(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2012 (01.03.2012)

PCT

(10) International Publication Number
WO 2012/027734 A1

(51) International Patent Classification:
A61N 1/36 (2006.01) *A61N 1/362* (2006.01)

(21) International Application Number:
PCT/US2011/049477

(22) International Filing Date:
29 August 2011 (29.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/377,499 27 August 2010 (27.08.2010) US

(71) Applicant *(for all designated States except US)*: **G&L CONSULTING, LLC** [US/US]; 640 Pompander Walk, Teaneck, NJ 07666 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GELFAND, Mark** [US/US]; 11 Avenue B, Apt. 4B, New York, NY 10009 (US). **LEVIN, Howard** [US/US]; 640 Pompander Walk, Teaneck, NJ 07666 (US).

(74) Agent: **NELSON, Jeffry, H.**; Nixon & Vanderhye P.C., 901 North Glebe Road, 11th Floor, Arlington, VA 22203-1808 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

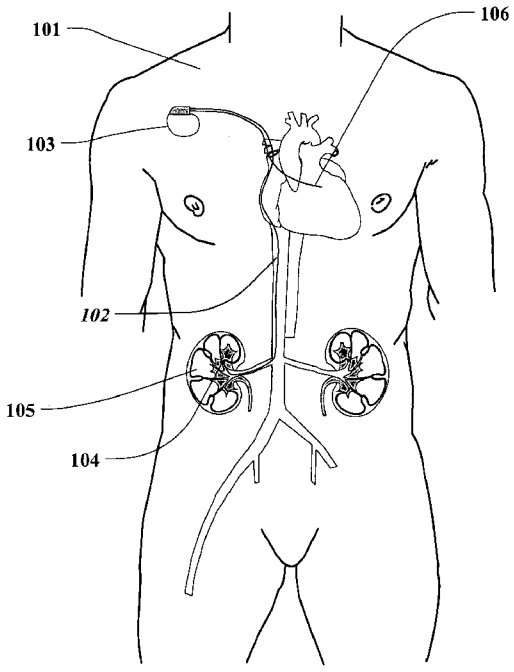
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: SYSTEM AND METHOD FOR ELECTRIC DIURESIS

(57) Abstract: An implantable medical device for treating fluid retention wherein stimulation is provided to the renal pelvis through a proximal transvenous lead system to induce a clinically significant increase in bilateral diuresis and natriuresis.

Figure 1



WO 2012/027734 A1

GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

SYSTEM AND METHOD FOR ELECTRIC DIURESIS

BACKGROUND OF THE INVENTION

[0001] The present invention relates generally to implantable medical devices and more particularly to a device and method for electric stimulation of a kidney to induce diuresis, natriuresis and blood pressure reduction.

[0002] I. Anatomy of the kidney and urine collection system.

[0003] The kidneys are organs that have numerous biological roles. Their primary role is to maintain the homeostatic balance of bodily fluids by filtering and secreting metabolites and minerals from the blood and excreting them, along with water, as urine.

[0004] The body mass, or parenchyma, of the kidney is divided into two major structures: superficial is the renal cortex and deep is the renal medulla. Grossly, these structures take the shape of 8 to 18 cone-shaped renal lobes, each containing renal cortex surrounding a portion of medulla called a renal pyramid. Between the renal pyramids are projections of cortex called renal columns. Nephrons, the urine-producing functional structures of the kidney, span the cortex and medulla. The initial filtering portion of a nephron is the renal corpuscle, located in the cortex, which is followed by a renal tubule that passes from the cortex deep into the medullary pyramids. Part of the renal cortex, a medullary

ray is a collection of renal tubules that drain into a single collecting duct.

[0005] The tip, or papilla, of each pyramid empties urine into a minor calyx, minor calyces empty into major calyces, and major calyces empty into the renal pelvis, which becomes the ureter. The ureters are muscular ducts that propel urine from the kidneys to the urinary bladder. It is now known that renal pelvis and ureters are more than just collection vessels for urine transport. Their walls include biologic sensors and nerve endings that play part in the control of body fluid volume.

[0006] The kidneys receive blood from the renal arteries, left and right, which branch directly from the abdominal aorta. Despite their relatively small size, the kidneys receive approximately 20% of the cardiac output.

[0007] Each renal artery branches into segmental arteries, dividing further into interlobar arteries which penetrate the renal capsule and extend through the renal columns between the renal pyramids. The interlobar arteries then supply blood to the arcuate arteries that run through the boundary of the cortex and the medulla. Each arcuate artery supplies several interlobular arteries that feed into the afferent arterioles that supply the glomeruli. The interstitum is the functional space in the kidney beneath the individual filters (glomeruli) which are rich in blood vessels. The interstitum absorbs fluid recovered from urine.

[0008] After filtration occurs the blood moves through a small network of venules that converge into interlobular veins. As with the arteriole distribution the veins follow the same pattern, the interlobular provide blood to the arcuate veins then back to the interlobar veins which come to form the renal vein exiting the kidney for drainage of blood into the inferior vena cava.

[0009] II. Innervation of the Kidney

[0010] The kidney both receives nervous system input from the rest of the body (termed, efferent nerve activity) and produces information which it sends back to the rest of the body (termed, afferent nerve activity).

[0011] The kidney and the urine collection system receive autonomic (mostly sympathetic) innervation, via the efferent nervous system. Autonomic nerves from the renal plexus and other sources follow the renal artery into the kidney through the renal hilus. The nerve fibers follow the branching pattern of the renal artery and serve as vasomotor fibers that regulate blood volume. Increased activity of the sympathetic efferent fibers can increase renin release, constrict arterioles and reduce urine output and salt excretion by the kidney.

[0012] Like other visceral organs, the kidneys also have a profuse sensory innervation. Electrophysiologic studies in the mammalian kidney have identified two major classes of sensory receptors of the renal afferent nerves, chemoreceptors (CRs), and mechanoreceptors (MRs).

