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(54) Title: SYSTEM AND METHOD FOR LOCATING AND IDENTIFYING FUNCTIONAL NERVES INNERVATING WALL OF ARTERIES

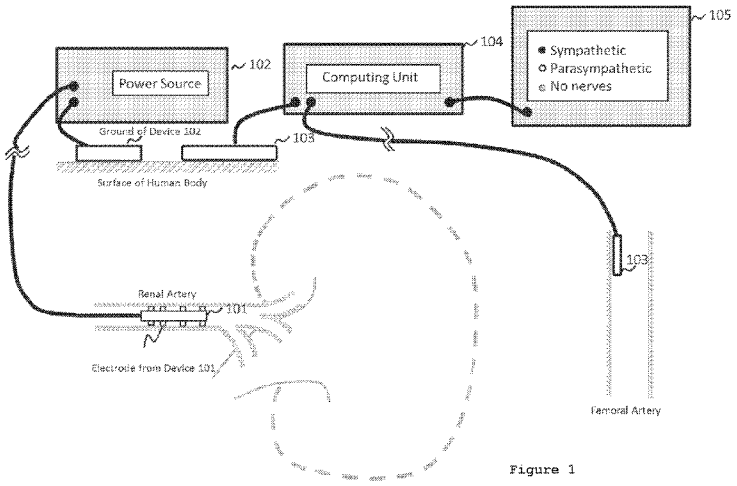

Figure 1

(57) Abstract: System and method for locating and identifying nerves innervating the wall of arteries such as the renal artery are disclosed. The present invention identifies areas on vessel walls that are innervated with nerves; provides indication on whether a dose of energy is delivered accurately to a targeted nerve; and provides immediate post-procedural assessment of the effect of the energy delivered to the nerve. The method includes at least the steps to evaluate a change in physiological parameters after a dose of energy is delivered to an arterial wall; and to determine the type of nerve that the energy was directed to (none, sympathetic or parasympathetic) based on the results of the evaluation. The system includes at least a device for delivering a dose of energy to the wall of an artery; sensors for detecting physiological signals from a subject; and indicators to display the results obtained using the said method.

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SYSTEM AND METHOD FOR LOCATING AND IDENTIFYING FUNCTIONAL NERVES INNERVATING WALL OF ARTERIES

[0001] This application claims benefit of U.S. Serial No.61/609,565, filed March 12, 2012 and U.S. Serial No. 61/527,893, filed August 26, 2011. The contents of the preceding applications are hereby incorporated in their entireties by reference into this application. Throughout this application, various publications are referenced. Disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

FIELD OF THE INVENTION

[0002] This invention relates to a system and method for accurate and precise location and identification of areas innervated with sympathetic and parasympathetic related nerves on an arterial wall during and after an energy delivery process.

BACKGROUND OF THE INVENTION

[0003] The fact that some cases of hypertension are resistant to treatment by pure pharmacological means has reignited the use of invasive techniques in treating these cases. Historically, surgical renal denervation was the prominent treatment for severe cases of hypertension prior to the introduction of orally administered anti-hypertensive drugs (Smithwick and Thompson, 1953). This type of conventional surgery was, however, extremely invasive and involved a major surgical procedure which greatly limits it practicality (DiBona, 2003). At least two clinical studies have, to a certain extent, provided support to the use of minimally invasive catheter-based radiofrequency (RF) renal nerve ablation in the treatment of resistant hypertension (Krum et al., 2009; Esler et al., 2009). Patients with hypertension resistant to the available anti-hypertensive drugs were selected for these studies and this interventional procedure demonstrated a 89% clinical success rate in lowering their blood pressure in a small and very selective patient population.

[0004] While there is growing interest in using such minimal invasive interventional techniques for treatment of hypertension, all systems on the market, including the Ardian Symplicity® Catheter System, are not optimally designed for this purpose. There are apparent shortcomings, even in the Ardian Symplicity® Catheter System, that limit the certainty of the interventional outcome.

[0005] An important aspect not considered in the current interventional systems and techniques, is the precision and accuracy in locating and delivering an effective dose of energy to a suitable ablation spot in the arterial wall. The current commonly accepted procedures for performing renal nerve ablation via catheters typically consists the steps of administering to the arterial wall 4 to 6 ablations, each made by 2 minutes of RF energies and spaced both longitudinally and rotationally along the inner wall of each renal artery. The ablations had to be delivered "blindly" in this helical manner because the exact location of the nerves innervating the renal artery with respect to the ablation catheter is unknown before and during the delivery of the ablation energy. An inaccurately directed dose of energy not only causes unnecessary damage to healthy tissues and non-sympathetic nerves but more importantly could not provide the promised solution for hypertension which the interventional procedure was intended for. In fact, in certain clinical settings other than the two published studies, the responder rate of the current "blind" type of interventional procedure could go as low as 50% (Medical devices: pg 1-2, February 22, 2012).

[0006] Theoretically, precise nerve ablation in the wall of an artery could be achieved by mapping the location of the nerves innervating the arterial wall prior to delivery of the dose of energy. By monitoring physiological parameters associated with the autonomic nervous systems such as the blood pressure, heart rate and muscle activity while a stimulus is delivered to a selected location on the arterial wall, the presence of autonomic nerves in the immediate vicinity of this location will be reflected from the changes in the monitored physiological parameters (Wang, US 2011/0306851 A1).

[0007] Further, the sympathetic and parasympathetic nerves of the autonomic nervous system often exert opposite effects in the human body including their control on blood pressure and heart rate. While ablation of the sympathetic nerves innervating the arterial walls will relieve hypertension, there is an equally possible chance that other tissues such as parasympathetic nerves are ablated in the "blind" type of interventional procedure. The result for decreasing or removal of nerve activity blindly may worsen the hypertension as could be inferred from several animal studies (Ueda et al., 1967; Beacham and Kunze, 1969; Aars and Akre, 1970; Ma and Ho, 1990; Lu et al. 1995).

[0008] The cause of failure in the current treatment was attributed to regeneration of the nerves after the ablation (Esler et al., 2010) and may also be related to both the inability to deliver the dose of energy to the targeted nerve and an insufficient dose of energy delivered for effective ablation. At present, the success of renal denervation is only assessed by the measurement of a

secondary effect known as norepinephrine spillover at least days after the interventional procedure (Krum et al., 2009) and lack a method for immediate post-procedural assessment. In order to improve the success rate of the interventional procedure, it is important to not only locate suitable ablation spots on the arterial wall, but also ensure that the energy is precisely and accurately delivered to a targeted nerve during the ablation process, and confirm immediately after the ablation that the dosage of energy delivered has effectively ablated the targeted nerve.

[0009] In response to the shortcomings of the current system and methods for nerve ablation, the present invention introduces improvements by providing a system and methods for accurate and precise location of suitable ablation spots on a renal arterial wall; ensuring sufficient ablation energy is accurately directed into a targeted nerve and to conduct immediate post-procedural assessment of nerve ablation.

SUMMARY OF THE INVENTION

[0010] It was with the preceding needs in mind that the present invention was developed. Embodiments of the disclosure are directed to system and method for accurate and precise location of areas innervated with nerves on an arterial wall; ensuring sufficient energy is accurately directed into a targeted nerve to elicit a desired response such as stimulation and ablation; and to conduct immediate post-procedural assessment of a sufficient nerve ablation. Further, the embodiments of the disclosure are also directed to provide an interface for clear representation of the location and type of nerves that are innervating the location being probed on the arterial wall.

[0011] The present invention provides a method for identifying the presence of functional sympathetic and parasympathetic nerves innervating the arterial walls in a human body with respect to the location of a dose of energy. The method comprises one or more of the steps of preparing a baseline of one or more of physiological parameters prior to the delivery of a dose of energy to the arterial wall; delivering a dose of energy to the arterial wall; detecting the physiological changes as a result of the delivered energy; rating the change based on a set of empirically pre-determined values; and determining if the area where the energy was delivered lies in the vicinity of functioning sympathetic or parasympathetic nerves based on the ratings.

[0012] In one embodiment, said method is used for locating suitable nerve ablation sites relevant to baroreflex including both sympathetic and parasympathetic systems in arterial walls prior to a nerve ablation procedure. In certain embodiments, the nerve ablation procedure is for

denervation of the renal artery. In another embodiment, the method is used for ensuring the accurate delivery of ablation energy to a targeted nerve in the arterial wall during a nerve ablation process. In a further embodiment, the method is used for immediate post-procedural assessment of the nerve ablation process to ensure that the targeted nerve has been ablated by the energy delivered in a nerve ablation procedure.

[0013] In certain embodiments, the energy is delivered to the arterial wall at dosage suitable for nerve stimulation. In other embodiments, the energy is delivered to the arterial wall at a dosage suitable for nerve ablation.

[0014] In one embodiment, the physiological parameters comprise blood pressure, heart rate, levels of biochemicals selected from epinephrine, norepinephrine, renin-angiotensin II and vasopressin, cardiac electrical activity, muscle activity, skeletal nerve activity, action potential of cells or other measurable reactions as a result of these physiological changes such as pupil response, electromyogram and vascular constriction.

[0015] In some embodiments, an area on the arterial wall that, upon stimulation, causes increase in blood pressure and heart rate is considered as innervated with sympathetic nerves while, in contrary, an area on the arterial wall that, upon stimulation, causes decrease in blood pressure and heart rate is considered as innervated with parasympathetic nerves.

[0016] In an embodiment, the energy for ablation is considered to be delivered accurately to a targeted nerve innervating the arterial wall when the physiological parameters deviate significantly from the baseline during the ablation process.

[0017] In one embodiment, the nerve ablation procedure is considered to be successful when an area, confirmed to be innervated with nerves with said method before the delivery of ablation energy, no longer leads to changes in the physiological parameters such as blood pressure and heart rate when stimulation energy is delivered to this spot.

[0018] The present invention also provides a system for locating and identifying nerves innervating an arterial wall. The system comprises one or more devices capable of delivering a dose of energy to an arterial wall; one or more sensors to receive signals of physiological parameters; one or more devices for analysis of signals from the sensors; and one or more indicators or panels capable of displaying the results of the analysis.

[0019] In one embodiment, the dose of energy delivered by the energy delivery device can be controlled to achieve either nerve stimulation or nerve ablation. In another embodiment, two separate devices are used to carry out nerve stimulation and nerve ablation independently.

[0020] In another embodiment, the energy delivered is one or more of electrical, mechanical, ultrasonic, radiation, optical and thermal energies.

[0021] In some embodiments, said sensors detect physiological parameters which comprise blood pressure, heart rate, levels of biochemicals selected from epinephrine, norepinephrine, renin-angiotensin II and vasopressin, cardiac electrical activity, muscle activity, skeletal nerve activity, action potential of cells and other measurable reactions as a result of the above such as pupil response, electromyogram and vascular constriction. In certain embodiments, the signals corresponding to the physiological parameters are detected with commercially available technologies known in the field.

[0022] In another embodiment, the device for digital analysis of the physiological signals is a microcontroller or computer.

[0023] In one embodiment, the analyzed results are displayed using different colored indicators. An area innervated with sympathetic nerves is represented with a green indicator and an area innervated with parasympathetic nerves is represented with a red indicator. In another embodiment, the analyzed data are displayed on a digital viewing panel.

[0024] In one embodiment, the set of indicators or panels may be built into devices in the system such as the energy delivery device. In certain embodiments, the set of indicators or panels may exist as a separate entity in the system.

BRIEF DESCRIPTION OF THE FIGURES

[0025] **Figure 1** is a schematic of a system of the present invention for locating and identifying functional nerves innervating the wall of an artery. The system comprises device **1** for delivery of energy to the arterial wall; power source **2** for powering device **1**; sensor **3** for detecting signals of physiological parameters; device **4** for analyzing the data from sensor **3**; and indicator **5** to display the results from device **4**.

[0026] **Figure 2** is a schematic diagram depicting the steps in an embodiment of the method to determine whether functioning sympathetic or parasympathetic nerves are in the vicinity of a dose of energy delivered to the arterial wall. The graphs illustrate possible recorded physiological signals.

[0027] **Figure 3** shows the experimental setup for acute pig experiments used in nerve mapping experiments.

[0028] **Figure 4A** shows Maximal and Minimal Effects of Left Renal Artery Stimulation on Arterial Systolic Pressure (ASP). Shown is arterial systolic pressure (ASP, as measured in mmHg) after an electrical stimulation in the left renal artery (LRA); baseline measures, as well maximal and minimal responses after the stimulation are shown.

[0029] **Figure 4B** shows Maximal and Minimal Effects of Left Renal Artery Stimulation on Arterial Diastolic Pressure (ADP). Shown is arterial diastolic pressure (ADP, as measured in mmHg) after an electrical stimulation in the left renal artery (LRA); baseline measures, as well as maximal and minimal responses after the stimulation are shown.

[0030] **Figure 4C** shows Maximal and Minimal Effects of Left Renal Artery Stimulation on Mean Arterial Pressure (MAP). Shown is mean arterial pressure (MAP, as measured in mmHG) after an electrical stimulation in the left renal artery (LRA); baseline measures, as well as maximal and minimal responses after the stimulation are shown.

[0031] **Figure 4D** shows Maximal and Minimal Effects of Left Renal Artery Stimulation on Heart Rate(HR). Shown are maximal and minimal changes in heart rate after left renal artery (LRA) electrical stimulation; baseline measures, as well as maximal and minimal heart rates after the stimulation are shown.

[0032] **Figure 5A** shows Maximal and Minimal Effects of Right Renal Artery Stimulation on Arterial Systolic Pressure (ASP). Shown is arterial systolic pressure (ASP, as measured in mmHg) after stimulation in the right renal artery (RRA); baseline measures, as well maximal and minimal responses after an electrical stimulation are shown.

