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Title: ANASTOMOTIC DEVICE AND METHOD FOR OPEN AND ENDOSCOPIC SURGICAL ANATOMOSIS

Abstract: The present invention relates to an anastomotic device comprising a tubular graft connector comprising a tube, wherein the tube is expandable, it is provided with a locking device locking the tube in an unexpanded position, as well as a releasing means arranged to release the locking device after an insertion into a vessel, duct, lumen etc.
TITLE
ANASTOMOTIC DEVICE AND METHOD FOR OPEN AND ENDOSCOPIC SURGICAL ANASTOMOSIS

DESCRIPTION
Technical field
The present invention relates to an anastomotic device and a method for open and endoscopic surgical anastomosis of blood vessels, such as arteries and veins, ducts, lumens or other tubular organs in endoscopic and/or open surgery, in particular for reinforcement of a vessel, and in particular with regard to arterial connections.

Background of the Invention
Vascular and by-pass surgery is a common modality for the treatment of occlusive vascular disease. Surgery typically involves a surgical incision and an exposure of the occluded vessel, whereupon a graft is attached to a sidewall of a target vessel or conduit. Mammary arteries, radial arteries, saphenous veins, or synthetic grafts (all referred to hereinafter as the conduit) are commonly used to join the occluded vessel (hereinafter the conduit distally of the occlusion). The proximal end of the by-pass graft is secured to the suitable conduit upstream the occlusion, e.g. the aorta or the same occluded vessel above the occlusion to divert the flow around the blockage. All occluded or diseased vessel tissue, such as a carotid artery or femoral artery can be similarly treated. Also in the same type of surgery any conduit can be arranged between an artery and a vein in dialysis patients.

Vascular anastomosis involves the attachment of vascular grafts to vessels in a patient. One type of anastomosis is an end-to-side anastomosis, which generally involves attaching an end of a graft to a sidewall of a target vessel at an opening in the sidewall. Another type is an end-to-end anastomosis, which generally involves attaching the end of a graft to the end of a target vessel. Typically, in these procedures, sutures or staples accomplish the attachment. Some conventional devices and methods for anastomosis are disclosed and described, for example, in U.S. Pat. Nos. 3,774,615; 4,368,736; 4,523,592; 4,607,637; and 4,907,591. One procedure that involves vascular anastomosis is coronary artery bypass surgery where an anastomosis is formed between a vascular graft and the ascending aorta.

Arterial connections were first introduced by Sabiston in 1963 providing a vein graft and Favaloro carried out the first IMA artery in 1975 using a graft similar to Sabiston.
While such surgical procedures are widely practiced they have certain inherent operative limitations. Suturing a graft conduit to the blood providing vessel, known as anastomosis, is a delicate surgical technique in particular on endoscopic surgery to accomplish the desired and optimum result. Complications must be avoided when connecting a bypass graft conduit. For example, it is important that the joint between the native vessel and the bypass graft conduit form a smooth uniform transition without narrowing or regional irregularities, which could reduce blood flow. Any protuberances, diameter changes, into the lumen could obstruct blood flow and may produce turbulence and increasing the risk of clotting and restenosis. The difference in size between the larger internal diameter of the bypass graft conduit and the typically smaller native artery may also produce unwanted turbulence in the blood. All of these characteristics can greatly diminish the effectiveness of the graft.


Sullivan et al. U.S. patent application Ser. No. 08/869,808, filed Jun. 5, 1997 (all of which are hereby incorporated by reference herein) show examples of medical procedures in which it is necessary to make one or more tubular connections between a patient's tubular body tissue structures and a tubular graft. The tubular graft may be either natural body tissue extracted from elsewhere in the patient's body, an artificial graft structure, or a combination of natural and artificial structures. In the exemplary procedures shown in the three references mentioned above it is typically necessary to connect an end of the graft to a sidewall of the patient's pre-existing body tubing (e.g., a blood vessel). The three aforementioned patent applications deal primarily with procedures that are performed to the greatest extent possible percutaneously and through lumens of a patient's tubular body structures. Thus a graft connector is sometimes needed that can be delivered and installed via such lumens. It is preferable that in such a graft connector a minimum of hardware be required to pass through the aperture in the side wall of the patient's tubular body structure to engage the graft connector, because hardware passing through an artificially created aperture can damage the aperture, or widen it more than necessary. At other times, a graft connector is needed that can be installed during more traditional surgical procedures.

It is important for a graft connector to be easy and quick to install (whether percutaneously or surgically), but to be secure after installation. It is typically preferable for a graft connector to be relatively flexible after installation so that it does not form an unnaturally rigid structure in the patient's body.

Notwithstanding the foregoing, a need still exists for systems and methods for effecting anastomosis which is quick, easy, effective and safe.

Atherosclerosis is a progressive disease process in which the flow within the lumen of an artery becomes restricted by a blockage, typically referred to as an atherosclerotic plaque. In the heart, as well as the periphery, a blockage of an artery can result in pain, dysfunction and even death. Numerous methods have been employed over the years to revascularize the tissue downstream of an arterial blockage. These methods include bypass grafting--using artificial, in-situ venous, or transplanted venous grafts, as well as angioplasty, atherectomy and most recently, laser transmyocardial revascularization. Bypass grafting has been extremely successful; however, the procedure requires extensive surgery. Recently, newer techniques such as the transthoracic endoscopic procedure being pursued by the company, Heartport, Inc. and Cardiothoracic Systems, Inc., illustrate the need for a less invasive method of bypassing coronary vessels. These procedures are very difficult to perform, and may not be widely applicable. While
transmyocardial laser revascularization, a technique in which small holes are drilled through the wall of the heart looks promising, the method of action is not yet well understood, and problems exist with the use of laser energy to create the channels. Yet clinicians are still very interested in the technique because it has the potential to be minimally invasive, and does not require the patient to be placed on cardiopulmonary bypass.

