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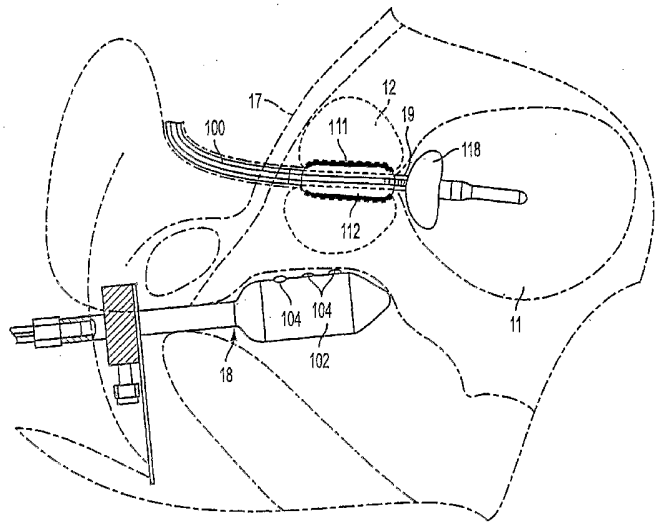
(54) Title: METHOD AND APPARATUS FOR TREATMENT OF TISSUE ADJACENT A BODILY CONDUIT WITH A COMPRESSION BALLOON



(57) Abstract: An apparatus for treatment of tissue within a body requiring thermotherapy includes a catheter to be inserted into a bodily conduit, an energy-emitting source disposed within the catheter, a compression balloon surrounding the energy-emitting source where the compression balloon has an inflated diameter that is greater than that of the bodily conduit in a relaxed state and an outside surface of the balloon is coated with one of gene modifiers and drug or medication, and means for activating the energy-emitting source to radiate energy to heat the drug-coated compression balloon and tissue to be treated whereby the heated drug-coated compression balloon effectively delivers the one of the gene modifiers and drug or medication to a target area of the diseased tissue. In addition, methods for using the above apparatus to treat diseased tissue are disclosed.

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METHOD AND APPARATUS FOR TREATMENT OF TISSUE ADJACENT A BODILY CONDUIT WITH A COMPRESSION BALLOON

Background of the Invention

1. Field of the Invention

The present invention generally relates to an apparatus and method for administering focused energy to a body using either a single energy applicator or multiple microwave applicators and compression of the body with a balloon filled with fluid, in order to treat visible tumors and microscopic malignant and benign cells in tissue with thermotherapy. In particular, the present invention relates to a transurethral catheter for thermal and warming therapy with compression of prostate tissue adjacent a urethra where the compression balloon is coated with a drug to create a drug-infused biological stent.

2. Description of the Prior Art

In order to treat the prostate with thermotherapy, it is necessary to heat a significant portion of the prostate gland while sparing healthy tissues in the prostate as well as the surrounding tissues including the urethral and rectal walls of a patient. The prostate gland encircles the urethra immediately below the bladder. The prostate, which is the most frequently diseased of all internal organs, is the site of a common affliction among older men, benign prostatic hyperplasia (BPH), acute prostatitis, as well as a more serious affliction, cancer. BPH is a nonmalignant, bilateral nodular tumorous expansion of prostate tissue occurring mainly in the transition zone of the prostate. Left untreated, BPH causes obstruction of the urethra that usually results in increased urinary frequency, urgency, incontinence, nocturia and slow or interrupted urinary stream.

Recent treatment of BPH includes transurethral microwave thermotherapy in which microwave energy is employed to elevate the temperature of tissue surrounding the prostatic urethra above about 45° C, thereby thermally damaging the tumorous prostate tissue. U.S. Patent Nos. 5,330,518 and 5,843,144 describe methods of ablating prostate tumorous tissue by transurethral thermotherapy, the subject matter of which is incorporated by reference. However, improvements still need to be made in this type of therapy to further maintain or enhance the patency of the urethra after the thermotherapy treatment. In particular, urine flow is not always improved despite ablation of the tumorous tissue causing

constriction of the urethra because edema produced by the transurethral thermotherapy treatment blocks the urethra passage resulting in patients treated by the above methods to be fitted with catheters for several days or weeks after the thermotherapy treatment.

U.S. Patent Nos. 5,007,437, 5,496,271 and 6,123,083 disclose transurethral catheters with a cooling balloon in addition to the anchoring or Foley balloon and are incorporated by reference herein. However, these patents circulate fluid, which acts as a coolant for removing heat preferentially from the non-prostatic tissue adjacent thereto, through the cooling balloons. The '083 patent further discloses the use of a thermotherapy catheter system taught by U.S. Patent No. 5,413,588 that employs chilled water between about 12°-15°C as the coolant. Chilled water significantly cools the urethra adjacent the cooling balloon. Likewise, the '271 patent describes a coolant as the fluid to keep the urethral wall temperatures cool. This chilling of the urethra does not aid in maintaining an opening within the heated urethra after the cooling balloon is removed, and reduces the therapeutic effect in the tissue immediately adjacent the urethral wall.

Another known alternative to thermal surgery, as described in U.S. Patent No. 5,499,994, is to insert a dilation balloon in the urethra and to expand the dilation balloon to compress the obstructed urethra. However, the expansion of the dilation balloon occurs over 24 hours and the patient still is not cured of the diseased prostate. Further, the expansion can cause adverse effects (e.g., tearing of the urethral walls). U.S. Patent No. 6,102,929 describes a post-operative procedure where the prostate tissue is expanded after the surgical procedure to enlarge the urethra to enable a patient to void comfortably. This expansion requires insertion of another device and requires the device to remain in the patient for a day or more.

In view of the fact that post-treatment catheters or other devices are still considered necessary by the medical community, further improvements are needed in thermotherapy to avoid the obstruction caused by edema and to maintain and enhance the opening of the urethra.

Summary of the Invention

The present invention is directed to an apparatus and a method for thermally treating tissue adjacent a bodily conduit, such as a urethra, while

preventing obstructions of the bodily conduit due to edema and delivering a drug or medicine to a targeted region. To achieve this object, the instant invention employs a catheter with an energy-emitting source and a compression balloon surrounding the energy-emitting source which is inflated by fluid that compresses, preps, and allows better energy coupling to the bodily conduit walls adjacent the compression balloon. The fluid inflating the compression balloon is maintained under pressure after the compression balloon is inflated to the desired diameter and, in a preferred embodiment, is not circulated so that heat is not carried away from the bodily conduit walls thereby improving the formation of the biological stent and sustaining the formation of the biological stent, especially in the area and tissue immediately adjacent to the compression balloon.

The compression balloon is coated with a drug or medicine or gene modifier, designed to aid in cancer treatment, cure infectious diseases, relieve pain, and/or to cause a stronger biological stent thus limiting the potential for restenosis. In conjunction with drug or medicine therapy, or alone, gene modifiers may coat the compression balloon for gene therapy. The heat from microwave, radio frequency, ultrasound or a like energy-emitting source, and/or light from any light emitting source, such as a laser, that is generated immediately adjacent to the coated compression balloon allow the gene modifier, drug or medicine to be effectively released, absorbed, and/ or activated into the target area. The compression balloon may be coated with any of the standard cytotoxic drugs so that may be released adjacent to the target area being treated for cancer, for example. If benign conditions surrounding a bodily conduit are being treated, antibiotics or other drugs that combat one of the infectious diseases or a benign condition, such as prostititus, may coat the compression balloon. Depending upon the treatment, a general pain relief medication may be coated on the outside of the compression balloon, alone or in combination with another drug or gene modifier for a specific disease that is readily accessible via a bodily conduit.

While the instant invention will be described with respect to a preferred embodiment where the bodily conduit is the urethra and prostatic tissue is to be treated by thermotherapy, the combination of compression, an energy source such as, microwaves, radio frequency, ultrasound, heated fluid or laser, and gene or drug therapy can be used to achieve the above goal in other bodily conduits or

intracavity sites including, but not limited to, cardiovascular, esophageal, nasal pharynx, and rectal cavities or organs accessible by body conduits such as lung, liver, ovaries, and etc. That is, it is a goal of the instant invention to open up bodily conduits so that the normal function of that conduit is not hampered and to treat both diseased and/or benign sites, as well as the relief of pain, by delivering applicable gene modifiers, drugs or medication to the targeted area. The power to the energy-emitting source for heat or light, and diameters and shaping of the compression balloon and catheter will vary depending upon the tissue or bodily conduit or organ to be treated and the coated material on the compression balloon.