[0033] **Figure 5B** shows Maximal and Minimal Effects of Right Renal Artery Stimulation on Arterial Diastolic Pressure (ADP). Shown is arterial diastolic pressure (ADP, as measured in

mmHg) after an electrical stimulation in the right renal artery (RRA); baseline measures, as well as maximal and minimal responses after the stimulation are shown.

[0034] **Figure 5C** shows mean arterial pressure (MAP, as measured in mmHg) after an electrical stimulation in the right renal artery (LRA); baseline measures, as well as maximal and minimal responses after the stimulation are shown.

[0035] **Figure 5D** shows Maximal and Minimal Effects of Right Renal Artery Stimulation on Heart Rate (HR). Shown are maximal and minimal changes in heart rate after right renal artery (RRA) electrical stimulation; baseline measures, as well as maximal and minimal heart rates after the stimulation are shown.

[0036] **Figure 6** shows the decreases in heart rate once intra-renal artery stimulations were applied to certain locations of renal artery.

[0037] **Figure 7A** shows Changes in Arterial Systolic Pressure (ASP) during Four Separated Renal Ablation in Left Renal Artery. Shown are the changes in arterial systolic pressure (ASP, as measured in mmHg) during four separate renal ablations in the left renal artery (LRA).

[0038] **Figure 7B** shows Changes in Arterial Diastolic Pressure (ADP) during Four Separated Renal Ablation in Left Renal Artery. Shown are changes in arterial diastolic pressure (ADP, as measured in mmHg) during four separate renal ablations in the left renal artery (LRA).

[0039] **Figure 7C** shows Changes in Mean Arterial Pressure (MAP) during Four Separated Renal Ablation in Left Renal Artery. Shown are changes in mean arterial pressure (MAP, as measured in mmHg) during four separate renal ablations in the left renal artery (LRA).

[0040] **Figure 7D** shows Changes in Heart Rate (HR) during Four Separated Renal Ablation in Left Renal Artery. Shown are changes in heart rate during four separate renal ablations in the left renal artery (LRA).

[0041] **Figure 8A** shows Changes in Arterial Systolic Pressure (ASP) during Four Separated Renal Ablation in Right Renal Artery. Shown are changes in arterial systolic pressure (ASP, as measured in mmHg) during four separate renal ablations in the right renal artery (RRA).

[0042] **Figure 8B** shows Changes in Arterial Diastolic Pressure (ADP) during Four Separated Renal Ablation in Right Renal Artery. Shown are changes in arterial diastolic pressure (ADP, as measured in mmHg) during four separate renal ablations in the right renal artery (RRA).

[0043] **Figure 8C** Changes in Mean Arterial Pressure (MAP) during Four Separated Renal Ablation in Right Renal Artery. Shown are changes in mean arterial pressure (MAP, as measured in mmHg) during four separate renal ablations in the right renal artery (RRA).

[0044] **Figure 8D** shows Changes in Heart Rate (HR) during Four Separated Renal Ablation in Right Renal Artery. Shown are changes in heart rate during four separate renal ablations in the right renal artery (RRA).

DETAILED DESCRIPTION OF THE INVENTION

[0045] This invention provides a system and method for locating sites innervated with functional nerves in the wall of arteries, particularly the renal artery, though persons skilled in the art will appreciate that nerves innervating other arteries or vessels in the human body may be located using this invention. The system comprises one or more devices capable of delivering a dose of energy to the wall of an artery; one or more sensors to receive inputs of physiological signals; one or more devices for analysis of signals from the sensors; and one or more indicators or panels capable of displaying the results of the analysis.

[0046] **Figure 1** depicts an exemplary system in accordance with an aspect of the invention, namely a renal denervation system using blood pressure and heart rate as the physiological parameters for identifying nerve response. The system comprises one or more of devices **1** for delivery of energy to the arterial wall which is in electrical communication with a power source **2**. System further comprises sensors **3** for detecting physiological signals in electrical communication with device **4** for analysis of the physiological signals. The indicator **5** in electrical communication with device **4** displays the result of the analysis from device **4**. Device **1**, in the form of a dual-function catheter, is shown inserted into the renal artery via minimal invasive interventional procedure in this embodiment. At least one of the electrodes of device **1** contacts the renal arterial wall at a defined location and is capable of delivering a dose of energy from the power source **2** for stimulation or ablation of the nerves that may be innervating the area of the arterial wall for which the electrode is in contact with. Sensors **3** detect changes in blood pressure and/or heart rate as energy sufficient for nerve stimulation or ablation is delivered from an electrode on device **1** to the

spot the electrode is contacting on the arterial wall. The signals from sensor **3** will be inputted to device **4** which will determine digitally whether the signal elicited is due to sympathetic or parasympathetic nerves, or the lack thereof. Indicator **5** will then display the result of the analysis from device **4**.

[0047] In one embodiment of the invention, device **1** is an invasive device inserted into an artery capable of delivering energy to a nerve innervating the artery, resulting in nerve stimulation or ablation. In another embodiment, device **1** is made up of two separate entities, one delivering the energy for nerve stimulation, and the other nerve ablation. In a different embodiment, device **1** is a single-electrode catheter or multi-electrode catheter.

[0048] In one embodiment, power source **2** delivers energy to the arterial wall via device **1**. In another embodiment, energy is delivered remotely through the human body by power source **2** into the arterial wall without device **1**. In a further embodiment, power source **2** is a multi-channel power source capable of delivering separate doses of energy independently to distinct locations on the arterial wall. In other embodiments, power source **2** is a single channel power source capable of delivering only 1 dose of energy each time. In another embodiment, the dosage of energy to be delivered by power source **2** is adjustable to induce different effects on a targeted nerve such as stimulation or ablation. In further embodiments, the energy delivered by power source **2** is one or more of electrical, mechanical, ultrasonic, radiation, optical and thermal energies.

[0049] In one embodiment, sensors **3** detect signals from physiological parameters comprising blood pressure, heart rate, levels of biochemicals selected from epinephrine, norepinephrine, renin-angiotensin II and vasopressin, cardiac electrical activity, muscle activity, skeletal nerve activity, action potential of cells and other measurable reactions as a result of the above such as pupil response, electromyogram and vascular constriction. In a further embodiment, sensors **3** detect said signals externally with or without contacting any part of the human body. In another embodiment, sensors **3** detect said signals inside the human body by placing into contact with, or in the vicinity of, the lumen of interest such as the renal artery orfemoral artery or any other artery. In yet another embodiment, sensor **3** could be a sensor from part of another equipment that is used in conjunction with this invention during the interventional procedure.

[0050] In an embodiment, device **4** is one or more microcontrollers or computers capable of digital analysis of the signals arising directly or indirectly from sensor **3**.

[0051] In one embodiment, indicator **5** is one or more digital viewing panels that display the result from the analysis of device **4**. In another embodiment, one or more results of said analysis from multiple locations on the arterial wall are simultaneously displayed on indicator **5**. In a further embodiment, indicator **5** also displays one or more the physiological signals from sensor **3**; energy related information from power source **2** such as current, frequency, voltage; tissue-electrode interface related information such as impedance; and information related to device **1** such as temperature. In certain embodiments, indicator **5** comprises a set of different colored lights each distinctly representing sympathetic nerve, parasympathetic nerve or no nerve. In other embodiments, indicator **5** represents the result from analysis of device **4** with texts, symbols, colors, sound or a combination of the above.

[0052] In certain embodiments, device **4** and indicator **5** are integrated as a single device and, in further embodiments, both device **4** and indicator **5** are integrated into power source **2**.

[0053] In yet another embodiment, sensor **3**, device **4** and indicator **5** exist independently from device **1** and power source **2** such that sensor **3**, device **4** and indicator **5** can be used with other external or invasive methods for energy delivery into the vessel wall such as high-intensity focused ultrasound.

[0054] The present invention additionally provides a method for identifying the presence of functional sympathetic or parasympathetic nerves innervating a selected area on the arterial wall based on changes in physiological parameters induced by a dose of energy. The method comprises one or more of the steps of preparing a baseline of the physiological parameters to be measured prior to the delivery of a dose of energy to the arterial wall; delivering a dose of energy to the arterial wall; detecting the physiological changes as a result of the delivered energy; rating the change based on a set of empirically pre-determined values; and, based on the ratings, determining if there are functional sympathetic or parasympathetic nerves in the vicinity of the site of energy delivery.

[0055] **Figure 2** is a flow chart illustrating the steps of the method for determining the presence of any functional sympathetic or parasympathetic nerve innervating a selected area of an arterial wall.

[0056] At **step 1**, physiological signals from sensor **3** are continuously recorded by device **4** to produce a reliable baseline reflective of any instantaneous changes in the signals.

[0057] Energy is then delivered by one of the electrodes in device **1** to the area on the arterial wall that this electrode is in contact with (**Step 2**). Sensor **3** detects any physiological change caused by the energy delivered, and the change is recorded as signals which are then sent to device **4**. (**Step 3**)

[0058] In **step 4**, device **4** determines the deviation of the physiological signals from the baseline of step **1** and, in **step 5**, determines the type of nerves innervating the area on the arterial wall based on the deviation from the baseline information.

[0059] In one embodiment, the physiological signals detected by sensor **3** comprises one or more of blood pressure, heart rate, levels of biochemicals selected from epinephrine, norepinephrine, renin-angiotensin II and vasopressin, cardiac electrical activity, muscle activity, skeletal nerve activity, action potential of cells and other observable body reactions as a result of the above such as pupil response and vascular constriction.

[0060] In an embodiment, the dosage of energy delivered in **step 2** is adjustable to induce different interactions with a targeted nerve such as nerve stimulation or nerve ablation.

[0061] In certain embodiments, the values of the physiological signals are measured using other external devices and inputted into device **4** prior to the energy delivery to replace the baseline formed by device **4**.

[0062] In one embodiment, the changes in physiological parameters are detected during or after the energy delivery process in step **2**. In another embodiment, the changes in physiological parameters are in the form of numerical values or waveforms. In further embodiments, the deviation from baseline of step **1** is evaluated by subtracting the baseline of step **1** from the signals.

[0063] In one embodiment, the empirically pre-determined set of values could be obtained from sets of clinical data or deduced from the experience of clinical physicians. In some embodiments, an area on the arterial wall is considered to be innervated with sympathetic nerves when energy delivered to the area causes an increase in heart rate by 10 beats per minute and/or an increase in blood pressure by 6 mmHg. In other embodiments, an area on the arterial wall is considered to be innervated with parasympathetic nerves when energy delivered to the area causes a decrease in heart rate by 5 beats per minute and/or a decrease in blood pressure by 2 mmHg.

[0064] In a further embodiment, the results of **step 5** will be displayed on indicator **5**.

[0065] In one embodiment, the method is used for identifying the suitable sites for nerve ablation in the arterial wall to disrupt baroreflex via sympathetic and parasympathetic nervous systems. In another embodiment, the method provides indication of whether the ablation energy is delivered accurately to the targeted nerves in the arterial wall. In a further embodiment, the method is used for immediate post-procedural assessment of nerve ablation.

[0066] The present invention also provides a method for locating or identifying a functional nerve innervating the wall of a blood vessel in a subject, comprising the steps of a) Delivering energy to one or more locations on said vessel wall sufficient to change one or more physiological parameters associated with the innervation of said vessel by a sympathetic or parasympathetic nerve; and b) Measuring said one or more physiological parameters after each delivery of energy, and determining the change from the corresponding parameters obtained without energy delivery to said vessel; wherein a lack of change in said physiological parameters in step b indicates the absence of a functional nerve at the location of energy delivery, a significant change in said physiological parameters in step b indicates the presence of a functional nerve at the location of energy delivery, and the direction of change in said physiological parameters in step b determines the nerve to be sympathetic or parasympathetic at the location of energy delivery. In one embodiment, the blood vessel is an artery, including a renal artery. In one embodiment, the functional nerve is related to baroreflex. In another embodiment, the subject of the method is a human or non-human animal. It is to be understood that a lack of change means that the change would be considered by someone skilled in the art to be negligible or statistically insignificant, and a significant change means that the change would be considered by someone skilled in the art to be meaningful or statistically significant.

[0067] In one embodiment, the method used for locating or identifying a functional nerve innervating the wall of a blood vessel in a subject comprises a step of delivering energy to a location where a nerve has been ablated, wherein a lack of change in said physiological parameters confirms nerve ablation. In one embodiment, the energy delivered is adjustable and consists of electrical, mechanical, ultrasonic, radiation, optical and thermal energies. In another embodiment, the energy delivered causes nerve stimulation or nerve ablation.

[0068] In one embodiment, the physiological parameters described in the method used for locating or identifying a functional nerve innervating the wall of a blood vessel in a subject are selected from blood pressure, heart rate, cardiac electrical activity, muscle activity, skeletal nerve activity, action potential of cells, pupil response, electromyogram, vascular constriction, and levels

of biochemicals selected from epinephrine, norepinephrine, renin-angiotensin II and vasopressin. In another embodiment, the functional nerve is a sympathetic or parasympathetic nerve.

[0069] In one embodiment, a system for locating or identifying a functional nerve innervating the wall of a blood vessel in a subject comprises: a) an energy-delivering device configured to deliver energy to one or more locations on said wall sufficient to stimulate a nerve innervating said vessel; b) One or more measuring devices for measuring one or more physiological parameters associated with the innervation of said blood vessel by a sympathetic or parasympathetic nerve, before or after energy is delivered to said nerve by said energy-delivering device; and c) a device configured to couple to the one or more measuring devices for displaying the location and identity of a nerve innervating said vessel wall. In one embodiment, the measuring devices are placed inside the vessel or outside the body. In another embodiment, the measuring devices comprise one or more microcontrollers or computers.

