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(54) Title: METHODS FOR TREATING ENDOLEAKS DURING ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSMS

(57) Abstract

Disclosed are methods for treating endoleaks arising from endovascular repair of abdominal aortic aneurysms. The disclosed methods involve the *in situ* sealing of endoleaks after placement of an endovascular prosthesis in the abdominal aorta. Sealing of endoleaks is achieved by injection of either a biocompatible polymer or prepolymer fluid composition into the endoleak which composition *in situ* solidifies to seal the leak. Preferably, the biocompatible fluid composition comprises a contrast agent to allow the clinician to visualize the sealing process.

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METHODS FOR TREATING ENDOLEAKS DURING ENDOVASCULAR REPAIR OF ABDOMINAL AORTIC ANEURYSMS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Patent Application Serial No. 09/273,120 filed March 19, 1999 which application is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to methods for treating endoleaks arising from endovascular repair of abdominal aortic aneurysms. Specifically, the methods of this invention involve the *in situ* sealing of endoleaks after placement of an endovascular prostheses in the abdominal aorta. Sealing of endoleaks is achieved by injection of a biocompatible fluid composition at the site of the endoleak which composition *in situ* solidifies and adheres to the vascular and/or prosthetic wall to seal the leak. Preferably, the biocompatible fluid composition comprises a contrast agent to allow the clinician to visualize the sealing process.

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The following publications, patent applications and patents are cited in this application as superscript numbers:

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[14] Castaneda-Zuniga, et al., *Interventional Radiology*, in Vascular Embolotherapy, Part 1, 1:9-32, Williams & Wilkins, Publishers (1992)

[15] Rabinowitz, et al., U.S. Patent No. 3,527,224, for *"Method of Surgically Bonding Tissue Together"*, issued September 8, 1970

[16] Hawkins, et al., U.S. Patent No. 3,591,676, for *"Surgical Adhesive Compositions"*, issued July 6, 1971

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[18] van Schie, et al., *"Successful Embolization of Persistent Endoleak from a Patent Inferior Mesenteric Artery"*, J. Endovasc. Surg., 4:312-315 (1997)

[19] Walker, et al., *"A Study of the Patency of the Inferior Mesenteric and Lumbar Arteries in the Incidence of Endoleak Following Endovascular Repair of Infra-renal Aortic Eneurysms"*, Clinical Radiology, 53:593-595 (1998)

All of the above publications, patent applications and patents are herein incorporated by reference in their entirety to the same extent as if each

individual publication, patent application or patent was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

Abdominal aortic aneurysms (AAA) represents a serious medical challenge and, when left untreated, eventual rupture of the aneurysm has significant morbidity associated therewith. When feasible, open surgery to repair the aortic aneurysm has been shown to be clinically successful.[1] However, open surgery is often not feasible especially in patients suffering from severe cardiac disease, renal disease or other conditions which contra-indicate open surgery. For example, conventional exposure of the infrarenal aorta necessitates a large abdominal incision, mobilization of the abdominal viscera, and retroperitoneal dissection which are associated with complications such as renal failure, pseudoaneurysms and bleeding. Infrarenal aortic clamping is also associated with an increased cardiac demand including an increase in left ventricular end diastolic volume and may be related to cardiac mortality.

Less invasive methods for treating abdominal aortic aneurysms avoid many of these problems and additionally result in reduced patient discomfort, reduced hospital stays and reduced care intensity.[5] Endovascular grafts have been investigated as one example of a less invasive method for the treatment of aneurysmal aortic disease. When compared to open surgery, endovascular grafting provides similar perioperative mortality rates notwithstanding the fact that endovascular grafting is often performed with individuals who are not candidates for open surgery due to one or more medical conditions which preclude such surgery.[1,4] One of the main concerns regarding endovascular grafting is the continued blood flow into the aneurysm after grafting which blood flow is termed in the art as an endoleak.[2] Endoleaks have been reported

in from about 7 to about 37% of endovascular aortic aneurysm repairs[3] with some reports placing this number as high as 44%.

Specifically, endovascular grafting requires catheter placement of an endovascular prosthesis at the abdominal aortic aneurysm site. Endoleaks arising after such grafting may be caused by incomplete sealing between the endovascular prosthesis and the aortic wall or by defects within the endovascular prosthesis. In addition, back bleeding from patent lumbar and inferior mesenteric arteries following placement of the endovascular prostheses in the aorta has also been recited as a potential cause of endoleaks.[6] There is uniform agreement that large endoleaks that lead to aneurysm enlargement necessitate treatment in order to prevent aneurysm rupture. It is also reported that the size of the endoleak does not appear to be a relevant factor for pressure transmission into the aneurysm.[3]

There are a variety of prophylactic and therapeutic treatment regimens for endoleaks reported in the literature. Prophylactic methods of inhibiting endoleaks by embolizing vasculature leading to the aneurysm, evidently with metallic coils, have been suggested and dismissed in an article by Walker, et al.[19] Therapeutic methods for endovascular repair include placement of additional stents within the prosthesis; insertion of metallic coils into the aneurysm space to induce thrombosis therein; and embolization of the inferior mesenteric artery using a prepolymer/water soluble contrast agent composition.[18]

The goal of such treatments is complete exclusion of the aneurysm from systemic blood flow. While complete exclusion is desirable, a secondary goal is to reduce intraaneursymal pressure (IAP) from blood flow into the aneurysm to acceptable levels thereby inhibiting the likelihood of rupture. In cases where no endoleaks arose after endovascular grafting, the mean IAP has been reported to be reduced by about 65%. However, when endoleaks arise,

it is reported that the mean IAP, while initially decreasing significantly, stabilized after a week at a reduction of only 22%. Moreover, the use of coils to induce thrombosis and thereby reduce IAP did not have any significant impact on the IAP.