Unlike known techniques that circulate fluid to remove heat from the urethral walls, the instant invention employs, in a preferred embodiment, low energy to heat tissue adjacent the bodily conduit walls and compression so that tissue further from the bodily conduit walls is easier to heat using a lower energy while still maintaining the temperature of the urethra above 30°C and avoiding overheating of the urethra. The Applicant believes that the urethral wall or targeted area should not be cooled by a circulating fluid as a biological stent or molded opening would not be formed effectively with cooled circulation fluid (i.e., fluid circulated into a patient in the range of 25°C - 30°C or lower). The lack of a circulating fluid is advantageous in that a lower energy may be used to therapeutically heat the prostate or other treatment site, as the heat is not drawn away from the treatment site when the fluid does not circulate or remains in the inflated compression balloon. Additionally, the lack of the circulating fluid does not detract from the heating and/activating or releasing of the gene modifier, drug and/or medicine disposed in the coated material on the compression balloon. While no circulation of the water is the preferred embodiment, a circulation of non-cooled fluid may also be used.

According to the exemplary invention, a select volume of collagen-containing tissue surrounding the urethra or an area immediately adjacent thereto is heated to a temperature of greater than 43 degrees C for a time sufficient to substantially destroy or modify the select volume of tissue. Prior to energizing the energy-emitting source, a preshaped coated compression balloon is filled with fluid to expand the urethral walls compressing the prostate thereby reducing blood flow in the prostate surrounding the urethral walls and as a result, the energy-

absorptive heating is more efficient in the region of constricted blood supply. The compression will also enlarge the surface area of the walls of the bodily conduit so that more drug is delivered efficiently per tissue area. In addition, compression of the area via the compression balloon could also lessen the distance from the surface of the balloon to the total targeted tissue thereby increasing the treatment zone if desired. The compression, together with the lack of a circulating fluid, theoretically enables a lower amount of energy than previously thought possible to heat the prostatic tissue or other tissues to therapeutic temperatures while causing the proteins of the urethral walls to become denatured or unraveled in the presence of the heat emitted from the energy-emitting source. That is, energy-emitting source 110 may be energized to a low power in the range of 0 watts to approximately 20 watts. Alternatively, the energy-emitting source alone may radiate heated fluid, such as water to provide the needed heat, or may be another energy source used in conjunction with heated fluid. As a result, it is envisioned that this preferred embodiment, in combination with a coated balloon, may provide a more permanent stent or a more effective treatment than thought possible with a lower treatment or release temperature, such as greater than or equal to 38 degrees C.

The fluid, which expands the compression balloon and remains inside the inflated balloon, does not detract from the denaturing process which forms the biological stent, as the fluid does not carry away heat from the urethral walls. In one aspect of this invention, the non-circulating fluid together with the material of the inflated balloon provides the ability to form a more lasting and efficient biological stent to the urethral wall or closed vesicle as the result of the heat, compression and the coated material. This invention addresses a new, improved and more effective method of thermotherapy by uniquely coating the compression balloon with a drug, gene therapy compound or other medicament, compressing the coated balloon with circulating or non-circulating fluid and activating the drug, gene therapy compound or other medicament of the coated material via either heat or light energy sources.

A second aspect of this invention is directed towards a targeted direct therapeutic delivery system with drug therapy and/or gene therapy compounds to treat the affected area. The non-circulating fluid is in direct contact with the

antenna or other energy-emitting source that emits the lower energy so that it provides a better coupling of the emitted lower energy to produce heat in the compressed prostatic tissues or other tissues. This is referred to as direct coupling technology as the non-circulating fluid conducts the energy emitted from the antenna or other source to the compressed prostatic tissues. Certain applications of the low energy-emitting apparatus according to the invention are envisioned where the inflation fluid would not be in direct contact with the antenna or other source and still would provide the necessary heat or light to therapeutically treat the diseased tissue. As a result of the fluid in the compression balloon coupling the low emitted energy to the prostate and urethra, air pockets in the balloon are minimized and thus, "hot spots", which occur as a result of the air pockets, are less of a problem thereby resulting in better patient tolerance to the heat treatment and better uniform heating to the entire prostate.

The heating of the proteins of the urethral walls to more than 43°C causes the proteins to become denatured or unraveled. The denaturing allows the urethral walls to conform to the expanded shape of the urethra created by the compression balloon and reduces the elasticity of the urethral walls so that a stent reinforcement period following the heating naturally solidifies the expanded shape resulting in a biological stent. That is, the expanded bodily conduit walls do not return to their previous shape after the compression balloon is deflated and removed thereby achieving a natural opening in the bodily conduit. The addition of a cytotoxic drug, for example, will aid to the ability in synergy with the heat or light to cause the biological stent, and/or cause activation and/or delivery of the desired drug or compound to also treat the affected tissue.

During the applications phase, a physical pulsing via compression and decompression of the compression balloon may be perform at various specified periods throughout the treatment to allow the rush of blood in and out of the compressed tissue. This physical or mechanical manipulation of the coated compression balloon also may be used in situations calling for a drug and/or a gene therapy compound so that the pulsing activates/ releases the compound material applied to a patient via an intravenous or injection method so that the compound, which is dependent on heat or light for activation or release, is delivered to the targeted tissue. This mechanical compression and decompression

can also aid in the mechanical fixation of the drugs and or gene therapy compounds to the targeted protein and/or DNA tissue. It is noted that this mechanical method fixation may cause the binding of the drugs and/or gene therapy compound disposed in the coated balloon to the protein and/or DNA. The resultant binding of the drug or gene therapy compound to the targeted protein and/or DNA is a major new innovation to ensure that the desired compound is effectively fixated or delivered to the targeted tissue.

According to a preferred embodiment of the invention, a stent reinforcement period of approximately up to 10 minutes or less follows the heating step. The stent reinforcement period maintains the pressure of the compression balloon after power to the energy-emitting source has been turned off so that a solidified expanded urethra is achieved minutes after thermotherapy and a catheter or other device is not necessary. The compression balloon during this reinforcement period also fixates the released drugs and/or gene therapy compounds within compressed tissue as a result of reduced blood flow.

Due to the fact that fluid is not circulated inside the balloon, the compression balloon may be made from either a compliant material, such as silicone material, or a non-compliant material, such as PET and still be easy to expand or be inflated by the fluid. In a preferred embodiment, the compression balloon is generally cylindrical with a sloped area on both sides of the compression balloon and is symmetrical along the length of the diameter according to a preferred embodiment. The position of the energy-emitting source in the preferred embodiment may be fixed. However, the compression balloon may be of any shape to create a desired mold or stent within a bodily conduit or urethra and may be asymmetrical along the length of the catheter. The use of a non-compliant material, such as PET, enables unique fixed expansion shapes to be formed when the balloon is inflated.

The compression balloon needs to maintain a pressure of about 5-25 psi against the urethral wall or other targeted tissue area along the length of the catheter with the preferred level of pressure being about 10-25 psi. Depending upon the size and shape of the compression balloon, the volume of fluid necessary to inflate or expand the balloon to its desired shape varies so that the appropriate amount of pressure is achieved in the inflated compression balloon. The

compression balloon may have a variable diameter along the length of the catheter and may be formed from a single balloon or multiple balloons.

The material of the compression balloon touching the urethral wall is very thin in contrast to the thickness of a traditional low temperature catheter, which is generally 5 times the thickness of the compression balloon material or up to 1 cm. A preferred thickness of the material of the inflated compression balloon touching the urethral wall could be less than approximately 2mm, and as a result of the compression, the transition zone between the fluid coupling and the prostatic tissue is minimized. In addition, the temperature of the fluid used to inflate the compression balloon is predetermined depending upon the application and varies over a range from about 0° to 50° C. This represents the starting temperature of the non-circulating fluid used to compress the balloon to the desired size and hardness. The fluid could be low lose or high lose depending on if the energy is to be either absorbed by the fluid or transparent through the fluid. The fluid may be heated to diffuse the energy uniformly in the bodily conduit or organ, or if a transparent fluid is employed, the heat generated by the energy-emitting source would heat the coated balloon directly and/or adjacent tissue. Again, the starting temperature of the fluid for inflating the compression balloon is dependent on the specific release and/or activation properties of the drugs and/or compounds disposed in the coated material. The beginning temperature of this fluid (before heating by the energy-emitting source) is envisioned to be from about 0 degrees to 50 degrees C.

According to the invention, a standard Foley bladder location balloon is disposed at the end of the catheter and a distal end of the compression balloon is mounted close to the neck of the Foley bladder balloon so that the distal end of the compression balloon is no greater than 2 cm away from the neck in the applications heating the prostate. For other sites, other forms of physical structures or imaging techniques are envisioned to provide direct placement to the delivery site. However, for example, in a preferred embodiment heating the prostate, the distal end of the compression balloon would be mounted within 1 cm of the bladder neck.