[0070] In one embodiment, said system displays the location and identity of a nerve as numbers, texts, symbols, colors, sound, waveforms, or a combination thereof.

[0071] In one embodiment, said system is used in a method for locating or identifying a functional nerve innervating the wall of a blood vessel in a subject, comprising the steps of a) Delivering energy to one or more locations on said vessel wall sufficient to change one or more physiological parameters associated with the innervation of said vessel by a sympathetic or parasympathetic nerve; and b) Measuring said one or more physiological parameters after each delivery of energy, and determining the change from the corresponding parameters obtained without energy delivery to said vessel; wherein a lack of change in said physiological parameters in step b indicates the absence of a functional nerve at the location of energy delivery, a significant change in said physiological parameters in step b indicates the presence of a functional nerve at the location of energy delivery, and the direction of change in said physiological parameters in step b determines the nerve to be sympathetic or parasympathetic at the location of energy delivery.

[0072] It will be appreciated by persons skilled in the art that the system and method disclosed herein may be used in nerve ablation of the renal artery to disrupt baroreflex via sympathetic and parasympathetic nervous systems but its application could be extended to any innervated vessels in the body.

[0073] The invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific examples are for

illustrative purposes only and should not limit the scope of the invention which is defined by the claims which follow thereafter.

[0074] It is to be noted that the transitional term "comprising", which is synonymous with "including", "containing" or "characterized by", is inclusive or open-ended and does not exclude additional, un-recited elements or method steps.

EXAMPLE 1
Locating nerves innervating an arterial wall

[0075] A method to locate nerves innervating an arterial wall via examination of the changes in physiological parameters after the delivery of a suitable dose of energy was designed and executed in acute pig experiments.

[0076] Three pigs (body weight from 50-52 kg) were anesthetized with intravenous injection of sodium pentobarbital at 15 mg/kg. The physiological parameters: systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were monitored. The experimental design and protocol are illustrated in **Figure 3**.

[0077] The ablation catheter used in this set of experiments was the 7F,B-Type, spacing 2-5-2mm, CELSIUS® RMT Diagnostic/Ablation Steerable Catheter (Biosense Webster, Diamond Bar, CA 91765, USA) and a Celsius radiofrequency generator (STOCKERT 70 RF Generator, Model Stockert GmbH EP-SHUTTLE ST-3205, STOCKERT GmbH, Freiburg, Germany).

[0078] Baselines for systolic, diastolic and mean arterial blood pressure and heart rate were measured before the delivery of electrical energy to different areas of the renal arterial wall. Mean arterial blood pressure and heart rate were then measured 5 seconds to 2 minutes after the delivery of energy to note for any effects. By recognizing that a significant change in blood pressure and heart rate to be associated with nerve stimulation, it was found that, although the segment of the arterial wall that is innervated varies in each animal, the method described herein has correctly located these areas in each of the animals giving a map of the innervated regions in the renal artery.

EXAMPLE 2
Relationship between Physiological Parameters and the Nerves Innervating an Arterial Wall

[0079] In order to demonstrate that energy delivered to different locations on an arterial wall may result in different effects on physiological parameters such as blood pressure and heart rate, and such characteristics can be capitalized on to identify the type of nerve innervating an

arterial wall, electrical energy was delivered to the innervated areas on the renal arterial walls of the pig model according to several strategies. Detailed parameters on the electrical energy delivered to Pig #1, Pig #2 and Pig #3 are shown in **Table 1**, **Table 2** and **Table 3** respectively.

[0080] In Pig #1, four separate stimulations took place in the left renal artery and two separate stimulations were performed in the right renal artery. As preliminary approaches, on the abdominal side of the left renal artery, two separate doses of electrical energy were delivered: one to the anterior wall and one to the posterior wall of the artery. On the kidney side of the left renal artery, two separate doses of electrical energy were delivered: one to the anterior wall and one to the posterior wall of the artery. Different effects of these energies on blood pressure and heart rate were observed. In the right renal artery, one dose of electrical energy was delivered to the renal artery on the abdominal side and the kidney side, respectively. The same stimulation strategy was used for Pig #2 and Pig #3.

[0081] The electrical energy delivered to different locations in the renal artery caused different effects on the systolic blood pressure, diastolic blood pressure, mean blood pressure and heart rate in all of the pigs tested. For instance, in response to the electrical energy delivered to the left kidney, the maximal change in systolic blood pressure was respectively 19.5 mmHg and 29 mmHg in Pig #1 and Pig #3; the minimal change of systolic blood pressure was respectively 2 mmHg and 1 mmHg in Pig #1 and Pig #3. However, in Pig #2, changes in systolic blood pressure were consistent when the electrical energy was delivered to either the abdominal aorta side or the kidney side. Furthermore, the stimulation location which caused the maximal effect or minimal effect varied from animal to animal, indicating that the distribution of renal autonomic nerves is not consistent between animals. These phenomenons in systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate during delivery of electrical energy to wall of the left renal artery were observed and further summarized in **Table 4A**, **4B**, **4C** and **4D**, respectively. Similar phenomenon in systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and heart rate during electrical stimulation in the right renal artery were also observed and further summarized in **Table 5A**, **5B**, **5C** and **5D**, respectively.

[0082] These data provide proof of concept for locating and identifying nerves innervating an arterial wall – specifically, that a substantial physiological response, in this case, the maximal increase or decrease in measured blood pressure, was induced by delivery of electrical energy via a catheter placed at a defined location where renal nerve branches are abundantly distributed. Averaged data (mean$\pm$SD) calculated from **Tables 4A-D** and **Tables 5A-D** are graphically represented in **Figure 4** and **Figure 5**, inclusive of all sub-figures.

Table 1
Renal Nerve Stimulation for Mapping

Pig #1:

Renal Artery	Stimulation Site		Stimulation Parameters
Left	Kidney side	Anterior Wall	15 V; 0.4ms; 400 Ohm; 17mA
		Posterior Wall	15 V; 0.4ms; 400 Ohm;28mA
	Abdominal Aorta Side	Anterior Wall	15 V;0.2ms; 400 Ohm;28mA
		Posterior Wall	15 V;0.2ms; 540 Ohm;28mA
Right	Kidney side		15 V; 0.2ms; 600 Ohm; 25mA
	Abdominal Aorta Side		15 V; 0.2ms; 520 Ohm; 25mA

Table 2
Renal Nerve Stimulation for Mapping

Pig #2:

Renal Artery	Stimulation Site	Stimulation Parameters
Left	Kidney side	15 V; 0.2ms; 580 Ohm; 26mA
	Abdominal Aorta Side	15 V; 0.2ms; 480 Ohm; 28mA
Right	Kidney side	15 V; 0.2ms; 520 Ohm; 28mA
	Abdominal Aorta Side	15 V; 0.2ms; 500 Ohm; 28mA

Table 3
Renal Nerve Stimulation for Mapping

Pig #3:

Renal Artery	Stimulation Site	Stimulation Parameters
Left	Kidney side	15 V; 9.9ms; 800 Ohm; 28mA
	Abdominal Aorta Side	15 V; 9.9ms; 800 Ohm; 28mA
Right	Kidney side	15 V; 9.9ms; 800 Ohm; 28mA
	Abdominal Aorta Side	15 V; 9.9ms; 800 Ohm; 28mA

Table 4A
Changes in Systolic Blood Pressure (SBP) During Electrical Stimulation in Left Renal Artery

	Left Renal Stimulation							
SBP	Maximal Responses (mmHg)				Minimal Responses (mmHg)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	131.5	151	19.5	AO Side	140	142	2	Renal Side
Pig 2	155	159	4	Renal Side	155	159	4	AO Side
Pig 3	173	202	29	Renal Side	169	170	1	AO Side
Average	153.2	170.7	17.5		154.7	157.0	2.3	
SD	20.8	27.4	12.6		14.5	14.1	1.5	

Table 4B
Changes in Diastolic Blood Pressure (DBP) During Electrical Stimulation in Left Renal Artery

	Left Renal Stimulation							
DBP	Maximal Responses (mmHg)				Minimal Responses (mmHg)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	99	108	9	AO Side	116	117	1	Renal Side
Pig 2	112	115	3	Renal Side	114	116	2	AO Side
Pig 3	119	139	20	Renal Side	110	115	5	AO Side
Average	110.0	120.7	10.7		113.3	116.0	2.7	
SD	10.1	16.3	8.6		3.1	1.0	2.1	

Table 4C
Changes in Mean Arterial Pressure (MAP) During Electrical Stimulation in Left Renal Artery

	Left Renal Stimulation							
MAP	Maximal Responses (mmHg)				Minimal Responses (mmHg)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	112.5	125	12.5	AO Side	123	128	5	Renal Side
Pig 2	130	133	3	Renal Side	131	132	1	AO Side
Pig 3	141	158	17	Renal Side	136	138	2	AO Side
Average	127.8	138.7	10.8		130.0	132.7	2.7	
SD	14.4	17.2	7.1		6.6	5.0	2.1	

Table 4D
Changes in Heart Rate (HR) During Electrical Stimulation in Left Renal Artery

	Left Renal Stimulation							
HR	Maximal Responses (beats/min)				Minimal Responses (beats/min)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	150	151	1	Renal Side	140	130	-10	Renal Side
Pig 2	126	132	6	AO Side	132	120	-12	Renal Side
Pig 3	138	142	4	Renal Side	159	150	-9	AO Side
Average	138.0	141.7	3.7		143.7	133.3	-10.3	
SD	12.0	9.5	2.5		13.9	15.3	1.5	

Table 5A

Changes in Systolic Blood Pressure (SBP) During Electrical Stimulation in Right Renal Artery

	Right Renal Stimulation							
SBP	Maximal Responses (mmHg)				Minimal Responses (mmHg)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	151.5	156	4.5	Renal Side	155	158	3	AO Side
Pig 2	153	166	13	Renal Side	157	162	5	AO Side
Pig 3	154	167	13	Renal Side	157	162	5	AO Side
Average	152.8	163.0	10.2		156.3	160.7	4.3	
SD	1.3	6.1	4.9		1.2	2.3	1.2	

Table 5B

Changes in Diastolic Blood Pressure (DBP) During Electrical Stimulation in Right Renal Artery

	Right Renal Stimulation							
DPB	Maximal Responses (mmHg)				Minimal Responses (mmHg)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	111.5	113	1.5	Renal Side	113	113	0	AO Side
Pig 2	113	119	6	Renal Side	114	117	3	AO Side
Pig 3	110	113	3	Renal Side	112	110	-2	AO Side
Average	111.5	115.0	3.5		113.0	113.3	0.3	
SD	1.5	3.5	2.3		1.0	3.5	2.5	

Table 5C

Changes in Mean Arterial Pressure (MAP) During Electrical Stimulation in Right Renal Artery

	Right Renal Stimulation							
MAP	Maximal Responses (mmHg)				Minimal Responses (mmHg)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	130	130	0	AO Side	131	130	-1	Renal Side
Pig 2	130	141	11	Renal Side	132	135	1	AO Side
Pig 3	127	130	3	Renal Side	130	131	1	AO Side
Average	129.0	133.7	4.7		131.0	132.0	1.0	
SD	1.7	6.4	5.7		1.0	2.6	2.0	

Table 5D
Changes in Heart Rate (HR) During Electrical Stimulation in Right Renal Artery

	Right Renal Stimulation							
HR	Maximal Responses (beats/min)				Minimal Responses (beats/min)			
Animal No.	Baseline	Maximal	Δ	Stimulation Location	Baseline	Minimal	Δ	Stimulation Location
Pig 1	141	146	5	AO Side	144	135	-9	Renal Side
Pig 2	135	147	12	Renal Side	120	117	-3	AO Side
Pig 3	129	135	6	Renal Side	126	123	-3	AO Side
Average	135.0	142.7	7.7		130.0	125.0	-5.0	
SD	6.0	6.7	3.8		12.5	9.2	3.5	

Table 6
Possible effects of stimulating renal nerves

Publication	Animal Model	Change of blood pressure when renal nerve stimulated	Change of heart rate when renal nerve stimulated
Ueda H, Uchida Y and Kamisaka K, *"Mechanism of the Reflex Depressor Effect by Kidney in Dog"*,	Dog	↓	N/A
Beacham WS and Kunze DL, *"Renal Receptors Evoking a Spinal Vasometer Reflex"*, J. Physiol., 1969, 201 (1): 73-85	Cat	↓	N/A
Aars H and Akre S *"Reflex Changes in Sympathetic Activity and Arterial Blood Pressure Evoked by Afferent Stimulation of the Renal Nerve"*, Acta Physiol. Scand., 1970, 78 (2): 184-188	Rabbit	↓	N/A
Ma G and Ho SY, *"Hemodynamic Effects of Renal Interoreceptor and Afferent Nerve Stimulation in Rabbit"*, Acta Physiol. Sinica, 1990, 42 (3): 262-268	Rabbit	↓	↓
Lu M, Wei SG and Chai XS, *"Effect of Electrical Stimulation of Afferent Renal Nerve on Arterial Blood Pressure, Heart Rate and Vasopressin in Rabbits"*, Acta Physiol. Sinica, 1995, 47 (5): 471-477	Rabbit	↓	↓

[0083] Among all the stimulation experiments performed in pigs according to the previously described protocol, certain locations in the renal arterial wall led to significant decreases

in heart rate without causing changes in the blood pressure or the change in blood pressure is minimal in comparison to the decrease in heart rate (**Figure 6**). Slight decreases in blood pressure, especially, diastolic blood pressure were often recorded. Out of the 56 data points inclusive of all 4 physiological parameters evaluated in the experiments, there were at least 1 data point from each physiological parameter that responded with the dose of energy by a drop or no/insignificant change in value; this accounted for over 23% of the data points in this experiment. These distinctive physiological changes in response to the stimulations appear to indicate that nerves innervating these locations are of parasympathetic nature and are different from those sympathetic nerves innervating the locations that results in increases in blood pressure and heart rate upon stimulation. **Table 6** summarized the effect of delivering a suitable dose of energy to the afferent renal nerve in different studies involving animal models of dogs, cats and rabbits. In conjunction with this invention, the studies in **Table 6** had demonstrated that it is not uncommon to induce effects akin to parasympathetic activity when a suitable dose of energy is delivered to the nerves innervating the kidney. In other words, there is an indication that, in the neural circuitry of the renal artery, there exist nerves that can induce parasympathetic activity rather than sympathetic activity and therefore should not be ablated when treating blood pressure related diseases.

