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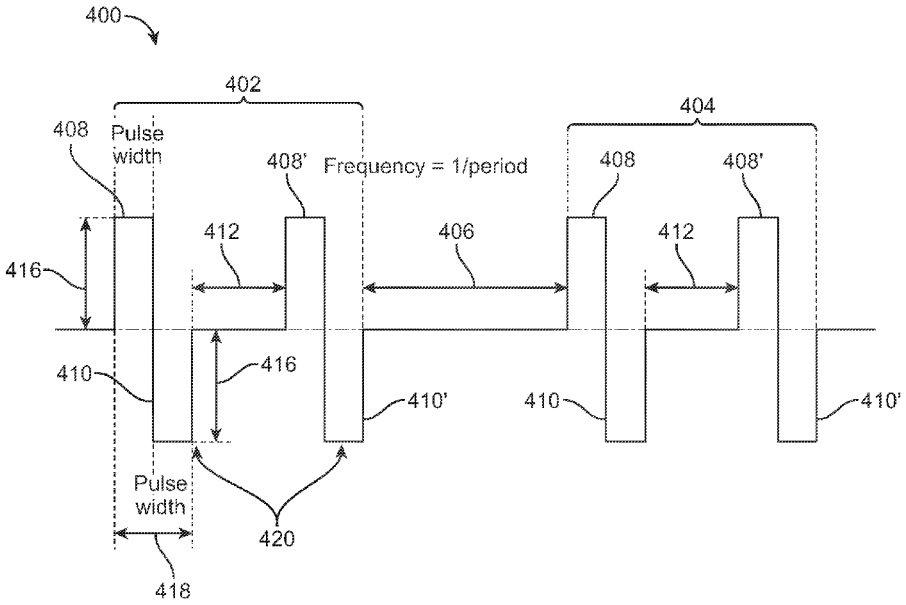


FIG. 21A

(57) Abstract: Devices, systems and methods are provided for delivering pulsed electric field (PEF) energy to tissue through one or more energy delivery bodies, each having one or more electrodes. The PEF energy is generated from a waveform having a variety of features. Waveform delays, such as inter-pulse delays, inter-cycle delays, inter-phase delays, inter-packet delays, inter-bundle delays, may be utilized within a treatment to obtain a desired outcome. In particular, these delays may be specifically manipulated to obtain particular desired outcomes. For example, one, some or all of these delays may be manipulated to control various aspects of PEF therapy so as to mitigate any associated risks, such as gas formation, electrical discharge, cavity formation, muscle contraction, and temperature rise, to name a few. In some embodiments, the delays distribute the period over which PEF energy is delivered, resulting in marked changes and optimization to the treatment delivery outcomes.

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[Continued on next page]

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PULSED ELECTRIC FIELD WAVEFORM MANIPULATION AND USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/007,233, filed April 8, 2020, entitled "PULSED ELECTRIC FIELD WAVEFORM MANIPULATION AND USE", and U.S. Provisional Patent Application No. 63/078,784, filed September 15, 2020, entitled "PULSED ELECTRIC FIELD WAVEFORM MANIPULATION AND USE". The disclosures of the foregoing applications are incorporated herein by reference in their entireties for all purposes.

BACKGROUND OF THE INVENTION

[0002] Various devices and methods have been developed to deliver therapeutic energy to the body for the treatment of diseases and afflictions. In some instances, such delivery is to tissues within a body lumen, passageway or similar anatomy, so as to treat diseased tissue along or within the walls of the passageway, or so as to affect diseases which are associated with a passageway or reachable through a passageway. Such devices typically include a flexible elongate shaft, so as to traverse tortuous luminal anatomy, and an energy delivery element mounted thereon to deliver such energy to remote or enclosed locations such as body lumens. Such devices have been developed to treat, for example, passageways of the lungs or blood vessels of the vasculature.

[0003] A variety of different types of energy have been used for therapeutic treatments, including radiofrequency energy, microwave energy, high intensity focused ultrasound (HIFU) energy, and pulsed electric field (PEF) energy, to name a few. PEF energy typically delivers high-energy discharges over very short periods. Thus, low-voltage energy from a DC power supply is transformed to high-intensity pulsed fields. The high-intensity energy is stored in capacitors to be discharged to the target tissue at different electric strengths (20–80 kV cm− 1) and times (< 1 s).

[0004] PEF energy is delivered in a manner so as to be non-thermal (i.e. below a threshold for causing cell death by thermal injury). Consequently, when extracellular matrices are present, the extracellular matrices are preserved, and the targeted tissue maintains its structural architecture including blood vessels and lymphatics. Thus, sensitive structures, such as biological lumens, blood vessels, nerves, etc, are able to be preserved which are critical to maintaining the integrity and functionality of the tissue. This provides a number of benefits. To begin, this allows for the treatment of tissues that are often considered untreatable by conventional methods. Target tissues that are near sensitive structures are typically unresectable by surgical methods due to the

inability to thoroughly and effectively surgically separate the tissue from the sensitive structures. Likewise, many conventional non-surgical therapies are contraindicated due to the potential for damage to the sensitive structures by the therapy or because the therapies are deemed ineffective due to the proximity of the sensitive structures. In addition, the ability to treat tissue near sensitive structures also provides a more comprehensive treatment in that malignant margins are not left near sensitive structures. Once tissue is treated, the survival of the structural architecture also allows for the natural influx of biological elements, such as components of the immune system, or for the introduction of various agents to further the therapeutic treatment.

[0005] However, a variety of risks are involved in using PEF energy. A few of such risks are described herein below.

Gas bubble formation

[0006] Typically, delivering PEFs in an ionic solution (saltwater, blood, interstitial fluid, etc.) will result in electrolytic reactions that affects the compounds within the solution, most notably separating water molecules resulting in hydrogen gas (at the active cathode) and chlorine gas (at the active anode) components. Thus, these gases are considered electrochemical generated gases. Alternating the PEF polarity during energy delivery will reduce the degree of bubble formation by alternating which item is being produced. However, this alone does not eliminate the generation of gas entirely, as the active periods during each phase of the polarity will continue to contribute to gas formation.

[0007] Gas bubble formation has a range of implications in clinical cases, which will vary with the location and application being targeted. In tissue destruction applications, whereby one or more electrodes are placed into the targeted region of tissue to deliver the PEFs either between the electrodes or in communication with a distant external dispersive pad, gas formation has been clearly visualized on ultrasound. It is routinely regarded as an inconsequential collateral effect of treatment delivery and has not been regarded as a confounding factor that alters treatment delivery. However, gas formation contributes to several effects, which may be desirable or undesirable depending on the application. In one consideration, the gas formation applies pressure to the adjacent tissue regions, and can distort tissue geometries, disrupt tissue architecture, or displace other materials within the tissue. In another consideration, gas formation could enter the bloodstream prior to dissolving. The circulating gaseous "bubble" could then travel through arterial pathways or subsequent veins to cause an embolism in the downstream tissues leading to ischemia, causing downstream cell and tissue death, pain, and other risks for

the patient. The bubble may also travel back through the systemic circulation prior to dissolving, and cause a pulmonary embolism, which could cause pain, morbidity, or patient death.

[0008] In addition to the gas formed by the induced electrochemical reactions, gas can also be formed by vaporization. Electric currents will increase the temperature of the ionic solution by Joule heating. In cases where the induced temperature exceeds the phase change value, vaporization of the water content will take place. Both vaporization and electrochemical generated gases show several orders of magnitude lower electric conductivity than ionic solutions. Thus, at the region of tissue being treated by the high voltage, high energy electric pulses, the resulting electric field inside the gas could be higher than the electric breakdown exhibited as a sparking electric arc, or a larger combustion event depending on the size, quantity, type, and distribution of gaseous bubbles being generated. This is a particular risk when the PEF protocol and tissue type results in the generation of a large amount of gas that is not readily removed from the local tissue environment. Such spark production, encouragement, and potential combustion events caused by bubble formation may result in high-current events affecting generator performance (or breaking the generator) as well as distortions of energy deposition patterns that affect treatment outcomes, producing risks including burned tissue, overtreated tissue, undertreated tissue, or a combination of these effects. These effects could all seriously affect the efficacy, morbidity, and potentially the mortality of the PEF therapy.

[0009] In another consideration for gas formation, the presence of the gas:liquid:tissue mixture will result in a heterogeneously altered electrical conductivity environment (in essence, the electric current may preferentially flow around or through the gas, changing its flow through the targeted tissue). This could result in higher energy concentrations in some regions and absent or reduced energy concentrations in others. This may inherently distort energy delivery and deposition, potentially affecting treatment efficacy, morbidity, and mortality of the procedure.

[0010] In addition to gas formation implications in solid tissue regions, the risks are also present and potentially compounded when delivering PEF treatments into fluid targets, such as blood within the vasculature or cardiopulmonary system. Of particular concern, gas bubbles generated in the left atrium and ventricle of the heart will rapidly be expelled by the heart into the aorta. These bubbles may enter the coronary circulation, the carotid vessels, or other blood vessels. If the bubbles do not dissolve back into the fluid, they may get lodged into the narrowing portions of the arteries, restricting or eliminating blood flow through these vessels, causing ischemia to the downstream tissues. Bubble formation has been found as a risk in cardiac treatments for indications such as atrial fibrillation by various energy modalities, including cryoablation, radiofrequency ablation, and PEF treatments. There is a significant risk for symptomatic and

asymptomatic cerebral ischemic events. In addition, the tendency for bubbles to float or move upwards makes them likely to enter the coronary artery on patients when placed in the supine position. Due to the likelihood and severity of issues that may be induced by gas formation during conventional procedures such as atrial fibrillation electrical isolation procedures, particular attention has been paid by clinicians and researchers to quantify and reduce the risk of these events in patients, including efforts to reduce or capture bubble formation. However, gas formation from PEF treatments has remained a standard collateral effect and patient risk.

Electrical Discharge

[0011] When delivering PEFs between electrodes, the generally high voltages employed can cause a breakdown in the delivery device, the tissue solid components, or the fluid in the tissue. This can cause an electrical discharge into this medium from the energized regions of the electrode. Electrical discharges can occur at the microscale, where they are not visible, or they can occur at a scale that is visible, generally manifesting as a visible “arc” or spark. The discharge is often accompanied by a pressure wave and audible sound than increases as the intensity of the discharge.

[0012] Discharges from the electrode cause a distortion in the quantity and distribution of the affecting items from the PEF therapy. They can concentrate the electric current into a focused area that causes stronger treatment effects (overtreatment) or burning from Joule heating in the region near the discharge. This may also reduce the electric current and subsequent electric field induced in the rest of the tissue (undertreatment). The electric breakdown of the current pathway may also result in a spike of electric current flowing through the system, which could increase the total electric current that must be generated by the PEF generator. Such spikes could exceed the PEF generating capacity of the generator or could cause high currents within the generator that damage the internal circuitry of the generator. In addition, electric discharge over ionic medium can generate reactive species (mainly nitrogen and oxygen) that will alter the composition of the medium having major impact on the pH of the solution and the normal biomolecule interaction.

[0013] Electrical discharges can commonly occur in PEF therapies due to the voltages used by these therapies. Bipolar electrode arrangements are particularly susceptible to major electrical arcing events due to the close proximity of the cathode and anode to each other, which may generate an electric discharge between electrodes also known as full discharge. This will induce a complete short-circuit if the voltage-to-distance ratio is not properly titrated. Permitting electrical discharges adds a degree of unpredictability and risk to the procedures. Avoiding them

may reduce the efficacy of the therapy by reducing the intensity of the therapy that may be delivered.

Cavity Formation

[0014] As a result of the electrical discharge, both visible and invisible, a pressure wave is generated, that is apparent as an audible "popping" tone. This tone is commonly encountered in many PEF therapies and accepted as a collateral effect of treatment delivery. However, when the discharge and the pressure wave is of sufficient intensity and repeated a sufficient number of times, the energy transferred and deposited into the tissue from this pressure wave can severely disrupt the tissue architecture and cells. The resulting effect is the accumulated generation of a defect or cavity within the tissue at the regions near the electrode, which experience the strongest intensity of these effects.

[0015] The generation of the cavity adds considerable risk to procedure deliveries in or near solid tissues and ductal systems. The resulting "shredding" and destruction of the tissue may damage sensitive structures, such as blood vessels, nerves, or other ductal systems such as the bile duct, urethra, ureter, or lymphatics. These shredding effects could result in hemorrhage, thrombus or emboli formation, or disruption of tissue function. Generally, PEF treatments are utilized in lieu of other therapies due to their ability to spare these sensitive structures. The formation of cavities from the therapy jeopardizes this benefit of most PEF therapies for tissue regions in close proximity (0.1-5mm) from the electrode.

[0016] In other instances, cavity formation and disruption via produced pressure waves may be desirable. For example, the disruption or dislodging of gallstones or kidney stones may be a target for this type of effect. Further, the fluid-filled cavity produced by these effects will generally be more conductive than the pre-existing tissue. Thus, continuing to deliver PEF (or other energy-based modalities) into this generated tissue cavity will serve to expand the applicable effects of the electrode, acting as a "virtual-electrode". Further, the conductive fluid will be a more homogeneous electrical conductivity and provide a more evenly distributed conduit for electrical flow, reducing the likelihood of electrical discharges into the tissue that may occur when electrical conductivities are heterogeneous. Therefore, at times it is desirable to control cavity formation resulting from PEF therapies.

Muscle Contraction

[0017] PEF therapies may induce their desirable clinical effects by altering the targeted tissue, however, this can also lead to the generation of action potentials in the nerves, especially motor

neurons, as well as skeletal muscle cells. The generation of action potentials in motor neurons can result in the generation of muscle contraction during energy delivery. Muscle contraction and the generation of nerve action potentials can be uncomfortable or painful if performed in conscious or semi-conscious patients. In addition, the electrodes delivering the therapy can move or dislodge, risking an alteration of treatment effect location. Moving electrodes may also puncture or damage sensitive tissues that were in proximity to the electrode locations at the beginning of treatment. These factors compound to safety concerns for the patient and user when delivering PEF therapies. Generally, contraction is worse as waveforms in a given polarity are longer, with DC being the worst and purely symmetrical biphasic being the least contractile for a given pulse length, and a strong correlation for asymmetric waveforms across the spectrum as they move from pure-symmetric to pure-DC (weaker to stronger).

[0018] In other instances, the induction of muscle contractions could be a desirable secondary (or primary) effect from PEF therapies. For example, it could be used in re-exciting tissue that has atrophied due to temporarily disconnected nerve fibers from injury or clinical procedures. In such an example, the PEFs could be delivered in proximity to the proximal or peripheral side of the motor neuron, inducing an action potential that excites the downstream skeletal muscle, retaining tone and preventing atrophy, as well as encouraging regeneration and recovery of the muscle and neurological tissues. Therefore, at times it is desirable to control and encourage the muscle contractions resulting from PEF therapies.

Temperature Rise

[0019] Delivery of energy to tissue results in Joule heating depending on the length of time the energy is applied along with other factors. When a packet or pulse of energy is delivered continuously, the energy for that individual portion is deposited concurrently, resulting in progressive temperature rise. This results in PEF therapies as having very high to extreme and rapid rises in temperature, especially at the tissue-electrode interface and regions within the first few mm of distance from the electrode(s). If appropriate mitigations are not taken, the cumulative temperature rise can result in thermal effect extents that could destroy the extracellular matrix architectural proteins (e.g., collagen), resulting in disruption of tissue function and potential dangers to the patient.

[0020] Consequently, improved therapies are desired to control these aspects of PEF and mitigate any associated risks. Such improvements should be safe, reliable, effective, easy to implement and cost efficient. At least some of these objectives will be met by the present invention.

SUMMARY OF THE INVENTION

[0021] Described herein are embodiments of apparatuses, systems and methods for treating target tissue. Likewise, the invention relates to the following numbered clauses:

[0022] 1. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising one or more packets of pulses to provide the treatment and comprising one or more delay periods which manipulates or reduces or avoids one or more secondary effects.

[0023] 2. A system as in claim 1, wherein the one or more secondary effects comprises bubble formation.

[0024] 3. A system as in claim 2, wherein bubble formation comprises formation of bubbles greater than or equal to 0.1mm in diameter.

[0025] 4. A system as in any of the above claims, wherein each of the pulses in the one or more packets of pulses has an on-time in a range 0.5 to 20 microseconds.

[0026] 5. A system as in any of claims 1-3, wherein each of the pulses in the one or more packets of pulses has a continuous on-time of up to 5 microseconds.

[0027] 6. A system as in any of the above claims, wherein each of the pulses has a duty cycle of less than or equal to 2.5 percent.

[0028] 7. A system as in any of the above claims, wherein the delay period is greater than or equal to 1 microsecond.

[0029] 8. A system as in claim 7, wherein the delay period is in a range of 1 to 250 microseconds.

[0030] 9. A system as in claim 7, wherein the delay period is in a range of 10-100 microseconds.

[0031] 10. A system as in claim 7, wherein the delay period is greater than or equal to 100 microseconds.

[0032] 11. A system as in claim 7, wherein the delay period is greater than or equal to 250 microseconds.

[0033] 12. A system as in claim 7, wherein the delay period is greater than or equal to 500 microseconds.

[0034] 13. A system as in claim 7, wherein the delay period is greater than or equal to 1000 microseconds.

[0035] 14. A system as in claim 7, wherein the at least one electrode is configured to be positioned within an ionic solution near the tissue and wherein the delay period is in a range of 100 microseconds to 10 milliseconds.

[0036] 15. A system as in claim 14, wherein the delay period is in a range of 250 microseconds to 1000 microseconds.

[0037] 16. A system as in claim 7, wherein the at least one electrode is configured to be positioned within the tissue and wherein the delay period is in a range of 10 microseconds to 1 millisecond.

[0038] 17. A system as in claim 16, wherein the delay period is in a range of 25 microseconds to 100 microseconds.

[0039] 18. As system as in any of the above claims, wherein the one or more packets of pulses comprises 100 packets and wherein each packet comprises 40 biphasic pulses.

[0040] 19. A system as in claim 1, wherein the one or more secondary effects comprises an electrical discharge event.

[0041] 20. A system as in claim 19, wherein the electrical discharge event comprises electrical arcing from at least one of the at least one electrode.

[0042] 21. A system as in any of claims 19-20, wherein each of the pulses in the one or more packets of pulses has an on-time in a range 1 to 50 microseconds.

[0043] 22. A system as in any of claims 18-20, wherein each of the pulses in the one or more packets of pulses has a continuous on-time in a range of up to 20 microseconds.

[0044] 23. A system as in any of claims 18-22, wherein each of the at least one packet of pulses has a duty cycle of less than or equal to 20 percent.

[0045] 24. A system as in claim 20, wherein the electrical discharge event comprises generation of a pressure wave against the tissue.

[0046] 25. A system as in claim 24, wherein the pressure wave is sufficient to generate a cavity within the tissue.

[0047] 26. A system as in claim 25, wherein each of the at least one packet of pulses has a duty cycle of less than or equal to 50 percent.

[0048] 27. A system as in any of claims 25-26, wherein each of the pulses in the one or more packets of pulses has an on-time in a range 10 to 100 microseconds.

[0049] 28. A system as in any of claims 25-26, wherein each of the pulses in the one or more packets of pulses has a continuous on time of up to 50 microseconds.

[0050] 29. A system as in any of claims 18-28, wherein the delay period is greater than or equal to 1 microsecond.

[0051] 30. A system as in claim 29, wherein the delay period is in a range of 1 to 500 microseconds.

[0052] 31. A system as in claim 29, wherein the delay period is in a range of 10-250 microseconds.

[0053] 32. A system as in claim 29, wherein the delay period is greater than or equal to 50 microseconds.

[0054] 33. A system as in claim 29, wherein the delay period is greater than or equal to 250 microseconds.

[0055] 34. A system as in claim 29, wherein the delay period is greater than or equal to 500 microseconds.

[0056] 35. A system as in claim 29, wherein the delay period is greater than or equal to 1000 microseconds.

[0057] 36. A system as in any of claims 18-29, wherein the at least one electrode is configured to be positioned within an ionic solution near the tissue and wherein the delay period is in a range of 50 microseconds to 10 milliseconds.

[0058] 37. A system as in claim 36, wherein the delay period is in a range of 250 to 1000 microseconds.

[0059] 38. A system as in any of claims 18-29, wherein the at least one electrode is configured to be positioned within the tissue and wherein the delay period is in a range of 100 microseconds to 10 milliseconds.

[0060] 39. A system as in claim 38, wherein the delay period is in a range of 250 to 2000 microseconds.

[0061] 40. A system as in any of claims 18-29, wherein the at least one electrode is configured to be positioned within a lumen wherein the tissue resides within a wall of the lumen and wherein the delay period is in a range of 10 microseconds to 10 milliseconds.

[0062] 41. A system as in claim 40, wherein the delay period is in a range of 50 to 500 microseconds.

[0063] 42. As system as in any of claims 18-41, wherein the one or more packets of pulses comprises 100 packets and wherein each packet comprises 40 biphasic pulses.

[0064] 43. A system as in claim 1, wherein the one or more secondary effects comprises a contraction of a muscle.

[0065] 44. A system as in claim 43, wherein the at least one electrode is configured to create a lesion having a width and wherein reducing or avoiding contraction of the muscle causes the at least one electrode maintain a position that does not move more than 25% of the width.

[0066] 45. A system as in claim 44, wherein the tissue comprises cardiac tissue and the lesion comprises a focal lesion.

[0067] 46. A system as in any of claims 43-45, wherein the delay period is greater than or equal to 5 milliseconds.

[0068] 47. A system as in claim 46, wherein the delay period is greater than or equal to 10 milliseconds.

[0069] 48. A system as in claim 46, wherein the delay period is in a range of 5 milliseconds to 1 second.

[0070] 49. A system as in claim 46, wherein the delay period is in a range of 5 to 100 milliseconds.

[0071] 50. A system as in claim 46, wherein the delay period is in a range of 5 to 10 milliseconds.

[0072] 51. A system as in claim 46, wherein the delay period is in a range of 10-30 milliseconds.

[0073] 52. A system as in claim 46, wherein the delay period is greater than or equal to 1000 microseconds.

[0074] 53. As system as in any of claims 43-52, wherein the one or more packets of pulses comprises 100 packets and wherein each packet comprises 40 biphasic pulses.

[0075] 54. A system as in any of claims 43-53, wherein the one or more packets of pulses comprise at least two packets separated by a packet delay period of at least 30 milliseconds.

[0076] 55. A system as in claim 54, wherein each of the packets are separated by a packet delay period of at least 30 milliseconds.

[0077] 56. A system as in any of the above claims, wherein the pulses comprise biphasic pulses and the delay period comprises an inter-phase delay between a positive phase and a negative phase of a biphasic pulse.

[0078] 57. A system as in claim 56, wherein each biphasic pulse comprises the inter-phase delay.

[0079] 58. A system as in any of the above claims, wherein the delay period comprises an inter-packet delay.

[0080] 59. A system as in claim 58, wherein the inter-packet delay is in a range of 30-5000 milliseconds.

[0081] 60. A system as in claim 59, wherein the inter-packet delay is 30-40 milliseconds.

[0082] 61. A system as in claim 59, wherein the inter-packet delay is 3000-5000 milliseconds.

[0083] 62. A system as in any of the above claims, wherein the delay period comprises an inter-pulse delay.

[0084] 63. A system as in any of the above claims, wherein the waveform comprises one or more bundles, wherein each bundle comprises two or more packets.

[0085] 64. A system as in claim 63, wherein each bundle comprises three packets and wherein each bundle is spaced apart so as to be delivered within an ST interval of a cardiac rhythm of the patient.

[0086] 65. A system as in claim 63, wherein the delay period comprises an inter-bundle delay.

[0087] 66. A system as in any of the above claims, wherein the waveform has a voltage amplitude of 500 to 4,000 volts.

[0088] 67. A system as in any of the above claims, wherein the waveform has a frequency of 300-800kHz.

[0089] 68. A system as in any of the above claims, wherein each of the one or more packets has 10-200 biphasic pulses.

[0090] 69. A system as in any of the above claims, wherein each of the one or more packets has 20-50 biphasic pulses.

[0091] 70. A system as in any of the above claims, wherein the treatment comprises 5 to 100 packets.

[0092] 71. A system as in any of the above claims, wherein the treatment comprises 10 to 60 packets.

[0093] 72. A system as in any of the above claims, further comprising a remote dispersive electrode positionable so that the energy is delivered in a monopolar manner.

[0094] 73. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising one or more packets of pulses to provide the treatment and comprising one or more delay periods which avoids a peak temperature in the tissue that would have been reached by delivery of the energy without the one or more delay periods.

[0095] 74. A system as in claim 73, wherein the peak temperature causes bubble formation.

[0096] 75. A system as in any of claims 73-74, wherein the peak temperature is 100 degrees Celsius.

[0097] 76. A system as in any of claims 73-75, wherein the peak temperature causes an electrical discharge.

[0098] 77. A system as in any of claims 73-76, wherein the delay period is greater than or equal to 5 milliseconds.

[0099] 78. A system as in claim 77, wherein the delay period is greater than or equal to 10 milliseconds.

[00100] 79. A system as in claim 77, wherein the delay period is in a range of 5 milliseconds to 1 second.

[00101] 80. A system as in claim 77, wherein the delay period is in a range of 5 milliseconds to 100 milliseconds.

[00102] 81. A system as in claim 77, wherein the delay period is in a range of 5 milliseconds to 10 milliseconds.

[00103] 82. A system as in claim 77, wherein the delay period is in a range of 10-30 milliseconds.

[00104] 83. A system as in any of claims 73-82, wherein the waveform comprises one or more bundles, wherein each bundle comprises two or more packets.

[00105] 84. A system as in claim 83, wherein each bundle comprises three packets and wherein each bundle is spaced apart so as to be delivered within an ST interval of a cardiac rhythm of the patient.

[00106] 85. As system as in any of claims 73-84, wherein the one or more packets of pulses comprises 100 packets and wherein each packet comprises 40 biphasic pulses.

[00107] 86. A system as in any of claims 73-85, wherein the pulses comprise biphasic pulses and the delay period comprises an inter-phase delay between a positive phase and a negative phase of a biphasic pulse.

[00108] 87. A system as in claim 86, wherein each biphasic pulse comprises the inter-phase delay.

[00109] 88. A system as in any of claims 73-85, wherein the delay period comprises an inter-packet delay.

[00110] 89. A system as in claim 88, wherein the inter-packet delay is in a range of 30-5000 milliseconds.

[00111] 90. A system as in claim 88, wherein the inter-packet delay is in a range of 30-40 milliseconds.

[00112] 91. A system as in claim 88, wherein the inter-packet delay is in a range of 3000-5000 milliseconds.

[00113] 92. A system as in any of claims 73-85, wherein the delay period comprises an inter-pulse delay.

[00114] 93. A system as in any of claims 73-92, wherein the waveform comprises one or more bundles, wherein each bundle comprises two or more packets.

[00115] 94. A system as in claim 93, wherein each bundle comprises three packets and wherein each bundle is spaced apart so as to be delivered within an ST interval of a cardiac rhythm of the patient.

[00116] 95. A system as in claim 93, wherein the delay period comprises an inter-bundle delay.

[00117] 96. A system as in any of claims 73-95, wherein the waveform has a voltage amplitude of 500 to 4,000 volts.

[00118] 97. A system as in any of claims 73-96, wherein the waveform has a frequency of 300-800kHz.

[00119] 98. A system as in any of claims 73-97, wherein each of the one or more packets has 10-200 biphasic pulses.

[00120] 99. A system as in any of claims 73-97, wherein each of the one or more packets has 20-50 biphasic pulses.

[00121] 100. A system as in any of claims 73-99, wherein the treatment comprises 5 to 100 packets.