The energy-emitting source, such as a microwave antenna, may be mounted within the compression balloon fixedly or movably. If the energy-

emitting source is movable, the maximum heating field may be moved forward or backward relative to the compression balloon. That is, the position of the energy-emitting portion can vary to optimize the heating of tissue for a particular therapy. The preferred location and movement, if any, of the energy-emitting source would depend on the size and shape of the compression balloon and the type of coated material or adjacent tissue to be treated. For example, a movable energy-emitting source (e.g., microwave antenna) could be used with compression balloons having a longer length. Alternatively, the energy-emitting source may be removable from one compression balloon and used with another compression balloon of differing length and diameter. This would provide a versatile apparatus, where the antenna can be used a multiple of times with different compression balloons. This feature together with less equipment needed to produce the thermocompression apparatus according to the invention makes the catheter apparatus easier and less expensive to manufacture.

Brief Description of the Drawings

These and other features and advantages of the invention will be further understood from the following detailed description of the preferred embodiment with reference to the accompanying drawings in which:

FIG. 1 is a vertical sectional view of a male pelvic region showing urinary organs affected by benign prostatic hyperplasia and an inserted catheter according to the invention with inflated compression and Foley balloons;

FIG. 2 is an enlarged portion of FIG. 1;

FIG. 3 is a plan view of the urethral catheter of the present invention;

FIG. 3a is a cross-sectional view of the urethral catheter of FIG. 3 taken along line a-a;

FIG. 4 illustrates the inflation of the compression balloon;

FIGS. 5a and 5b are schematic, cross-sectional views of a urethra showing the compression balloon in the uninflated and inflated states, respectively to illustrate the expansion of the urethral walls and prostate according to the invention; and

FIG. 6 is a schematic cross-sectional view of the urethra illustrating an inflated, asymmetric compression balloon according to the invention.

Detailed Description of the Invention

The present invention is directed to a device and a method for thermally treating tissue adjacent a bodily conduit, such as a urethra, while preventing obstructions of the bodily conduit due to edema and delivering a drug or medicine to a targeted region of the tissue to be treated. Examples and alternatives of the method and apparatus according to the present invention will be described and illustrated below after a brief discussion of collagen.

Collagen is a principal component of connective tissue and fibromuscular tissues. Collagen also has known properties such as plastic remodeling when subjected to high temperatures (e.g. about 60° C to 70° C). Specific remodeling temperatures are generally more exactly identifiable for a type and age of tissue in a particular location of the body. In the embodiment according to the invention, Applicant theorizes that the remodeling temperature is lowered as a result of the bodily conduit being reshaped and the tissue adjacent to the conduit being compressed to significantly reduce the blood flow. General principles of collagen and collagen reactivity to thermal treatment are known in the art and are described in the following articles, amongst others: Gustavson, The Chemistry and Reactivity of Collagen, Academic Press, Inc., New York, 1956, specifically including p.p. 211-220; Agah et. al., Rate Process Model For Arferial Tissue Thermal Damage: Implications on Vessel Photocoagulation, Lasers in Surgery and Medicine, 15:176-184 (1994); Trembly et. al., Combined Microwave Heating and Surface Cooling of the Cornea, IEEE Transactions On Biomedical Engineering, Vol. 38, No. 1, 1991, Stringer et. al., Shrinkage Temperature of Eye Collagen, Nature, No. 4965, pp. 1307.

Of specific interest, collagen is found in fibromuscular tissue and other interstitial connective tissue forming part of or surrounding various ducts in the body. For example, the urethra is a duct in the lower urinary tract that passes fluid from the bladder, through the prostate, and out of the body via the penis. Proximal portions of the prostatic urethra are surrounded by a ring of fibromuscular tissue and by interstitial tissue in the prostate, both types of tissue including collagen. Manipulation of this collagen in the method of the present invention is used to remedy various dysfunctions of the prostate and/or urethra, such as benign prostatic hyperplasia. Accordingly, the urethra is one example of a duct in the

body having collagen rich surrounding tissue and a diameter that must be carefully controlled to maintain normal function, which is addressed by the method of the present invention.

A method and apparatus for thermally treating tissue adjacent a bodily conduit, such as an urethra, according to the invention, delivers a gene compound or drug or medicine to a targeted tissue area and maintains the expanded diameter of the urethra into a selected urethral shape after microwave thermotherapy treatment for benign prostatic hyperplasia to restore patency to the urethra , as illustrated in Figures. 1-6. Figure 1 is a vertical sectional view of a male pelvic region showing the effect of benign prostatic hyperplasia (BPH) on the urinary organs. Urethra 10 is a duct leading from bladder 11, through prostate 12 and out orifice 13 of penis end 14. Benign tumorous tissue growth within prostate 12 around urethra 10 causes constriction of urethra 10, which interrupts the flow of urine from bladder 11 to orifice 13. The tumorous tissue of prostate 12, which encroaches urethra 10 and causes the constriction (not shown, as compression balloon 112 is inflated), can be effectively removed by heating and necrosing the encroaching tumorous tissue. This is accomplished, according to the invention, by inserting an energy-emitting source containing catheter 100 into a bodily conduit (e.g., urethra) so that the energy-emitting source 110 is positioned in a region of an organ (e.g., prostate) in order to radiate energy to heat the tissue to be treated adjacent the bodily conduit. Ideally, with the present invention, periurethral tumorous tissue of prostate 12 anterior and lateral to urethra 10 is heated and necrosed while avoiding unnecessary and undesirous damage to urethra 10 and to adjacent healthy tissues, such as external sphincter 17, rectum 18, and bladder neck 19.

Figure 2 is an enlarged sectional view of Figure 1 illustrating specific anatomical features including urethra 10 and bladder 11 and showing catheter 100 with an inflated compression balloon 112 and an inflated Foley or anchoring balloon 118. As shown on Figures 1-4, the instant invention employs a catheter 100 with an energy-emitting source 110 and a compression balloon 112 surrounding the energy-emitting portion of source 110, which is filled with a warmed fluid to inflate the same under pressure and to maintain the warmth of the urethra walls adjacent the compression balloon. Compression balloon 112 may be

coated with a material 111 including at least one gene modifier (gene therapy compound) and drug or medicine that is designed to aid in cancer treatment, cure infectious diseases, relieve pain and/or cause a stronger biological stent. A selective heating of benign tumorous tissue in prostate 12 (transurethral thermotherapy) is made possible by energy-emitting-containing catheter 100 of the present invention. The energy-emitting source 110 may produce heat from microwaves, radio frequency, ultrasound or like energy. The heat from energy-emitting source 110 and/or light from any light-emitting source, such as a laser, can activate and release the at least one gene modifier and drug or medication into the target tissue area. Thus, the heat of the energy-emitting source and/or light of a light-emitting source heats the adjacent tissue to a temperature to ablate diseased tissue and acts in synergy with coated material 111 to activate and release the gene modifier, drug or medication so that gene or drug is absorbed into the targeted tissue. A rectal probe 102 with a number of sensors is inserted into rectum 18 and measures the amount of heat generated by the absorbed emitted energy at the rectal wall.

As shown in Figure 2, three sensors 104 are mounted on probe 102. The sensors are preferably integrally mounted at differing radial locations on the probe and spaced approximately 1 centimeter from one another. Foley balloon 118 is inserted into a patient's bladder so that the proximal end of the compression balloon is located at the patient's prostate immediately distal of the bladder neck. The length of compression balloon 112 varies depending upon the size of a patient's bladder. A typical length of the compression balloon would be about 40 millimeters and the length can range from 25 to 60 millimeters. The material 111 with at least one of a gene modifier, drug or medication coating compression balloon 112 may cover the entire length of the compression balloon to release a gene modifier, drug or medication to the adjacent tissue. In other embodiments, the coating of compression balloon 112 with material 111 may be positioned on a portion of the compression balloon so that the gene modifier, drug or medication is released to the desired target area. The compression balloon may be coated with any of the standard cytotoxic drugs used for the treatment of cancer, an antibiotic to treat a benign condition or an infectious disease, and/or pain medication used for the general relief of pain. For example, in order to treat benign prostate

hyperplasia, the compression balloon 112 may be coated with a material 111 with one of Proscar, Hytrin, Flowmax, Cadora, or a drug that improves the symptoms or cures prostatic diseases. Depending upon the treatment, a general pain relief medication may be coated on the outside of the compression balloon, alone or in combination with another drug or gene modifier for a specific disease that is readily accessible via a bodily conduit.