EXAMPLE 3

Ensuring energy is directed to a target nerve during ablation

[0084] Subsequent to the studies for locating and identifying nerves in an arterial wall, energies at dosage suitable for ablations were also delivered to the innervated spots in the renal arterial wall of the same pigs. Four ablations were each delivered to the left and to the right renal arteries starting from the kidney side and moving to the abdominal aorta side in the order of movement from the anterior, to the posterior, to the superior and then to the inferior wall; each ablation was $\leq$ 5mm apart from the location of the previous ablation and the electrode head (catheter tip) of the ablation catheter was turned 90 degrees after each ablation. Based on the literature (Krum 2009, 2010), low energy level (5-8 watts) should be used for renal ablation; therefore, 5 watts and 8 watts were used for renal ablation. For left renal artery ablation, the energy level applied was 5 watts and the time length of ablation was 120 seconds; for the right renal artery, the ablation energy level applied was 8 watts and the time length was 120 seconds. The temperature at the ablation site was measured to be from 40°C to 50°C. The physiological parameters: systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate were examined during ablations. The data clearly showed that ablation at different locations within the renal artery resulted in differing changes in blood pressure and heart rate, further demonstrating that changes in physiological parameters such as blood pressure and heart rate can be used as indicators for an

accurate delivery of ablation energy to a targeted nerve and provided further evidence that distribution of the nerves in the arterial wall varied case by case.

[0085] Changes in systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate during four separate renal ablations in the renal arteries of the left kidney were summarized in **Figures 7A**, **7B**, **7C** and **7D**, respectively. Changes in arterial systolic and diastolic pressure, mean arterial pressure and heart rate during four separate renal ablations in the renal arteries of the right kidney were summarized in **Figures 8A**, **8B**, **8C** and **8D**, respectively.

REFERENCES

1. Aars, H. and Akre, S., (1970), Reflex Changes in Sympathetic Activity and Arterial Blood Pressure Evoked by Afferent Stimulation of the Renal Nerve, Acta Physiol. Scand., 78 (2): 184-188.
2. Beacham, W.S. and Kunze, D.L., (1969), Renal Receptors Evoking a Spinal Vasometer Reflex, J. Physiol., 201 (1): 73-85.
3. DiBona, G.F. (2003), Neural control of the kidney: past, present and future, Hypertension, 41: 621-624.
4. Esler, M., Schlaich, M., Sobotka, P. et al., (2009) Catheter-based renal denervation reduces total body and renal noradrenaline spillover and blood pressure in resistant hypertension, Journal of Hypertension, 27(suppl 4):s167.
5. Esler, M. et al., (December 4, 2010), Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomized controlled study, The Lancet, 376: 1903-1909.
6. Krum, H., Schlaich, M., Whitbourn, R., Sobotka, P.A., Sadowski, J., Krzysztof, Bartus, K., Kapelak, B., Walton, A., Sievert, H., Thambar, S., Abraham, W.T., and Esler, M., (April 2009), Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study, The Lancet, 373(9671):1275-1281.
7. Lu, M., Wei, S.G. and Chai, X.S., (1995), Effect of Electrical Stimulation of Afferent Renal Nerve on Arterial Blood Pressure, Heart Rate and Vasopressin in Rabbits, Acta Physiol. Sinica, 47 (5): 471-477.
8. Ma, G. and Ho, S.Y., (1990), Hemodynamic Effects of Renal Interoreceptor and Afferent Nerve Stimulation in Rabbit, Acta Physiol. Sinica, 42 (3): 262-268.
9. Medical devices: pg 1-2, February 22, 2012.
10. Smithwick, R.H., and Thompson, J.E., (August 15, 1953), Splanchnicectomy for essential hypertension; results in 1,266 cases. J Am Med Association, 152(16):1501-1504.
11. Ueda, H., Uchida, Y., and Kamisaka, K., (1967), Mechanism of the Reflex Depressor Effect by Kidney in Dog, Jpn. Heart J., 8 (6): 597-606.
12. Wang, J., Mapping sympathetic nerve distribution for renal ablation and catheters for the same, US patent application no. 2011/0306851 A1, filed August 26, 2011.

2012303696 08 Apr 2014

Claims

The claims defining the invention are as follows:

1. A method of mapping parasympathetic or sympathetic renal nerve for treatment of disease caused by systemic renal nerve hyperactivity, comprising the steps of:

a) introducing a catheter into the lumen of a renal artery such that the tip of said catheter contacts a site on the inner renal artery wall;

b) measuring one or more physiological parameters to obtain baseline measurements before introducing electrical current to the site, said physiological parameters are selected from the group consisting of systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate;

c) applying electrical stimulation by introducing electrical current to the site via the catheter, wherein said electrical current is controlled to be sufficient to elicit changes in said physiological parameters when there is an underlying nerve at the site; and

d) measuring said physiological parameters at a specific time interval after each electrical stimulation, wherein an increase of said physiological parameters over the baseline measurements after said electrical stimulation would indicate that a sympathetic renal nerve has been mapped at said site; a decrease of said physiological parameters over the baseline measurements after said electrical stimulation would indicate that a parasympathetic renal nerve has been mapped at said site.

2. The method of claim 1, wherein said catheter is an ablative catheter currently in use to treat cardiac arrhythmias.

3. The method of claim 1, wherein said catheter is an ablative catheter designed specifically for mapping renal nerves for ablative procedures.

4. The method of claim 1, further comprises the step of applying radiofrequency energy through the catheter to the site identified in step (d) for ablation of the underlying nerve to treat disease caused by systemic renal nerve hyperactivity.

5. The method of claim 4, further comprises repeating the steps (b) to (d) on the ablated site, wherein a lack of change in said physiological parameters confirms nerve ablation.

6. A system when used for mapping parasympathetic or sympathetic renal nerve, comprising:

(i) a catheter configured to deliver electrical current to one or more locations on the inner renal artery wall sufficient to stimulate a nerve innervating said renal artery;

(ii) one or more measuring devices for measuring one or more physiological parameters associated with the innervation of said renal artery, wherein said physiological parameters are selected from the group consisting of systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate;

(iii) a computing device configured to couple to the one or more measuring devices, wherein said computing device computes a baseline for said physiological parameters prior to delivery of said electrical current and computes any increase or decrease in the physiological parameters against said baseline after delivery of said electrical current; and

(iv) a display device for displaying the location or identity of a nerve innervating said inner renal artery wall, wherein said display device will display signal for sympathetic nerve when the physiological parameter increases relative to said baseline, and wherein said display device will display signal for parasympathetic nerve when the physiological parameter decreases relative to said baseline.

7. The system of claim 6, wherein said measuring devices are placed inside the renal artery, femoral artery or outside the body.

8. The system of claim 6, wherein said catheter could also deliver ablative energy selected from the group consisting of radiofrequency, mechanical, ultrasonic, radiation, optical and thermal energies.

9. The system of claim 6, wherein said computing device comprises one or more microcontrollers or computers.

10. The system of claim 6, wherein the location or identity of the parasympathetic or sympathetic nerve is displayed as

numbers, texts, symbols, colors, sound, waveforms, or a combination thereof.

11. Use of the system of any one of claims 6-10 for mapping parasympathetic or sympathetic renal nerve according to the method of claim 1.

Figure 1

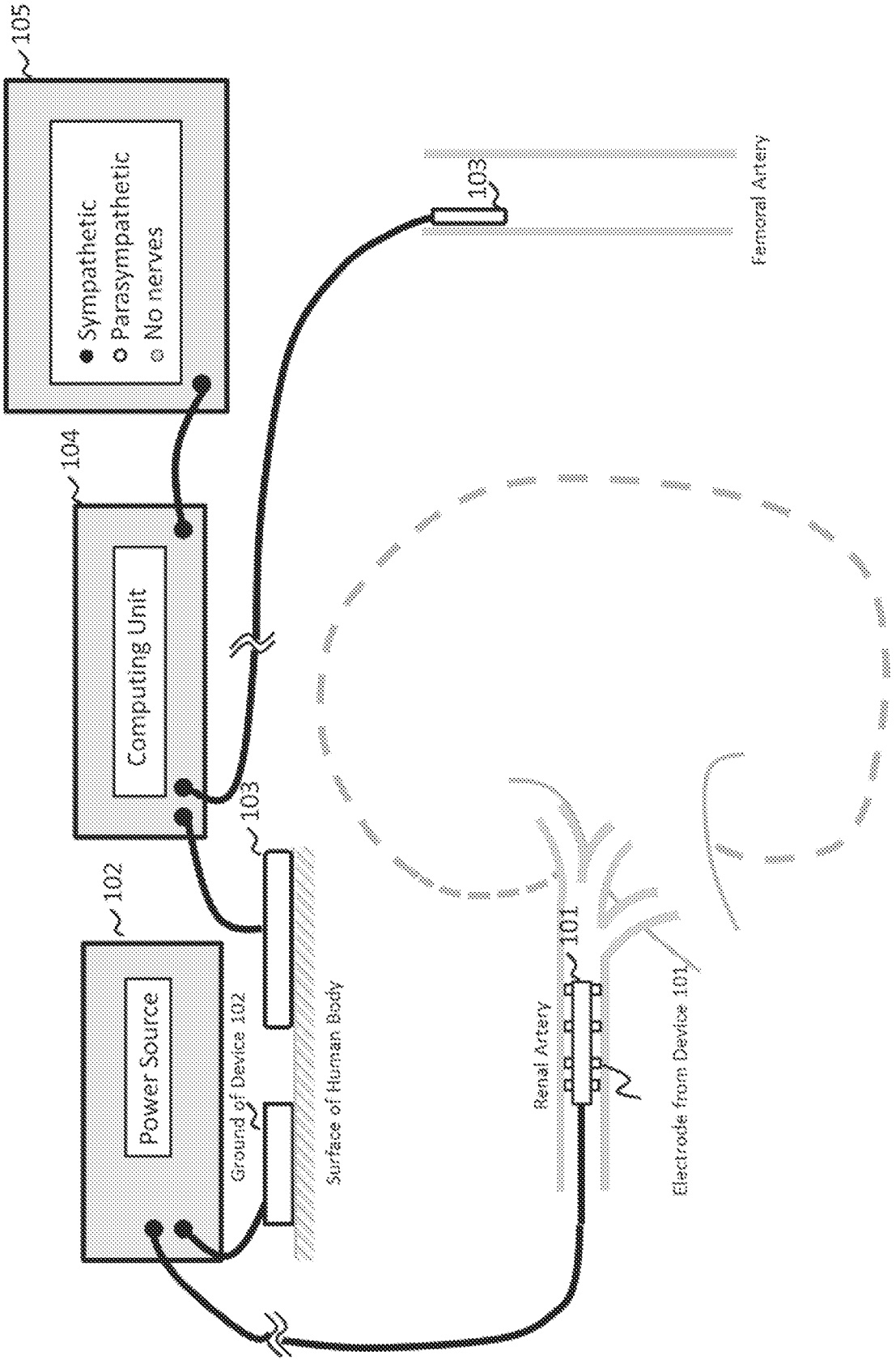
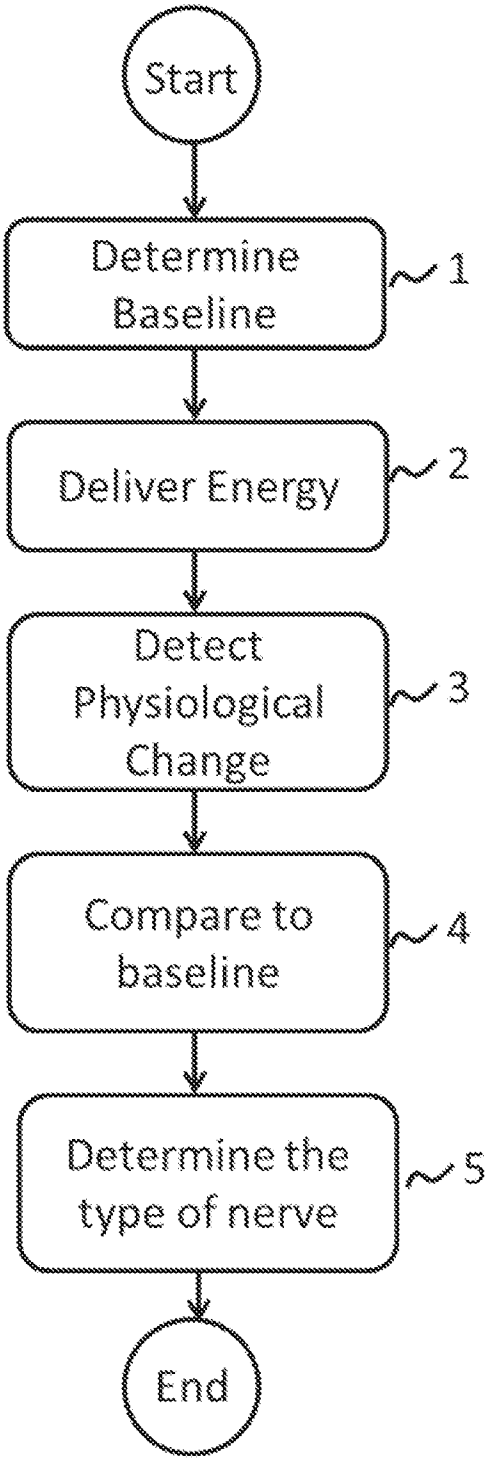
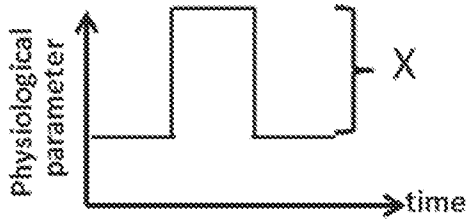

