METHODS AND APPARATUS FOR THERMALLY-INDUCED RENAL NEUROMODULATION

Inventors: Denise Demarais, Los Gatos, CA (US); Andrew Wu, Foster City, CA (US); Hanson Gifford III, Woodside, CA (US); Mark Deen, Mountain View, CA (US)

Correspondence Address:
PERKINS COIE LLP
PATENT-SEA
P.O. BOX 1247
SEATTLE, WA 98111-1247 (US)

Assignee: Ardian, Inc., Palo Alto, CA

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ABSTRACT

Methods and apparatus are provided for thermally-induced renal neuromodulation. Thermally-induced renal neuromodulation may be achieved via direct and/or via indirect application of thermal energy to heat or cool neural fibers that contribute to renal function, or of vascular structures that feed or perfuse the neural fibers. In some embodiments, parameters of the neural fibers, of non-target tissue, or of the thermal energy delivery element, may be monitored via one or more sensors for controlling the thermally-induced neuromodulation. In some embodiments, protective elements may be provided to reduce a degree of thermal damage induced in the non-target tissues. In some embodiments, thermally-induced renal neuromodulation is achieved via delivery of a pulsed thermal therapy.
Thermal Heating Mechanism

Moderate Heating
(45°C > Temperature > 37°C)

↓RSNA

Substantial Heating
(Temperature ≥ 45°C)

↓RSNA

FIGURE 15A

Thermal Cooling Mechanism

Non-Freezing
(37°C > Temperature > 0°C)

↓RSNA

Freezing
(Temperature ≤ 0°C)

↓RSNA

Nerve injury

Nerve injury

FIGURE 15B
METHODS AND APPARATUS FOR THERMALLY-INDUCED RENAL NEUROMODULATION

REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application No. 60/816,999 filed on Jun. 28, 2006. The present application is also a Continuation-In-Part application of co-pending U.S. patent application Ser. No. 10/408,665, filed on Apr. 8, 2003, which claims the benefit of U.S. Provisional Application Nos. (a) 60/370,190, filed on Apr. 8, 2002, (b) 60/413,575, filed on Oct. 3, 2002, and (c) 60/442,970, filed on Jan. 29, 2003. Furthermore, this application is a Continuation-In-Part application of co-pending U.S. patent application Ser. No. 11/189,563, filed on Jul. 25, 2005, which is a Continuation-In-Part application of U.S. patent application Ser. No. 11/129,765, filed on May 13, 2005, and which claims the benefit of U.S. Provisional Application Nos. (a) 60/616,254, filed on Oct. 5, 2004, and (b) 60/624,793, filed on Nov. 2, 2004. Furthermore, this application is a Continuation-In-Part application of co-pending U.S. patent application Ser. No. 11/504,117, filed on Aug. 14, 2006.

[0002] All of these applications are incorporated herein by reference in their entireties.

INCORPORATION BY REFERENCE

[0003] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

TECHNICAL FIELD

[0004] The present invention relates to methods and apparatus for neuromodulation. More particularly, the present invention relates to methods and apparatus for achieving renal neuromodulation via thermal heating and/or cooling mechanisms.

BACKGROUND

[0005] Heart Failure or Chronic Heart Failure (“CHF”) is a condition that occurs when the heart becomes damaged and reduces blood flow to the organs of the body. If blood flow decreases sufficiently, kidney function becomes altered, which results in fluid retention, abnormal hormone secretions, and increased constriction of blood vessels. These results increase the workload of the heart and further decrease the capacity of the heart to pump blood through the kidneys and circulatory system.

[0006] It is believed that progressively decreasing perfusion of the kidneys is a principal non-cardiac cause perpetuating the downward spiral of CHF. Moreover, the fluid overload and associated clinical symptoms resulting from these physiologic changes result in additional hospital admissions, poor quality of life and additional costs to the health care system.

[0007] In addition to their role in the progression of CHF, the kidneys play a significant role in the progression of Renal Failure or Chronic Renal Failure (“CRF”), Renal Disease or End-Stage Renal Disease (“ESRD”), Hypertension (pathologically high blood pressure) and other cardiovascular diseases. The functions of the kidneys can be summarized under three broad categories: filtering blood and excreting waste products generated by the body’s metabolism; regulating salt, water, electrolyte and acid-base balance; and secreting hormones to maintain vital organ blood flow. Without properly functioning kidneys, a patient will suffer water retention, reduced urine flow, and accumulation of waste toxins in the blood and body. These conditions result from reduced renal function or renal failure (kidney failure) and are believed to increase the workload of the heart. In a CHF patient, renal failure will cause the heart to further deteriorate as fluids are retained and blood toxins accumulate due to the poorly functioning kidneys.

[0008] It has been established in animal models that the heart failure condition results in abnormally high sympathetic activation of the kidneys. An increase in renal sympathetic nerve activity leads to decreased removal of water and sodium from the body, as well as increased renin secretion. Increased renin secretion leads to vasoconstriction of blood vessels supplying the kidneys, which causes decreased renal blood flow. Reduction of sympathetic renal nerve activity, e.g., via denervation, may reverse these processes.

[0009] Applicants have described methods and apparatus for treating renal disorders by applying a pulsed electric field, preferably non-thermal, to neural fibers that contribute to renal function. See, for example, Applicants’ co-pending U.S. patent application Ser. Nos. (a) 11/129,765, filed on May 13, 2005, (b) Ser. No. 11/189,563, filed on Jul. 25, 2005, and (c) Ser. No. 11/363,867, filed Feb. 27, 2006, all of which are incorporated herein by reference in their entireties. A pulsed electric field (“PEF”) may initiate renal denervation or other types of neuromodulation via irreversible electropropagation or other processes. The PEF may be delivered from apparatus positioned intravascularly, extracorporal, intra- or extravascularly or a combination thereof. Additional methods and apparatus for achieving renal neuromodulation via localized drug delivery (such as by a drug pump or infusion catheter) or use of a stimulation electric field are described in co-owned and co-pending U.S. patent application Ser. No. 10/408,665, filed Apr. 8, 2003, and U.S. Pat. No. 6,978,174, both of which are incorporated herein by reference in their entireties.

[0010] A potential challenge of using non-thermal PEF systems for treating renal disorders is to selectively electroporate target cells without affecting other cells. For example, it may be desirable to irreversibly electroporate renal nerve cells that travel along or in proximity to renal vasculature, but it may not be desirable to damage the smooth muscle cells of which the vasculature is composed. As a result, an overly aggressive course of non-thermal PEF therapy may persistently injure the renal vasculature, but an overly conservative course of non-thermal PEF therapy may not achieve the desired renal neuromodulation.

[0011] Applicants have also described methods and apparatus for monitoring changes in tissue impedance or conductivity in order to determine the effects of pulsed electric field therapy. Such changes in tissue can be used to determine an extent of electroporation and/or its degree of irreversibility in target or non-target tissue. See, for example, Applicant’s co-pending U.S. patent application
Ser. No. 11/233,814, filed Sep. 23, 2005, which is incorporated herein by reference in its entirety. However, in some patients it may be difficult or impractical to achieve such real-time monitoring when utilizing non-thermal pulsed electric field neuromodulatory mechanisms. This can result in insufficient neuromodulation to achieve a desired treatment outcome, and thus re-intervention may be necessary to complete the treatment. Conversely, an overly aggressive course of relatively unmonitored or uncontrolled therapy may induce undesirable and/or persistent damage in non-target tissue. Thus, it would be desirable to achieve renal neuromodulation via more easily monitored and/or controlled neuromodulatory mechanisms.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Several embodiments of the present invention will be apparent upon consideration of the following detailed description, taken in conjunction with the accompanying drawings, in which like reference characters refer to like parts throughout, and in which:

[0013] FIG. 1 is a schematic view illustrating human renal anatomy.

[0014] FIG. 2 is a schematic isometric detail view showing the location of the renal nerves relative to the renal artery.

[0015] FIG. 3 is a schematic side view, partially in section, illustrating an example of an extravascular method and apparatus for thermal renal neuromodulation.

[0016] FIGS. 4A-4C are schematic side views, partially in section, illustrating examples of intravascular methods and apparatus for thermal renal neuromodulation.

[0017] FIGS. 5A and 5B are schematic side views, partially in section, illustrating an alternative embodiment of the intravascular methods and apparatus of FIGS. 4 comprising wall-contact electrodes.

[0018] FIGS. 6A and 6B are schematic side views, partially in section, illustrating an alternative embodiment of the intravascular methods and apparatus of FIG. 4 comprising alternative wall-contact electrodes.