[00122] 101. A system as in any of claims 73-99, wherein the treatment comprises 10 to 60 packets.

[00123] 102. A system as in any of claims 73-101, further comprising a remote dispersive electrode positionable so that the energy is delivered in a monopolar manner.

[00124] 103. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of pulses to provide the treatment

wherein each pulse has a pulse length and at least one of the at least one packet comprises a delay having a delay period that is at least twice the pulse length.

[00125] 104. A system as in claim 103, wherein the delay period is at least ten times the pulse length.

[00126] 105. A system as in any of claims 103-104, wherein the at least one packet has a packet length at least 50 times the delay period.

[00127] 106. A system as in claim 105, wherein the at least one packet has a packet length at least 100 times the delay period.

[00128] 107. A system as in any of claims 103-106, wherein the delay comprises an inter-pulse delay.

[00129] 108. A system as in claim 107, wherein the pulses are biphasic pulses and the inter-pulse delay is an inter-cycle delay.

[00130] 109. A system as in any of claims 103-106, wherein the pulses are biphasic pulses and the delay comprises inter-phase delay.

[00131] 110 .A system as in any of claims 103-109, wherein the delay period comprises 250 to 1000 microseconds.

[00132] 111. A system as in any of claims 103-110, wherein the at least one packet comprises at least 25 pulses.

[00133] 112. A system as in claim 111, wherein the at least one packet comprises at least 40 pulses.

[00134] 113. A system as in any of claims 103-112, wherein the least one packet is separated from an adjacent packet by an inter-packet delay of at least 30 microseconds.

[00135] 114. A system as in claim 113, wherein the least one packet is separated from an adjacent packet by an inter-packet delay of 100-5000 microseconds.

[00136] 115. A system as in any of claims 103-114, wherein the treatment comprises 5-100 packets.

[00137] 116. A system as in claim 115, wherein the treatment comprises 10-60 packets.

[00138] 117. A system as in any of claims 103-116, wherein the waveform has a voltage amplitude of 500-10,000 volts.

[00139] 118. A system as in any of claims 103-117, wherein each pulse has a pulse length of 1.66 microseconds.

[00140] 119. A system as in any of claims 103-117, wherein each pulse has a pulse length of 2.5 microseconds.

[00141] 120. A system as in any of claims 103-117, wherein each pulse has a pulse length of 20 microseconds.

[00142] 121. A system as in any of claims 103-120, further comprising a remote dispersive electrode positionable so that the energy is delivered in a monopolar manner.

[00143] 122. A system as in any of claims 103-121, wherein the delay period is of sufficient length to reduce or avoid bubble formation near the at least one electrode.

[00144] 123. A system as in any of claims 103-122, wherein the delay period is of sufficient length to reduce or avoid an electrical discharge event near the least one electrode.

[00145] 124. A system as in any of claims 103-123, wherein the delay period is of sufficient length to reduce or avoid cavity formation in the tissue.

[00146] 125. A system as in any of claims 103-124, wherein the delay period is of sufficient length to reduce or avoid contraction of a muscle of the patient.

[00147] 126. A system as in any of claims 103-125, wherein the delay period is of sufficient length to

[00148] avoid a peak temperature in the tissue that would have been reached by delivery of the energy without the one or more delay periods.

[00149] 127. A system as in claim 126, wherein the peak temperature causes bubble formation.

[00150] 128. A system as in any of claims 126-127, wherein the peak temperature is 100 degrees Celsius.

[00151] 129. A system as in any of claims 126-128, wherein the peak temperature causes an electrical discharge.

[00152] 130. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of biphasic pulses to provide the treatment wherein each biphasic pulse comprises an inter-phase delay in a range of 250 to 1000 microseconds.

[00153] 131. A system as in claim 130, wherein the waveform has a voltage amplitude of 500-10,000 volts.

[00154] 132. A system as in any of claims 130-131, wherein each pulse has a pulse length of 1.66 microseconds.

[00155] 133. A system as in any of claims 130-131, wherein each pulse has a pulse length of 2.5 microseconds.

[00156] 134. A system as in any of claims 130-131, wherein each pulse has a pulse length of 20 microseconds.

[00157] 135. A system as in any of claims 130-134, wherein the delay period is of sufficient length to reduce or avoid bubble formation near the at least one electrode.

[00158] 136. A system as in any of claims 130-135, wherein the delay period is of sufficient length to reduce or avoid an electrical discharge event near the least one electrode.

[00159] 137. A system as in any of claims 130-136, wherein the delay period is of sufficient length to reduce or avoid cavity formation in the tissue.

[00160] 138. A system as in any of claims 130-137, wherein the delay period is of sufficient length to reduce or avoid contraction of a muscle of the patient.

[00161] 139. A system as in any of claims 130-138, wherein the delay period is of sufficient length to

[00162] avoid a peak temperature in the tissue that would have been reached by delivery of the energy without the one or more delay periods.

[00163] 140. A system as in claim 139, wherein the peak temperature causes bubble formation.

[00164] 141. A system as in any of claims 139-140, wherein the peak temperature is 100 degrees Celsius.

[00165] 142. A system as in any of claims 139-141, wherein the peak temperature causes an electrical discharge.

[00166] 143. A system as in any of claims 130-142, further comprising a remote dispersive electrode positionable so that the energy is delivered in a monopolar manner.

[00167] 144. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising 2-60 packets of pulses to provide the treatment wherein each packet includes at least one delay period of in a range of 250 to 1000 microseconds.

[00168] 145. A system as in claim 144, wherein the waveform has a voltage amplitude of 500-10,000 volts.

[00169] 146. A system as in any of claims 144-145, wherein each pulse has a pulse length of 1.66 microseconds.

[00170] 147. A system as in any of claims 144-145, wherein each pulse has a pulse length of 2.5 microseconds.

[00171] 148. A system as in any of claims 144-145, wherein each pulse has a pulse length of 20 microseconds.

[00172] 149. A system as in any of claims 144-148, wherein the delay period is of sufficient length to reduce or avoid bubble formation near the at least one electrode.

[00173] 150. A system as in any of claims 144-149, wherein the delay period is of sufficient length to reduce or avoid an electrical discharge event near the least one electrode.

[00174] 151. A system as in any of claims 144-150, wherein the delay period is of sufficient length to reduce or avoid cavity formation in the tissue.

[00175] 152. A system as in any of claims 144-151, wherein the delay period is of sufficient length to reduce or avoid contraction of a muscle of the patient.

[00176] 153. A system as in any of claims 144-152, wherein the delay period is of sufficient length to

[00177] avoid a peak temperature in the tissue that would have been reached by delivery of the energy without the one or more delay periods.

[00178] 154. A system as in claim 153, wherein the peak temperature causes bubble formation.

[00179] 155. A system as in any of claims 153-154, wherein the peak temperature is 100 degrees Celsius.

[00180] 156. A system as in any of claims 153-155, wherein the peak temperature causes an electrical discharge.

[00181] 157. A system as in any of claims 144-156, further comprising a remote dispersive electrode positionable so that the energy is delivered in a monopolar manner.

[00182] 158. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of pulses having a delay period wherein the at least one packet has a packet length at least 50 times the delay period.

[00183] 159. A system as in claim 158, wherein the at least one packet has a packet length at least 100 times the delay period.

[00184] 160. A system as in any of claims 158-159, wherein each pulse has a pulse length of 1.66 microseconds.

[00185] 161. A system as in any of claims 158-159, wherein each pulse has a pulse length of 2.5 microseconds.

[00186] 162. A system as in any of claims 158-159, wherein each pulse has a pulse length of 20 microseconds.

[00187] 163. A system as in any of claims 158-162, wherein the delay period is of sufficient length to reduce or avoid bubble formation near the at least one electrode.

[00188] 164. A system as in any of claims 158-163, wherein the delay period is of sufficient length to reduce or avoid an electrical discharge event near the least one electrode.

[00189] 165. A system as in any of claims 158-164, wherein the delay period is of sufficient length to reduce or avoid cavity formation in the tissue.

[00190] 166. A system as in any of claims 158-165, wherein the delay period is of sufficient length to reduce or avoid contraction of a muscle of the patient.

[00191] 167. A system as in any of claims 158-166, wherein the delay period is of sufficient length to
avoid a peak temperature in the tissue that would have been reached by delivery of the energy without the one or more delay periods.

[00192] 168. A system as in claim 167, wherein the peak temperature causes bubble formation.

[00193] 169. A system as in any of claims 167-168, wherein the peak temperature is 100 degrees Celsius.

[00194] 170. A system as in any of claims 167-169, wherein the peak temperature causes an electrical discharge.

[00195] 171. A system as in any of claims 167-170, further comprising a remote dispersive electrode positionable so that the energy is delivered in a monopolar manner.

[00196] 172. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of pulses wherein each pulse has a

duty cycle of less than or equal to 50 percent so as to reduce or avoid one or more secondary effects.

[00197] 173. A system as in claim 172, wherein the one or more secondary effects comprises cavity formation in the tissue.

[00198] 174. A system as in claim 172, wherein each pulse has a duty cycle of less than or equal to 20 percent.

[00199] 175. A system as in claim 174, wherein the one or more secondary effects comprises an electrical discharge event.

[00200] 176. A system as in claim 172, wherein each pulse has a duty cycle of less than or equal to 2.5 percent.

[00201] 177. A system as in claim 176, wherein the one or more secondary effects comprises bubble formation.

[00202] 178. A system as in claim 177, wherein bubble formation comprises formation of bubbles greater than or equal to 0.1mm in diameter.

[00203] 179. A system for treating tissue comprising:

an electrode positionable near the tissue; and

a generator in electrical communication with the electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy treats the tissue, wherein the energy is generated from a waveform having a particular delay period between pulses selected to affect gas formation, external electrical discharge, muscle contraction, cavity formation, and/or temperature rise.

[00204] 180. A method of influencing at least one secondary effect of pulsed electric field therapy comprising:

selecting a particular delay period between portions of a pulsed electric field waveform so as to influence the at least one secondary effect.

[00205] 181. A method as in claim 1, wherein the at least one secondary effect comprises gas formation.

[00206] 182. A method as in claim 1, wherein the at least one secondary effect comprises electric discharge.

[00207] 183. A method as in claim 1, wherein the at least one secondary effect comprises cavity formation.

[00208] 184. A method as in claim 1, wherein the at least one secondary effect comprises muscle contraction.

[00209] 185. A method as in claim 1, wherein the at least one secondary effect comprises temperature rise.

[00210] These and other embodiments are described in further detail in the following description related to the appended drawing figures.

INCORPORATION BY REFERENCE

[00211] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[00212] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[00213] Fig. 1 illustrates an embodiment of a pulsed electric field waveform having pulses that are monophasic and are separated by an inter-pulse delay that is measured from one polarity pulse to the next pulse of the same polarity.

[00214] Fig. 2 illustrates an embodiment of a pulsed electric field waveform having pulses that are biphasic wherein each cycle is comprised of one polarity pulse followed by an opposite polarity pulse.

[00215] Fig. 3 illustrates an embodiment of a pulsed electric field waveform having pulses that are biphasic such as in Fig. 2, however in this embodiment the opposite polarity pulses are separated by an inter-phase delay.

[00216] Fig. 4 illustrates example pulses grouped in bursts or packets.

[00217] Fig. 5 illustrates example packets grouped into batches or bundles.

[00218] Figs. 6A-6C provides ultrasound images which illustrate bubble formation under various conditions when an energy delivery body is submerged into a saline bath.

[00219] Figs. 7A-7B illustrates an example comparison between the effects of different sized cycle delays on electrical discharge.

[00220] Figs. 8A-8B illustrate the effects of identical pulsed electric field treatment protocols, apart from different cycle delays, delivered to liver tissue. Fig. 8A illustrates the result of using a waveform having a cycle delay of approximately 50ns which resulted in

significant tissue cavity format. Fig. 8B illustrates the result of using the same waveform but with a cycle delay of approximately 1000μs.

[00221] Fig. 9, illustrates Nodes of Ranvier occurring along a myelinated axon where the axolemma (axon membrane) is exposed to the extracellular space.

[00222] Fig. 10 illustrates modeling of myelinated axon regions are modeled as electrical components.

[00223] Figs. 11A-11D illustrates the charging and discharging behavior of a motor neuron in response to pulsed electric field waveforms having no or low cycle delay versus a larger cycle delay.

[00224] Fig. 12 illustrates the effect of cycle delay on muscle stimulation threshold.

[00225] Fig. 13 illustrates amplitude and distribution of a temperature rise from a pulsed electric field protocol generated by a numerical simulation.

[00226] Figs. 14A-14B illustrate the temperature distribution at the time of maximum temperature rise as related to Fig. 13.

[00227] Fig. 15 provides an overview illustration of an example therapeutic system for use in delivering specialized pulsed electric field energy.

[00228] Fig. 16 illustrates another embodiment of a treatment device configured for use in delivering the specialized pulsed electric field energy, particularly configured to deliver focal therapy.

[00229] Fig. 17 illustrates a portion of the heart showing a cut-away of the right atrium and left atrium along with the treatment device of Fig. 16 disposed therein.

[00230] Fig. 18 illustrates treatment of the tissue surrounding the opening of the left inferior pulmonary vein in a point by point fashion with the use of the treatment device of Fig. 16.

[00231] Fig. 19A-19B illustrate another embodiment of a therapeutic energy delivery catheter or device.

[00232] Figs. 20A-20B illustrate another embodiment of a treatment system.

[00233] Fig. 21A illustrates an embodiment of a waveform of a signal prescribed by an energy delivery algorithm.

[00234] Fig. 21B illustrates various examples of biphasic pulses having an inter-phase time therebetween.

[00235] Fig. 21C illustrates further examples of waveforms having unequal voltages.

[00236] Fig. 21D illustrates further examples of waveforms having unequal pulse widths.

[00237] Fig. 21E illustrates an example waveform prescribed by another energy delivery algorithm wherein the waveform is monophasic.

[00238] Fig. 21F illustrates further examples of waveforms having monophasic pulses.

[00239] Fig. 21G illustrates further examples of waveforms having such phase imbalances.

[00240] Fig. 21H illustrates an example of a waveform having imbalances in both positive and negative voltages.

[00241] Fig. 22 is a graph illustrating portions of a sample electrocardiogram (ECG) trace of a human heart highlighting periods wherein it is desired to deliver energy pulses to the lung passageway via the energy delivery body.

DETAILED DESCRIPTION OF THE INVENTION

[00242] Specific embodiments of the disclosed devices, systems, and methods will now be described with reference to the drawings. Nothing in this detailed description is intended to imply that any particular component, feature, or step is essential to the invention.

[00243] A variety of different types of energy have been used for therapeutic treatments of patients, including radiofrequency (RF) energy, microwave (MW) energy, high intensity focused ultrasound (HIFU) energy, and pulsed electric field (PEF) energy, to name a few. These energy modalities differ according to the waveform of the electric signal provided by the generator. When possible, they are categorized according to the electromagnetic spectrum. The electromagnetic spectrum covers electromagnetic waves with frequencies ranging from below one hertz to above 10^{25} hertz, corresponding to wavelengths from thousands of kilometers down to a fraction of the size of an atomic nucleus. This frequency range is divided into separate bands, and the electromagnetic waves within each frequency band are called by different names; beginning at the low frequency (long wavelength) end of the spectrum these are: radio waves, microwaves, terahertz waves, infrared, visible light, ultraviolet, X-rays, and gamma rays at the high-frequency (short wavelength) end. The electromagnetic waves in each of these bands have different characteristics, such as how they are produced, how they interact with matter, and their practical applications.

[00244] RF energy is the lowest portion in the electromagnetic spectrum familiar as a medium of analog and modern digital wireless communication system. It spreads in the range between 3 kHz and 300 GHz and is a continuous waveform. Waveforms having a frequency in the RF range have been manipulated to change from a continuous waveform to a pulsed waveform. Thus, energy is applied intermittently, in pulses or short bursts of pulses. Pulsed RF or pulsed electric fields (PEF) provide different effects on cellular tissue than continuously

delivered RF because cells react differently over the time that the energy is applied. For example, RF ablation causes cell death due to thermal damage to the cells while PEF cause cell death by non-thermal (i.e. below a threshold for causing thermal ablation) effects. Such cell death maintains extracellular matrices so that the targeted tissue maintains its structural architecture including blood vessels and lymphatics. Thus, sensitive structures, such as biological lumens, blood vessels, nerves, etc., are able to be preserved which are critical to maintaining the integrity and functionality of the tissue.

[00245] Fig. 1 illustrates an embodiment of a PEF waveform 10 having pulses 12 that are monophasic and are separated by an inter-pulse delay 14 that is measured from one polarity pulse to the next pulse of the same polarity. Thus, the inter-pulse delay 14 may be considered a DC pulse delay. Fig. 2 illustrates an embodiment of a PEF waveform 10 having two pulses 12 that are each biphasic wherein each cycle is comprised of one polarity phase 12a followed by an opposite polarity phase 12b. In this embodiment, there is no delay between these two opposite polarity phases 12a, 12b, however there is an inter-cycle delay 16 between the cycles (i.e. biphasic pulses). It may be appreciated that inter-cycle delays are a form of inter-pulse delays wherein the pulses are biphasic pulses. Fig. 3 illustrates an embodiment of a PEF waveform 10 having pulses 12 that are biphasic such as in Fig. 2, however in this embodiment the opposite polarity phases 12a, 12b are separated by a switch delay or inter-phase delay 18.

[00246] In some instances, pulses 12 are grouped in bursts or packets 20, such as illustrated in Fig. 4. Here, five packets 20 are illustrated, each packet 20 being comprised of a plurality of cycles or biphasic pulses. The packets 20 are separated by inter-packet delays 22. It may be appreciated that packets 20 may be comprised of a variety of different types of pulses (e.g. monophasic, biphasic, etc.) and the same or differing polarities. For example, in some embodiments, a packet 20 is comprised of a series of pulses 12 of the same polarity, followed by a switch in polarity for one or more pulses 12, which may or may not be followed by subsequent switches in polarity for one or more additional pulses 12.

[00247] Optionally, in some instances, packets 20 are grouped into batches or bundles 24, such as illustrated in Fig. 5. Here, two bundles 24 are illustrated, each bundle 24 being comprised of three packets 20. The bundles 24 are separated by inter-bundle delays 26. Typically, the energy is applied to the patient so that the inter-bundle delays 26 are synced with the heartbeat, wherein the inter-bundle delays 26 occur during the sensitive portions of the heartbeat. Thus, energy is applied outside of sensitive portions of the heartbeat so as to avoid inducing arrhythmias. In some embodiments, energy is delivered during the R-T interval of a patient's ECG rhythm. In other embodiments, the PEF energy is delivered agnostic to the

location in the ECG waveform. Biphasic waveforms, in particular, are able to be delivered in this manner safely without disrupting the normal electrophysiological behavior of the heart. Thus, bundles may be used for reasons such as expediting treatments, with varying inter-bundle delays 26 that are established for other reasons, such as thermal mitigation. Alternately, packets 20 can be delivered in quick succession, without bundling of the packets. These packets may be delivered synchronously or asynchronously to the ECG rhythm.

[00248] Typically, a treatment is considered the period of energy delivery to a target area before moving to the next target area. For example, when treating a passageway of a lung, an energy delivery device may comprise an electrode that circumferentially contacts an inner surface of a segment of the lung passageway. The energy from the waveform may be applied continuously, or the user may start and stop energy activation/application. In either case, energy is delivered to the electrode until the segment of target tissue receiving the energy is desirably treated. Energy delivery is then ceased, and the electrode is repositioned within the lung passageway so as to treat a new segment of target tissue (either overlapping or not overlapping with the first segment of target tissue). Each period of energy delivery to a target area before moving to the next target area is considered a treatment. Thus, a patient would typically undergo a plurality of treatments within a lung during a procedure.

[00249] When treating a portion of the heart, such as when ablating portions of heart to treat atrial fibrillation, an energy delivery device may comprise an electrode having a blunt tip that contacts a surface of the atrium or pulmonary vein. In such instances, energy is delivered from the tip to the cardiac tissue to create ablation at the area of contact. This is repeated as the tip is moved to various locations, so as to create a circular or linear ablation which blocks electrical conduction through the cardiac tissue. Again, a treatment is considered the period of energy delivery to a target area before moving to the next target area. Thus, a full conduction block would typically involve a plurality of treatments, wherein each treatment is comprised of one or more activations.

[00250] In summary, for the purposes described herein, a treatment typically comprises the entire period of PEF delivery to affect a targeted section of tissue that is delivered from one electrode (or set of electrodes) to another electrode (or set of electrodes) before moving one of the electrodes. Likewise, an activation typically comprises the PEF treatment delivery for a single "start" sequence initiated by a user. Multiple activations may be delivered in a single treatment. The time between activations would be determined by the user and any secondary constraints on PEF delivery (such as synchronization with a cardiac rhythm, time for temperature to return to baseline, or due to incidental incomplete treatment delivery of the first activation).

[00251] The PEF waveforms are delivered to tissue through one or more energy delivery bodies, each having one or more electrodes. Ultimately, the physical arrangement of electrodes forms a circuit. Electrodes may behave as the cathode or anode, or both, at any given time within a packet, a series of pulses, a cycle, an activation, or any other period that separates two pulses. When electrodes that partially or fully create the electrical circuit are in the same regional proximity, particularly in or near the targeted tissue, the system is referred as bipolar or multipolar electrode arrangements. Multipolar arrangements would apply when more than two polarity orientations are used, such as one electrode set at 1000 V, a second at 500 V, and a third at 0V, whereby the 2nd electrode is known to be a negative polarity to the first electrode, but a positive polarity to the third electrode. When one or more of the electrodes in the circuit are placed separate at a distant, non-targeted region of tissue (e.g., a dispersive pad) this arrangement is referred as a monopolar electrode arrangement. These descriptions are for convenience, and descriptions of the use of the concepts described herein for either of these arrangements may be interpreted as applicable to other arrangements of electrodes.

[00252] Energy delivery may be actuated by a variety of mechanisms, such as with the use of an actuator 132 on the device 102 or a foot switch operatively connected to the generator 104. Such actuation typically provides a single energy dose or activation. The energy dose is typically defined by the number of packets delivered and the voltage of the packets. Each energy dose delivered to the target tissue is configured to maintain the temperature at or in the target tissue below a threshold for thermal ablation, particularly thermal ablation or denaturing of stromal proteins in the basement membrane or deeper submucosal extracellular protein matrices. In addition, the doses may be titrated or moderated over time so as to further reduce or eliminate thermal buildup during the treatment procedure. Instead of inducing thermal damage, defined as extracellular protein coagulation at sites of danger to therapy, the energy dose provides energy at a level which induces treatment of the condition without damaging sensitive tissues.

[00253] It may be appreciated that the delays described herein (e.g. inter-pulse delay 14, inter-cycle delay 16, inter-phase delay 18, inter-packet delay 22, inter-bundle delay 26, etc.) may be consistent or varied throughout a packet 20, bundle 26 and/or treatment depending on the type of waveform. Likewise, some delays may not be present because they are zero or because they are not relevant to the waveform (e.g. if no bundles 24 are present, there are no inter-bundle delays 26 due to irrelevancy). Inter-pulse delays 14 may be consistent throughout a packet 20 of pulses 12, or they may change over the course of the packet 20. For example, a first inter-pulse delay may be 50ns, followed by a second inter-pulse delay of 1ms, after which the sequence is repeated. There may be sub-patterns within a packet 20 wherein a given sequence of pulses 12 of

comparable with varying polarities is repeated (e.g.: up, up, down, delay, up, up, down, ...; up, up, down, down, up, delay, down, up, up, down, down, ...; etc), these sub-patterns are referred to as a series of pulses. Each series of pulses has the same pattern which defines it as a series. However, each series may have differing characteristics such as having pulses of differing polarity, differing pulse widths, differing amplitudes, and differing inter-phase and/or interpulse delays in differing patterns. In some embodiments, different series are positioned in a repeating sequence., Thus, in some embodiments, there are relevant intra-series delays from any given pulse to the subsequent pulse, and a secondary range of inter-series delays between the given series.

[00254] In some embodiments, inter-pulse delays 14 are consistent over the course of a packet 20 and in other embodiments, the inter-pulse delays 14 vary within a packet 20. In some embodiments, the duty cycle of pulses comprising a packet ranges from <0.01% to 100%. In some embodiments, a treatment comprises identical packets 20, wherein each packet 20 has consistent inter-pulse delays 14 or inconsistent inter-pulse delays 14. In other embodiments, a treatment comprises at least two different types of packets 20, wherein each of the at least two different types of packets 20 has consistent inter-pulse delays 14 yet the inter-pulse delays 14 differ between the at least two different types of packets 20. Or in other embodiments, at least one of the at least two different types of packets 20 has inconsistent inter-pulse delays 14 that differs from the other. Typically, when bundles 24 are present, the inter-bundle delay 26 is consistent when synced with a cardiac rhythm, however it may be appreciated that the inter-bundle delay 26 may vary either with the patient changes in cardiac rhythm or upon other treatment delivery protocol constraints.

[00255] In any case, it may be appreciated that any combination of delays (e.g. inter-pulse delay 14, inter-cycle delay 16, inter-phase delay 18, inter-packet delay 22, inter-bundle delay 26, etc.) may be utilized within a treatment to obtain a desired outcome. In particular, these delays may be specifically manipulated to obtain particular desired outcomes. For example, one, some or all of these delays may be manipulated to control various aspects of PEF therapy so as to mitigate any associated risks, such as gas formation, electrical discharge, cavity formation, muscle contraction, and temperature rise, to name a few. In some embodiments, the delays distribute the period over which (high) voltage PEF energy is delivered, resulting in marked changes and optimization to the treatment delivery outcomes. In some embodiments, the range of delays described herein are between 0s and 100ms.

[00256] In some embodiments, the delay periods are manipulated to distribute the pace of energy delivery and permit resolution and decay of certain effects prior to them inducing effects

from their accumulation. When applying PEFs for biological cell and tissue manipulation, where charge accumulation and decay is at a different timescale than the other effects, it is possible to accumulate treatment effect on the cell with multiple cycles or series of pulses, but without causing a variety of secondary treatment effects, such as gas formation, electrical discharge, cavity formation, muscle contraction, and temperature rise, to name a few. In other instances, these secondary accumulated treatment effects may be desirable to initiate or enhance therapy outcomes, and thus the delays will be selected to encourage these effects, which again are done in a manner that does not alter the primary objective of inducing cellular and tissue responses to the PEFs. These examples of secondary effects are not an exhaustive list and other secondary effects desired to be manipulated may also be controlled by selecting appropriate delays.

Gas Formation

[00257] In some embodiments, delays are manipulated to discourage the gas formation generated by PEF therapies. As mentioned previously, in order for molecular bonds to break, thereby forming gas, energy needs to be delivered for a sufficient period of time. Further, once gas has formed, it aggregates over time and coalesces into collectively larger regions, forming progressively larger bubbles. The larger the bubbles, the longer the time taken for the bubbles to resorb into fluid. These processes can be diminished or avoided by skillfully introducing delays into the waveform. Such delays provide energy in time periods insufficient to form any or any substantial quantities of gas and/or insufficient to allow any bubbles that may have been generated to grow large enough to avoid dissolution. The total energy being delivered is not altered by such manipulation the delays, thereby preserving the overall treatment effect. Thus, with the proper choice of delays, it may be possible for gas formation to be avoided or for bubbles to entirely re-dissolve or re-form into other molecules.

