



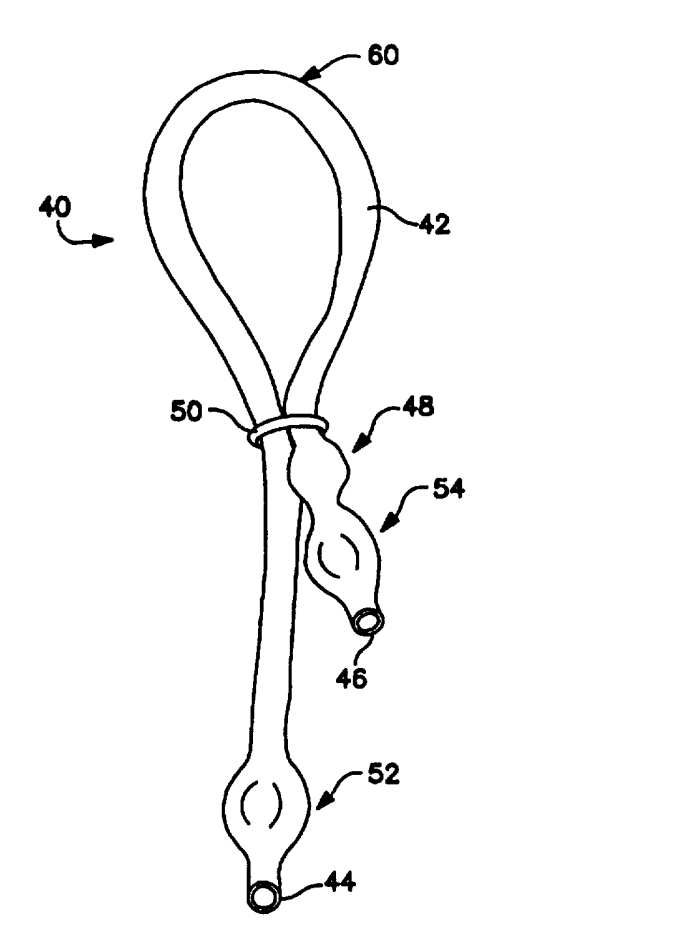
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(54) Title: VENOUS FLOW CONTROL ELEMENT FOR MAINTAINING PENILE ERECTION

(57) Abstract

A venous flow control device is provided for assisting in the maintenance of a penile erection or in preventing urinary incontinence. The device is a tubular structure having an integral fastening means, and is adapted to be secured in a loop configuration about the penis to provide an adjustable radial constrictive force about the base of the penis. Methods for using the device are also provided.



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VENOUS FLOW CONTROL ELEMENT FOR
MAINTAINING PENILE ERECTION

Technical Field

5 The present invention relates generally to venous flow control devices useful for maintaining erection of the penis during sexual intercourse. More particularly, the invention pertains to a tubular device adapted to be secured in a loop configuration about an individual's penis in either a pre-scrotal or post-scrotal position. The invention additionally relates to methods of using the device to control venous flow from the penis,
10 and to use in conjunction with the administration of pharmacologically active agents.

Background of the Invention

 Generally, an erection is produced by a blood flow imbalance caused by increased arterial blood flow into the erectile tissues of the penis in the presence of restricted veinal
15 blood flow from the penis. This imbalance enables the erectile tissue to become engorged with blood and causes penile enlargement or erection. The physiological events associated with the erectile process include a vascularization which increases arterial blood flow into the penis as well as a concurrent veno-constriction from the expanding cavernosa compression against the tunica, thereby causing an imbalance in blood flow
20 rates to and from the penis. Erection persists as long as the venous outflow is less than the arterial inflow.

 The erectile process can fail for a number of reasons, resulting in any one of a number of erectile dysfunctions, including impotence. "Impotence" is the consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse. It
25 has been estimated that approximately 10 million American men are impotent (R. Shabsigh et al., "Evaluation of Erectile Impotence," *Urology* 32:83-90 (1988); W.L. Furlow, "Prevalence of Impotence in the United States," *Med. Aspects Hum. Sex.* 19:13-16 (1985)). Impotence is recognized to be an age-dependent disorder, with an incidence of 1.9 percent at 40 years of age and 25 percent at 65 years of age (A.C. Kinsey et al.,
30 "Age and Sexual Outlet," in *Sexual Behavior in the Human Male*, A.C. Kinsey et al., eds., Philadelphia, PA: W.B. Saunders, 218-262 (1948)). In 1985 in the United States,

impotence accounted for more than several hundred thousand outpatient visits to physicians (National Center for Health Statistics, National Hospital Discharge Survey, 1985, Bethesda, MD, Department of Health and Human Services, 1989 DHHS publication no. 87-1751).

5 A number of causes of impotence have been identified, including vasculogenic, neurogenic, endocrinologic and psychogenic. See Das, S., *Int. J. Impotence Res.* 6:183-189 (1984). Impotence may result from various physiological or psychological conditions which cause the blood flow rates to and from the penis to remain substantially in balance, thereby preventing the concomitant retention of blood in the penis, which is necessary to
10 induce and maintain an erection. Impotence can also be a side effect of various classes of therapeutic drugs, or can be associated with various diseases, including diabetes, multiple sclerosis and sickle cell anemia. Impotence resulting from any one of these causes can be exacerbated by additional factors such as cigarette smoking, a poor diet, or the like.

 A frequent physiological condition associated with impotence relates to "venous
15 leakage" wherein the penile venous system is not sufficiently compressed during the erectile process, permitting excessive drainage of blood from penile tissue and subsequent detumescence or erectile failure. Diagnostic tests (e.g., cavernosography) have shown that upwards of 40% of impotent men suffer from some degree of venous leakage.

 Numerous treatments for impotence are known in the art, and include
20 psychological therapies, hormonal therapy, administration of various vasodilators, surgery (e.g., vascular surgery or implantation of penile prostheses), vacuum devices and various external aids such as penile splints and constriction devices. See e.g., Krane, et al., *N. Eng. J. Med.* 321(24):1648-1659 (1989). In light of the recognition that penile inflow arteries are principally within the deep interior of the organ, and that penile return veins
25 are disposed both within the deep interior and subdermally, adjacent to the surface of the organ, a number of devices have been described wherein the blood flow from the penis may be restricted using external devices such as constriction bands. These devices are adapted to be placed about the penis at a location closely adjacent to the body trunk. Thus, the blood flow from the penis via the peripheral veins is impeded while the blood
30 flow to the penis via the deeply embedded arteries remains substantially unimpeded, thereby assisting in the achievement and/or maintenance of an erection (Sidi et al., *Urol.*

Clin. N. America 17:19-21 (1990); U.S. Patent No. 2,581,114 to Larson; U.S. Patent No. 3,461,863 to Sullinger; U.S. Patent No. 4,203,432 to Koch; U.S. Patent No. 4,967,738 to March; U.S. Patent No. 5,027,800 to Rowland).

