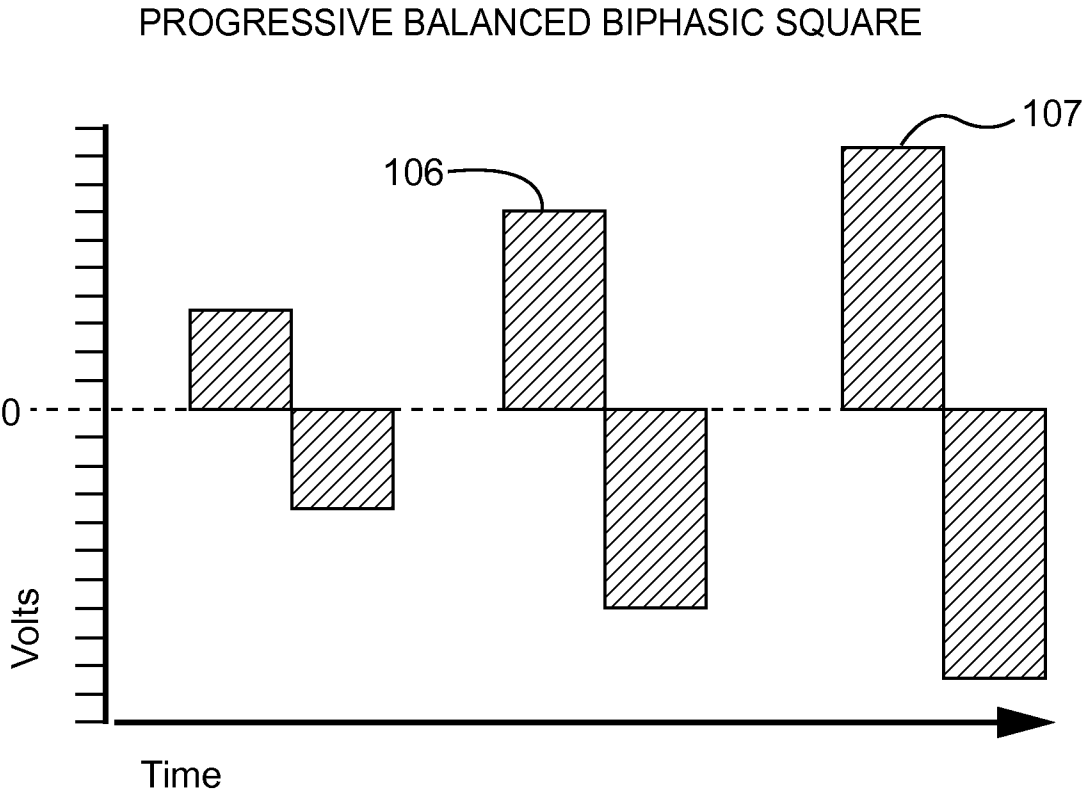


FIG. 4

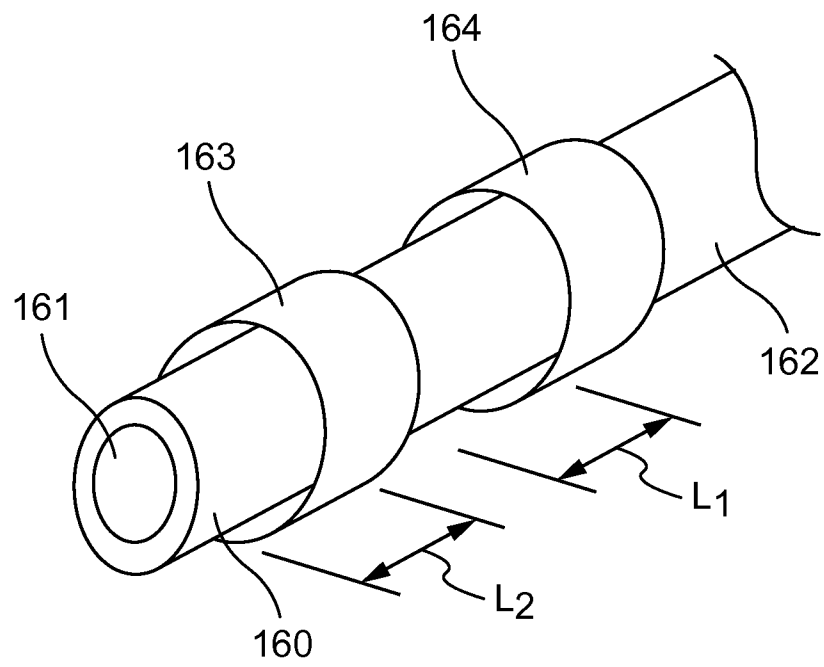


FIG. 5

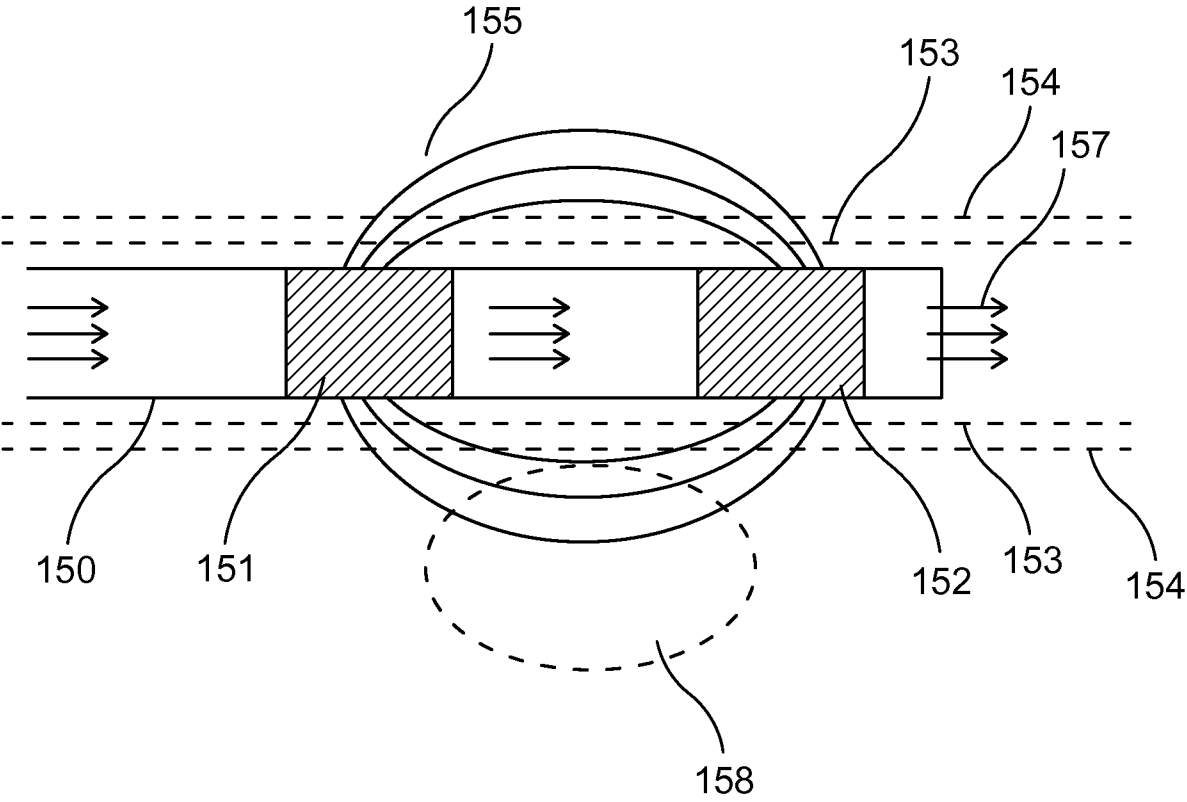


FIG. 6

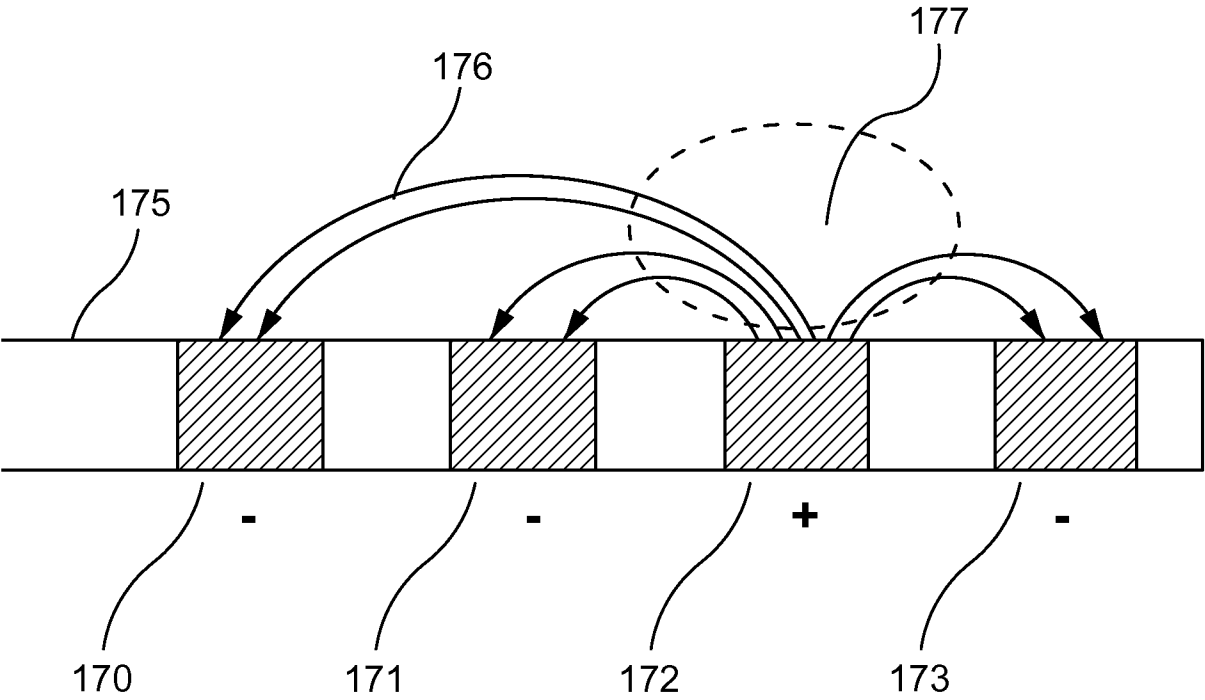


FIG. 7

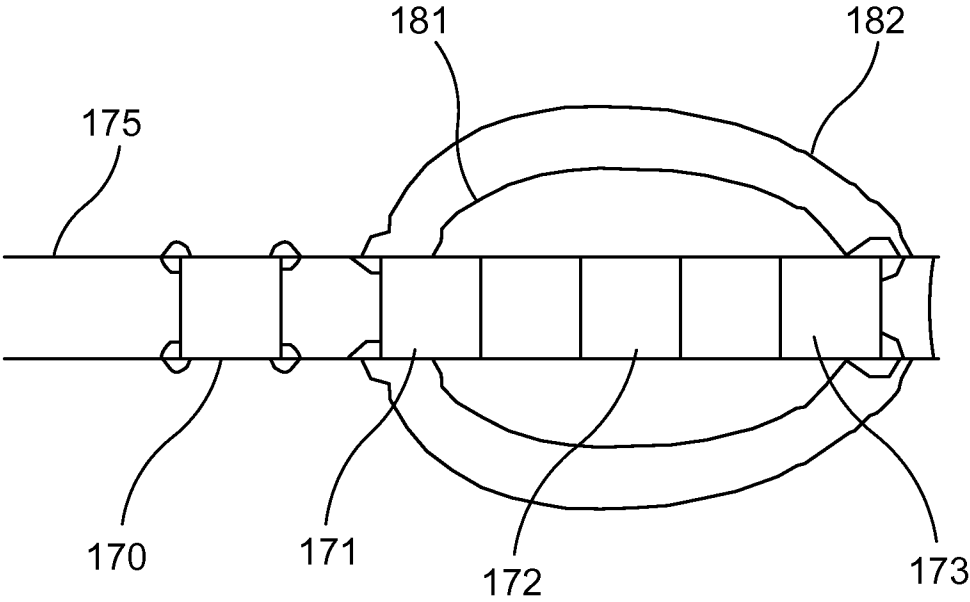


FIG. 8

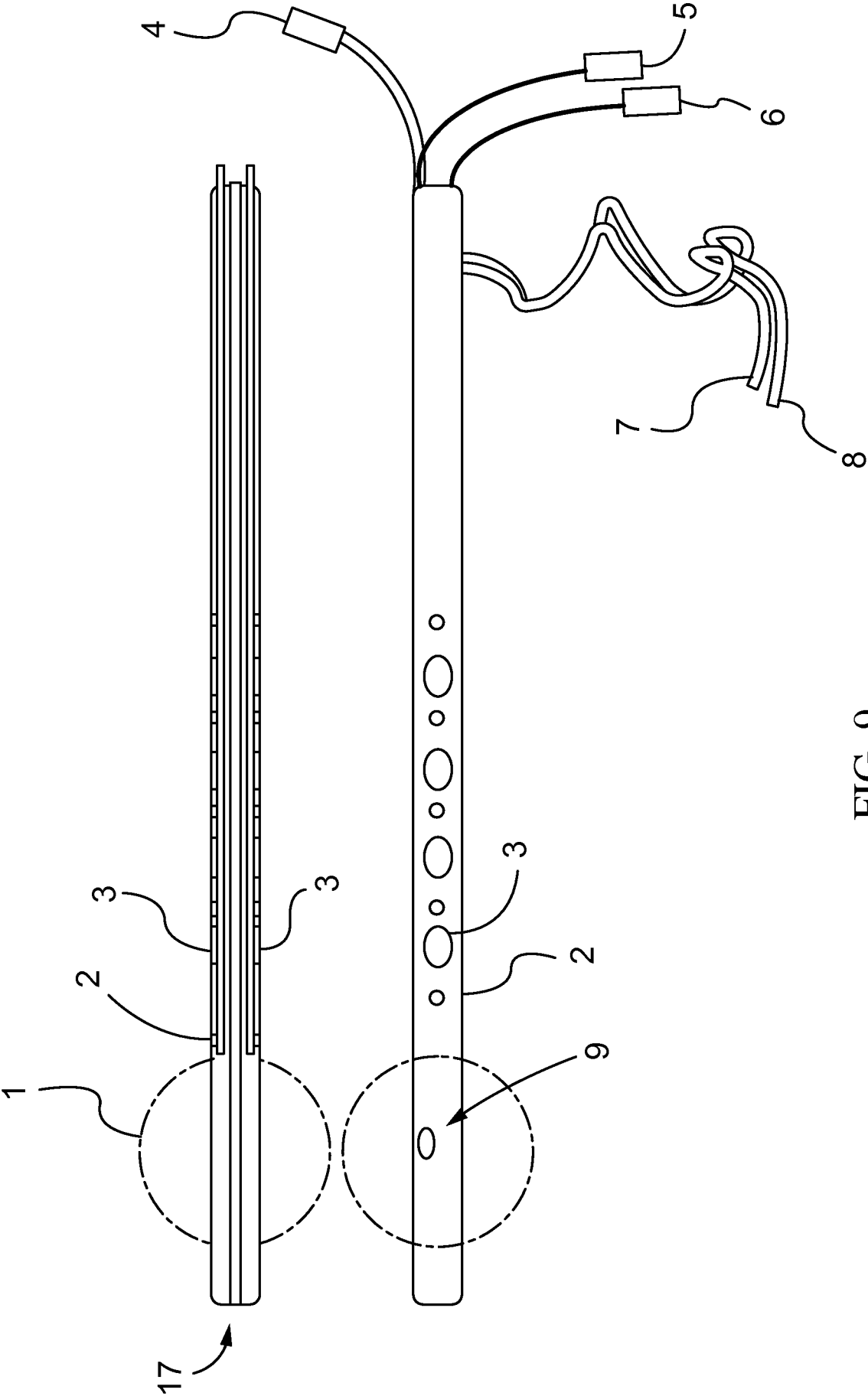


FIG. 9

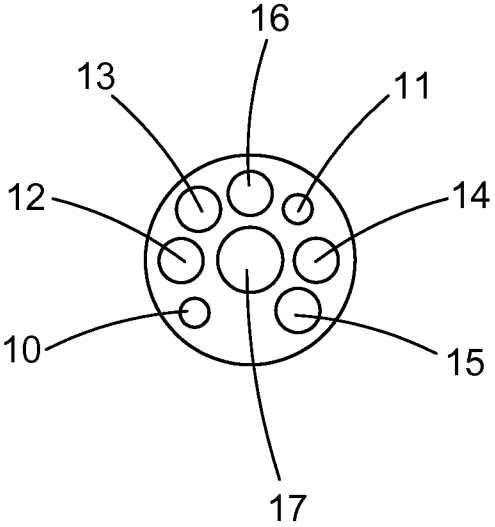


FIG. 10

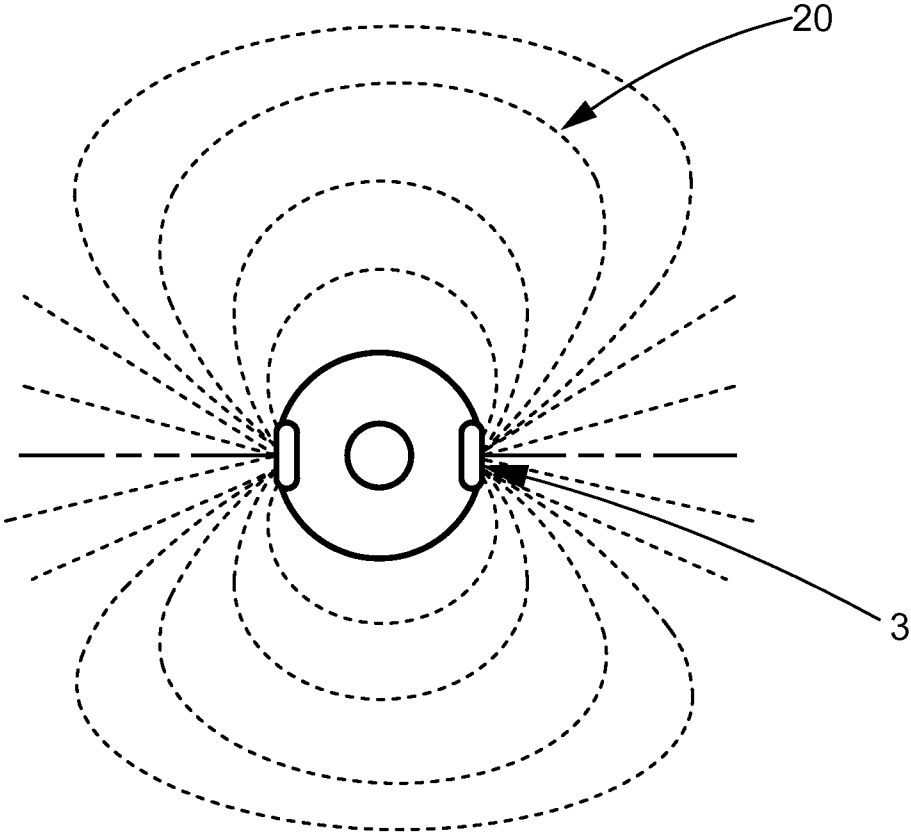


FIG. 11

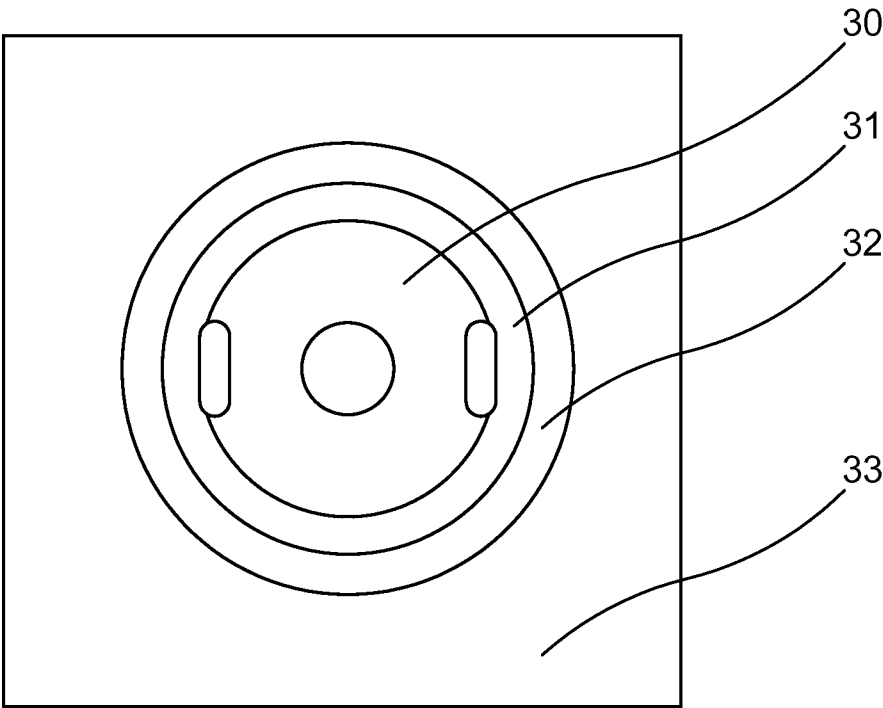


FIG. 12

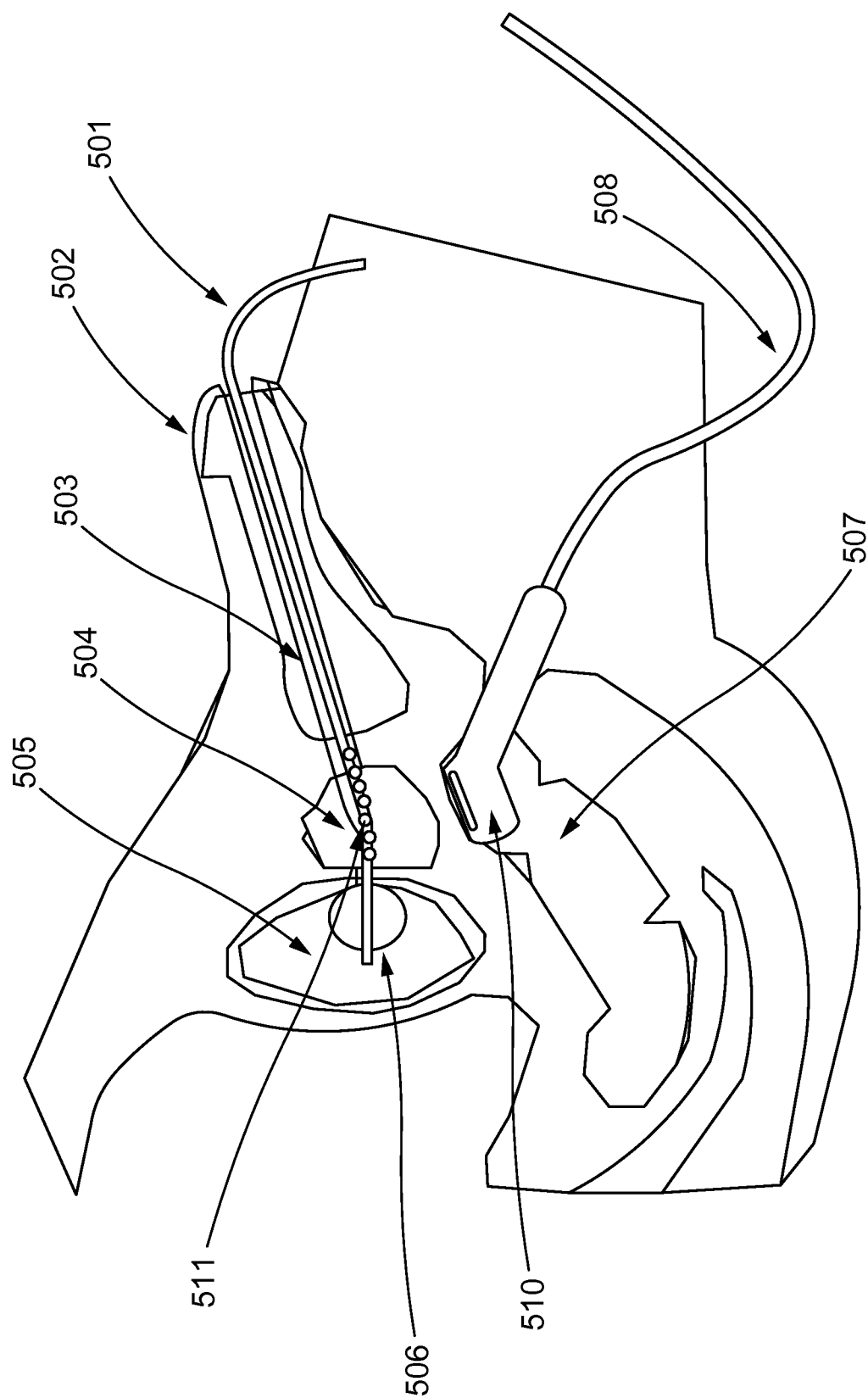


