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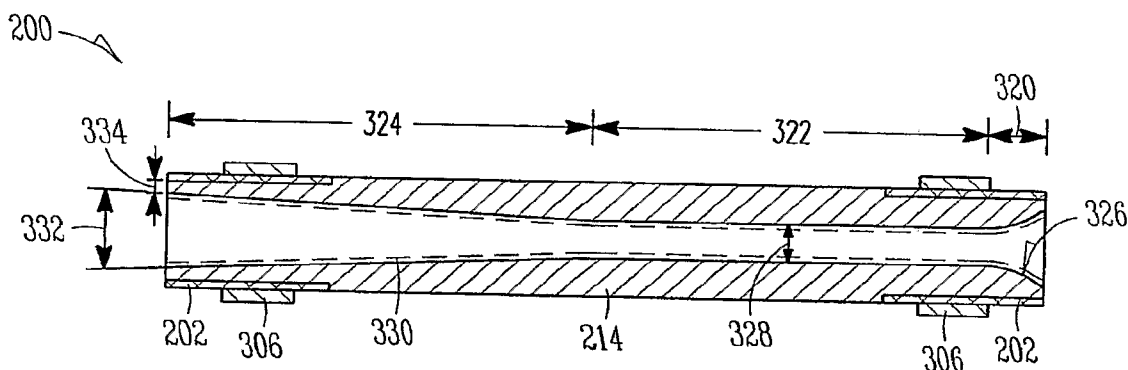
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(57) Abstract: Blood flow restrictors are discussed. In some examples, a restrictor apparatus includes a converging entry portion, a diverging exit portion, and optionally a narrowed portion therebetween to restrict the flow of blood through an arteriovenous graft from a subject's artery to a subject's vein. The structure of the restrictor apparatus decreases the pressure and volume of blood flow between the subject's artery and vein to reduce or prevent hyperplasia or stenosis on the venous side, an increased load on the heart, or blood steal, among other things. The restrictor apparatus can be separate from, but couplable to, the arteriovenous graft. Alternatively, the restrictor apparatus can be integral with the arteriovenous graft. Methods of forming and using the restrictor apparatus are also discussed.



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ARTERIOVENOUS GRAFT BLOOD FLOW CONTROLLERS AND METHODS

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CLAIM OF PRIORITY

Benefit of priority is hereby claimed to U.S. Patent Application Serial Number 60/823,242, filed on August 22, 2006, which is herein incorporated by reference.

10

TECHNICAL FIELD

This patent document pertains generally to vascular access systems, apparatuses, and methods. More particularly, but not by way of limitation, this patent document pertains to arteriovenous graft blood flow controllers and methods.

15

BACKGROUND

A number of medical procedures, such as hemodialysis, chemotherapy, transfusions, etc., require repeated access to a subject's vascular anatomy. In hemodialysis, for example, blood is removed from the subject's artery, treated with a dialysis machine that cleanses the blood of toxins (such as potassium and urea, as well as free water), and introduced back into the subject at a vein. Hemodialysis is typically conducted in a dedicated facility, either in a special room in a hospital or a clinic that specializes in hemodialysis. Hemodialysis sessions typically last about 3-6 hours and occur about 3 times per week for the duration of the subject's life or until the subject receives a kidney transplant.

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For hemodialysis to be effective, large volumes of blood must be removed rapidly from the subject's body, passed through the dialysis machine, and returned to the subject. A number of operations have been developed to provide access to the circulatory system of a subject to connect the subject to the dialysis machine. The three primary modes of access to the blood in hemodialysis include an intravenous catheter, an arteriovenous fistula, or an arteriovenous graft. The type of access is typically influenced by factors such as the degree of the subject's renal (i.e., kidney) failure or the condition of his or her vasculature.

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Catheter access typically consists of a plastic catheter with two lumens. The catheter is inserted into a large vein (typically in a limb) to allow withdrawal of relatively large flows of blood using one lumen. This blood is fed through the dialysis device, and returned to the subject via the other lumen. However, using the catheter
5 access mode almost always allows less blood flow than that of a well functioning arteriovenous fistula or graft.

Arteriovenous fistulas and grafts comprise second and third modes, respectively, of access to the blood in hemodialysis. To create an arteriovenous fistula, a vascular surgeon joins an artery and a vein together (typically in an upper
10 extremity) through anastomosis. Since this bypasses the capillaries, blood flows at a very high rate through the arteriovenous fistula as compared to typical vessel flow. During treatment, two needles or cannulas are inserted into the arteriovenous fistula, one to draw blood and the other to return it. The advantages of arteriovenous fistula use include relative absence of a potential foreign body reaction, as there is no
15 exogenous material involved in their formation, and higher blood flow rates that translate to more effective dialysis. However, if an arteriovenous fistula permits very high flow, then excessive "blood steal" can result in inadequate flow to the distal extremities of that limb. This may result in cold extremities of such limb, cramping pains, or tissue damage.

20 Arteriovenous grafts are much like arteriovenous fistulas, except that an artificial vessel made of a synthetic material is used to join the artery and vein. As such, arteriovenous grafts may result in foreign body reactions. However, arteriovenous grafts can typically be ready for use as a dialysis conduit soon after surgical implantation, unlike arteriovenous fistulas. Arteriovenous grafts are often
25 used when the subject's native vasculature does not permit using an arteriovenous fistula.

While the high blood flow rates of arteriovenous fistulas and grafts are thought to reduce the likelihood of thrombosis, there can be a number of complications including high output heart failure and a distal blood steal syndrome resulting from

such flow. In addition, very high flow may result in thrombosis resulting from venous hyperplasia or stenosis occurring either at the graft-vein anastomosis or centrally in the subclavian or axillary veins.

5

OVERVIEW

Blood flow restrictors are discussed. In some examples, a restrictor apparatus includes a converging entry portion, a diverging exit portion, and optionally a narrowed portion therebetween to restrict the flow of blood through an arteriovenous graft from a subject's artery to a subject's vein. The structure of the restrictor apparatus decreases the pressure and volume of blood flow between the subject's artery and vein to reduce or prevent hyperplasia or stenosis on the venous side, an increased load on the heart, or blood steal, among other things. The restrictor apparatus can be separate from, but couplable to, the arteriovenous graft. Alternatively, the restrictor apparatus can be integral with the arteriovenous graft. Methods of forming and using the restrictor apparatus are also discussed.

10

In Example 1, an apparatus comprises at least one blood flow restrictor apparatus including, a restrictor entry portion, including a fixed dimensioned convergent first lumen that tapers to substantially match an interior diameter of an arterial portion of an arteriovenous graft; and a restrictor exit portion, including a fixed dimensioned divergent second lumen that tapers to substantially match an interior diameter of a venous portion of the arteriovenous graft.

15

In Example 2, the apparatus of Example 1 optionally comprises a restrictor narrowed portion disposed between the restrictor entry portion and the restrictor exit portion, the restrictor narrowed portion including a fixed dimensioned third lumen connecting the first and second lumens, the third lumen having a smaller interior diameter than at least a portion of the first and second lumens, the third lumen substantially matching adjacent interior diameters of the first and second lumens.

20

In Example 3, the apparatus of Example 2 is optionally configured such that the interior diameter of the third lumen is substantially constant.

In Example 4, the apparatus of at least one of Examples 2 or 3 is optionally configured such that the interior diameter of the third lumen is at least about 1.5 millimeters.

5 In Example 5, the apparatus of at least one of Examples 2-4 optionally comprises a biologically active layer on an interior surface of at least a portion of at least one of the first lumen of the restrictor entry portion, the second lumen of the restrictor exit portion, or the third lumen of the restrictor narrowed portion.

10 In Example 6, the apparatus of at least one of Examples 1-5 optionally comprises the arterial portion of the arteriovenous graft, sized and shaped to be coupled to the restrictor entry portion; and the venous portion of the arteriovenous graft, sized and shaped to be coupled to the restrictor exit portion.

15 In Example 7, the apparatus of Example 6 is optionally configured such that the arterial portion of the arteriovenous graft includes an arterial end portion anastomosable with an artery of a subject and a portion configured to receive an arterial hemodialysis cannula; and the venous portion of the arteriovenous graft includes a venous end portion anastomosable with a vein of the subject and a portion configured to receive a venous hemodialysis cannula.

20 In Example 8, the apparatus of at least one of Examples 6 or 7 is optionally configured such that the restrictor apparatus comprises a structure that is separate from, but couplable to, at least one of the arterial portion of the arteriovenous graft or the venous portion of the arteriovenous graft.

25 In Example 9, the apparatus of Example 8 is optionally configured such that the restrictor apparatus comprises a reduced outer diameter portion on at least one of the restrictor entry portion or the restrictor exit portion, the reduced diameter portion sized and shaped to be inserted within an interior diameter of at least one of the arterial portion of the arteriovenous graft or the venous portion of the arteriovenous graft.

In Example 10, the apparatus of Example 9 optionally comprises at least one annular clamp sized and shaped to be disposed around a portion of the arteriovenous

graft and the reduced diameter portion of the restrictor apparatus to couple the arteriovenous graft to the at least one restrictor apparatus.

5 In Example 11, the apparatus of at least one of Examples 1-10 is optionally configured such that the outward taper of the divergent second lumen of the restrictor exit portion includes an exit angle, with respect to a coaxial central axis of the second lumen, of less than or equal to about 6 degrees.

10 In Example 12, the apparatus of at least one of Examples 1-11 is optionally configured such that the outward taper of the divergent second lumen of the restrictor exit portion includes an exit angle, with respect to a coaxial central axis of the second lumen, that is small enough to substantially inhibit blood clot formation.

In Example 13, the apparatus of at least one of Examples 1-12 is optionally configured such that the convergent first lumen of the restrictor entry portion includes a radially curved entry having a radius of curvature of at least about 2 millimeters.

15 In Example 14, the apparatus of at least one of Examples 1-13 is optionally configured such that the convergent first lumen of the restrictor entry portion includes an entry angle, with respect to a coaxial central axis of the first lumen, of less than or equal to about 6 degrees.

20 In Example 15, the apparatus of at least one of Examples 1-14 is optionally configured such that the restrictor apparatus comprises a structure that is separate from, but couplable within, the arteriovenous graft.

In Example 16, the apparatus of at least one of Examples 1-15 is optionally configured such that the restrictor apparatus comprises a structure that is integrated with the arteriovenous graft as a unitary device.

25 In Example 17, the apparatus of at least one of Examples 1-16 is optionally configured such that at least a portion of the restrictor apparatus includes a rigid material that is substantially non-penetrable by a hemodialysis cannula.

In Example 18, a method of restricting a flow of blood through an arteriovenous graft system comprises guiding a converging of the flow of blood from a first fluid lumen defined by a first interior diameter wall of an arteriovenous graft to a

second fluid lumen defined by a fixed interior diameter wall of a narrowed portion of at least one restrictor apparatus; and guiding a diverging of the flow of blood from the second fluid lumen defined by the fixed interior diameter wall of the narrowed portion of the restrictor apparatus back to a third fluid lumen defined by a second interior
5 diameter wall of the arteriovenous graft.

In Example 19, the method of Example 18 optionally comprises subcutaneously implanting the arteriovenous graft system.

In Example 20, the method of Example 19 is optionally configured such that subcutaneously implanting the arteriovenous graft system includes subcutaneously
10 implanting an arterial end portion of the arteriovenous graft, a venous end portion of the arteriovenous graft, and the restrictor apparatus located between the arterial and venous end portions.

In Example 21, the method of Example 20 optionally comprises anastomizing the arterial end portion to an artery; and anastomizing the venous end portion to a
15 vein.

In Example 22, the method of at least one of Examples 20 or 21 optionally comprises inserting an arterial cannula into the arterial end portion; inserting a venous cannula into the venous end portion; performing hemodialysis using the arterial and venous cannulas; using the restrictor apparatus located between the arterial and venous
20 cannulas to restrict blood flow bypassing the arterial and venous cannulas through the arteriovenous graft during the hemodialysis; and removing the arterial and venous cannulas from the respective arterial and venous end portions.