[00258] Even if the delays are insufficient for complete elimination of the gas from resorbing into the fluid, is the delays may be sufficient to prevent the meaningful aggregation of the gases into larger bubbles. In such instances, the smaller bubbles are migrating and beginning to resorb prior to the next onset of energy and additional gas formation. In this way, the bubbles do not coalesce into large bubbles. Importantly, the size of the bubble also relates to its effects in the body. A small (<0.1mm diameter) bubble typically will resorb in the order of seconds and is generally too small to induce a meaningful ischemic event. Thus, bubbles produced at this size typically do not pose a meaningful threat to patient safety. Conversely, larger bubbles (>0.1mm) may take minutes or longer to resorb and may disrupt or occlude blood vessels. Therefore, even if bubble generation cannot be eliminated entirely, suppressing the size and quantity of bubbles

produced to only those that are clinically insignificant and/or will resorb quickly may be equally effective.

[00259] In some embodiments, when delivering PEF therapies in blood (an electrolytic fluid) in a monopolar fashion (i.e. with the use of a remotely positioned return electrode) using 7F tip cardiac ablation focal electrode catheter, the suppression of the amount and size of produced gas formation may begin setting in when cycle delays of 1μs are present in a waveform having pulses 12 that are biphasic (1μs duration) and have a voltage of 3000V. In other embodiments, a comparable energy delivery begins showing meaningful reductions in gas formation when cycle delays are 10 or 20μs, with a complete elimination of hyperechoic bubbles when cycle delays are greater than or equal to 150 μs.

[00260] Figs. 6A-6C provides ultrasound images which illustrate bubble formation under various conditions when an energy delivery body 108 (e.g. electrode) is submerged into a saline bath. Fig. 6A illustrates a baseline image of an energy delivery body 108, indicated by an arrow, wherein no energy is being delivered. Thus, this image serves as a control. A shadow artifact is highlighted at the arrowhead. Fig. 6B illustrates energy delivery by the energy delivery body 108 wherein the waveform has a cycle delay of 50ns. This shows an extensive degree of hyperechoic bubbles being generated and visualized on the screen. Fig. 6D illustrates energy delivery by the energy delivery body 108 wherein the waveform has the same parameters as in Fig. 6B, however the waveform has a cycle delay of 1ms. As shown, no bubbles are visible anywhere within the imaging window.

[00261] Thus, in some embodiments, when delivering PEF therapies in blood or any electrolytic fluid, adjacent to a target tissue, such as in cardiac or vascular clinical applications, gas formation can be eliminated with the use of delays, such as cycle delays or other delays, in the range of 100μs -10,000μs, preferably 100μs -1000μs, such as 250μs-1000μs. It may be appreciated that in some embodiments delays are 100μs, 150μs, 200μs, 250μs, 300μs, 400μs, 500μs, 600μs, 700μs, 800μs, 900μs, 1000μs, in the range of 100-250μs, 250-500μs, 500-1000μs, greater than 250μs, greater than 500μs, greater than 1000μs, 1000-5,000μs, 1000-10,000μs, to name a few. In some embodiments, when delivering PEF to solid tissues, such as when the energy deliver body 108 is positioning into a target tissue, gas formation can be eliminated with the use of delays, such as cycle delays or other delays, in the range of 10μs-1000μs, preferably 25μs-100μs. It may be appreciated that in some embodiments delays are 10μs, 20μs, 25μs, 30μs, 40μs, 50μs, 60μs, 70μs, 80μs, 90μs, 100μs, in the range of 10-100μs, 25-500μs, 500-1000μs, greater than 25μs, greater than 50μs, greater than 100μs, to name a few.

Electrical Discharge

[00262] In some instances, when energy is delivered from an energy delivery body 108 to the patient, electric current concentrates and accumulates in a focal region around the energy delivery body 108. At a point, the cumulative energy delivery exceeds the breakdown potentials of the energy delivery body 108 material or the surrounding tissue or fluid. This causes electrical discharge events (e.g. sudden flow of electricity, such as arcing) from the energy delivery body 108 to the nearby tissue, fluid, or cells. However, the introduction of appropriate waveform delays permits relaxation of charge buildup in the fluids and tissue materials. Thus, by introducing delays, the energy delivery is not constant, thus allowing for relaxation of the charge buildup at various times prior to resuming energy delivery. With a sufficient number and duration of delays, discharge events can be prevented. The sufficient number and duration of delays to prevent discharge is related to the energy and intensity of the treatment protocol; higher voltages will involve longer delays.

[00263] Electrical discharge events are very likely in PEF therapies that involve waveforms having voltages in the range of 500-5000 V to invoke their therapeutic effects, especially when using bipolar electrode arrangements. It may be appreciated that electrical discharge events can occur outside of this range depending on specific conditions, particularly when energy is delivered via bipolar electrodes. For these ranges of parameters, delays (e.g. cycle delays, etc.) of 50, 250, 500, or 1000 μs and beyond may be most appropriate at retaining the predominant degree of treatment effect while also preventing electrical arcing discharge.

[00264] Figs. 7A-7B illustrates an example comparison between the effects of different sized cycle delays on electrical discharge. Here, an energy delivery body 108 was immersed in a saline bath and delivered a PEF treatment until a visible electric discharge was encountered. The waveform was comprised of a plurality of pulses 12 forming a packet 20 having an on-time of 300μs. This 300μs on-time packet was delivered at progressively higher voltages until a visible electrical discharge event was encountered. After this, the on-time was decreased, and the voltage was continued to be increased until an electric discharge was again visible. Fig. 7A illustrates a waveform having a very small cycle delay (50ns). Fig. 7B illustrates a waveform having a modest cycle delay (50μs). Notably, the 50μs cycle delay trial set shows an increase of 78% in electric current that may be delivered before an electric discharge was noted when compared to a very small, ~50ns, cycle delay. Thus, this modest cycle delay was shown to markedly increase the amount of energy that can be delivered by the electrode prior to an electric discharge. This cycle delay is well below the realm where a reduced efficacy in treatment effect may be encountered (depending on cell size and properties, most likely begins to occur in the 5-

10ms cycle delay range). This greater resilience to electrical arcing was demonstrated to remain for all packet on-times tested in this series.

[00265] It may be appreciated that the design of the energy delivery body 108 or the physical arrangements of the energy delivery bodies 108 also play a role. When the design or arrangement of the energy delivery bodies 108 encourage concentration of electric currents, such as smaller contact areas or regions of sharp boundaries on the energy delivery bodies 108, longer delays are utilized to mitigate electrical discharge events.

[00266] Thus, in some embodiments, when delivering PEF therapies in blood or any electrolytic fluid, adjacent to a target tissue, such as in cardiac or vascular clinical applications, electric discharge can be eliminated with the use of delays, such as cycle delays or other delays, in the range of 50μs -10,000μs, preferably 250μs -1000μs. It may be appreciated that in some embodiments delays are 50μs, 100μs, 150μs, 200μs, 250μs, 300μs, 400μs, 500μs, 600μs, 700μs, 800μs, 900μs, 1000μs, in the range of 50-250μs, 250-500μs, 500-1000μs, greater than 250μs, greater than 500μs, greater than 1000μs, 1000-5,000μs, 1000-10,000μs, to name a few. In some embodiments, when delivering PEF to solid tissues, such as when the energy deliver body 108 is positioning into a target tissue, electric discharge can be eliminated with the use of delays, such as cycle delays or other delays, in the range of 100μs-10,000μs, preferably 250μs-2000μs. It may be appreciated that in some embodiments delays are 100μs, 200μs, 250μs, 300μs, 400μs, 500μs, 600μs, 700μs, 800μs, 900μs, 1000μs, 1500μs, 2000μs, in the range of 250-500μs, 250-1000μs, 500-1000μs, 1000-2000μs, greater than 250μs, greater than 500μs, greater than 1000μs, to name a few. In some embodiments, when delivering PEF to luminal targets (e.g. airways), such as when the energy delivery body 108 is positioned within the lumen of a target tissue having no conductive fluid, electric discharge can be eliminated with the use of delays, such as cycle delays or other delays in the range of 10μs-10,000μs, preferably 50μs-500μs. It may be appreciated that in some embodiments delays are 10μs, 20μs, 30μs, 40μs, 50μs, 60μs, 70μs, 80μs, 90μs, 100μs, 200μs, 300μs, 400μs, 500μs, in the range of 50-100μs, 100-250μs, 250-500μs, 1000-10,000μs, greater than 50μs, greater than 250μs, greater than 500μs, greater than 1000μs to name a few.

Cavity Formation

[00267] As mentioned, when electrical discharge does occur a pressure wave is generated that is apparent as an audible "popping" tone. When the discharge and the pressure wave is of sufficient intensity and repeated a sufficient number of times, the energy transferred and deposited into the tissue from this pressure wave can severely disrupt the tissue architecture and

cells. The resulting effect is the accumulated generation of a defect or cavity within the tissue at the regions near the electrode, which experience the strongest intensity of these effects.

[00268] By incorporating delays between the energized portions of the waveform, such as within a PEF packet, time is permitted for resolution of physical effects at a molecular level before these effects accumulate into a pressure wave capable of generating a tissue cavity. This results in a more distributed deposition of energy into the tissue, reducing or eliminating the pressure waves that occur as a result of PEF therapies. Thus, the introduction of cycle delays and other delays into the waveform can be used to mitigate or eliminate the generation of cavities. This can be harnessed to increase the predictability of the treatment effect outcome, and also be used to eliminate the dangers associated with the cavity formation, such as the disruption of vasculature integrity, fistula formation, or damage to other sensitive tissues.

[00269] Figs. 8A-8B illustrate the effects of identical PEF treatment protocols, apart from different cycle delays, delivered to liver tissue T. Fig. 8A illustrates the result of using a waveform having a cycle delay of approximately 50ns which resulted in significant tissue cavity C formation. Fig. 8B illustrates the result of using the same waveform but with a cycle delay of approximately 1000μs. Thus, the same amount of energy is delivered. As shown, such a longer cycle delay is able to entirely eliminate the large cavities formed in the liver tissue T.

[00270] One collateral benefit of cavity elimination is more efficient energy deposition into tissue by potentially eliminating gaps at the tissue-electrode interface. This could result in the generation of larger treatment effects.

[00271] In some embodiments, when delivering PEF to solid tissues, such as when the energy deliver body 108 is positioning into a target tissue, cavity formation can be eliminated with the use of delays, such as cycle delays or other delays, in the range of 100μs-10,000μs, preferably 250μs-2000μs. It may be appreciated that in some embodiments, delays are 100μs, 200μs, 250μs, 300μs, 400μs, 500μs, 600μs, 700μs, 800μs, 900μs, 1000μs, 1500μs, 2000μs, in the range of 250-500μs, 250-1000μs, 500-1000μs, 1000-2000μs, greater than 250μs, greater than 500μs, greater than 1000μs, to name a few.

Muscle Contraction

[00272] Cells and tissues closest to the energy delivery bodies 108 are the most intensely affected cells and tissue in PEF therapies. It is possible to subject these cells and tissues to the accumulated generation of treatment effects while avoiding or preventing the generation of action potentials in distant motor neurons and skeletal muscle (as well as cardiac and smooth muscle). This is achieved with the use of biphasic pulses and is further achieved with delays

within the waveform. It has been found that the charging and relaxation characteristics of these distant motor neurons involve longer duration cycle delays to prevent their occurrence. For example, 10ms, 20ms, 30ms, 40ms, or 50ms cycle delays may be used.

[00273] In some instances, desired cycle delays are determined at least in part by numerical simulations of action potential generation. In some embodiments, a model is utilized that is based on an array of Nodes of Ranvier between myelinated regions of axons. Referring to Fig. 9, Nodes of Ranvier NR, also known as myelin-sheath gaps, occur along a myelinated axon MA where the axolemma AA (axon membrane) is exposed to the extracellular space. Nodes of Ranvier NR are uninsulated and highly enriched in ion channels, allowing them to participate in the exchange of ions required to regenerate the action potential. Nerve conduction in myelinated axons MA occurs in a manner in which the action potential seems to "jump" from one node NR to the next along the axon MA. This results in faster conduction of the action potential.

[00274] Referring to Fig. 10, the myelinated axon MA regions are modeled as resistors for the intracellular environment. Each node NR is comprised of a membrane for the cell that separates the intracellular environment from the extracellular environment and is modeled as a capacitor in parallel with a leakage resistor and voltage source. When exposed to an electric field, the myelinated axon MA begins charging along the capacitor. When the electric field is removed (e.g. the pulse is ceased for a delay period), the charge accumulation on the myelinated axon MA begins discharging. Thus, the ability for a PEF therapy to induce an action potential in motor neurons relates to the effective duty cycle of the PEF waveform.

[00275] This concept is conveyed in Figs. 11A-11D. Fig. 11A illustrates an example PEF waveform 10 having no or low cycle delay 16 and Fig. 11B provides a schematic depiction of the charging 62 and discharging 64 behavior of a motor neuron. Two packets 20 of the waveform 10 are depicted, separated by an inter-packet delay 22. As the packet 20 is delivered, the motor neuron incrementally charges throughout the delivery. After a period of time, the accumulated transmembrane potential induces an action potential (indicated by dashed line 66). The motor neuron then begins discharging upon commencement of the inter-packet delay 22. This repeats for each later packet 20.

[00276] Fig. 11C illustrates an example PEF waveform 10 having larger cycle delay 16 than the waveform of Fig. 11A. Fig. 11D provides a schematic depiction of the charging 62 and discharging 64 behavior of the motor neuron. As the waveform 10 is delivered, the motor neuron incrementally charges throughout the delivery, however discharging begins upon commencement of the cycle delay 16. Thus, it is apparent that the inclusion of larger cycle delays 16 results in constraining the accumulated transmembrane potential below that which

would induce an action potential (below the dashed line 66). For a given active period of energy delivery, a characteristic delay for that waveform and electric field intensity exists that prevents accumulated axon charge from reaching the threshold that induces an action potential.

[00277] Properties for the mathematical model are selected to mimic that of motor neuron axons. By utilizing the model, it is found that benefits of cycle delays 16 to mitigate muscle contractions begin occurring at cycle delays of 10ms and plateau at cycle delays of 1 second, as illustrated in Fig. 12. Thus, this is the modeled effective range to limit muscle contraction. It should be noted that these ranges will change relative to the intensity, phase-behavior (monophasic or biphasic or varying asymmetry levels of biphasic), other parameters of the PEF waveform (total packet on-time, etc), geometry of the electrode arrangement (bipolar, multipolar, or monopolar), and the proximity of a given motor neuron to the PEF electrode(s) for whether an action potential is ultimately induced in the neuron. Muscle cells (skeletal, cardiac, smooth) will also have similar effects and characteristics affecting their susceptibility to contraction, though at different inherent sensitivities based on the inherent characteristics and specific properties of these cells.

[00278] Depending on the specifics of the PEF waveform, as cycle delays 16 are increased generally from 5ms up to and beyond 10ms, there is a chance that the total volume of tissue treated by the PEFs will begin to decrease. However, the closest cells to the energized electrode will still remain affected and thus treated by the tissue. Thus, although treatment effects will vary as cycle delays 16 begin ranging into the 10s of milliseconds, it is still possible to generate meaningful treatment outcomes using cycle delays that will reduce or eliminate muscle contraction. Conversely, short to eliminated delays could be used to encourage additional muscle contraction, where desired.

[00279] In some embodiments, when delivering PEF to solid tissues, such as when the energy deliver body 108 is positioning into a target tissue, muscle contraction can be reduced or eliminated with the use of delays, such as cycle delays or other delays, in the range of 5ms-100ms, preferably 10-30ms. In some embodiments, when delivering PEF to luminal targets (e.g. airways), such as when the energy delivery body 108 is positioned within the lumen of a target tissue having no conductive fluid, muscle contraction can be reduced or eliminated with the use of cycle delays in the range of 5ms-100ms, preferably 10-30ms. In either case, it may be appreciated that in some embodiments delays are 5ms, 10ms, 25ms, 30ms, 40ms, 50ms, 60ms, 70ms, 80ms, 90ms, 100ms, in the range of 5-10ms, 10-20ms, 20-30ms, greater than 5ms, greater than 10ms, greater than 15ms, greater than 30ms, to name a few.

Temperature Rise

[00280] As described herein, introducing and manipulating delay periods between active periods of a PEF waveform distributes the energy deposition into the tissue over a longer period of time. This significantly affects the shape and amplitude of the temperature rise spike that characteristically occurs for PEF therapies during the pulse delivery period, particularly at the region very close to the electrode (tissue-electrode interface). This improves the safety of the treatment, reduces the chance for collateral tissue effects, and reduces the chances for electrical discharge events, including sparking or arc formation, by eliminating the potential for hot-spots in the tissue or fluid that would encourage arcing. Thus, introduction of cycle delays can be used to significantly improve treatment outcomes by attenuating the peak temperatures that occur.

[00281] Referring to Fig. 13, calculation of the amplitude and distribution of a temperature rise from a PEF protocol can be generated by a numerical simulation. In this example, three PEF protocols are compared, each comprising a waveform 10 having a single packet 20 of biphasic pulses 12. A first PEF protocol includes no cycle delays, a second PEF protocol includes 1ms cycle delays 16 and a third PEF protocol includes 10ms cycle delays 16. As shown in Fig. 13, the general mm-scale distribution of temperatures exceeding 50°C was comparable between the protocols having no cycle delays and 1ms cycle delays. However, the instantaneous spike in max temperature at the tissue-electrode interface is dramatically different. The protocol having no cycle delay generated maximum temperatures of ~175°C, while the protocol having 1ms cycle delays reached a peak temperature of ~80°C, and the protocol having 10ms cycle delays muted the maximum temperature rise to ~55°C. The temperature distribution at the time of maximum temperature rise is illustrated in Figs. 14A-14B, thus reflecting a different duration into the packet for the 0ms delay (Fig. 14A) versus the 1ms delay (Fig. 14B). Thus, the introduction and manipulation of cycle delays 16 induces a marked, scalable, effect on thermal effects that occur to the tissue.

[00282] It should be noted that these values are at the immediate tissue-electrode boundary, where maximum temperatures are encountered, followed by a very steep decline in temperature. Once the packet is completed, there is a steep decline in temperature as well. Thus, while these values indicate very high temperatures, they do not indicate that significant degrees of thermal damage would occur from the modeled PEF therapy at mm-scale distances into the tissue from the electrode. However, the mitigated temperature peaks would significantly reduce the potential generation of harmful thermal damage and protein denaturation in close proximity to the electrode, as well as reduce the chances of generating electrical discharge events. These are two of the key benefits for utilizing cycle delays in these procedures.

[00283] Thus, in some embodiments, when delivering PEF therapies in blood or any electrolytic fluid, adjacent to a target tissue, such as in cardiac or vascular clinical applications, peak temperatures can be reduced with the use of delays, such as cycle delays or other delays, in the range of 200μs -20,000μs, preferably 500μs -10,000μs. In some embodiments, when delivering PEF to solid tissues, such as when the energy deliver body 108 is positioning into a target tissue, peak temperatures can be reduced with the use of delays, such as cycle delays or other delays, in the range of 200μs -20,000μs, preferably 500μs -10,000μs. In either case, it may be appreciated that in some embodiments delays are 500μs, 1000μs, 2000μs, 3000μs, 4000μs, 5000μs, 6000μs, 7000μs, 8000μs, 9000μs, 10,000μs, in the range of 200-500μs, 500-1000μs, 500-1000μs, 1000-10,000μs, 10,000-20,000μs, greater than 200μs, greater than 500μs, greater than 1000μs, to name a few.

[00284] In some embodiments, when delivering PEF to luminal targets (e.g. airways), such as when the energy delivery body 108 is positioned within the lumen of a target tissue having no conductive fluid, peak temperatures can be reduced with the use of delays, such as cycle delays or other delays, in the range of 100μs-10,000μs, preferably 200μs-1000μs. In either case, it may be appreciated that in some embodiments delays are 100μs, 200μs, 300μs, 400μs, 500μs, 600μs, 700μs, 800μs, 900μs, 1000μs, in the range of 100-200μs, 100-500μs, 500-1000μs, 500-1000μs, 1000-10,000μs, greater than 200μs, greater than 500μs, greater than 1000μs, to name a few.

Comparisons of Delay Ranges to Control Effects

[00285] Overall, the susceptibility and sensitivity for a given therapy to each secondary treatment effect, such as gas formation, electrical discharge, cavity formation, muscle contraction, and temperature rise, will vary. Table 1, below, summarizes the potential most applicable ranges of delays that may be used to mitigate these effects for various targeted tissue varieties. Notably, this table focuses on applications to mitigate the secondary effects, but there are other times when these effects may want to be encouraged, and thus a different range of delays may be applicable for a given therapeutic target.

Table 1. Summary Table of Basic Cycle Delays

Target	Electrode(s) Location	Objective	Cycle Delay General Range (Targeted Range)
Cardiac/Vascular	In blood, adjacent to target tissue	Eliminate gas formation	100μs – 10ms (250-1000μs)

		Eliminate electric discharge	50µs – 10ms (250-1000µs)
		Increase treatment effect	100µs – 10ms (500µs-5ms)
		Reduce peak temperatures	200µs-20ms (500µs-10ms)
		Reduce muscle contraction	5ms – 100ms (10-30ms)
Solid Tissues	Placed into target tissue	Eliminate gas formation	10µs – 1ms (25 – 100µs)
		Eliminate electric discharge	100µs – 10ms (250-2000µs)
		Increase treatment effect	100µs – 10ms (500µs-5ms)
		Eliminate cavity formation	100µs – 10ms (250-2000µs)
		Reduce muscle contraction	5ms – 100ms (10-30ms)
		Reduce peak temperatures	200µs-20ms (500µs-10ms)
Luminal Targets (airways, etc)	Within lumen of target tissue, no conductive fluid	Eliminate electric discharge	10µs – 10ms (50-500µs)
		Increase treatment effect	100µs – 10ms (500µs-2ms)
		Reduce muscle contraction	5ms – 100ms (10-30ms)
		Reduce peak temperatures	100µs-10ms (200µs-1ms)

[00286] Thus, the inclusion and manipulation of various delays within PEF waveforms, particularly phase delays, cycle delays 16, and/or inter-packet delays 20, provides a powerful tool to dramatically improve treatment outcomes. This is achieved by eliminating or reducing

the risks associated with secondary effects inherently caused by PEF therapies due to their nature of delivering high voltage electric pulses. These effects and benefits will apply regardless of the ranges of energy delivered in the waveform.

[00287] Thus, methods have been provided for controlling the secondary effects described above (e.g. gas formation, electrical discharge, muscle contraction, cavity formation and temperature rise) by controlling the duration and/or sequences of the constituent delays comprising a PEF treatment waveform contained within a cycle, series, packet, bundle, and/or activation that comprises what is collectively referred as the PEF waveform. It may be appreciated that although the examples and embodiments described herein focus on cycle delays 16, such information (e.g. example ranges for delay values, delay positions, number of delays, delay types, etc.) applies to any delay or combination of delays in a PEF waveform. Different types of delays, alone or in combination, may have the same effect by allowing a particular treatment effect while spreading out the energy delivery so as to mitigate various secondary effects. Thus, in some instances, manipulation of the timing of the energy delivery can be achieved in various ways with the same or similar outcome. Such effects may also be influence by electrode arrangements.

[00288] In an effort to provide sufficient examples of the various parameter combinations and outcome effects, Table 2 is provided hereinbelow. Table 2 provides a variety of combinations of treatment scenarios including electrode shape, circuit type, various parameter values and treatment effects. Example minimum values for cycle delays 16 to avoid various secondary effects (e.g. bubble formation, arcing, cavity formation) are provided given the particular scenario. Thus, it is apparent that delay values are dependent on a variety of factors related to the treatment protocol, however unifying concepts are elucidated as described herein-throughout.

[00289] Table 2.

Treatment Effect (depth)	Electrode shape	Circuit Type	Frequency kHz	Cycle Count	Packets	Amperage A	Calculated impedance ohms	Calculated Voltage, kV	Min Cyc delay to avoid bubbles, µs	Min Cyc delay to avoid arcing, µs	Min Cyc delay to avoid cavity, µs
~5mm	Focal tip	Monopolar	400	45	12	19	100	1900	10	0	0
~6.5mm	Focal tip	Monopolar	400	45	21	22	100	2200	50	0	0
~8mm	Focal tip	Monopolar	400	45	30	25	100	2500	100	10	0
~10mm	Focal tip	Monopolar	400	45	30	30	100	3000	200	40	5
~8mm	1/2 surface area of Focal tip	Monopolar	400	45	30	25	100	2500	200	20	10
~8mm	Focal tip	Monopolar	Mono-phasic	10µs pulses, 10 cycs total	30	15	100	1500	200	50	30
~10mm	Focal tip	Monopolar	200	20	30	22	100	2200	300	60	35
Treatment Effect (width)	Electrode shape	Circuit Type	Frequency kHz	Cycle Count	Packets	Amperage A	Calculated impedance, ohms	Calculated Voltage, kV	Min Cyc delay to avoid bubbles, µs	Min Cyc delay to avoid arcing, µs	Min Cyc delay to avoid cavity, µs
~1 cm	Needle	Monopolar	400	40	100	22	150	3300	150	250	100
~2 cm	Needle	Monopolar	100	10	100	22	150	3300	200	300	200
~3 cm	Needle	Monopolar	80	8	100	26.7	150	4000	500	350	250
~1 cm	Needle	Monopolar	Mono-phasic	10µs pulses, 10 pulses total	30	22	150	3300	50	25	10

[00290] When reducing secondary effects, a primary principle underlying the use of these methods is that the delays are too short for complete discharge of accumulated charge distortions and/or recovery of the cell and organelles from the effects induced by the pulsed electric field (e.g., cell polarization, ATP depletion, etc). Thus, the repeated exposure of the targeted cells and tissue to a subsequent pulse, pulses, or series of pulses following the initial pulse or series of pulses results in the accumulation of injury to the cell, which ultimately increases its susceptibility to macromolecule transport (drugs, genetic material, etc) or results in its death (phagocytized, programmed cell death (parthanatos, pyroptosis, apoptosis, etc), necrosis, etc). Thus, the efficacy of the PEF therapy remains, at a consistent or altered extent, while the secondary effects are controlled.

[00291] Regarding these methods, the secondary effects may be reduced when delays are selected of sufficient duration whereby the induction of one or more of these behaviors is attenuated or prevented entirely. The effects may also be selectively encouraged, such as by using delays that are sufficiently low so as to foster their occurrence, especially when subsequent pulses within a portion of the waveform are of similar polarity arrangement. For example, in some instances, gas formation may be used to the advantage of the clinician via mechanisms such as physically disrupting the treatment environment. This may be used for purposes such as encouraging cell death, encouraging cell susceptibility to cytoactive agents, increasing mixing efficiency for infusions, and other potential uses. Therefore, at times it is desirable to control and encourage the formation of gas resulting from PEF therapies. However, for convenience,

methods are primarily described herein to reduce the secondary (acellular) effects that may occur as a result of PEF therapies.

Waveform Lengths

[00292] When introducing and/or manipulating delays in a PEF waveform, various characteristics of the waveform may change. For example, when introducing or increasing cycle delays 16 in a packet 20 of a PEF waveform 10, the time to complete a packet will increase. It may be appreciated that such increase in packet duration or completion time will not increase packet on-time if the only change is an increase in delays. If a treatment is determined by delivering a particular number of packets 20, then the treatment time will increase with an increase in packet duration. Likewise, if inter-packet delays 26 are introduced or increased, the treatment time will also increase if the treatment comprises more than one packet.

[00293] In some instances, PEF waveforms without delays are delivered in pulses or packets that are 100µs in length. When using a waveform having a base frequency of 400kHz, the waveform has 400,000 cycles per second or one cycle is 2.5µs long. Thus, in such instances the packet would comprise 40 cycles. If a cycle delay of 250µs was introduced to such a packet (e.g. after each cycle within the packet), the packet length or packet duration would increase by 10,000µs for a total packet duration of 10,100µs. Table 3, below, illustrates the total packet time for a variety of introduced cycle delays (e.g. 250µs, 500µs,1000 µs) in comparison to the packet duration for conventional PEF waveforms. In this table, a cycle delay is introduced after each cycle within the packet. This behavior is the same for phase-delays instead of cycle delays.