105
Sympathetic
Parasympathetic
No nerves
104
Computing Unit
102
Power Source
103
103
Femoral Artery
Ground of Device 102
Surface of Human Body
Renal Artery
101
Electrode from Device 101

Figure 2





X > a => sympathetic nerve
X < -b => parasympathetic nerve
X = 0 => no functioning nerves

where values of a and b were determined empirically from a large statistical group

Figure 3

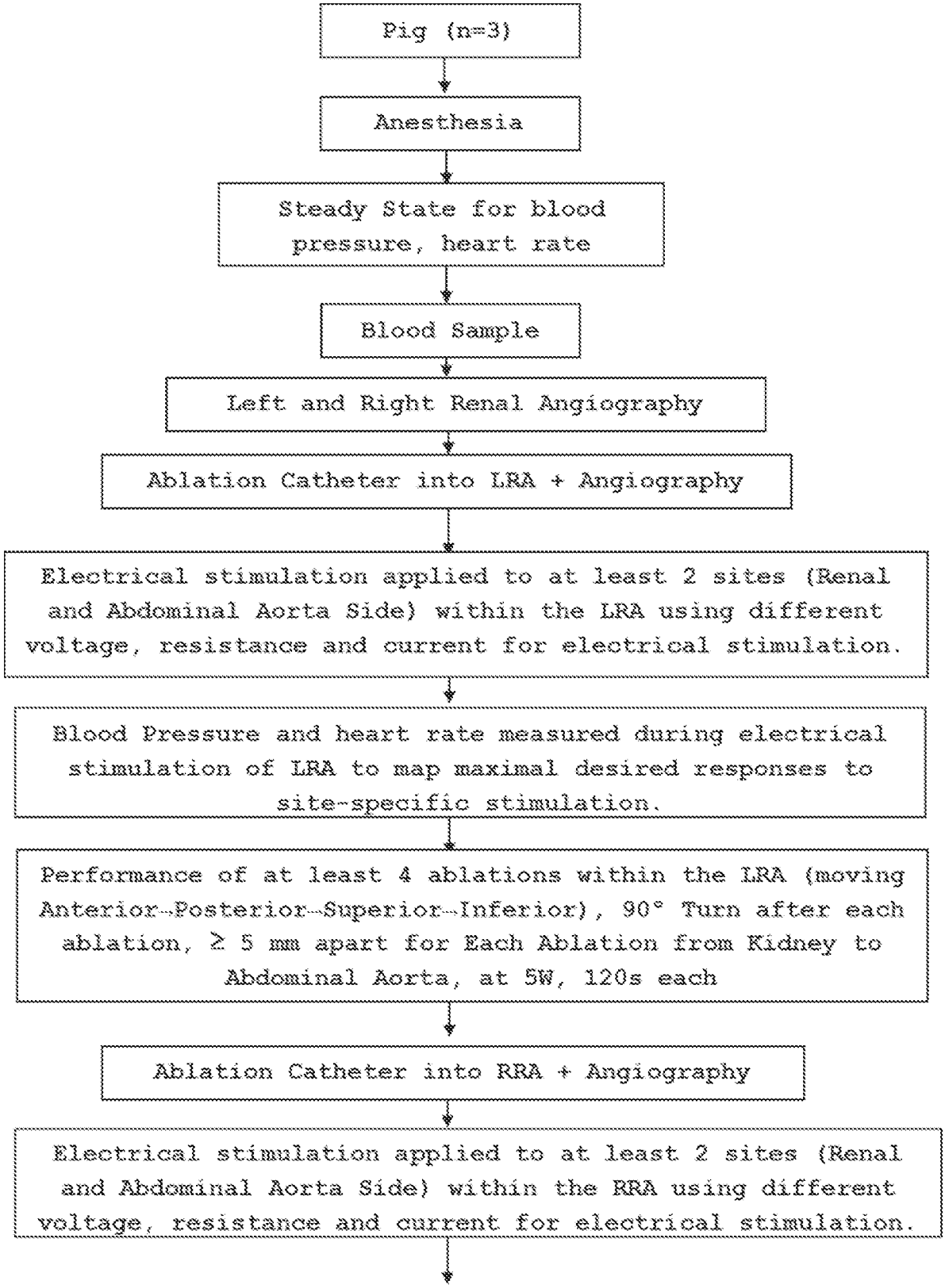
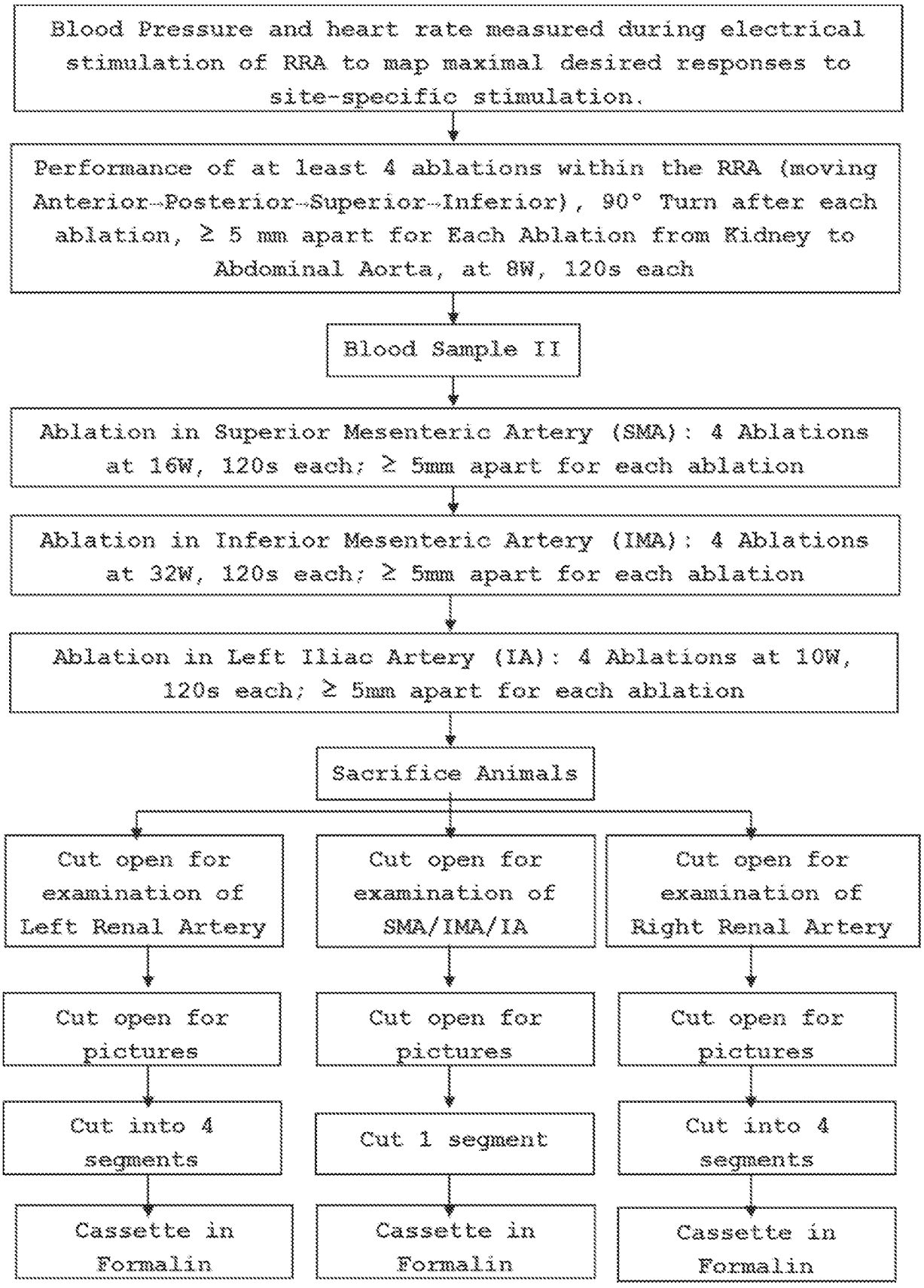
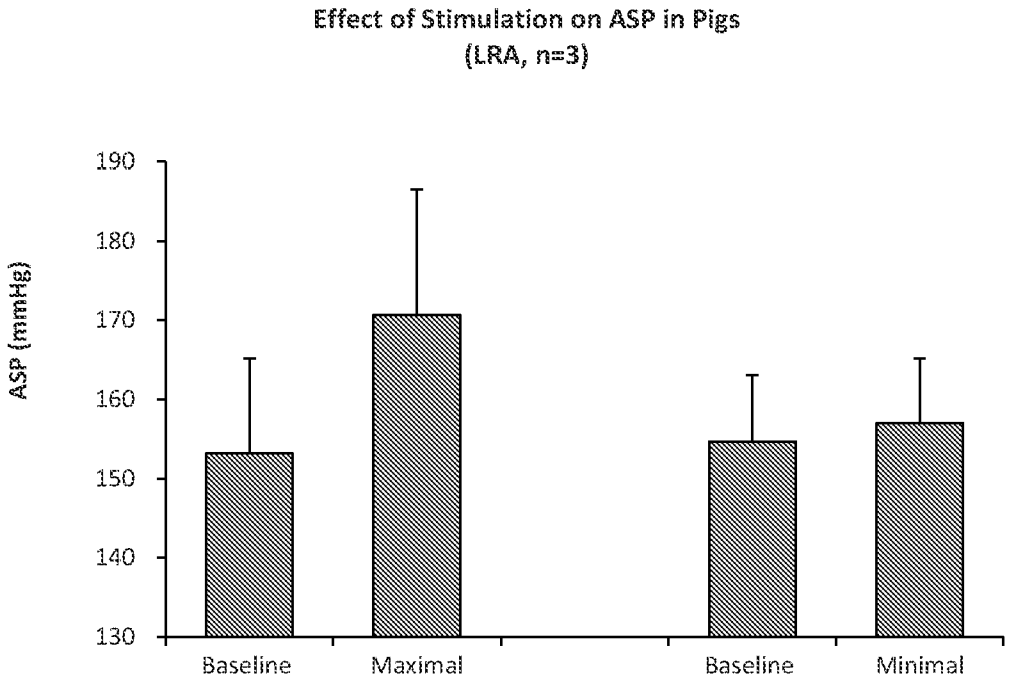

Pig (n=3)
Anesthesia
Steady State for blood pressure, heart rate
Blood Sample
Left and Right Renal Angiography
Ablation Catheter into LRA + Angiography
Electrical stimulation applied to at least 2 sites (Renal and Abdominal Aorta Side) within the LRA using different voltage, resistance and current for electrical stimulation.
Blood Pressure and heart rate measured during electrical stimulation of LRA to map maximal desired responses to site-specific stimulation.
Performance of at least 4 ablations within the LRA (moving Anterior→Posterior→Superior→Inferior), 90° Turn after each ablation, ≥ 5 mm apart for Each Ablation from Kidney to Abdominal Aorta, at 5W, 120s each
Ablation Catheter into RRA + Angiography
Electrical stimulation applied to at least 2 sites (Renal and Abdominal Aorta Side) within the RRA using different voltage, resistance and current for electrical stimulation.