Catheter 100 would be around 18 French (French is a measurement equal to .333 mm or .013 inch). Since the average diameter of a male adult human is about 22 French, the deflated compression balloon 112 that surrounds the catheter would add approximately 2 French so that diameter of catheter 100 and balloon 112 would be less than that of the patient's urethra for ease of insertion and less pain for the patient. Multi-lumen shaft 100 and associated molded parts are preferably extruded of a medical grade polymer sold by Concept Polymer Incorporated under the trademark C-Flex™. The compression balloon is preferably molded from a medical grade polyester material sold by Allied under the trademark PET™, that has a limit of stretch based on its initial maximum molded shape. Alternative materials can include a silicone material manufactured by Dow Corning Inc. under the trade name Silastic R ™ type Q7-4850 and type Q7-4765, for the shaft extrusion and the molded manifold, and Elastosil type LR3003/30Us for the anchoring balloon 118. The material of catheter 100 preferably has a Shore D hardness between 50D and 80D.

After full insertion (i.e., the deflated Foley balloon reaching into the patient's bladder), a fluid (sterile water) is pumped through the Foley inflation valve 113 thereby to inflate Foley balloon 118 and hold the catheter within the patient's urethra. Inflation valve 113 maintains fluid in the Foley balloon with the desired pressure so that the catheter is anchored in the patient. However, the catheter is still capable of limited longitudinal movement with respect to the urethra. After Foley balloon 118 has been inflated, a warmed fluid, preferably a low-loss liquid (e.g., deionized or sterile water), is slowly pumped through the one or more catheter inflation/circulation lumens 120 (Figure 3a) into the prostate compression balloon 112 to inflate the same expanding the urethral walls and maintaining the temperature of the urethral walls above 30°C. The diameter of the inflated compression balloon would be approximately in the range of 25 - 60

French, preferably in the range of about 40-60 French. Approximately 20-30cc of fluid should fill compression balloon 112 so that its outer surface expands the bodily conduit. The warmed fluid used to inflate compression balloon 112 is preferably a minimally energy absorptive solution which conducts microwaves to the tissue to be heated more efficiently. Thus, the fluid which fills compression balloon 112 serves to compress and prep the bodily conduit and adjacent tissue surrounding the bodily conduit prior to energizing the energy-emitting source 110. In addition, the fluid provides means to couple the emitted energy to the bodily conduit walls adjacent the compression balloon to provide a more efficient heating of the tissue. Depending upon the application and the gene modifier and/or drug to be released from the coated material 111, the fluid may be a high-lose liquid or a low-lose liquid to either diffuse the heat or light or act transparent so that the heat or light is effectively delivered to release and/or activate the coated material in an efficient and uniform manner.

A typical implementation of a catheter according to the invention is shown in Figure 3. Foley balloon 118 is deflated in this Figure. As shown on the left-hand side of the Figure, a Foley inflation valve 113, a warmed, sterile-fluid intake 115a and a sterile-fluid outtake 115b are provided to receive fluid. The sterile-fluid intake and outtake 115a, 115b enable the circulation of sterile fluid in the compression balloon, if desired, during thermotherapy and maintain the desired pressure to achieve the specific fluid flow pattern and distribution of fluid within the balloon. In an embodiment where circulation of the fluid is not desired, fluid may enter fluid intake 115a and valves known to those skilled in the art and may maintain the desired pressure of the fluid filled in the compression balloon. After the stent reinforcement period described below, the fluid may be removed from the compression balloon via outtake 115b. A central lumen 126 receives the energy-emitting source 110, which may be an antenna in the form of a coaxial cable. As shown in Figure 3a, protrusions 127 are formed in central channel 126 in order to keep energy-emitting source 110 centralized inside catheter 100 and to create channels for the removal of the filled fluid. Protrusions 127 enable the distance between the energy-emitting source and outside wall of the catheter to remain constant thereby ensuring a consistent heating pattern at the energy-emitting portion of the source 110. The energy emitting source 110 is directed

coupled to the low-loss liquid to maximize emitted power and to cool the shaft of the energy-emitted source.

As shown in Figure 4, orifices 122, 124 are employed in one or more of catheter lumens 120 on both sides of compression balloon 112 so that warmed fluid can be pumped through lumens 120 into compression balloon 112 at one end to fill the same and pumped out at the other end to remove the fluid. In one embodiment, the warmed water may be circulated into lumens 120, pumped into compression balloon 112 to fill the same and exit through central orifice 126, which holds an energy-emitting source 110, such as a microwave antenna to flow out of catheter 100 external of a patient. The placement and diameter of the orifices 122, 124 enables sufficient fluid flow, if desired, and pressure of about 10-25 psi to be maintained in compression balloon 112 during the entire thermotherapy treatment. In a preferred embodiment, an outtake-fluid-side channel is fitted with a restrictive orifice 116 to control the compression balloon pressure so that the compression balloon may be filled with the incoming fluid under the appropriate pressure. If no flow of the fluid pumped into compression balloon 112 is desired, a valve of the restrictive orifice 116 may act as a stopper plug, or, if some fluid flow is desired, the valve may be opened to determine the amount of fluid flow. The restrictive orifice 116, in an alternative embodiment, can be located immediately external to the catheter in the connective tubing (e.g., 115a, 115b) used to connect the catheter to the external fluid warming pumping system (Figure 3b). The pressurization of the warmed fluid filled in the compression balloon 112 is such that air pockets are reduced in the inflated balloon. Accordingly, air pockets in the compression balloon, which may result in "hot spots" causing burns on the urethral walls, are avoided. This results in the desired compression of the prostatic urethral tissue, without burning the urethral walls, which is maintained during and after the thermotherapy treatment.

It is desired to heat the diseased prostate tissue to a therapeutic temperature (greater than about 43°C) while maintaining the temperature of the non-prostate tissue lining the urethra above 30°C. The non-prostate tissue includes the urethral wall and adjacent tissue and is disposed between the energy-emitting source 110 and prostatic tissue 12. According to the invention, the energy-emitting source 110 is energized or activated to heat a portion of the tissue to be treated that

surrounds the bodily conduit to a temperature of about 43°C or lower depending upon the coated balloon and treatment to be performed. The tissue is heated to the determined temperature for a time sufficient to destroy a heated portion of the tissue to be treated via the heat generated by the energy-emitting source. The energy-emitting portion 110a of source 110 is disposed in catheter 100 so that it rests within the compression balloon 112. Energy-emitting portion 110a preferably emits an irradiating microwave field, which varies as an inverse function (e.g., inverse square) of the distance between the energy-emitting portion 110a (e.g., microwave antenna) and the tissue to be heated. Consequently, the non-prostatic tissue of urethral wall 10, which is closer to energy-emitting portion 110a than prostatic tissue 12, would be heated to a higher temperature than the prostatic tissue to be treated. Likewise, proximate prostatic tissue would be heated to a higher temperature than more distal prostatic tissue. Upon completion of the time sufficient to destroy a diseased or targeted tissue area, the generation of heat by energy-emitting source 110 is terminated.

U.S. Patent No. 5,007,437 to Sterzer discloses the use of a balloon to compress the prostate tissue and to move the urethral wall away from the microwave antenna, which produces the heat. This method reduced the microwave field intensity and the resultant heat produced at the urethral wall by moving the urethral wall further from the heat-producing antenna. However, Sterzer also employed a circulating fluid to continuously cool the urethral wall while the urethral wall was inflated. Applicant recognized that this circulating coolant was preventing the urethral wall and adjacent prostatic tissue from reaching a temperature sufficient to denature the protein or enable plastic remodeling. As a result, Applicant theorized that the use of an inflated prostate compression balloon together with the circulation of warmed fluid would mitigate the denaturing problem, as shown in Figures 5a and 5b.

Figures 5a and 5b respectively show a cross-section of a deflated compression balloon and a cross-section of an inflated compression balloon. The radial distances from energy-emitting source 110, for example a microwave antenna, to distal prostatic tissue 202 and proximal tissue 204, which includes the urethral wall and adjacent non-prostatic tissue, when compression balloon 112 is deflated are smaller than those distances are when compression balloon 112 is

inflated. As shown, inflated compression balloon 112 forms a symmetrical toroid extending around the entire circumference of the urethral catheter. Specifically, the radial distance R_{1b} from energy-emitting source 110 to the inner circumference of proximal tissue 204 with inflated compression balloon 112 is significantly larger than the corresponding radial distance R_{1a} with deflated compression balloon 112. Similarly, the radius R_{2b} to the inner circumference of prostate tissue 202 with inflated compression balloon 112 is significantly larger than the corresponding radial distance R_{2a} with deflated compression balloon 112. Because prostate tissue is soft and compressible, the difference between the outer and inner radii R_{3b} and R_{2b} of prostate tissue 202 with inflated compression balloon 112 is substantially reduced with respect to the corresponding difference between radii R_{3a} and R_{2a} with deflated compression balloon 112.