In Example 23, the method of Example 22 is optionally configured such that restricting blood flow includes permitting blood flow through the arterial and venous
25 cannulas of at least 300 cubic centimeters per minute during the hemodialysis.

In Example 24, the method of Example 22 is optionally configured such that restricting blood flow includes permitting blood flow through the arterial and venous cannulas of at least 400 cubic centimeters per minute during the hemodialysis.

In Example 25, a method of forming a restrictor apparatus comprises forming a convergent first lumen that tapers to substantially match an interior diameter of an arterial portion of an arteriovenous graft in a restrictor entry portion; forming a divergent second lumen that tapers to substantially match an interior diameter of a venous portion of the arteriovenous graft in a restrictor exit portion; and forming a third lumen connecting the first and second lumens in a restrictor narrowed portion, the third lumen having a fixed interior diameter smaller than at least a portion of the first and second lumens, the third lumen substantially matching adjacent interior diameters of the first and second lumens.

In Example 26, the method of Example 25 optionally comprises incorporating the restrictor apparatus with the arteriovenous graft extending from the arterial end portion to the opposite venous end portion.

In Example 27, the method of Example 26 is optionally configured such that incorporating the restrictor apparatus with the arteriovenous graft comprises cutting the arteriovenous graft between the arterial end portion and the venous end portion; and coupling the restrictor apparatus between the arterial end portion and the venous end portion of the arteriovenous graft.

In Example 28, the method of Example 26 is optionally configured such that incorporating the restrictor apparatus with the arteriovenous graft includes disposing the restrictor apparatus within an interior diameter wall of the arteriovenous graft.

In Example 29, the method of Example 26 is optionally configured such that incorporating the restrictor apparatus with the arteriovenous graft includes forming an arteriovenous graft having an integrated restrictor apparatus.

In Example 30, the method of at least one of Examples 25-29 is optionally configured such that forming the first lumen includes forming an entry angle of less than or equal to about 6 degrees between a wall of the first lumen and a coaxial axis defining a center of the first lumen.

In Example 31, the method of at least one of Examples 25-30 is optionally configured such that forming the second lumen includes forming an exit angle of less

than or equal to about 6 degrees between a wall of the second lumen and a coaxial axis defining a center of the second lumen.

In Example 32, the method of at least one of Examples 25-31 is optionally configured such that forming the first lumen includes forming a convergent curved wall having a radius of curvature of at least about 2 millimeters.

In Example 33, the method of at least one of Examples 25-32 is optionally configured such that forming the third lumen includes forming an effective interior diameter of the third lumen of at least about 1.5 millimeters.

In Example 34, the method of at least one of Examples 25-33 optionally comprises disposing a biologically active layer on an interior surface of at least one of the first, second, or third lumens.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not necessarily drawn to scale, like numerals describe similar components throughout the several views. The drawings illustrate generally, by way of example, but not by way of limitation, various embodiments discussed in the present document.

- FIG. 1 is a plan view of a hemodialysis system and an environment in which the hemodialysis system can generally be used.
- FIG. 2A is a schematic view of an arteriovenous graft and an environment in which the graft can be used.
- FIG. 2B is a schematic view of an arteriovenous graft system and an environment in which the graft system can be used.
- FIG. 2C is a detailed view of an arteriovenous graft system and an environment in which the graft system can be used.
- FIG. 3A is a schematic view of portions of an arteriovenous graft system, as constructed in accordance with an embodiment.

- FIG. 3B is a side cross-sectional view along line 3B-3B of FIG. 3A illustrating interior portions of the arteriovenous graft system of FIG. 3A.
- 5 FIG. 3C is a transverse cross-sectional view along line 3C-3C of FIG. 3A illustrating the varying diameters of the arteriovenous graft system of FIG. 3A.
- FIG. 4A is a schematic view of portions of an arteriovenous graft system, as constructed in accordance with an embodiment.
- 10 FIG. 4B is a side cross-sectional view along line 4B-4B of FIG. 4A illustrating interior portions of the arteriovenous graft system of FIG. 4A.
- FIG. 4C is a transverse cross-sectional view along line 4C-4C of FIG. 4A illustrating the varying diameters of the arteriovenous graft system of FIG. 4A.
- 15 FIG. 5 is a summary chart from a computer simulation listing blood flow properties when using and not using a restrictor apparatus, as constructed in accordance with an embodiment.
- FIG. 6A is a schematic view of a hemodialysis system not including a restrictor apparatus and one or more measurement devices used for *in vivo* experimentation.
- 20 FIG. 6B is a schematic view of a hemodialysis system including a restrictor apparatus and one or more measurement devices used for *in vivo* experimentation.
- 25 FIG. 6C is a group data chart summarizing *in vivo* experimentation results of a hemodialysis system including and not including a restrictor apparatus, as constructed in accordance with an embodiment.

FIG. 7 illustrates an example method of forming an arteriovenous graft system, including forming a restrictor apparatus having fixed dimensions.

5 FIG. 8 illustrates an example method of restricting a flow of blood through an arteriovenous graft system.

DETAILED DESCRIPTION

Healthy kidneys not only clean blood by filtering out extra water and wastes, but they also produce hormones that help maintain strong bones and healthy blood.
10 When a subject's kidneys fail, numerous debilitating effects are experienced by the subject, including rising blood pressure, accumulation of fluids and toxic wastes in the subject's body and insufficient red blood cell production. Treatment is therefore required to artificially replace the work of the failed kidneys.

A hemodialysis machine acts as an artificial kidney to remove toxins and water
15 from the subject's blood. Hemodialysis generally uses a special filter (typically a dialyzer **102**) to clean the blood. FIG. 1 illustrates a hemodialysis system **100** and a subject **104** with which the hemodialysis system can be used. The hemodialysis system **100** generally includes a dialysis machine **106**, one or more cannulas **108**, **110**, and an arteriovenous graft **202** (FIG. 2A). As shown in FIG. 2A, the arteriovenous graft **202** extends from an arterial end portion **204**, which can be anastomosed with a
20 subject's artery **206**, to a venous end portion **208**, which can be anastomosed with a subject's vein **210**.

As shown in FIG. 2C, an arterial cannula **108** and a venous cannula **110** can be inserted into the arteriovenous graft **202** near the graft-artery anastomosis **220** and
25 graft-vein anastomosis **222**, respectively. Then, as shown in FIG. 1, blood from the subject **104** can be drawn via the arterial cannula **108** at the arterial side of the arteriovenous graft and received by the dialysis machine **106** where it is dialyzed (i.e., cleansed). After being dialyzed, the blood can be returned to the subject **104** at the venous side of the arteriovenous graft via the venous cannula **110**.

To filter the blood efficiently, the dialysis machine **106** typically requires a blood flow rate of about 400 cubic centimeters per minute (i.e., 400 cc/min). To supply such a high blood flow rate while preventing vessel wall collapse as the dialysis machine **106** extracts blood, a relatively large diameter graft (e.g., a graft about 6 millimeters in tubular interior diameter) is used. However, such large diameter grafts can cause high output heart failure, atrophy of one or more peripheral limbs, such as a hand **212** (FIG. 2A), or thrombosis secondary to venous hyperplasia or stenosis occurring either at the graft-vein anastomosis **222** (FIG. 2C) or centrally in the subclavian or axillary veins.

The present inventors have recognized a need for, among other things, cost-effective vascular access systems, apparatuses, and methods that reduce the excess circulatory load obligated by a relatively large diameter arteriovenous graft **202** and lessen the blood steal of such graft **202** by reducing flow through it, without encouraging clotting, and while still maintaining a high flow rate during dialysis. Accordingly, the present inventors have developed a blood flow restrictor apparatus **214** for use with the arteriovenous graft **202** (collectively referred to as an arteriovenous graft system **200** (*see, e.g.*, FIGS. 2B, 2C, 3A, 3B, 4A, and 4B)). The restrictor apparatus **214** is sized and shaped to, among other things, reduce the basal (non-hemodialysis state) blood flow through the arteriovenous graft **202**, while still allowing the flow rates typical for efficient dialysis. In some examples, the restrictor apparatus **214** can, additionally or alternatively, reduce recirculation of dialyzed blood, thereby facilitating the obtaining of cleaner blood in less time. Reducing recirculation of dialyzed blood increases hemodialysis efficiency, which can lessen the hemodialysis treatment time requirements for subjects **104** with renal failure.

Examples

An example of a right arm **216** of a subject **104** (FIG. 1) subcutaneously implanted with an arteriovenous graft system **200** is shown in FIG. 2B. In this example, the arteriovenous graft system **200** includes a tubular or similar arteriovenous graft **202** and an integral or separable blood flow restrictor apparatus

214. The arteriovenous graft system **200** is generally connected between a subject's artery **206**, such as one of the brachial, ulnar, or radial arteries, and a subject's vein **210**, such as the cephalic vein.

FIG. **2C** illustrates in more detail, a portion of the subject's right arm **216** and
5 the arteriovenous graft system **200** subcutaneously implanted therein. The arteriovenous graft system **200** provides a shunted path of low blood flow resistance that allows a substantial portion of the arterial blood flowing through the subject's artery **206** to be diverted at the graft-artery sewn anastomosis **220**, through the arteriovenous graft **202** and restrictor apparatus **214**, to the subject's vein **210** at the
10 graft-vein sewn anastomosis **222**, such as during the blood diversion of a hemodialysis session.

During hemodialysis, an arterial cannula **108** and a venous cannula **110** are inserted into the arteriovenous graft **202** near the graft-artery anastomosis **220** and the graft-vein anastomosis **222**, respectively. Blood is drawn from the subject **104** (FIG.
15 **1**) upstream of the restrictor apparatus **214** via the arterial cannula **108** at the arterial end portion **204** of the arteriovenous graft **202**, sent through a dialysis machine **106** (FIG. **1**) where it is dialyzed, and returned to the subject **104** downstream of the restrictor apparatus **214** at the venous end portion **208** of the arteriovenous graft **202** via the venous cannula **110**. In one example, but as may vary, the venous cannula **110**
20 and the arterial cannula **108** are inserted into the subject's skin about 2-3 centimeters or more apart, which translates to about 8-10 centimeters or more separation on the arteriovenous graft **202** due to a U-shape implantation configured, such as is shown in FIG. **2C**. This 8-10 centimeters or more separation reduces or prevents recirculation of dialyzed blood through the arteriovenous graft **202**. The blood flow restrictor
25 apparatus **214** can be placed or located in the arteriovenous graft **202** between such insertion points of the arterial cannula **108** and the venous cannula **110**. The blood flow restrictor apparatus **214** permits the requisite high flow from the arterial cannula **108** and through the venous cannula **110** during dialysis, but restricts the blood flow through the fixed dimensions of the restrictor apparatus itself, during and between

hemodialysis sessions. This reduces the complications associated with a high flow rate arteriovenous graft, such as high output heart failure, atrophy of the distal hand **212**, or thrombosis secondary to venous hyperplasia or stenosis occurring either at the graft-vein anastomosis **222** or centrally in the subclavian or axillary veins, as
5 discussed above.

To prevent insertion of one or both of the arterial **108** or venous **110** cannula into the restrictor apparatus **214**, the restrictor apparatus **214** itself can include a non-puncturable structure (*see, e.g.*, FIGS. **3A-3B**) or a rigid collar **402** or other puncture resistant covering can be disposed around an exterior of the restrictor apparatus **214**
10 (*see, e.g.*, FIGS. **4A-4B**).

In certain examples, the arteriovenous graft **202** includes a tubular structure composed of or including a synthetic material, such as GORETEX™ manufactured by W.L. Gore & Associates, Inc. of Newark, DE. Additionally or alternatively, the arteriovenous graft **202** can include a woven or other self-sealing material made of any
15 of a variety of one or more biocompatible materials, including biocompatible polymers, metals, alloys, or a combination thereof, such as polyester, polytetrafluoroethylene, polyethylene, polypropylene, polyurethane, silicone, stainless steel, titanium, or platinum, some of which are manufactured by Gish Biomedical, Inc. of Rancho Santa Margarita, CA.