FIG. 13

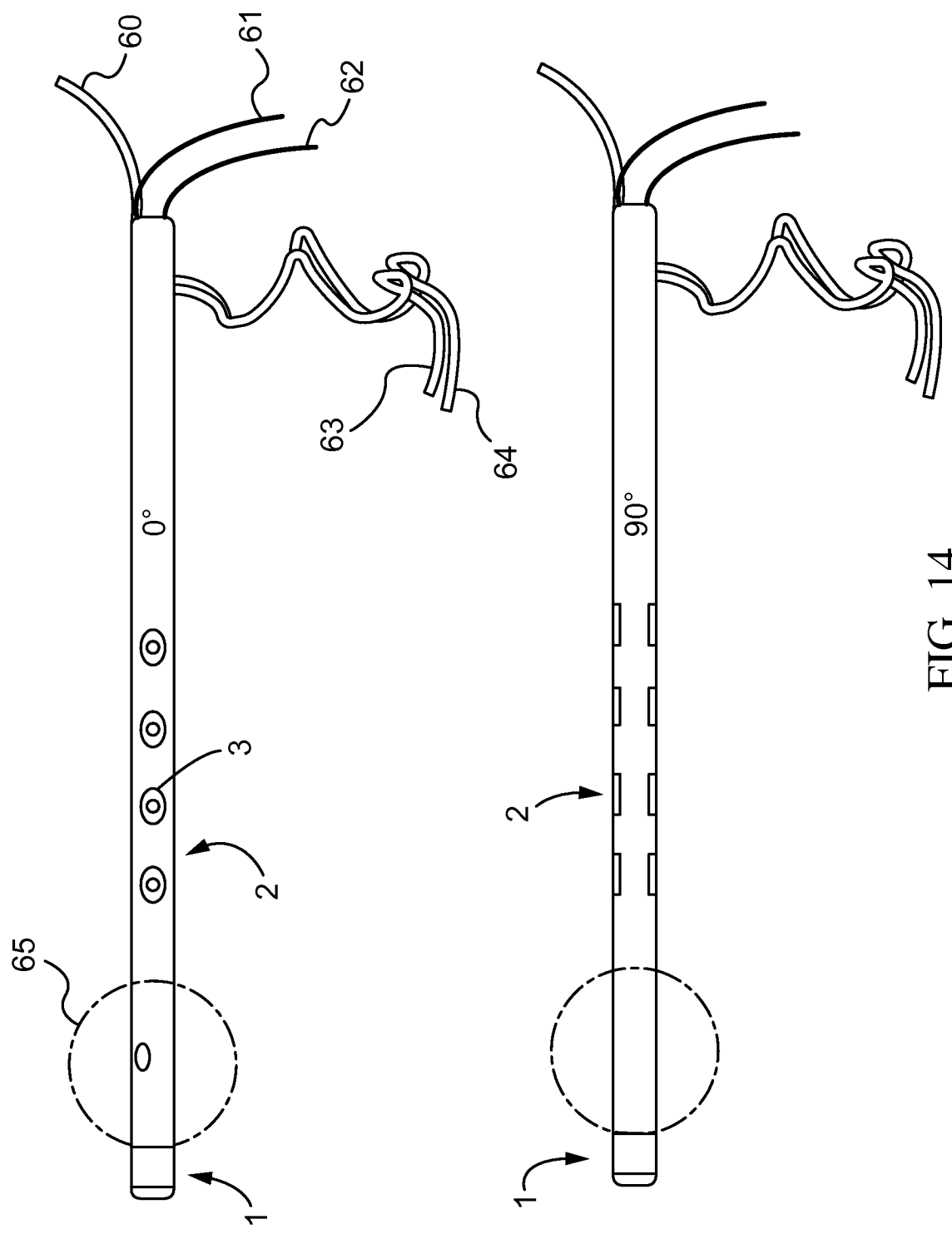


FIG. 14

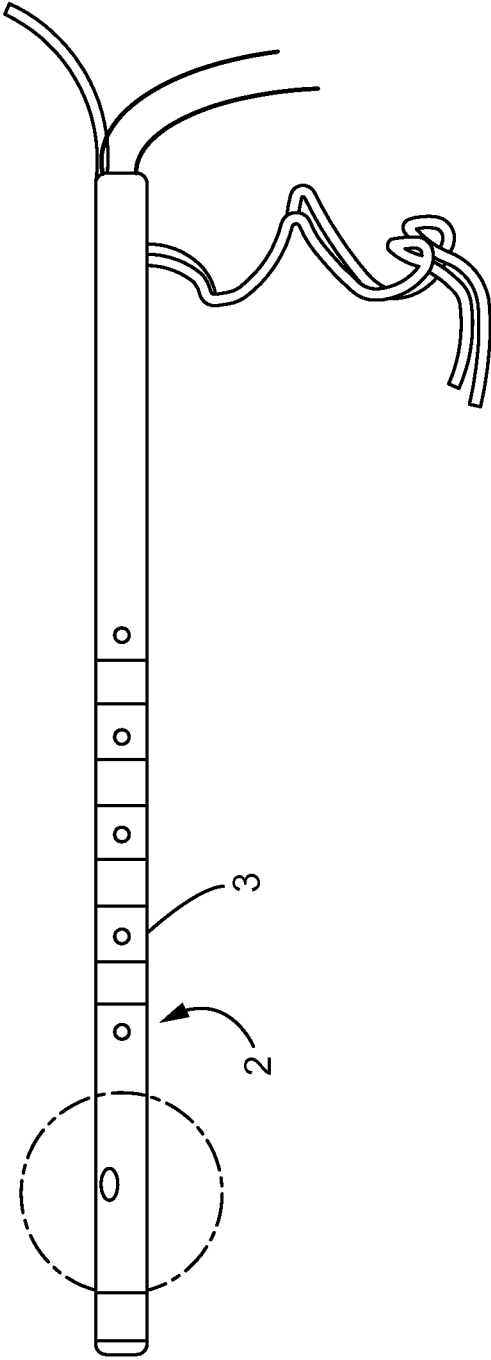


FIG. 15

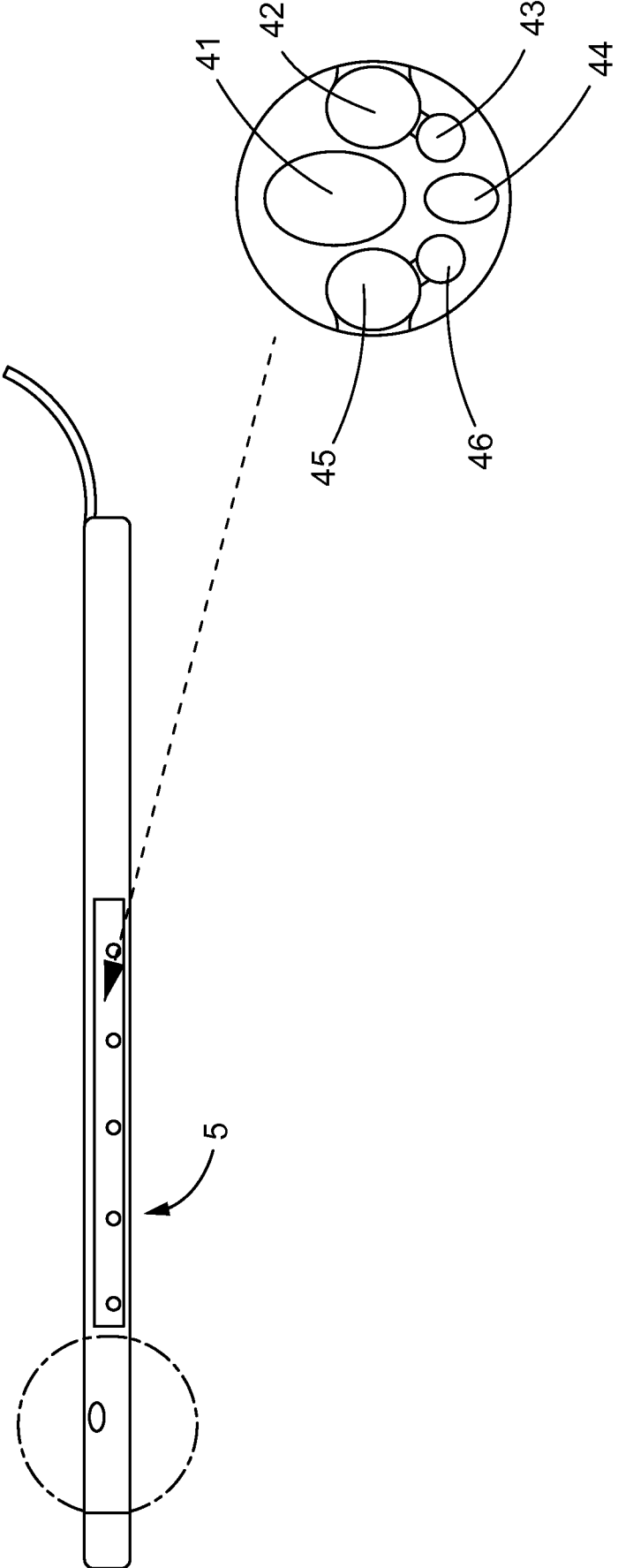


FIG. 16

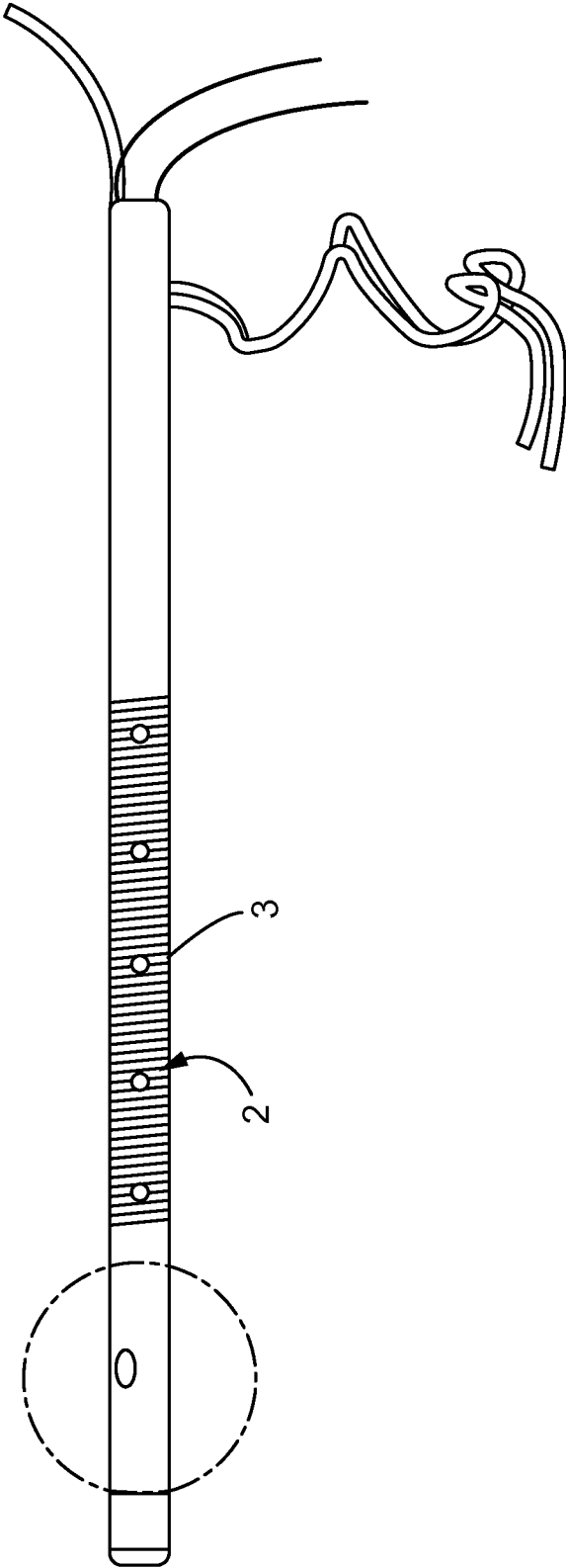


FIG. 17

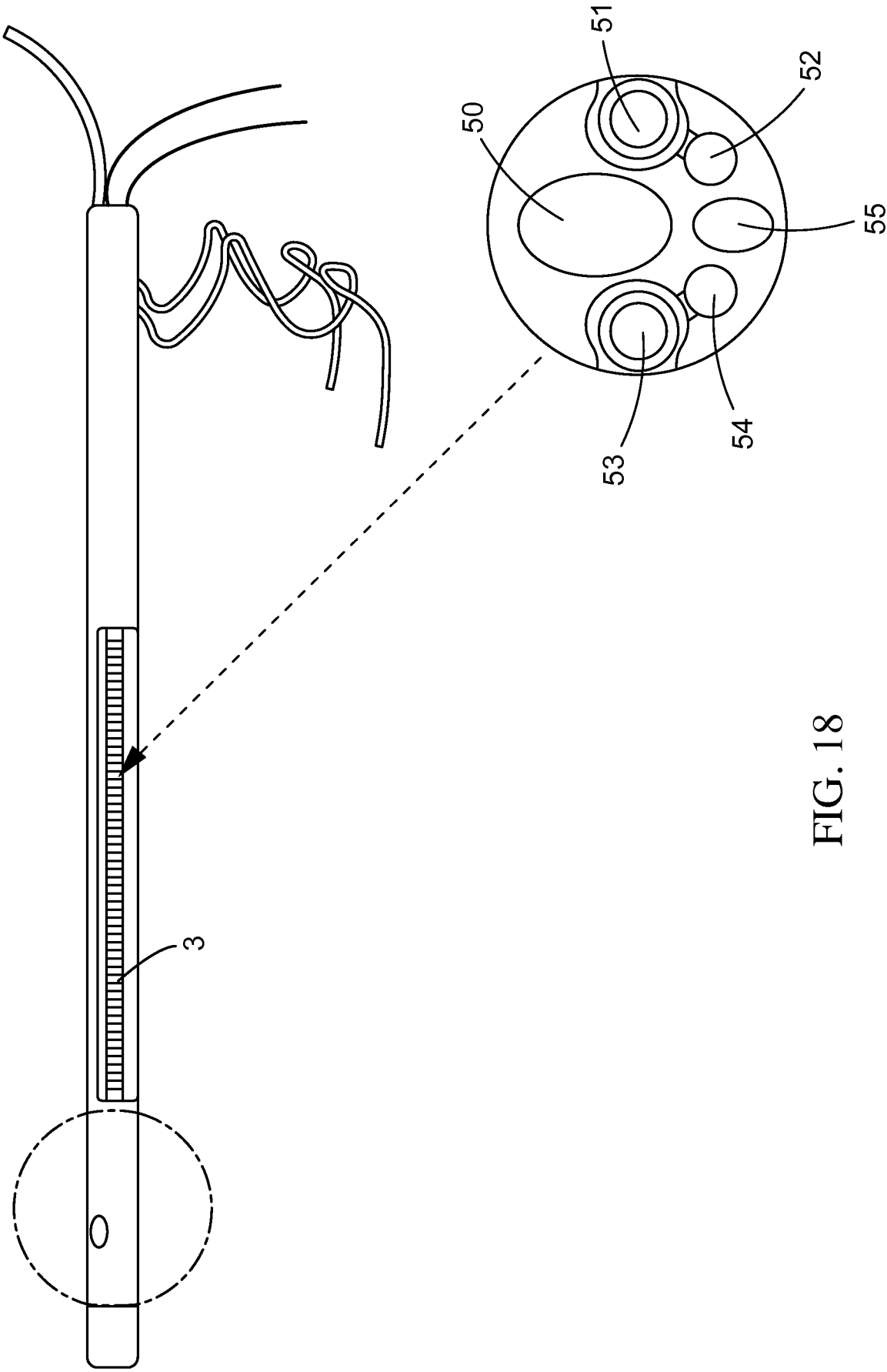


FIG. 18

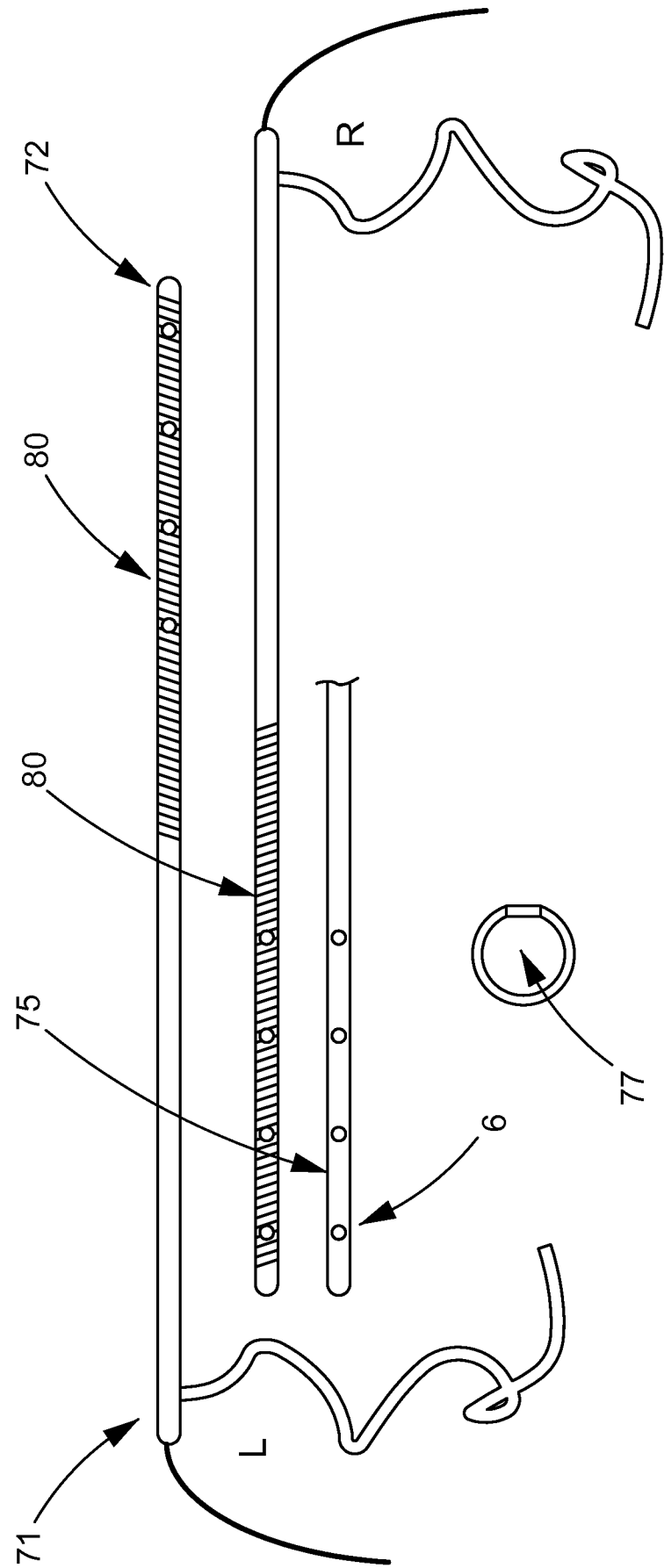


FIG. 19

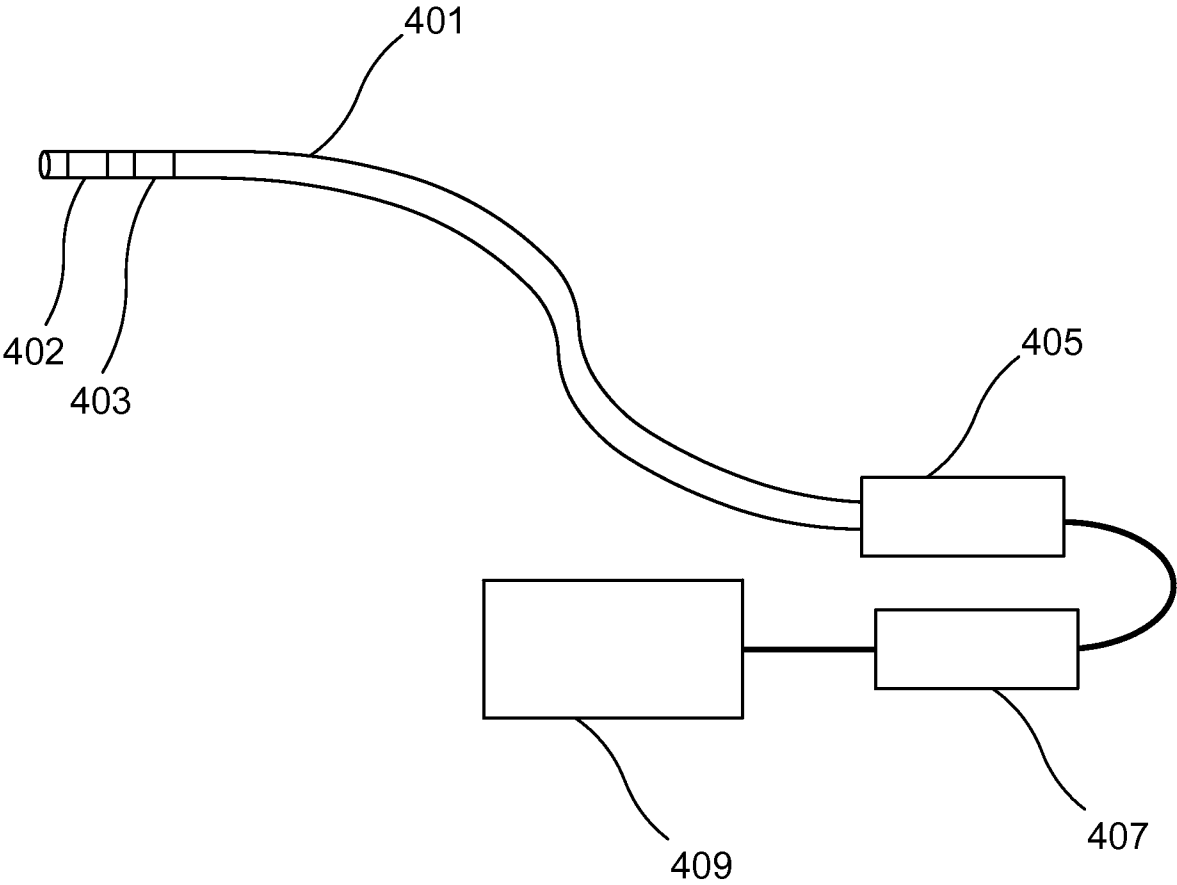


FIG. 20

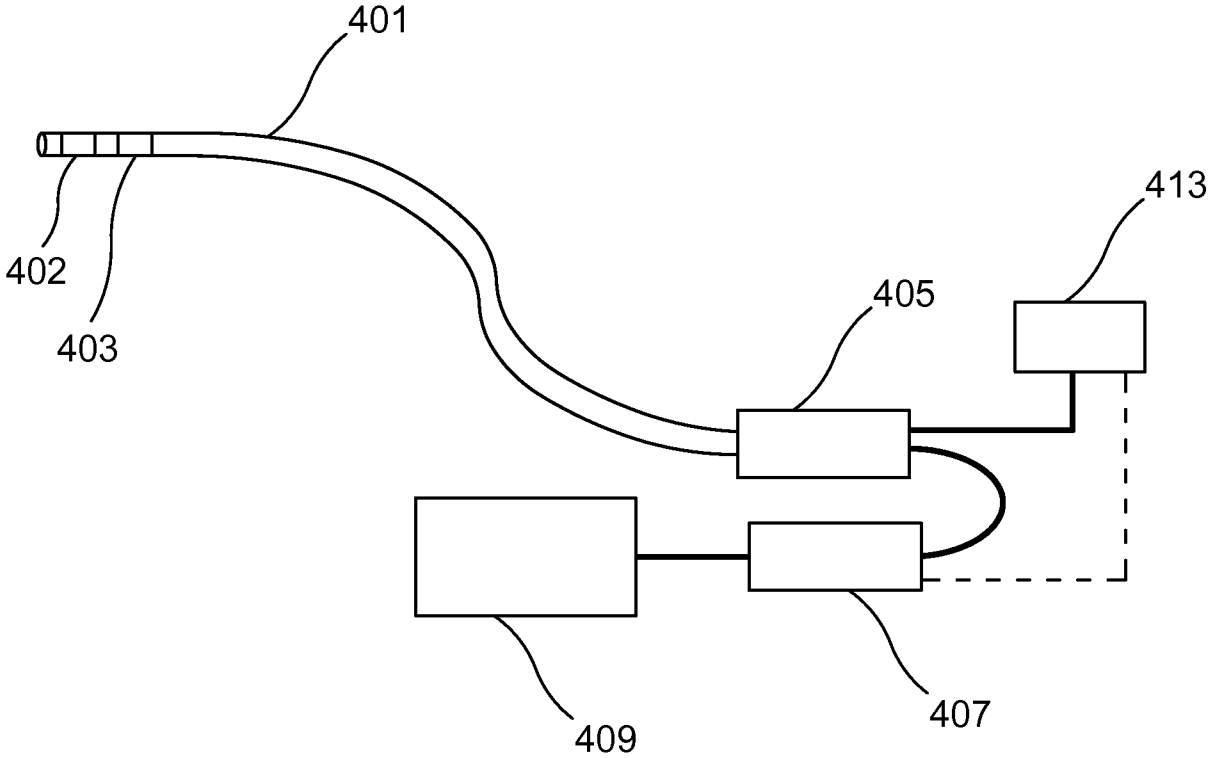


FIG. 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/035592**A. CLASSIFICATION OF SUBJECT MATTER****A61B 18/14(2006.01)i, A61N 1/30(2006.01)i**