5 More particularly, U.S. Patent No. 2,581,114 to Larson describes a constriction device consisting of an elongated elastic tube with a rigid U-shaped yoke which provides the "socket" of a ball-and-socket coupling means for fastening the device in place about the penis and impeding venous outflow. U.S. Patent No. 3,461,863 to Sullinger describes an adjustable constriction device consisting of a loop of flexible tubing having two apertures arranged at one end of the tubing which allow the other end to pass through and provide a means for fastening the device in place. Sullinger further describes the importance of the relative spacing of the two apertures and tube wall thickness to prevent or resist slippage of the device in response to increased tension. Sidi et al. describe a multi-component tourniquet device comprised of flexible tubing, an associated elongate locking mechanism, and a separate release loop. The flexible tubing is routed through a first aperture in the locking mechanism, doubled back to form a loop, and routed through a second aperture in the locking mechanism. The device is described for use in conjunction with the intracavernosal administration of drugs in the diagnosis and treatment of impotence.

15 Although these devices, as well as other types of constriction or clamping devices known in the art, are capable of restricting blood flow from the penis, these devices are subject to several disadvantages in the treatment or prevention of erectile failure. One common disadvantage involves a lack of a means to adjust constrictive tension, rendering it difficult or impossible to control the degree of veinal outflow restriction necessary to prevent erectile failure. Insufficient restriction may prevent such devices from maintaining an erection, and too much restriction may result in user discomfort, numbness and insensitivity, and may even result in damage to the penile tissue if left in place for an extended period of time. Prior devices which may exert excessive constriction can cause substantial or complete restriction of arterial blood flow into the penis, resulting in serious injury. Further, since the degree of veinal restriction provided by prior devices depends in part on the stage of the individual's erection, a problem arises when such devices are

adjusted to a particular tightness suitable for achieving an initial erection that subsequently becomes too restrictive thereafter.

Other approaches to inducing erection and preventing erectile failure include physiological treatments such as injection of a vasoactive drug directly into a corpora cavernosa. See, for example, U.S. Patent Nos. 4,127,118 to Latorre, 4,766,889 to Trick et al., and 4,857,059 to Rey et al. Commonly used drugs include α -adrenergic blocking agents such as the long acting phenoxybenzamine and the short acting phentolamine, smooth muscle relaxants such as papaverine, prostaglandins having vasoactive function such as prostaglandin-E₁ (PGE₁) and combinations thereof. See Kursh et al., *Urol. Clin. of No. America* 15(4):625-629 (1988), and Ishii et al., *J. of Urol.* 141:323-325 (1989). Yet another approach involves topical application of an agent such as a vasodilator directly to the various skins or mucosa of the penis. Commonly used agents include hydralazine, sodium nitroprusside, phenoxybenzamine and phentolamine (see U.S. Patent No. 4,801,587 to Voss et al.). Although such therapies provide sufficient prevention of erectile failure in some individuals, loss of erection upon lying down or incomplete response to the vasoactive drugs at high dosages may be manifestations of excessive venous outflow from the penis. In such instances, the concurrent use of a venous outflow control device may be indicated.

Accordingly, there remains a need for a therapeutic device adapted for application to the penis that is useful to treat or prevent erectile failure. Such a device must be capable of providing readily adjustable control over venous outflow, whereby proper use thereof enhances retention of blood within an individual's penis without substantially obstructing arterial inflow or becoming too constrictive during the erectile process. Further, there remains a need for a venous flow control device which may be employed to supplement or improve the efficacy of physiological treatments for erectile failure, such as in the therapeutic administration of vasoactive or androgenic agents and the like. The devices may be used to reduce the required dosage, and/or to render effective a dosage which is ineffective in the absence of the device. That is, the administered agent remains within the penis for an extended period of time, and enhances the effectiveness of the drug therapy. It is also desirable that any such device be simple in structure, so as to provide ease and economy of manufacture.

Disclosure of the Invention

Accordingly, a novel device for the treatment or prevention of erectile dysfunction is provided. The device is an adjustable venous flow control ("VFC") device that is formed from a length of flexible tubing capable of providing readily adjustable venous flow control when applied to the penis and an integral fastening means. The therapeutic device can thus be used to effectively enhance retention of blood within the penis without substantially obstructing arterial inflow or becoming too constrictive during the erectile process.

The invention is also directed to a method of maintaining penile erection in a male individual by encircling the penis with an adjustable VFC device as provided herein, and securing the device at a selected tension to assist in preventing excess venous outflow from the individual's erect penis. The method can also be used to enhance penile erection, for example by enhancing penile size achieved with erection.

It is still a further object of the invention to provide a method of treating erectile dysfunction in a male individual by encircling the individual's penis with an adjustable venous flow control device and selecting a desired tension setting, then administering a pharmacologically active agent to the individual, whereby the device prevents excess venous outflow from the penis and, when the agent is administered locally, causes enhanced retention of the agent within the penis. That is, when used in conjunction with local pharmaceutical therapy, for example, transurethral drug administration, the device helps retain the drug within the penis to allow transfer to the corpus cavernosum for an extended period of time. Use of the therapeutic device in this manner may render effective an otherwise ineffective dose of a pharmacologically active agent, and/or may reduce the dosage of the agent necessary to provide a therapeutic effect.

The invention also provides a method for preventing urinary incontinence in a male individual using a VFC device as provided herein, and involves tensioning the device about the penis to prevent involuntary passage of urine from the urethra.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art in light of an examination of the following, or may be learned by practice of the invention.

Brief Description of the Drawings

Figure 1 is a perspective view of a venous flow control device in a loop configuration.

5 Figure 2 is a cross-sectional view of the device of Figure 1 showing an integral fastening means disposed within the tubing of the device.

Figure 3 is a perspective view of an alternative venous flow control device in a loop configuration.

Figure 4 is a cross-sectional view of the device of Figure 3 showing optional finger grasping means disposed within the tubing of the device.

10 Figure 5 is a pictorial representation of a venous flow control device in use.

Modes for Carrying Out the Invention

Before describing the present invention in detail, it is to be understood that the present invention is not limited to specific materials, configurations or particular methods
15 of use, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly
20 dictates otherwise. Thus, for example, reference to "a vasoactive agent" refers to one or more such agents, reference to "an androgenic agent" includes a mixture of two or more such agents, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

25 The term "elasticity" as used herein refers to the capability of a solid material to change shape and size under the influence of opposing forces, to sustain such deformation without permanent loss of size or shape, and to recover its original configuration when the forces are removed. Further, an "elastomer" or "an elastomeric material" generally refers to any material which exhibits elasticity.

30 The elasticity of a material selected for use herein will derive from a wide variety of factors such as tensile strength and tube wall thicknesses. Tensile strength refers to the

maximum stress that a stretched material can withstand without tearing. The elasticity of a material may be qualified and quantified in a wide variety of ways. One feature of the elastic materials used to make the present devices relates to the flexibility of the material in response to deforming forces, and the capability of the material to regain its original shape after being deformed within its elastic limits.