The human body may react to introduction of the synthetic materials of an arteriovenous graft **202**. The body's reaction may include thrombus formation in or around the arteriovenous graft **202**. While woven graft materials, such as GORETEX™, may not be recognized by the subject's body as a foreign body to the same degree as non-woven materials, woven materials may still experience some
25 degree of body reaction, such as inflammation. For this reason, the arteriovenous grafts **202** can be made larger in interior diameter than what is needed to accommodate the dialysis machine's **106** (FIG. 1) about 400 cc/min requisite blood flow. This larger size, in turn, can result in high volume blood flow (e.g., 800-900 cc/min), which may further result in hyperplasia, among other things. Hyperplasia is a

condition that may occur when the higher pressure/volume of the arterial flow crosses the boundary from the relatively non-compliant arteriovenous graft **202** to the more compliant outflow vein **210** at the venous anastomosis **222**. The resultant intima hyperplasia in the vein **210** adjacent to the anastomosis **222** may lead to progressive stenosis and eventually premature clotting and arteriovenous graft **202** occlusion. In addition to hyperplasia and stenosis, the large obligate shunted blood volumes may lead to an increased load on the heart and blood steal that results in poor circulation at the extremity beyond or distal to the arteriovenous graft **202**.

The restrictor apparatus **214** comprises a size and shape that reduces the pressure and volume of blood flow through the arteriovenous graft **202** (e.g., by about 40-50%) generally without thrombus formation, and accordingly may reduce or eliminate the above discussed problems with hyperplasia, stenosis, increased heart load, or blood steal. Further, the restrictor apparatus **214** still allows adequate blood flow typically needed by the dialysis machine **106** during dialysis sessions (e.g., about 400 cc/min blood flow; however, in certain circumstances about 300 cc/min may suffice). In certain examples, the arteriovenous graft **202** is about 5-6 inches long and about 6 millimeters in interior diameter outside the region of the restrictor apparatus **214**. As shown, the implanted shape of the arteriovenous graft **202** between the subject's artery **206** and vein **210** can generally resemble a U-shape (i.e., make an approximate 180 degree change in direction). In one such example, the restrictor apparatus **202** is disposed on a generally straight leg portion of the U-shape. In another example, the restrictor apparatus **202** comprises a pliable (i.e., bendable) material and is disposed on a curved portion of the U-shape. As phantomly shown, the subject's vein **210** can be ligated **270** upstream of the graft-vein anastomosis **222**.

Although the present examples focus on an arteriovenous graft system **200** subcutaneously implanted within a subject's arm **216** (see, e.g., FIG. 2B), the present subject matter is not so limited. The arteriovenous graft system **200** can alternatively be implanted in any suitable location of the subject's body **104** (FIG. 1). For instance,

in certain examples, the arteriovenous graft system 200 can be implanted within a subject's leg 112 (FIG. 1).

FIG. 3A illustrates portions of an example of an arteriovenous graft system 200. The arteriovenous graft system 200 comprises an arteriovenous graft 202 and a restrictor apparatus 214. As shown, the restrictor apparatus 214 can comprise a structure separate from, but couplable to, the arteriovenous graft 202. In certain examples, the arteriovenous graft 202 comprises a tubular structure having an arterial end portion 204 and a venous end portion 208. The restrictor apparatus 214 can be interposed between the arterial 204 and venous 208 end portions and coupled to adjacent tubular arteriovenous graft 202 portions via reduced apparatus diameter portions 302. The reduced apparatus diameter portions 302 create a shoulder 304 on the restrictor apparatus 214 to which the arterial 204 and venous 208 end portions can abut against when the tubular graft portions 204, 208 are fitted over the reduced apparatus diameter portions 302. The arteriovenous graft 202 and the restrictor apparatus 214 can be securely coupled to one another via stainless steel clamps 306, such as those manufactured by Oetiker, Inc. of Marlette, MI. Advantageously, clamp materials such as stainless steel and the like are durable, non-corrosive, and non-thrombogenic.

As discussed above, blood from the subject 104 (FIG. 1) flows from an artery 206 (FIG. 2C), through the shunted arteriovenous graft 202 and restrictor apparatus 214, and into a vein 210 (FIG. 2C). To connect the subject 104 to a dialysis machine 106, an arterial 108 and a venous 110 cannula (FIG. 2C) are inserted through the skin and into the arteriovenous graft 202. Blood is removed from the subject 104 through the arterial cannula 108, circulated through the dialysis machine 106, and returned to the subject 104 through the venous cannula 110. In certain examples, the arteriovenous graft 202 comprises a woven material 308 configured to be punctured by the cannulas 108, 110 and to self-seal upon their removal. In other examples, the arteriovenous graft 202 can include dedicated cannula injection portions, which include a self-sealing material, such as silicone or the like.

FIG. 3B is a side cross-sectional view taken along line 3B-3B of FIG. 3A and illustrates the interior structure of one example of an arteriovenous graft system 200. The arteriovenous graft system 200, according to this example, includes an arteriovenous graft 202 coupled to an intermediately disposed restrictor apparatus 214. 5 The arteriovenous graft 202 is securely coupled to the restrictor apparatus 214 via one or more annular clamps 306, such as stainless-steel annular clamps. As shown, but as may vary, the restrictor apparatus 214 can include a side cross-sectional profile having three portions including a restrictor entry portion 320, a restrictor narrowed portion 322, and a restrictor exit portion 324. In another example, the restrictor apparatus 214 10 can include a side cross-sectional profile having two portions including a restrictor entry portion 320 and a restrictor exit portion 324. Each of the restrictor entry portion 320, the restrictor narrowed portion 322, and the restrictor exit portion 324, if present, have specified fixed internal dimensions (i.e., interior diameters and longitudinal lengths) based on one or more desired blood flow characteristics. Like most foreign 15 objects introduced into a subject's body, it is advantageous to keep the exterior size of the restrictor apparatus 214 small.

In this example, the interior structure of the restrictor apparatus 214 includes a restrictor entry portion 320 having a radius of curvature, a constant diameter restrictor narrowed portion 322, and a gently tapered diverging restrictor exit portion 324. It is 20 desirable to have a smooth transition between the arteriovenous graft 202 and the restrictor apparatus 214. A restrictor entry portion 320 having a large entry radius 326 reduces turbulence, which causes platelets in the blood to collide, and which can induce clot formation. To reduce or avoid turbulent blood flow, varying examples of the restrictor apparatus 214 comprise an entry having a radius of curvature of about 2 25 millimeters or more. As shown, the restrictor entry portion 320 tapers from (1) a diameter substantially similar to an interior diameter of the arteriovenous graft 202 on a first end of the restrictor entry portion 320 to (2) the diameter of the restrictor narrowed portion 322 on a second end of the restrictor entry portion 320.

The restrictor narrowed portion **322** is generally smooth and generally maintains a fixed and constant diameter **328** along its length. The generally smooth finish of the restrictor narrowed portion **322** helps to prevent thrombosis by not encouraging turbulent blood flow. A longer restrictor narrowed portion **322** will
5 generally further reduce blood flow, but should not be so long as to encourage clotting. In certain examples, the restrictor narrowed portion **322** includes a length of between 1-100 millimeters, such as about 25 millimeters. In certain examples, the effective interior diameter of the restrictor narrowed portion **322** is at least about 1.5 millimeters. In certain other examples, the effective interior diameter of the restrictor
10 narrowed portion **322** is at least about 2.5 millimeters, which is believed to stop high viscous shear rates and to successfully reduce the flow of blood through the arteriovenous graft system **200**.

To inhibit thrombus formation, the restrictor apparatus **214** can comprise a coating of a biologically active layer **330** (e.g., an anti-thrombogenic coating), such as
15 that manufactured by Carmeda of Upplands Vasby, Sweden, which effectively reduces the interior diameter **328** of the restrictor narrowed portion **322**. Thus, in certain examples, the pre-coating interior diameter **328** of the restrictor narrowed portion **322** is about 2.8-3.0 millimeters, such that when the biologically active layer **330** is taken into account, the effective interior diameter **328** of the restrictor narrowed portion is
20 about 2.5 millimeters or more. The biologically active layer **330** can be applied to the surface of the restrictor narrowed portion **322** by coating, spraying, dipping, or vapor deposition. Such layer **330** can extend along the linear length as phantomly shown in FIG. **3B**, or be localized to a particular area.

The restrictor exit portion **324** is shown gently tapered having an exit angle
25 **332**. Computer simulation indicates that an exit angle **332** of about 6 degrees or less advantageously inhibits or prevents blood flow separation or flow turbulence. As shown, the restrictor exit portion **324** diverges from the diameter **328** of the restrictor narrowed portion **322** on a first end to a diameter that is substantially similar to the interior diameter of the arteriovenous graft **202** on a second end. In certain examples,

a step **334** of about 0.5 millimeters or less can exist at the exit of the restrictor apparatus **214** so that there is essentially no discontinuity between the exit portion **324** of the restrictor and the interior diameter of the arteriovenous graft **202**.

Together, in at least one example, the restrictor entry portion **320**, the restrictor narrowed portion **322**, and the restrictor exit portion **324** decrease the dynamic pressure and volume of blood flow passing through the arteriovenous graft system **200**. This lessens the blood steal from a limb **212** (FIG. **2B**) peripheral to the arteriovenous graft system **200** and reduces the blood flow loads on the heart and veins, all without affecting needed dialysis flow rates and without encouraging clotting. The amount of flow restriction provided by the restrictor apparatus **214** is dependent on the interior diameter and length of the apparatus, such as the interior diameter and length of the restrictor narrowed portion **322**. For instance, a longer restrictor narrowed portion **322** generally results in greater flow restriction, but may result in clotting if too long. On the other hand, a shorter restrictor narrowed portion **322** generally results in less flow restriction and can therefore be less effective in reducing blood steal (*see, e.g.*, FIG. **5**). A greater restrictor narrowed portion diameter **328** generally results in less clotting, but also less restriction and more blood steal. Advantageously, the separate structure restrictor apparatus **214** illustrated in FIGS. **3A-3C** can be used with a conventional vascular access graft, such as by retrofitting the restrictor apparatus **214** into an intermediate portion of an existing arteriovenous graft **202** that has been cut into two pieces. Alternatively, the separate structure restrictor apparatus **214** can be disposed (e.g., slid) within a conventional vascular access graft.

FIG. **3C** is a transverse cross-section along line **3C-3C** of FIG. **3A** and illustrates the varying diameters of one example of an arteriovenous graft system **200**. Taken at an outermost end of a reduced diameter portion **302** (FIG. **3A**), the cross-section shown in FIG. **3C** shows an annular clamp **306** encircling a tubular arteriovenous graft **202** and the tapered restrictor entry portion **320**. As shown, the restrictor entry portion **320** tapers to an interior diameter **328** of the restrictor narrowed

portion 322. While FIGS. 3A-3C illustrate a traverse cross-section of the arteriovenous graft system 200 having a circular configuration, the traverse cross-section can also be oval or some other configuration.

FIG. 4A illustrates portions of another example of an arteriovenous graft system 200. In this example, the arteriovenous graft system 200 comprises an arteriovenous graft 202 and an integral restrictor apparatus 214. Unlike the restrictor apparatus 214 of FIGS. 3A-3C, the restrictor apparatus 214 of FIGS. 4A-4C together with the arteriovenous graft 202 comprise a unitary construction. The restrictor apparatus 214 can be encircled or surrounded, at least in part, by a relatively non-penetrable (i.e., non-puncturable) collar 402. This prevents cannula 108, 110 (FIG. 2C) insertions into the restrictor apparatus and helps permit a caregiver to be able to palpate the restrictor to determine its position. In certain examples, the collar 402 comprises a rigid biocompatible material, such as a biocompatible metal (e.g., titanium or stainless-steel) or a biocompatible plastic.