In view of existing problems associated with endovascular repair of endoleaks, the accepted treatment for these endoleaks is open surgery. However, the mortality rates for open surgery of endoleaks is higher than either initial open surgery for the abdominal aortic aneurysm or for the initial endovascular repair of the aneurysm.

In view of the above, reliable endovascular methods to inhibit endoleaks after endovascular graft repair of abdominal aortic aneurysms is desirable.

SUMMARY OF THE INVENTION

This invention is directed to methods for treating endoleaks arising from endovascular repair of abdominal aortic aneurysms. These methods provide for delivery of a fluid composition to the sites of endoleaks in the abdominal aorta which fluid composition, *in situ*, forms a coherent solid mass which adheres to vascular and/or prosthetic wall to seal the endoleak.

In a preferred embodiment, the fluid composition comprises a biocompatible polymer, a biocompatible solvent and a contrast agent to allow the clinician to visualize the procedure. In a further preferred embodiment, the contrast agent is a water insoluble contrast agent characterized by having an average particle size of about 10 μm or less.

In another preferred embodiment, the fluid composition comprises a biocompatible prepolymer and a contrast agent which, again, is employed to allow the clinician to visualize the procedure. In a further preferred

embodiment, the contrast agent is a water insoluble contrast agent characterized by having an average particle size of about 10 μm or less.

Accordingly, in one of its method aspects, this invention provides a method for sealing endoleaks in a patient arising from endovascular repair of abdominal aortic aneurysms which method comprises:

identifying an abdominal aortic aneurysm in a patient;

endovascularly repairing said aneurysm by catheter delivery of an endovascular prosthesis to the site of said aneurysm thereby inhibiting blood flow into the aneursym;

identifying one or more endoleaks in said patient; and

delivering to the site or sites of the endoleak in said patient a sufficient amount of a fluid composition comprising a biocompatible solvent and a biocompatible polymer under conditions wherein the fluid composition forms a coherent adhesive mass *in situ* at said site or sites thereby sealing the endoleaks.

In one preferred embodiment, the fluid composition further comprises a contrast agent to permit the clinician to detect the composition *in vivo*. The contrast agent can be either water soluble or water insoluble and preferably is water insoluble.

In another preferred embodiment, the fluid composition is delivered by a microcatheter, by a needle or any other access device.

Methods further comprising the step of delivering a detectable agent, such as a contrast agent, through the catheter or needle after it has been inserted into the artery and detecting the agent to confirm that the catheter has the proper placement prior to delivery of the fluid composition to the site of the endoleak are also provided.

In another of its method aspects, this invention is directed to a method for treating abdominal aortic aneurysms in a patient which method comprises:

identifying an abdominal aortic aneurysm in a patient;

endovascularly repairing said aneurysm by catheter delivery of an endovascular prosthesis to the site of said aneurysm thereby inhibiting blood flow into the aneurysm;

identifying the presence of one or more endoleaks in said patient;

delivering to the site or sites of endoleaks in said patient a sufficient amount of a fluid composition comprising a biocompatible prepolymer and a water insoluble contrast agent under conditions wherein the fluid composition forms a coherent mass *in situ* which adheres to the walls of the vascular site and/or prosthesis thereby sealing the endoleaks.

In a preferred embodiment, the fluid composition is delivered by either a microcatheter or by a needle.

This invention is also directed to kits of parts for use in endovascular treatment of aneurysms in a patient including sealing of endoleaks arising from such repair. In one embodiment, this kit comprises the following components:

(a) a fluid composition which is selected from the group consisting of (i) a biocompatible polymer and a biocompatible solvent and (ii) a biocompatible prepolymer and a water insoluble contrast agent which fluid composition forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm; and

(c) a catheter suitable for delivering an endovascular prosthesis to the aneurysm.

In a preferred embodiment, this kit further comprises an endovascular prosthesis.

In another embodiment, this kit comprises the following components:

(a) a fluid composition which is selected from the group consisting of (i) a biocompatible polymer and a biocompatible solvent and (ii) a biocompatible prepolymer and a water insoluble contrast agent which fluid composition forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm; and

(c) an endovascular prosthesis.

In a preferred embodiment, this kit further comprises a catheter suitable for delivering an endovascular prosthesis to the aneurysm.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed, in part, to novel methods for sealing endoleaks in a patient which methods deliver endovascularly a fluid composition to the site of the endoleak which composition solidifies *in situ* to seal the endoleak. Specifically, the fluid compositions used herein provide for formation of a coherent adhesive mass which forms *in situ* thereby sealing endoleaks thereby overcoming complications heretofore associated with such leaks.

However, prior to discussing this invention in further detail, the following terms will first be defined:

The term "sealing an endoleak" refers to a process wherein a fluid composition is injected at the site of the endoleak arising, for example, at or adjacent the site of an abdominal aortic aneurysm treated with an endovascular prosthesis. After delivery, the fluid composition solidifies *in situ* to seal the endoleak. Any endoleak can be treated in the methods of this invention

including endoleaks arising, for example, from incomplete sealing between the endovascular prosthesis and the aortic wall, from defects within the endovascular prosthesis as described below, and/or from retrograde flow from patent lumbar and inferior mesenteric arteries following placement of the endovascular prosthesis in the aorta.