Renal CRs are of two types, CR1 and CR2. Both respond to renal ischemia, but only CR2 reacts to alterations in the electrolyte composition of the renal pelvis. MRs are of three types, each sensitive to arterial perfusion pressure (MRa), venous pressure (MRv), and uretero-pelvic pressure (MRu). These sensory receptors with their specific activities can reflect the physical and chemical states of the kidney in diuretic and antidiuretic states, as well as in pathologic conditions such as chronic hypoxia, hypertension, and ischemic renal failure. Activation of these renal sensory receptors, thus an increase in afferent renal nerve activity, could initiate systemic effects, such as the central control of blood pressure and volume but also local reflexes termed the "renorenal reflex". Therefore, these renal sensory receptors can play an important role in the regulation of body fluid homeostasis.

[0013] III. Physiological and Clinical Relevance of Renal Pelvic Receptor Activation.

[0014] Chemical and mechanical (by stretching) stimulation of the urine collection space causes diuresis, natriuresis (from both kidneys) and reduces blood pressure. These effects are well researched and are unquestionable. For example infusion of hypertonic saline or pressurization of renal pelvis caused said effects in animals and humans. The phenomenon was observed normal specimens and in a variety of disease models.

[0015] DiBona and Kopp demonstrated in a number of papers that the reno-renal reflex is normally activated

by a rise in pressure or sodium concentration in the collecting system, the renal pelvis and the ureters.

[0016] Physiologically, the reno-renal reflex increases renal blood flow, GFR, diuresis, natriuresis and reduces blood pressure both by promoting sodium excretion and by a direct effect on brainstem sympathetic ganglions. Increasing afferent renal nerve activity via injection of sodium into the renal pelvis leads to a decrease in efferent sympathetic nerve activity and both ipsilateral and contralateral diuresis and natriuresis..

[0017] In summary, the renal pelvis chemo- and mechanoreceptors (baroreceptors) activate the reno-renal reflex via afferent nerve activity integrated at the level of the spinal cord to modulate diuresis and natriuresis of both the ipsilateral and contralateral kidneys.

[0018] The inventors are unaware of conclusive data that electro-stimulation of the baroreceptors, chemoreceptors or nerves involved in the reno-renal reflex will produce the same effect. Nevertheless, historic experience with the carotid sinus baroreflex strongly suggests that electric activation of the same physiologic pathways is possible.

[0019] Therapeutic modulation and modification of these afferent nerve signals that originate inside the kidney is proposed by the inventors. The main therapeutic purpose of this modification of neural signals is to increase sodium excretion (natriuresis) and water

excretion (diuresis) in patients with fluid retention, primarily from Congestive Heart Failure (CHF). In addition down modulation (reduction) of afferent neural activity from the kidney should yield systemic benefits, such as vasodilation of peripheral blood vessels and reduction of blood pressure.

[0020] IV. Motivation for Therapy.

[0021] CHF is an enormous health issue for patients, health care system and most hospitals. Heart failure represents roughly 2.2 million admissions per year and it costs the health care system roughly $23 billion to treat these patients. Further, there is a subgroup of 200,000 Class IV patients that account for 800,000 admissions. Unfortunately, while this group of 200,000 represents only 13% of the CHF patient population, they are responsible for almost 50% of the cost of CHF hospitalizations due to complications like pulmonary edema and other co-morbidities associated with very sick CHF patients.

[0022] The symptom that typically drives the CHF patients to the hospital is acute fluid overload. The current treatment is to put them on an IV form of the diuretic that most likely has already failed them in the oral form. It may take 2-4 days to remove the 2-4 liters of excess fluid using IV diuretics. The blood ultrafiltration therapy can remove fluid faster but is expensive and requires special skills and sophisticated technology.

[0023] Up to one in three heart failure patients who take diuretic drugs experience diuretic resistance: when the process of eliminating excess sodium and water stops before enough fluid has been removed from the patient's body. In patients with mild heart failure and good kidney function, diuretic resistance is uncommon. However, diuretic resistance occurs more often in patients with moderate or severe heart failure.

[0024] There is also a significant clinical need to prevent patients from becoming fluid overloaded earlier in the course of heart failure, even before patients become diuretic resistant. Many patients, specifically those in early and late Class III and earlier in Class IV CHF could avoid problems associated with fluid overload (e.g., shortness of breath, inability to perform activities of daily living and reduced heart function) by preventing the development of fluid .

[0025] Most device-based therapies that treat fluid overload are utilized only after significant fluid overload has occurred due to the complexity, invasiveness or difficulty of performing the therapy. It would be desirable to have a therapy that clinicians would be comfortable with initiating earlier in the course of heart failure that would be able to stop or slow the occurrence of fluid overload.

[0026] There is therefore a long felt, large unmet clinical need for innovation in the area of safe and effective induced diuresis therapies. The clinical need includes a need for diuresis therapies administered to

patients at home, when needed and before the patient becomes short of breath and require admission to the hospital. Further, there is a clinical need for induced diuresis in patients that become diuretic resistant.

BRIEF DESCRIPTION OF THE INVENTION

[0027] A device, system and method have been invented that, in one embodiment, stimulates chemoreceptors and baroreceptors and associated intra-renal nerves in the urine collection space and specifically in the renal pelvis of the kidney. These receptors are nerve endings that conduct information to the CNS via afferent nerves. Stimulation results in the induced physiologic response similar to the natural reno-renal reflex. Patients with fluid retention, heat failure and hypertension are expected to benefit from natriuresis, diuresis and vascular vasodilation.

[0028] The inventors propose a novel implantable electrode and lead designs, insertion methods for the electrode and lead that will allow a novel electrode placement in close proximity to the renal pelvis using transvenous access and an IPG configured to generate electrical stimulus signals to activate the baroreceptors in the renal pelvis.