[00294] Table 3.

	# of packets	# cycles per packet	Total packet time (µs)	% on-time during total packet time
No delays	1	40	100	100%
With 250µs cycle delays	1	10	2,525	0.99%
With 250µs cycle delays	1	25	6,313	0.99%
With 250µs cycle delays	1	50	12,625	0.99%
With 250µs cycle delays	1	100	25,250	0.99%
With 500µs cycle delays	1	10	5,025	0.50%

With 500µs cycle delays	1	25	12,563	0.50%
With 500µs cycle delays	1	50	25,125	0.50%
With 500µs cycle delays	1	100	50,250	0.50%
With 1000µs cycle delays	1	10	10,025	0.25%
With 1000µs cycle delays	1	25	25,063	0.25%
With 1000µs cycle delays	1	50	50,125	0.25%
With 1000µs cycle delays	1	100	100,250	0.25%

[00295] In some embodiments, the inclusion of delays may increase the packet duration to a range of approximately 1000 to 200,000 microseconds, such as 2,000µs, 5,000µs, 10,000µs, 20,000µs, 25,000µs, 30,000µs, 40,000µs, 50,000µs, 60,000µs, 70,000µs, 80,000µs, 90,000µs, 100,000µs, 110,000µs, 120,000µs, 130,000µs, 140,000µs, 150,000µs, 160,000µs, 170,000µs, 180,000µs, 190,000µs, 200,000µs, 1000-2000µs, 1000-3000µs, 1000-4000µs, 1000-5000µs, 1000-10,000µs, 10,000-20,000µs, 10,000-30,000µs, 10,000-40,000µs, 10,000-50,000µs, 50,000-100,000µs, 50,000-150,000µs, 50,000-200,000µs, greater than 10,000µs, greater than 25,000 µs, greater than 50,000µs, greater than 100,000µs, greater than 200,000µs to name a few.

[00296] It may be appreciated that Table 3 illustrates a small sample of combinations. Waveforms can include delays of any length, any number of delays and any type of delay (i.e. not limited to cycle delays). The delays may be consistent (e.g. same length, same position, etc., throughout waveform) or inconsistent (e.g. at least one of differing length, at least one in differing position or skipping position, differing between packets, differing between batches, etc.). Likewise, different base frequencies may be used. Further, any number of packets may be present in a waveform and any number of batches may be present, including no batches. In any case, the introduction of these types of delays significantly increases the packet time, as illustrated above. However, such increases have minimal impact on overall treatment time given the relatively small timescale of such increases. In other words, the tolerable limit for treatment times during a procedure is well beyond such increases due to inclusion of delays.

Delivery Devices and Systems

[00297] Typically, the energy is delivered with the use of systems and devices designed for the particular clinical application. With sufficient access, energy can be delivered to any

target within the body of the patient. In some embodiments, the systems and devices are designed for endoluminal access to target tissue throughout the body, particularly in locations previously considered inaccessible to percutaneous approaches. Endoluminal access allows treatment of target tissue from within various lumens in the body. Lumens are the spaces inside of tubular-shaped or hollow structures within the body and include passageways, canals, ducts and cavities to name a few. Example luminal structures include blood vessels, esophagus, stomach, small and large intestines, colon, bladder, urethra, urinary collecting ducts, uterus, vagina, fallopian tubes, ureters, kidneys, renal tubules, spinal canal, spinal cord, and others throughout the body, as well as structures within and including such organs as the lung, heart and kidneys, to name a few. In some embodiments, the target tissue is accessed via the nearby luminal structure. In some instances, a treatment device 102 is advanced through various luminal structures or branches of a luminal system to reach the target tissue location. For example, when accessing a target tissue site via a blood vessel, the treatment device 102 may be inserted remotely and advanced through various branches of the vasculature to reach the target site. Likewise, if the luminal structure originates in a natural orifice, such as the nose, mouth, urethra or rectum, entry may occur through the natural orifice and the treatment device 102 is then advanced through the branches of the luminal system to reach the target tissue location. Alternatively, a luminal structure may be entered near the target tissue via cut-down or other methods. This may be the case when accessing luminal structures that are not part of a large system or that are difficult to access otherwise.

[00298] Target tissues include any of the luminal structures themselves, tissue nearby these luminal structures and any tissue accessible from these endoluminal approaches or other approaches, such as percutaneous, laparoscopic or open surgical approaches. These include cells, tissues and/or organs in the integumentary, skeletal, muscular, nervous, endocrine, cardiovascular, lymphatic, respiratory, digestive, urinary, and reproductive systems, to name a few. Examples cells, tissues and/or organs include luminal structures themselves, soft tissues throughout the body located near luminal structures and solid organs accessible from luminal structures, including but not limited to liver, pancreas, gall bladder, kidney, prostate, ovary, lymph nodes and lymphatic drainage ducts, underlying musculature, bony tissue, brain, eyes, thyroid, etc.

[00299] Examples of systems which may utilize waveform manipulations such as described herein include the tissue modification systems (e.g., energy delivery catheter systems) described in commonly assigned patent applications including international patent application number PCT/US2017/039527 titled "GENERATOR AND A CATHETER WITH AN

ELECTRODE AND A METHOD FOR TREATING A LUNG PASSAGEWAY," international patent application number PCT/US2018/067501 titled "METHODS, APPARATUSES, AND SYSTEMS FOR THE TREATMENT OF DISORDERS", international patent application number PCT/US2018/067504 titled "OPTIMIZATION OF ENERGY DELIVERY FOR VARIOUS APPLICATIONS", international patent application number PCT/US2020/028844 titled "DEVICES, SYSTEMS AND METHODS FOR THE TREATMENT OF ABNORMAL TISSUE", and international patent application number PCT/US2020/042260 titled "TREATMENT OF THE REPRODUCTIVE TRACT WITH PULSED ELECTRIC FIELDS", international patent application number PCT/US2020/066205 titled "TREATMENT OF CARDIAC TISSUE WITH PULSED ELECTRIC FIELDS", all of which are incorporated herein by reference for all purposes.

[00300] Fig. 15 provides an overview illustration of an example therapeutic system 100 for use in delivering the specialized PEF energy. In this embodiment, the system 100 comprises an elongate device 102 comprising a shaft 106 having a distal end 103 and a proximal end 107. The device 102 includes an energy delivery body 108 which is generically illustrated as a dashed circle near the distal end 103 of the shaft 106. It may be appreciated that the energy delivery body 108 may take a variety of forms having structural differences which encumber the drawing of a single representation, however individual example embodiments will be described and illustrated herein. The energy delivery body 108 may be mounted on or integral with an exterior of the shaft 106 so as to be externally visible. Or, the energy delivery body 108 may be housed internally within the shaft 106 and exposed by advancing from the shaft 106 or retracting the shaft 106 itself. Likewise, more than one energy delivery body 108 may be present and may be external, internal or both. In some embodiments, the shaft 106 is comprised of a polymer, such as an extruded polymer. It may be appreciated that in some embodiments, the shaft 106 is comprised of multiple layers of material with different durometers to control flexibility and/or stiffness. In some embodiments, the shaft 106 is reinforced with various elements such as individual wires or wire braiding. In either case, such wires may be flat wires or round wires. Wire braiding has a braid pattern and in some embodiments the braid pattern is tailored for desired flexibility and/or stiffness. In other embodiments, the wire braiding that reinforces the shaft 106 may be combined advantageously with multiple layers of material with different durometers to provide additional control of flexibility and/or stiffness along the length of the shaft.

[00301] In any case, each energy delivery body 108 comprises at least one electrode for delivery of the PEF energy. Typically, the energy delivery body 108 comprises a single delivery

electrode and operates in a monopolar arrangement which is achieved by supplying energy between the energy delivery body 108 disposed near the distal end 103 of the device 102 and a return electrode 140 positioned upon the skin of the patient. It will be appreciated, however, that bipolar energy delivery and other arrangements may alternatively be used. When using bipolar energy delivery, the device 102 may include a plurality of energy delivery bodies 108 configured to function in a bipolar manner or may include a single energy delivery body 108 having multiple electrodes configured to function in a bipolar manner. The device 102 typically includes a handle 110 disposed near the proximal end 107. The handle 110 is used to maneuver the device 102, and typically includes an actuator 132 for manipulating the energy delivery body 108. In some embodiments, the energy delivery body 108 transitions from a closed or retracted position (during access) to an open or exposed position (for energy delivery) which is controlled by the actuator 132. Thus, the actuator 132 typically has the form of a knob, button, lever, slide or other mechanism. It may be appreciated that in some embodiments, the handle 110 includes a port 111 for introduction of liquids, agents, substances, tools or other devices for delivery through the device 102. Example liquids include suspensions, mixtures, chemicals, fluids, chemotherapy agents, immunotherapy agents, micelles, liposomes, embolics, nanoparticles, drug-eluting particles, genes, plasmids, and proteins, to name a few.

[00302] The device 102 is in electrical communication with a generator 104 which is configured to generate the PEF energy. In this embodiment, the generator 104 includes a user interface 150, one or more energy delivery algorithms 152, a processor 154, a data storage/retrieval unit 156 (such as a memory and/or database), and an energy-storage sub-system 158 which generates and stores the energy to be delivered. In some embodiments, the user interface 150 on the generator 104 is used to select the desired treatment algorithm 152. In other embodiments, the algorithm 152 is automatically selected by the generator 104 based upon information obtained by one or more sensors, which will be described in more detail in later sections. A variety of energy delivery algorithms may be used. In some embodiments, one or more capacitors are used for energy storage/delivery, however any other suitable energy storage element may be used. In addition, one or more communication ports are typically included.

[00303] As illustrated in Fig. 15, the distal end 103 of the device 102 is typically advanceable through a delivery device, such as an endoscope 10. Endoscopes 10 typically comprise a control body 12 attached to an elongate insertion tube 14 having a distal tip 16. The endoscope 10 has an interior lumen accessible by a port 18 into which the distal end 103 of the device 102 passes. The shaft 106 of the device 102 advanceable through the interior lumen and exits out of the distal tip 16. Imaging is achieved through the endoscope 10 with the use of a

light guide tube 20 having an endoscopic connector 22 which connects to a light and energy source. The distal tip 16 of the endoscope may be outfitted with visualization technologies including but not limited to video, ultrasound, laser scanning, etc. These visualization technologies collect signals consistent with their design and transmit the signal either through the length of the shaft over wires or wirelessly to a video processing unit. The video processing unit then processes the video signals and displays the output on a screen. It may be appreciated that the endoscope 10 is typically specific to the anatomical location to which it is being used, such as gastroscopes (upper GI endoscopy, which includes the stomach, esophagus, and small intestine (duodenum)), colonoscopes (large intestine), bronchoscopes (lungs), laryngoscopes (larynx), cystoscopes (urinary tract), duodenoscopes (small intestine), enteroscopes (digestive system), ureteroscopes (ureter), hysteroscopes (cervix, uterus), etc. It may be appreciated that in other embodiments, the device 102 is deliverable through a catheter, sheath, introducer, needle or other delivery system.

[00304] Once a target tissue area has been approached endoluminally, energy can be delivered to the target tissue in a variety of ways. In one arrangement, an energy delivery body 108 is positioned within a body lumen and energy is delivered to the target tissue that is has entered the body lumen, through at least a portion of the lumen wall to target tissue either within the lumen wall and/or at least partially surrounding the lumen wall or through the lumen wall to target tissue outside and nearby the lumen wall. In another arrangement, the energy delivery body 108 is advanced through the lumen wall and inserted within or near target tissue outside of the lumen wall. It may be appreciated that such arrangements may be combined, involving at least two energy delivery bodies 108, one positioned within the body lumen and one extending through the wall of the body lumen. In some embodiments, each of the energy delivery bodies 108 function in a monopolar manner (e.g. utilizing a return electrode placed at a distance). In other embodiments, at least some of the energy delivery bodies 108 function in a bipolar manner (e.g. utilizing an energy delivery body 108 as a return electrode). Optionally, each of two energy delivery bodies 108 may be positioned on opposite sides of a lumen wall and function in a bipolar manner so as to treat tissue therebetween (e.g. within the lumen wall). Since the lumen itself is preserved throughout the treatment, these delivery options are possible and allow treatment of tissue in, on or nearby the lumen itself. Such delivery of therapy allows access to previously inaccessible tissue, such as tumors or diseased tissue that has invaded lumen walls or has wrapped at least partially around a body lumen, too close to be surgically removed or treated with conventional focal therapies. Many conventional focal therapies, such as treatment with

thermal energy, damage or destroy the structure of the lumen walls due to thermal protein coagulation, etc.

[00305] The endoscopic approach also lends itself to monopolar energy delivery. As mentioned, monopolar delivery involves the passage of current from the energy delivery body 108 (near the distal end of the device 102) to the target tissue and through the patient to a return pad 140 positioned against the skin of the patient to complete the electric current circuit. Thus, in some embodiments, the device 102 includes only one energy delivery body 108 or electrode. This allows the device 102 to have a low profile so as to be positionable within smaller body lumens. This also allows deep penetration of tissue surrounding the energy delivery body 108. Likewise, when penetrating the lumen wall with such devices, only one penetration is needed per treatment due to the use of only one energy delivery body 108. It may be appreciated that additional penetrations may occur due to various device designs or treatment protocols, however in some embodiments, the monopolar delivery design reduces the invasiveness of the procedure, simplifies the device and treatment design and provides superior treatment zones in target tissue.

[00306] In contrast, bipolar delivery involves the passage of current through target tissue between two electrodes either on the same energy delivery body 108, on different energy delivery bodies 108 or by other arrangements. Most conventional energy therapies are bipolar and are typically percutaneous. Such therapies involve multiple penetrations of the skin, increasing discomfort, prolonging healing and adding complexity to the procedure. It may be appreciated that although the systems described herein may be utilized in a variety of formats, including bipolar and percutaneous arrangements, the device features will typically be combined in a manner that reduces overall invasiveness and provides better outcomes.

[00307] Fig. 16 illustrates another embodiment of a treatment device 102 configured for use in delivering the specialized PEF energy, particularly configured to deliver focal therapy. In this embodiment, the device 102 comprises an elongate shaft 106 having at least one energy delivery body 108 near its distal end 103 and a handle 110 near its proximal end 107. In this embodiment, the at least one energy delivery body 108 comprises a “focal electrode” having a cylindrical shape. The cylindrical shape has a circular, substantially flat face or curved face for positioning against tissue. In some embodiments, the device 102 has an overall length of 50-150cm, preferably 100-125cm, more preferably 110-115cm. Likewise, in some embodiments, it has a 7 Fr outer diameter 3-15Fr, preferably 4-12Fr, more preferably 7-8.5Fr. It may be appreciated that in some embodiments, the shaft 106 has a deflectable end portion 121 and optionally the deflectable end portion 121 may have a length of 50-105mm resulting in curves with diameters ranging from approximately 15 to 55mm. Deflection may be achieved by a

variety of mechanism including a pull-wire which extends to the handle 110. Thus, the handle 110 is used to manipulate the device 102, particularly to steer the distal end 103 during delivery and treatment. Energy is provided to the device 102, and therefore to the at least one energy delivery body 108, via a cable 13 that is connectable to the generator 104.

[00308] In some embodiments, the treatment device 102 of Fig. 16 is utilized for treating cardiac tissues, particularly for treating arrhythmias, such as atrial fibrillation. Fig. 17 illustrates a portion of the heart H showing a cut-away of the right atrium RA and left atrium LA. The largest pulmonary veins are the four main pulmonary veins (right superior pulmonary vein RSPV, right inferior pulmonary vein RIPV, left superior pulmonary vein LSPV and left inferior pulmonary vein LIPV), two from each lung that drain into the left atrium LA of the heart H. In some embodiments, treatment of atrial fibrillation involves placing the treatment device 102 deep within the pulmonary vein and gradually withdrawing to the ostium, proximal to the mapping catheter. Mapping and treatment then commences.

[00309] In some embodiments, the tissue surrounding the opening of the left inferior pulmonary vein LIPV is treated in a point by point fashion with the use of the treatment device 102 (with assistance of mapping) to create a circular treatment zone around the left inferior pulmonary vein LIPV, as illustrated in Fig. 18. In some instances, specialized navigation software can be used to allow appropriate positioning of the treatment catheter 120. The delivery electrode 122 is positioned near or against the target tissue area, and energy is provided to the delivery electrode 122 so as to create a treatment area A. Since the energy is delivered to a localized area (focal delivery), the electrical energy is concentrated over a smaller surface area, resulting in stronger effects than delivery through an electrode extending circumferentially around the lumen or ostium. It also forces the electrical energy to be delivered in a staged regional approach, mitigating the potential effect of preferential current pathways through the surrounding tissue. These preferential current pathways are regions with electrical characteristics that induce locally increased electric current flow therethrough rather than through adjacent regions. Such pathways can result in an irregular electric current distribution around the circumference of a targeted lumen, which thus can distort the electric field and cause an irregular increase in treatment effect for some regions and a lower treatment effect in other regions. This may be mitigated or avoided with the use of focal therapy which stabilizes the treatment effect around the circumference of the targeted region. Thus, by providing the energy to certain regions at a time, the electrical energy is "forced" across different regions of the circumference, ensuring an improved degree of treatment circumferential regularity. Fig. 18 illustrates the repeated application of energy in point by point fashion around the left inferior pulmonary vein LIPV with

the use of the treatment device 102 to create a circular treatment zone. As illustrated, in this embodiment each treatment area A overlaps an adjacent treatment area A so as to create a continuous treatment zone. The size and depth of each treatment area A may depend on a variety of factors, such as parameter values, treatment times, tissue characteristics, etc. It may be appreciated that the number of treatment areas A may vary depending on a variety of factors, particularly the unique conditions of each patient's anatomy and electrophysiology. In some embodiments, the number of treatment areas A include one, two, three, four, five, six, seven, eight, nine, ten, fifteen, twenty, twenty five, thirty or more.

[00310] When all the electrical connections between the atrium and the vein have been treated, there is electrical silence within the pulmonary vein, with only the far field atrial signal being recorded. Occasionally spikes of electrical activity are seen within the pulmonary vein with no conduction to the rest of the atrium; these clearly demonstrate electrical discontinuity of the vein from the rest of the atrial myocardium.

[00311] It may be appreciated that in various embodiments the treatment device 102 includes a variety of specialized features. For example, in some embodiments, the device 102 includes a mechanism for real time measurement of the contact force applied by the catheter tip to a patient's heart wall during an ablation procedure. In some embodiments, this mechanism is included in the shaft 120 and comprises a tri-axial optical force sensor which utilizes white light interferometry. By monitoring and modifying the applied force throughout the procedure, the user is able to better control the device 102 so as to create more consistent and effective lesions.

[00312] Referring back to Fig. 16, in some embodiments, the device 102 includes one or more additional electrodes 109 (e.g. ring electrodes) positioned along the shaft 120, proximal to the energy delivery body 108. In some embodiments, some or all of the electrodes 109 can be used for stimulating and recording (for electrophysiological mapping), so a separate cardiac mapping catheter is not needed when using device 102 for ablation.

[00313] In some embodiments, the device 102 includes a thermocouple temperature sensor, optionally embedded in the energy delivery body 108. Likewise, in some embodiments the device 102 includes a lumen which may be used for irrigation and/or suction. In some embodiments, the device 102 includes one or more sensors that can be used to determine temperature, impedance, resistance, capacitance, conductivity, permittivity, and/or conductance, to name a few. In some embodiments, one or more of the electrodes act as the one or more sensors. In other embodiments, the one or more sensors are separate from the electrodes. Sensor data can be used to plan the therapy, monitor the therapy and/or provide direct feedback via the processor 154, which can then alter the energy-delivery algorithm 152. For example, impedance

measurements can be used to determine not only the initial dose to be applied but can also be used to determine the need for further treatment, or not.

[00314] It may be appreciated that in some embodiments the system 100 includes an automated treatment delivery algorithm that dynamically responds and adjusts and/or terminates treatment in response to inputs such as temperature, impedance at various voltages or AC frequencies, treatment duration or other timing aspects of the energy delivery pulse, treatment power and/or system status.

[00315] As mentioned previously, one or more energy delivery algorithms 152 are programmable, or can be pre-programmed, into the generator 104 for delivery to the patient P. The one or more energy delivery algorithms 152 specify electric signals which provide energy delivered to the walls of the heart which are non-thermal (e.g. below a threshold for thermal ablation; below a threshold for inducing coagulative thermal damage), reducing or avoiding inflammation, and/or preventing denaturation of stromal proteins in the luminal structures. In general, the algorithm 152 is tailored to affect tissue to a pre-determined depth and/or volume and/or to target specific types of cellular responses to the energy delivered.

[00316] Fig. 19A illustrates another embodiment of a therapeutic energy delivery catheter or device 102. In this embodiment, the device 102 has an elongate shaft 106 with at least one energy delivery body 108 near its distal end and a handle 110 at its proximal end. The device 102 is connectable to a generator 104 as part of a treatment system 100. Connection of the device 102 to the generator 104 provides electrical energy to the energy delivery body 108, among other features. In this embodiment, the energy delivery body 108 includes a plurality of wires or ribbons 120, constrained by a proximal end constraint 122 and a distal end constraint 124, and forms a spiral-shaped basket serving as an electrode. In an alternative embodiment, the wires or ribbons are straight instead of formed into a spiral-shape (i.e., configured to form a straight-shaped basket). In still another embodiment, the energy delivery body 108 is laser cut from a tube. It may be appreciated that a variety of other designs may be used. For example, Fig. 19B illustrates an energy delivery body 108 having a paddle shape. In this embodiment, the energy delivery body 108 is comprised of a plurality of wires or ribbons 120 arranged so as to form a flat pad or paddle. Such an energy delivery body 108 is flexible so as to be retracted into the shaft 106. Referring back to Fig. 19A, in this embodiment the energy delivery body 108 is self-expandable and delivered to a targeted area in a collapsed configuration. This collapsed configuration can be achieved, for example, by placing a sheath 126 over the energy delivery body 108. The instrument shaft 106 (within the sheath 126) terminates at the proximal end constraint 122, leaving the distal end constraint 124 essentially axially unconstrained and free to

move relative to the shaft 106 of the device 102. Advancing the sheath 126 over the energy delivery body 108 allows the distal end constraint 124 to move forward, thereby lengthening/collapsing and constraining the energy delivery body 108.

[00317] As shown in this example, the device 102 includes a handle 110 at its proximal end. In some embodiments, the handle 110 is removable, such as by pressing a handle removal button 130. In this embodiment, the handle 110 includes an energy delivery body manipulation knob or actuator 132 wherein movement of the actuator 132 causes expansion or retraction/collapse of the basket-shaped electrode. In this example, the handle 110 also includes a working port snap 134 for optional connection with an endoscope or other type of visualization device and a cable plug-in port 136 for connection with the generator 104. It may be appreciated that a variety of types of visualization may be used, including angiography (optionally including markers), computed tomography, optical coherence tomography, ultrasound, and direct video visualization, to name a few.

[00318] In this embodiment, the therapeutic energy delivery device 102 is connectable with the generator 104 along with a dispersive (return) electrode 140 applied externally to the skin of the patient P. Thus, in this embodiment, monopolar energy delivery is achieved by supplying energy between the energy delivery body 108 disposed near the distal end of the device 102 and the return electrode 140. It will be appreciated, however, that bipolar energy delivery and other arrangements may alternatively be used. When using bipolar energy delivery, the therapeutic energy delivery device 102 may differ in overall design, such as to include a plurality of energy delivery bodies 108, or may appear similar in overall design, such as to include a single energy delivery body 108 which is configured to function in a bipolar manner. In some instances, bipolar energy delivery allows for the use of a lower voltage to achieve the treatment effect, as compared to monopolar energy delivery. In a bipolar configuration, the positive and negative poles are close enough together to provide a treatment effect both at the electrode poles and in-between the electrode poles. This can spread the treatment effect over a larger, shallower surface area thus requiring a lower voltage to achieve the treatment effect, compared to monopolar. Likewise, this lower voltage may be used to reduce the depth of penetration.

[00319] As mentioned previously, one or more energy delivery algorithms 152 are programmable, or can be pre-programmed, into the generator 104 for delivery to the patient. The one or more energy delivery algorithms 152 specify electric signals which provide energy delivered to the tissue that are non-thermal (e.g. below a threshold for thermal ablation; below a threshold for inducing coagulative thermal damage), reducing or avoiding inflammation, and/or

preventing denaturation of stromal proteins in the luminal structures. In general, the algorithm 152 is tailored to affect tissue to a pre-determined depth and/or to target specific types of cellular responses to the energy delivered. It may be appreciated that depth and/or targeting may be affected by parameters of the energy signal prescribed by the one or more energy delivery algorithms 152, the design of the device 102 (particularly the one or more energy delivery bodies 108), and/or the choice of monopolar or bipolar energy delivery. Typically, depths of up to 0.01cm, up to 0.02cm, 0.01-0.02cm, up to 0.03cm, 0.03-0.05cm, up to 0.05cm, up to 0.08cm, up to 0.09cm, up to 0.1cm, up to 0.2cm, up to 0.5cm, up to 0.7cm, up to 1.0cm, up to 1.5cm, up to 2.0cm, up to 2.5cm, up to 3.0cm, up to 3.5cm, up to 4.0cm, up to 4.5cm, or up to 5.0cm, to name a few. These depths may be larger for circumferentially focal targets, or they may exist for entire circumferential depths through a lumen and parenchymal tissue.

[00320] Figs. 20A-20B illustrate another embodiment of a treatment system 100. Here, the system 100 is configured to treat target tissue that is located at least partially outside of a body lumen wherein treatment may benefit from originating the treatment energy at a distance from the body lumen. In this embodiment, the system 100 comprises an energy delivery device 102 connectable with a generator 104. It may be appreciated that many of the system components described above are utilized in this embodiment of the system 100, such as particular aspects of the device 102, generator 104 and other accessories. Therefore, such description provided above is applicable to the system 100 described herein below. The main differences are related to the energy delivery body 108.

[00321] Here, the device 102 comprises a shaft 106 having a distal end 103, a proximal end 107 and at least one lumen 105 extending at least partially therethrough. Likewise, the device 102 also includes at least one energy delivery body 108. In this embodiment, an energy delivery body 108 has the form of a probe 500 that is disposed within the lumen 105 of the shaft 106. The probe 500 has a probe tip 502 that is advanceable through the lumen 105 and extendable from the distal end 103 of the shaft 106 (expanded in Fig. 20A to show detail). In this embodiment, the tip 502 has a pointed shape configured to penetrate tissue, such as to resemble a needle. Thus, in this embodiment, the probe tip 502 is utilized to penetrate the lumen wall W and surrounding tissue so that it may be inserted into the target tissue external to the body lumen. Thus, the probe 500 has sufficient flexibility to be endoluminally delivered yet has sufficient column strength to penetrate the lumen wall W and target tissue. In some embodiments, the device 102 has markings to indicate to the user the distance that the probe tip 502 has been advanced so as to ensure desired placement.