FIG. 4B is a side cross-sectional view taken along line 4B-4B of FIG. 4A and illustrates the interior structure of another example of an arteriovenous graft system 200. The arteriovenous graft system 200, in this example, includes an arteriovenous graft 202 integrated with a restrictor apparatus 214. As shown, the restrictor apparatus 214 can include a side cross-sectional profile that includes a restrictor entry portion 420, a restrictor narrowed portion 422, and a restrictor exit portion 424. Each of the restrictor entry portion 420, the restrictor narrowed portion 422, and the restrictor exit portion 424 have specified fixed internal dimensions (i.e., interior diameters and longitudinal lengths), which can be established based on one or more desired blood flow characteristics. For instance, the arteriovenous graft system 200 can include varying interior dimensions in the vicinity of the restrictor apparatus 214 such that the walls are thicker at the restrictor entry portion 420, the restrictor narrowed portion 422, and the restrictor exit portion 424 than at the arterial 204 and venous 208 end portions of the arteriovenous graft 202 (FIG. 4A).

In this example, the interior structure of the restrictor apparatus 214

includes a gently tapered converging restrictor entry portion **420**, a constant diameter restrictor narrowed portion **422**, and a gently tapered diverging restrictor exit portion **424**. It is believed to be desirable to have a smooth transition between the interior diameter of the arteriovenous graft **202** and that of the restrictor apparatus **214**. A
5 restrictor entry portion **420** having as large (or near as large) as entry radius **326** (FIG. **3B**) as possible may reduce turbulence, which causes platelets in the blood to collide and may induce clot formation. To avoid turbulent blood flow, in certain examples, the restrictor apparatus **214** includes an entry having a radius of curvature of at least about 2 millimeters. As another example, FIG. **4B** shows an example in which the
10 restrictor entry portion **420** can include a converging tapered entry angle **418** of about 6 degrees or less.

The restrictor narrowed portion **422** is generally smooth and maintains a fixed and constant diameter **428** along its length. The generally smooth finish of the restrictor narrowed portion **422** helps to prevent thrombosis by not encouraging
15 turbulent blood flow. A longer restrictor narrowed portion **422** further reduces blood flow; however, the restrictor narrowed portion **422** should not be so long as to reduce flow to an extent that encourages clotting. In certain examples, the restrictor narrowed portion **422** comprises a length between 1-100 millimeters, such as about 25 millimeters. In certain examples, the effective interior diameter of the restrictor
20 narrowed portion **322** is at least about 1.5 millimeters. In certain other examples, the effective interior diameter of the restrictor narrowed portion **322** is at least about 2.5 millimeters, which is expected to stop high viscous shear rates and to successfully reduce the flow of blood through the arteriovenous graft system **200**.

The restrictor exit portion **424** is shown gently tapered having an exit angle
25 **432**. An exit angle **432** of about 6 degrees or less advantageously prevents blood flow separation and flow turbulence. As shown, the restrictor exit portion **424** diverges from the diameter **428** of the restrictor narrowed portion **422** on a first end to a diameter substantially similar to the interior diameter of the arteriovenous graft **202** on a second end. A step **434** of about 0.5 millimeters or less can exist at the exit of the

restrictor apparatus **214** so that there is essentially no discontinuity between the restrictor and the interior diameter of the arteriovenous graft **202**.

In certain examples, the restrictor entry portion **420**, the restrictor narrowed portion **422**, and the restrictor exit portion **424** decrease the dynamic pressure and volume of blood flow passing through the arteriovenous graft system **200**. This lessens the blood steal from a peripheral limb **212** (FIG. **2B**) and reduces the blood flow load on the heart and veins, all without affecting needed dialysis flow rates and without encouraging clotting. The amount of flow restriction provided by the restrictor apparatus **214** depends on its interior diameter and length, such as the interior diameter and length of the restrictor narrowed portion **322**. For instance, a longer narrowed portion **422** will further reduce flow, but may result in clotting if too long. A greater diameter **428** of the narrowed portion will result in less clotting, but also less flow restriction.

FIG. **4C** is a transverse cross-section along line **4C-4C** of FIG. **4A** and illustrates the varying diameters of one example of an arteriovenous graft system **200**. Taken at an end of the restrictor apparatus **214**, the cross-section shown in FIG. **4C** shows a collar **402** about the walls of the restrictor apparatus **214** and the tapered restrictor entry portion **420**. As shown, the restrictor entry portion **420** tapers to an interior diameter **428** of the restrictor narrowed portion **422**. While FIGS. **4A-4C** illustrate a traverse cross-section of the arteriovenous graft system **200** having a circular configuration, the traverse cross-section can also be oval or some other configuration.

FIG. **5** is a summary chart **500** from a computer simulation comparing the simulated blood flow properties within a subject **104** (FIG. **1**) and in an arteriovenous graft **202** or an arteriovenous graft system **200** (FIG. **2B**) (including an arteriovenous graft **202** and a restrictor apparatus **214** (FIG. **2B**)) implanted within the subject. Line **502** of the summary chart **500** lists the simulated blood flow properties occurring within the subject **104** and in the arteriovenous graft **202** (which does not include a restrictor apparatus **214**). Lines **504** and **506** of the summary chart **500** list the

simulated blood flow properties occurring within the subject 104 and in arteriovenous graft systems 200 including restrictor narrowed portions 322 (*see, e.g.*, FIG. 3B) of 25 millimeters and 45 millimeters in length, respectively. The computer simulation according to this example assumes a graft tubular interior diameter of about 6 millimeters, an effective interior diameter 328 of the restrictor narrowed portion 322 of about 2.5 millimeters, and a divergent exit angle 332 of about 6 degrees with respect to a coaxial central axis of the restrictor apparatus 214.

As shown, the peripheral blood steal 508 occurring within the subject 104 implanted with a non-restrictive arteriovenous graft 202 is simulated as being much greater than the peripheral blood steal 508 occurring within the subject 104 implanted with a restrictive arteriovenous graft system 200. More specifically, the peripheral blood steal 508 occurring within the subject 104 implanted with the arteriovenous graft system 200 including a 25 millimeter long restrictor narrowed portion 322 was simulated as being about 33% less than the peripheral blood steal 508 occurring within the subject 104 implanted with the non-restrictive arteriovenous graft 202; while the blood steal 508 within the subject 104 implanted with the arteriovenous graft system 200 including a 45 millimeter long restrictor narrowed portion 322 was simulated as being about 42% less the peripheral blood steal 508 occurring within the subject 104 implanted with the non-restrictive arteriovenous graft 202.

According to at least one study, such as is found in Sutera, S. P. and Mehrjardi, M.H., *Deformation and Fragmentation of Human Red Blood Cells in Turbulent Shear Flow*, Biophysical Journal, Vol. 5 (1975): 1-10, wall shear stress 510 in an arteriovenous graft 202 or graft system 200 should be less than approximately 2000 dynes/centimeter². As shown in the summary chart 500, the wall shear stress 510 is 135 dynes/centimeter² and 400 dynes/centimeter² in the non-restrictive arteriovenous graft 202 and the restrictive arteriovenous graft system 200, respectively.

Using information about the wall shear stress 510, platelet stimulation factor 512 and predicted percent hemolysis 514 can be calculated. The platelet stimulation factor 512 can be calculated by taking the product of (wall shear stress) x (blood

residence time in the arteriovenous graft)^{0.452}. According to Wootton, D. M. and Ku, D. N., *Fluid Mechanics of Vascular Systems, Diseases, and Thrombosis*, Annu. Rev. Biomed. Eng. (1999) 01:299-329, the platelet stimulation factor **512** should be less than 1000. As shown in the summary chart **500**, the platelet stimulation factor **512** is 200 and 650 in the non-restrictive arteriovenous graft **202** and the restrictive arteriovenous graft system **200**, respectively. The predicted percent hemolysis **514** can be estimated using a model formula proposed by Giersiepen, M., Wurzing, L. J., Opitz, R., and Reul, H., *Estimation of Shear Stress-Related Blood Damage in Heart Valve Protheses – in vitro Comparison of 24 Aortic Valves*, The International Journal of Artificial Organs 13.5 (1990): 300-306. According to Giersiepen et al., the predicted percent hemolysis **514** is equal to the product of $(3.62 \times 10^{-5}) \times (\text{wall shear stress (in Pa)})^{2.416} \times (\text{blood residence time in the arteriovenous graft})^{0.785}$. As shown in the summary chart **500**, predicted percent hemolysis is 2.2, 6.1, and 7.6 in the non-restrictive arteriovenous graft **202**, the arteriovenous graft system **200** including the 25 millimeter long restrictor narrowed portion **322**, and the arteriovenous graft system **200** including the 45 millimeter long restrictor narrowed portion **322**, respectively.

Other simulated information summarized in the chart **500** includes the maximum strain rate in the arteriovenous graft **516** and the maximum strain rate at the graft-artery anastomosis **518**. As shown, the maximum strain rate in graft **516** is simulated as being 2000 and 18000 in the non-restrictive arteriovenous graft **202** and the restrictive arteriovenous graft system **200**, respectively; while the maximum strain rate at the graft-artery anastomosis **518** is simulated as being 20000 and 10000, respectively.

To experimentally illustrate the utility of the present blood flow restrictor apparatus **214**, *in vivo* experiments were performed on three pigs ranging in body weight from about 44.0-47.7 kilograms. In each of the pigs, as respectively shown in FIGS. 6A and 6B, an arteriovenous graft **202** or an arteriovenous graft system **202** (including an arteriovenous graft **202** and a restrictor apparatus **214**) was subcutaneously implanted. Each arteriovenous graft **202** extended from an arterial end

portion 204 to a venous end portion 208. The arterial end portion 204 was anastomosed 220 to a pig's artery (e.g., iliac artery) 206, while the venous end portion 208 was anastomosed 222 to a pig's vein (e.g., iliac vein) 210.

Each of the pigs was further instrumented with one or more measurement
5 devices, such as one or more blood flow rate detectors 602, blood pressure detectors, SVO2 detectors, or respiration detectors, for data gathering purposes. Some of the parameters measured by the one or more measurement devices included iliac blood flow upstream to the arteriovenous graft 202, iliac blood flow downstream to the arteriovenous graft 202, blood flow through the arteriovenous graft 202, mean aortic
10 blood pressure, systolic blood pressure, mean iliac venous pressure upstream of the arteriovenous graft 202, continuous cardiac output, continuous cardiac index, and SVO2. FIGS. 6A and 6B illustrate example placement of three blood flow rate detectors 602A-C used to measure iliac blood flow upstream to the arteriovenous graft 202, iliac blood flow downstream to the arteriovenous graft 202, and blood flow
15 through the arteriovenous graft 202. As shown, a first blood flow rate detector 602A can be disposed upstream of the arteriovenous graft 202 in the iliac artery 206, a second blood flow rate detector 602B can be disposed downstream of arteriovenous graft 202 in the iliac artery 206, and a third blood flow rate detector 602C can be disposed in the arteriovenous graft 202.

20 Using the three blood flow rate detectors 602A-C, blood flow rates through each pig were measured with (FIG. 6B) and without (FIG. 6A) the restrictor apparatus 214. In addition, blood flow rates through each pig were measured with and without a dialysis machine 102 present. As discussed above, blood from each pig can be drawn via an arterial cannula 108 (FIG. 2C) at the arterial side 204 of the arteriovenous graft
25 202 and received by the dialysis machine 102 where it is dialyzed. After being dialyzed, the blood can be returned to the pig at the venous side 208 of the arteriovenous graft 202 via a venous cannula 110 (FIG. 2C). For this *in vivo* experiment, blood was drawn from the arteriovenous graft 202, via the arterial cannula 108, at a rate of 400 milliliters per minute.

FIG. 6C provides a chart 650 summarizing the results of the *in vivo* experimentation performed on the three pigs. In brief, when the dialysis machine 102 was turned off, it was found that on average blood flow via the arteriovenous graft 202 was reduced (0.51 ± 0.03 vs. 0.28 ± 0.03 liters/minute) when the restrictor apparatus 214 was present (i.e., integrated with the arteriovenous graft 202 as a unitary body or interposed between the arterial 204 and venous 208 end portions of the arteriovenous graft 202). Without the restrictor apparatus 214 present, the arteriovenous graft 202 on average caused iliac blood flow to increase from 0.15 ± 0.12 to 0.61 ± 0.12 liters/minute (306.7%). With the restrictor apparatus 214 present, the arteriovenous graft 202 on average caused iliac blood to increase from 0.15 ± 0.12 to 0.40 ± 0.1 liters/minute (166.7%).