[0019] FIGS. 7A and 7B are schematic side views, partially in section, illustrating other alternative embodiments of the intravascular methods and apparatus of FIG. 4 comprising multiple wall-contact electrodes.

[0020] FIGS. 8A-8H are schematic side views, partially in section, illustrating embodiments of the intravascular methods and apparatus of FIG. 4 comprising one or more wall-contact electrodes, as well as optional blood flow occlusion and thermal fluid injection.

[0021] FIG. 9 is a schematic side view, partially in section, illustrating an example of an intra-to-extravascular method and apparatus for thermal renal neuromodulation.

[0022] FIG. 10 is a schematic side view, partially in section, of an alternative embodiment of the method and apparatus of FIG. 8 configured for thermal renal neuromodulation via direct application of thermal energy.

[0023] FIG. 11 is a schematic side view, partially in section, illustrating a method and apparatus for thermal renal neuromodulation comprising a thermoelectric element suitable for direct application of thermal energy to target neural fibers.

[0024] FIG. 12 is a schematic side view, partially in section, illustrating another method and apparatus for thermal renal neuromodulation comprising a thermoelectric element.

[0025] FIGS. 13A and 13B are schematic side views, partially in section, illustrating a method and apparatus for thermal renal neuromodulation via high-intensity focused ultrasound.

[0026] FIG. 14 is a schematic side view, partially in section, illustrating an alternative embodiment of the apparatus and method of FIGS. 13.

[0027] FIGS. 15A and 15B are schematic diagrams for classifying the various types of thermal neuromodulation that may be achieved with the apparatus and methods of the present invention.

DETAILED DESCRIPTION

A. Overview

[0028] The following describes several embodiments of methods and apparatus for renal neuromodulation via thermal heating and/or thermal cooling mechanisms. Many embodiments of such methods and apparatus may reduce renal sympathetic nerve activity. Thermally-induced (via heating and/or cooling) neuromodulation may be achieved via apparatus positioned proximate target neural fibers, such as being positioned (a) within renal vasculature (i.e., positioned intravascularly), (b) extravascularly, (c) intra-to-extravascularly, or (d) a combination thereof. Thermal neuromodulation by heating or cooling may be caused by directly effecting or otherwise altering the neural structures that are subject to the thermal stress. Additionally or alternatively, the thermal neuromodulation may at least in part be due to alteration of arteries, arterioles, capillaries, or veins or other vascular structures which perfuse the target neural fibers or surrounding tissue. Furtherstill, the modulation may at least in part be caused by electroproportion of the target neural fibers or of surrounding tissue.

[0029] As used herein, thermal heating mechanisms for neuromodulation include both thermal ablation and non-ablative thermal injury or damage (e.g., via sustained heating or resistive heating). Thermal heating mechanisms may include raising the temperature of target neural fibers above a desired threshold to achieve non-ablative thermal injury, or above a higher temperature) to achieve ablative thermal injury. For example, the target temperature can be above body temperature (e.g., approximately 37°C) but less than about 45°C for non-ablative thermal injury, or the target temperature can be about 45°C or more for the ablative thermal injury.

[0030] As used herein, thermal cooling mechanisms for neuromodulation include non-freezing thermal slowing of nerve conduction and/or non-freezing thermal nerve injury, as well as freezing thermal nerve injury. Thermal cooling mechanisms may include reducing the temperature of target neural fibers below a desired threshold, for example, below the body temperature of about 37°C (e.g., below about 20°C) to achieve non-freezing thermal injury. Thermal cooling
mechanisms also may include reducing the temperature of the target neural fibers below about 0°C, e.g., to achieve freezing thermal injury.

[0031] In addition to monitoring or controlling the temperature during thermal neuromodulation, the length of exposure to thermal stimuli may be specified to affect an extent or degree of efficacy of the thermal neuromodulation. In many embodiments, the length of exposure to thermal stimuli is longer than instantaneous exposure, such as longer than about 30 seconds, or even longer than 2 minutes. In certain specific embodiments, the length of exposure can be less than 10 minutes, but this should in no way be construed as the upper limit of the exposure period. Exposure times measured in hours, days or longer, may be utilized to achieve desired thermal neuromodulation.

[0032] When conducting neuromodulation via thermal mechanisms, the temperature threshold discussed previously may be determined as a function of the duration of exposure to thermal stimuli. Additionally or alternatively, the length of exposure may be determined as a function of the desired temperature threshold. These and other parameters may be specified or calculated to achieve and control desired thermal neuromodulation.

[0033] In some embodiments, thermally-induced renal neuromodulation may be achieved by directly applying thermal cooling or heating energy to the target neural fibers. For example, a chilled or heated fluid can be applied at least proximate to the target neural fiber, or heated or cooled elements (e.g., a thermoelectric element or a resistive heating element) can be placed in the vicinity of the neural fibers. In other embodiments, thermally-induced renal neuromodulation may be achieved via indirect generation and/or application of the thermal energy to the target neural fibers, such as through application of a ‘thermal’ electric field, high-intensity focused ultrasound, laser irradiation, or other suitable energy modalities to the target neural fibers. For example, thermally-induced renal neuromodulation may be achieved via delivery of a pulsed or continuous thermal electric field to the target neural fibers, the electric field being of sufficient magnitude and/or duration to thermally induce the neuromodulation in the target fibers (e.g., to heat or thermally ablate or necrose the fibers). Additional and alternative methods and apparatus may be utilized to achieve thermally-induced renal neuromodulation, as described hereinafter.

[0034] When utilizing thermal heating mechanisms for thermal neuromodulation, protective cooling elements, such as convective cooling elements, optionally may be utilized to protect smooth muscle cells or other non-target tissue from undesired thermal effects during the thermally-induced renal neuromodulation. Likewise, when utilizing thermal cooling mechanisms, protective heating elements, such as convective heating elements, may be utilized to protect the non-target tissue. Non-target tissue additionally or alternatively may be protected by focusing the thermal heating or cooling energy on the target neural fibers so that the intensity of the thermal energy outside of the target zone is insufficient to induce undesired thermal effects in the non-target tissue. When thermal neuromodulation is achieved via thermal energy delivered intravascularly, the non-target tissue may be protected by utilizing blood flow as a conductive and/or convective heat sink that carries away excess thermal energy (hot or cold). For example, when blood flow is not blocked, the circulating blood may remove excess thermal energy from the non-target tissue during the procedure. The intravascularly-delivered thermal energy may heat or cool target neural fibers located proximate to the vessel to modulate the target neural fibers while blood flow within the vessel protects non-target tissue of the vessel wall from the thermal energy. For example, the thermal energy can target neural fibers within the adventitia to necrose or ablate the target fibers while the blood flow protects tissue in the vessel wall.

[0035] One drawback of using a continuous, intravascularly-delivered thermal energy therapy in the presence of blood flow to achieve desired intravascularly-induced neuromodulation is that the feasible thermal magnitude (e.g., power) and/or duration of the therapy may be limited or insufficient. This can be caused by the limited heat capacity of the blood flowing through the blood vessel to remove excess thermal energy from the vessel wall to mitigate damage or necrosis to the non-target tissue. Pulsed RF electric fields or other types of pulsed thermal energy may facilitate greater thermal magnitude (e.g., higher power), longer total duration and/or better controlled intravascular renal neuromodulation therapy compared to a continuous thermal energy therapy. For example, a pulsed thermal therapy may allow for monitoring of effects of the therapy on target or non-target tissue during the interval between the pulses. This monitoring data optionally may be used in a feedback loop to better control therapy, e.g., to determine whether to continue or stop treatment, and it may facilitate controlled delivery of a higher power or longer duration therapy.

[0036] Furthermore, the time interval between delivery of thermal energy pulses may facilitate additional convective or other cooling of the non-target tissue of the vessel wall compared to applying an equivalent magnitude or duration of continuous thermal energy. Without being limited to theory, this may occur because blood flow through the blood vessel may convectively cool (heat) the non-target tissue of the vessel wall with which the blood contacts faster than target neural fibers positioned outside of the vessel.

[0037] When providing a pulsed thermal therapy, this difference in the heat transfer rate between the tissue of the blood vessel wall and the relatively remote target neural fibers may be utilized to ablate, necrose or otherwise modulate the target neural fibers without undesirably affecting the non-target tissue. The pulsed thermal energy therapy may be applied with greater thermal magnitude and/or of longer total duration (i.e., the cumulative duration of all thermal energy pulses within the therapy) than a continuous thermal therapy. Heat transfer from the vessel wall to the blood (or vice versa) during the off-time or low-energy interval between the thermal energy pulses facilitates the greater magnitude/longer duration delivery with moderated damage to the non-target tissue.