The term "biocompatible polymer" refers to polymers which, in the amounts employed, are non-toxic, chemically inert, and substantially non-immunogenic when used internally in the patient and which, while soluble in the biocompatible solvent, are substantially insoluble in blood. Suitable biocompatible polymers include, by way of example, cellulose acetates[7,10-11] (including cellulose diacetate[9]), ethylene vinyl alcohol copolymers[8,12], hydrogels (e.g., acrylics), polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof.[13] Preferably, the biocompatible polymer does not induce chronic inflammation when employed *in vivo*.

The particular biocompatible polymer employed is not critical and is selected relative to the viscosity of the resulting polymer solution, the solubility of the biocompatible polymer in the biocompatible solvent, and the like. Such factors are well within the skill of the art.

Preferred biocompatible polymers include cellulose diacetate and ethylene vinyl alcohol copolymer. Cellulose diacetate polymers are either commercially available or can be prepared by art recognized procedures. In a preferred embodiment, the number average molecular weight, as determined by gel permeation chromatography, of the cellulose diacetate composition is from about 25,000 to about 100,000 more preferably from about 50,000 to about 75,000 and still more preferably from about 58,000 to 64,000. The weight average molecular weight of the cellulose diacetate composition, as determined by gel permeation chromatography, is preferably from about

50,000 to 200,000 and more preferably from about 100,000 to about 180,000. As is apparent to one skilled in the art, with all other factors being equal, cellulose diacetate polymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight polymers. Accordingly, adjustment of the viscosity of the composition can be readily achieved by mere adjustment of the molecular weight of the polymer composition.

Ethylene vinyl alcohol copolymers comprise residues of both ethylene and vinyl alcohol monomers. Small amounts (e.g., less than 5 mole percent) of additional monomers can be included in the polymer structure or grafted thereon provided such additional monomers do not alter the sealing properties of the composition. Such additional monomers include, by way of example only, maleic anhydride, styrene, propylene, acrylic acid, vinyl acetate and the like.

Ethylene vinyl alcohol copolymers are either commercially available or can be prepared by art recognized procedures. Preferably, the ethylene vinyl alcohol copolymer composition is selected such that a solution of 6 weight percent of the ethylene vinyl alcohol copolymer, 35 weight percent of a tantalum contrast agent in DMSO has a viscosity equal to or less than 60 centipoise at 20°C. As is apparent to one skilled in the art, with all other factors being equal, copolymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight copolymers. Accordingly, adjustment of the viscosity of the composition as necessary for catheter delivery can be readily achieved by mere adjustment of the molecular weight of the copolymer composition.

As is also apparent, the ratio of ethylene to vinyl alcohol in the copolymer affects the overall hydrophobicity/hydrophilicity of the composition which, in turn, affects the relative water solubility/insolubility of the

composition as well as the rate of precipitation of the copolymer in an aqueous solution (e.g., blood). In a particularly preferred embodiment, the copolymers employed herein comprise a mole percent of ethylene of from about 25 to about 60 and a mole percent of vinyl alcohol of from about 40 to about 75. These compositions provide for requisite precipitation rates suitable for use in sealing endoleaks arising from endovascular repair of an abdominal aortic aneurysm.

The term "contrast agent" refers to a biocompatible (non-toxic) radiopaque material capable of being monitored during injection into a mammalian subject by, for example, radiography or fluoroscopy. The contrast agent can be either water soluble or water insoluble. Examples of water soluble contrast agents include metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine.

The term "water insoluble contrast agent" refers to a water insoluble (i.e., has a water solubility of less than 0.01 mg/ml at 20°C), radiopaque material capable of being monitored during injection into a mammalian subject by, for example, radiography or fluoroscopy. Examples of water insoluble contrast agents include tantalum, tantalum oxide and barium sulfate, which are commercially available in the proper form for *in vivo* use. Methods for preparing such water insoluble biocompatible contrast agents having an average particle size of about 10 μm or less are described below. Other water insoluble contrast agents include gold, tungsten and platinum.

The term "biocompatible solvent" refers to an organic material liquid at least at body temperature of the mammal in which the biocompatible polymer is soluble and, in the amounts used, is substantially non-toxic. Suitable biocompatible solvents include, by way of example, ethanol, acetone, dimethylsulfoxide, analogues/homologues of dimethylsulfoxide, ethyl lactate, and the like. Aqueous mixtures with the biocompatible solvent can also be

employed provided that the amount of water employed is sufficiently small that the dissolved polymer precipitates upon contact with the blood. Preferably, the biocompatible solvent is dimethylsulfoxide (DMSO).

The term "encapsulation" as used relative to the contrast agent being encapsulated in the polymer precipitate is not meant to infer any physical entrapment of this agent within the precipitate much as a capsule encapsulates a medicament. Rather, this term is used to mean that an integral coherent precipitate forms which does not separate into individual components.

The term "adheres to" as used herein means that the composition formed *in situ* retains the position/location where the polymer mass formed after injection and thereby functions to seal the endoleak. This term does not necessarily infer that the composition acts as an adhesive although in the case of, for example, a cyanoacrylate prepolymer, the solid composition formed may, in fact, be adhesive.

The term "biocompatible prepolymer" refers to materials which polymerize *in situ* to form a polymer and which, in the amounts employed, are non-toxic, chemically inert, and substantially non-immunogenic when used internally in the patient and which are substantially insoluble in blood. Suitable biocompatible prepolymers include, by way of example, cyanoacrylates[14,15,16], hydroxyethyl methacrylate, silicone prepolymers, and the like. The prepolymer can either be a monomer or a reactive oligomer[16]. Preferably, the biocompatible prepolymer does not induce chronic inflammation when employed *in vivo*.