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)

A61B 18/14; A61N 1/05; A61F 2/00; A61B 17/39; A61N 1/30

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: ablation, prostate, voltage pulse, control, cooling fluid, cardiac defibrillator, trans-rectal probe, heater

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6272384 B1 (SIMON et al.) 07 August 2001	1-9, 16-19, 21, 26-28
A	See column 2, line 34-column 7, line 30; claims 1-20; and figure 1.	10-15, 20, 22-25
A	US 2006-0217703 A1 (CHORNENKY et al.) 28 September 2006	1-28
	See paragraphs [0029]-[0066]; claims 1-17, 21; and figures 1-9.	
A	US 6009351 A (FLACHMAN, JONATHAN L.) 28 December 1999	1-28
	See column 1, line 56-column 6, line 36; claims 1-18; and figures 1-5B.	
A	US 6517534 B1 (MCGOVERN et al.) 11 February 2003	1-28
	See column 5, line 49-column 26, line 54; claims 1-25; and figures 1-17.	
A	US 5334193 A (NARDELLA, PAUL C.) 02 August 1994	1-28
	See column 2, line 45-column 8, line 50; claims 1-9; and figures 1-6.	



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

23 September 2015 (23.09.2015)

Date of mailing of the international search report

02 October 2015 (02.10.2015)

Name and mailing address of the ISA/KR

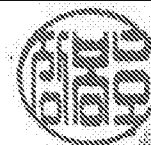
International Application Division
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon Metropolitan City, 35208,
Republic of Korea

Facsimile No. +82-42-472-7140

Authorized officer