[0029] The electrodes are integrated on transvenous leads, similar to pacemaker leads that are connected to an Implantable Pulse Generator (IPG), such as an implantable stimulator or pacemaker. The IPG contains power electronics, electronic control logic and software needed to implement the therapy by generating electrical

impulses applied via an electrode(s) to a location on the patient proximate to the electrode. For example, the renal urine space, e.g., the renal pelvis, may be stimulated by an IPG having a transvenous lead and electrode assembly. The electrode is lodged in one of the interlobar or and segmental veins that merge and exit as a single renal vein in most people. The IPG delivers electrical impulses to the electrode, which apply the impulses to the interlobar or segmental vein(s). The impulses are generated in the IPG by the power electronics based on commands from the electronic control logic and associated software.

[0030] The renal vein usually lies anterior to the renal artery at the renal hilum. The left renal vein is longer than the right renal vein. The left renal vein averages 6 to 10 cm in length and will normally course anteriorly between the superior mesenteric artery and the aorta before emptying into the medial aspect of the inferior vena cava. The right renal artery averages 2 to 4 cm in length and joins the lateral aspect of the inferior vena cava. Unlike the right renal vein, the left renal vein receives several tributaries before joining the inferior vena cava. It receives the left adrenal vein superiorly, the left gonadal vein inferiorly, and a lumbar vein posteriorly.

[0031] The novel device, system and method disclosed herein takes advantage of the anatomy of renal veins to place stimulation electrodes in close proximity to targeted receptors and nerves in the urine collection space of the kidney, such as in the renal pelvis and

upper ureter. The stimulation electrodes activate baroreceptors, e.g., chemoreceptors and mechanoreceptors, in the renal pelvis to evoke such effects as the reno-renal reflex. The stimulation electrodes may be inserted without invasive surgical placement of artificial devices in the urine space where foreign materials can cause encrustation or kidney stones.

[0032] A method has been conceived to treat a patient comprising: artificially stimulating a chemoreceptor or a baroreceptor associated with a nerve in or proximate to the urine generation space or urine collection space of the patient; wherein the artificial stimulation promotes the production of urine by the patient. The vascular space may be proximate to a urine generation area, e.g., kidney, renal pelvis or ureter, or urine collection area, urethra and bladder, of the patient. The vascular space may be innervated by chemoreceptors and baroreceptors.

[0033] The method may further comprise placement of an electrode in a vascular space of the patient and the stimulation includes applying energy through the electrode to the vascular space to stimulate the chemoreceptor or baroreceptor. The electrode may be mounted on a flexible lead and the placement of the electrode includes extending the electrode and lead through the venous system of the patient into the vascular space. The vascular space may be in the kidney, in the hilum of the kidney, an arcuate vein, an interlobar vein or a renal vein. The electrode may be placed in at least one of the interlobar and segmental veins that merge and exit as a single renal vein of the

kidney. Further, the electrode may be secured to a wall of a vein, wherein the wall includes the chemoreceptor or baroreceptor.

[0034] The stimulating may include applying an electrical current to activate afferent neural signaling. The stimulation may be applied by a stimulation device proximate to a renal pelvis of the patient. The artificial stimulation is provided by an implantable pulse generator (IPG) implanted in the patient.

[0035] The method may further include selecting the patient for the treatment by determining the patient is suffering from at least one of chronic heart failure (CHF), fluid retention and sodium retention.

[0036] An apparatus has been conceived to artificially stimulate urine production in a patient comprising: a stimulation device, e.g., IPG, generating a urine production stimulation signal; a probe insertable to be proximate to an urine collection space or a urine generation space of the patient, wherein the probe communicates with the stimulation device, and instructions stored in a non-transitory memory of the stimulation device, wherein the instructions are executed by a processor in the stimulation device to cause the stimulation device to generate the stimulation signal and transmit the signal to the probe. The stimulation signals may include electrical signals and the probe includes an electrode to transmit the electrical signals to the urine collection space or the urine generation

space. The probe may be insertable in a vein of a kidney and the kidney is in the urine generation space.

[0037]

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] A preferred embodiment and best mode of the invention is illustrated in the attached drawings where identical reference numerals indicate identical structure throughout the figures and where multiple instances of a reference numeral in a figure show the identical structure at another location to improve the clarity of the figures, and where:

[0039] Figure 1 is a schematic diagram of the patient treated with the renal stimulation device.

[0040] Figure 2 is a schematic diagram of the kidney with an implanted stimulation electrode.

[0041] Figure 3 is a schematic diagram of the kidney with alternative stimulation electrodes.

DETAILED DESCRIPTION OF THE INVENTION

[0042] FIGURE 1 shows a patient 101 being treated with an IPG 103 implanted in a pocket of the patient's chest, similar to where a cardiac pacemaker is conventionally implanted. The IPG 103 is connected to a renal lead 102 equipped with the distal stimulation electrode 104. The distal end electrode 104 is implanted in a suitable internal vein of the kidney 105. The lead is threaded

through the connected branches of venous system by a cardiologist under fluoroscopic guidance. The distal section of the lead may be positioned by the cardiologist in the renal veins, such as in the renal pelvis. There can be a plurality of electrodes (See Fig. 3) positioned along the length of the distal section of the lead. The plurality of leads may be used to increase the effects of the stimulation, as compared to a lead having a single electrode.

[0043] An example of an IPG 103 can be the CVRx Rheos System (Minneapolis, MN) for Baroreflex Activation Therapy® used for treatment of hypertension by stimulation of carotid sinus baroreceptors. Other commercially available IPGs are the Genesis IPG manufactured by the Advanced Neuromodulation Systems, Inc. (Plano, Tex.) and used to control pain, and the Medtronic, Inc. (Minneapolis, Minn.) Synergy ® Neurostimulation System. These and other similar state-of-the-art stimulators are fully implantable, battery powered, externally programmable and operate with a variety of implantable leads and electrodes adapted for long time implantation in the body. With some modifications, stimulators available from CVRx, Medtronic, Cyberonics and Advanced Neuromodulation Systems can be adapted for this invention. Alternatively, a manufacturing company with right expertise can develop a dedicated stimulator for the invention if the parameters of stimulation are defined.