Compositions

The compositions used in the methods of this invention are fluid compositions characterized by the fact that these compositions form a coherent mass *in vivo* which adheres to the vascular and/or prosthetic wall at the site of

the endoleak thereby sealing the leak. The fluid compositions employed in the methods of this invention are polymer or prepolymer compositions prepared by conventional methods whereby each of the components is added and the resulting composition mixed or stirred together until the overall composition is substantially homogeneous.

In one embodiment, fluid polymer compositions preferably comprise a biocompatible polymer, a biocompatible solvent and optionally a contrast agent. Such compositions can be prepared by adding sufficient amounts of the biocompatible polymer to the biocompatible solvent to achieve the effective concentration for the polymer composition. Preferably, the polymer composition will comprise from about 2.5 to about 12.0 weight percent of the biocompatible polymer composition based on the total weight of the polymer composition and more preferably from about 4 to about 5.4 weight percent. If necessary, gentle heating and stirring can be used to effect dissolution of the biocompatible polymer into the biocompatible solvent, e.g., 12 hours at 50°C.

When employed, sufficient amounts of the contrast agent are then added to the biocompatible polymer/solvent composition to achieve the effective concentration for the complete composition. Preferably, the composition will comprise from about 10 to about 40 weight percent of the contrast agent and more preferably from about 20 to about 40 weight percent and even more preferably about 30 weight percent. Insofar as the contrast agent may not be soluble in the biocompatible solvent (e.g., a water insoluble contrast agent), stirring is employed to effect homogeneity of the resulting suspension.

In order to enhance formation of the suspension, the particle size of the water insoluble contrast agent is preferably maintained at about 10 μm or less and more preferably at from about 1 to about 5 μm (e.g., an average size of about 2 μm). In one preferred embodiment, the appropriate particle size of

the contrast agent is prepared, for example, by fractionation. In such an embodiment, a water insoluble contrast agent such as tantalum having an average particle size of less than about 20 microns is added to an organic liquid such as ethanol (absolute) preferably in a clean environment. Agitation of the resulting suspension followed by settling for approximately 40 seconds permits the larger particles to settle faster. Removal of the upper portion of the organic liquid followed by separation of the liquid from the particles results in a reduction of the particle size which is confirmed under an optical microscope. The process is optionally repeated until a desired average particle size is reached.

When no contrast agent is employed, the biocompatible solvent is preferably employed at a concentration of from 88 to about 97.5 weight percent of the biocompatible polymer composition based on the total weight of the polymer composition and more preferably from about 90 to about 95 weight percent.

When a contrast agent is employed, the biocompatible solvent is preferably employed at a concentration of from 52 to 87.5 weight percent based on the total weight of the composition; more preferably from about 54.8 to about 76 weight percent; and even more preferably 64.8 to about 66 weight percent. Typical examples of suitable concentrations of individual components are given in the table below:

Example	Polymer	Solvent	Contrast Agent
A	2.5 weight %	97.5 weight %	--
B	8 weight %	92 weight %	--
C	2.5 weight %	87.5 weight %	10 weight %
D	8 weight %	82 weight %	10 weight %
E	2.5 weight %	57.5 weight %	40 weight %
F	8 weight %	52 weight %	40 weight %
G	8 weight %	72 weight %	20 weight %
H	2.5 weight %	67.5 weight %	30 weight %
I	8 weight %	62 weight %	30 weight %
J	4 weight %	66 weight %	30 weight %
K	5.4 weight %	64.6 weight %	30 weight %

The particular order of addition of components to the biocompatible solvent is not critical and stirring of the resulting solution/suspension is conducted as necessary to achieve homogeneity of the composition. Preferably, mixing/stirring of the composition is conducted under an anhydrous atmosphere at ambient pressure. The resulting composition is heat sterilized and then stored preferably in sealed amber bottles or vials until needed.

Each of the polymers recited herein is commercially available but can also be prepared by methods well known in the art. For example, polymers are typically prepared by conventional techniques such as radical, thermal, UV, γ irradiation, or electron beam induced polymerization employing, as necessary, a polymerization catalyst or polymerization initiator to provide for the polymer composition. The specific manner of polymerization is not

critical and the polymerization techniques employed do not form a part of this invention.

In order to maintain solubility in the biocompatible solvent, the polymers described herein are preferably not cross-linked.

In another embodiment, the fluid compositions comprise prepolymer compositions which preferably comprise a biocompatible prepolymer and a water insoluble contrast agent. Such compositions can be prepared by adding sufficient amounts of the contrast agent to the solution (e.g., liquid prepolymer) to achieve the effective concentration for the complete composition. Preferably, the prepolymer composition will comprise from about 10 to about 40 weight percent of the contrast agent and more preferably from about 20 to about 40 weight percent and even more preferably about 30 weight percent. The water insoluble contrast agent is typically not soluble in the biocompatible prepolymer composition and stirring is employed to effect homogeneity of the resulting suspension. In order to enhance formation of the suspension, the particle size of the contrast agent is preferably maintained at about 10 μm or less and more preferably at from about 1 to about 5 μm (e.g., an average size of about 2 μm).