CHANG, Bong Ho

Telephone No. +82-42-481-3353



INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US2015/035592**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.: 29
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 29 pertains to a method for treatment of the human body by surgery, and thus relates to a subject matter which the International Searching Authority is not required to search, under PCT Article 17(2)(a)(i) and PCT Rule 39.1(iv).
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 any 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/US2015/035592

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6272384 B1	07/08/2001	None	
US 2006-0217703 A1	28/09/2006	US 2003-0060856 A1 US 2004-0059389 A1 US 2010-0262067 A1 US 2014-0107643 A1 US 2015-0112333 A1 US 6994706 B2 US 7130697 B2 US 7765010 B2 US 8634929 B2 US 8958888 B2	27/03/2003 25/03/2004 14/10/2010 17/04/2014 23/04/2015 07/02/2006 31/10/2006 27/07/2010 21/01/2014 17/02/2015
US 6009351 A	28/12/1999	WO 99-03535 A1	28/01/1999
US 6517534 B1	11/02/2003	AU 1999-27639 A1 AU 1999-32920 A1 AU 2000-43308 A1 AU 4330800 A US 2001-0003798 A1 US 2001-0018585 A1 US 2003-0060819 A1 US 6440127 B2 US 6447505 B2 US 6692493 B2 WO 00-59394 A1 WO 99-40859 A1 WO 99-40860 A1	30/08/1999 30/08/1999 23/10/2000 23/10/2000 14/06/2001 30/08/2001 27/03/2003 27/08/2002 10/09/2002 17/02/2004 12/10/2000 19/08/1999 19/08/1999
US 5334193 A	02/08/1994	EP 0703803 A1 JP 08-505544 A WO 94-11059 A1	14/07/1999 18/06/1996 26/05/1994