The term "erectile dysfunction" as used herein intends a periodic or consistent inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse. The present method of "treating" erectile dysfunction includes "preventing" erectile dysfunction as well.

As used herein, the term "drug" or "pharmacologically active agent" intends a compound or composition of matter which, when administered to an organism (human or animal) induces a desired therapeutic effect. Preferred pharmacologically active agents used in conjunction with the invention are vasoactive and androgenic agents.

The terms "transurethral," "intraurethral" or "urethral" as used to specify the preferred mode of administration of pharmacologically active agents, refer to delivery of at least one such agent onto the urethral mucosa such that the agent contacts the lining of the urethra and passes therethrough into the vascular system of the spongiosa, glans and the corpora cavernosa of the penis.

The term "topical" is used herein to refer to a mode of administration of various agents at, or immediately beneath, the point of application to the skin or mucosa. A large number of chemical agents can be applied to the various skins or urethral mucosa of the penis for their local and sometimes systemic effects.

By "transdermal" delivery, applicants intend to include both transdermal (or "percutaneous") and transmucosal administration, i.e., delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream.

By an "effective" amount of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition being treated, the drug or agent being employed, the mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective"

amount in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

In one embodiment, the invention relates to a venous flow control device adapted for application to the penis. The device can be used to maintain a penile erection, enhance a penile erection, or help in the treatment of incontinence. Referring to Figure 1, one embodiment of such a device is generally indicated at **10**. The device **10** is formed from a length of tubing having a central section **12** flanked by a distal end **14** and a proximal end **16**. The central section of the tubing has a substantially uniform diameter. The length of the tubing may be selected to custom fit any individual user in either a pre-scrotal or post-scrotal position.

The device **10** further includes an integral fastening means adapted to hold and secure the tubing in the form of a loop having an adjustable size. The integral fastening means is provided in part by a substantially rigid, enlarged segment of tubing **18** substantially adjacent to the proximal end **16** of the tubing. The enlarged segment of tubing operates in combination with an associated annular ring **20** to provide a ball and ring coupling configuration. Specifically, a loop, indicated at **22**, is formed by folding a portion of the central section **12** of the tubing on itself and threading the folded section through the ring **20**. The central opening of the ring is dimensioned such that the tubing may be maintained in a loop formation; however, the overall size of the loop **22** is readily adjustable by pulling a desired length of the tubing through the ring. Once the loop has been adjusted to a particular size, the device is locked by sliding the ring **20** into close engagement with the enlarged segment **18** of the tubing. As shown in Figure 1, the enlarged segment of tubing has a larger diameter than that of the central section **12** of the tubing. This feature prevents the passage of the enlarged section through the annular ring and allows the device **10** to be maintained in the form of loops having various sizes. The device **10** is thus quite simple in structure and can be formed from readily available materials such as surgical tubing and O-ring gaskets. This provides ease and economy of manufacture, particularly when compared to prior composite constriction devices which employ structurally complicated and/or specialized components.

The tubing **12** may be manufactured from any number of materials, and the selection of a particular material will depend on criteria such as user sensitivities,

therapeutic device regulatory guidelines and/or a number of material characteristics. Preferably, the device is formed from a highly stretchable, flexible elastomeric material which has sufficient tensile strength to withstand a substantial degree of stretch and maintains its elasticity over time and repeated use.

5 Particularly preferred materials for tubing **12** include natural gum rubber, surgical rubber or latex rubber, as well as synthetic elastomers such as silicones and copolymers well known in the art. Latex rubber exhibits particularly preferred elastomeric characteristics, but may cause sensitization in a small percentage of the population. These materials can also include one or more colorants, typically present at about 0.5 to 10
10 wt. %. An example of a preferred latex material is an off-white colored latex containing titanium dioxide (typically about 6 wt. %).

 Silicone tubing structures are also well known in the art. Silicone tubing is generally capable of full recovery after deformation, and can be sealed or bonded to render structures air-tight, i.e., using silicone that has been liquified by heating. Other
15 materials which are useful herein include, but are not limited to, natural and synthetic elastomers such as butyl rubber, polyurethane rubber, polysiloxane elastomers such as methyl vinyl polysiloxane or the like, block copolymers such as Kraton® (Shell Oil Company, Houston, TX) or the like, ethylene/propylene copolymers, polyisobutylene, chloroprene polymers, polybutadiene, polyisoprene and natural rubbers. Additional
20 materials will be readily apparent to those of skill in the art. Tubing structures formed from such materials may be fabricated using conventional techniques, e.g., compression, transfer or injection molding procedures.

 Ring **20** can comprise any material which is sufficiently rigid to hold its shape. The ring should have a smooth surface to facilitate device assembly and adjustment of
25 loop size. In addition, the ring material preferably has a coefficient of static friction with respect to the tubing material which allows the tubing to easily slide within and against the ring when the size of the loop is being adjusted. Particularly preferred ring materials include polycarbonates (such as Lexan®) or polystyrenes. Another preferred ring material is polytetrafluoroethylene, such as wherein the annular ring **20** comprises a Teflon® O-
30 ring. It has been found herein that Lexan® exhibits particularly superior frictional characteristics when used in combination with latex tubing materials.

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Referring now to Figures 1 and 2, the enlarged segment 18 of tubing is provided by a substantially spherical body 24 within the tubing at the proximal end 16 thereof. The spherical body has a diameter greater than that of the diameter of the remainder of the tubing. When the body is inserted into the tubing, then, the tubing stretches about the body to provide a substantially rigid, enlarged tubing segment. Body 24 is held in place adjacent to the proximal end 16 of the tubing and, because of the grip provided by the stretched tubing material, resists any lateral movement within the tubing. The body 24 is generally formed from a metallic material, a substantially nondeformable polymeric material, or other rigid materials. For example, body 24 may comprise a polyethylene or polypropylene ball. Here again, the fact that commonly available materials such as polyethylene or polypropylene may be used reduces the cost and difficulty of manufacturing the present devices.

In a related embodiment of the invention, a VFC device is provided with grasping means which facilitate the manipulation and adjustment of the device. Referring to Figure 3, one such device is shown generally at 40. The device 40 is formed from tubing having a central section 42 flanked by a distal end 44 and a proximal end 46. The device 40 also includes an adjustable integral fastening means that can maintain the tubing in the form of a loop of adjustable size, wherein the integral fastening means comprises the operative combination of a substantially rigid, enlarged segment of tubing 48 adjacent to the proximal end 46 of the tubing and an associated ring 50. The device has been assembled as previously described to provide a loop, generally indicated at 60. A first grasping means 52 is present adjacent to the distal end 44 of the tubing. A second grasping means 54 is present between the proximal end 46 of the tubing and the enlarged segment 48 of the tubing. The first and second grasping means generally comprise areas of tubing having increased diameter with respect to the diameter of the remainder of the tubing. These areas provide finger grasps or ears that allow an individual to manipulate the device more easily, such as when adjusting the device in place about the individual's penis.