[0044] In one embodiment of the invention, a sensing and pacing lead of a stimulator or pulse generator (that

can be an implantable IPG or a temporary lead that is externally driven) is placed in a vena cava and maneuvered into the renal vein which is adjacent or substantially in proximity to the renal pelvis of the kidney or the junction of renal pelvis and ureter or renal part of the ureter. It is understood that the vascular anatomy of the human kidney varies and in different cases different veins can be more suitable of the purpose of lead placement.

[0045] The disclosed embodiment illustrates an embodiment of the invention that combines a renal stimulation device and applying signals delivered by an IPG, which may be a cardiac pacemaker. Patients with CHF and hypertension often require cardiac pacing, ICD and CRT therapy. As these patients already have or are about to receive an implanted cardiac pacemaker, the pacemaker may generate signals for an additional pacing lead 106 positioned in the patient's heart chamber and a renal lead 102. The lead 102 may be a conventional atrial, ventricular or coronary vein lead. Further, ICD shocking coils can be added to the IPG such that the IPG can generate relatively large electrical shock signals that are to be applied to the renal lead 102. The control electronics and logic circuits in the pacemaker may also be configured to generate signals for the renal lead.

[0046] The renal lead 102 may be an insulated wire, or several wires, that are electrically connected to the IPG. The wire can include several insulated conductors from individual electrodes arranged on the distal end of the lead 102. The wires may be extremely flexible in

order to withstand the twisting and bending caused by body movement and respiration that affects kidneys and renal veins. The renal lead 102 may include a connector pin, lead body, fixation mechanism and electrode(s). The Connector Pin is the portion of the lead that is inserted into a connector block on the IPG. The Lead Body is an insulated metal wire that carries electrical energy from the pacemaker to the electrode(s) placed in the renal veins. The Fixation Mechanism is optional and may be a small mechanism near the tip of the lead that holds the lead electrodes to the muscle or other tissue proximate to the electrode(s). The electrode(s) may be a bare or otherwise exposed metal electric contact located at the end of the lead. The electrode delivers the electrical energy from the IPG to the renal tissue.

[0047] Medication can be added where a lead electrode touches the tissue. Regardless of whether a lead is placed on the nerve, muscle or connective tissue, the location where the lead touches the tissue naturally produces an inflammatory response. This response is similar to what is observed when the skin is scraped or cut: the area around the scrape is red and may result in a scar as your body repairs itself. By placing a steroid drug at the tip of the lead, some leads (such as for example the Medtronic CapSure pacing leads) reduce this inflammation. The steroid dose, typically 1 mg, is administered over a period of several weeks. The use of steroids can help extend stimulator battery life because less scar tissue means lower resistance (lead impedance) and thus less current required for the electrical pulse that stimulates the nerve.

[0048] FIGURE 2 is a schematic diagram of one embodiment of the invention showing relevant renal anatomy. Urine is collected in the pelvis 208 of the kidney 105 and drains into the ureter 209. Interlobular 206, arcuate 202 , interlobar 205, and segmental 203 and 204 veins successively merge and exit as a single renal vein 201. It is understood that in some patients there may be two renal veins.

[0049] Stimulation electrode 104 (typically cathode) is shown in one of the interlobar veins. Although an interlobar vein is a possible implantation site, renal anatomy is variable and other veins can be suitable candidates if they are located close to the renal pelvis that is the target of stimulation. Injection of radiocontrast material can be used to illuminate renal pelvis, where contrast tends to naturally accumulate, to assist placement of leads under fluoroscopic guidance.

[0050] Lead 102 is threaded through the venous system of the patient and electrically connects the electrode 104 to the IPG 103. In this embodiment the metal enclosure of the IPG 103 serves as the indifferent electrode to close the electric circuit and enable the flow of current between the cathode electrode 104 and the metal case of IPG 103 implanted under the patient's skin. This modality of stimulation is called monopolar stimulation. Monopolar stimulation has advantages or broader capture field and simplicity but other (such as bipolar or multipolar) stimulation modalities are often preferred since they limit the effect on untargeted

structures such as untargeted nerves in the parenchyma of the kidney.

[0051] FIGURE 3 shows an embodiment of the invention that implements a more complex stimulation scheme. First stimulation lead 102 and second stimulation lead 302 are inserted using conventional interventional techniques known to interventional cardiologists in two separate interlobar veins of the kidney. Preferably the leads are located on two different sides of the renal pelvis 208. Both leads are equipped with two or more stimulation electrodes 104, 301, 304 and 303. These electrodes are electrically connected to the electronics inside the IPG 103. The electronics is capable of using any combination of electrodes as cathodes and anodes selectively. Operator can use a remote programmer to perform operations known as current stirring to achieve best therapeutic effect. For example current can be applied between the electrodes 104 and 301 to achieve bipolar stimulation. Alternatively stimulation can be applied between electrodes 104 and 303 and 301 and 304 where electrodes 104 and 303 are cathodes. Alternatively any electrode or any number of electrodes can be used as cathodes with the case of the IPG 103 serving as anode for current return. It is understood that in the art of nerve stimulation multiple cathode electrodes are often beneficial since they allow engagement of more nerve fibers and nerve endings such as receptors. Although two electrodes per lead are shown, it is understood that modern technology allows placement of up to ten ring electrodes on the stimulation lead. Experts believe that

if necessary even more electrodes can be added to the lead design.

[0052] The onset and duration of the stimulation is under the control of logic embedded in the IPG. It is expected that the therapy will be dispensed with a fixed duration of pulses that can last several hours. Stimulation onset can be programmed to start at certain times of the day or by the remote control operated by the patient or physician. It should be clear that other strategies for setting the duration and timing of stimulation are within the scope of the invention.

[0053] The logic embedded in the IPG may be executable program instructions stored in a non-transitory memory of the IPG and executed by a processor in the IPG. The program instructions, when executed by the processor, cause the IPG to generate stimulation signals, e.g., electrical pulses, delivered to the renal lead 102 of the stimulation electrode 104 or the electrodes 104, 301, 303 and 304 of the stimulation leads 102 and 302. The instructions may be determine the timing, duration, shape and magnitude of the stimulation signals generated by the IPG and applied to the electrodes. The instructions may be selected or modified by a health care professional, e.g., a physician, or the patient using a wireless programming device which wirelessly communicates with the IPG.