[0038] In addition or as an alternative to utilizing the patient’s blood as a heat sink to establish the difference in heat transfer rates, a thermal fluid (hot or cold) may be injected, infused or otherwise delivered into the vessel to remove excess thermal energy and protect the non-target tissues. The thermal fluid may, for example, comprise a saline or other biocompatible fluid that is heated, chilled or at a room temperature. The thermal fluid may, for example,
be injected through the device catheter or through a guide catheter at a location upstream from an energy delivery element, or at other locations relative to the tissue for which protection is sought. The thermal fluid may be injected in the presence of blood flow or with the flow temporarily occluded.

[0039] Occlusion of flow in combination with thermal fluid delivery may facilitate good control over the heat transfer kinetics along the non-target tissues. For example, the normal variability in blood flow rate between patients, which would vary the heat transfer capacity of the blood flow, may be controlled for by transferring thermal energy between the vessel wall and a thermal fluid that is delivered at a controlled rate. Use of injected thermal fluids to remove excess thermal energy from non-target tissues to relatively protect the non-target tissues during therapeutic treatment of target tissues may be utilized in body lumens other than blood vessels.

[0040] In some embodiments, methods and apparatus for real-time monitoring of an extent or degree of neuromodulation or denervation (e.g., an extent or degree of thermal damage) in tissue innervated by the target neural fibers and/or thermal damage in the non-target tissue may be provided. Likewise, real-time monitoring of the thermal energy delivery element may be provided. Such methods and apparatus may, for example, comprise a thermocouple or other temperature sensor for measuring the temperature of the monitored tissue or of the thermal energy delivery element. Other parameters that can be measured include the power, total energy delivered, or impedance. Monitoring data may be used for feedback control of the thermal therapy. For example, intravascularly-delivered thermal therapy may be monitored and controlled by acquiring temperature or impedance measurements along the wall of the vessel in the vicinity of the treatment zone, and/or by limiting the power or duration of the therapy.

[0041] To better understand the structures of several embodiments of devices described below, as well as the methods of using such devices for thermally-induced renal neuromodulation, a description of the renal anatomy in humans is provided.

B. Renal Anatomy Summary

[0042] With reference to FIG. 1, the human renal anatomy includes the kidneys K, which are supplied with oxygenated blood by the renal arteries RA. The renal arteries are connected to the heart via the abdominal aorta AA. Deoxygenated blood flows from the kidneys to the heart via the renal veins RV and the inferior vena cava IVC.

[0043] FIG. 2 illustrates a portion of the renal anatomy in greater detail. More specifically, the renal anatomy also includes renal nerves RN extending longitudinally along the lengthwise dimension L of renal artery RA, generally within the adventitia of the artery. The renal artery RA has smooth muscle cells SMC that surround the arterial circumference and spiral around the angular axis θ of the artery. The smooth muscle cells of the renal artery accordingly have a lengthwise or longer dimension extending transverse (i.e., non-parallel) to the lengthwise dimension of the renal artery. The misalignment of the lengthwise dimensions of the renal nerves and the smooth muscle cells is defined as “cellular misalignment.”

C. Embodiments of Apparatus and Methods for Neuromodulation

[0044] FIGS. 3-14 illustrate examples of systems and methods for thermally-induced renal neuromodulation. FIG. 3 shows one embodiment of an extravascular apparatus 200 that includes one or more electrodes configured to deliver a thermal electric field to renal neural fibers for renal neuromodulation via heating. The apparatus 200 of FIG. 3 is configured for temporary extravascular placement; however, it should be understood that partially or completely implantable extravascular apparatus additionally or alternatively may be utilized. Applicants have previously described extravascular pulsed electric field systems, for example, in co-pending U.S. patent application Ser. No. 11/189,563, filed Jul. 25, 2005, which has been incorporated herein by reference in its entirety.

[0045] The specific embodiment of the apparatus 200 shown in FIG. 3 comprises a laparoscopic or percutaneous system having a probe 210 configured for insertion in proximity to the track of the renal neural supply along the renal artery, vein, hilum and/or within Gerota’s fascia under a suitable guidance system. The probe 210 can have at least one electrode 212 for delivering a thermal electric field therapy. The electrode(s) 212, for example, may be mounted on a catheter and electrically coupled to a thermal electric field generator 50 via wires 211. The electrode 212 can be passed through the probe 210, or in an alternative embodiment the electrode 212 may be mounted to the probe 210. The probe 210 may have an electrical connector to couple the electrode 212 to the field generator 50.

[0046] The field generator 50 is located external to the patient. The generator, as well as any of the electrode embodiments described herein, may be utilized with any embodiment of the present invention for delivery of a thermal electric field with desired field parameters, e.g., parameters sufficient to thermally or otherwise induce renal neuromodulation in target neural fibers via heating and/or electroporation. It should be understood that electrodes of embodiments described herein after may be electrically connected to the generator even though the generator is not explicitly shown or described with each embodiment. Furthermore, the field generator optionally may be positioned internally within the patient. Further still, the field generator may additionally or may be replaced with an alternative thermal energy generator, such as a thermoelectric generator for heating or cooling (e.g., a Peltier device), or a thermal fluid injection system for heating or cooling, etc.

[0047] The electrode(s) 212 can be individual electrodes that are electrically independent of each other, a segmented electrode with commonly connected contacts, or a continuous electrode. A segmented electrode may, for example, be formed by providing a slotted tube fitted onto the electrode, or by electrically connecting a series of individual electrodes. Individual electrodes or groups of electrodes 212 may be configured to provide a bipolar signal. The electrodes 212 may be dynamically assignable to facilitate monopolar and/or bipolar energy delivery between any of the electrodes and/or between any of the electrodes and a remote electrode. Such a remote electrode may be attached externally to the patient’s skin, e.g., to the patient’s leg or flank. In FIG. 3, the electrodes 212 comprise a bipolar
electrode pair. The probe 210 and the electrodes 212 may be similar to the standard needle or trocar-type used clinically for RF nerve block. Alternatively, the apparatus 200 may comprise a flexible and/or custom-designed probe for the renal application described herein.

[0048] In FIG. 3, the probe 210 has been advanced through a percutaneous access site P into proximity with a patient's renal artery RA. The probe pierced the patient's Gerota's fascia F, and the electrodes 212 are advanced into position through the probe and along the annular space between the patient's artery and fascia. Once properly positioned, the target neural fibers may be heated via a pulsed or continuous electric field delivered across the bipolar electrodes 212. Such heating may, for example, ablate or cause non-ablative thermal injury to the target neural fibers to at least partially denervate the kidney innervated by the target neural fibers. The electric field also may induce reversible or irreversible electroporation in the target neural fibers, which may compliment the thermal injury induced in the neural fibers. After treatment, the apparatus 200 may be removed from the patient to conclude the procedure.

[0049] Referring now to FIGS. 4A and 4B, several embodiments of intravascular systems for thermally-induced renal neuromodulation are described. Applicants have previously described intravascular pulsed electric field systems, for example, in co-pending U.S. patent application Ser. No. 11/129,765, filed May 13, 2005, which has been incorporated herein by reference in its entirety. In one embodiment, an apparatus 300 comprises a catheter 302 having an optional positioning element 304, shaft electrodes 306a and 306b disposed along the shaft of the catheter, and optional radiopaque markers 308 disposed along the shaft of the catheter in the region of the positioning element 304. The positioning element 304 can be a balloon, an expandable wire basket, other mechanical expander that holds the electrodes 306a-b at a desired location relative to the vessel. The electrodes 306a-b can be arranged such that the electrode 306a is near a proximal end of the positioning element 304 and the electrode 306b is near the distal end of the positioning element 304. The electrodes 306 are electrically coupled to the field generator 50 (see FIG. 3) for delivery of a thermal electric field for heating of target neural fibers. In an alternative embodiment, one or more of the electrodes may comprise Peltier electrodes for cooling the target neural fibers to modulate the fibers.