The grasping means 52 and 54 can be formed by compressing the tubing at its distal and proximal ends 44 and 46 to provide substantially flattened areas of increased diameter. When the tubing comprises an elastomeric or flexible material, the flattened areas can be formed using heat sealing techniques, or a bonding agent such as a suitable

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adhesive. However, the grasping means are preferably provided by bodies that are contained within the tubing. Referring now to Figures 3 and 4, the first 52 and second 54 grasping means are formed from annular bodies 56 and 58, respectively, which are contained within the tubing at the distal and proximal ends thereof. The annular bodies 56 and 58 have diameters sufficient to cause the tubing to stretch into flattened discs of increased diameter relative to the diameter of the central section 42 of the tubing. The annular bodies also serve to close and substantially seal the VFC device at both ends. In this manner, one possible source of contamination is avoided by closing off the interior of the tubing. The device 40 can thus be effectively re-used in a sanitary fashion by cleaning the surface using soap and water.

Referring now to Figure 5, the device 40 is shown in place about the base of an individual's penis 80 in a post-scrotal position. The device is first brought into a loop configuration by passing a portion of the tubing through the ring 50. An initial setting is established by drawing a sufficient length of tubing through the ring to provide a loop 60 of maximum size. The size of the loop is maintained by locking the device with the ball and ring coupler. The device can then be applied by grasping the loop 60 and stretching the tubing to increase the size of the loop. The penis is inserted through the stretched loop and the device slid over the shaft of the penis until it is positioned around the base thereof. As depicted in Figure 5, the VFC device 40 is preferably positioned with the distal and proximal ends, 44 and 46, of the tubing arranged to one side of the shaft of the penis with the enlarged portion of tubing 48 protruding through the annular ring 50 above the remaining section of tubing that passes through the ring. Device 40 is adjusted by grasping the distal end 44 of the tubing at the first finger grip 52 and pulling the tubing until the loop 60 is tightened as desired about the base of the penis or around both the base of the penis and the scrotum.

In use, the VFC device is tightened to provide increased circumferential tension about the penis. In particular, the distal end 44 is grasped and pulled downwardly to draw the tubing through the ring, thereby decreasing the size of the loop 60. The device is maintained at its tensioned setting by the resilient engagement of the enlarged segment 48 of tubing with both the ring 50 and a portion of the central section 42 that passes through the ring. Thus, the device 40 provides an even, radial compressive force on the penis

sufficient to limit the outflow of blood from the penis during the erectile process without substantially obstructing arterial inflow.

As the penis becomes erect, the VFC device may be further tightened or loosened as necessary to achieve and/or maintain erection and comfort. The ball and ring coupling provided by the integral fastening means serves to maintain the selected tension setting by
5 resisting movement in response to outward pressure exerted by the penis during the erectile process. However, as the penis develops increased turgidity, the extent of outward pressure may reach a threshold where the VFC device needs to be re-adjusted to a decreased tension setting by providing a slightly greater loop size. This loosening
10 operation involves grasping the proximal end 46 of the tubing at the second finger grip 54 and pulling the tubing upward to partially disengage the enlarged segment 48 of the tubing from its coupling seat in the annular ring 50. In this manner, the size of the loop 60 can be incrementally increased to provide delicate control over the tension provided by the device.

The ability to control and adjust the degree of tension provided by the VFC device
15 allows the individual to avoid excessive venous flow occlusion which can prevent deep tissue transfer throughout the cavernosa, resulting in occurrence of a partial erection, e.g., an erection occurring distal to the device. Excessive occlusion can lead to a hinged erection such as those failed erections that have been encountered with prior pump and
20 occlusive band devices. By contrast, the adjustable pressure exerted by the VFC device allows only the superficial venous and spongiosal systems to be effected, allowing the entire length of the cavernosa to fill to yield a normal erection.

Accordingly, the invention provides a safe and effective means to assist an individual in the maintenance of a penile erection. The devices emulate the normal
25 erectile process by providing vaso-constriction such as that normally effected by sphincter muscles at the base of the penis to interrupt the veinal blood flow therefrom during erection, thereby causing an imbalance in blood flow rates to and from the penis. When properly adjusted, the devices supply a radial compressive force effective to impede blood flow from the penis via the peripheral veins, while blood flow to the penis via the deeply
30 embedded arteries remains substantially unimpeded. Thus, the devices interrupt venous leakage and are useful in the maintenance of an erection.

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In another embodiment of the invention, a method is provided for maintaining a penile erection in a human individual using the VFC device. In order to carry out the method, a VFC device is provided as described above, having a tubing length sufficient to fit around the base of an individual's penis, in either a pre-scrotal or post-scrotal position. When used in the pre-scrotal position, the tubing encircles the base of the penis and passes behind the scrotum at the junction of the pubis. Some individuals may find that such pre-scrotal positioning is more comfortable or more effective than post-scrotal application. In both positions, the device is used to encircle the base of the penis and is brought into a tensioned setting by drawing on one end of the tubing such that the size of the loop is decreased. As explained above, this helps restrict venal out-flow from the penis. The device may optionally be applied to the individual's penis after enlargement to help maintain an erection, such as when the user does not require assistance in achieving an erection. The device can also be used to enhance penile erection, or to enhance penile size attained with erection.

The invention also extends to a method for treating erectile dysfunction in a male individual wherein application of the device is coupled with therapeutic administration of a selected pharmaceutical agent, typically a vasoactive or androgenic agent, within the context of a dosing regimen effective to assist in the treatment of erectile dysfunction. Suitable dosage regimens will be known to those skilled in the art or may be readily determined. The amount of active agent administered will, of course, be dependent on the subject being treated, the mode of administration, and the judgment of the prescribing physician.

Suitable pharmaceutical agents are vasoactive agents including, but not limited to: nitrates such as nitroglycerin, isosorbide dinitrate, erythryl tetranitrate, amyl nitrate, sodium nitroprusside, molsidomine, linsidomine chlorhydrate ("SIN-1") and S-nitroso-N-acetyl-d,l-penicillamine ("SNAP"); long and short acting α -blockers such as phenoxybenzamine, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prazosin, trimazosin, alfuzosin, tamsulosin and indoramin; ergot alkaloids such as ergotamine and ergotamine analogues, e.g., acetergamine, brazergoline, bromerguride, cianergoline, delorgotriple, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotriple, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide,

proterguride and terguride; antihypertensive agents such as diazoxide, hydralazine and minoxidil; vasodilators such as nimodipine, pinacidil, cyclandelate, dipyridamole and isoxsuprine; chlorpromazine; haloperidol; yohimbine; trazodone; naturally occurring prostaglandins such as PGE₁, PGA₁, PGB₁, PGF_{1 α} , 19-hydroxy-PGA₁, 19-hydroxy-PGB₁,
5 PGE₂, PGA₂, PGB₂, 19-hydroxy-PGA₂, 19-hydroxy-PGB₂, PGE₃, PGF_{3 α} ; semisynthetic or synthetic derivatives of natural prostaglandins, including carboprost tromethamine, dinoprost tromethamine, dinoprostone, lipoprost, gemeprost, metenoprost, sulprostone and tiaprostone; and vasoactive intestinal peptides.