[0054] Stimulation of afferent nerves to elicit physiologic response is generally known. For example, carotid sinus nerve stimulation is well known through

developments at Medtronic, Inc., of Minneapolis, Minn. In the 1960s to early 1970s, Medtronic produced and marketed two carotid sinus nerve stimulators for treatment of hypertension, the "Barostat," and angina, the "Angistat." These devices lowered blood pressure, decreased myocardial work and oxygen consumption, and thereby alleviated hypertension and angina. CVRx Inc. (Maple Grove, MN) is developing an implantable device to treat patients with high blood pressure based on stimulation of carotid sinus baroreceptors. This new device is called the Rheos™ Baroreflex Hypertension Therapy System. This system is made up of 3 major components: Rheos Implantable Pulse Generator, Rheos Carotid Sinus Leads, and Programmer.

[0055] The implantable pulse generator provides (IPG) control and delivery of the activation energy through the leads and electrode. The leads conduct activation energy from the implantable pulse generator to desired stimulation site.

[0056] The implantable pluse generator may be a computer programmed device that executes a program electronically stored in the device. The programmer system provides the ability to non-invasively communicate with the pulse generator. A surgical implant procedure is used to place the pulse generator under the skin for example in the low back. The electrodes are placed on the renal veins and the leads run under the skin and are connected to the pulse generator.

[0057] U.S. Patent 6,522,926 describes a method of intravascular and extravascular stimulation of baroreceptors to stimulate coronary artery baroreceptors. Devices for stimulation of baroreceptors are adaptable for use as stimulation of baroreceptors proximate to the urine generation and collection spaces of a patient.

[0058] The IPG may be programmed to generate short stimulation pulses in a range of 50 to 500 microseconds to stimulate receptors and afferent nerves. By way of example, the IPG may generate electrical stimulation signals of 50-150 microseconds at frequency in a range of 20 to 40 Hertz (such as 30 Hz). These electrical stimulations may be applied to the renal blood vessels of a kidney. Such stimulation is known from scientific literature to excite nerve tissue and generate nerve signals. The stimulation of the nerve tissue is expected to result in benefit to the patient primarily by causing secretion of sodium and water. The secretion of sodium and water should relieve a patient suffering from CHF, excess fluid or excess sodium.

[0059] Another example of an implantable stimulator IPG is the Vagus Nerve Stimulation (VNS™) with the Cyberonics NeuroCybernetic Prosthesis (NCP®) System used for treatment of epilepsy. It is manufactured by Cyberonics Inc. IPGs from different manufacturers are virtually identical across application areas, usually varying only in the patterns of stimulating voltage pulses, style or number of electrodes used, and the programmed parameters. The basic implantable system consists of a pacemaker-like titanium case enclosing the power source and

microcircuitry that are used to create and regulate the electrical impulses. An extension lead attached to this generator carries the electrical pulses to the electrode lead that is implanted or attached to the nerves or tissues to be stimulated.

[0060] The wires, leads and the stimulator can be fully implanted at the time of surgery. Alternatively wires or leads can cross the skin and connect to the signal generator outside of the body. An implantable stimulator can be implanted later during a separate surgery or the use of an external stimulator can be continued.

[0061] It is understood that the IPG can be also a cardiac pacemaker and can have more leads. It is expected that in future cardiac pacemakers will have even more leads connecting them to various parts of the anatomy. The leads can combine sensing and pacing electrodes as known and common in the field. The IPG is equipped with the programmable logic that enables it to sense signals, process the information, execute algorithms and send out electric signals to the leads.

[0062] The stimulation can be a pulse train or series of pulse bursts pulse burst that can, for example, consist of individual unipolar or biphasic (of alternating polarity) pulses. Pulse duration can be chosen from values between 0.05 to 0.5 milliseconds and delivered at frequency of 5 to 100 Hz, based on the existing general experience with nerve stimulation, to elicit baroreflex. It is preferred to apply pulses of lowest possible amplitude and duration that will ensure

the desired response without causing undesired activation of electrical or mechanical activity of the tissues.

[0063] The amount of energy required to cause these undesired stimulations varies. It may be desired to alter the stimulation pattern after the implantation. The amount of energy delivered an be altered by changing either the pulse duration, pulse amplitude or both. The energy required depends on the impedance of tissue between the electrode and the baroreceptors and on the energy losses in the interface. Based on the existing experience, pulses in the range of 0.25 to 5.0 V should be sufficient to transvenously stimulate receptors in the renal urinary space. It is desired to maintain amplitude below the level that can cause irregular heartbeats (arrhythmias) and muscle contractions, inadvertent heart muscle contraction, skeletal muscle twitching and pain. It is possible to include means to adjust these parameters after the implantation, using the stimulator's telemetry capability.

[0064] If the stimulation source is the constant current source, the stimulation intensity's range can be, for example, about 0.5 mA to 50 mA. Both monophasic and biphasic waveforms potentially can be used. The amplitude and frequency may vary burst to burst or pulse by pulse - within the same burst of pulses - for a single burst waveform. The burst duration can be in the range of 0.1 to 0.25 seconds, the ultimate limiting factor being the duration of the ventricular refractory period.

[0065] The IPG intelligence, e.g., a microprocessor housed in the implant, may adjust the stimulation burst shape, pulse shape, frequency of pulses and amplitude of pulses to set or control the blood pressure. The system may also adjust the rate of rise and fall of the pulse amplitude within the burst to create ramps of variable shape. The microprocessor or monitors the heart, such as by sensing electric signals from the heart, e.g., ECG signals, pressure signals from a pressure sensor or oxygen saturation signals from an oxygen saturation sensor in the heart or vascular system. The microprocessor executes an algorithm that determines the burst shape, pulse shape, frequency of pulses and/or amplitude of pulses based on the sensor input signals.