[0050] The positioning element 304 optionally may center or otherwise position the electrodes 306a and 306b within a vessel. Additionally, as in FIG. 4A, the positioning element may comprise an impedance-altering element that alters the impedance between electrodes 306a and 306b during the therapy to direct the thermal electric field across the vessel wall. This may reduce the level of energy required to achieve desired renal neuromodulation and may reduce a risk of undesirably affecting non-target tissue. Applicants have previously described use of a suitable impedance-altering element in co-pending U.S. patent application Ser. No. 11/266, 993, filed Nov. 4, 2005, which is incorporated herein by reference in its entirety. When the positioning element 304 comprises an inflatable balloon as in FIG. 4A, the balloon may serve as both a centering element for the electrodes 306 and as an impedance-altering electrical insulator for directing an electric field delivered across the electrodes, e.g., for directing the electric field into or across the vessel wall for modulation of target neural fibers. Electrical insulation provided by the positioning element 304 may reduce the magnitude of applied energy or other parameters of the thermal electric field necessary to achieve desired heating at the target fibers.

[0051] Furthermore, the positioning element 304 optionally may be utilized as a cooling element and/or a heating element. For example, the positioning element 304 may be inflated with a chilled fluid that serves as a heat sink for removing heat from tissue that contacts the element. Conversely, the positioning element 304 optionally may be a heating element by inflating it with a warmed fluid that heats tissue in contact with the element. The thermal fluid optionally may be circulated and/or exchanged within the positioning element 304 to facilitate more efficient conductive and/or convective heat transfer. Thermal fluids also may be used to achieve thermal neuromodulation via thermal cooling or heating mechanisms, as described in greater detail herein below. The positioning element 304 (or any other portion of apparatus 300) additionally or alternatively may comprise one or more sensors for monitoring the process. In one embodiment, the positioning element 304 has a wall-contact thermocouple 310 (FIG. 4A) for monitoring the temperature or other parameters of the target tissue, the non-target tissue, the electrodes, the positioning element and/or any other portion of the apparatus 300.

[0052] The electrodes 306 can be individual electrodes (i.e., independent contacts), a segmented electrode with commonly connected contacts, or a single continuous electrode. Furthermore, the electrodes 306 may be configured to provide a bipolar signal, or the electrodes 306 may be used together or individually in conjunction with a separate patient ground pad for monopolar use. As an alternative or in addition to placement of the electrodes 306 along the central shaft of the catheter 302, as in FIGS. 4A and 4B, the electrodes 306 may be attached to the positioning element 304 such that they contact the wall of the renal artery RA. In such a variation, the electrodes may, for example, be affixed to the inside surface, outside surface or at least partially embedded within the wall of the positioning element. FIG. 4C, described hereinafter, illustrates one example of wall-contact electrodes, while FIGS. 5-8 illustrate alternative examples of wall-contact electrodes.

[0053] In use, the catheter 302 may be delivered to the renal artery RA as shown, or it may be delivered to a renal vein or to any other vessel in proximity to neural tissue contributing to renal function, in a low profile delivery configuration through a guide catheter or other device. Alternatively, catheters may be positioned in multiple vessels for thermal renal neuromodulation, e.g., within both the renal artery and the renal vein. Techniques for pulsed electric field renal neuromodulation in multiple vessels have been described previously, for example, in co-pending U.S. patent application Ser. No. 11/451,728, filed Jul. 12, 2006, which is incorporated herein by reference in its entirety.

[0054] Once the positioning element 304 is at a desired location within the renal vasculature, it may be expanded into contact with an interior wall of the vessel. A thermal electric field then may be delivered via the electrodes 306 across the wall of the artery. The electric field thermally modulates the activity along neural fibers that contribute to
renal function via heating. In several embodiments, the thermal modulation at least partially denervates the kidney innervated by the neural fibers via heating. This may be achieved, for example, via thermal ablation or non-ablative damage of the target neural fibers. The electric field also may induce electroporation in the neural fibers.

[0055] In the embodiment of FIG. 4A, the positioning element 304 illustratively comprises an inflatable balloon, which may preferentially direct the electric field as discussed. In the embodiment of FIG. 4B, the positioning element comprises an expandable wire basket that substantially centers the electrodes 306 within the vessel without blocking blood flow through the vessel. During delivery of the thermal electric field (or of other thermal energy), the blood may act as a heat sink for conductive and/or convective heat transfer to remove excess thermal energy from the non-target tissue. This protects the non-target tissue from undesired thermal effects. This effect may be enhanced when blood flow is not blocked during energy delivery, as in the embodiment of FIG. 4B.

[0056] Using the patient’s blood as a heat sink is expected to facilitate delivery of longer or greater magnitude thermal treatments with reduced risk of undesired effects to the non-target tissue, which may enhance the efficacy of the treatment at the target neural fibers. Although the embodiment of FIG. 4B illustratively comprises a positioning element for centering the electrodes without blocking flow, it should be understood that the positioning element may be eliminated and/or that the electrodes may be attached to the positioning element such that they are not centered in the vessel upon expansion of the centering element. In such embodiments, the patient’s blood may still mitigate excess thermal heating or cooling to protect non-target tissues.

[0057] One drawback of using a continuous, intravascularly-delivered thermal energy therapy in the presence of blood flow to achieve desired intravascularly-induced neuromodulation is that the feasible thermal magnitude (e.g., power) and/or duration of the therapy may be limited or insufficient. This can occur because the capacity of the blood to remove heat is limited, and thus the blood flowing through the blood vessel may not remove enough excess thermal energy from the vessel wall to mitigate or avoid undesirable effects in the non-target tissue. Use of a pulsed thermal energy therapy, such as a pulsed thermal RF electric field, may facilitate greater thermal magnitude (e.g., higher power), longer total duration and/or better controlled intravascular renal neuromodulation therapy compared to a continuous thermal energy therapy. For example, the effects of the therapy on target or non-target tissue may be monitored during the intervals between the pulses. This monitoring data optionally may be used in a feedback loop to better control the therapy, e.g., to determine whether to continue or stop treatment, and it may facilitate controlled delivery of a higher power or longer duration therapy.

[0058] Furthermore, the off-time or low-energy intervals between thermal energy pulses may facilitate additional convective or other cooling of the non-target tissue of the vessel wall compared to use of a continuous thermal therapy of equivalent magnitude or duration. This may occur because blood flow through the blood vessel can convectively cool (heat) the non-target tissue of the vessel wall faster than the target neural fibers positioned outside of the vessel wall.

[0059] When providing a pulsed thermal therapy, the difference in heat transfer rates between tissue of the blood vessel wall and the relatively remote target neural fibers may be utilized to ablate, necrose or otherwise modulate the target neural fibers without producing undesirable effects in the non-target tissue. As a result, the pulsed thermal energy therapy may be applied with greater thermal magnitude and/or of longer total duration (i.e., the cumulative duration of all thermal energy pulses) compared to a continuous thermal therapy. The higher heat transfer rate at the vessel wall during the intervals between the thermal energy pulses facilitates the greater magnitude/longer duration delivery.

[0060] In addition or as an alternative to utilizing the patient’s blood as a heat sink to create a difference in the heat transfer rates, a thermal fluid (hot or cold) may be injected, infused or otherwise delivered into the vessel to remove excess thermal energy and protect the non-target tissues. The thermal fluid may, for example, comprise saline or another biocompatible fluid that is heated, chilled or at room temperature. The thermal fluid may, for example, be injected through the device catheter or through a guide catheter at a location upstream from an energy delivery element, or at other locations relative to the tissue for which protection is sought. The thermal fluid may be injected in the presence of blood flow or with the blood flow temporarily occluded.

[0061] In several embodiments, the occlusion of the blood flow in combination with thermal fluid delivery may facilitate good control over the heat transfer kinetics along the non-target tissues. For example, the normal variability in blood flow rate between patients, which would vary the heat transfer capacity of the blood flow, may be controlled for by transferring thermal energy between the vessel wall and a thermal fluid that is delivered at a controlled rate. Furthermore, this method of using an injected thermal fluid to remove excess thermal energy from non-target tissues in order to protect the non-target tissues during therapeutic treatment of target tissues may be utilized in body lumens other than blood vessels.

[0062] One or more sensors, such as the thermocouple 310 of FIG. 4A, may be used to monitor the temperature(s) or other parameter(s) at the electrodes 306, the wall of the vessel and/or at other desired locations along the apparatus or the patient’s anatomy. The thermal neuromodulation may be controlled using the measured parameter(s) as feedback. This feedback may be used, for example, to maintain the parameter(s) below a desired threshold. For example, the parameter(s) may be maintained below a threshold that may cause undesired effects in the non-target tissues. With blood flowing through the vessel, more thermal energy may be carried away, which may allow for longer or higher energy treatments than when blood flow is blocked in the vessel.