Prazosin, prostaglandin E₁ and prostaglandin E₂ are particularly preferred
10 vasoactive agents herein. Additionally, simultaneous administration of two or more vasoactive agents may be desirable and in some cases exhibit a synergistic effect. The combinations are administered within the context of an effective dosing regimen to take advantage of the combined effect. Preferred combinations of vasoactive agents include, for example, combinations of an α -blocker with a prostaglandin such as the combination
15 of prazosin with prostaglandin E₁.

Other pharmaceutical agents useful herein are androgenic agents including, but not limited to: the naturally occurring androgens androsterone, testosterone and
dehydroepiandrosterone (DHEA); pharmaceutically acceptable esters of testosterone; and pharmaceutically acceptable derivatives of testosterone. Testosterone esters are generally
20 formed from the hydroxyl group present at the C-17 position, and particularly preferred esters are the enanthate, propionate, cypionate and phenylacetate esters of testosterone. Exemplary pharmaceutically acceptable derivatives of testosterone include, but are not limited to, methyltestosterone, testolactone, oxymetholone and fluoxymesterone.

Transurethral administration of the agent is preferred although not essential. Use
25 of the VFC device in conjunction with transurethral administration of the agent allows for the enhanced retention of the administered agent within the penis. The agent will typically be administered in a pharmaceutical composition comprising an effective amount of the agent, a vehicle suitable for transurethral drug delivery, and, optionally, a transurethral permeation enhancer. The vehicle is selected from any of a number of
30 common materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with other

components of the composition in a deleterious manner. Other types of components may be incorporated into the pharmaceutical composition as well, for example, surfactants, preservatives (e.g., antioxidants), stabilizers, enzyme inhibitors, and the like, as will be appreciated by those skilled in the art of drug formulation preparation and delivery.

5 As explained in PCT Publication No. WO91/16021, transurethral administration of a pharmaceutical agent can be carried out in a number of different ways. For example, the agent can be introduced into the urethra from a flexible tube, squeeze bottle, pump or aerosol spray. The agent may also be contained in coatings, pellets or suppositories which are absorbed, melted or bioeroded in the urethra. In certain embodiments, the
10 selected agent may be included in a coating on the exterior surface of a penile insert.

Various transurethral drug delivery devices are known in the art, and can be used in the practice of the methods herein. Such devices generally deliver the agent at least about 3 cm into the urethra, and preferably at least about 7 cm into the urethra. Examples of devices suited to deliver a drug transurethrally include those described and illustrated in
15 WO91/16021. The devices can either be manufactured under sterile conditions, thereby eliminating the need for post-manufacturing sterilization, or they can be manufactured under non-sterile conditions and then subsequently sterilized by any suitable technique, e.g., radiation sterilization.

Transurethral compositions may further include one or more permeation enhancers
20 which increase the permeability of the urethral wall to agents administered as described herein and thereby increase the rate at which those agents enter the bloodstream. Transurethral permeation enhancers useful herein include, but are not limited to, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide (C₁₀MSO), polyethylene glycol monolaurate (PEGML),
25 propylene glycol, glycerol monolaurate, lecithin, the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone® from Nelson Research & Development Co., Irvine, CA), alcohols, or the like.

Further, to facilitate insertion of the transurethral agent, a pharmaceutical composition may include a coating having lubricating properties. Such coatings may
30 contain materials such as polyethylene glycol ("PEG"), propylene glycol, or hydroxy alkyl celluloses, for example, which are or become slippery upon insertion into the

urethra. Materials such as glycerol monolaurate, polyethylene glycol monolaurate, and glycerol monolaurate, for example, may combine permeation enhancing properties with lubricating properties.

5 The pharmaceutical composition may additionally include one or more enzyme inhibitors designed to inhibit any agent-degrading enzymes which may be present in the urethra. Such enzyme inhibiting compounds may be determined by those skilled in the art by reference to the pertinent literature and/or using routine experimental methods.

10 In other aspects of the invention, the pharmaceutical agent may be administered topically, transdermally or by any other available and effective means such as by intracavernosal injection. However, transurethral administration is preferred. Nevertheless, it may sometimes be desirable to deliver the agent using an alternative mode of administration.

15 In connection with administration of pharmaceutical agents, the VFC devices of the invention provide a particularly useful adjunct in the treatment of erectile dysfunction in serving to prevent the flow of blood from the penis, thereby increasing the transient retention of a locally administered agent within the penis. As will be appreciated by those skilled in the art, increased retention of such agents within the penis serves to improve the effectiveness of drug administration. For example, concurrent use of the VFC device as described herein results in from at least a two-fold to a ten-fold or greater increase in the dose response efficacy of an administered vasoactive agent in the treatment of erectile dysfunction. Thus, these devices may be used to render effective an otherwise ineffective dose of a vasoactive agent, such as when a user has experienced incomplete response to drug administration due to excessive venous leakage. Furthermore, use of the present devices in connection with drug administration allows lower dosages of pharmaceutical agents to be used.

25 The terminal shaft and glans of the human penis have extensive vascular interconnections with the interior of the corpus cavernosa. The extent of such vascularization, although variable, is sufficient to cause drug transfer problems in topical and transdermal drug administration. Adsorption of topically applied agents through the skin of the penis is generally not sufficiently rapid to overcome the concomitant superficial venous drainage, the drainage of the glans, and distal non-cavernosa transfer

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into the spongiosa, each of which serve to clear the agent from the penis. Thus, prior attempts at topical or transdermal application of agents to the skin of the penis in the treatment of erectile dysfunction have not provided consistent satisfactory erections in light of the minimal cavernosal transfer caused by exodus of the agents from the cavernosum.

However, use of a VFC device as described herein in conjunction with topical, transdermal or intracavernosal administration of therapeutic agents enables enhanced drug retention in the corpora cavernosa and results in enhanced effectiveness of drug therapy. The VFC device applies a mild, adjustable pressure about the periphery of the penis which is sufficient to occlude the superficial venous and spongiosa drainage. Drug transfer problems are thus avoided, and the administered agent is retained within the penis, allowing movement into the corpus cavernosa. This produces smooth muscle response and a consistent erectile response.