Other information gleaned from the *in vivo* experimentation performed on the three pigs is as follows. It was found that sufficient blood flow for performing hemodialysis can still be obtained acutely after implanting the restrictor apparatus 214 in the arteriovenous graft 202. Regarding CO (which was measured in two of the three pigs), it was found that the arteriovenous graft 202 caused CO to increase from 3.7 to 4.8 liters/minute (29.7%) and from 2.9 to 3.2 liters/minute (9.4%) – an average increase of 21% – without the restrictor apparatus 214 present. With the restrictor apparatus 214 present, the arteriovenous graft 202 caused CO to increase from 4.1 to 5 liters/minute (22%) and from 2.1 to 2.5 liters/minute (19.1%) – an average increase of also 21%. It was further found that arterial pressure, systolic aortic pressure, and mean iliac venous pressure were not substantially altered depending on whether or not the restrictor apparatus 214 was or was not present.

FIG. 7 illustrates an example method 700 of forming an arteriovenous graft system. At 702, a restrictor apparatus having fixed dimensions is formed. According to varying examples, forming the restrictor apparatus comprises forming a restrictor entry portion, a restrictor exit portion, and a optionally a restrictor narrowed portion therebetween. The restrictor entry portion includes a convergent first lumen that tapers outward on a first end to substantially match an interior diameter of an arterial

portion of an arteriovenous graft. In one example, the first lumen includes an entry angle of less than or equal to about 6 degrees between the wall of the first lumen and a coaxial axis defining a center of the first lumen. In another example, the first lumen includes a convergent curved wall having a radius of curvature of at least 2
5 millimeters.

Options for the restrictor exit and restrictor narrowed portions are as follows. In varying examples, the restrictor exit portion includes a divergent second lumen that tapers outward on a second end to substantially match an interior diameter of a venous portion of the arteriovenous graft. In one example, the second lumen includes an exit
10 angle of less than or equal to about 6 degrees between the wall of the second lumen and a coaxial axis defining a center of the second lumen. In varying examples, the restrictor narrowed portion includes a third lumen connecting the first and second lumens. The third lumen is narrower than at least a portion of the first and second
lumens and substantially matches adjacent interior diameters of the first and second
15 lumens (i.e., substantially matches a second end of the first lumen and a first end of the second lumen). In one example, the third lumen includes an effective interior diameter of at least 2.5 millimeters.

At 704, the restrictor apparatus is incorporated with an arteriovenous graft. According to certain examples, the incorporation of the restrictor apparatus with the
20 arteriovenous graft includes cutting the arteriovenous graft between an arterial and a venous end portion thereof and securely coupling the restrictor apparatus to such graft portions. According to other examples, the incorporation of the restrictor apparatus with the arteriovenous graft includes disposing the restrictor apparatus within an interior diameter wall of the arteriovenous graft. According to still other examples,
25 the incorporation of the restrictor apparatus with the arteriovenous graft includes the formation of an arteriovenous graft having an integrated restrictor apparatus. Optionally, at 706, an interior surface of at least one of the first, second, or third lumens of the restrictor apparatus is coated with a biologically active layer.

FIG. 8 illustrates an example method 800 of restricting a flow of blood through an arteriovenous graft system including an arteriovenous graft and at least one restrictor apparatus. At 802, the arteriovenous graft system is subcutaneously implanted within a subject between a subject's artery and vein. The at least one restrictor apparatus is located between an arterial end portion and a venous end portion of the arteriovenous graft. The arterial end portion of the arteriovenous graft is anastomosed to the subject's artery, while the venous end portion of the arteriovenous graft is anastomosed to the subject's vein.

At 804, a converging of a flow of blood from a first fluid lumen defined by a first interior diameter wall of the arteriovenous graft is guided to a second fluid lumen defined by a fixed interior diameter wall of a narrowed portion of the at least one restrictor apparatus. At 806, a diverging of the flow of blood from the second fluid lumen defined by the fixed interior diameter wall of the narrowed portion of the restrictor apparatus is guided to a third fluid lumen defined by a second interior diameter wall of the arteriovenous graft.

At 808, an arterial cannula is inserted into the arterial end portion of the arteriovenous graft, and at 810, a venous cannula is inserted into the venous end portion of the arteriovenous graft. At 812, hemodialysis is performed on the flow of blood drawn by the arterial cannula and thereafter, the cleansed blood returned to the subject via the venous cannula. During the hemodialysis, the blood flow bypassing the arterial and venous cannulas through the arteriovenous graft is restricted using the restrictor apparatus. Upon completion of the hemodialysis, the arterial and venous cannulas are removed from the respective arterial and venous end portions of the arteriovenous graft.

Closing Notes:

The above Detailed Description includes references to the accompanying drawings, which form a part of the Detailed Description. The drawings show, by way of illustration, specific embodiments in which the invention can be practiced. These embodiments are also referred to herein as "examples." All publications, patents, and

patent documents referred to in this document are incorporated by reference herein in their entirety, as though individually incorporated by reference. In the event of inconsistent usages between this document and those documents so incorporated by reference, the usage in the incorporated reference(s) should be considered

5 supplementary to that of this document; for irreconcilable inconsistencies, the usage in this document controls.

In this document, the terms “a” or “an” are used, as is common in patent documents, to include one or more than one, independent of any other instances or usages of “at least one” or “one or more.” In this document, the term “or” is used to
10 refer to a nonexclusive or, such that “A or B” includes “A but not B,” “B but not A,” and “A and B,” unless otherwise indicated. In this document, the term “subject” is used to include the term “patient.” In the appended claims, the terms “including” and “in which” are used as the plain-English equivalents of the respective terms “comprising” and “wherein.” Also, in the following claims, the terms “including” and
15 “comprising” are open-ended, that is, a system, device, article, or process that includes elements in addition to those listed after such a term in a claim are still deemed to fall within the scope of that claim. Moreover, in the following claims, the terms “first,” “second,” and “third,” etc. are used merely as labels, and are not intended to impose numerical requirements on their objects.

20 The above description is intended to be illustrative, and not restrictive. For example, the above-described examples (or one or more features thereof) may be used in combination with each other. Other embodiments can be used, such as by one of ordinary skill in the art upon reviewing the above description. Also, in the above Detailed Description, various features may be grouped together to streamline the
25 disclosure. This should not be interpreted as intending that an unclaimed disclosed feature is essential to any claim. Rather, inventive subject matter may lie in less than all features of a particular disclosed embodiment. Thus, the following claims are hereby incorporated into the Detailed Description, with each claim standing on its own as a separate embodiment. The scope of the invention should be determined with

reference to the appended claims, along with the full scope of equivalents to which such claims are entitled.

5 The Abstract is provided to comply with 37 C.F.R. §1.72(b), to allow the reader to quickly ascertain the nature of the technical disclosure. It is submitted with the understanding that it will not be used to interpret or limit the scope or meaning of the claims.

WHAT IS CLAIMED IS:

1. An apparatus comprising:
at least one blood flow restrictor apparatus including:
a restrictor entry portion, including a fixed dimensioned convergent first lumen that tapers to substantially match an interior diameter of an arterial portion of an arteriovenous graft; and
a restrictor exit portion, including a fixed dimensioned divergent second lumen that tapers to substantially match an interior diameter of a venous portion of the arteriovenous graft.
2. The apparatus of claim 1, comprising a restrictor narrowed portion disposed between the restrictor entry portion and the restrictor exit portion, the restrictor narrowed portion including a fixed dimensioned third lumen connecting the first and second lumens, the third lumen having a smaller interior diameter than at least a portion of the first and second lumens, the third lumen substantially matching adjacent interior diameters of the first and second lumens.
3. The apparatus of claim 2, wherein the interior diameter of the third lumen is substantially constant.
4. The apparatus of claims 2 or 3, wherein the interior diameter of the third lumen is at least about 1.5 millimeters.
5. The apparatus of any of claims 2-4, comprising a biologically active layer on an interior surface of at least a portion of at least one of the first lumen of the restrictor entry portion, the second lumen of the restrictor exit portion, or the third lumen of the restrictor narrowed portion.

6. The apparatus of any of claims 1-5, comprising:
 - the arterial portion of the arteriovenous graft, sized and shaped to be coupled to the restrictor entry portion; and
 - the venous portion of the arteriovenous graft, sized and shaped to be coupled to the restrictor exit portion.
7. The apparatus of claim 6, wherein:
 - the arterial portion of the arteriovenous graft includes an arterial end portion anastomosable with an artery of a subject and a portion configured to receive an arterial hemodialysis cannula; and
 - the venous portion of the arteriovenous graft includes a venous end portion anastomosable with a vein of the subject and a portion configured to receive a venous hemodialysis cannula.
8. The apparatus of claims 6 or 7, wherein the restrictor apparatus comprises a structure that is separate from, but couplable to, at least one of the arterial portion of the arteriovenous graft or the venous portion of the arteriovenous graft.
9. The apparatus of claim 8, wherein the restrictor apparatus comprises a reduced outer diameter portion on at least one of the restrictor entry portion or the restrictor exit portion, the reduced diameter portion sized and shaped to be inserted within an interior diameter of at least one of the arterial portion of the arteriovenous graft or the venous portion of the arteriovenous graft.
10. The apparatus of claim 9, comprising at least one annular clamp sized and shaped to be disposed around a portion of the arteriovenous graft and the reduced diameter portion of the restrictor apparatus to couple the arteriovenous graft to the at least one restrictor apparatus.

11. The apparatus of any of claims 1-10, wherein the outward taper of the divergent second lumen of the restrictor exit portion includes an exit angle, with respect to a coaxial central axis of the second lumen, of less than or equal to about 6 degrees.

12. The apparatus of any of claims 1-11, wherein the outward taper of the divergent second lumen of the restrictor exit portion includes an exit angle, with respect to a coaxial central axis of the second lumen, that is small enough to substantially inhibit blood clot formation.

13. The apparatus of any of claims 1-12, wherein the convergent first lumen of the restrictor entry portion includes a radially curved entry having a radius of curvature of at least about 2 millimeters.

14. The apparatus of any of claims 1-13, wherein the convergent first lumen of the restrictor entry portion includes an entry angle, with respect to a coaxial central axis of the first lumen, of less than or equal to about 6 degrees.

15. The apparatus of any of claims 1-14, wherein the restrictor apparatus comprises a structure that is separate from, but couplable within, the arteriovenous graft.

16. The apparatus of any of claims 1-15, wherein the restrictor apparatus comprises a structure that is integrated with the arteriovenous graft as a unitary device.

17. The apparatus of any of claims 1-16, wherein at least a portion of the restrictor apparatus includes a rigid material that is substantially non-penetrable by a hemodialysis cannula.

18. A method of restricting a flow of blood through an arteriovenous graft system comprising:

guiding a converging of the flow of blood from a first fluid lumen defined by a first interior diameter wall of an arteriovenous graft to a second fluid lumen defined by a fixed interior diameter wall of a narrowed portion of at least one restrictor apparatus; and

guiding a diverging of the flow of blood from the second fluid lumen defined by the fixed interior diameter wall of the narrowed portion of the restrictor apparatus back to a third fluid lumen defined by a second interior diameter wall of the arteriovenous graft.

19. The method of claim 18, comprising subcutaneously implanting the arteriovenous graft system.

20. The method of claim 19, wherein subcutaneously implanting the arteriovenous graft system includes subcutaneously implanting an arterial end portion of the arteriovenous graft, a venous end portion of the arteriovenous graft, and the restrictor apparatus located between the arterial and venous end portions.

21. The method of claim 20, comprising:
anastomizing the arterial end portion to an artery; and
anastomizing the venous end portion to a vein.

22. The method of claims 20 or 21, comprising:
inserting an arterial cannula into the arterial end portion;
inserting a venous cannula into the venous end portion;
performing hemodialysis using the arterial and venous cannulas;

using the restrictor apparatus located between the arterial and venous cannulas to restrict blood flow bypassing the arterial and venous cannulas through the arteriovenous graft during the hemodialysis; and

removing the arterial and venous cannulas from the respective arterial and venous end portions.