[0063] As discussed, when utilizing intravascular apparatus to achieve thermal neuromodulation, in addition or as an alternative to central positioning of the electrode(s) within a blood vessel, the electrode(s) optionally may be configured to contact an internal wall of the blood vessel. Wall-contact electrode(s) may facilitate more efficient transfer of a thermal electric field across the vessel wall to target neural fibers, as compared to centrally-positioned electrode(s). In some embodiments, the wall-contact electrode(s) may be delivered to the vessel treatment site in a reduced profile configuration, then expanded in vivo to a deployed configu-
ration wherein the electrode(s) contact the vessel wall. In some embodiments, expansion of the electrode(s) is at least partially reversible to facilitate retrieval of the electrode(s) from the patient’s vessel.

[0064] FIG. 4C depicts an embodiment of an apparatus 400 having one or more wall-contact electrodes 306. One or more of the struts of the expandable basket positioning element 304 may comprise a conductive material that is insulated in regions other than along segments that contact the vessel wall and form electrode(s) 306. The electrode(s) may be used in either a bipolar or a monopolar configuration. Furthermore, the electrode(s) may comprise sensor(s), e.g., impedance or temperature sensors, for monitoring and/or controlling the effects of the thermal energy delivery. The sensors, for example, can be thermocouples.

[0065] FIGS. 5A and 5B depict an alternative embodiment of an intravascular apparatus 500 having electrodes configured to contact the interior wall of a vessel. The apparatus 500 of FIGS. 5A and 5B is an alternative embodiment of the apparatus 100 of FIGS. 4A and 4B wherein the proximal electrode 306a of FIGS. 4A and 4B has been replaced with a wall-contact electrode 306a'. The wall-contact electrode 306a' comprises a proximal connector 312a that connects the electrode to the shaft of the catheter 302 and is electrically coupled to the pulse generator. The apparatus 500 also has a plurality of extensions 314a that extend from the proximal connector 312a and at least partially extend over a surface of positioning element 304. The extensions 314a optionally may be selectively insulated such that only a selective portion of the extensions, e.g., the distal tips of the extensions, are electrically active. The electrode 306a' optionally may be fabricated from a slotted tube, such as a stainless steel or shape-memory (e.g., NiTi) slotted tube. Furthermore, all or a portion of the electrode may be gold-plated to improve radiopacity and/or conductivity.

[0066] As seen in FIG. 5A, the catheter 302 may be delivered over a guide wire 4 to a treatment site within the patient’s vessel with the electrode 306a' positioned in a reduced profile configuration. The catheter 302 optionally may be delivered through a guide catheter 303 to facilitate such reduced profile delivery of the wall-contact electrode. When positioned as desired at a treatment site, the electrode 306a' may be expanded into contact with the vessel wall by expanding the positioning element 304 (shown in FIG. 5B). A thermal monopolar or bipolar electric field then may be delivered across the vessel wall and between the electrodes 306a' and 306b to induce thermal neuremodulation, as discussed previously. The optional positioning element 304 may alter impedance within the blood vessel and more efficiently route the electrical energy across the vessel wall to the target neural fibers.

[0067] After terminating the electric field, the electrode 306a' may be returned to a reduced profile, and the apparatus 300 may be removed from the patient or repositioned in the vessel. For example, the positioning element 304 may be collapsed (e.g., deflated), and the electrode 306a' may be contracted by withdrawing the catheter 302 within the guide catheter 303. Alternatively, the electrode may be fabricated from a shape-memory material biased to the collapsed configuration, such that the electrode self-collapses upon collapse of the positioning element.

[0068] Although in FIGS. 5A and 5B the electrode 306a' is expanded into contact with the vessel wall, it should be understood that the electrode alternatively may be fabricated from a self-expanding material biased such that the electrode self-expands into contact with the vessel wall upon positioning of the electrode distal of the guide catheter 303. A self-expanding embodiment of the electrode 306a' may obviate a need for the positioning element 304 and/or may facilitate maintenance of blood flow through the blood vessel during delivery of an electric field via the electrode. After delivery of the electric field, the self-expanding electrode 306a' may be returned to a reduced profile to facilitate removal of the apparatus 300 from the patient by withdrawing the catheter 302 within the guide catheter 303.

[0069] FIGS. 6A and 6B depict another embodiment of an apparatus 600 and methods for delivering a field using a wall-contact electrode. As an alternative to the proximal connector 312a of the electrode 306a' of FIGS. 5A and 5B, the electrode 306a" of FIGS. 6A comprises a distal connector 316a for coupling the electrode to the shaft of catheter 302 on the distal side of the positioning element 304. The distal connector enables the electrode to extend over the entirety of the positioning element 304 and may facilitate contraction of the electrode 306a" after thermal neuromodulation. For example, the electrode 306a" can be contracted by proximally retracting the proximal connector 312a relative to the catheter 302 during or after contraction of the positioning element 304. FIG. 6A shows the electrode 306a" in the reduced profile configuration, and FIG. 6B shows the electrode in the expanded configuration in which the conductive portions contact the vessel wall.

[0070] FIGS. 7A and 7B show additional alternative embodiments of methods and an apparatus 700. In FIGS. 7A and 7B, the apparatus 700 comprises the proximal electrode 306a' of FIGS. 5A and 5B, and a distal wall-contact electrode 306b'. The embodiment of FIG. 7A comprises proximal and distal positioning elements 304a and 304b, respectively, for expanding the proximal and distal wall-contact electrodes 306a' and 306b', respectively, into contact with the vessel wall. The embodiment of FIG. 7B comprises only a single positioning element 304, but the distal wall-contact electrode 306b' is proximal facing and positioned over the distal portion of the positioning element 304 to facilitate expansion of the distal electrode 306b'. In the embodiment of FIG. 7B, the extensions of the proximal and distal electrodes optionally may be connected along non-conductive connectors 318 to facilitate collapse and retrieval of the electrodes post-treatment.

[0071] A bipolar electric field may be delivered between the proximal and distal wall-contact electrodes, or a monopolar electric field may be delivered between the proximal and/or distal electrode(s) and an external ground. Having both the proximal and distal electrodes in contact with the wall of the vessel may facilitate more efficient energy transfer across the wall during delivery of a thermal electric field, as compared to having one or both of the proximal and distal electrodes centered within the vessel.

[0072] FIGS. 8A-8I illustrate additional embodiments of the apparatus and methods that can comprise one or more wall-contact electrodes, blood flow occlusion features, and thermal fluid injection functions. The embodiments of FIGS. 8 are described as monopolar devices, but it should be understood that any or all of the embodiments may be configured or operated as bipolar devices. Furthermore,
although blood flow occlusion and thermal fluid injection are described in combination with wall-contact electrode(s), it should be understood that such occlusion and injection features may be provided in combination with electrode(s) that do not contact the vessel wall.

[0073] As discussed previously, in addition or as an alternative to utilizing the patient’s blood as a heat sink to create different heat transfer rates between target neural fibers and non-target tissue of the wall of the vessel within which thermal energy is delivered, a thermal fluid (hot or cold) may be injected, infused or otherwise delivered into the vessel. The thermal fluid may further remove excess thermal energy and protect the non-target tissue. When delivering thermal RF therapy, the thermal fluid may, for example, comprise chilled or room temperature saline (e.g., saline at a temperature lower than the temperature of the vessel wall during the therapy delivery). The thermal fluid may be injected through the device catheter or through a guide catheter at a location upstream from an energy delivery element, or at other locations relative to the tissue for which protection is sought. The thermal fluid may be injected in the presence of blood flow or with blood flow temporarily occluded. The occlusion of blood flow in combination with thermal fluid delivery may facilitate good control over the heat transfer kinetics along the non-target tissues, as well as injection of fluid from a downstream location.

[0074] FIGS. 8A and 8B show an embodiment of an apparatus 800 that comprises the catheter 802 having an element 804, which may be used to position the apparatus within the vessel and/or to occlude blood flow. The element 804 may comprise an inflatable balloon. The apparatus 800 can further have an active monopolar electrode 806 located proximally from the element 804 such that inflation of the element 804 blocks blood flow downstream of the electrode 806. The monopolar electrode 806 illustratively comprises multiple extensions 814, and it should be understood that any desired number of extensions may be provided, including a single extension. The monopolar electrode is utilized in combination with a remote electrode, such as a ground pad, positioned external to the patient. The apparatus can also comprise an infusion port 805 between the element 804 and the monopolar electrode 806.