The ability to control and adjust the tension provided by the novel VFC device also allows for use in methods to prevent urinary incontinence. Accordingly, in a further embodiment of the invention, a method is provided for preventing involuntary passage of urine from the urethra in an incontinent male individual. The method involves encircling the base of the penis with a VFC device as provided herein. The device can be tensioned about the penis to occlude the urethra and prevent involuntary passage of urine therethrough. The device can be readily loosened when the individual wishes to void, and then re-tensioned. In a related embodiment, the VFC device can be structured so as to exert additional pressure on the urethra.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

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Example 1Use of Venous Flow Control Device to Provide Improved
Erectile Response to Transurethral Drug Administration

Transurethral and intracavernosal administration of alprostadil (prostaglandin E₁)
5 has been shown to be effective in the treatment of erectile dysfunction. However, some
patients are still unable to achieve adequate veno-occlusion using such local
pharmacotherapy. Accordingly, the venous flow control (VFC) device 40 depicted in
Figures 3 and 4 was used in conjunction with transurethral alprostadil administration in
patients previously unresponsive to transurethral therapy alone to assess the ability of the
10 device to supplement or improve the efficacy of such pharmacotherapy in the treatment of
impotence.

The experimental group included eight individuals who had been nonresponsive to
transurethral alprostadil therapy in the treatment of erectile dysfunction. Each individual
underwent color-flow duplex ultrasound evaluation following a 500 μ g dose of alprostadil
15 administered transurethrally. Drug was administered to each individual twice: on one day
without the VFC device; and, on a separate day, with the VFC device. The order of
administration of alprostadil with or without the device was randomized throughout the
experimental group. When the VFC device was used, the loop was positioned about the
base of the penis and tensioned firmly prior to transurethral alprostadil administration.
20 Tension provided by the device was adjusted for comfort 10 minutes after drug
administration. Peak systolic velocity (PSV) and end diastolic velocity (EDV) were
measured after drug administration, and the values obtained were used to calculate the
erectile resistivity index (RI). Subjective patient observations of penile rigidity were also
recorded and scored on a scale of 1-5, wherein 1 = no response, and 5 = rigid.

25 Evaluation of the results of the investigation showed that use of the VFC device
with transurethral alprostadil administration increased the mean (\pm SE) reported penile
rigidity to 3.6 ± 0.4 , from a mean of 2.4 ± 0.3 obtained without use of the device ($p =$
 0.02). Six out of the eight individuals in the experimental group who had previously
failed transurethral alprostadil therapy were able to achieve an erection sufficient for
30 intercourse by using the VFC device in connection with the pharmacotherapy. The mean
duration of erection sufficient for intercourse also increased significantly, from 1.3 ± 1.3

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minutes without the device, to 14 ± 3.6 minutes with the device ($p=0.01$). Hemodynamic measurements using duplex ultrasound showed an increase in RI (0.67 to 0.78, $p=0.07$), as well as a trend toward a decrease in end diastolic velocity (EDV), when the VFC device was used. No significant difference in peak systolic velocity was observed
5 between measurements obtained after transurethral alprostadil administration alone, or transurethral alprostadil administration in conjunction with use of the VFC device.

Accordingly, the results indicate that use of the VFC device in combination with transurethral alprostadil administration can improve both penile rigidity and the duration of an erection that is sufficient for intercourse.

Claims:

1. A device for application to a human penis and adapted to maintain a penile erection, comprising:

5 a length of flexible tubing having a distal end, a proximal end, and a central section having a substantially uniform diameter; and

an integral fastening means adapted to secure the tubing in the form of a loop of adjustable size, comprising a substantially rigid, enlarged segment of tubing substantially adjacent to the proximal end of the tubing and a ring through which a loop of the central
10 section of tubing may be passed, wherein the ring is dimensioned to maintain the tubing in the form of a loop while also allowing adjustment of the size of the loop, and further wherein the enlarged segment of tubing has a diameter which prevents its passage through the ring.

15 2. The device of claim 1, wherein the substantially rigid, enlarged segment of tubing is provided by a substantially spherical body contained within the tubing.

3. The device of claim 1, wherein the tubing is comprised of a latex material.

20 4. The device of claim 3, wherein the latex material comprises about 0.5 to 10 wt. % pigment.

5. The device of claim 1, wherein the length of the tubing is such that the loop fits around a penis.

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6. The device of claim 1, wherein the length of the tubing is such that the loop fits around both a penis and the scrotum at the junction of the pubis.

7. The device of claim 1, wherein the tubing further comprises first and
30 second grasping means respectively arranged adjacent to the distal and proximal ends of

the tubing, wherein the enlarged segment of tubing is between said first and second grasping means and substantially adjacent to the second grasping means.

8. A method for maintaining penile erection in a male individual, comprising:

5 (a) providing (i) a length of tubing sufficient to encircle a penis, having a distal end, a proximal end and a central section, (ii) an integral fastening means comprising a substantially rigid, enlarged segment of tubing substantially adjacent to the proximal end of the tubing, and (iii) a ring through which a portion of the central section of the tubing has been passed to define a loop of adjustable size; and

10 (b) encircling the base of the individual's penis with said loop and tensioning the device thereabout to provide circumferential tension sufficient to prevent excess venous outflow from the penis, wherein tensioning comprises pulling on the distal end of the tubing to reduce the size of the loop and bring the enlarged segment of tubing into close locking engagement with both the ring and a central section of the tubing.

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9. The method of claim 8, further including the step of reducing the circumferential tension provided by the tensioned device during erection so as to retain blood within the penis without substantially obstructing arterial inflow.

20

10. The method of claim 9, wherein reducing the tension is carried out by pulling on the proximal end of the tubing to disengage the enlarged segment of tubing from its close locking engagement with the ring and the central section of the tubing, thereby allowing the size of the loop to be increased.

25

11. A method of maintaining penile erection in a human individual, comprising:

(a) providing (i) a length of tubing sufficient to encircle the penis and pass behind the scrotum at the junction of the pubis, having a distal end, a proximal end and a central section, (ii) an integral fastening means comprising a substantially rigid, enlarged segment of tubing substantially adjacent to the proximal end of the tubing, and (iii) a ring through

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which a portion of the central section of the tubing has been passed to define a loop of adjustable size; and

(b) positioning the loop provided in part (a) so as to encircle the individual's penis and pass behind the scrotum at the junction of the pubis and tensioning the device thereabout to provide circumferential tension sufficient to prevent excess venous outflow from the penis, wherein tensioning comprises pulling on the distal end of the tubing to reduce the size of the loop and bring the enlarged segment of tubing into close locking engagement with both the ring and the central section of the tubing.

10 12. The method of claim 11, further including the step of reducing the circumferential tension provided by the tensioned device during erection so as to retain blood within the penis without substantially obstructing arterial inflow.

15 13. The method of claim 12, wherein reducing the tension is carried out by pulling on the proximal end of the tubing to disengage the enlarged segment of tubing from its close locking engagement with the ring and the portion of the central section of the tubing, thereby allowing the size of the loop to be increased.