Consequently, the inflated compression balloon causes the prostate 12 to be compressed from the urethral wall thereby decreasing the thickness of the tissue between the compressed wall of the urethra and the margins of the prostate capsule. Consequently, the distance between the medicated coating 111 of compression balloon 112 and the targeted tissue area may be reduced thereby increasing the treatment zone. The more distal tissue 202 is not as compressed as the tissue more proximal to the urethra 204. Since the actual tissue thickness through which the energy emitted by the energy-emitting source 110 is less, the energy deposited is more evenly distributed throughout the entire prostate capsule. This makes it possible to heat the prostatic tissue more evenly and to higher therapeutic temperatures without heating any part of the non-prostatic tissue beyond its maximum safe temperature. This can be achieved with lower energy levels being emitted from the energy-emitting source 110 than previously thought possible. In addition, the compression of the tissue surrounding the inflated compression balloon in a bodily conduit enlarges the surface area that the coated compression balloon come into contact with thereby efficiently delivering more gene or drug per tissue area.

At the same time the inflated compression balloon 112 constricts the blood flow in the compressed prostate so that the irradiated heat is not carried away by the natural blood flow and thus makes this tissue more susceptible to heating by the emitted energy. Since the overall tissue thickness is reduced, the amount of

energy required to effectively heat the prostate tissue 204 to a therapeutic temperature is reduced. Conversely, in typical non-compressed therapies, the amount of energy required to raise the temperature of the more distal prostatic tissue 202, that may be adjacent to the rectal wall to a maximize safe temperature of 41°C will be significantly higher than that required according to the invention. Thus, it is possible to heat the prostatic tissue more evenly and to higher temperatures without heating any part of the non-prostatic tissue beyond its safe maximum temperature.

In order to heat proximal tissue 204 above a predetermined collagen transition temperature during a microwave thermotherapy treatment, warmed fluid above 30°C, preferably in the range of about 31°C - 60°C, fills compression balloon 112, in contrast to a coolant. As a result, the urethral wall and adjacent tissue are maintained at a temperature so that they are sufficiently denatured and a natural biological stent can be formed in the bodily conduit and adjacent tissue after the thermotherapy treatment.

The warming of the urethral wall above 30°C and maintaining of this temperature serves to denature the proteins of the urethral wall; but does not heat the urethral wall beyond a maximum safe temperature. This denaturing allows the urethral walls to conform to the expanded shape of the urethra created by compression balloon 112 and reduces the elasticity of the urethral walls so that a stent reinforcement period following the heating of the thermotherapy treatment naturally solidifies the expanded shape resulting in a biological stent. That is, the expanded urethral walls do not return to their previous shape after the compression balloon is deflated and removed thereby achieving a natural opening in the a bodily conduit, such as a urethra.

The stent reinforcement period that follows the termination of the heating of the prostatic tissue requires that the compression balloon remain inflated at the desired pressure of 10-25 psi for up to about 10 minutes. During this reinforcement period, the pressure of the filled fluid in the compression balloon should be maintained in order to solidify the biological stent. In addition, the pressurized compression balloon during this reinforcement period can fixate the released drugs and/or gene therapy drugs compounds within the compressed tissue as a result of the reduced blood flow. That is, the stent reinforcement period

maintains the pressure of the compression balloon after power to the energy-emitting source has been turned off so that drugs and/or gene therapy compounds released from the coated compression balloon fixate in a targeted tissue area and a solidified expanded urethra is achieved minutes after thermotherapy so that a urine drainage catheter or other device is not necessary.

During the stent reinforcement period, additional heat may be applied to compression balloon 112 to aid in the activation and release of the gene compounds and/or drugs in material 111 coating the outside of balloon 112 and the absorption of one the gene compounds or drugs into the targeted tissue area. The additional heat may be delivered to the compression balloon via one of hot water, radio-frequency, laser, microwave, ultrasound and infrared. It is envisioned that the additional energy may be applied to the tissue from outside of the bodily conduit. Applicant theorizes that the additional heat may result in a long-lasting or sustained biological stent being formed. The step of applying additional heat either alone or in conjunction with an appropriate, intravenously injected drug may provide pain relief, reduction of lesions and the healing of diseased tissue.

Compression balloon 112 is generally cylindrical with a sloped area on both sides of the compression balloon and is symmetrical along the length of the diameter according to a preferred embodiment. However, compression balloon 112 may be of any shape to create a desired mold or stent within a bodily conduit or urethra. As shown in Figure 6, the compression balloon 112' on catheter 100 is designed so that it inflates asymmetrically around catheter 100. The asymmetrical balloon 112' inflates a bodily conduit so that a region of tissue adjacent the bodily conduit receives more or less radiate energy from the energy- emitting source 110 depending upon the width of the inflated compression balloon 112'. The wider the inflated compression balloon, the more compressed the tissue adjacent the bodily conduit becomes and the adjacent tissue is moved further from the heat producing source. It is envisioned that a coated, compression balloon inserted into a bodily conduit other than a prostatic urethra the bodily conduit is other than a prostatic urethra and the inflated compression balloon may be expanded to a diameter that is up to five times greater than a diameter of the bodily conduit in its normal and functioning size.

Compression balloon 112 preferably should be maintain about 10-25 psi against the urethral wall along the length of the catheter with the preferred level of pressure being about 15 psi. However, depending upon the size and strength of the bodily conduit, the compression balloon may be inflated to a pressure lower than or greater than the preferred range for a prostatic urethra. In another embodiment, compression balloon may be mechanically manipulated so that alternating compression and decompression of the compression balloon occurs against the bodily conduit to be treated so that at least one of a gene modifier, and a drug or medication of coated material 111 is effectively delivered and fixated to a target area of the tissue to be treated. That is, the act of compression and decompression physically manipulates the bodily conduit against the coated material 111 causing a released gene modifier or drug to fixate to a targeted area. The act of compression or decompression of compression balloon 112, which is coated with material 111, may cause the binding of the at least one of a gene modifier and a drug or medication to protein or DNA of the bodily conduit wall and/or adjacent tissue.

In another aspect of the invention, a gene modifier or a drug or medication may be injected intravenously into tissue to be treated by thermotherapy. The injected gene modifier or drug or medication can be intravenously injected adjacent the target area of diseased tissue so that a targeted direct therapeutic delivery system efficiently delivers the gene compound or medication to the affected area. It is envisioned that this direct therapeutic delivery system may be employed with a heat alone or a heat plus compression thermotherapy treatment. Of course, a compression balloon with coated material may be used in a heat plus compression thermotherapy treatment if additional gene compounds or medication is desired to be delivered to the targeted tissue area.

Although the present invention has been described with reference to preferred embodiments, workers skilled in the art will recognize that changes may be made in form and detail without departing from the spirit and scope of the invention.

WE CLAIM:

1. A method of thermotherapy and/or activation and release of gene modifiers or drugs for treating tissue adjacent a bodily conduit comprising the steps of:

inserting an energy-emitting source containing catheter into a bodily conduit so that an energy-emitting source is positioned in a region of the prostate in order to radiate energy that heats tissue to be treated adjacent the bodily conduit;

inflating a compression balloon on the catheter that surrounds the energy-emitting source with a fluid wherein the compression balloon is coated with at least one of a gene modifier, and a drug or medication;

energizing the energy-emitting source and heating a portion of the tissue to be treated surrounding the bodily conduit to a temperature and for a time sufficient to destroy a heated portion of the tissue to be treated via the heat generated by the energy-emitting source wherein one of the heat of the energized energy-emitting source and warmed fluid one of releases, activates and enhances the at least one of the gene modifier, and the drug or medication coated on the compression balloon; and

terminating the generation of heat by the energy-emitting source upon completion of the time sufficient to destroy the heated portion of the tissue.

2. The method according to Claim 1, further comprising the step of alternating compression and decompression of the compression balloon against the bodily conduit to be treated so that the at least one of a gene modifier, and a drug or medication is effectively delivered to a target area of the tissue to be treated.

3. The method according to Claim 1, wherein the drug coated on the compression balloon is one of a standard cytotoxic drug used for the treatment of cancer, an antibiotic used to treat one of a benign condition and any infectious disease, and pain medication for the general relief of pain.