23. The method of claim 22, wherein restricting blood flow includes permitting blood flow through the arterial and venous cannulas of at least 300 cubic centimeters per minute during the hemodialysis.

24. The method of claim 22, wherein restricting blood flow includes permitting blood flow through the arterial and venous cannulas of at least 400 cubic centimeters per minute during the hemodialysis.

25. A method of forming a restrictor apparatus comprising:

forming a convergent first lumen that tapers to substantially match an interior diameter of an arterial portion of an arteriovenous graft in a restrictor entry portion;

forming a divergent second lumen that tapers to substantially match an interior diameter of a venous portion of the arteriovenous graft in a restrictor exit portion; and

forming a third lumen connecting the first and second lumens in a restrictor narrowed portion, the third lumen having a fixed interior diameter smaller than at least a portion of the first and second lumens, the third lumen substantially matching adjacent interior diameters of the first and second lumens.

26. The method of claim 25, comprising incorporating the restrictor apparatus with the arteriovenous graft extending from the arterial end portion to the opposite venous end portion.

27. The method of claim 26, wherein incorporating the restrictor apparatus with the arteriovenous graft comprises:

cutting the arteriovenous graft between the arterial end portion and the venous end portion; and

coupling the restrictor apparatus between the arterial end portion and the venous end portion of the arteriovenous graft.

28. The method of claim 26, wherein incorporating the restrictor apparatus with the arteriovenous graft includes disposing the restrictor apparatus within an interior diameter wall of the arteriovenous graft.

29. The method of claim 26, wherein incorporating the restrictor apparatus with the arteriovenous graft includes forming an arteriovenous graft having an integrated restrictor apparatus.

30. The method of any of claims 25-29, wherein forming the first lumen includes forming an entry angle of less than or equal to about 6 degrees between a wall of the first lumen and a coaxial axis defining a center of the first lumen.

31. The method of any of claims 25-30, wherein forming the second lumen includes forming an exit angle of less than or equal to about 6 degrees between a wall of the second lumen and a coaxial axis defining a center of the second lumen.

32. The method of any of claims 25-31, wherein forming the first lumen includes forming a convergent curved wall having a radius of curvature of at least about 2 millimeters.

33. The method of any of claims 25-32, wherein forming the third lumen includes forming an effective interior diameter of the third lumen of at least about 1.5 millimeters.

34. The method of any of claims 25-33, comprising disposing a biologically active layer on an interior surface of at least one of the first, second, or third lumens.

100

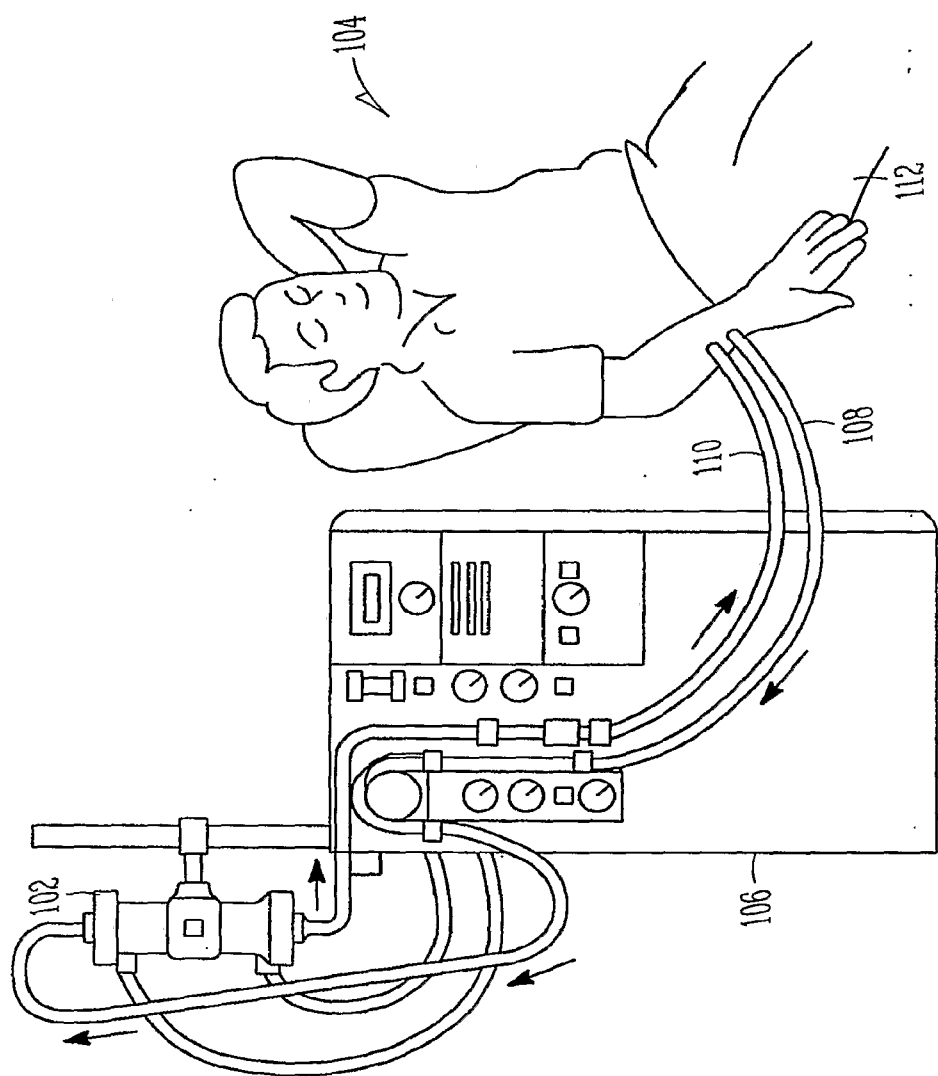
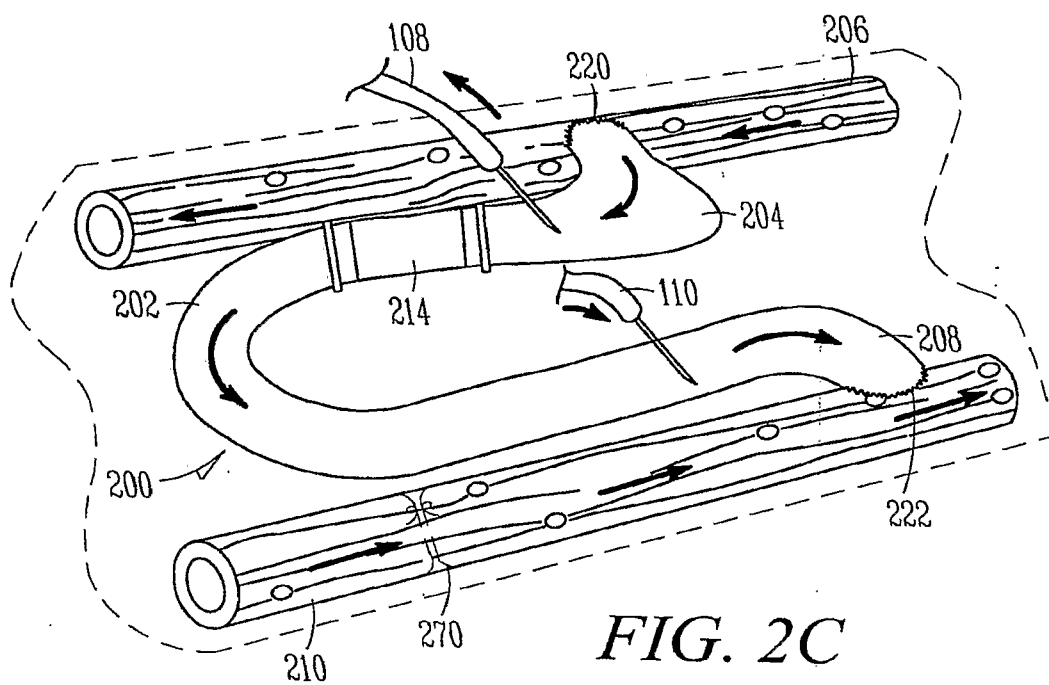
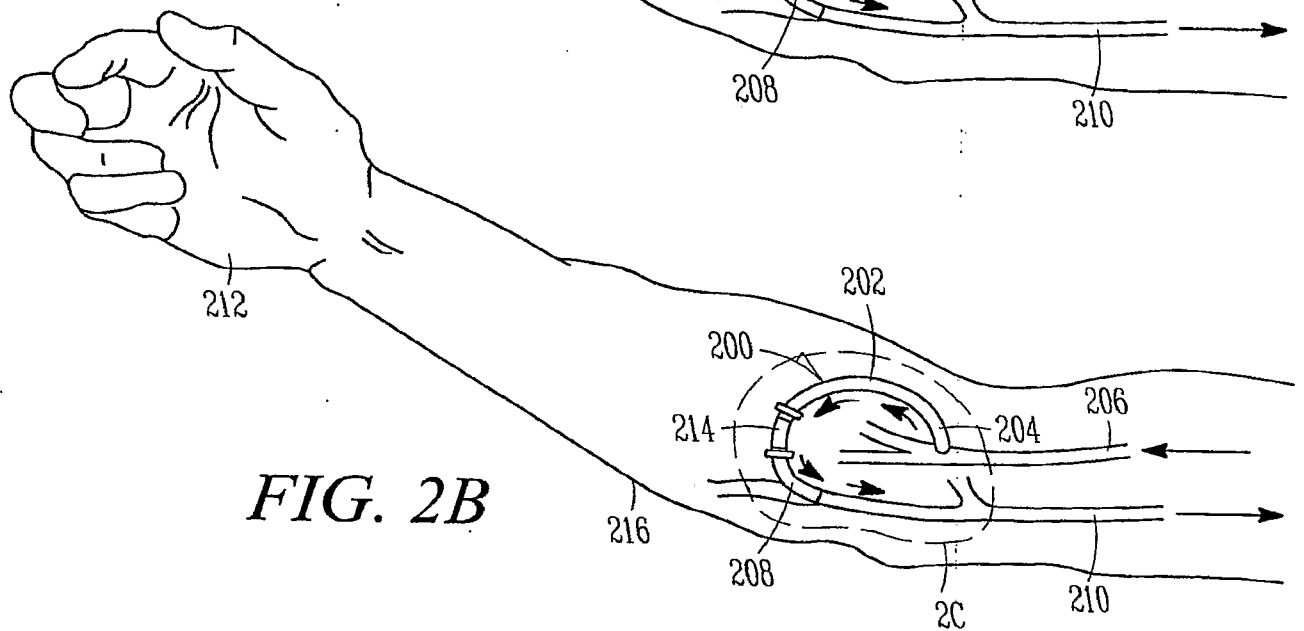
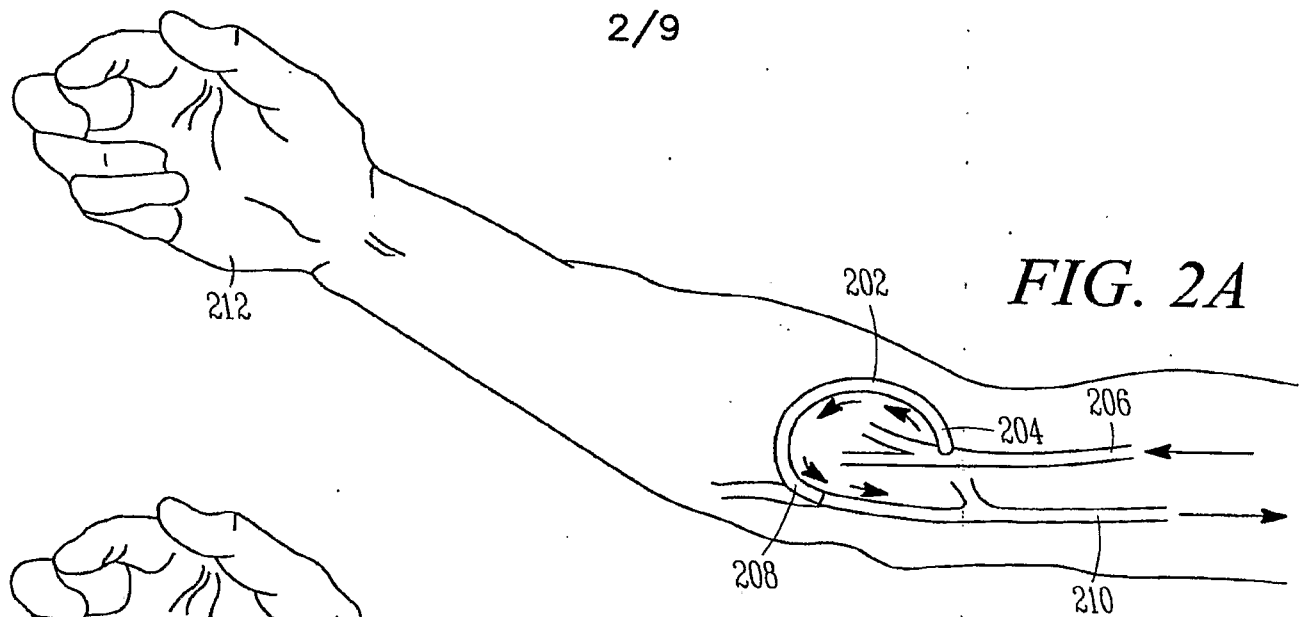