[00322] In some embodiments, the probe extends from the distal end 103 of the shaft 106 approximately less than 0.5 cm, 0.5 cm, 1 cm, 2 cm, 3 cm, 4 cm, 5 cm, 6 cm, 7 cm, 8 cm or more than 8 cm. In some embodiments, the probe extends 1-3 cm or 2-3 cm from the distal end of the shaft 106. In some embodiments, the probe is 18 gauge, 19 gauge, 20 gauge, 21 gauge, 22 gauge, 23 gauge, 24 gauge, or 25 gauge. In some embodiments, the probe 500 is comprised of a conductive material so as to serve as an electrode. Thus, the electrode would have the size of the exposed probe. Example materials include stainless steel, nitinol, cobalt-chromium alloy, copper, and gold. Thus, in these embodiments, the PEF energy is transmittable through the probe 500 to the probe tip 502. Consequently, the shaft 106 is comprised of an insulating material or is covered by an insulating sheath. Example insulating materials include polyimide, silicone, polytetrafluoroethylene, and polyether block amide. The insulating material may be consistent or varied along the length of the shaft 106 or sheath. Likewise, in either case, the insulating material typically comprises complete electrical insulation. However, in some embodiments, the insulating material allows for some leakage current to penetrate.

[00323] When the probe 500 is energized, the insulting shaft 106 protects the surrounding tissue from the treatment energy and directs the energy to the probe tip 502 (and any exposed portion of the probe 500) which is able to deliver treatment energy to surrounding tissue. Thus, the tip 502 acts as a delivery electrode and its size can be selected based on the amount of exposed probe 500. Larger electrodes can be formed by exposing a greater amount of the probe 500 and smaller electrodes can be formed by exposing less. In some embodiments, the exposed tip 502 (measured from its distal end to the distal edge of the insulating shaft) during energy delivery has a length of 0.1cm, 0.2 cm, 0.3 cm, 0.4 cm, 0.5 cm, 0.6 cm,0.7 cm, 0.8 cm, 0.9 cm, 1 cm, 2 cm, 3 cm, greater than 3 cm, up to 8cm, less than or equal to 0.1cm, less than or equal to 0.3cm, less than or equal to 0.5 cm, less than or equal to 1 cm, 0.2-0.3 cm, 0.1-0.5 cm, 0.1-1 cm, and all ranges and subranges therebetween. In addition to changing the size of the electrode, the tip 502 is retractable into the shaft 106 to allow for atraumatic endoscopic delivery and is then advanceable as desired to reach the target tissue. In this embodiment, advancement and retraction are controlled by an actuator 132 (e.g. knob, button, lever, slide or other mechanism) on a handle 110 attached to the proximal end 107 of the shaft 106. It may be appreciated that the shaft 106 itself may be advanced toward the target tissue, with or without advancing the probe from the distal end 103 of the shaft 106. In some embodiments, the distal end of the shaft 106 is advanced up to 20 cm into the tissue, such as from an external surface of a luminal structure or from an external surface of the body of the patient.

[00324] The handle 110 is connected to the generator 104 with the use of a specialized energy plug 510. The energy plug 510 has a first end 512 that connects to the handle 110 and a second end 514 the connects to the generator 104. The connection of the first end 512 with the handle 110 is expanded for detail in Fig. 20B. In this embodiment, the first end 512 has an adapter 516 that includes a connection wire 518 extending therefrom. The connection wire 518 is insertable into the proximal end of the probe 500 within the handle 110. This allows the energy to be transferred from the generator 104, through the connection wire 518 to the probe 500. Thus, the probe 500 is able to be electrified throughout its length, however only the exposed tip 502 delivers energy to the tissue due to the presence of the insulated shaft 106.

[00325] The devices, systems and methods described herein may be used on their own or in combination with other treatments. Such combinatory treatment may be applicable to cancer treatment in particular. For example, the PEF treatment described herein may be used in combination with a variety of non-surgical therapies, neoadjuvant and adjuvant therapies such as radiotherapy, chemotherapy, targeted therapy/immunotherapy, focal therapy, gene therapy, plasmid therapy, to name a few. Example focal therapies include microwave ablation, radiofrequency ablation, cryoablation, high intensity focused ultrasound (HIFU), and other pulsed electric field ablation therapies. Such combination may condition the tissue for improved responsiveness and in some cases a synergistic response that is greater than either of the therapies alone. In addition, the PEF treatments described herein may lead to an abscopal effect due to the nature of the therapy.

Energy Algorithms

[00326] The PEF energy is provided by one or more energy delivery algorithms 152. In some embodiments, the algorithm 152 prescribes a signal having a waveform comprising a series of energy packets wherein each energy packet comprises a series of high voltage pulses. In such embodiments, the algorithm 152 specifies parameters of the signal such as energy amplitude (e.g., voltage) and duration of applied energy, which is comprised of the number of packets, number of pulses within a packet, and the fundamental frequency of the pulse sequence, to name a few. Additional parameters may include switch time or inter-phase delay between polarities in biphasic pulses, dead time or cycle delay between biphasic cycles, and rest time or inter-packet delay between packets. In some embodiments, there is a fixed rest period between packets and in other embodiments packets are gated to the cardiac cycle and are thus variable with the patient's heart rate. There may be a deliberate, varying rest period algorithm or no rest period

may also be applied between packets. A feedback loop based on sensor information and an auto-shutoff specification, and/or the like, may be included.

[00327] Fig. 21A illustrates an embodiment of a waveform 400 of a signal prescribed by an energy delivery algorithm 152. Here, two packets are shown, a first packet 402 and a second packet 404, wherein the packets 402, 404 are separated by an inter-packet delay or rest period 406. In this embodiment, each packet 402, 404 is comprised of a first biphasic cycle (comprising a first positive pulse peak 408 and a first negative pulse peak 410) and a second biphasic cycle (comprising a second positive pulse peak 408' and a second negative pulse peak 410'). The first and second biphasic pulses are separated by a cycle delay or dead time 412 (i.e., a pause) between each pulse. In this embodiment, the biphasic pulses are symmetric so that the set voltage 416 is the same for the positive and negative peaks. Here, the biphasic, symmetric waves are also square waves such that the magnitude and time of the positive voltage wave is approximately equal to the magnitude and time of the negative voltage wave.

A. Voltage

[00328] The voltages used and considered may be the tops of square-waveforms, may be the peaks in sinusoidal or sawtooth waveforms, or may be the RMS voltage of sinusoidal or sawtooth waveforms. In some embodiments, the energy is delivered in a monopolar fashion and each high voltage pulse or the set voltage 416 is between about 500 V to 10,000 V, particularly about 3500 V to 4000 V, about 3500 V to 5000 V, about 3500 V to 6000 V, including all values and subranges in between including about 250 V, 500 V, 1000 V, 1500 V, 2000V, 2500 V, 3000 V, 3500 V, 4000 V, 4500 V, 5000 V, 5500 V, 6000 V to name a few. Voltages delivered to the tissue may be based on the setpoint on the generator 104 while either taking in to account the electrical losses along the length of the device 102 due to inherent impedance of the device 102 or not taking in to account the losses along the length, i.e., delivered voltages can be measured at the generator or at the tip of the instrument.

[00329] It may be appreciated that the set voltage 416 may vary depending on whether the energy is delivered in a monopolar or bipolar fashion. In bipolar delivery, a lower voltage may be used due to the smaller, more directed electric field. The bipolar voltage selected for use in therapy is dependent on the separation distance of the electrodes, whereas the monopolar electrode configurations that use one or more distant dispersive pad electrodes may be delivered with less consideration for exact placement of the catheter electrode and dispersive electrode placed on the body. In monopolar electrode embodiments, larger voltages are typically used due to the dispersive behavior of the delivered energy through the body to reach the dispersive

electrode, on the order of 10cm to 100cm effective separation distance. Conversely, in bipolar electrode configurations, the relatively close active regions of the electrodes, on the order of 0.5mm to 10cm, including 1mm to 1cm, results in a greater influence on electrical energy concentration and effective dose delivered to the tissue from the separation distance. For instance, if the targeted voltage-to-distance ratio is 3000 V/cm to evoke the desired clinical effect at the appropriate tissue depth (1.3mm), if the separation distance is changed from 1mm to 1.2mm, this would result in a necessary increase in treatment voltage from 300 to about 360 V, a change of 20%.

B. Frequency

[00330] It may be appreciated that the number of biphasic cycles per second of time is the frequency when a signal is continuous. In some embodiments, biphasic pulses are utilized to reduce undesired muscle stimulation, particularly cardiac muscle stimulation. In other embodiments, the pulse waveform is monophasic and there is no clear inherent frequency. Instead, a fundamental frequency may be considered by doubling the monophasic pulse length to derive the frequency. In some embodiments, the signal has a frequency in the range 100kHz-1MHz, more particularly 100kHz - 1000kHz. In some embodiments, the signal has a frequency in the range of approximately 100-600 kHz which typically penetrates the lumen wall so as to treat or affect particular cells somewhat deeply positioned, such as submucosal cells or smooth muscle cells. In some embodiments, the signal has a base frequency or fundamental frequency in range of approximately 600kHz -1000kHz or 600 kHz - 1 MHz which typically penetrates the lumen wall so as to treat or affect particular cells somewhat shallowly, such as epithelial or endothelial cells. It may be appreciated that at some voltages, frequencies at or below 100-250 kHz may cause undesired muscle stimulation. Therefore, in some embodiments, the signal has a frequency in the range of 400 - 800 kHz or 500-800 kHz, such as 500 kHz, 550 kHz, 600 kHz, 650 kHz, 700 kHz, 750 kHz, 800 kHz. In particular, in some embodiments, the signal has a frequency of 600 kHz. In addition, cardiac synchronization is typically utilized to reduce or avoid undesired cardiac muscle stimulation during sensitive rhythm periods. It may be appreciated that even higher frequencies may be used with components which minimize signal artifacts.

C. Voltage-Frequency Balancing

[00331] The frequency of the waveform delivered may vary relative to the treatment voltage in synchrony to retain adequate treatment effect. Such synergistic changes would include

the decrease in frequency, which evokes a stronger effect, combined with a decrease in voltage, which evokes a weaker effect. For instance, in some cases the treatment may be delivered using 3000 V in a monopolar fashion with a waveform frequency of 800kHz, while in other cases the treatment may be delivered using 2000 V with a waveform frequency of 400 kHz.

[00332] When used in opposing directions, the treatment parameters may be manipulated in a way that makes it too effective, which may increase muscle contraction likelihood or risk effects to undesirable tissues, such as cartilage for airway treatments. For instance, if the frequency is increased and the voltage is decreased, such as the use of 2000 V at 800 kHz, the treatment may not have sufficient clinical therapeutic benefit. Opposingly, if the voltage was increased to 3000 V and frequency decreased to 400 kHz, there may be undesirable treatment effect extent to collateral sensitive tissues. In some cases, the over-treatment of these undesired tissues could result in morbidity or safety concerns for the patient, such as destruction of cartilaginous tissue in the airways sufficient to cause airway collapse, or destruction of smooth muscle in the GI tract sufficient to cause interruption of normal peristaltic motion. In other cases, the overtreatment of the untargeted or undesirable tissues may have benign clinical outcomes and not affect patient response or morbidity if they are overtreated.

D. Packets

[00333] As mentioned, the algorithm 152 prescribes a signal having a waveform comprising a series of energy packets wherein each energy packet comprises a series of high voltage pulses. The cycle count 420 is half the number of pulses within each biphasic packet. Referring to Fig. 21A, the first packet 402 has a cycle count 420 of two (i.e. four biphasic pulses). In some embodiments, the cycle count 420 is set between 1 and 100 per packet, including all values and subranges in between. In some embodiments, the cycle count 420 is up to 5 pulses, up to 10 pulses, up to 25 pulses, up to 40 pulses, up to 60 pulses, up to 80 pulses, up to 100 pulses, up to 1,000 pulses or up to 2,000 pulses, including all values and subranges in between.

[00334] The packet duration is determined by the cycle count, among other factors such as inserted delays. In some embodiments, packet durations are in the range of approximately 50 to 1000 microseconds, such as 50 μs, 60 μs, 70 μs, 80 μs, 90 μs,100 μs, 125 μs, 150 μs, 175 μs, 200 μs, 250 μs, 100 to 250 μs, 150 to 250 μs, 200 to 250 μs, 500 to 1000 μs to name a few. In other embodiments, the packet durations are in the range of approximately 100 to 1000 microseconds, such as 150 μs, 200 μs, 250 μs, 500 μs, or 1000 μs. In some embodiments, the inclusion of delays may increase the packet duration to a range of approximately 1000 to

200,000 microseconds, such as 2,000μs, 5,000μs, 10,000μs, 20,000μs, 25,000μs, 30,000μs, 40,000μs, 50,000μs, 60,000μs, 70,000μs, 80,000μs, 90,000μs, 100,000μs, 110,000μs, 120,000μs, 130,000μs, 140,000μs, 150,000μs, 160,000μs, 170,000μs, 180,000μs, 190,000μs, 200,000μs, 1000-2000μs, 1000-3000μs, 1000-4000μs, 1000-5000μs, 1000-10,000μs, 10,000-20,000μs, 10,000-30,000μs, 10,000-40,000μs, 10,000-50,000μs, 50,000-100,000μs, 50,000-150,000μs, 50,000-200,000μs, greater than 10,000μs, greater than 25,000 μs, greater than 50,000μs, greater than 100,000μs, greater than 200,000μs to name a few.

E. Waveforms

[00335] Fig. 21A illustrates an embodiment of a waveform 400 having symmetric pulses such that the voltage and duration of pulse in one direction (i.e., positive or negative) is equal to the voltage and duration of pulse in the other direction. Fig. 21B illustrates an example waveform 400 prescribed by another energy delivery algorithm 152 wherein the waveform 400 has voltage imbalance. Here, two packets are shown, a first packet 402 and a second packet 404, wherein the packets 402, 404 are separated by a rest period 406. In this embodiment, each packet 402, 404 is comprised of a first biphasic cycle (comprising a first positive pulse peak 408 having a first voltage V1 and a first negative pulse peak 410 having a second voltage V2) and a second biphasic cycle (comprising a second positive pulse peak 408' having first voltage V1 and a second negative pulse peak 410' having a second voltage V2). Here the first voltage V1 is greater than the second voltage V2. The first and second biphasic cycles are separated by dead time 412 between each pulse. Thus, the voltage in one direction (i.e., positive or negative) is greater than the voltage in the other direction so that the area under the positive portion of the curve does not equal the area under the negative portion of the curve. This unbalanced waveform may result in a more pronounced treatment effect as the dominant positive or negative amplitude leads to a longer duration of same charge cell membrane charge potential. In this embodiment, the first positive peak 408 has a set voltage 416 (V1) that is larger than the set voltage 416' (V2) of the first negative peak 410. Fig. 21C illustrates further examples of waveforms having unequal voltages. Here, four different types of packets are shown in a single diagram for condensed illustration. The first packet 402 is comprised of pulses having unequal voltages but equal pulse widths, along with no inter-phase delays and dead times. Thus, the first packet 402 is comprised of four biphasic pulses, each comprising a positive peak 408 having a first voltage V1 and a negative peak 410 having a second voltage V2). Here the first voltage V1 is greater than the second voltage V2. The second packet 404 is comprised of pulses having unequal voltages but symmetric pulse widths (as in the first pulse 402), with inter-phase delays equal to

cycle delays. The third packet 405 is comprised of pulses having unequal voltages but symmetric pulse widths (as in the first pulse 402), with inter-phase delays that are shorter than cycle delays. The fourth packet 407 is comprised of pulses having unequal voltages but symmetric pulse widths (as in the first pulse 402), with inter-phase delays that are greater than cycle delays. It may be appreciated that in some embodiments, the positive and negative phases of biphasic waveform are not identical, but are balanced, where the voltage in one direction (i.e., positive or negative), is greater than the voltage in the other direction but the length of the pulse is calculated such that the area under the curve of the positive phase equals the area under the curve of the negative phase.

[00336] In some embodiments, imbalance includes pulses having pulse widths of unequal duration. In some embodiments, the biphasic waveform is unbalanced, such that the voltage in one direction is equal to the voltage in the other direction, but the duration of one direction (i.e., positive or negative) is greater than the duration of the other direction, so that the area under the curve of the positive portion of the waveform does not equal the area under the negative portion of the waveform.

[00337] Fig. 21D illustrates further examples of waveforms having unequal pulse widths. Here, four different types of packets are shown in a single diagram for condensed illustration. The first packet 402 is comprised of pulses having equal voltages but unequal pulse widths, along with no inter-phase delays and cycle delays. Thus, the first packet 402 is comprised of four biphasic pulses, each comprising a positive peak 408 having a first pulse width PW1 and a negative peak 410 having a second pulse width PW2). Here the first pulse width PW1 is greater than the second pulse width PW2. The second packet 404 is comprised of pulses having equal voltages but unequal pulse widths (as in the first pulse 402), with inter-phase delays equal to cycle delays. The third packet 405 is comprised of pulses having equal voltages but unequal pulse widths (as in the first pulse 402), with inter-phase delays that are shorter than cycle delays. The fourth packet 407 is comprised of pulses having equal voltages but unequal pulse widths (as in the first pulse 402), with inter-phase delays that are greater than cycle delays.

[00338] Fig. 21E illustrates an example waveform 400 prescribed by another energy delivery algorithm 152 wherein the waveform is monophasic, a special case of imbalance whereby there is only a positive or only a negative portion of the waveform. Here, two packets are shown, a first packet 402 and a second packet 404, wherein the packets 402, 404 are separated by an inter-packet delay or rest period 406. In this embodiment, each packet 402, 404 is comprised of a first monophasic pulse 430 and a second monophasic pulse 432. The first and second monophasic pulses 430, 432 are separated by a cycle delay or dead time 412 between

each cycle. This monophasic waveform could lead to a more desirable treatment effect as the same charge cell membrane potential is maintain for longer durations. However, adjacent muscle groups will be more stimulated by the monophasic waveform, compared to a biphasic waveform.

[00339] Fig. 21F illustrates further examples of waveforms having monophasic pulses. Here, four different types of packets are shown in a single diagram for condensed illustration. The first packet 402 is comprised of pulses having identical voltages and pulse widths, with no switch times or inter-phase delays (because the pulses are monophasic) and a cycle delay equal to the active time. In some cases, there may be cycle delay duration than the active time of a given pulse. Thus, the first packet 402 is comprised of three monophasic pulses 430, each comprising a positive peak. In instances where the dead time is equal to the active time, the waveform may be considered unbalanced with a fundamental frequency representing a cycle period of 2x the active time and no dead time. The second packet 404 is comprised of monophasic pulses 430 having equal voltages and pulse widths (as in the first packet 402), with larger cycle delays. The third packet 405 is comprised of monophasic pulses 430 having equal voltages and pulse widths (as in the first packet 402), and even larger cycle delays. The fourth packet 407 is comprised of monophasic pulses 430 having equal voltages and pulse widths (as in the first packet 402), with yet larger cycle delays.

[00340] In some embodiments, an unbalanced waveform is achieved by delivering more than one pulse in one polarity before reversing to an unequal number of pulses in the opposite polarity. Fig. 21G illustrates further examples of waveforms having such phase imbalances. Here, four different types of packets are shown in a single diagram for condensed illustration. The first packet 402 is comprised of four cycles having equal voltages and pulse widths, however, opposite polarity pulses are intermixed with monophasic pulses. Thus, the first cycle comprises a positive peak 408 and a negative peak 410. The second cycle is monophasic, comprising a single positive pulse with no subsequent negative pulse 430. This then repeats. The second packet 404 is comprised of intermixed biphasic and monophasic cycles (as in the first packet 402), however the pulses have unequal voltages. The third packet 405 is comprised of intermixed biphasic and monophasic cycles (as in the first packet 402), however the pulses have unequal pulse widths. The fourth packet 407 is comprised of intermixed biphasic and monophasic pulses (as in the first packet 402), however the pulses have unequal voltages and unequal pulse widths. Thus, multiple combinations and permutations are possible. Fig. 21H illustrates an example of a waveform having imbalances in both positive and negative voltages. Here a packet is shown having a first positive pulse peak 408 and a first negative pulse peak 410

having a greater voltage than a second positive pulse peak 408' and a second negative pulse peak 410'. These differing cycles repeat throughout the packet.

[00341] Regarding the utility of unequal waveforms, the unbalanced TMP manipulation achieved reduces the implications of biphasic cancellation. There is a correlative relationship between the degree of imbalance, approaching a monopolar waveform as fully unbalanced, and the intensity of TMP manipulation. This will result in proportional relationship between the extent of treatment effect as well as the degree of muscle contraction. Thus, approaching more unbalanced waveforms will enable stronger treatment effects at the same voltage and frequency (if applicable) for biphasic waveforms than those produced from purely balanced biphasic waveforms. For example, the treatment effect evoked by a 830ns-415ns-830ns-etc pulse length sequence within a packet will have the pulse constituting the second half of the cycle being half the duration of the original phase. This will restrict the induction of TMP manipulation by the second phase of the cycle, but will also generate less reversed TMP, enabling a stronger effect from the original polarity in the subsequent cycle at the original length. In another example, the "positive" portion of the waveform may be 2500V, with the "negative" portion being 1500V (2500-1250-2500- etc V), which will induce comparable effects on TMP polarization as that which was described for the pulse duration imbalance. In both of these cases, the manipulation of the opposing polarity intensity will result in cumulative stronger TMP manipulation for the positive pulse in the cycle. This will thus reduce the effects of biphasic cancellation and will generate stronger treatment effects than a protocol of 830-830-830ns or 2500-2500-2500V, despite the deposition of less total energy delivered to the tissue. In this way, it is possible to deliver less total energy to the tissue but evoke the desired treatment effect when TMP manipulations are integral to the treatment mechanism of action.

[00342] Extended further, the fully unbalanced waveforms would not include any opposite polarity component but may still include brief portions of pulses delivered in just the positive phase. An example of this is a packet that contains 830ns of positive polarity, an 830ns pause with no energy delivered, followed by another 830ns of positive polarity, and so forth. The same approach is true whether considering the pulse length imbalance or the voltage imbalance, as the absence of a negative pulse is equivalent to setting either of these parameters to zero for the "negative" portion.

[00343] However, appropriate treatment delivery considers that the advantages offered by biphasic waveforms, namely the reduction of muscle contraction, resulting from biphasic cancellation will likewise be reduced. Therefore, the appropriate treatment effect extent is balanced against the degree of acceptable muscle contraction. For example, an ideal voltage

imbalance may be 2500-1000-2500-... V, or 2500-2000-2500-...V; or 830-100-830-...ns, or 830-500-830-...ns.

[00344] It may be appreciated that in some embodiments the pulses are sinusoidal in shape rather than square. One benefit of a sinusoidal shape is that it is balanced or symmetrical, whereby each phase is equal in shape. Balancing may assist in reducing undesired muscle stimulation. It may be appreciated that in other embodiments the pulses have decay-shaped waveforms.

Alternative Delivery Approaches

[00345] As mentioned previously, in most embodiments, access is minimally invasive and relies on endoluminal approaches. However, it may be appreciated that other approaches, such as percutaneous, laparoscopic or open surgical approaches, may be used in some situations.

[00346] In some embodiments, when accessing percutaneously, the shaft 106 of the device 102 is passed through a delivery device that penetrates the skin layer into the underlying tissue. In some embodiments, the delivery device comprises a needle that is inserted through the skin and directed toward the target tissue. The shaft 106 is then advanced through the needle. In some embodiments, the probe tip 502 is shaped to assist in penetrating tissue, such as a pointed shape. Thus, the shaft 106 may be advanced through tissue to the desired location therein. Once desirably positioned, energy is delivered through the probe tip 502 to treat the target tissue. It may be appreciated that the probe tip 502 may also be advanced from the shaft 106 into the tissue and/or a conductive element 560 may be advanced into the tissue wherein the energy is delivered from the conductive element 560.

[00347] In other embodiments, when accessing percutaneously, the shaft 106 of the device 102 is rigid so as to be able to penetrate the skin layer without the use of a delivery device. In such embodiments, the probe tip 502 is typically shaped to assist in penetrating tissue, such as a pointed shape. Thus, the shaft 106 itself is advanced into the tissue to the desired location therein. Once desirably, positioned, energy is delivered through the probe tip 502 to treat the target tissue. It may be appreciated that the probe tip 502 may also be advanced from the shaft 106 into the tissue and/or a conductive element 560 may be advanced into the tissue wherein the energy is delivered from the conductive element 560.

[00348] In laparoscopic approaches, the shaft 106 of the device 102 is passed through a laparoscope which has been inserted through a small incision. These small incisions provide reduced pain, reduced hemorrhaging and shorter recovery time in comparison to open surgery. In some embodiments, the probe tip 502 is shaped to assist in penetrating tissue, such as a

pointed shape. Thus, the shaft 106 may be advanced through tissue to the desired location therein. Once desirably positioned, energy is delivered through the probe tip 502 to treat the target tissue.

[00349] In open surgical approaches, the shaft 106 of the device 102 may also be passed through a delivery device or the device 102 may penetrate the tissue directly. In either case, once desirably positioned, energy is delivered through the probe tip 502 to treat the target tissue.

Cardiac Synchronization

[00350] In some embodiments, the energy signal is synchronized with the patient's cardiac cycle to prevent induction of cardiac arrhythmias. Thus, the patient's cardiac cycle is typically monitored with the use of an electrocardiogram (ECG). Referring to Fig. 22, a typical ECG trace 600 includes a repeating cycle of a P wave 602 representing atrial depolarization, a QRS complex 604 representing ventricular depolarization and atrial repolarization, and a T wave 606 representing ventricular repolarization. To safely deliver energy within the airway in close proximity to the heart, synchronization between energy delivery and the patient's cardiac cycle is employed to reduce the risk of cardiac arrhythmia. High voltage energy can trigger a premature action potential within the cardiac muscle as the delivered energy increases the cardiac muscle cell membrane permeability allowing ion transport, which can induce cardiac arrhythmias, especially ventricular fibrillation. To avoid cardiac arrhythmias, the electrical energy is delivered to the airway in a fashion that is outside the "vulnerable period" of the cardiac muscle. Within one cardiac cycle (heartbeat), the vulnerable period of the ventricular muscle is denoted on an ECG by the entire T wave 606. Typically, for ventricular myocardium, the vulnerable period coincides with the middle and terminal phases of the T wave 606. However, when high energy pulses are delivered in close proximity to the ventricle, the vulnerable period can occur several milliseconds earlier in the heartbeat. Therefore, the entire T wave can be considered to be within the vulnerable period of the ventricles.

[00351] The remaining parts of a cardiac cycle are the P wave 602 and the QRS complex 604, which both include periods when atrial or ventricular muscle is refractory to high voltage energy stimuli. If high voltage energy pulses are delivered during the muscle's refractory period, arrhythmogenic potential can be minimized. The ST segment 608 (interval between ventricular depolarization and repolarization) of the first cardiac cycle and the TQ interval 610 (interval including the end of the first cardiac cycle and the mid-point of the second cardiac cycle) are the periods where high voltage energy can be delivered without induction of cardiac arrhythmia due

to the cardiac muscle depolarized state (refractory period). Fig. 22 includes shaded boxes that indicate example portions of the cardiac cycle during which energy can be applied safely.

[00352] It may be appreciated that in some embodiments, components for acquiring the electrocardiogram 170 are integrally formed as part of the generator 104. If the cardiac monitor is limited to acquiring up to a 5-lead ECG, and it may be beneficial to incorporate additional leads into the system. This would further eliminate the need to use the communications port 167 to receive cardiac sync pulses. Rather, the processor 154 can be configured to detect the R-waves directly and to assess the integrity of the entire QRS complex.

[00353] As used herein, the terms "about" and/or "approximately" when used in conjunction with numerical values and/or ranges generally refer to those numerical values and/or ranges near to a recited numerical value and/or range. In some instances, the terms "about" and "approximately" can mean within ± 10% of the recited value. For example, in some instances, "about 100 [units]" can mean within ± 10% of 100 (e.g., from 90 to 110). The terms "about" and "approximately" can be used interchangeably.