[0075] In FIG. 8A, the catheter 802 may be advanced within the renal artery RA in a reduced profile delivery configuration. In FIG. 81, once properly positioned, the electrode 806 may be actively expanded, or it may self-expand by removing a sheath, the guide catheter or another type of restraint from the electrode. The expanded electrode 806 contacts the vessel wall. The element 804 may be expanded before, during or after expansion of the electrode to properly position the electrode within the vessel and/or to occlude blood flow within the renal artery downstream of the electrode. A monopolar electric field may be delivered between the active electrode 806 and the external ground. The electric field may, for example, comprise a pulsed or continuous RF electric field that thermally induces neuro-modulation (e.g., necrosis or ablation) in the target neural fibers. The thermal therapy may be monitored and controlled, for example, via data collected with thermocouples 810, impedance sensors or other sensors.

[0076] To increase the power that may be delivered or the duration of the thermal treatment without undesirably affecting non-target tissue, a thermal fluid infusate I may be injected through the injection port 805 of the catheter 802 to cool (heat) the non-target tissue. This is expected to mitigate undesired effects in the non-target tissue. The infusate may, for example, comprise chilled saline that removes excess thermal energy (hot or cold) from the wall of the vessel during thermal RF therapy.

[0077] Convective or other heat transfer between the non-target vessel wall tissue and the infusate I may facilitate cooling (heating) of the vessel wall at a faster rate than cooling (heating) occurs at the target neural fibers. This difference in the heat transfer rates between the wall of the vessel and the target neural fibers may be utilized to modulate the neural fibers. Furthermore, when utilizing a pulsed thermal therapy, the higher heat transfer rate at the wall relative to the target neural fibers may allow for relatively higher power or longer duration therapies compared to continuous thermal therapies. Also, the interval between pulses may be used to monitor and/or control effects of the therapy.

[0078] FIG. 8C shows an embodiment of another apparatus 801 with wall-contact electrodes, a flow occlusion feature, and a thermal fluid injection function. In FIG. 8C, the occlusion element 804 is coupled to the guide wire G, which may comprise an infusion lumen, and the infusate I is delivered through a distal outlet of the catheter 802. As will be apparent, the occlusion element alternatively may be coupled to a separate catheter or sheath rather than to the guide wire. Also, the infusate may, for example, be delivered through the guide wire lumen or through an additional lumen or annulus of the catheter 802. FIG. 8D illustrates another embodiment of an apparatus 830 wherein the occlusion element 804 is positioned proximal or upstream of the electrode(s) 806, and the infusate I is delivered at a position distal of the occlusion element but proximal of the electrode(s).

[0079] FIG. 8E is an embodiment of an apparatus 840 with occlusion elements 804 positioned both proximal and distal of the electrode(s) 806. In addition to having a first injection port 805a, the catheter 802 comprises an aspiration port 805b. Separate lumens can extend through the catheter for injection and aspiration of the infusate I via the ports 805. Providing both injection and aspiration of the infusate facilitates good control over the flow dynamics of the infusate, and thereby the heat transfer kinetics of the infusate. For example, providing aspiration and injection at the same rate may provide consistent heat transfer kinetics between the vessel and the electrode(s).

[0080] FIG. 8F illustrates another embodiment of an apparatus 850 having a catheter 852 comprising a wall-contact electrode 856 that may be moved into contact with the vessel wall via an elongated member 857. In this embodiment, the elongated member 857 is distally connected to the catheter in the vicinity of the electrode 856. The elongated member may be configured for self expansion, or it may extend through port 805 of the catheter 852 and through a lumen of the catheter to a proximal location for manipulation by a medical practitioner. The proximal section of the elongated member may be advanced relative to the catheter 852 by the medical practitioner such that the member assumes the illustrated curved profile.

[0081] Upon expansion of the elongated member, the catheter 852 is deflected such that the electrode 856 coupled
to the catheter shaft contacts the vessel wall. Optionally, element 804 may be expanded to facilitate positioning of the electrode via the elongated member and/or to block flow through the vessel. The element 804 can be coupled to the guide or delivery catheter 803. Infusate 1 optionally may be delivered through the catheter 803 as shown.

[0082] FIG. 8G is an embodiment of an apparatus 860 comprising a shaped or self-expanding electrode 866. The electrode 866 may be delivered to a treatment site within catheter 803, and then it moves to a preselected shape after it has been removed from the lumen of the catheter 803. For example, the electrode 866 can be removed from the catheter by advancing the catheter 802 and/or retracting the catheter 803. The electrode 866 contacts the vessel wall for delivery of therapy. Optionally, the catheter 802 may be rotated to rotate the electrode relative to the vessel wall and angularly reposition the electrode. The therapy may be delivered at a singular angular position or at multiple angular positions. Additionally or alternatively, multiple angularly spaced electrodes 866 may be positioned within the vasculature, as shown in FIG. 8H. In addition to angular spacing, the electrodes may be longitudinally spaced to facilitate treatment over a longitudinal segment of the vessel, e.g., to achieve a circumferential treatment along the longitudinal segment rather than along a cross-section.

[0083] In addition to extravascular and intravascular systems for thermally-induced renal neuromodulation, intra-to-extravascular systems may be provided. The intra-to-extravascular systems may, for example, have electrode(s) that are delivered to an intravascular position, and then at least partially passed through/across the vessel wall to an extravascular position prior to delivery of a thermal electric field. Intra-to-extravascular positioning of the electrode(s) may place the electrode(s) in closer proximity to target neural fibers for delivery of a thermal electric field, as compared to fully intravascular positioning of the electrode(s). Applicants have previously described intra-to-extravascular pulsed electric field systems, for example, in co-pending U.S. patent application Ser. No. 11/324,188, filed Dec. 29, 2005, which is incorporated herein by reference in its entirety.

[0084] FIG. 9 illustrates one embodiment of an intra-to-extravascular (“ITEV”) system for thermally-induced renal neuromodulation is described. ITEV system 900 comprising a catheter 922 having (a) a plurality of proximal electrode lumens terminating at proximal side ports 924, (b) a plurality of distal electrode lumens terminating at distal side ports 926, and (c) a guidewire lumen 923. The catheter 922 preferably comprises an equal number of proximal and distal electrode lumens and side ports. The ITEV system 900 also includes proximal needle electrodes 928 that may be advanced through the proximal electrode lumens and the proximal side ports 924, as well as distal needle electrodes 929 that may be advanced through the distal electrode lumens and the distal side ports 926.

[0085] The catheter 922 comprises an optional expandable positioning element 930, which may comprise an inflatable balloon or an expandable basket or cage. In use, the positioning element 930 may be expanded prior to deployment of the needle electrodes 928 and 929 in order to position or center the catheter 922 within the patient’s vessel (e.g., within renal artery RA). Centering the catheter 922 is expected to facilitate delivery of all needle electrodes to desired depths within/external to the patient’s vessel (e.g., to deliver all of the needle electrodes approximately to the same depth). In FIG. 9, the illustrated positioning element 930 is between the proximal side ports 924 and the distal side ports 926, and thus the positioning element 930 is between the delivery positions of the proximal and distal electrodes. However, it should be understood that the positioning element 930 additionally or alternatively may be positioned at a different location or at multiple locations along the length of the catheter 922 (e.g., at a location proximal of the side ports 924 and/or at a location distal of the side ports 926).

[0086] As illustrated in FIG. 9, the catheter 922 may be advanced to a treatment site within the patient’s vasculature over a guidewire (not shown) via the lumen 323. During intravascular delivery, the electrodes 928 and 929 may be positioned such that their non-insulated and sharpened distal surfaces are positioned within the proximal and distal vessels, respectively. Once at a treatment site, a medical practitioner may advance the electrodes via their proximal regions that are located external to the patient. Such advancement causes the distal regions of the electrodes 928 and 929 to exit side ports 924 and 926, respectively, and pierce the wall of the patient’s vasculature such that the electrodes are positioned extravascularly via an ITEV approach.

[0087] The proximal electrodes 928 can be connected to an electric field generator 50 as active electrodes, and the distal electrodes 929 can serve as return electrodes. In this manner, the proximal and distal electrodes form bipolar electrode pairs that align the thermal electric field with a longitudinal axis or direction of the patient’s vasculature. As will be apparent, the distal electrodes 929 alternatively may comprise the active electrodes and the proximal electrodes 928 may comprise the return electrodes. Furthermore, the proximal and/or the distal electrodes may comprise both active and return electrodes. Further still, the proximal and/or the distal electrodes may be utilized in combination with an external ground for delivery of a monopolar thermal electric field. Any combination of active and distal electrodes may be utilized, as desired.