FIG. 1

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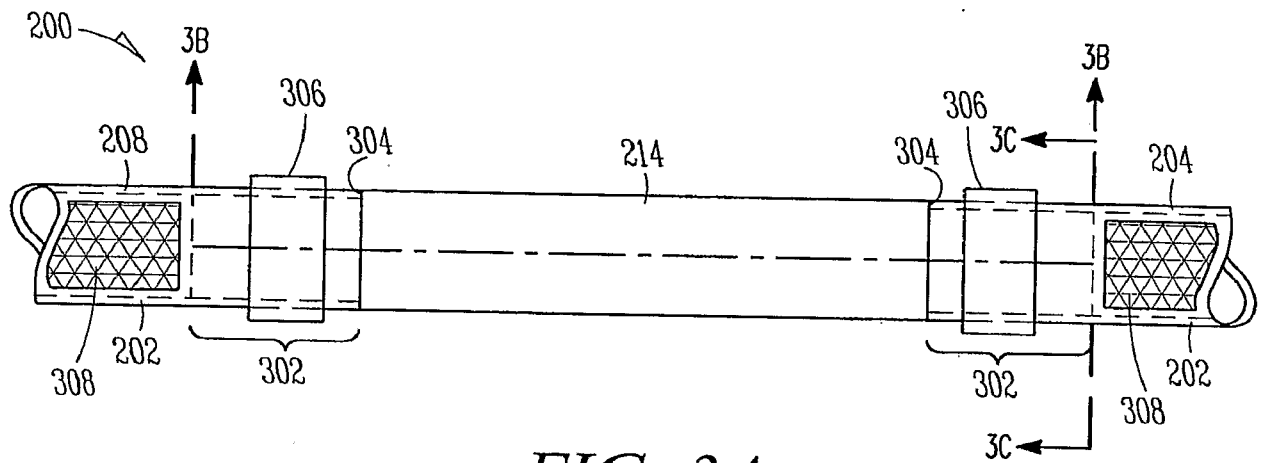


FIG. 3A

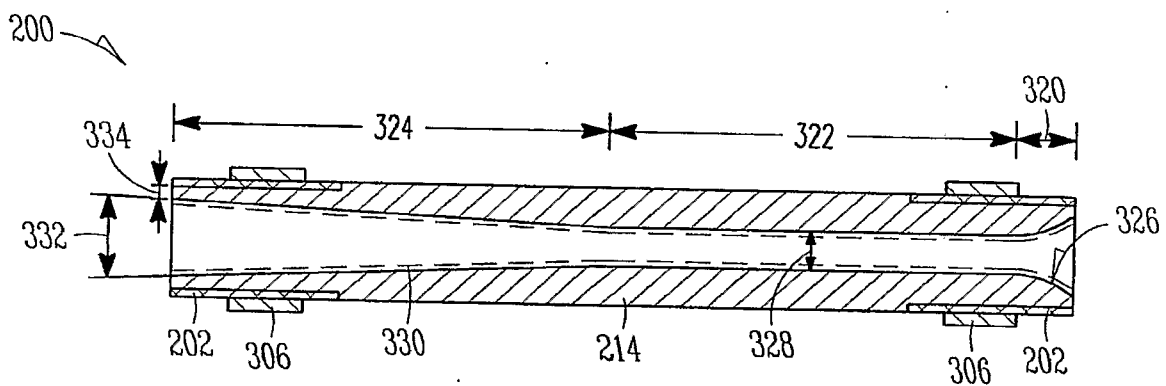


FIG. 3B

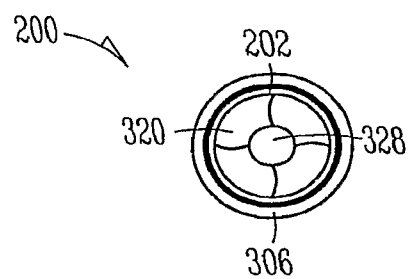


FIG. 3C

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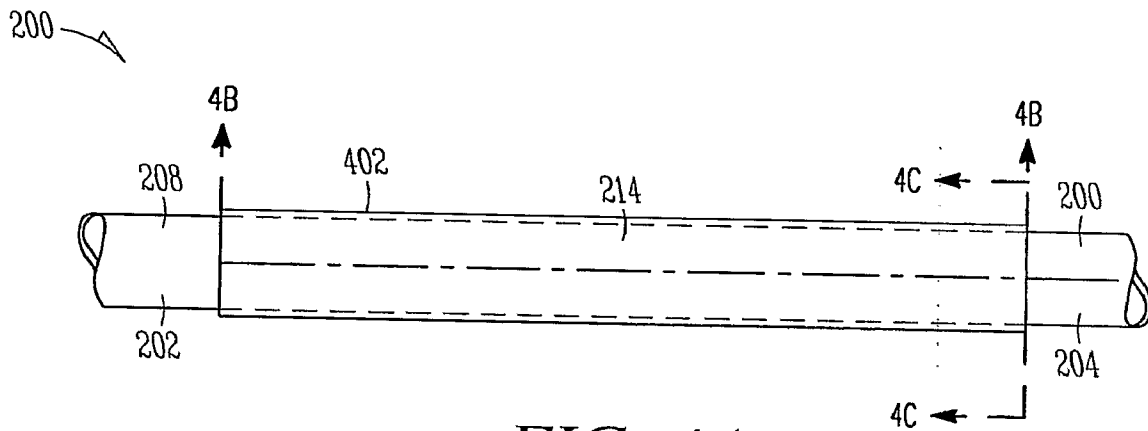


FIG. 4A

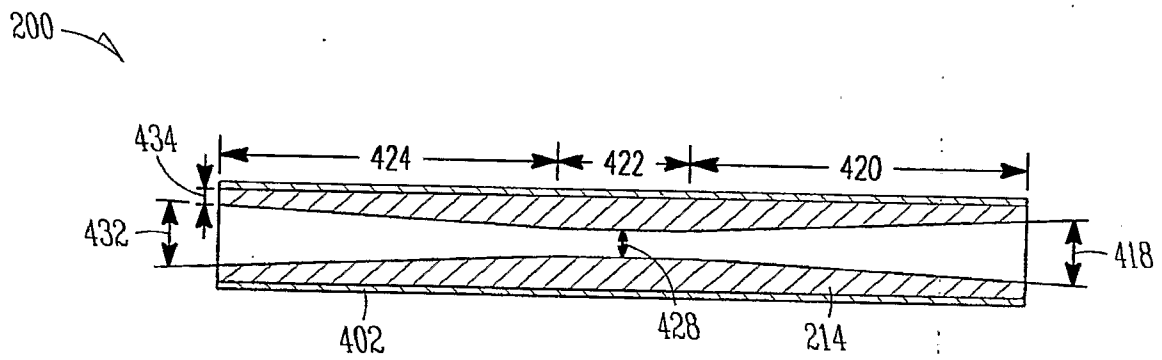


FIG. 4B

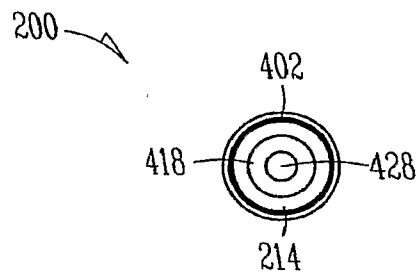


FIG. 4C

COMPUTER SIMULATION BLOOD FLOW PROPERTIES

500						
	508	510	512	514	516	518
RESTRICTION	BLOOD STEAL (ml/min)	WALL SHEAR STRESS (dynes/cm ²) (SHOULD BE < 2000)	PLATELET STIMULATION FACTOR (SHOULD BE < 1000)	PREDICTED % HEMOLYSIS	MAX STRAIN RATE IN GRAFT	MAX STRAIN RATE AT ANASTOMOSIS
NONE - 6mm GRAFT ONLY	780	135	200	2.2	2000	20000
2.5mm SHORT (25mm LONG)	520	400	650	6.1	18000	10000
2.5mm LONG (45mm LONG)	450	-	-	7.6	-	

502

504

506

FIG. 5

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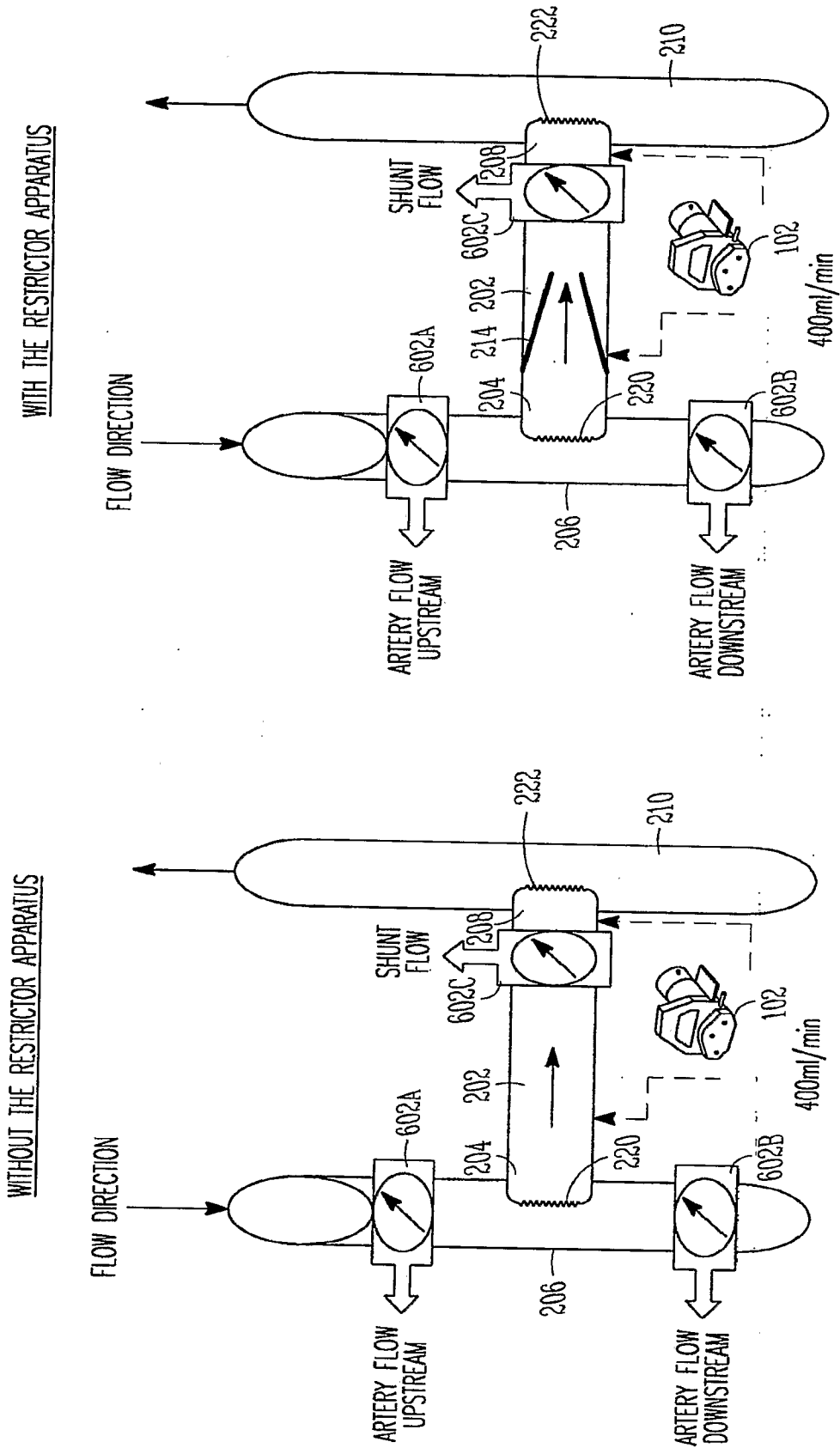