When the prepolymer is liquid, the use of a biocompatible solvent is not absolutely necessary but may be preferred to provide for an appropriate viscosity, etc. in the composition. Preferably, when employed, the biocompatible solvent will comprise from about 30 to about 90 weight percent of the biocompatible prepolymer composition based on the total weight of the prepolymer composition and more preferably from about 60 to about 80 weight percent. When a biocompatible solvent is employed, the prepolymeric composition typically comprises from about 10 to about 50 weight percent of the prepolymer based on the total weight of the composition. Typical

examples of suitable concentrations of individual components are given in the table below:

Example	Prepolymer	Solvent	Contrast Agent
L	90 weight %	--	10 weight %
M	85 weight %	--	15 weight %
N	80 weight %	--	20 weight %
O	70 weight %	--	30 weight %
P	60 weight %	--	40 weight %
Q	50 weight %	30 weight %	20 weight %
R	10 weight %	80 weight %	10 weight %
S	40 weight %	30 weight %	40 weight %
T	50 weight %	40 weight %	10 weight %
U	40 weight %	40 weight %	30 weight %
V	30 weight %	30 weight %	40 weight %

In a particularly preferred embodiment, the prepolymer is a cyanoacrylate ester which is preferably employed in the absence of a biocompatible solvent. When so employed, the cyanoacrylate composition is selected to have a viscosity of from about 5 to about 20 centipoise at 20°C.

The particular order of addition of components is not critical and stirring of the resulting suspension is conducted as necessary to achieve homogeneity of the composition. Preferably, mixing/stirring of the composition is conducted under an anhydrous atmosphere at ambient pressure. The resulting composition is sterilized and then stored preferably in sealed amber bottles or vials until needed.

Methods

The compositions described above can then be employed in methods for the catheter assisted sealing of endoleaks formed by endovascular repair of an abdominal aortic aneurysm by an endovascular prosthesis.

Specifically, endovascular repair of such aneurysms involves the introduction of an endovascular prosthesis into the abdominal aortic aneurysm which is an art recognized procedure described, for example, by Parodi.[17] This procedure typically consists of dissection of the femoral artery at the groin and introduction of an endovascular prosthesis inside the abdominal aortic aneurysm. Upon insertion, the prosthesis excludes the aneurysm sac from the systemic vascular circulation thereby repairing the aneurysm. Suitable endovascular prostheses for endovascular repair of abdominal aortic aneurysms are well known in the art and are described, for example, by Beebe, et al.[5] Such prostheses, by themselves, do not form part of this invention. Similarly, catheters for delivering such endovascular prostheses to the site of the abdominal aortic aneurysm are also well known in the art and are commercially available. Such catheters, by themselves, also do not form part of this invention.

In any event, in the methods of this invention, a sufficient amount of the fluid composition described above is introduced at the site of the endoleak via a catheter or needle delivery means preferably under fluoroscopy so that sealing of the endoleak can be visualized. The specific amount of fluid composition employed is dictated by the total size of the endoleak, whether penetration of the fluid composition into the aneurysm is desirable and/or achievable and other factors such as the concentration of polymer/prepolymer in the composition, the rate of solids formation, etc. Such factors are well within the skill of the art.

Prior to sealing the endoleak in the manner described above, the clinician would first identify the site or sites of the endoleak which typically include the interface of the aortic wall to the end of the endovascular prosthesis; defects within the endovascular prosthesis such as at juncture points between segments of the prosthesis which permit blood flow through the prosthesis itself; and retrograde flow from patent lumbar and inferior mesenteric arteries following placement of the endovascular prosthesis in the aorta.

Access to these sites of endoleaks can be achieved by microcatheter retrograde access via the patent lumbar and/or inferior mesenteric arteries or by endovascular methods or percutaneous puncture at the site of the endoleak. After access is achieved, delivery of the fluid composition proceeds as described above.

One particularly preferred method for catheter delivering the compositions described in the methods of this invention to the site of the endoleak is via a small diameter medical catheter. The particular catheter employed is not critical provided that polymeric catheter components are compatible with the fluid composition (i.e., the catheter components will not readily degrade in the fluid composition). In this regard, it is preferred to use polyethylene in the catheter components because of its inertness in the presence of the fluid composition described herein. Other materials compatible with the fluid compositions can be readily determined by the skilled artisan and include, for example, other polyolefins, fluoropolymers (e.g., Teflon™), silicone, etc.

Another particularly preferred method for the catheter injection of the polymer composition of this invention is described by Greff, et al., U.S. Patent No. 5,830,178 which issued on November 3, 1998 and which is incorporated herein by reference in its entirety.

When a fluid composition comprising a biocompatible polymer is introduced at the site of the endoleak, the biocompatible solvent diffuses rapidly into the blood and a solid coherent mass forms *in situ* which precipitate is the water insoluble polymer with any contrast agent encapsulated therein. Without being limited to any theory, it is believed that initially, a soft gel to spongy solid precipitate forms upon contact with the blood which mass adheres to the vascular or prosthetic wall thereby sealing the endoleak.

When a fluid composition comprising a biocompatible prepolymer is introduced at the site of the endoleak, the prepolymer polymerizes *in situ* to form a solid coherent mass or film with any water insoluble contrast agent encapsulated therein. This mass adheres to the vascular and/or prosthetic wall thereby sealing the endoleak.

When a contrast agent is employed in the fluid composition, sealing of the endoleak by this composition can be confirmed by injection of an independent contrast agent such iopamidol (50:50 mixture with saline) into the blood flow of the aorta. Failure of this contrast agent to reach the aneurysm sac as visualized by fluoroscopy confirms sealing of the endoleak.

The sealing of endoleaks can be conducted during the surgical repair of the abdominal aortic aneurysm or in a separate surgical procedure conducted subsequent to the surgical repair. All that is required is the determination of the location of the endoleaks in the patient and introduction of the fluid composition to seal such endoleaks.

The methods of this invention are preferably conducted by using kits of parts comprising two or more of the components necessary to effect the endoleak repair protocol. For example, in one embodiment, this kit comprises the following components:

(a) a fluid composition comprising a composition selected from the group consisting of (i) a biocompatible polymer and a biocompatible solvent

and (ii) a biocompatible prepolymer and a water insoluble contrast agent which fluid composition forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm; and

(c) a catheter suitable for delivering an endovascular prosthesis to the aneurysm.