20 14. A method for treating erectile dysfunction in a male individual, comprising:
(a) administering a pharmacologically active agent to the individual;
(b) providing (i) a length of tubing sufficient to encircle a penis, having a distal end, a proximal end and a central section, (ii) an integral fastening means comprising a substantially rigid, enlarged segment of tubing substantially adjacent to the proximal end of the tubing, and (iii) a ring through which a portion of the central section of the tubing has been passed to define a loop of adjustable size; and

25 (c) encircling the base of the individual's penis with said loop and tensioning the device thereabout to provide circumferential tension sufficient to prevent excess venous outflow from the penis and cause enhanced retention of the agent within the penis, wherein tensioning comprises pulling on the distal end of the tubing to reduce the size of the loop and bring the enlarged segment of tubing into close locking engagement with both
30 the ring and a portion of the central section of the tubing.

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15. A method for treating erectile dysfunction in a male individual, comprising:

(a) administering a pharmacologically active agent to the individual;

(b) providing (i) a length of tubing sufficient to encircle the penis and pass behind the scrotum at the junction of the pubis, having a distal end, a proximal end and a central section, (ii) an integral fastening means comprising a substantially rigid, enlarged segment of tubing substantially adjacent to the proximal end of the tubing, and (iii) a ring through which a portion of the central section of the tubing has been passed to define a loop of adjustable size; and

(c) positioning the loop so as to encircle the individual's penis and pass behind the scrotum at the junction of the pubis, and tensioning the device thereabout to provide circumferential tension sufficient to prevent excess venous outflow from the penis and cause enhanced retention of the agent within the penis, wherein tensioning comprises pulling on the distal end of the tubing to reduce the size of the loop and bring the enlarged segment of tubing into close locking engagement with both the ring and a portion of the central section of the tubing.

16. The method of claims 14 or 15, wherein the agent is administered locally.

17. The method of claim 16, wherein the agent is administered transurethraly.

18. The method of claims 14 or 15, wherein the agent is a vasoactive agent.

19. The method of claims 14 or 15, wherein the agent is an androgenic agent.

20. A method for preventing urinary incontinence in a male individual, comprising:

(a) providing (i) a length of tubing sufficient to encircle a penis, having a distal end, a proximal end and a central section, (ii) integral fastening means comprising a substantially rigid, enlarged segment of tubing substantially adjacent to the proximal end of the tubing, and (iii) a ring through which a portion of the central section of the tubing has been passed to define a loop of adjustable size; and

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(b) encircling the base of the individual's penis with said loop and tensioning the device thereabout to provide circumferential tension sufficient to prevent involuntary passage of urine from the individual's urethra, wherein tensioning comprises pulling on the distal end of the tubing to reduce the size of the loop and bring the enlarged segment
5 of tubing into close locking engagement with both the ring and a portion of the central section of the tubing.