[00354] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

WHAT IS CLAIMED IS:

1. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising one or more packets of pulses to provide the treatment and comprising one or more delay periods which manipulates or reduces or avoids one or more secondary effects.

2. A system as in claim 1, wherein the one or more secondary effects comprises bubble formation.

3. A system as in any of the above claims, wherein each of the pulses in the one or more packets of pulses has an on-time in a range 0.5 to 20 microseconds.

4. A system as in any of claims 1-3, wherein each of the pulses in the one or more packets of pulses has a continuous on-time of up to 5 microseconds.

5. A system as in any of the above claims, wherein each of the pulses has a duty cycle of less than or equal to 2.5 percent.

6. A system as in any of the above claims, wherein the delay period is greater than or equal to 1 microsecond.

7. A system as in claim 6, wherein the delay period is in a range of 1 to 250 microseconds.

8. A system as in claim 6, wherein the delay period is in a range of 10-100 microseconds.

9. A system as in claim 6, wherein the delay period is greater than or equal to 100 microseconds.

10. A system as in claim 6, wherein the delay period is greater than or equal to 250 microseconds.

11. A system as in claim 6, wherein the delay period is greater than or equal to 1000 microseconds.

12. A system as in claim 1, wherein the one or more secondary effects comprises an electrical discharge event.

13. A system as in claim 12, wherein the electrical discharge event comprises electrical arcing from at least one of the at least one electrode.

14. A system as in any of claims 12-13, wherein each of the pulses in the one or more packets of pulses has an on-time in a range 1 to 50 microseconds.
15. A system as in any of claims 12-13, wherein each of the pulses in the one or more packets of pulses has a continuous on-time in a range of up to 20 microseconds.
16. A system as in any of claims 12-15, wherein each of the at least one packet of pulses has a duty cycle of less than or equal to 20 percent.
17. A system as in claim 12, wherein the electrical discharge event comprises generation of a pressure wave against the tissue.
18. A system as in claim 17, wherein the pressure wave is sufficient to generate a cavity within the tissue.
19. A system as in claim 18, wherein each of the at least one packet of pulses has a duty cycle of less than or equal to 50 percent.
20. A system as in any of claims 18-19, wherein each of the pulses in the one or more packets of pulses has an on-time in a range 10 to 100 microseconds.
21. A system as in any of claims 18-19, wherein each of the pulses in the one or more packets of pulses has a continuous on time of up to 50 microseconds.
22. A system as in any of claims 12-21, wherein the delay period is greater than or equal to 1 microsecond.
23. A system as in claim 22, wherein the delay period is in a range of 1 to 500 microseconds.
24. A system as in claim 22, wherein the delay period is in a range of 10-250 microseconds.
25. A system as in claim 1, wherein the one or more secondary effects comprises a contraction of a muscle.
26. A system as in claim 25, wherein the at least one electrode is configured to create a lesion having a width and wherein reducing or avoiding contraction of the muscle causes the at least one electrode maintains a position that does not move more than 25% of the width.
27. A system as in any of claims 25-26, wherein the delay period is greater than or equal to 5 milliseconds.
28. A system as in claim 27, wherein the delay period is greater than or equal to 10 milliseconds.
29. A system as in claim 27, wherein the delay period is in a range of 5 milliseconds to 1 second.

30. A system as in claim 27, wherein the delay period is in a range of 5 to 10 milliseconds.
31. A system as in any of claims 25-30, wherein the one or more packets of pulses comprise at least two packets separated by a packet delay period of at least 30 milliseconds.
32. A system as in claim 31, wherein each of the packets are separated by a packet delay period of at least 30 milliseconds.
33. A system as in any of the above claims, wherein the pulses comprise biphasic pulses and the delay period comprises an inter-phase delay between a positive phase and a negative phase of a biphasic pulse.
34. A system as in any of the above claims, wherein the delay period comprises an inter-packet delay.
35. A system as in claim 34, wherein the inter-packet delay is in a range of 30-5000 milliseconds.
36. A system as in claim 35, wherein the inter-packet delay is 30-40 milliseconds.
37. A system as in claim 35, wherein the inter-packet delay is 3000-5000 milliseconds.
38. A system as in any of the above claims, wherein the delay period comprises an inter-pulse delay.
39. A system as in any of the above claims, wherein the waveform comprises one or more bundles, wherein each bundle comprises two or more packets.
40. A system as in claim 39, wherein each bundle comprises three packets and wherein each bundle is spaced apart so as to be delivered within an ST interval of a cardiac rhythm of the patient.
41. A system as in claim 39, wherein the delay period comprises an inter-bundle delay.
42. A system as in any of the above claims, wherein the waveform has a voltage amplitude of 500 to 4,000 volts.
43. A system as in any of the above claims, wherein the waveform has a frequency of 300-800kHz.
44. A system as in any of the above claims, wherein each of the one or more packets has 10-200 biphasic pulses.
45. A system as in any of the above claims, wherein each of the one or more packets has 20-50 biphasic pulses.
46. A system as in any of the above claims, wherein the treatment comprises 5 to 100 packets.

47. A system as in any of the above claims, wherein the treatment comprises 10 to 60 packets.

48. A system as in any of the above claims, further comprising a remote dispersive electrode positionable so that the energy is delivered in a monopolar manner.

49. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising one or more packets of pulses to provide the treatment and comprising one or more delay periods which avoids a peak temperature in the tissue that would have been reached by delivery of the energy without the one or more delay periods.

50. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of pulses to provide the treatment wherein each pulse has a pulse length and at least one of the at least one packet comprises a delay having a delay period that is at least twice the pulse length.

51. A system as in claim 50, wherein the delay period is at least ten times the pulse length.

52. A system as in any of claims 50-51, wherein the at least one packet has a packet length at least 50 times the delay period.

53. A system as in claim 52, wherein the at least one packet has a packet length at least 100 times the delay period.

54. A system as in any of claims 50-53, wherein the delay comprises an inter-pulse delay.

55. A system as in claim 54, wherein the pulses are biphasic pulses and the inter-pulse delay is an inter-cycle delay.

56. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of biphasic pulses to provide the treatment wherein each biphasic pulse comprises an inter-phase delay in a range of 250 to 1000 microseconds.

57. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising 2-60 packets of pulses to provide the treatment wherein each packet includes at least one delay period of in a range of 250 to 1000 microseconds.

58. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of pulses having a delay period wherein the at least one packet has a packet length at least 50 times the delay period.

59. A system for treating tissue of a patient comprising:

at least one electrode positionable near the tissue; and

a generator in electrical communication with the at least one electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy provides a treatment to the tissue, wherein the energy is generated from a waveform comprising at least one packet of pulses wherein each pulse has a duty cycle of less than or equal to 50 percent so as to reduce or avoid one or more secondary effects.

60. A system as in claim 59, wherein the one or more secondary effects comprises cavity formation in the tissue.

61. A system as in claim 59, wherein each pulse has a duty cycle of less than or equal to 20 percent.

62. A system as in claim 61, wherein the one or more secondary effects comprises an electrical discharge event.

63. A system as in claim 59, wherein each pulse has a duty cycle of less than or equal to 2.5 percent.

64. A system as in claim 63, wherein the one or more secondary effects comprises bubble formation.

65. A system for treating tissue comprising:

an electrode positionable near the tissue; and

a generator in electrical communication with the electrode, wherein the generator includes at least one energy delivery algorithm that provides pulsed electric field energy to the electrode so that the energy treats the tissue, wherein the energy is generated from a waveform having a particular delay period between pulses selected to affect gas formation, external electrical discharge, muscle contraction, cavity formation, and/or temperature rise.

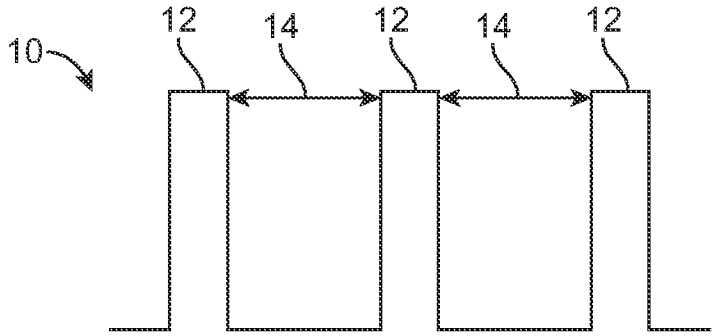


FIG. 1

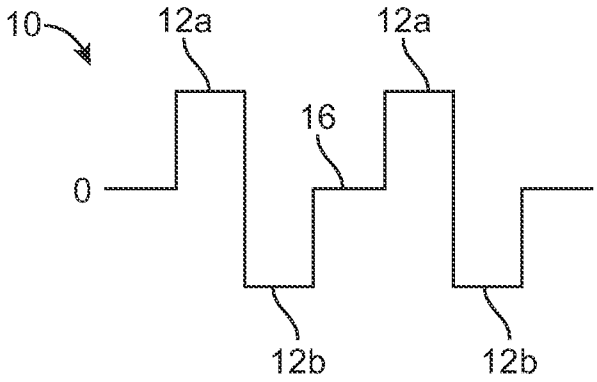


FIG. 2

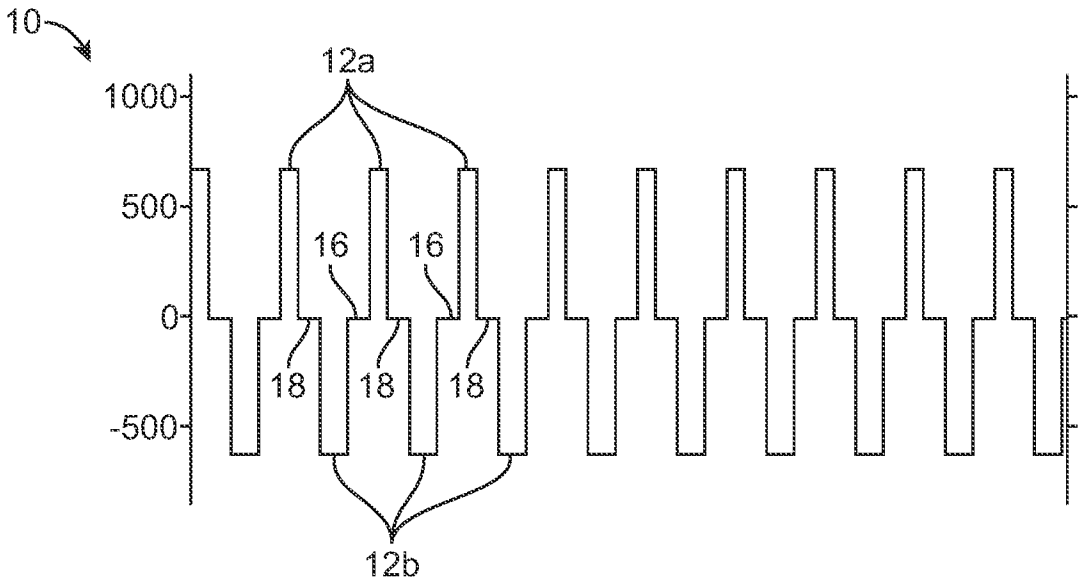


FIG. 3

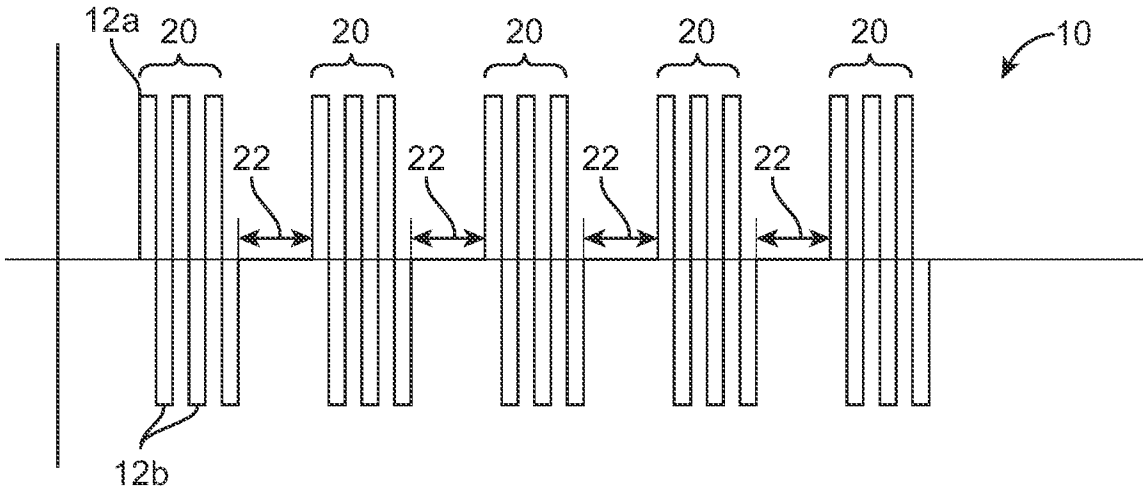

12a
20
20
20
20
20
10
22
22
22
22
12b

FIG. 4

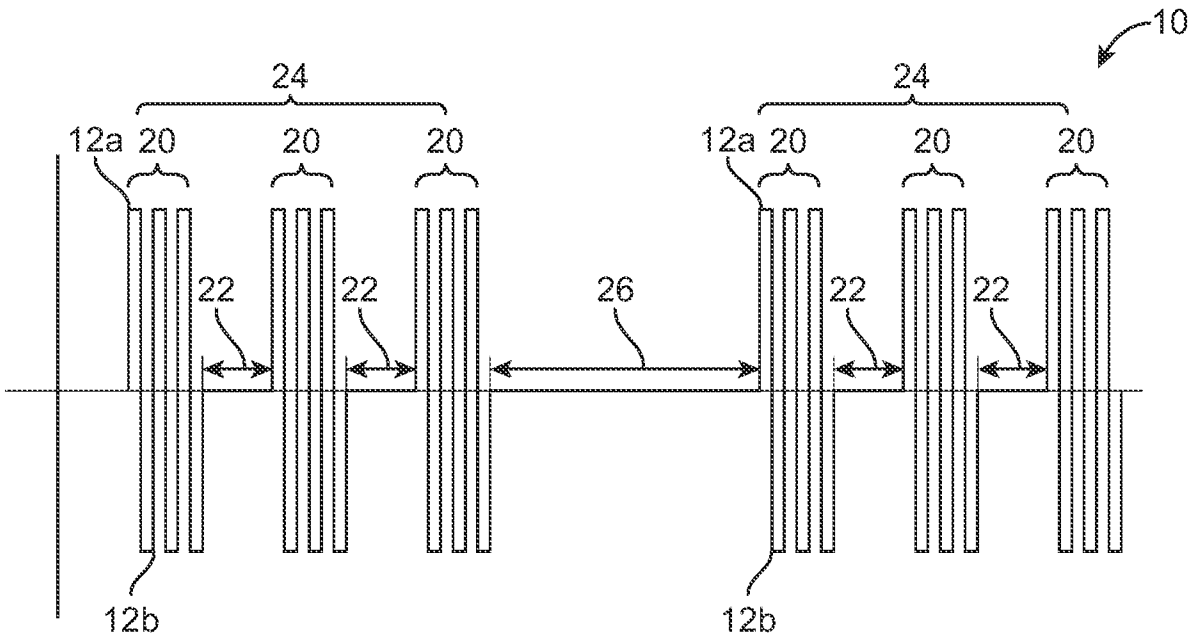

10
24
24
12a
20
20
20
12a
20
20
20
22
22
26
22
22
12b
12b

FIG. 5

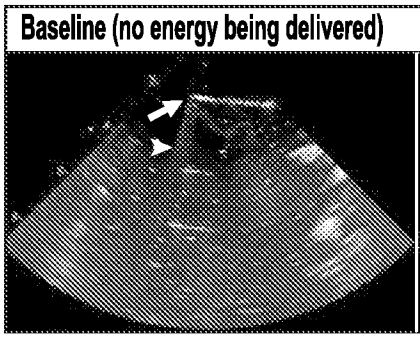


FIG. 6A

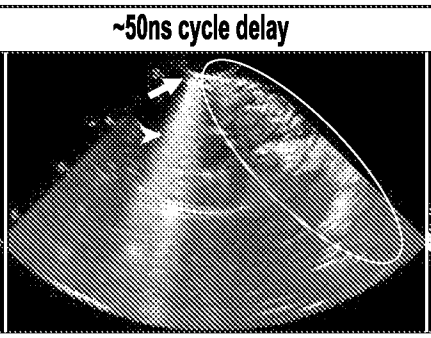


FIG. 6B

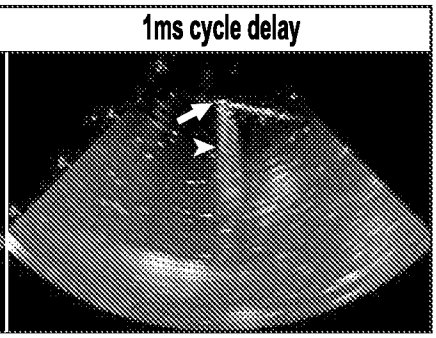


FIG. 6C

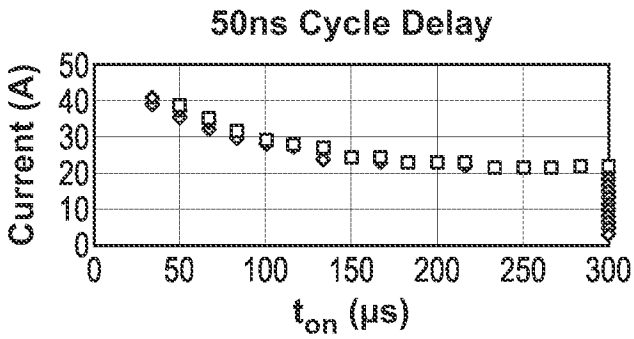


FIG. 7A

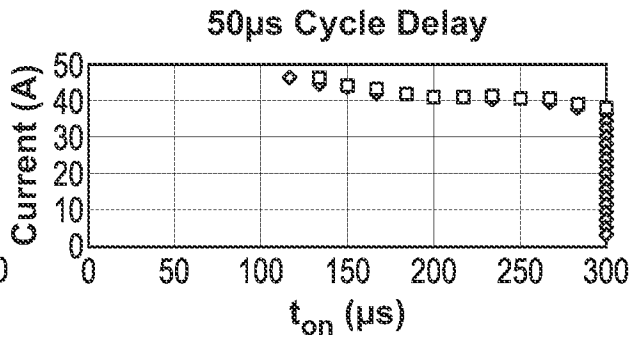


FIG. 7B

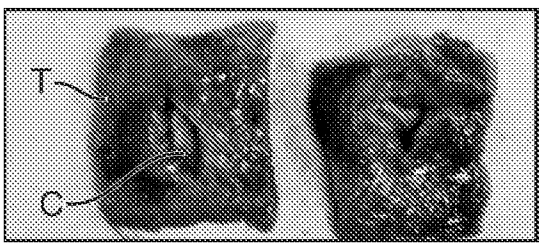


FIG. 8A

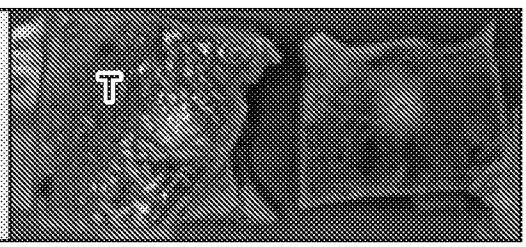


FIG. 8B

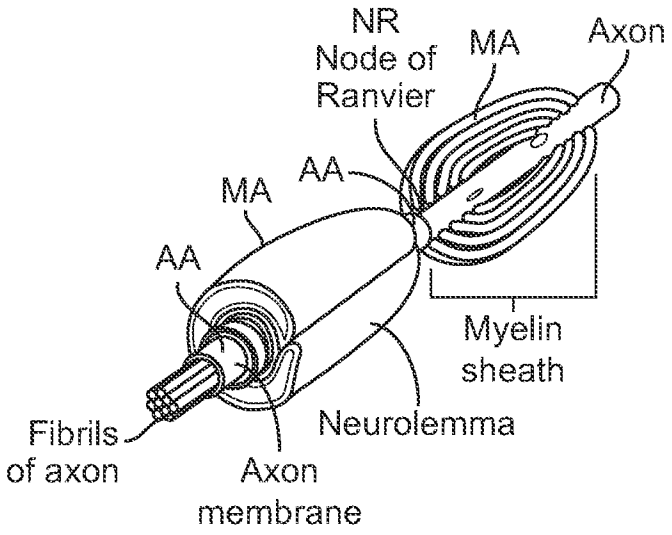


FIG. 9

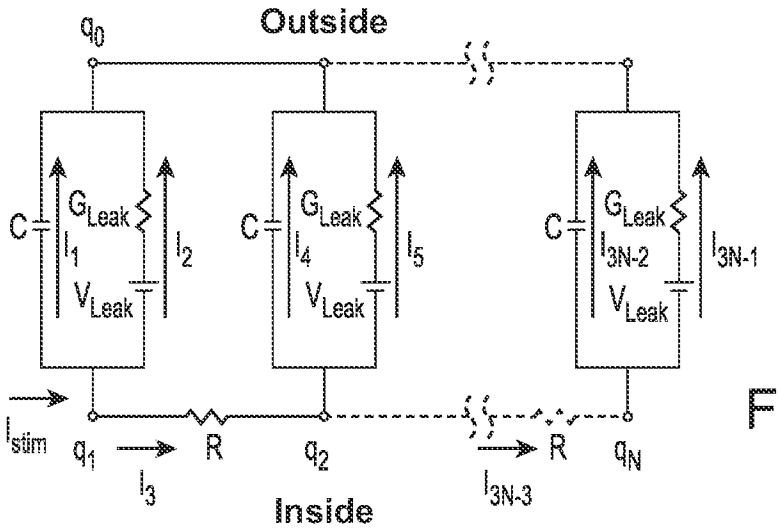


FIG. 10

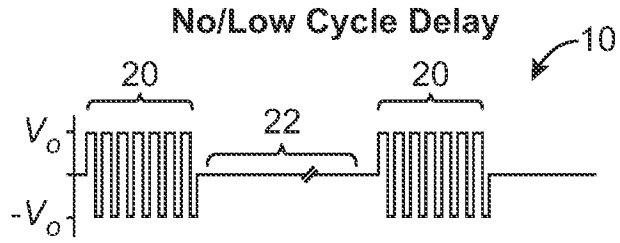


FIG. 11A

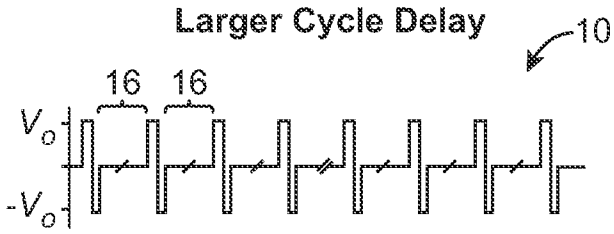


FIG. 11C

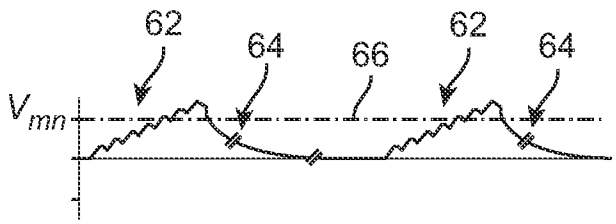


FIG. 11B

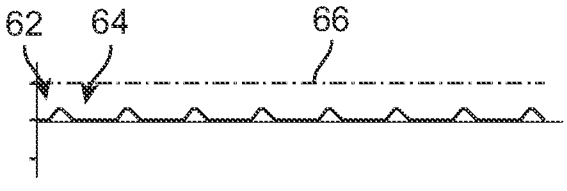


FIG. 11D

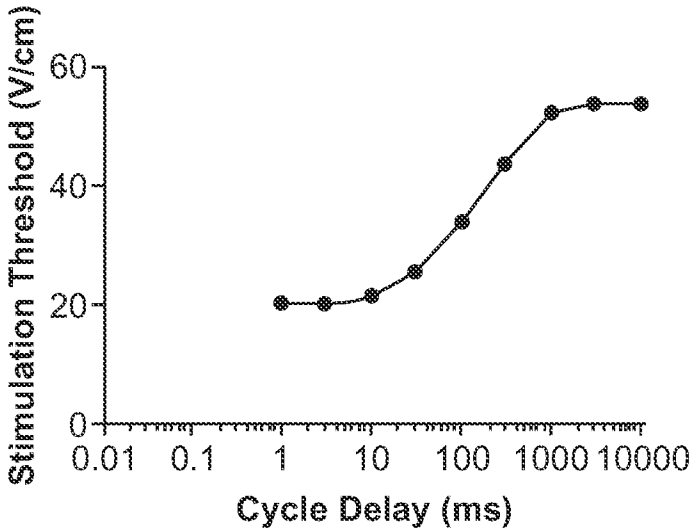

Stimulation Threshold (V/cm)
60
40
20
0
0.01
0.1
1
10
100
1000
10000
Cycle Delay (ms)

FIG. 12

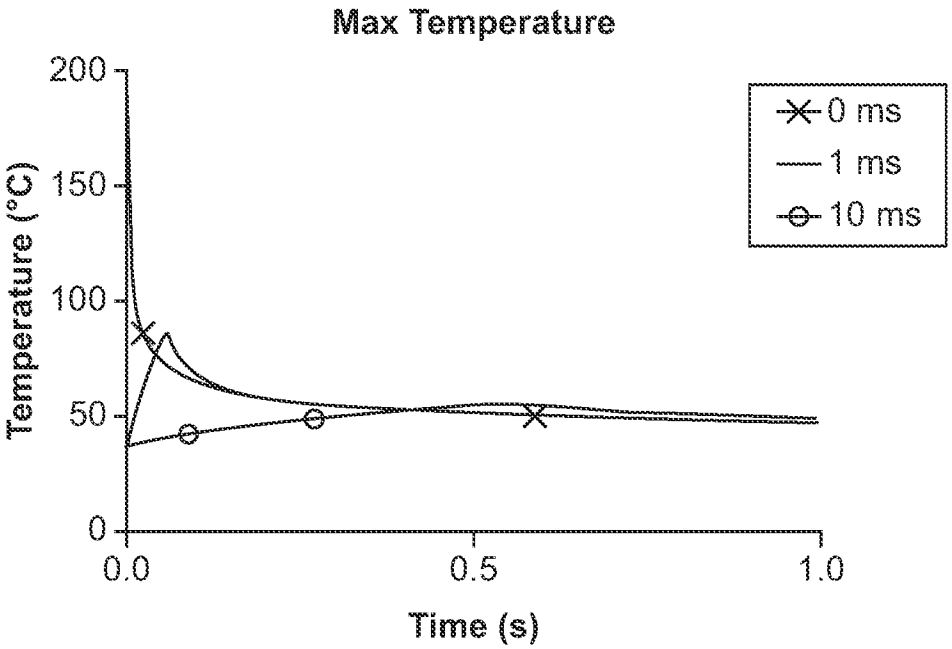

Max Temperature
Temperature (°C)
200
150
100
50
0
0.0
0.5
1.0
Time (s)
0 ms
1 ms
10 ms