[0066] While the invention has been described in connection with what is presently considered to be the most practical and preferred embodiment, it is to be understood that the invention is not to be limited to the disclosed embodiment, but on the contrary, is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A method to treat a patient comprising:

artificially stimulating a chemoreceptor or a baroreceptor associated with a nerve in or proximate to the urine generation space or urine collection space of the patient;

wherein the artificial stimulation promotes the production of urine by the patient.

2. The method of claim 1 further comprising placement of an electrode in a vascular space of the patient and the stimulation includes applying energy through the electrode to the vascular space to stimulate the chemoreceptor or baroreceptor.

3. The method of claim 2 wherein the vascular space is proximate to a urine generation or collection area of the patient.

4. The method of claim 2 wherein the vascular space is proximate to the urine space of the kidney.

5. The method of claim 4 where said urine space is space is innervated by chemoreceptors and baroreceptors.

6. The method of claim 5 wherein the urine space is at the renal pelvis or ureter of the kidney.

7. The method of claim 2 wherein the electrode is mounted on a flexible lead and the placement of the

electrode includes extending the electrode and lead through the venous system of the patient into the vascular space.

8. The method of claims 2 or 8 wherein the vascular space is in the kidney.

9. The method of claim 8 wherein the vascular space is at least one of a hilum of the kidney, an arcuate vein, an interlobar vein and a renal vein.

10. The method of claim 2 wherein the placement step includes positioning the electrode in at least one of the the interlobar and segmental veins that merge and exit as a single renal vein of the kidney.

11. The method of claims 2 or 10 wherein the placement step includes securing the electrode to a wall of a vein, wherein the wall includes the chemoreceptor or baroreceptor.

12. The method of any of claims 1 to 11 wherien the step of stimulating includes applying an electrical current to activate afferent neural signaling

13. The method of any of claims 1 to 12 wherein the artificial stimulation includes electrical stimulation.

14. The method of any of claims 1 to 13 further comprising placing a stimulation device proximate to a renal pelvis of the patient and wherein the step of artificially stimulating includes activating the stimulation device.

15. The method of any of claims 1 to 14 further comprising selecting the patient for the treatment by determining the patient is suffering from at least one of chronic heart failure (CHF), fluid retention and sodium retention.

16. The method of any of claims 1 to 15 wherein the artificial stimulation is provided by an implantable pulse generator (IPG) implanted in the patient.

17. The method of any of claims 1 to 16 wherein the urine generation space includes a kidney of the patient.

18. An apparatus to artificially stimulate urine production in a patient comprising:

a stimulation device generating a urine production stimulation signal;

a probe insertable to be proximate to an urine collection space or a urine generation space of the patient, wherein the probe communicates with the stimulation device, and

instructions stored in a non-transitory memory of the stimulation device, wherein the instructions are executed by a processor in the stimulation device to cause the stimulation device to generate the stimulation signal and transmit the signal to the probe.

19. The apparatus of claim 18 wherein stimulation device is an implantable pulse generating device.

20. The apparatus of claim 18 or 19 wherein the stimulation signals include electrical signals and the probe includes an electrode to transmit the electrical signals to the urine collection space or the urine generation space.

21. The apparatus of claims 18 to 20 wherein the probe is insertable in a vein of a kidney and the kidney is in the urine generation space.