Figure 3 (Cont'd)

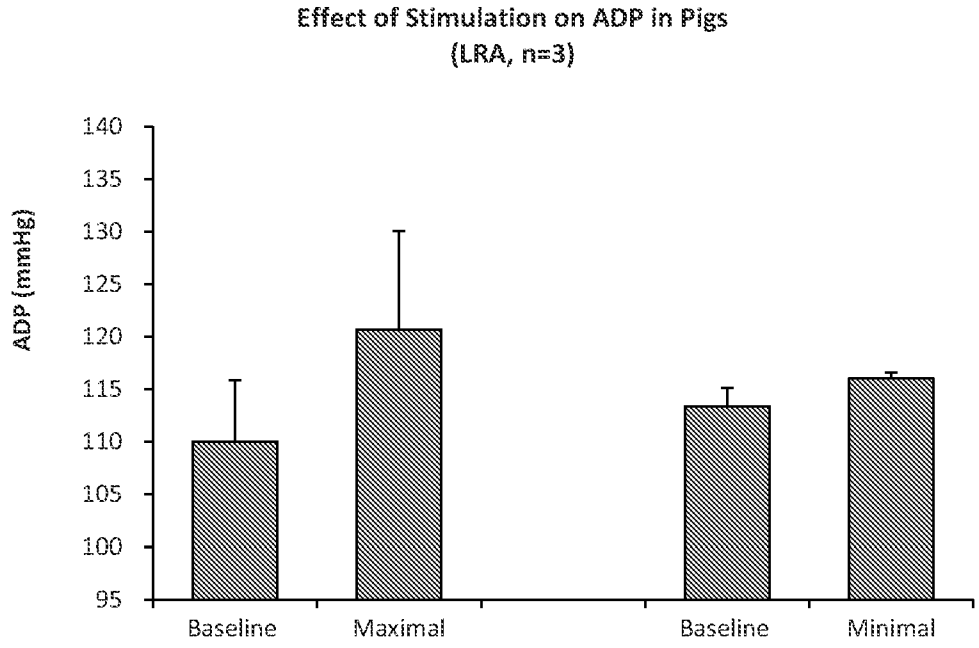


Figures 4A-4B

4A

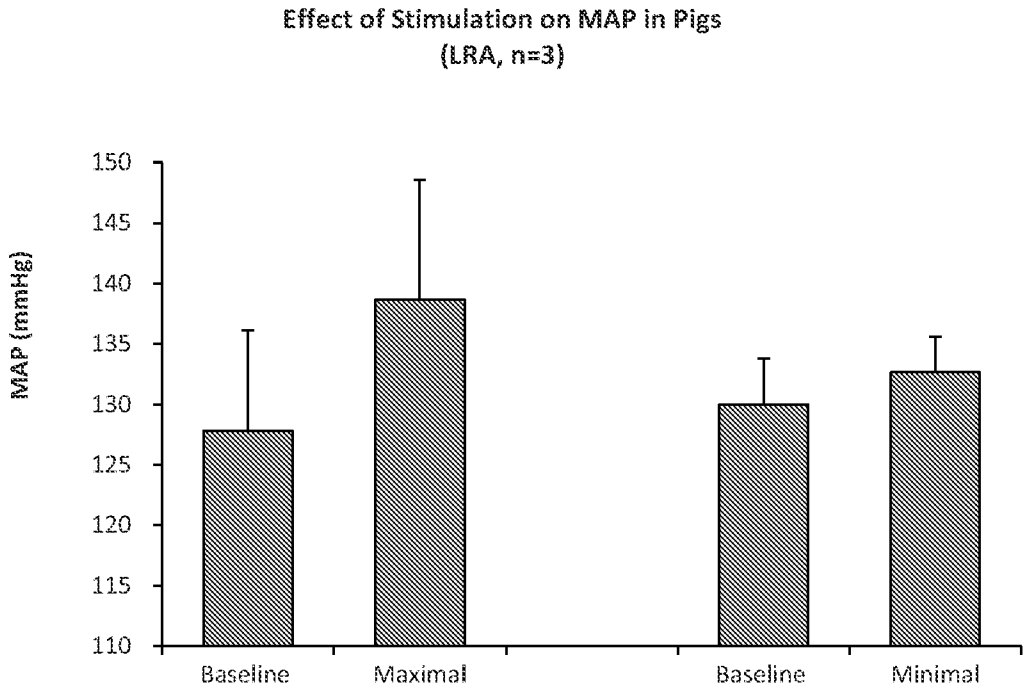


4B

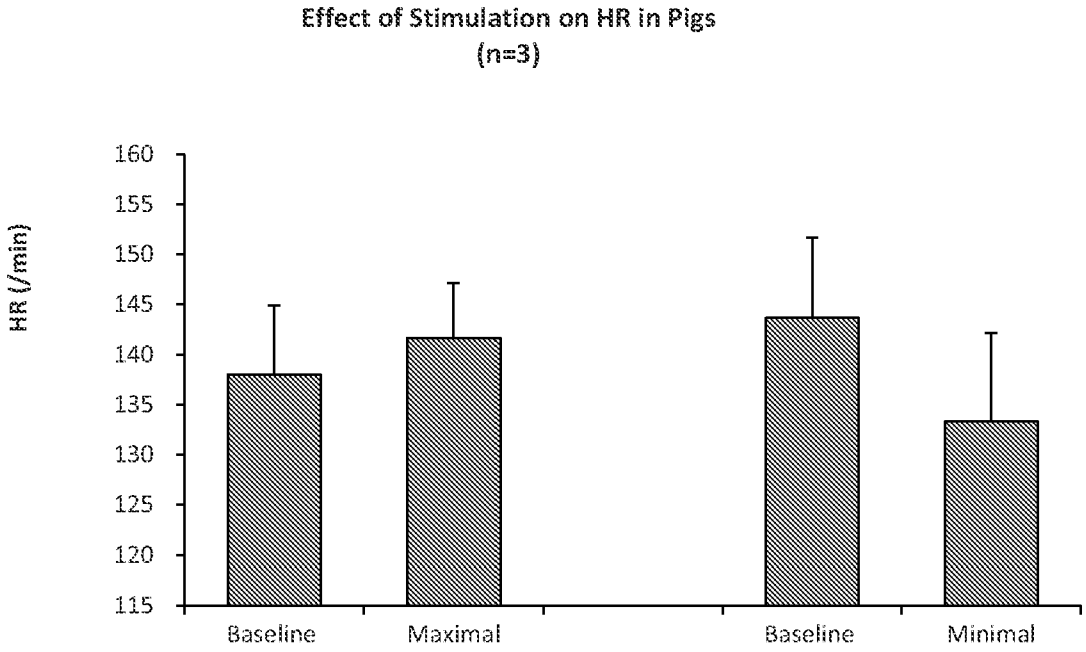


Figures 4C-D

4C

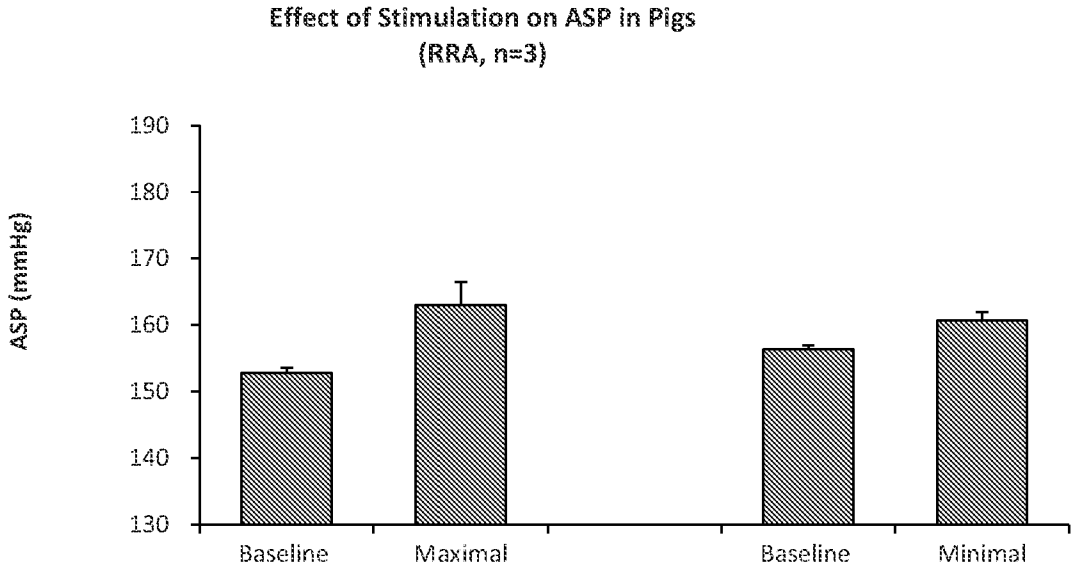


4D

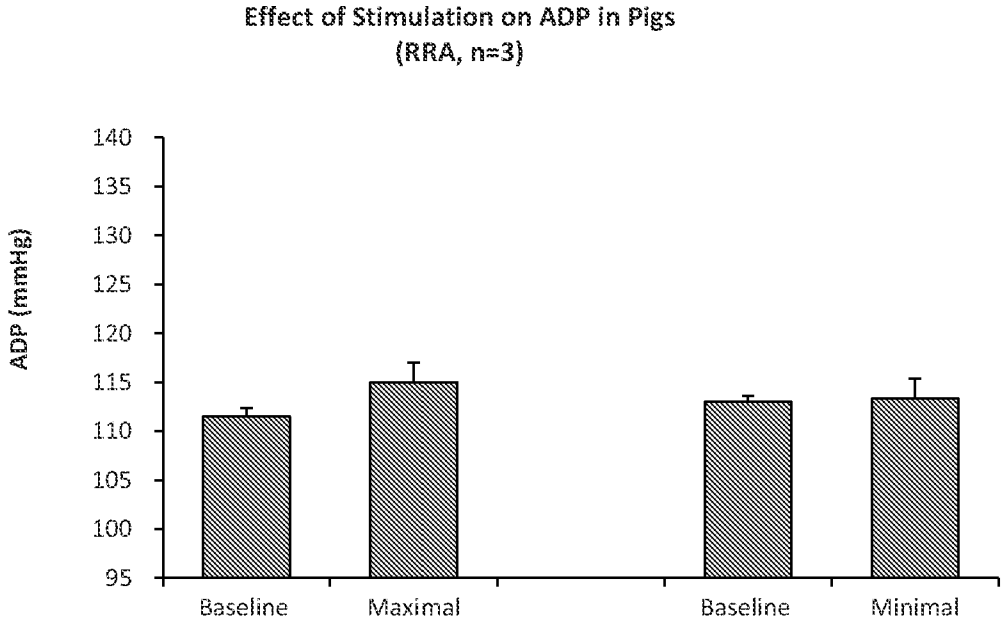


Figures 5A-5B

5A

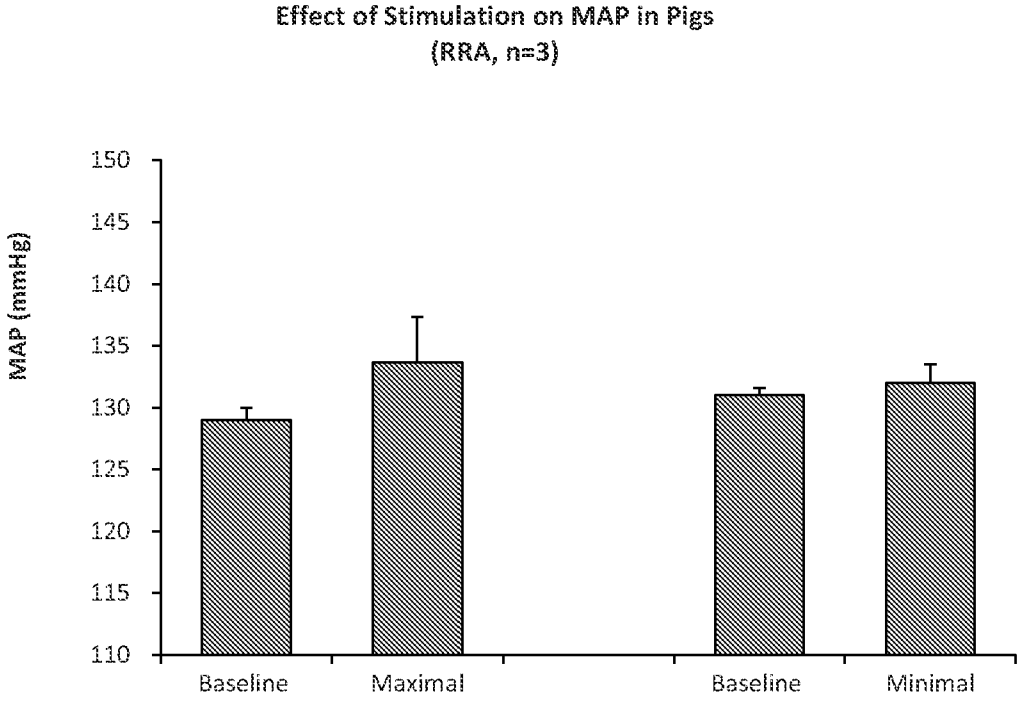