[0088] When the electrodes 928 and 929 are connected to an electric field generator and positioned extravascularly, and with the positioning element 930 optionally expanded, delivery of the thermal electric field may proceed to achieve desired renal neuromodulation via heating. The electric field also may induce electroporation. After achievement of the thermally-induced renal neuromodulation, the electrodes may be retracted within the proximal and distal lumens, and the positioning element 930 may be collapsed for retrieval. The ITEV system 900 then may be removed from the patient to complete the procedure. Additionally or alternatively, the system may be repositioned to provide therapy at another treatment site, such as to provide bilateral renal neuromodulation.

[0089] Cooling elements, such as convective cooling elements, may be utilized to protect non-target tissues like smooth muscle cells from thermal damage during thermally-induced renal neuromodulation via heat generation. Non-target tissues may be protected by focusing the thermal energy on the target neural fibers such that an intensity of the
thermal energy is insufficient to induce thermal damage in non-target tissues distant from the target neural fibers.

[0090] Although FIGS. 3-7 and 9 illustratively show bipolar apparatus, it should be understood that monopolar apparatus alternatively may be utilized as in FIGS. 8A-8H. For example, an active monopolar electrode may be positioned intravascularly, extravascularly or intra-to-extravascularly in proximity to target neural fibers that contribute to renal function. A return electrode may be attached to the exterior of the patient or positioned in the patient apart from the active electrodes. Finally, a thermal electric field may be delivered between the in vivo monopolar electrode and the remote electrode to effectuate desired thermally-induced renal neuromodulation. Monopolar apparatus additionally may be utilized for bilateral renal neuromodulation.

[0091] The embodiments of FIGS. 3-9 illustratively describe methods and apparatus for thermally-induced renal neuromodulation via delivery of thermal electric fields that modulate the target neural fibers. However, it should be understood that alternative methods and apparatus for thermally-induced (via both heating and cooling) renal neuromodulation may be provided. For example, electric fields may be used to cool and modulate the neural fibers with thermoelectric or Peltier elements. Also, thermally-induced renal neuromodulation optionally may be achieved via direct application of thermal energy to the target neural fibers. Such direct thermal energy may be generated and/or transferred in a variety of ways, such as via resistive heating, via delivery of a heated or chilled fluid (see FIGS. 10 and 12), via a Peltier element (see FIG. 11), etc. Thermally-induced renal neuromodulation additionally or alternatively may be achieved via application of high-intensity focused ultrasound to the target neural fibers (see FIG. 13). Additional and alternative methods and apparatus for thermally-induced renal neuromodulation may be used in accordance with the present invention.

[0092] With reference now to FIG. 10, an alternative embodiment of an apparatus 1000 and methods for thermally-induced neuromodulation via direct application of thermal energy is described. In the embodiment of FIG. 10, the electrodes 928 and 929 of FIG. 9 have been replaced with infusion needles 1028 and 1029, respectively. A thermal fluid F may be delivered through the needles to the target neural fibers. The thermal fluid may be heated in order to raise the temperature of the target neural fibers above a desired threshold. For example, the temperature of the neural fibers can be raised above a body temperature of about 37° C., or above a temperature of about 45° C. Alternatively, the thermal fluid may be cooled to reduce the temperature of the target neural fibers below a desired threshold. For example, the neural fibers can be cooled to below the body temperature of about 37° C., or further cooled below about 20° C., or still further cooled below a freezing temperature of about 0° C. As will be apparent, in addition to intra-to-extravascular delivery of a thermal fluid, the thermal fluid may be delivered intravascularly (e.g., may inflate and/or be circulated through a balloon member), extravascularly (e.g., may be circulated through a vascular cuff), or a combination thereof.

[0093] In addition or as alternative to injection of a thermal fluid to the target neural fibers through infusion needles 1028 and 1029, an alternative neuromodulatory agent, such as a drug or medicament, may be injected to modulate, necrose or otherwise block or reduce transmission along the target neural fibers. Examples of alternative neuromodulatory agents include, but are not limited to, phenol and neurotoxins, such as botulinum toxin. Additional neuromodulatory agents, per se known, will be apparent to those of skill in the art.

[0094] FIG. 11 shows another method and apparatus 1100 for thermal renal neuromodulation via direct application of thermal energy to the target neural fibers. The apparatus 1100 comprises renal artery cuff 1102 having one or more integrated thermoelectric elements that are electrically coupled to an internal or external power supply 1104. The thermoelectric element utilizes the well-known Peltier effect (i.e., the establishment of a thermal gradient induced by an electric voltage) to achieve thermal renal neuromodulation.

[0095] An electric current is passed from the power supply 1104 to the thermoelectric element of the cuff 1102. The thermoelectric element can comprise two different metals (e.g., a p-type and an n-type semiconductor) that are connected to each other at two junctions. The current induces a thermal gradient between the two junctions, such that one junction cools while the other is heated. Reversal of the polarity of the voltage applied across the two junctions reverses the direction of the thermal gradient. Either the hot side or the cold side of the thermoelectric element faces radially inward in order to heat or cool, respectively, the target neural fibers that travel along the renal artery to achieve thermal renal neuromodulation. Optionally, the radially outward surface of the thermoelectric element may be insulated to reduce a risk of thermal damage to the non-target tissues. The cuff 1102 may comprise one or more temperature sensors, such as thermocouples, for monitoring the temperature of the target neural fibers and/or of the non-target tissues.

[0096] FIG. 12 shows another method and apparatus 1200 utilizing the Peltier effect. The apparatus 1200 comprises an implanted or external pump 1202 connected to a renal artery cuff 1204 via inlet fluid conduit 1206a and outlet fluid conduit 1206b. The inlet fluid conduit transfers fluid from the pump to the cuff, while the outlet fluid conduit transfers fluid from the cuff to the pump to circulate fluid through the cuff. A reservoir of fluid may be located in the cuff, the pump and/or in the fluid conduits.

[0097] The pump 1202 further comprises one or more thermoelectric or other thermal elements in heat exchange contact with the fluid reservoir for cooling or heating the fluid that is transferred to the cuff to thermally modulate the target neural fibers. The apparatus 1200 optionally may have controls for automatic or manual control of fluid heating or cooling, as well as fluid circulation within the cuff. Furthermore, the apparatus may comprise temperature and/or renal sympathetic neural activity monitoring or feedback control. Although the apparatus illustratively is shown unilaterally treating neural fibers innervating a single kidney, it should be understood that bilateral treatment of neural fibers innervating both kidneys alternatively may be provided.

[0098] Thermal renal neuromodulation alternatively may be achieved via pulsed or continuous high-intensity focused ultrasound. High intensity focused ultrasound also may induce reversible or irreversible electroporation in the target neural fibers. Furthermore, the ultrasound may be delivered
over a full 360° (e.g., when delivered intravascularly) or over a radial segment of less than 360° (e.g., when delivered extravascularly, intra- extravascularly, or a combination thereof). FIGS. 13A and B illustrate an embodiment of an ultrasonic apparatus 1300 comprising a catheter 1302, one or more ultrasound transducers 1304 positioned along the shaft of the catheter, and an inflatable balloon 1306 around the transducers 1304. The ultrasound transducers 1304 are coupled to an ultrasound signal generator via conductors 1307. The balloon 1306 can have an acoustically reflective portion 1308 for reflecting an ultrasound wave and an acoustically transmissive portion 1309 the wave through which the ultrasonic energy can pass. In this manner, the wave may be focused as shown at a focal point or radius P positioned a desired focal distance from the catheter shaft. In an alternative embodiment, the transducers may be attached directly to the balloon.

[0099] The focal distance may be specified or dynamically variable such that the ultrasonic wave is focused at a desired depth on target neural fibers outside of the vessel. For example, a family of catheter sizes may be provided to allow for a range of specified focal distances. A dynamically variable focal distance may be achieved, for example, via calibrated expansion of the balloon.

[0100] Focusing the ultrasound wave may produce a reverse thermal gradient that protects the non-target tissues and selectively affect the target neural fibers to achieve thermal renal neuromodulation via heating. As a result, the temperature at the vessel wall may be less than the temperature at the target tissue. FIG. 13A shows the apparatus 1300 in a reduced delivery and retrieval configuration, and FIG. 13B shows the apparatus 1300 in an expanded deployed configuration.

[0101] FIG. 14 shows an alternative embodiment of an ultrasonic apparatus 1400 having a catheter 1402, a conductor 1403, and concave ultrasound transducers 1401. The concave ultrasound transducers 1404 direct the energy to a specific focal point P, and as such the concave transducers 1404 eliminate the need of the reflective portion of the balloon 366 (e.g., the balloon may be acoustically transmissive at all points).