Figure 1

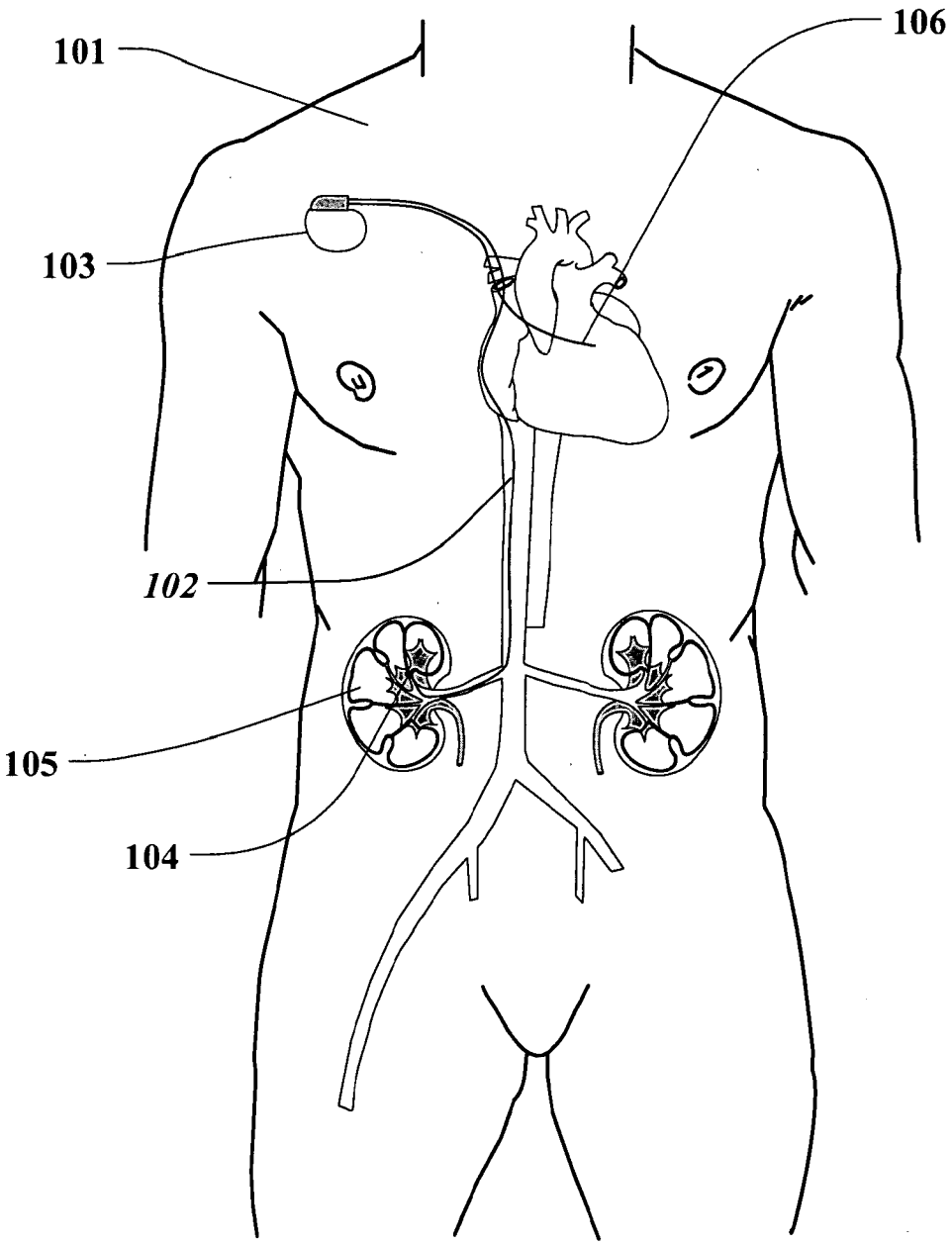


Figure 2

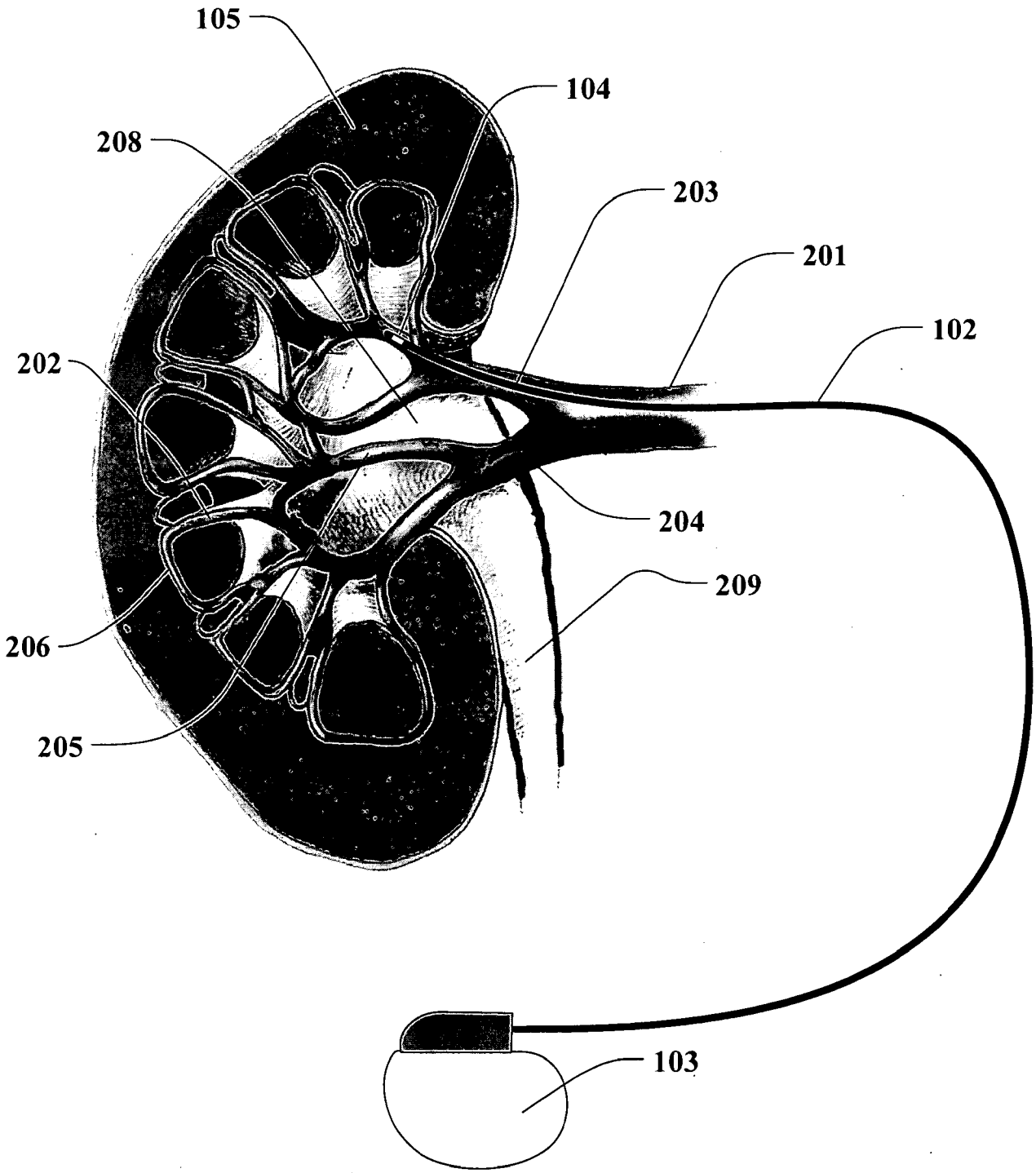
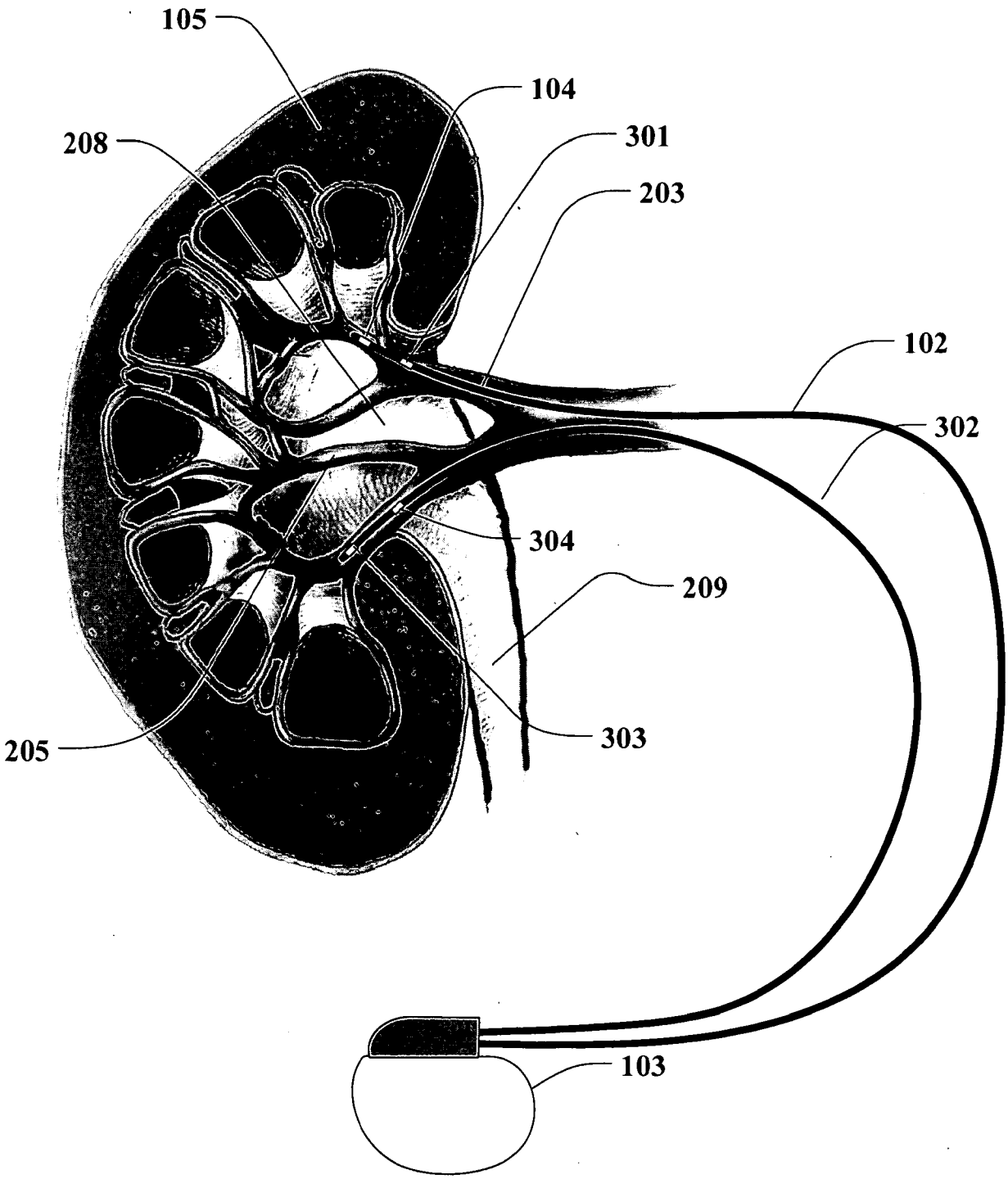