5B



Figures 5C-5D

5C



5D

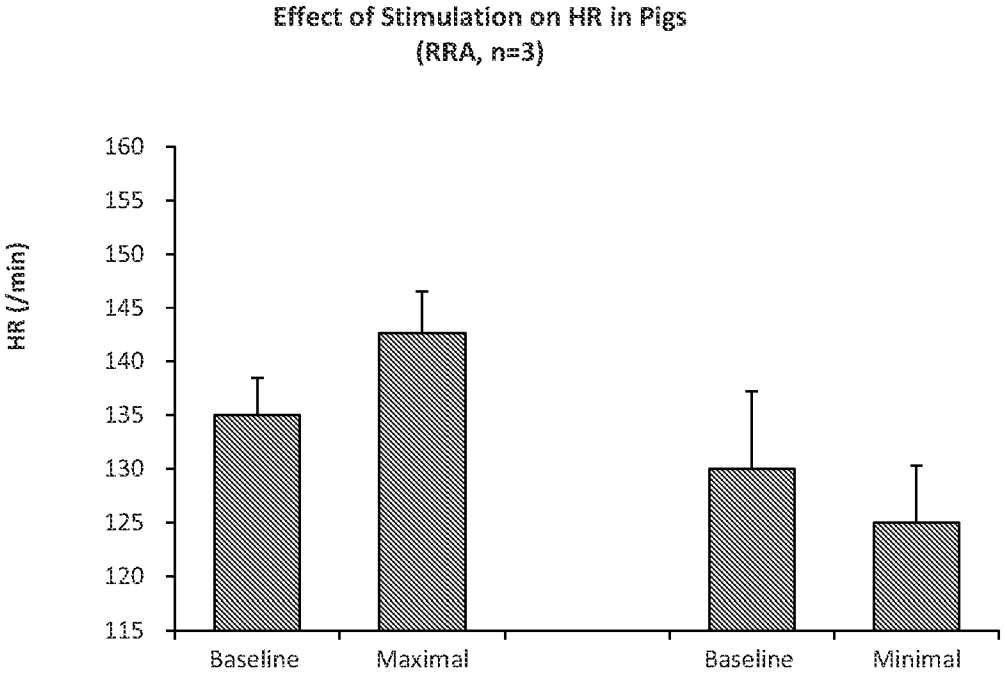
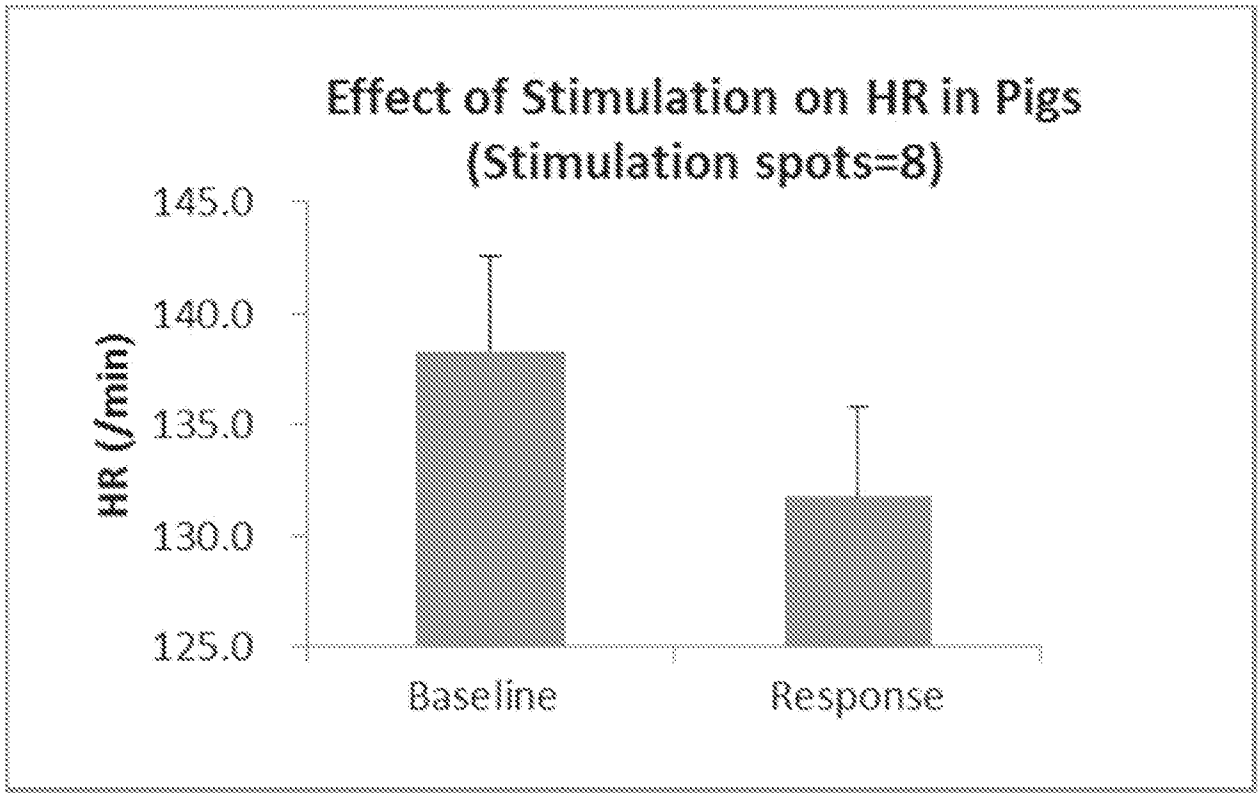
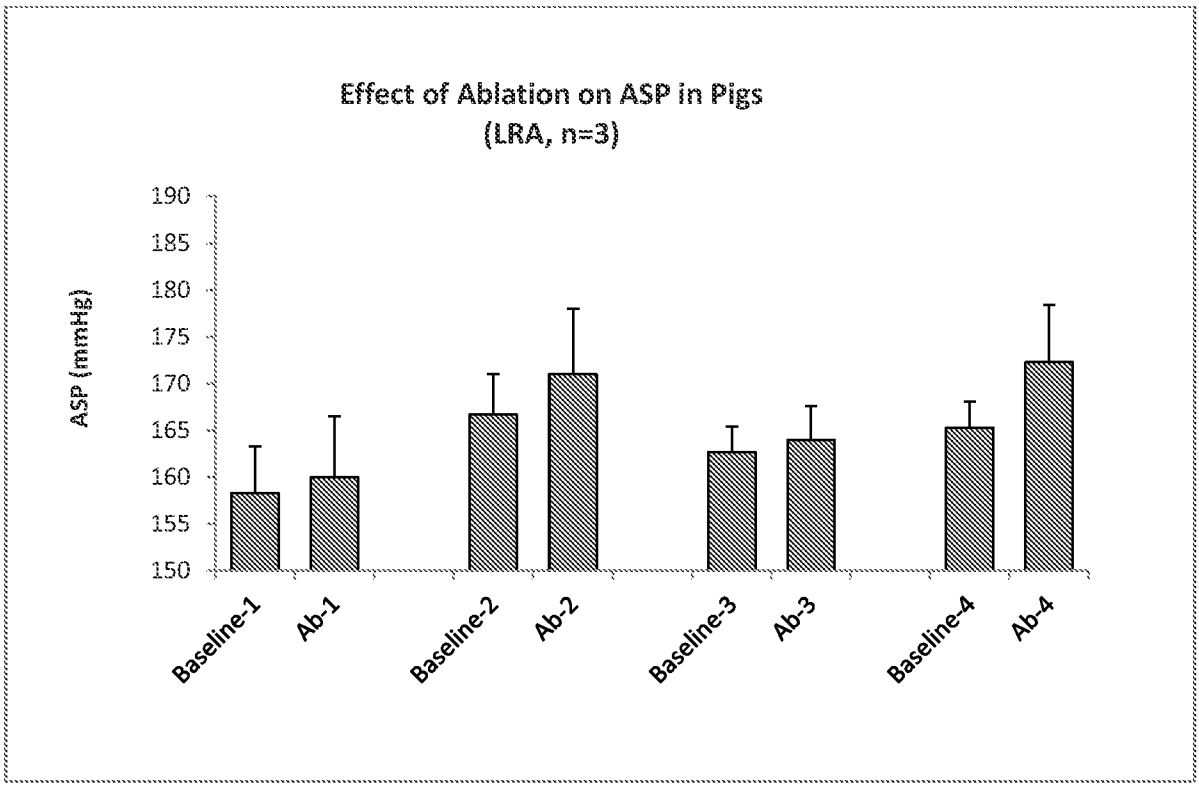


Figure 6

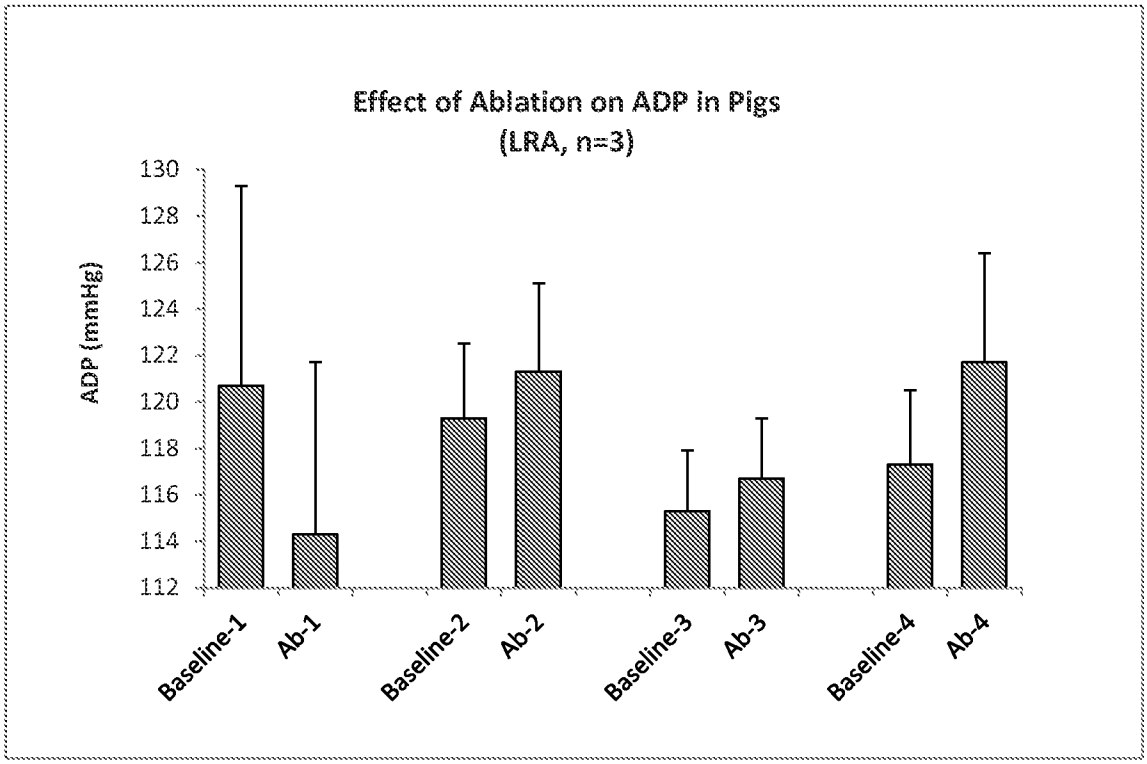

Effect of Stimulation on HR in Pigs
(Stimulation spots=8)
HR (/min)
145.0
140.0
135.0
130.0
125.0
Baseline
Response