In a preferred embodiment, this kit further comprises an endovascular prosthesis.

In another embodiment, this kit comprises the following components:

(a) a fluid composition comprising a composition selected from the group consisting of (i) a biocompatible polymer and a biocompatible solvent and (ii) a biocompatible prepolymer and a water insoluble contrast agent which fluid composition forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm; and

(c) an endovascular prosthesis.

In a preferred embodiment, this kit further comprises a catheter suitable for delivering an endovascular prosthesis to the aneurysm.

Utility

The methods described herein are useful in reducing or eliminating blood flow through an endoleak into an endovascularly repaired aneurysm thereby reducing or eliminating the possible rupture of the aneurysm. Accordingly, these methods find use in human and other mammalian subjects

requiring closure of such endoleaks. Additionally, when a water insoluble contrast agent is employed, the stability of the closure can be monitored weeks, months or even years after sealing by non-invasive fluoroscopic techniques. Resealing of the endoleak is also facilitated by the presence of the water insoluble contrast agent which permits the clinician to readily identify the site of treated endoleaks.

It is contemplated that the procedures set forth above can be employed for sealing endoleaks arising from insertion of an endovascular prosthesis at vascular sites other than the abdominal aorta. Such prostheses could be used to repair aneurysms and other vascular diseases at vascular sites such as peripheral vessels.

The following examples are set forth to illustrate the claimed invention and are not to be construed as a limitation thereof.

EXAMPLES

Unless otherwise stated, all temperatures are in degrees Celsius. Also, in these examples and elsewhere, the following abbreviations have the following meanings:

atm	=	atmospheres
cc	=	cubic centimeter
cm	=	centimeter
DMSO	=	dimethylsulfoxide
EVOH	=	ethylene vinyl alcohol copolymer
g	=	gram
hrs	=	hours
IM	=	intramuscularly
in.	=	inch
IU	=	international units
IV	=	intravenously
kg	=	kilogram
mg	=	milligram
min.	=	minute

mL	=	milliliter
mm	=	millimeter
PTFE	=	polytetrafluoroethylene
sec.	=	seconds
SQ	=	subcutaneously
μm	=	micron

Example 1

The purpose of this example is to demonstrate the preparation of a fluid polymer composition useful in the methods of this invention.

Specifically, an EVOH polymer composition was prepared as follows:

Composition

A) 8 g EVOH;

B) 30 g tantalum having an average particle size of about 3 μm (narrow size distribution); and

C) 100 mL DMSO.

Component A) was added to Component C) at 50°C and stirred for 2 hrs on a hot plate under an argon blanket. To this resulting composition was added Component B and the resulting mixture was mixed until homogeneous.

Example 2

This example illustrates sealing of endoleaks arising from endovascular repair of an abdominal aortic aneurysm in a dog model. The following illustrates the protocol employed:

Equipment Used

0.035/0.038 3J Guide Wires (Cook, Bloomington, IN)
10-14F Introducer Sheaths (Daig, Minnetonka, MN)
Angioplasty Balloon Catheters (10x2/ 10x4/ 10x6/ 16x2/16x4 18x2/18x4) - (Blue Max and XXL; Meditech, MA)

4mm Aortic Punch (Medtronic, Minneapolis, Minn.)
Palmaz Stents: P4014, P5014 (Johnson and Johnson Interventional Systems, New Jersey)

Infusion Catheters (Easy Rider™ 3F, Micro Therapeutics, Irvine, CA)
Microguide Wire (Silver Speed™, Micro Therapeutics, Irvine, CA)
Composition of Example 1
Contrast Media -Hypaque-76™ (Nycomed, Princeton, NJ)
7 and 8F Guiding Catheters (Medtronics, Minneapolis, MN)
10 mm and 12 mm diameter polyethylene terephthalate Wallgrafts™ (Schneider, Boston Scientific, Natick, MA)
5F Angiographic Catheters (Cordis, Miami Lakes, FL)

Pre-surgical Procedures

The animal was fasted 24 hrs prior to surgery and then pre-anesthetized with 0.01 mg/kg Glycopyrrolate SQ followed by anesthetization with a combination of Butorphanol, Xylazine, and Telazol. This combination was given such that 6.6 /kg Telazol is given IM. Next, the animal was intubated and connected to Isoflurane gas anesthesia of 1-3%.

A 20 gauge catheter was placed into the cephalic vein of the animal and 0.9% saline was administered intravenously at a rate of 1-4 mL/kg/hr and then 15 mL blood was collected for CBC liver profile.

A standard sterile surgical preparation and draping was utilized. The carotid or femoral artery was exposed via vessel cutdown and distal and proximal hemostatic loops placed. An arteriotomy was then performed and the introducer sheath (10-14F) was advanced into the artery lumen. The sheath and artery was then secured.

After the introducer was placed, the animal was IV heparinized with 100 units of heparin/kg of body weight.

A 7-8 F guiding catheter was introduced over a standard 0.035 inch, 3 mm "J" guide wire. A flush anteroposterior projection aortogram was obtained with use of contrast media, and the mediolateral diameter of the dog infrarenal aorta was measured with the use of the markers on the pigtail as standardization. A flat film X-ray was required during the contrast arteriography.

In accordance of the measurements of the infrarenal aorta, a Palmaz stent was deployed into the infrarenal aorta on a 10-16 mm diameter, 4 cm long angioplasty balloon with use of fluoroscopic guidance. Then the infrarenal aortic stent was overdilated to 1.5-2.0 its measured normal diameter in the dog at 6-8 atm using a standard pressure gauge for a single inflation lasting 30 sec.