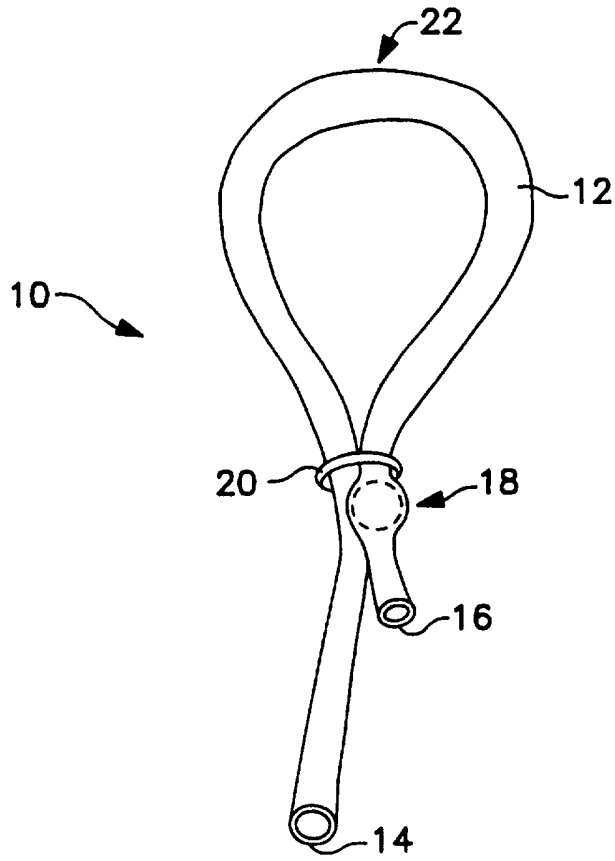


FIG. 1

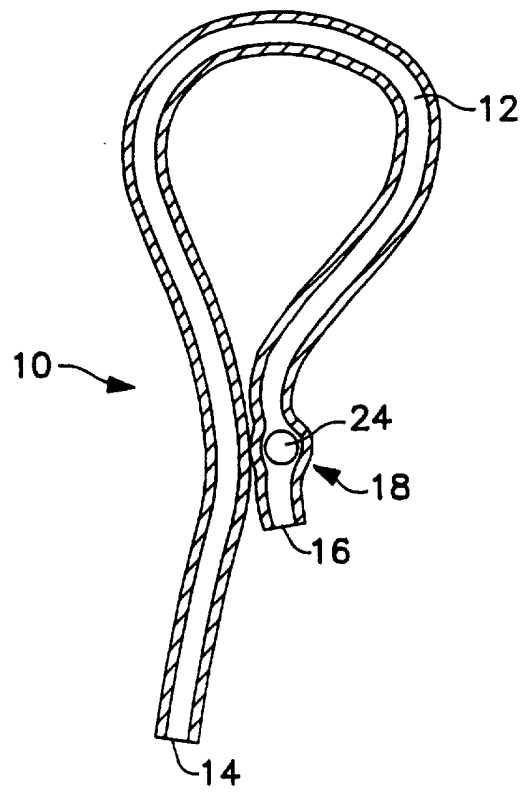


FIG. 2

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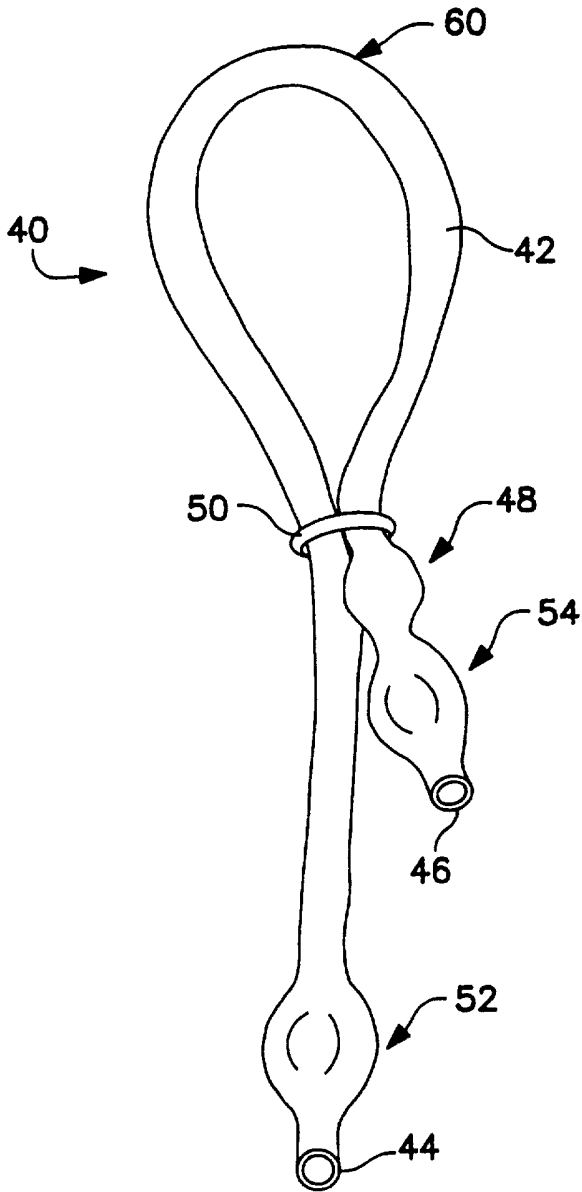


FIG. 3

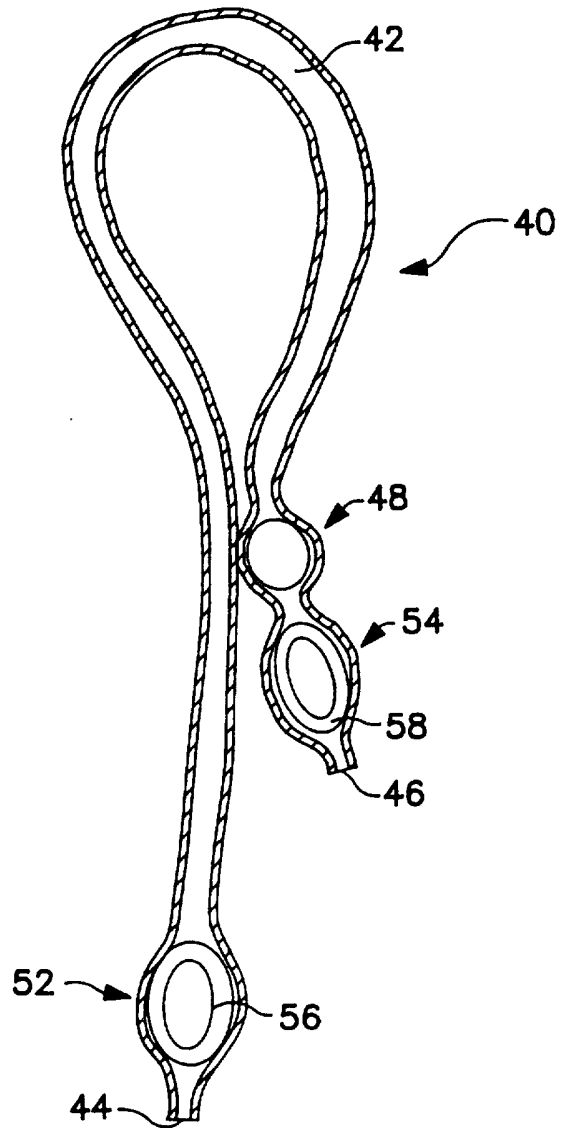


FIG. 4

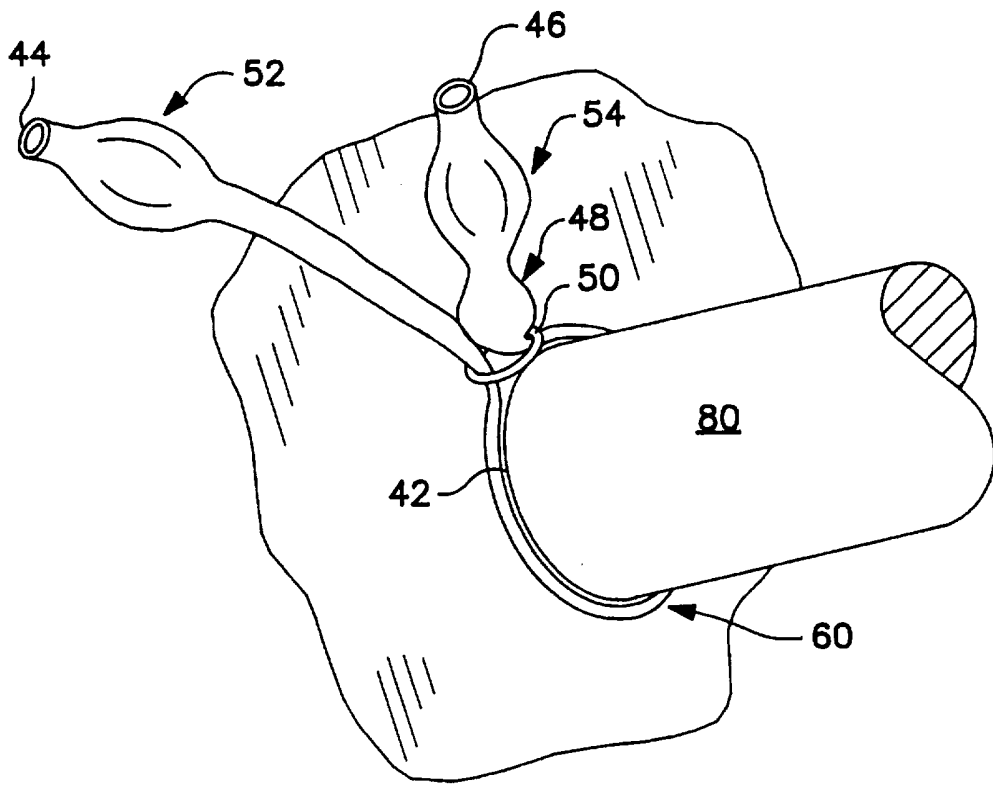


FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/10617

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61F5/41 A61F2/00

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 581 114 A (LARSON) 1 January 1952 cited in the application	1-13
Y	see column 1, line 47 - column 3, line 5; figures 1-6	14-20
Y	WO 91 16021 A (ALZA CORP) 31 October 1991 see claims 1-6; figure 3	14-19
Y	WO 90 11063 A (DACOMED CORP) 4 October 1990 see claim 10	20
A	US 3 461 863 A (SULLINGER GLEN R) 19 August 1969 cited in the application	
	-/--	

Further documents are listed in the continuation of box C.

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
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- "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)
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- "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
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- "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

19 September 1997

Date of mailing of the international search report

21/11/1997

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Authorized officer

Sánchez y Sánchez, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/10617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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		JP 63132825 A	04-06-88
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