Figure 3



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/049477

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N1/36
ADD. A61N1/362

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61N

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/067360 A2 (BAR-YOSEPH GILL [IL]; POLSKY ALON [IL]; NEPHERA LTD) 17 June 2010 (2010-06-17) abstract page 40, lines 22-29; figures 4, 6, 7 page 45, lines 25-29 page 61, line 17 - page 66, line 17	18-21
X	US 2007/173899 A1 (LEVIN HOWARD R [US] ET AL) 26 July 2007 (2007-07-26) paragraphs [0092] - [0094], [0114]; figures 3, 11	18-21
X	US 2008/119907 A1 (STAHMANN JEFFREY E [US]) 22 May 2008 (2008-05-22) paragraphs [0029] - [0036], [0059] - [0061]; figure 2	18-21

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2011	01/12/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Smit, Jos

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/049477

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 804 905 A1 (ARDIAN INC [US]) 11 July 2007 (2007-07-11) paragraphs [0033], [0129] - [0142]; figure 20	18-21
X,P	US 2010/249865 A1 (ZHANG YUNLONG [US] ET AL) 30 September 2010 (2010-09-30)	18-21
X,P	US 2011/093026 A1 (WARIAR RAMESH [US] ET AL) 21 April 2011 (2011-04-21)	18-21
A	WO 2007/146834 A2 (ARDIAN INC [US]; DEMARAIS DENISE [US]) 21 December 2007 (2007-12-21)	18-21
A	US 2007/260281 A1 (HASTINGS ROGER [US] ET AL) 8 November 2007 (2007-11-08)	18-21

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2011/049477

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-17
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Claims Nos.: 1-17

Claims 1-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT - Method for treatment of the human or animal body by therapy. In particular, claims 1-17 comprise the step of artificially stimulating a chemoreceptor or a baroreceptor of a patient.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2011/049477

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010067360 A2	17-06-2010	CA 2746343 A1	17-06-2010
		EP 2376189 A2	19-10-2011
		WO 2010067360 A2	17-06-2010
US 2007173899 A1	26-07-2007	NONE	
US 2008119907 A1	22-05-2008	AU 2007325818 A1	05-06-2008
		EP 2121123 A1	25-11-2009
		JP 2010510025 A	02-04-2010
		US 2008119907 A1	22-05-2008
		WO 2008066732 A1	05-06-2008
EP 1804905 A1	11-07-2007	NONE	
US 2010249865 A1	30-09-2010	US 2010249865 A1	30-09-2010
		WO 2010111349 A1	30-09-2010
US 2011093026 A1	21-04-2011	US 2011093026 A1	21-04-2011
		WO 2011049716 A1	28-04-2011
WO 2007146834 A2	21-12-2007	CA 2655099 A1	21-12-2007
		CN 101489624 A	22-07-2009
		EP 2029223 A2	04-03-2009
		JP 2009539565 A	19-11-2009
		WO 2007146834 A2	21-12-2007
US 2007260281 A1	08-11-2007	CA 2651032 A1	15-11-2007
		EP 2015835 A2	21-01-2009
		JP 2009535188 A	01-10-2009
		US 2007260281 A1	08-11-2007
		WO 2007131015 A2	15-11-2007