4. The method according to Claim 3, wherein the benign condition is prostititus or an inflammation surrounding a bodily conduit.

5. The method according to Claim 2, wherein the step of compression or decompression physically manipulates the bodily conduit to fixate the at least one of a gene modifier and drug or medication into the targeted area.

6. The method according to Claim 2, wherein the step of compression or decompression physically manipulates the bodily conduit and surrounding tissue to cause binding of the at least one of a gene modifier and drug or medication to protein or DNA of the bodily conduit and surrounding tissue.

7. The method according to Claim 1, wherein the drug coated on the compression balloon is used to cure prostatic diseases.

8. The method according to Claim 7, wherein the drug coated on the compression balloon is one of Proscar, Hytrin, Flowmax and Cadora and is used to treat benign prostate hyperplasia.

9. The method according to Claim 1, further comprising the step of applying one of additional heat or light to the compression balloon after the termination of heat generated by the energized energy-emitted source wherein the additional heat or light one of releases, activates and enhances the at least one of a gene modifier, and a drug or medication coated on the compression balloon.

10. The method according to Claim 9, wherein the additional heat or light is delivered to the compression balloon via one of hot water, radio-frequency, laser, microwave, ultrasound and infrared.

11. The method according to Claim 9, wherein the amount of heat or light generated in the step of applying at least one of additional heat and light provides significant absorption of at least one of a gene modifier, and a drug or medication of the coated compression balloon through the bodily conduit so that the at least one of the gene modifier, and the drug or medication reaches the target area.

12. The method according to Claim 9, wherein the amount of heat or light generated in the step of applying at least one of additional heat and light releases

and/or activates the at least one of a gene modifier, and a drug or medication of the coated compression balloon resulting in a sustained biological stent.

13. The method according to Claim 1, wherein the fluid inflating the compression balloon is one of a high lose fluid and a low lose fluid depending upon whether the heat or light applied via the energy-emitting source is to be diffused or not as it travels through the compression balloon.

14. The method according to Claim 9, wherein the amount of heat or light generated in the step of applying at least one of additional heat and light is sufficient for at least one of treatment or reduction of lesions, pain relief and healing of diseased tissue.

15. An apparatus for treatment of tissue within a body requiring thermotherapy, said apparatus comprising:

a) a catheter to be inserted into a bodily conduit;

b) an energy-emitting source disposed within said catheter;

c) a compression balloon surrounding the energy-emitting source within said catheter, said compression balloon having an inflated diameter that is greater than that of the bodily conduit in a relaxed state and having an outside surface of the balloon coated with at least one of a gene modifier and a drug or medication;

d) anchoring means for positioning said energy-emitting source and said compression balloon adjacent the tissue to be treated;

e) means for activating the energy-emitting source to radiate energy to heat the coated, compression balloon and tissue to be treated wherein the heat of the energized energy-emitting source one of releases, activates and enhances the at least one of the gene modifier, and the drug or medication coated on the compression balloon; and

f) means for terminating the radiation of energy from the energy-emitting source upon completion of the time period to destroy diseased tissue whereby the heated, coated compression balloon effectively delivers the at least one of the gene modifier, and the drug or medication to a target area of the diseased tissue.

16. The apparatus according to claim 15, further comprising means for inflating the coated, compression balloon to a sufficient pressure thereby expanding the bodily conduit and ensuring that a surface of the coated, compression balloon is in direct contact with the bodily conduit.

17. The apparatus according to claim 15, further comprising means for alternating compression and decompression of the coated, compression balloon against the bodily conduit to be treated causing physical manipulation of the bodily conduit so that the at least one of a gene modifier, and a drug or medication of the coated, compression balloon is effectively delivered to a target area of the tissue to be treated.

18. The apparatus according to claim 15, further comprising means for maintaining the pressure of the inflated compression balloon during and after thermotherapy.

19. The apparatus according to claim 16, wherein the bodily conduit is a prostatic urethra and the inflated compression balloon is approximately 40 to 60 French.

20. The apparatus according to claim 16, wherein the bodily conduit is other than a prostatic urethra and the inflated compression balloon is expanded to a diameter that is up to five times greater than a diameter of the bodily conduit in its normal and functioning size.

21. The apparatus according to Claim 15, wherein the bodily conduit is a prostatic urethra and the pressure of the inflated compression balloon is approximately in the range of about 10-25 psi.

22. A method of thermotherapy for treating tissue adjacent a bodily conduit comprising the steps of:

inserting an energy-emitting source containing catheter into a bodily conduit so that an energy-emitting source is positioned in a region of the prostate

in order to radiate energy that heats tissue to be treated adjacent the bodily conduit;

inflating a compression balloon on the catheter that surrounds the energy-emitting source with a fluid and upon inflating the compression balloon to the desired dimension, stopping circulation of the fluid;

energizing the energy-emitting source to a low power where the amount of power depends upon the bodily conduit being treated;

heating a portion of the tissue surrounding the bodily conduit to a sufficiently high temperature, depending upon the coated, compression balloon and the treatment to be performed, for a time sufficient to destroy a heated portion of the tissue via the energy-emitting source; and

terminating the heating of the tissue upon completion of the time sufficient to destroy the heated portion of the tissue.

23. The method of claim 22, wherein the low power in the range of 0 watts to approximately 20 watts.

24. The method according to claim 22, wherein the sufficiently high temperature is approximately 43 degrees C.

25. The method according to claim 22, wherein fluid is one of non-ionizing water and sterile water.

26. The method according to claim 22, wherein the compression balloon has a length, the heated portion of the tissue is a treatment zone and the length of the treatment zone depends on the length of the compression balloon.

27. The method according to claim 26, wherein the length of the compression balloon is in the range of approximately 25 millimeters to 60 millimeters.

28. A method of thermotherapy for treating tissue adjacent a bodily conduit comprising the steps of:

injecting at least one of a gene modifier, and drug or medication into an area adjacent the tissue to be treated;

inserting an energy-emitting source containing catheter into a bodily conduit so that an energy-emitting source is positioned in a region of the prostate in order to radiate energy that heats tissue to be treated adjacent the bodily conduit;

inflating a compression balloon on the catheter that surrounds the energy-emitting source with a fluid;

alternating compression and decompression of the compression balloon against the bodily conduit to be treated so that the bodily conduit and surrounding tissue is mechanically manipulated causing at least one of the intravenously injected gene modifier, and the drug or medication to be effectively delivered to a target area of the tissue to be treated;

energizing the energy-emitting source to a low power in the range of 0 watts to approximately 20 watts;

heating a portion of the tissue surrounding the bodily conduit to a temperature of approximately 43°C for a time sufficient to destroy a heated portion of the tissue via the energy-emitting source; and

terminating the heating of the tissue upon completion of the time sufficient to destroy the heated portion of the tissue wherein the inflated compression balloon reduces blood flow in the tissue being treated and tissue adjacent the bodily conduit is maintained at a temperature above 30°C to produce a biological stent.

29. The method according to claim 1, wherein the activation and release of gene modifiers or drugs from the coated compression balloon causes an immune response for the treatment or management of the tissue to be treated.

30. The apparatus according to claim 15, wherein the activation and release of gene modifiers or drugs from the coated compression balloon causes an immune response for the treatment or management of the diseased tissue.