FIG. 6A

FIG. 6B

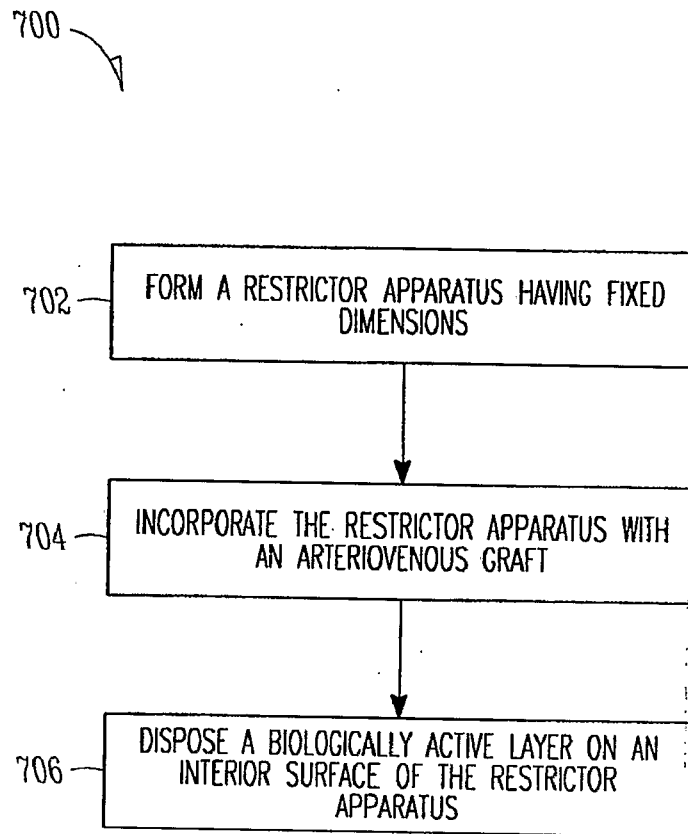
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650

		IN	VIVO	Group Data		(EXPERIMENTAL RESULTS)							
				Shunt Flow(L/min)	A Flow-D(L/min)	A Flow-U(L/min)	MAP(mmHg)	MPV(mmHg)	ASP(mmHg)	CCO	CCI	SV02	VSP (mmHg)
		<u>No Device</u>											
		<u>Shunt On</u>											
Pig 1				0.49	0.221	0.73	52	21	75				24
Pig 2				0.49	0.07	0.6	57	25	72	4.8	3.8	83	31.5
Pig 3				0.55	0.015	0.485	57	24	78	3.2	2.8	88	26.2
		Mean		0.51	0.102	0.605	55.3	23.7	75.5	4	3.3	85.5	27.2
		SD		0.03	0.11	0.12	2.89	2.52	3.00	1.13	0.71	3.54	3.9
		<u>Shunt Off</u>											
Pig 1				0	0.32	0.28	50	22	78				23.5
Pig 2				0	0.12	0.1	61	26	75	3.7	3	84	31.3
Pig 3				0	0.06	0.06	59	24	78	2.9	2.8	84	26.6
		Mean		0.0000	0.1667	0.1467	56.6667	24.0000	77.0000	3.3000	2.9000	84.0000	27.1333
		SD		0.00	0.14	0.12	5.88	2.00	1.73	0.57	0.14	0.00	3.9
		<u>Device On</u>											
		<u>Shunt On</u>											
Pig 1				0.28	0.22	0.5	53	21	75				23.8
Pig 2				0.25	0.11	0.39	60	26	76	5	3.9	85	30.9
Pig 3				0.305	0.035	0.3	59	24	79	2.5	2.3	86	25.7
		Mean		0.2783	0.1217	0.3967	57.3333	23.6667	76.6667	3.7500	3.1000	85.5000	26.8000
		SD		0.03	0.09	0.10	3.79	2.52	2.08	1.77	1.13	0.71	3.7
		<u>Shunt Off</u>											
Pig 1				0	0.28	0.29	54	22	77.5				24.1
Pig 2				0	0.1	0.1	62	26	76	4.1	3.6	83	31.6
Pig 3				0	0.06	0.07	65	24	76	2.1	1.8	81	26.1
		Mean		0.0000	0.1467	0.1533	60.3333	24.0000	76.5000	3.1000	2.7000	82.0000	27.2667
		SD		0.00	0.12	0.12	5.69	2.00	0.87	1.41	1.27	1.41	3.9
		<u>Device On</u>											
		<u>Dialysis Pump On: 400ml/min</u>											
Pig 1				0.07	0.19	0.8	50	22	89				23
Pig 2				0.07	0.04	0.51	61	23	74	4.2	3.7	89	27.4
Pig 3				0.01	0.02	0.42	57	25	77	3.8	3.1	88	27.3
		Mean		0.0500	0.0833	0.5767	56.0000	23.3333	73.3333	3.9000	3.4000	88.5000	25.9000
		SD		0.03	0.09	0.20	5.57	1.53	4.04	0.42	0.42	0.71	2.50
		<u>Dialysis Pump Off</u>											
Pig 1				0.11	0.22	0.3	48	21	68.9				24.5
Pig 2				0.22	0.13	0.3	57	24	70	3.1	2.8	84	27.9
Pig 3				0.28	0.04	0.3	57	25	77	3.8	3.1	85	27.1
		Mean		0.2033	0.1300	0.3000	54.0000	23.3333	71.9667	3.3500	2.9500	84.5000	26.5000
		SD		0.09	0.09	0.00	5.20	2.08	4.39	0.35	0.21	0.71	1.80
		<u>No Device</u>											
Pig 1				0.5	0.19	0.6	48	21	65				23.4
Pig 2				0.35	0.06	0.39	59	23	71	4	3.4	84	25.7
Pig 3				0.59	0.01	0.48	63	24	83	3.5	3	92	26.6
		Mean		0.4800	0.0867	0.4900	56.6667	22.6667	73.0000	3.7500	3.2000	88.0000	25.2333
		SD		0.12	0.09	0.11	7.77	1.53	9.17	0.35	0.28	5.66	1.7
		<u>Dialysis Pump On: 400ml/min</u>											
Pig 1				0.21	0.18	0.77	48	22	65.9				23.3
Pig 2				-0.05	0.05	0.44	58	26	69	3.4	3	81	27.7
Pig 3				0.08	0.02	0.48	58	23	79	4	3.5	89	27.5
		Mean		0.0800	0.0833	0.5633	54.6667	23.6667	71.3000	3.7000	3.2500	85.0000	26.1667
		SD		0.13	0.09	0.18	5.77	2.08	8.85	0.42	0.35	5.65	2.50
		<u>Dialysis Pump Off</u>											
Pig 1				0.43	0.2	0.58	50	22	66.7				23.6
Pig 2				0.35	0.08	0.4	58	26	69	3.1	2.7	81	27.2
Pig 3				0.52	0.02	0.49	63	24	83	3.5	3	91	27.4
		Mean		0.4333	0.1000	0.4900	57.0000	24.0000	72.9000	3.3000	2.8500	86.0000	26.0667
		SD		0.09	0.09	0.09	6.56	2.00	8.82	0.28	0.21	7.07	2.10

FIG. 6C

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*FIG. 7*

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800

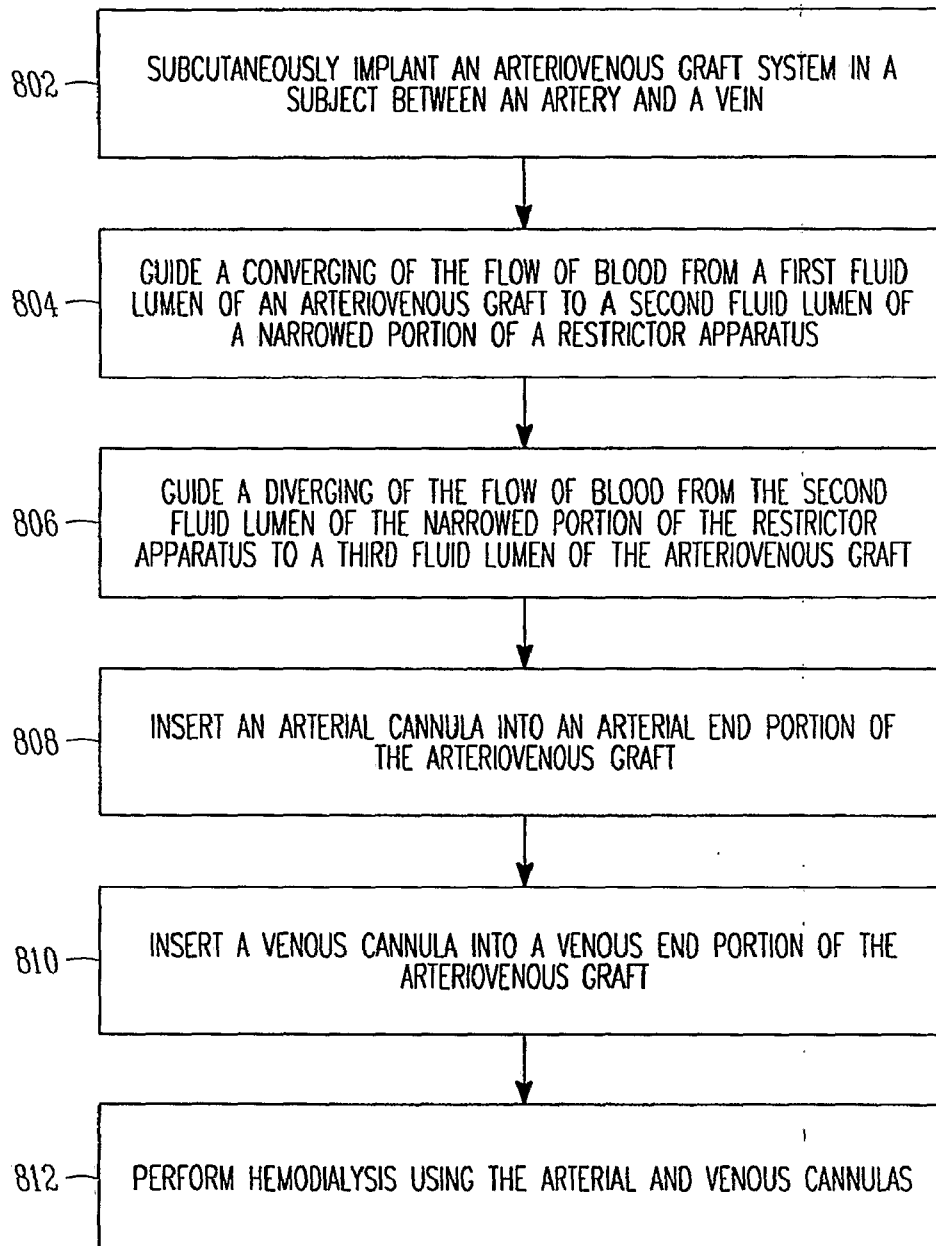


FIG. 8