FIG. 13

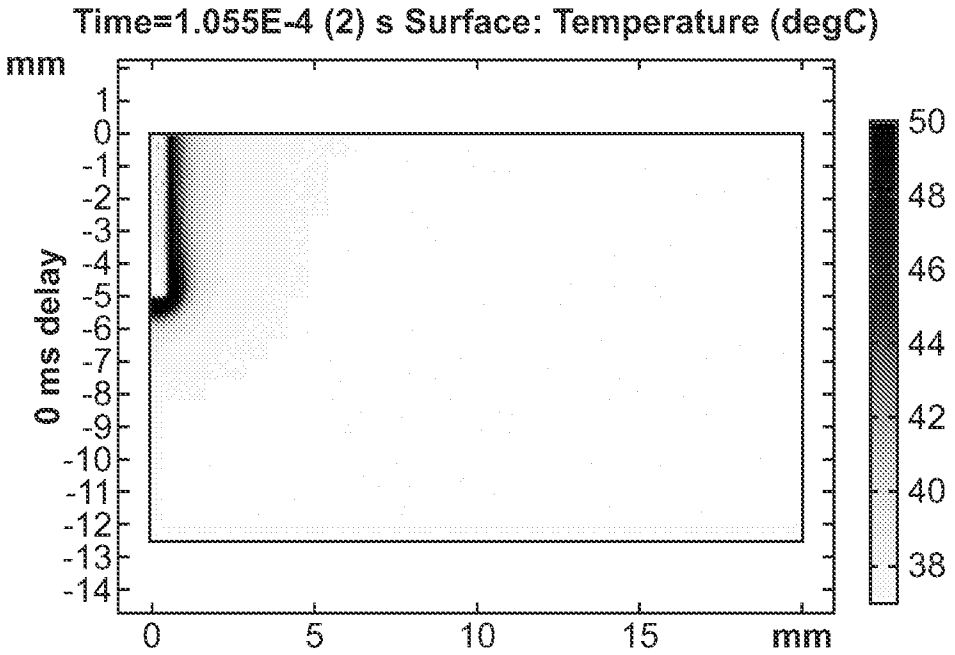


FIG. 14A

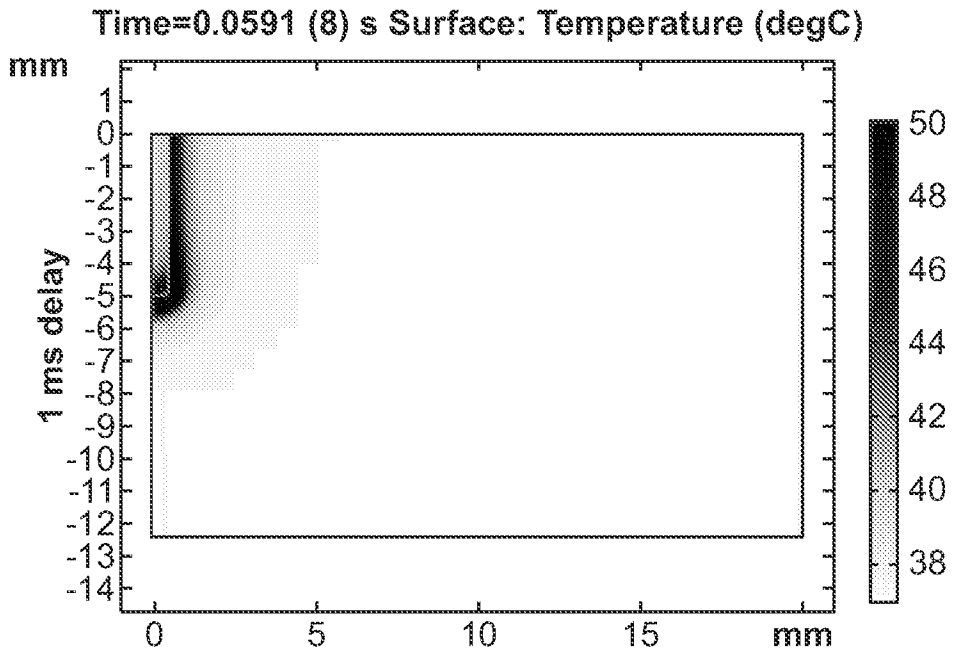


FIG. 14B

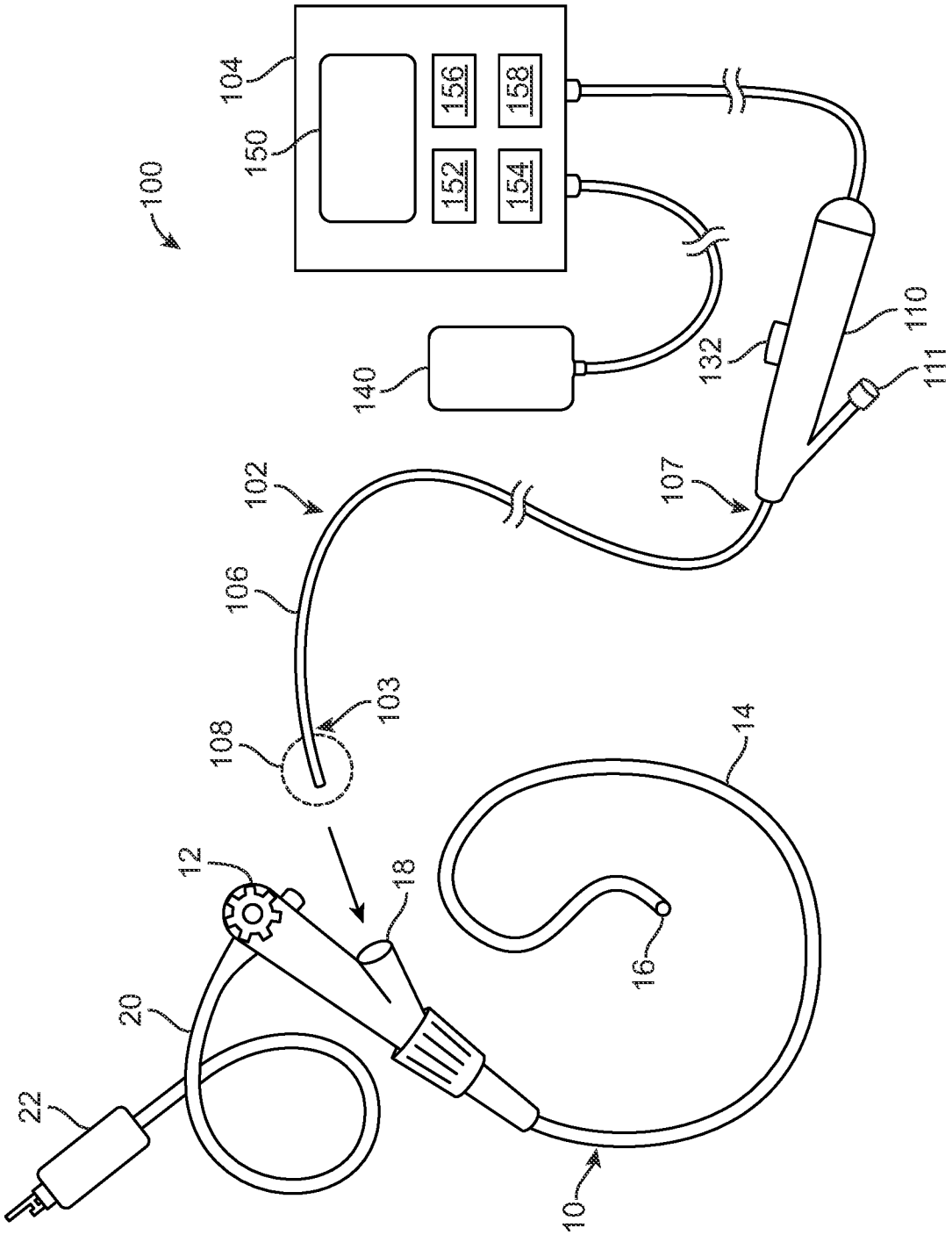

100
104
150
156
158
152
154
140
132
110
111
102
107
106
103
108
14
12
18
16
20
22
10

FIG. 15

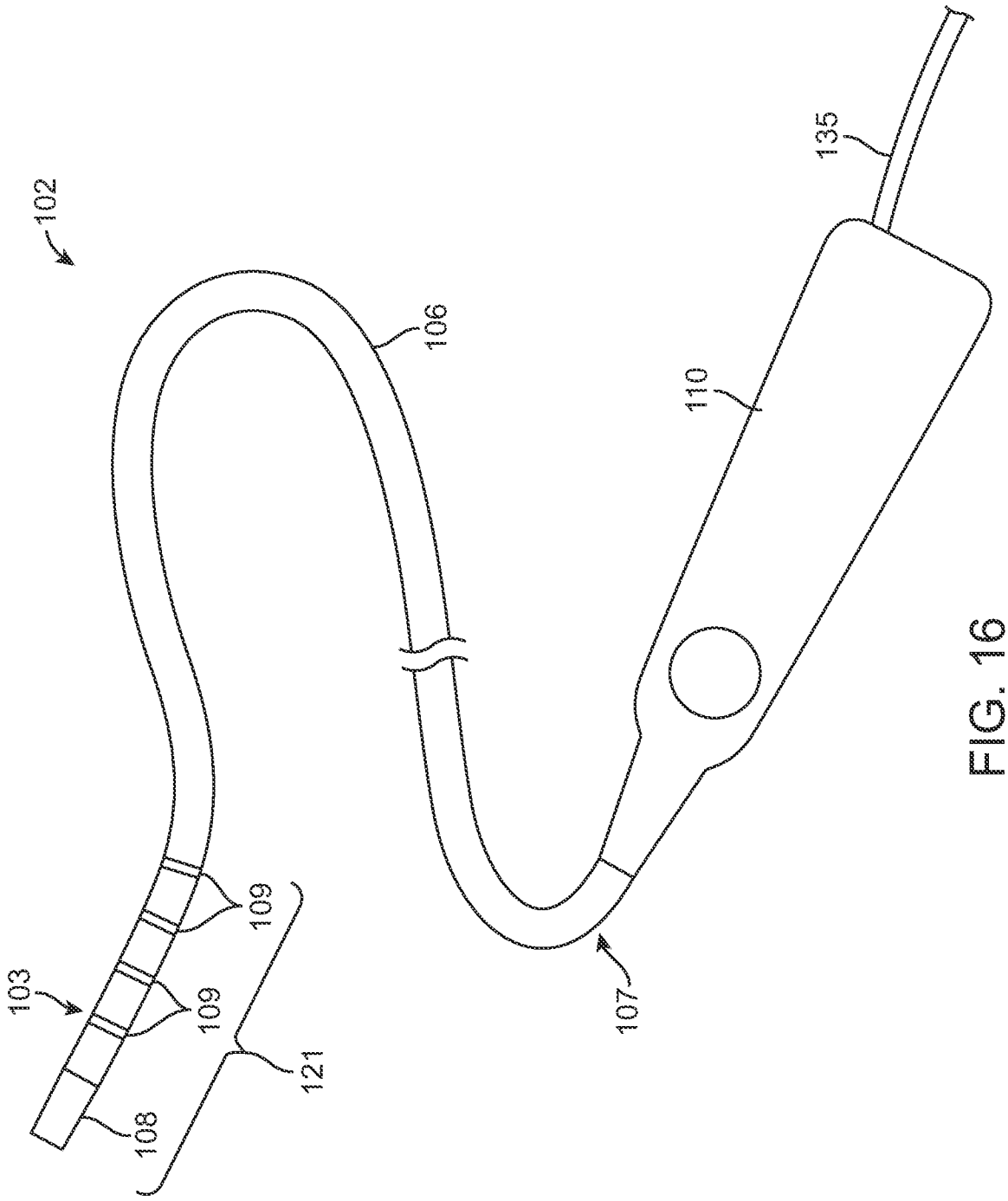


FIG. 16

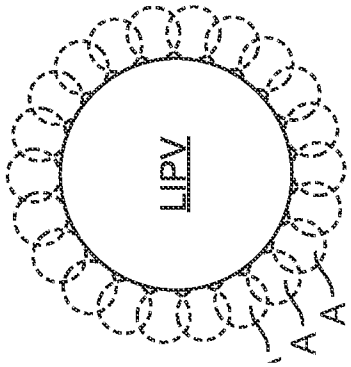


FIG. 18

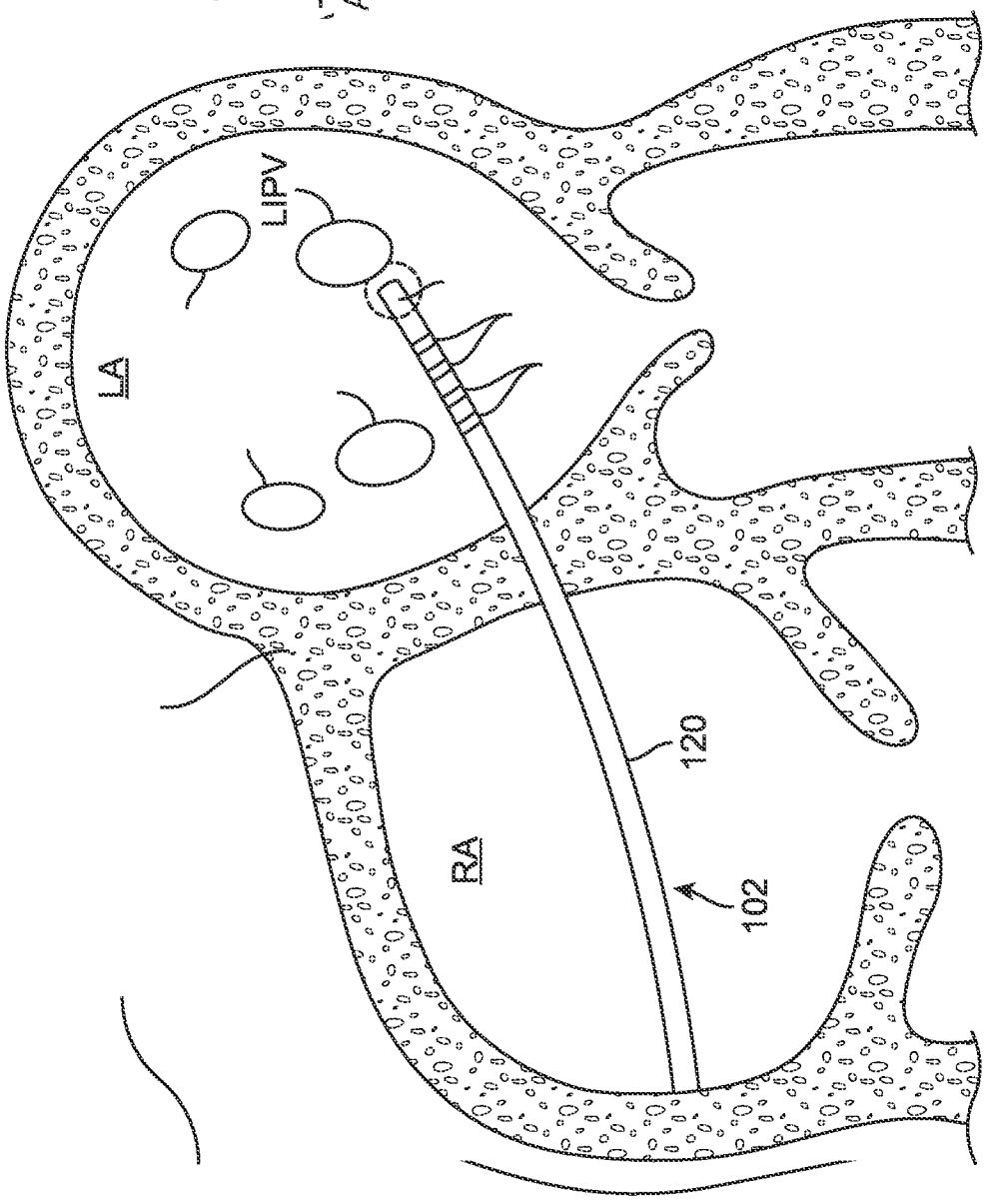


FIG. 17

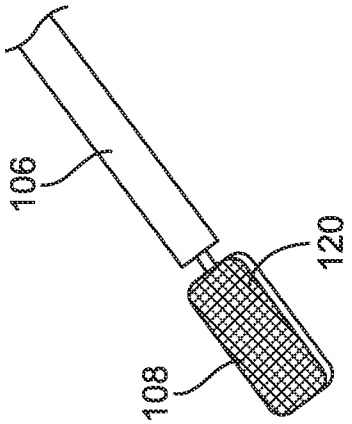


FIG. 19B

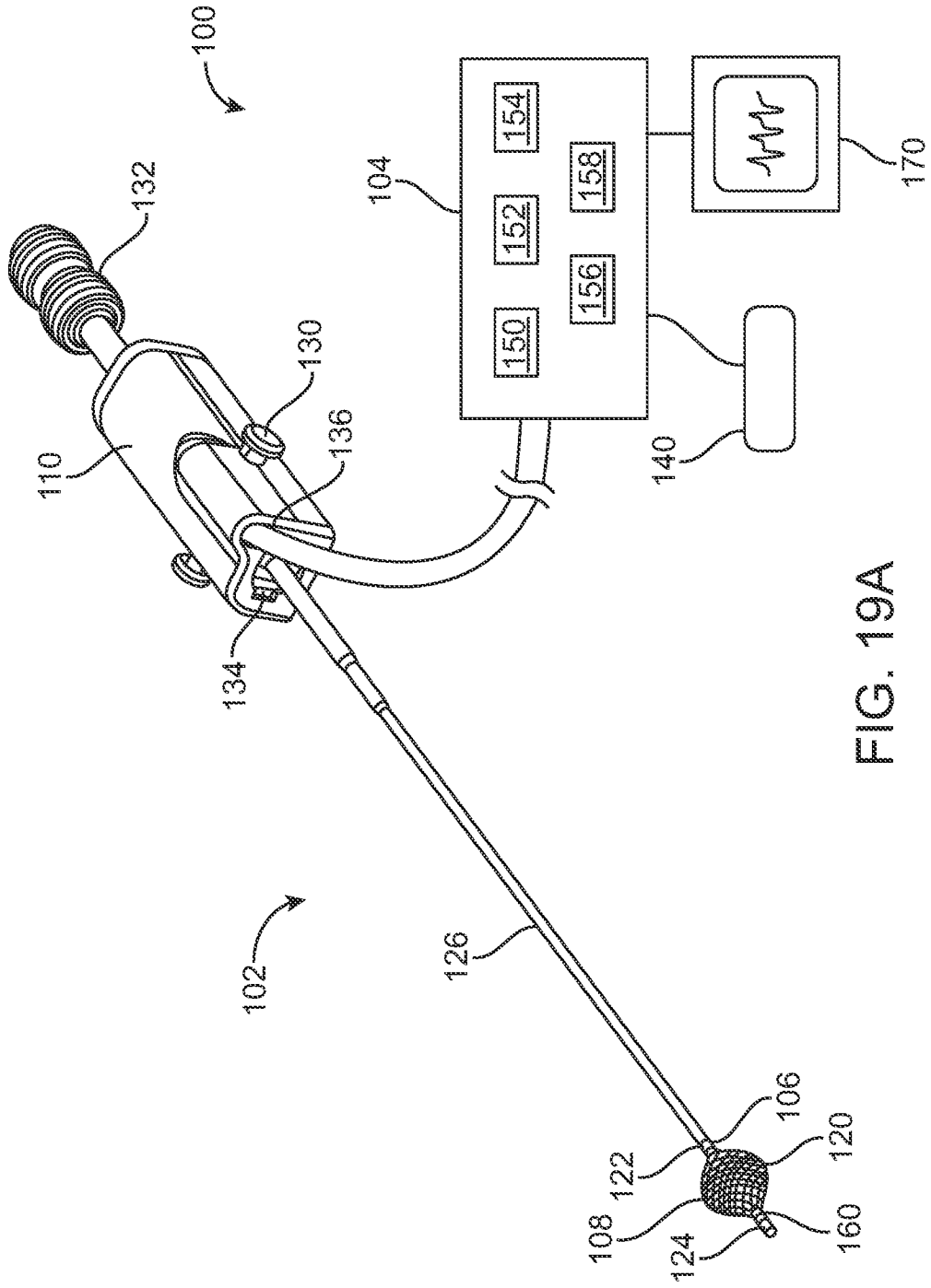


FIG. 19A

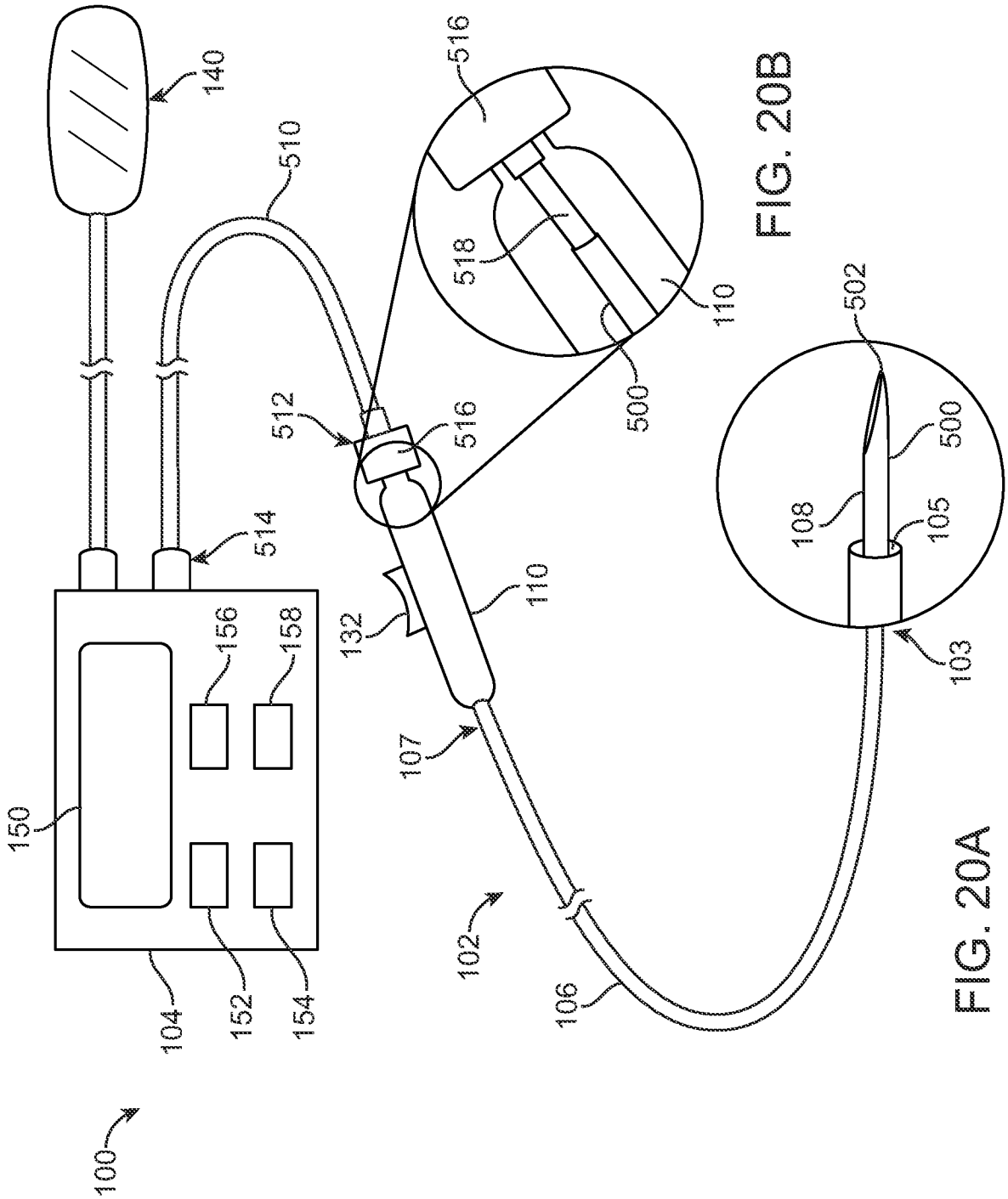


FIG. 20B

FIG. 20A

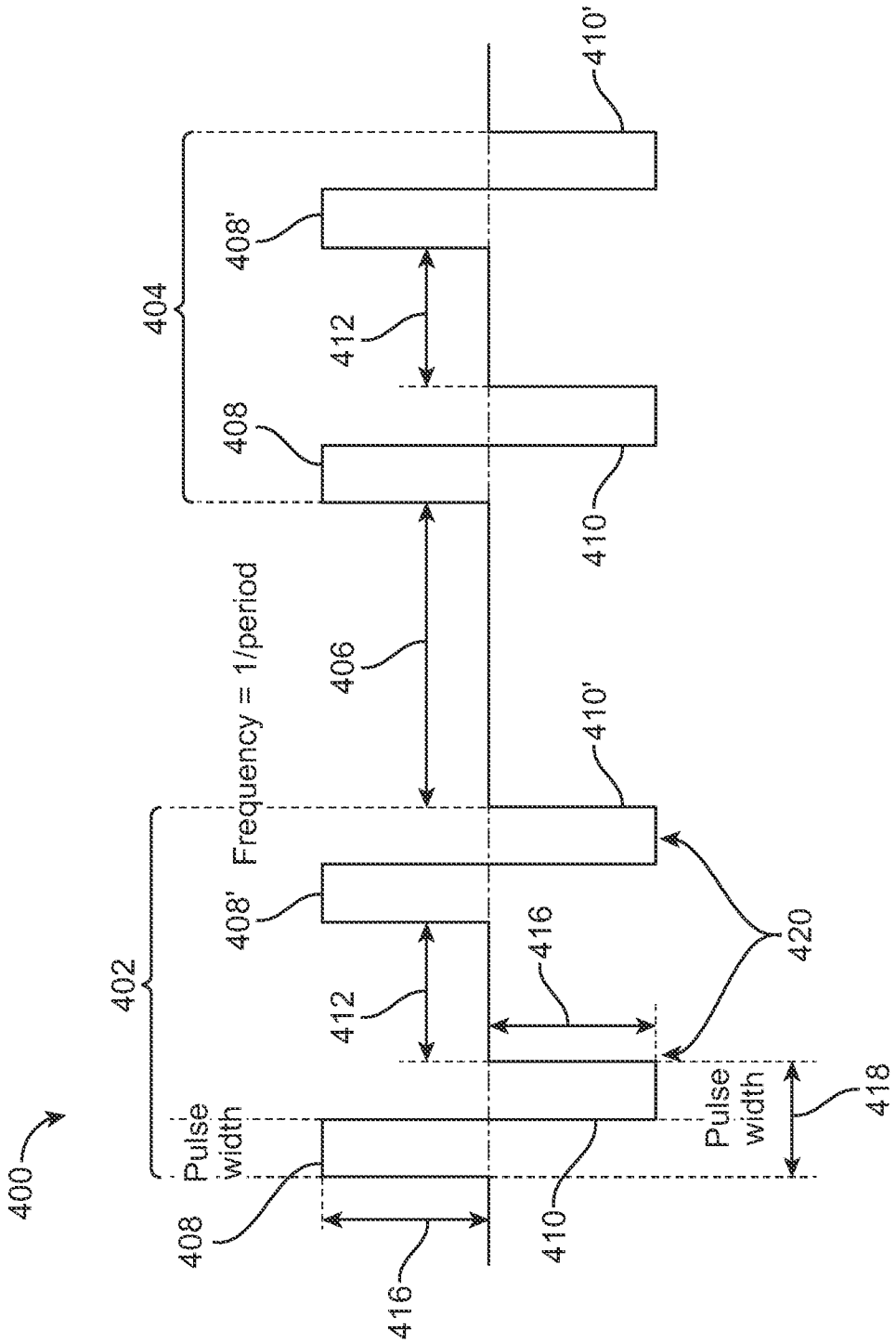

400
402
404
406
408
408'
410
410'
412
416
418
420
Frequency = 1/period
Pulse width
Pulse width