The balloon was removed over a wire and replaced with the measuring pigtail catheter. A repeat aortogram was obtained and the abdominal aortic aneurysm was measured in the animal. A flat film with and without contrast media injections was obtained with all prostheses in the field of view.

A Wallgraft was then inserted with the model AAA. Each Wallgraft was medially perforated with a 4 mm aortic punch which produced a graft defect that was the source of the endoleak. These endografts were placed coaxially within the aneurysms.

A repeat aortogram was obtained. A flat film with and without contrast media injections was obtained with all prostheses in the field of view.

Upon completion, the arteriotomy was closed with interrupted polypropylene sutures and the surrounding tissue were sutured. The animal was allowed to recover before being returned to a cage.

At the conclusion of surgery, the animal was given approximately 25,000 IU/kg procaine and benzathine penicillin SQ.

Post-operatively, the animal received 325 mg/day of aspirin for 6 weeks and ampicillin 1 g/day for 3 days.

Endoleak Treatment

After 1 week, a CT-scan with and without contrast media was performed on the dog. A major leak at the graft defect (4 mm hole) that involved flow through a number of lumbar arteries and the distal stent graft to the aortic wall interface seal was noted. The animal was returned to a second phase of the study.

Treatment of the endoleaks was performed immediately after the CT scan. The animal had been fasted 24 hours prior to surgery and then pre-anesthetized with 0.01 mg/kg Glycopyrrolate SQ followed by anesthetization with a combination of Butorphanol, Xylazine, and Telazol. This combination was given such that 6.6 mg/kg Telazol is given IM. Next, the animal was intubated and connected to Isoflurane gas anesthesia of 1-3%.

A 20 gauge catheter was placed into the cephalic vein of the animal and 0.9% saline was administered intravenously at a rate of 1-4 mL/kg/hr.

A standard sterile surgical preparation and draping was utilized. The carotid or femoral artery was exposed via vessel cutdown and distal and proximal hemostatic loops placed. An arteriotomy was then performed and the introducer sheath (10-12F) was advanced into the carotid artery lumen. The sheath and artery were then secured.

After the introducer has been placed, the animal was IV heparinized with 100 units of heparin/kg of body weight.

A 7-8 F guiding catheter was introduced over a standard 0.035 inch, 3 mm J guide wire. A flush anteroposterior projection aortogram was obtained with the use of contrast media. The endoleaks were observed. A flat film X-

ray with and without contrast media injections was obtained with the aneurysm in the field of view.

The guiding catheter was removed and a 5F guiding catheter was placed adjacent to the 4 mm "hole". A small amount of contrast was given to confirm the position of the endoleak.

A microguide wire (0.010 inch) was passed through 5 F catheter and through the endograft hole. An infusion microcatheter was positioned over the wire and inside the aneurysm sac and about 1 cc of the fluid composition of Example 1 was administered under fluoroscopy until complete seal of the endoleak was achieved with filling of the lumber arteries and around the cuff or interface of the stent graft to the aortic wall. Contrast injection confirmed no blood flow through this endoleak pathway. Flat films were taken to document the results.

Follw-up aortography and CT scan was performed 5 weeks later, confirming successful treatment of the endoleaks. The above data demonstrates that the methods of this invention effectively seal endoleaks *in vivo*.

Example 3

This example illustrates the procedures used to access a simulated endoleak within the aneurysm sac after placement of the prosthesis within the AAA. Specifically, this example employs the following protocol.

A 25 kg male dog was prepared and anesthetized per Example 2 above. An abdominal midline incision was then made and the descending aorta exposed. A 15 mm arteriotomy was made in the aorta and a patch of fascia was sutured onto this opening creating an aneurysm of a size of about 4.5 x 3.5 x 4.0 cm. Three 4F Fogarty balloon catheters were placed into the aneursym via the carotid artery under fluoroscopy and each balloon catheter

was then filled with contrast solution comprising 1:1 saline:Hypaque 76 (0.25 cc, 0.25 cc and 0.5 cc respectively). A 12 mm x 5 cm Wall stent graft was placed within the aorta and over the aneurysm opening. To access the aneurysm sac through the graft, a 6 F guide catheter was placed into the aorta to the graft via the femoral artery and a 22 G x 40 cm needle introduced through the guide catheter. The needle tip was bent about 45 degrees. Under fluoroscopy, the graft wall was punctured and the needle tip advanced into the aneurysm sac. Each of the three filled balloons was successfully located and punctured to release the contrast agent which was visualized via fluoroscopy. To complete this simulation, a sufficient amount of the composition of Example 1 was then injected through the needle to fill the aneurysm sac. This composition, upon contact with the blood in the aneurysm sac solidified.

From the foregoing description, various modifications and changes in the above described methods will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

WHAT IS CLAIMED IS:

1. A method for sealing endoleaks in a patient arising from endovascular repair of abdominal aortic aneurysms which method comprises:

identifying an abdominal aortic aneurysm in a patient;

endovascularly repairing said aneurysm by catheter delivery of an endovascular prosthesis to the site of said aneurysm thereby inhibiting blood flow into the aneurysm;

identifying one or more endoleaks in a patient; and

delivering through a microcatheter to the site or sites of endoleaks in said patient a sufficient amount of a fluid composition comprising a biocompatible solvent and a biocompatible polymer under conditions wherein the fluid composition forms a coherent adhesive mass *in situ* thereby sealing the endoleaks.