[0102] The apparatus described above with respect to FIGS. 3-14 optionally may be used to quantify the efficacy, extent or cell selectivity of thermally-induced renal neuromodulation in order to monitor and/or control the neuromodulation. As discussed previously, the apparatus may further comprise one or more sensors, such as thermocouples or imaging transducers, for measuring and monitoring one or more parameters such as (a) temperature rise or drop above or below certain thresholds is expected to thermally ablate, (b) target neural fibers and/or (c) non-target tissues. For example, a temperature rise or drop above or below certain thresholds is expected to thermally ablate, non-ablatively injure, freeze or otherwise damage the target neural fibers to thereby modulate the target neural fibers.

[0103] FIGS. 15A and 15B classify the various types of thermal neuromodulation that may be achieved with the apparatus and methods of the present invention. FIGS. 15A and 15B are provided only for the sake of illustration and should in no way be construed as limiting. FIG. 15A classifies thermal neuromodulation due to heat exposure. As shown, exposure to heat in excess of a body temperature of about 37°C, but below a temperature of about 45°C, may induce thermal injury via moderate heating of the target neural fibers or of vascular structures that perfuse the target fibers. For example, this may induce non-ablative thermal injury in the fibers or structures. Exposure to heat above a temperature of about 45°C, or above about 60°C, may induce thermal injury via substantial heating of the fibers or structures. For example, such higher temperatures may thermally ablate the target neural fibers or the vascular structures. In some patients, it may be desirable to achieve temperatures that thermally ablate the target neural fibers or the vascular structures, but that are less than about 90°C, or less than about 85°C, or less than about 80°C, and/or less than about 75°C. Regardless of the type of heat exposure utilized to induce the thermal neuromodulation, a reduction in renal sympathetic nerve activity ("RSNA") is expected.

[0104] As seen in FIG. 15B, thermal cooling for neuromodulation includes non-freezing thermal slowing of nerve conduction and/or nerve injury, as well as freezing thermal nerve injury. Non-freezing thermal cooling may include reducing the temperature of the target neural fibers or of the vascular structures that feed the fibers to temperatures below the body temperature of about 37°C, or below about 20°C, but above the freezing temperature of about 0°C. This non-freezing thermal cooling may either slow nerve conduction or may cause direct neural injury. Slow nerve conduction may use continuous or intermittent cooling of the target neural fibers to sustain the desired thermal neuromodulation, while direct neural injury may require only a discrete treatment to achieve sustained thermal neuromodulation. Thermal cooling for neuromodulation also may include freezing thermal nerve injury by reducing the temperature of the target neural fibers or of the vascular structures that feed the fibers to temperatures below the freezing point of about 0°C. Regardless of the type of cold exposure utilized to induce the thermal neuromodulation (freezing or non-freezing), a reduction in renal sympathetic nerve activity ("RSNA") is expected.

[0105] It is expected that thermally-induced renal neuromodulation, whether delivered extravascularly, intravascularly, intra-extravascularly or a combination thereof, may alleviate clinical symptoms of CHF, hypertension, renal disease, myocardial infarction, atrial fibrillation, contrast nephropathy and/or other cardio-renal diseases for a period of months (potentially up to six months or more). This time period may be sufficient to allow the body to heal; for example, this period may reduce the risk of CHF onset after an acute myocardial infarction to thereby alleviate a need for subsequent re-treatment. Alternatively, as symptoms recurr, or at regularly scheduled intervals, the patient may receive repeat therapy. Thermally-induced renal neuromodulation also may systemically reduce sympathetic tone.

[0106] Although preferred illustrative variations of the present invention are described above, it will be apparent to those skilled in the art that various changes and modifications may be made thereto without departing from the invention. It is intended in the appended claims to cover all such changes and modifications that fall within the true spirit and scope of the invention.

I/We claim:

1. A method for thermally-induced renal neuromodulation, the method comprising:
positioning a thermal apparatus at least proximate to a neural fiber that contributes to renal function; and delivering pulsed energy via the thermal apparatus to modulate a function of the neural fiber via thermal effects.
2. The method of claim 1, wherein positioning the thermal apparatus further comprises delivering the device via an approach chosen from the group consisting of intravascularly, extravascularly, intra-to-extravascularly and combinations thereof.
3. The method of claim 1, wherein delivering the pulsed energy further comprises directly applying pulsed thermal energy to the neural fiber.
4. The method of claim 1, wherein delivering the pulsed energy further comprises indirectly applying pulsed thermal energy to the neural fiber.
5. The method of claim 1, wherein delivering the pulsed energy further comprises delivering a pulsed thermal electric field to the neural fiber via at least one electrode.
6. The method of claim 5, wherein positioning the thermal apparatus further comprises intravascularly delivering the device, and wherein delivering a pulsed thermal electric field to the neural fiber via at least one electrode further comprises delivering the pulsed thermal electric field via at least one wall-contact electrode.
7. The method of claim 1 further comprising monitoring a parameter of at least one of the neural fiber, a non-target tissue or the apparatus during thermally-induced modulation of the function of the neural fiber.
8. The method of claim 7 further comprising controlling the delivery of the pulsed energy in response to the monitored parameter.
9. The method of claim 1 further comprising actively protecting non-target tissue during thermal modulation of the neural fiber.
10. The method of claim 9, wherein actively protecting the non-target tissue further comprises reducing a degree of thermal damage induced in the non-target tissue.
11. The method of claim 9, wherein actively protecting the non-target tissue further comprises delivering a thermal fluid to a vicinity of the non-target tissue.
12. The method of claim 9, wherein actively protecting the non-target tissue further comprises delivering a thermal fluid to a vicinity of the non-target tissue.
13. The method of claim 1, wherein delivering the pulsed energy further comprises delivering pulsed high intensity focused ultrasound to the neural fiber.
14. The method of claim 1, wherein delivering the pulsed energy further comprises heating the neural fiber via the pulsed thermal energy.
15. The method of claim 1, wherein delivering the pulsed energy further comprises cooling the neural fiber via the pulsed thermal energy.
16. Apparatus for thermally-induced renal neuromodulation, the apparatus comprising:
- a pulse generator configured to provide pulsed thermal energy;
- a device configured for delivery within a blood vessel to a vicinity of a neural fiber that contributes to renal function; and a thermal modulation element supported by the device, the thermal modulation element being configured to expand from a first dimension to a second dimension, wherein the thermal modulation element is configured to (a) contact a wall of the blood vessel upon expansion of the thermal modulation element to the second dimension within the blood vessel, and (b) transmit the pulsed thermal energy relative to the neural fiber to thermally induce modulation of a function of the neural fiber upon expansion of the thermal modulation element to the second dimension within the blood vessel.
17. The apparatus of claim 16, wherein the thermal modulation element is configured to self-expand from the first dimension to the second dimension.
18. The apparatus of claim 16, wherein the device further comprises an expandable member that is at least proximate to the thermal modulation element, the expandable member being configured to expand the thermal modulation element from the first dimension to the second dimension.
19. The apparatus of claim 16, wherein the thermal modulation element is configured for direct application of the pulsed thermal energy relative to the neural fiber.
20. The apparatus of claim 16, wherein the thermal modulation element is configured for indirect application of the pulsed thermal energy relative to the neural fiber.
21. The apparatus of claim 16, wherein the thermal modulation element further comprises at least one electrode configured to deliver a pulsed thermal electric field relative to the neural fiber.
22. The apparatus of claim 16, wherein the apparatus further comprises at least one sensor.
23. The apparatus of claim 22, wherein the sensor is configured to monitor a physiological parameter of the neural fiber.
24. The apparatus of claim 22, wherein the sensor is configured to monitor a physiological parameter of non-target tissue.
25. The apparatus of claim 22, wherein the sensor is configured to monitor a parameter of the apparatus.
26. The apparatus of claim 22 further comprising a feedback control in communication with the sensor.
27. The apparatus of claim 16, wherein the apparatus further comprises a protective element configured to reduce a degree of thermal damage induced in non-target tissue.
28. The apparatus of claim 16, wherein the thermal modulation element further comprises at least one thermal element configured to deliver the pulsed thermal energy relative to the neural fiber.
29. The apparatus of claim 16, wherein the thermal modulation element further comprises a high intensity focused ultrasound element.
30. The apparatus of claim 16, wherein the thermal modulation element further comprises a thermal fluid.
31. The apparatus of claim 27, wherein the protective element comprises an infusion element configured to infuse a thermal fluid in a vicinity of the non-target tissue.
32. The apparatus of claim 16 further comprising an occlusion element configured to temporarily occlude blood flow within the blood vessel.