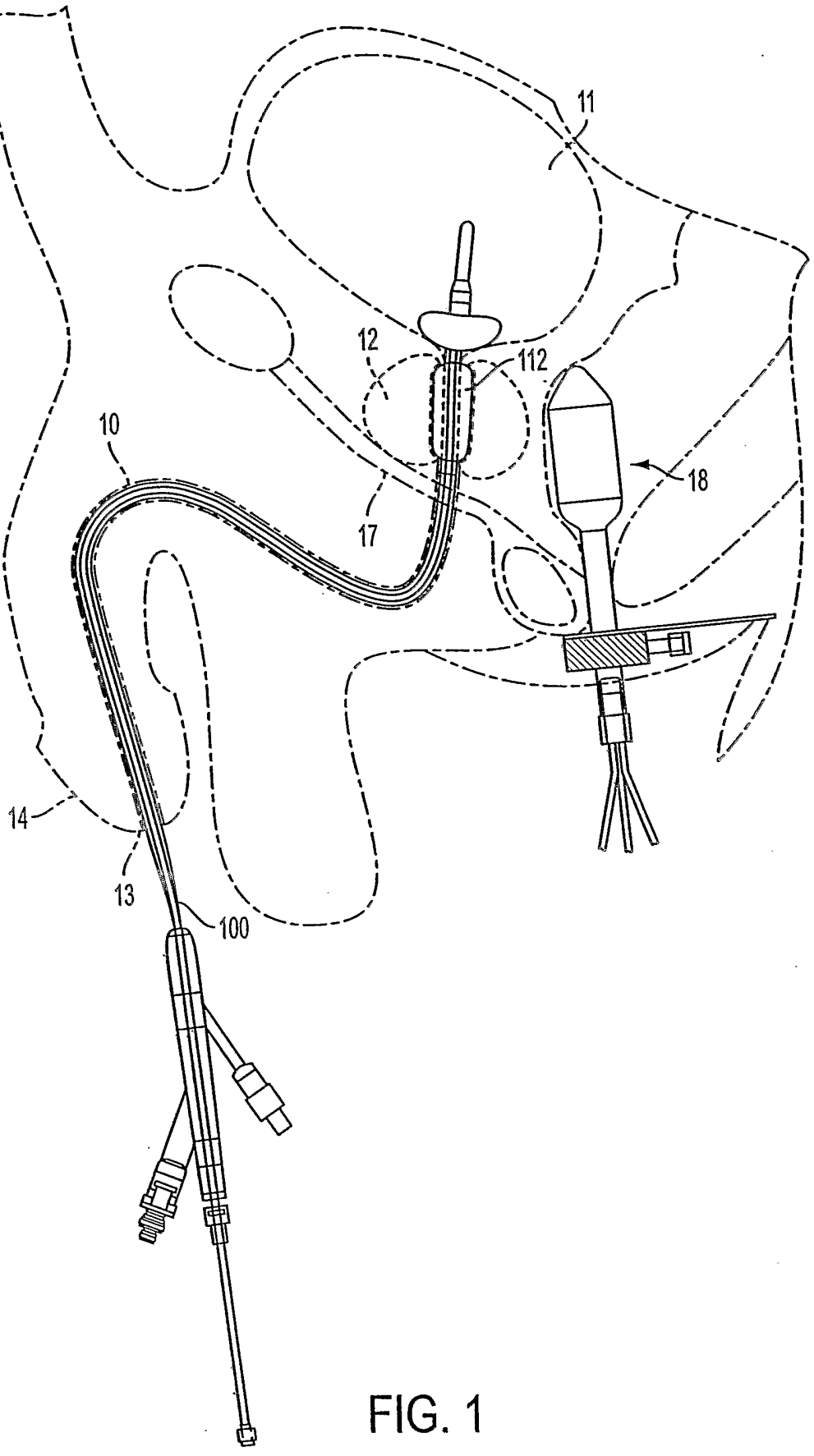

FIG. 1

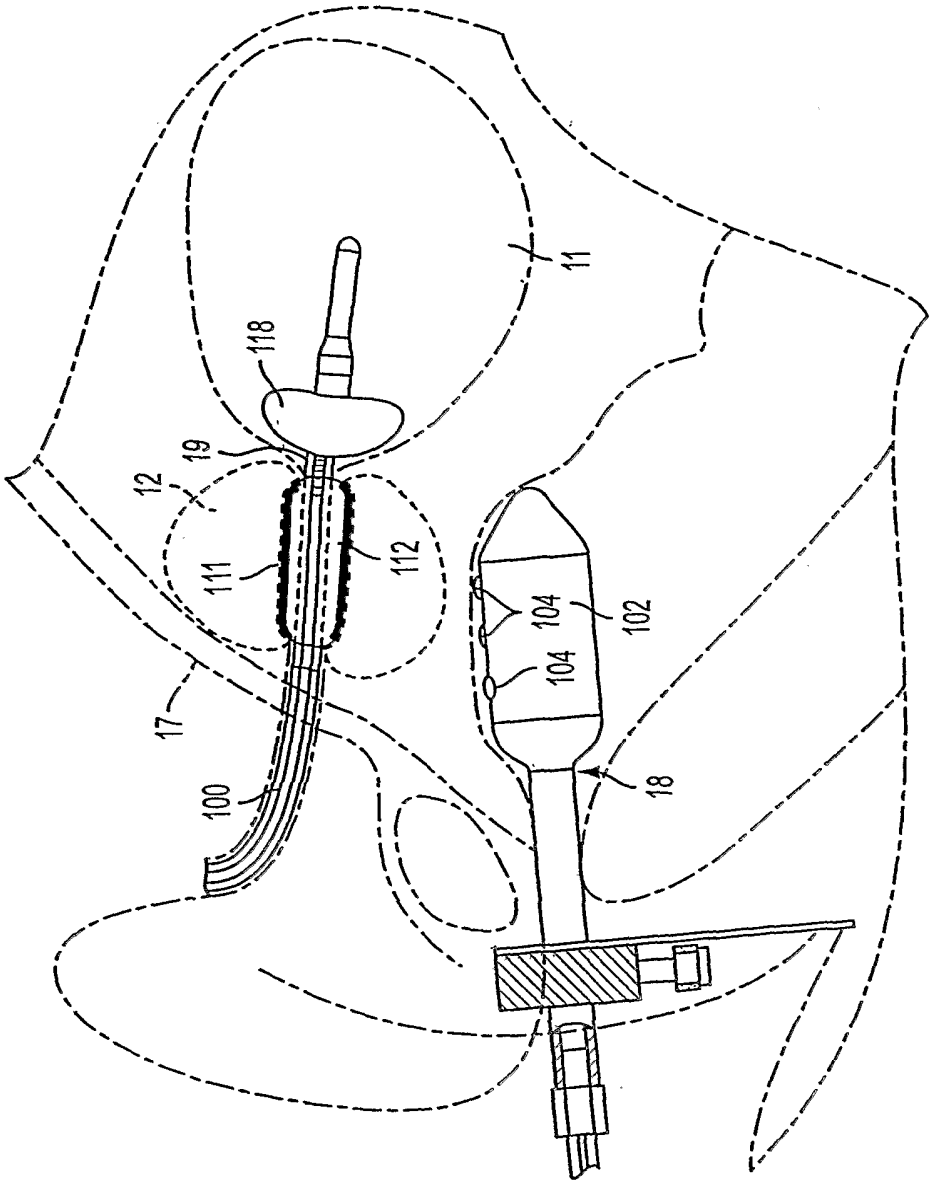

FIG. 2

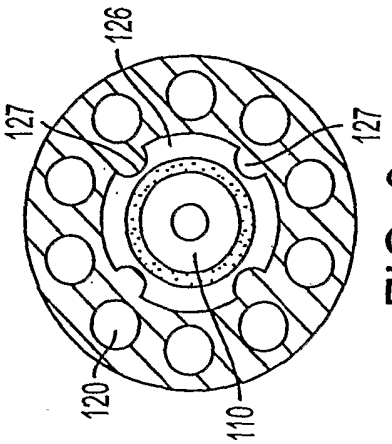

FIG. 3a

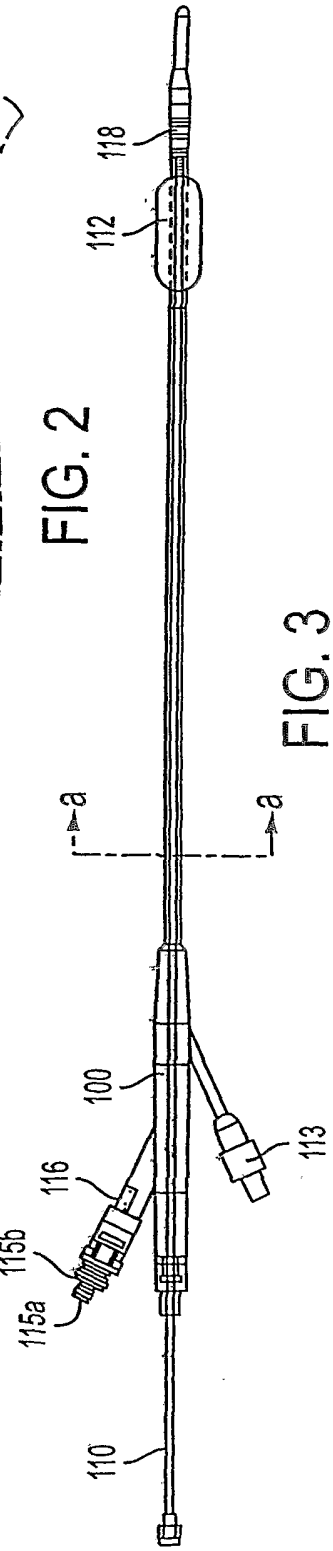

FIG. 3

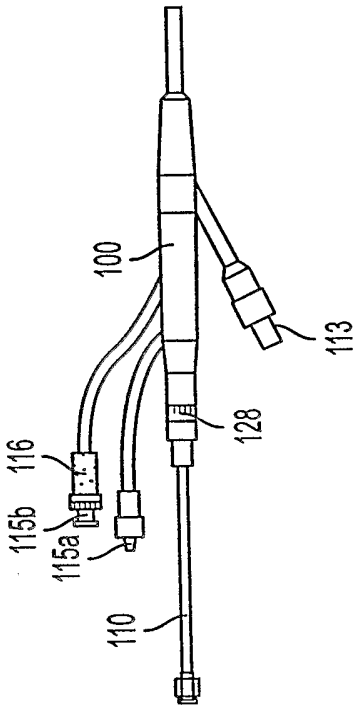
100
113
128
116
115b
115a
110

FIG. 3b

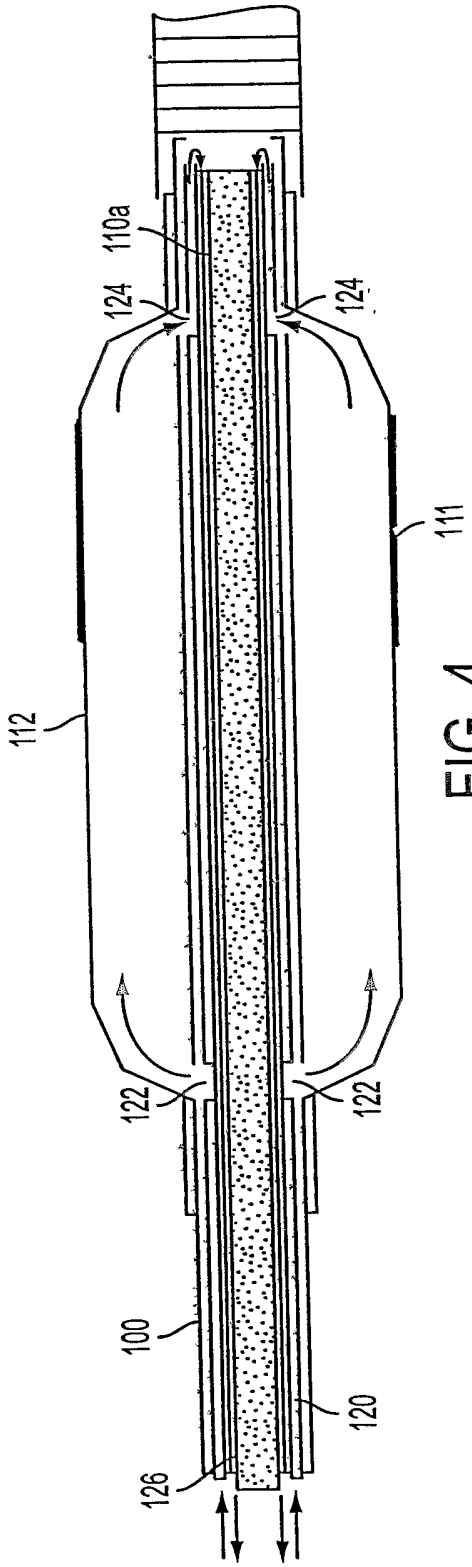
110a
124
124
111
112
122
122
100
120
126

FIG. 4

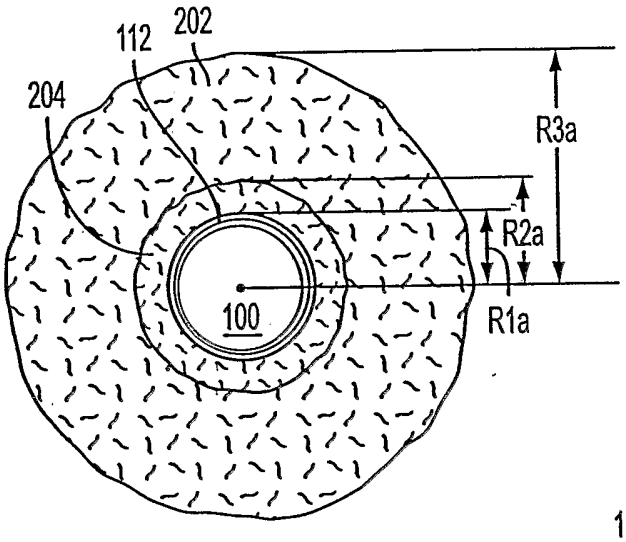

FIG. 5a

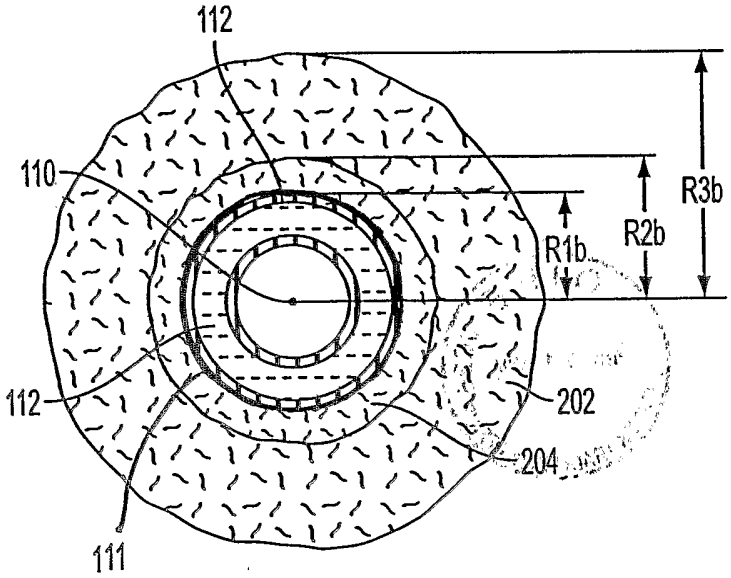

FIG. 5b

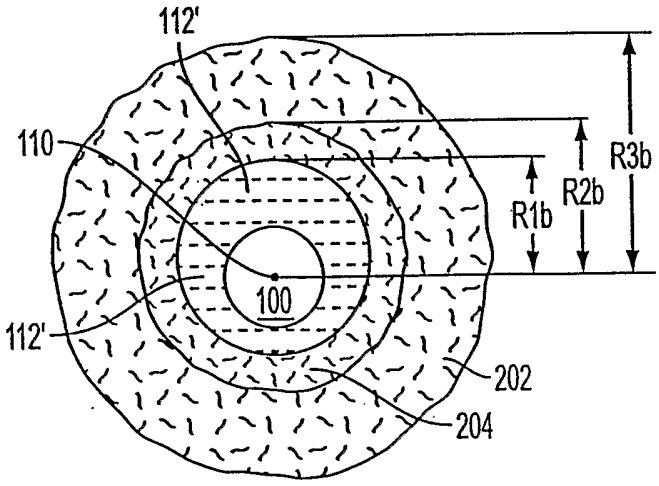

FIG. 6

INTERNATIONAL SEARCH REPORT

national Application No
T/US2004/014768

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B18/18 A61M25/10 A61F7/12

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)
IPC 7 A61B A61M A61F

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.
Y	US 2003/055470 A1 (MON JOHN ET AL) 20 March 2003 (2003-03-20) paragraph '0029! - paragraph '0048!; figures 2,3a	15,16, 18-21
Y	US 6 524 274 B1 (BARRY JAMES J ET AL) 25 February 2003 (2003-02-25) column 3, line 62 - column 4, line 32 example 2	15,16, 18-21
Y A	US 4 955 377 A (LENNOX CHARLES D ET AL) 11 September 1990 (1990-09-11) column 3, line 10 - column 7, line 65; figure 1	15,16, 18-20 21

-/--

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

[X] Patent family members are listed in 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
24 November 2004	06/12/2004

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Artikis, T

INTERNATIONAL SEARCH REPORT

International Application No
/US2004/014768

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/069619 A1 (FENN ALAN J ET AL) 10 April 2003 (2003-04-10) abstract paragraph '0060! paragraph '0131! - paragraph '0133!	15-18
A	US 2002/151844 A1 (WANG LIXIAO ET AL) 17 October 2002 (2002-10-17) abstract paragraph '0010! paragraph '0032! - paragraph '0034!; figures 4,5	15,16

ternational application No.
PCT/US2004/014768

INTERNATIONAL SEARCH REPORT

Box 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.: 1-14,22-30
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy and surgery

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 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 fee, this Authority did not invite payment of any additional fee.

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.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/014768

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