2. The method according to Claim 1 wherein said biocompatible polymer is selected from the group consisting of cellulose acetate polymers, ethylene vinyl alcohol copolymers and polyacrylates.

3. The method according to Claim 2 wherein said biocompatible polymer is a cellulose acetate polymer or an ethylene vinyl alcohol copolymer.

4. The method according to Claim 1 wherein said biocompatible solvent is selected from the group consisting of dimethylsulfoxide, ethanol, ethyl lactate, and acetone.

5. The method according to Claim 4 wherein said biocompatible solvent is dimethylsulfoxide.

6. The method according to Claim 1 wherein the composition further comprises a contrast agent.

7. The method according to Claim 6 wherein said contrast agent is a water insoluble contrast agent.

8. The method according to Claim 7 wherein said water insoluble contrast agent is selected from the group consisting of tantalum, tantalum oxide, tungsten, and barium sulfate.

9. The method according to Claim 7 wherein said water insoluble contrast agent is characterized by having an average particle size of about 10 μm or less.

10. The method according to Claim 6 wherein said contrast agent is a water soluble contrast agent.

11. The method according to Claim 10 wherein said water soluble contrast agent is selected from the group consisting of metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine.

12. A method for sealing endoleaks in a patient arising from endovascular repair of abdominal aortic aneurysms which method comprises:

identifying an abdominal aortic aneurysm in a patient;

endovascularly repairing said aneurysm by catheter delivery of an endovascular prosthesis to the site of said aneurysm thereby inhibiting blood flow into the aneurysm;

identifying one or more endoleaks in a patient; and

delivering through a microcatheter to the site or sites of endoleaks in said patient a sufficient amount of a fluid composition comprising a biocompatible prepolymer, a water insoluble contrast agent and, when necessary to provide for a fluid composition, a biocompatible solvent wherein said delivery is conducted under conditions wherein the fluid composition forms a coherent adhesive mass *in situ* thereby sealing the endoleaks.

13. The method according to Claim 12 wherein said water insoluble contrast agent is selected from the group consisting of tantalum, tantalum oxide, tungsten, and barium sulfate.

14. The method according to Claim 12 wherein said water insoluble contrast agent is characterized by having an average particle size of about 10 μm or less.

15. The method according to Claim 12 wherein the biocompatible prepolymer is selected from the group consisting of cyanoacrylates, hydroxyethyl methacrylate and silicon prepolymers.

16. A kits of parts for use in sealing endoleaks arising from endovascular repair of an aneurysm which comprises:

(a) a fluid composition which forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm; and

(c) a catheter suitable for delivering an endovascular prosthesis to the aneurysm.

17. The kit of parts according to Claim 16 which kit further comprises an endovascular prosthesis.

18. A kits of parts for use in sealing endoleaks arising from endovascular repair of an aneurysm which comprises:

(a) a fluid composition which forms a coherent mass in the presence of blood which mass adheres to the vascular surface and/or the surface of the endovascular prosthesis;

(b) a catheter suitable for delivering the fluid composition to an endoleak site formed from endovascular repair of an aneurysm; and

(c) an endovascular prosthesis.

19. The kit of parts according to Claim 18 which kit further comprises a catheter suitable for delivering an endovascular prosthesis to the aneurysm.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07399

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61M 5/00, 29/00
US CL :Please See Extra Sheet.
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)

U.S. : Please See Extra Sheet.

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 practicable, search terms used)

WEST, STN ONLINE, BIOSIS, EMBASE
search terms: embolizing, embolization, endoleaks, leaks, aneurysm, abdominal aneurysm

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAN SCHIE. G. et al. Successful Embolization of Persistent Endoleak From a Patent Inferior Mesenteric Artery. J Endovasc Surg. 1997. Vol. 4. pages 312-315, especially abstract and page 313.	1-2, 6, 12, 15
Y	WHITE. G. et al. Endoleak as a Complication of Endoluminal Grafting of Abdominal Aortic Aneurysms: Classification, Incidence, Diagnosis, and Management. J Endovasc Surg. 1997. Vol. 4. Pages 152-168, especially pages 160-167	1-15
Y	WAIN. R. et al. Endoleaks after Endovascular Graft Treatment of Aortic Aneurysms: Classification, Risk Factors, and Outcome. J Vasc Surg. January 1998. Vol. 27. No. 1. Pages 69-80, especially pages 71-72.	1-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"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
"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)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 10 MAY 2000	Date of mailing of the international search report 03 AUG 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHAHNAM SHARAREH Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07399

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,695,480 A (EVANS et al) 09 December 1997 (09.12.97), see column 12 lines 15-67, column 9 lines 1-46, column 14 lines 1-35.	1-19
Y	US 5,749,894 A (ENGELSON) 12 May 1998 (12.05.98), abstract, see column 8 lines 11-67, column 9 lines 45-63.	1-15
Y	US 5,868,778 A (GERSHONY et al) 09 February 1999 (09.02.99), see abstract, column 6 lines 16-21, column 8 lines 20-67.	1-19
Y	JP 406,107,549 (MANDAI et al) 19 April 1994, see attached abstract translation.	1-15
Y	US 5,749,922 A (SLEPIAN et al) 12 May 1998 (12.05.98), see column 6 lines 5-45, column 8 lines 30-47, column 12 lines 1-10.	1-19
Y, P	KARCH. L. et al. Algrithm for the Diagnosis and Treatment of Endoleaks. Am J Surg. September 1999. Vol. 178. pages 225-231, see abstract	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/07399

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

604/264, 53, 49
424/1.29, 9.4, 426, 443
523/113, 115

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

604/264, 53, 49
424/1.29, 9.4, 426, 443
523/113, 115