Figures 7A-7B

7A

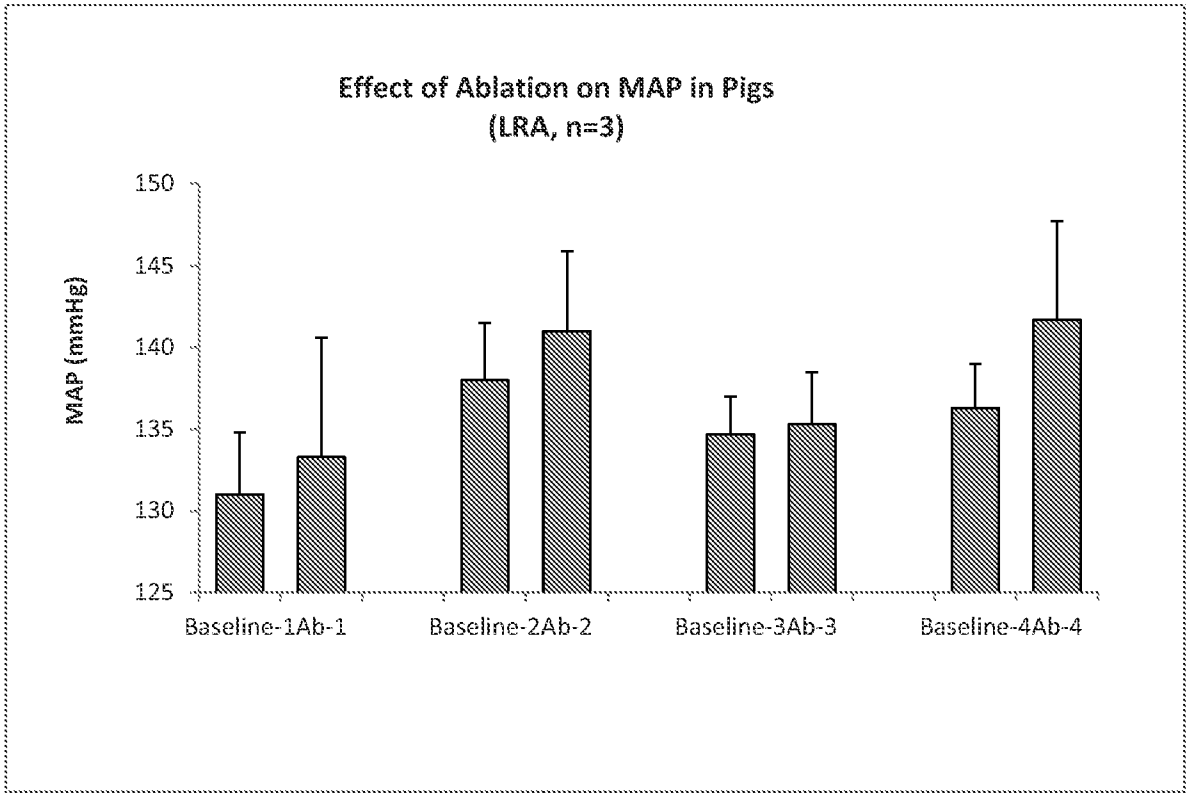


7B

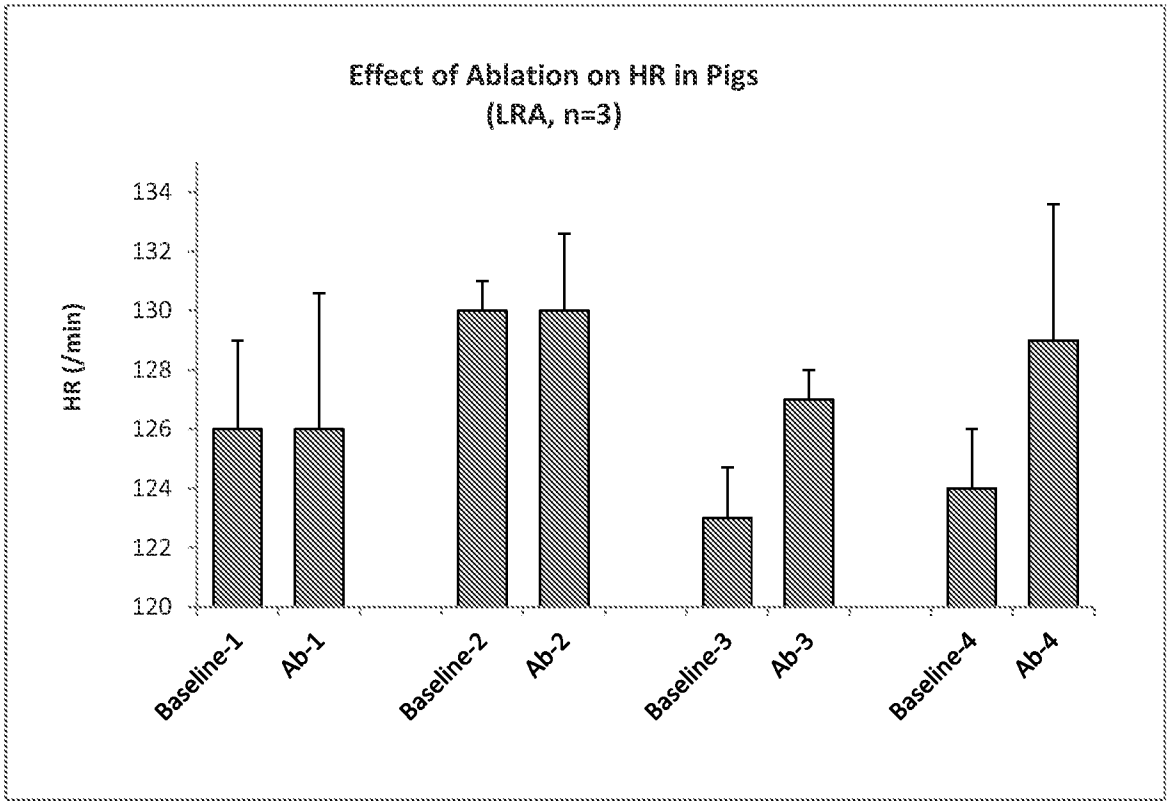


Figures 7C-7D

7C

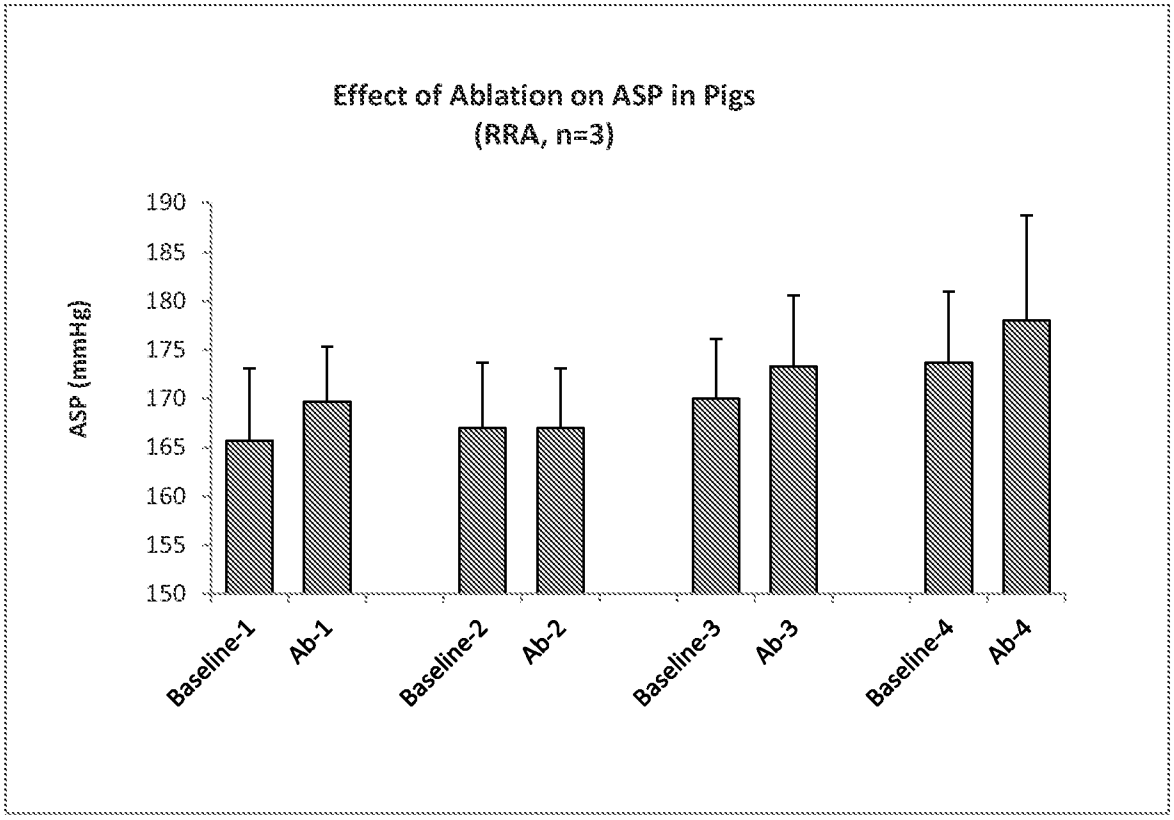


7D

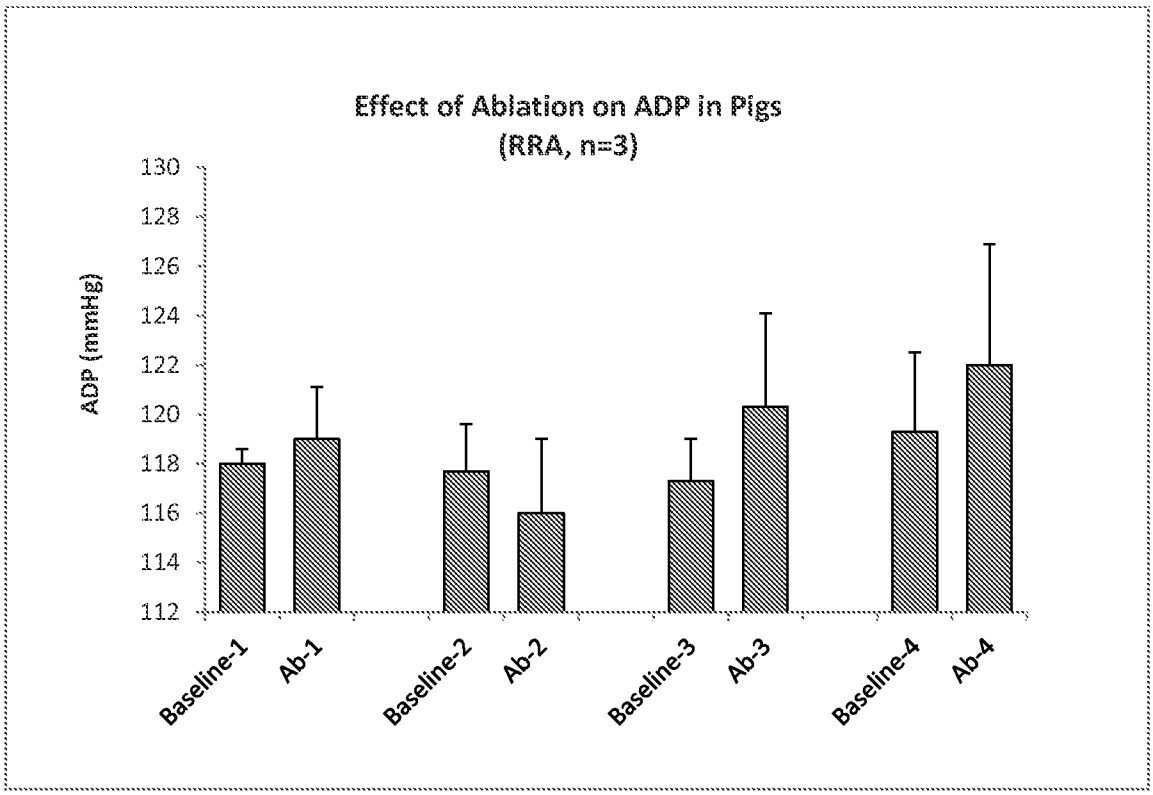


Figures 8A-8B

8A

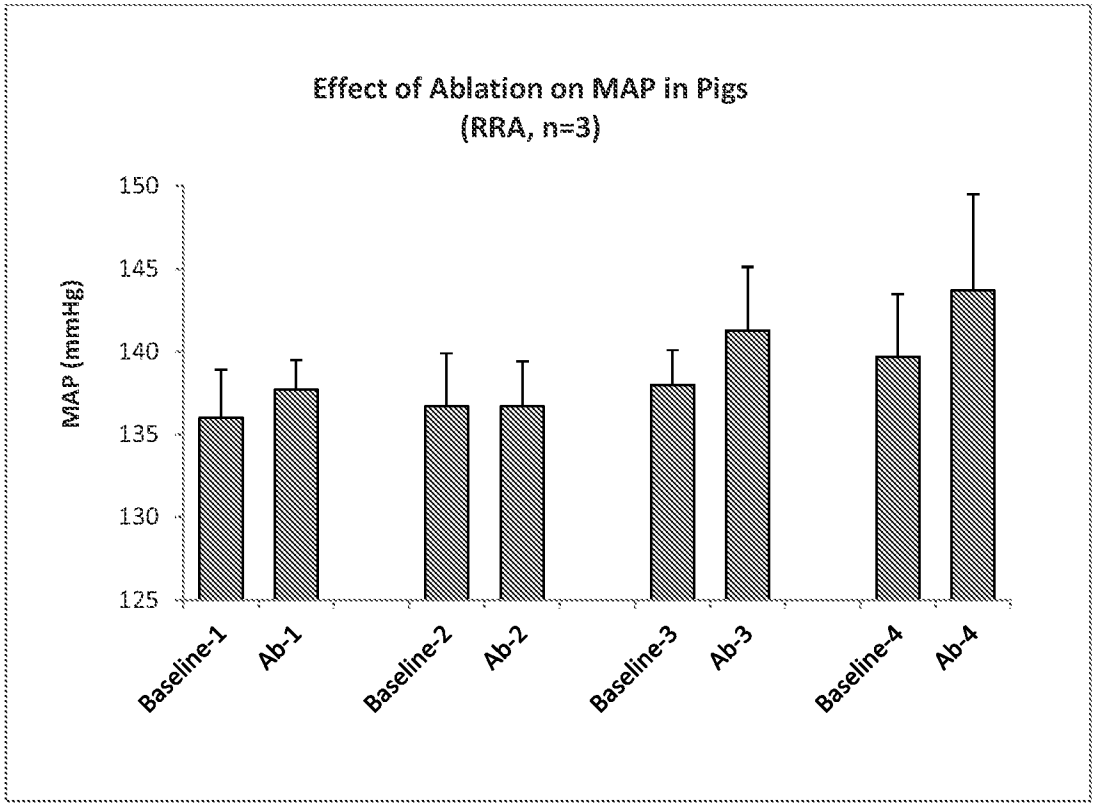
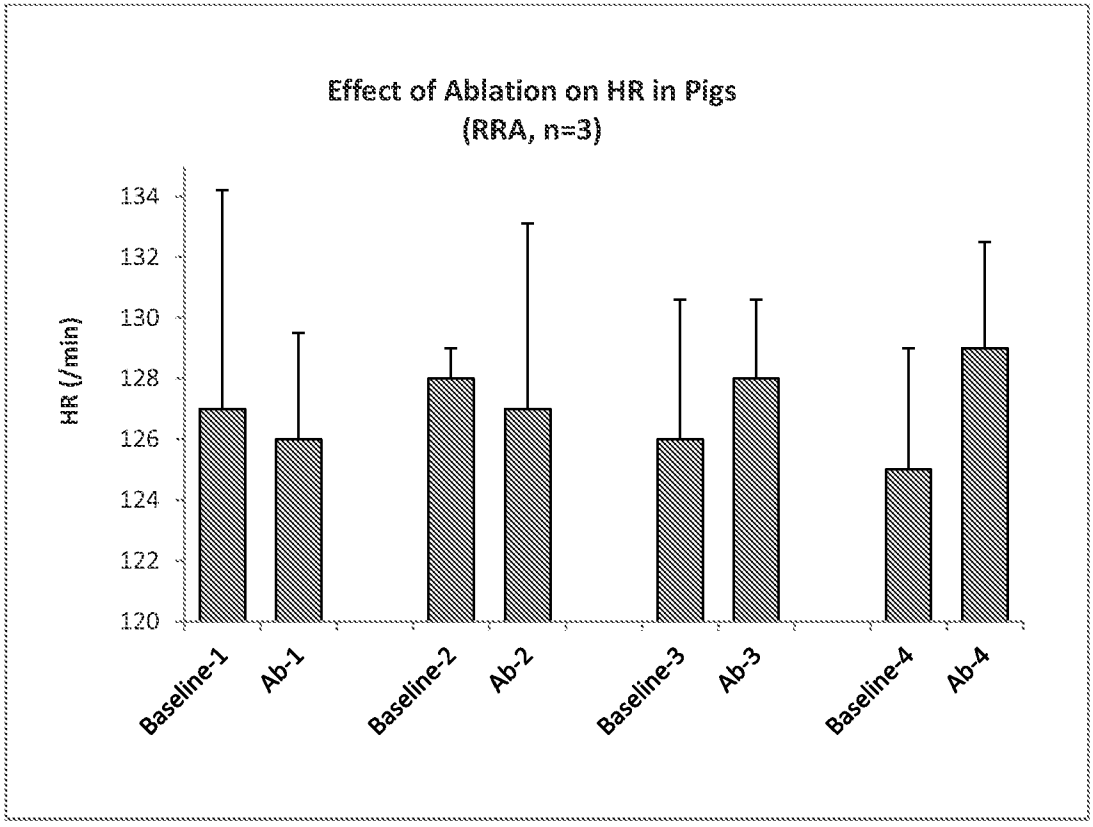


8B



Figures 8C-8D

8C



8D