FIG. 21A

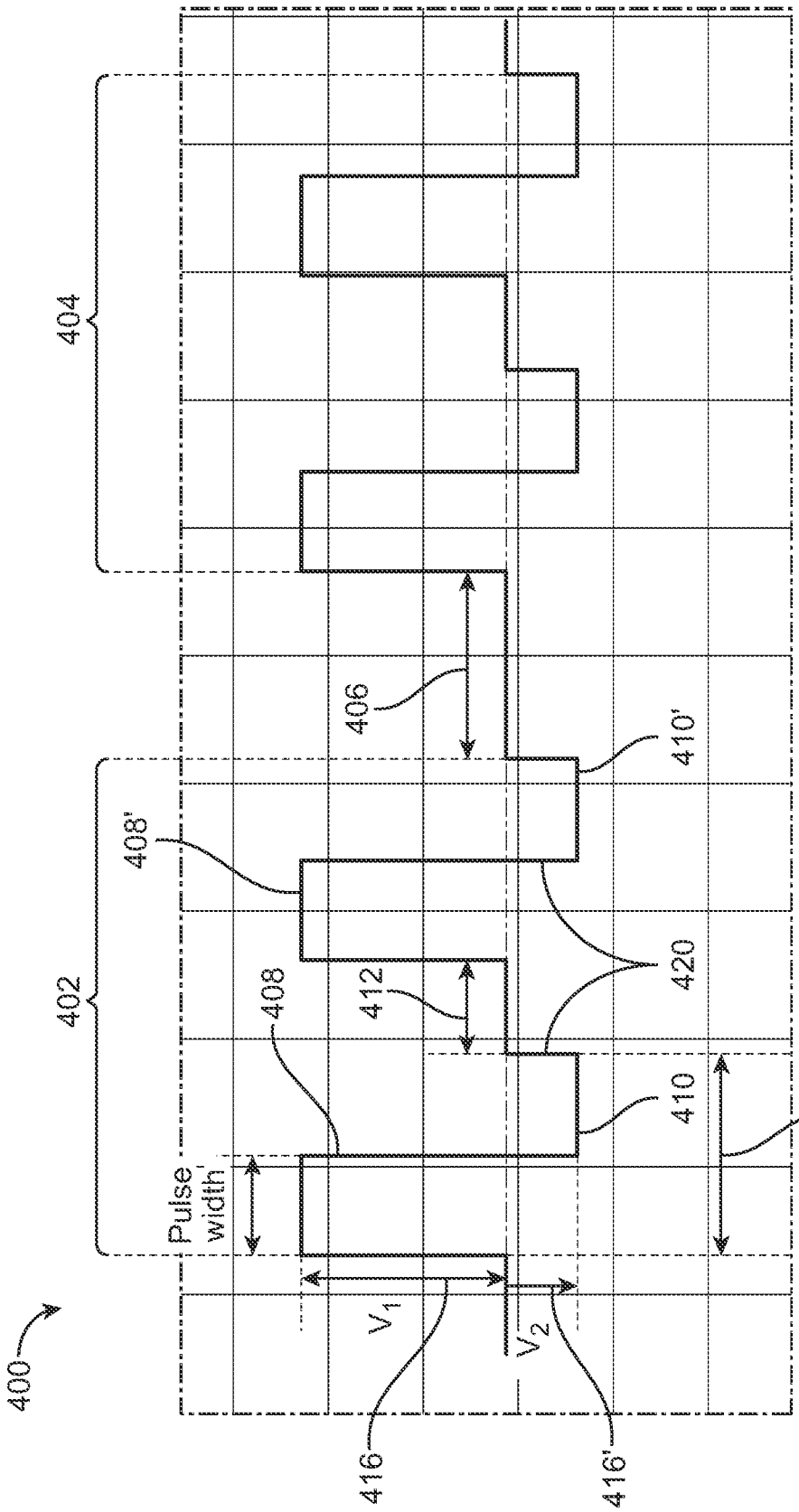

400
402
404
406
408
408'
410
410'
412
416
416'
418
420
Pulse width
V_1
V_2

FIG. 21B

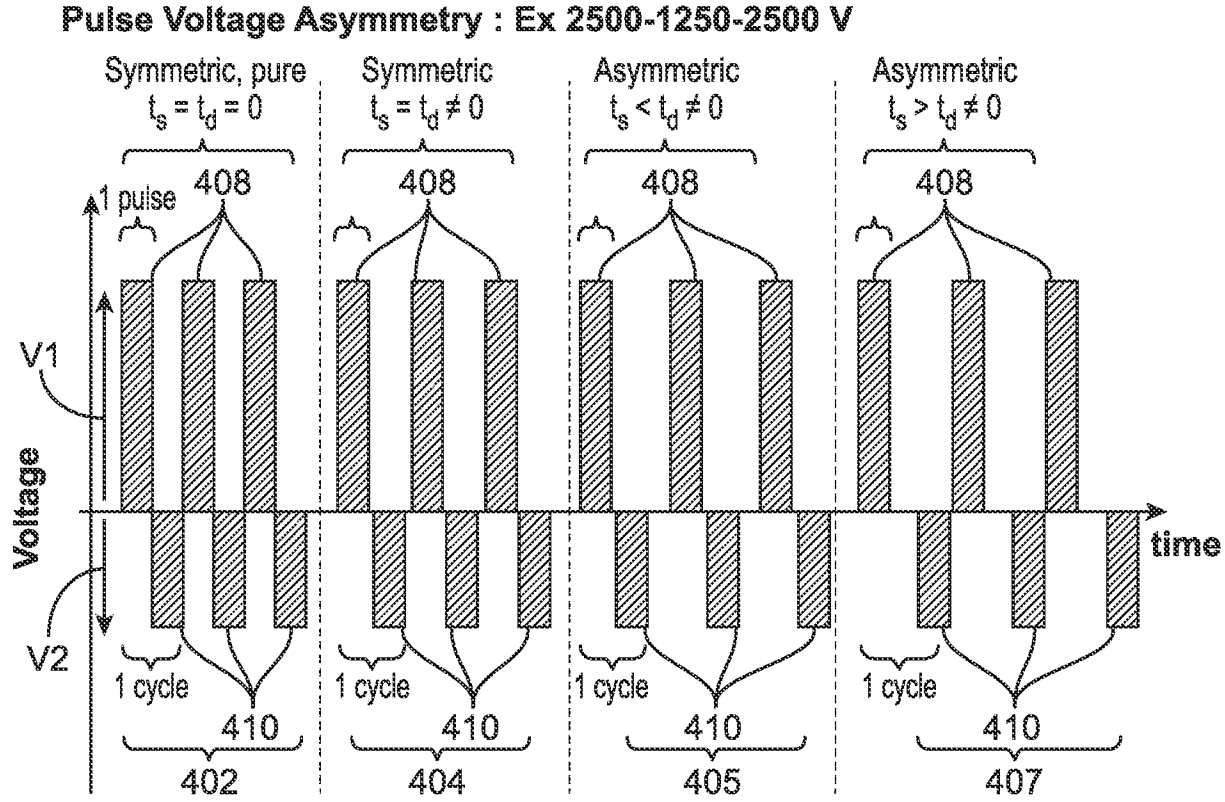


FIG. 21C

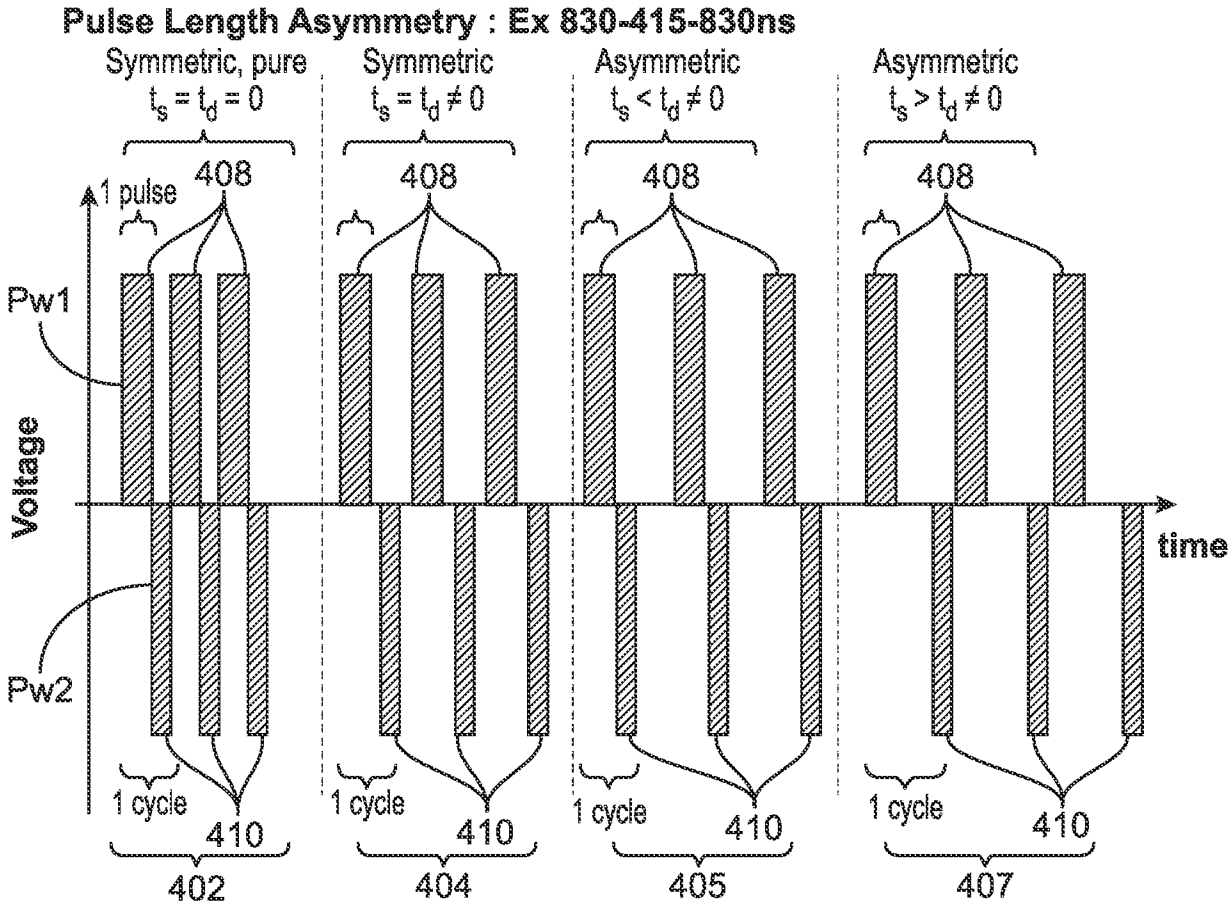


FIG. 21D

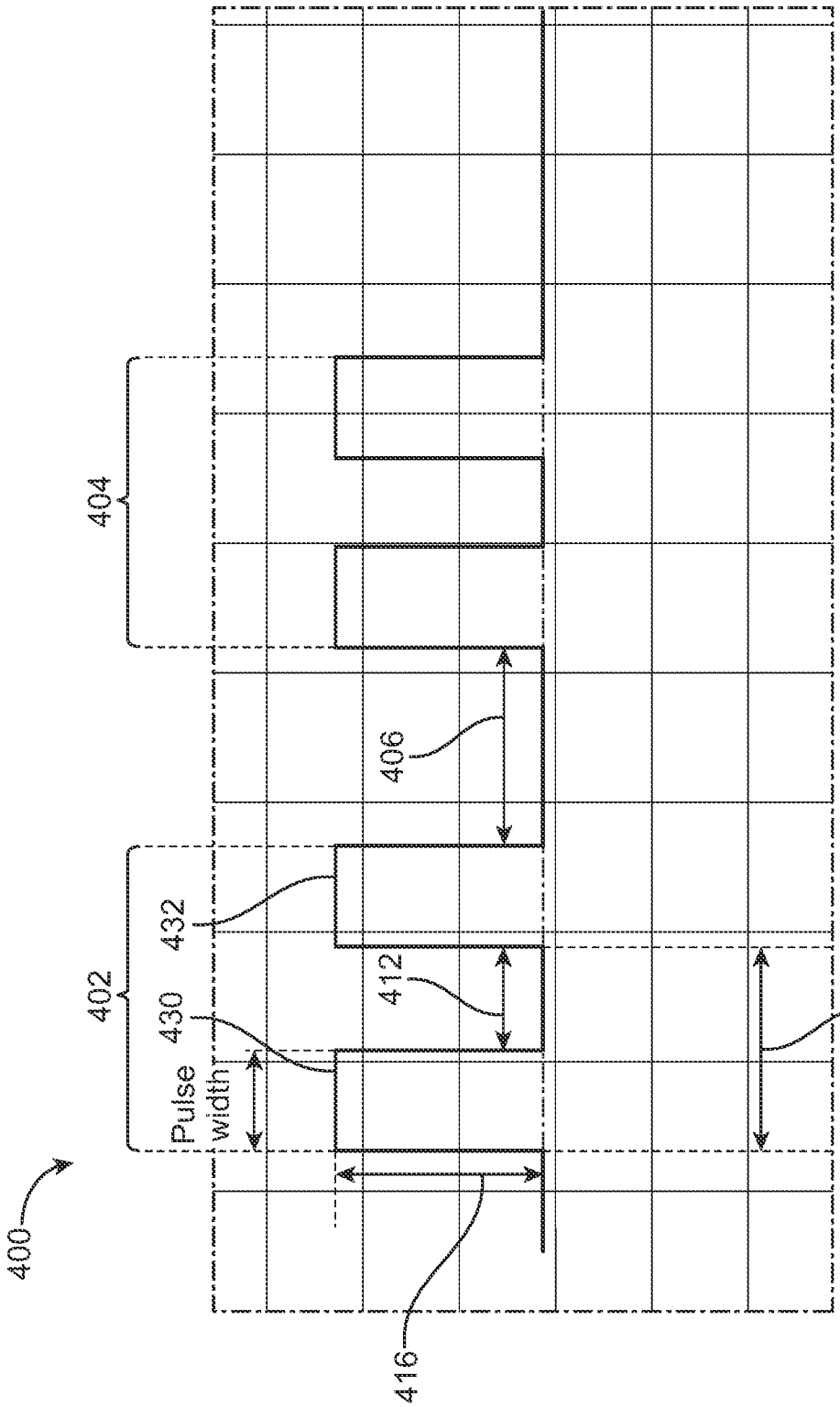


FIG. 21E

Pulse Asymmetry (pulse length and/or pulse voltage) :
Ex 2500V@830ns - 0 - 2500V@830ns

Note: Because no opposing polarity, there is no appreciable difference when considering t_s V. t_d

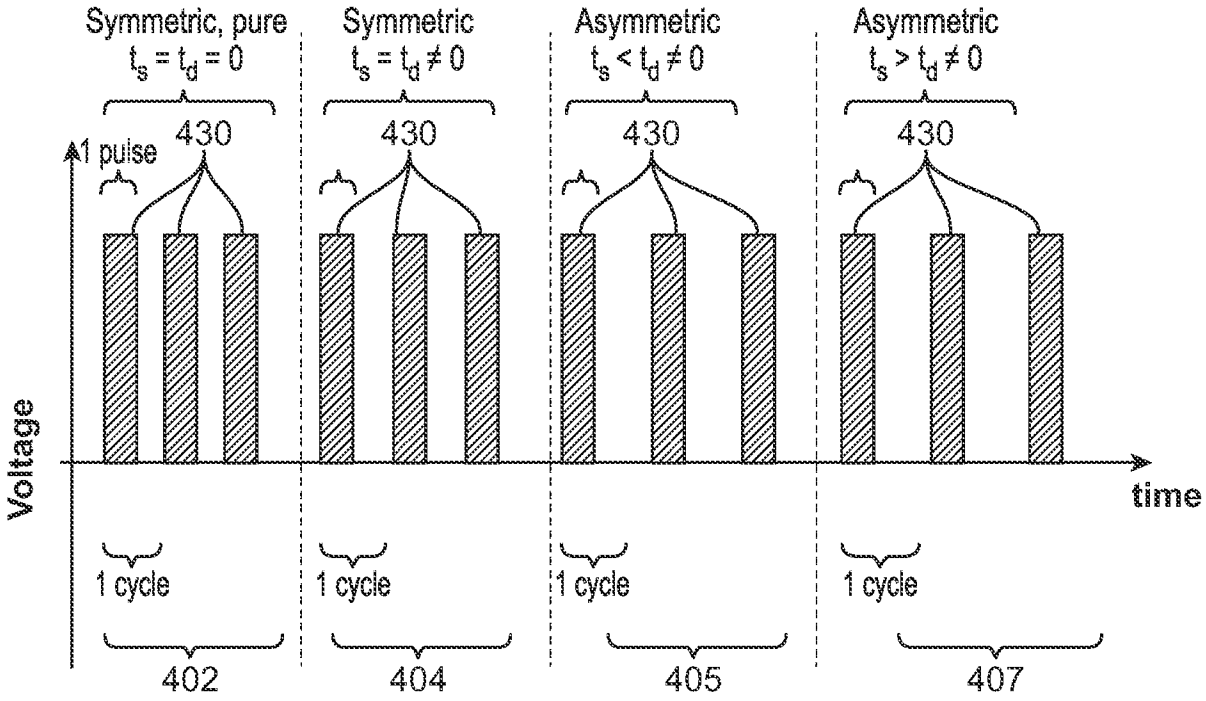


FIG. 21F

Pulse Voltage and Timing Variable Asymmetry : Multiple combinations and permutations possible

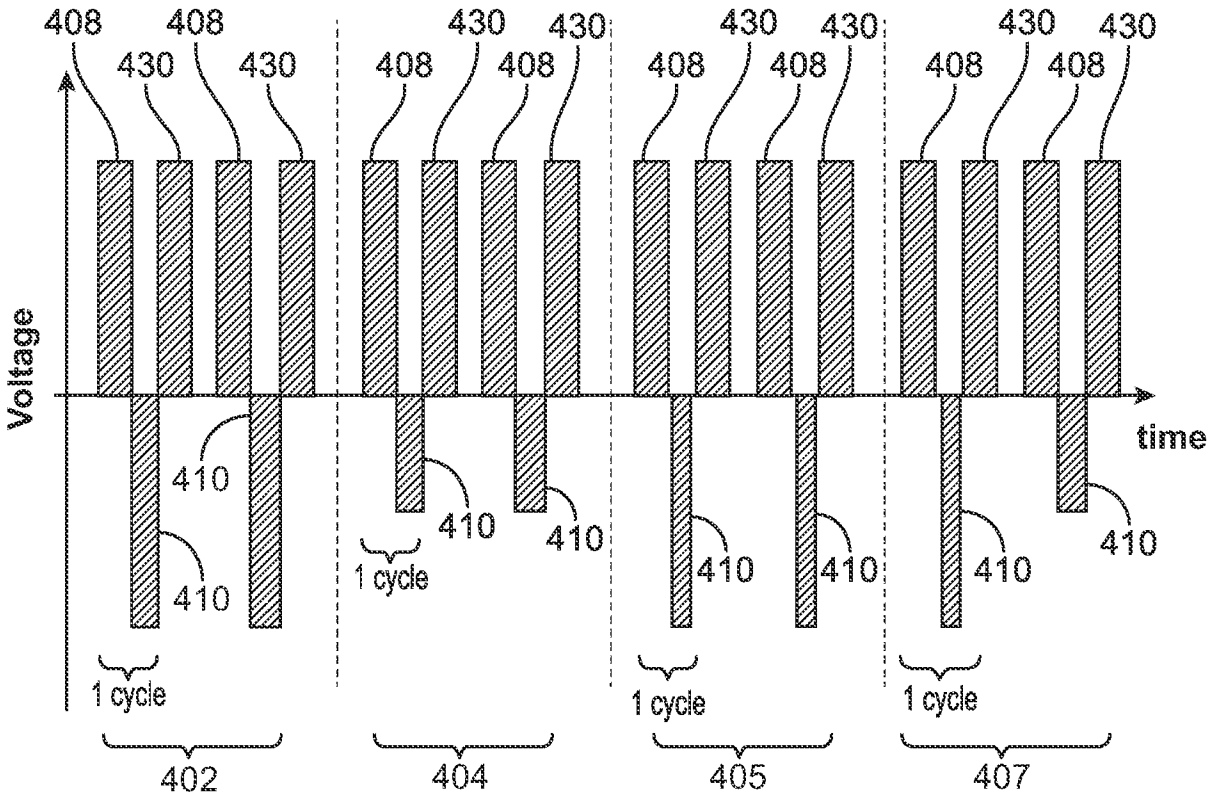


FIG. 21G

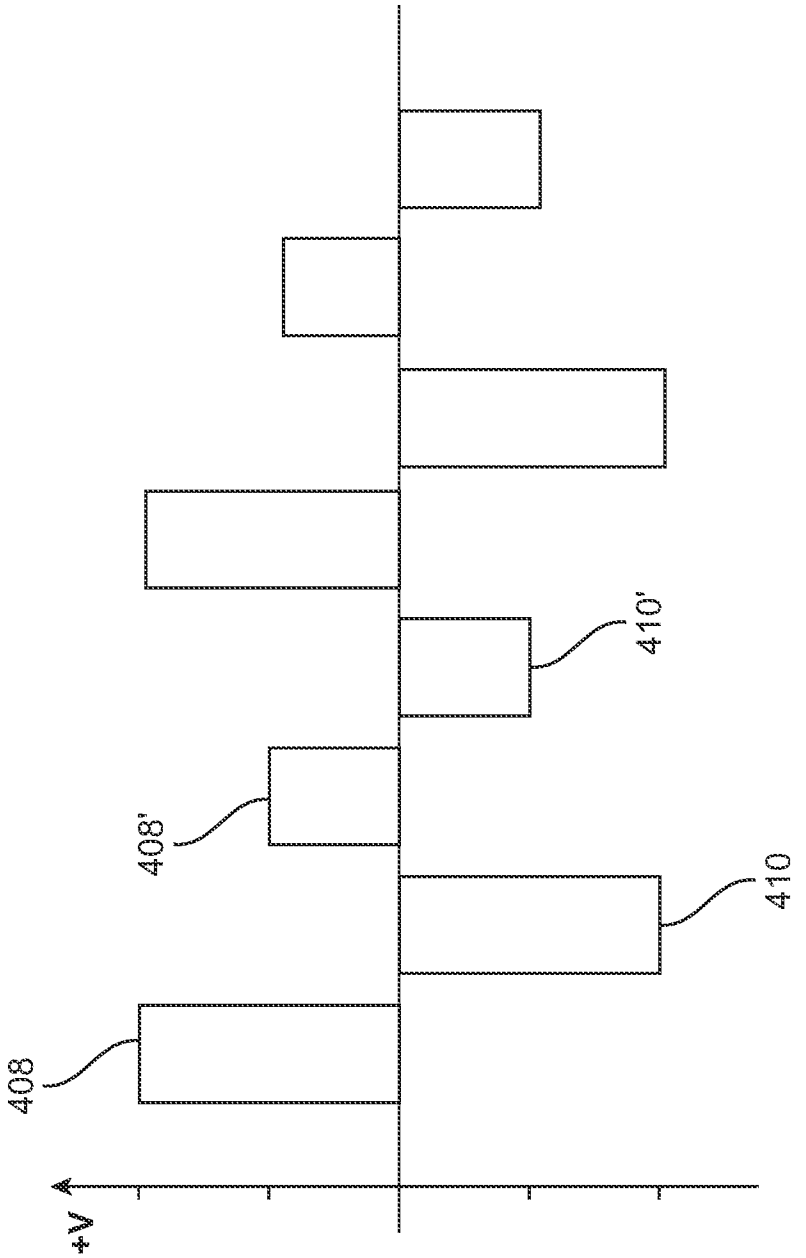


FIG. 21H

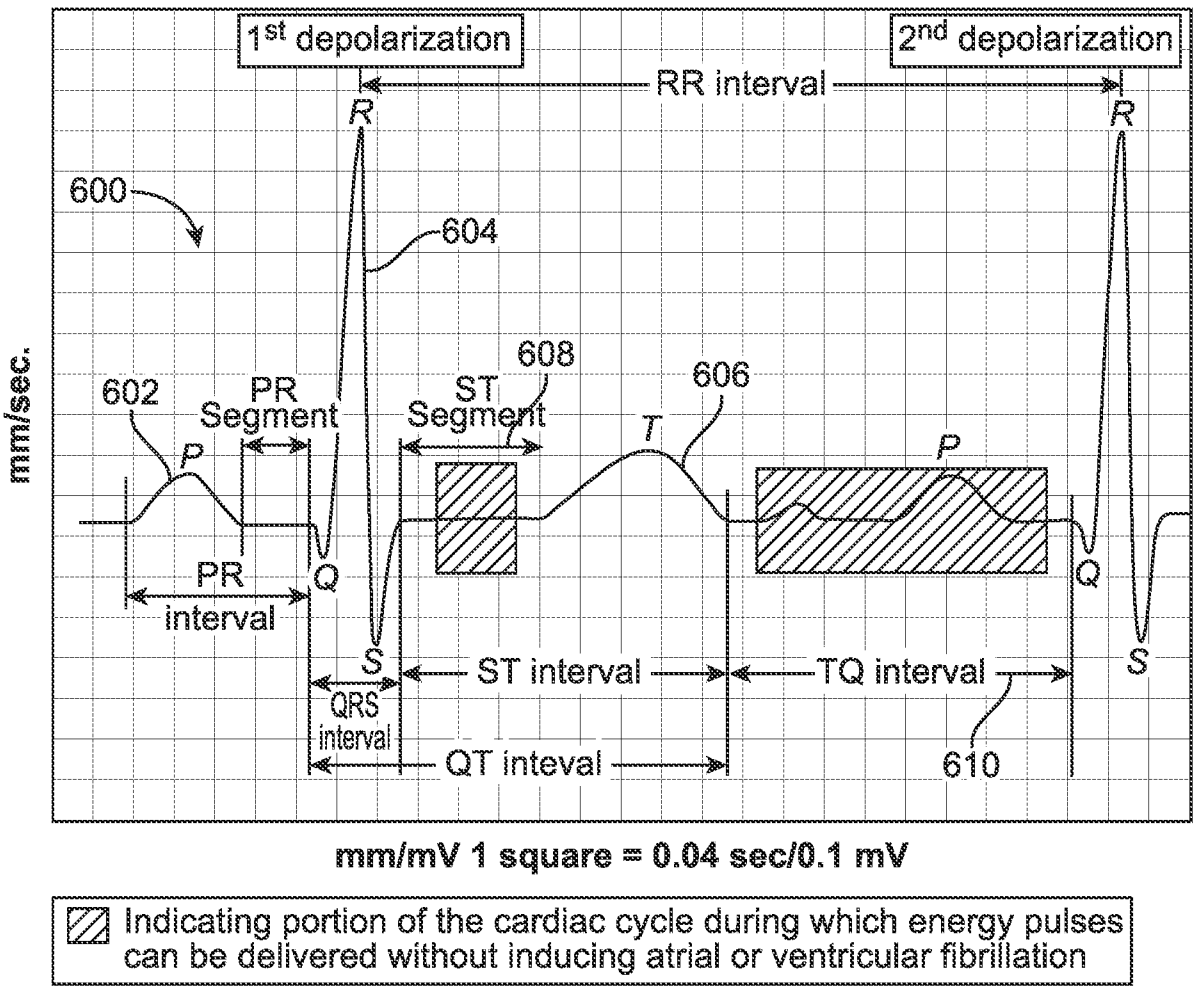

1st depolarization
2nd depolarization
RR interval
R
R
600
604
608
606
602
PR Segment
ST Segment
T
P
P
PR interval
Q
Q
S
ST interval
TQ interval
S
QRS interval
QT inteval
610
mm/sec.
mm/mV 1 square = 0.04 sec/0.1 mV
Indicating portion of the cardiac cycle during which energy pulses can be delivered without inducing atrial or ventricular fibrillation

FIG. 22