In the 1970s several cardiovascular surgeons experimented with the use of cardiac veins for revascularization. The procedure was for use on patients, which had severely diffuse stenotic coronary vessels. The technique involved using an intervening graft from the internal mammary artery or an aortic attachment to an saphenous vein. Instead of sewing the grafts to the distal coronary artery, the grafts were attached to the coronary or cardiac vein in the same location. The proximal portion of the vein was then ligated to prevent a shunt, and the patient was then taken off cardiopulmonary bypass, and chest was closed. In this model, the vein were "arterialized", allowing flow in a retrograde fashion in a effort to bring oxygenated blood to the venules and capillaries of the heart. The success of this technique varied greatly, and was for the most part abandoned. Problems included stenosis at the anastomosis, intracardiac hemorrhages from ruptured venules, and thrombosis of the grafts.

The devices, systems and methods proposed in this disclosure suggest a new method of percutaneous or minimally invasive surgical revascularization. Here, the cardiac veins may either be arterialized, or may be simply used as by-pass grafts. There is no literature to suggest that this has been ever been attempted. While in-situ by-pass grafts have been made in the periphery, still an incision is made to attach and ligate the vein ends. Another procedure, which bears some resemblance to this technique, is called the TIPS procedure--transjugular intrahepatic portosystemic shunt. In this procedure a stent is advanced into liver tissue to connect the portal vein to the inferior vena cava. While this procedure can be accomplished percutaneously, it is not for the purpose of revascularization of an organ or to bypass a blockage within a vessel, does not permit retrograde flow within either of the two vessels, is not performed with an accompanying embolization, and requires the use of a stent. Further, the devices and methods used in that setting are too large and do not have the directional capability necessary for use in smaller vessels such as those found in the heart.

Open surgery was for many years the only way to gain access to tissues to perform a surgical maneuver. With the advent of optics, various endoscopic procedures were developed. Initially, these procedures utilized natural orifices such as the urinary tract,
oral cavity, nasal canal and anus. Most recently, new techniques using transabdominal and transthoracic ports have been developed. These thoroscopic or laparoscopic procedures essentially use instruments, which are long-shafted versions of their counterparts in open surgery. General anesthesia is usually required, and there are still several smaller wounds, which require healing.

One major problem of the T-shaped graft conduits of hitherto used design is the confluence of body liquid partly from the occluded area side, and partly from the graft conduit side. These fluid streams together forms a flow, which is larger than the single stream, which means that there is a risk for further occlusions or other complications.

OBJECTS OF THE INVENTION
Accordingly, it is a general object of this invention to provide an anastomosis system and method of use which addresses that problem.

It is a further object of this invention to provide an anastomotic coupling of particular utility for use in arterial and/or venous surgery which does not impede blood flow and which minimizes the blood turbulence which would normally result from a size differential between the two tubular bodies, e.g., the graft and the native blood vessel to which it is grafted.

It is a further object of this invention to provide an anastomotic fitting which provides a connection between a autologous or non-autologous vascular graft and the native blood vessel to which it is to be connected with a smooth uniform transition and which decreases in cross-sectional area in a controlled manner to reduce the possibility of blood turbulence therethrough.

It is a further object of this invention to provide a system and method of use for quickly, easily and safely effecting the anastomosis of vessels, ducts, lumens or other tubular organs.

It is a further object of this invention to provide an anastomotic coupling device for effecting the anastomosis of vessels, ducts, lumens or other tubular organs which is arranged for quick and sure placement with minimal chance of error.

It is a further object of this invention to provide a device for joining the ends of interrupted tubes or tubular organs of various sizes and functions, including, but not limited to, arteries, veins, lymphatic ducts, oviducts, urethras, intestines and the like.
It is a further object of the subject invention to provide a system for rapidly connecting two tubular bodies, e.g., a bypass graft to a native artery, without the need for sutures.

It is a further object of this invention to provide an anastomosis device for effecting the quick and easy anastomosis of two vessels, ducts, lumens or other tubular organs to each other while minimizing the chances for tissue necrosis.

It is a further object of this intervention to provide a device which improves body’s response to implantation. This means can be obtained either by a mere design of the device or by introducing pharmacologically active agents as such or through gene transfer to the tissues surrounding the device.

SUMMARY OF THE INVENTION

These and other objects of the instant invention are achieved by providing a system for effecting the bypass or other anastomosis of a portion of a native blood vessel, duct, lumen or other tubular organ within the body of a living being with another vessel, duct, lumen, or other tubular organ, e.g., a graft conduit. The native blood vessel, duct, lumen or tubular organ has a wall with an opening provided therein. The system comprises an anastomosis device for connecting the graft conduit to the native blood vessel, duct, lumen or tubular organ to establish a passageway for carrying fluid, e.g., blood, between the graft conduit and the native vessel.

Thus the invention in particular relates to an anastomotic device comprising a tubular graft connector comprising a tube, wherein the tube is expandable, it is provided with a locking device locking the tube in an unexpanded position, as well as a releasing means arranged to release the locking device after an insertion into a vessel, duct, lumen etc.

In accordance with one preferred aspect of the invention, the deployment instrument is arranged to dilate a portion of the native vessel contiguous with the opening to facilitate the introduction of at least a portion of the anastomosis device within the native vessel.

In accordance with another preferred aspect of the invention, the anastomosis device includes a passageway extending therethrough, which decreases in cross-sectional area to provide a path for fluid, e.g., blood, to flow therethrough between the graft conduit and the native vessel while minimizing turbulence therein.
In accordance with another preferred aspect of the intervention, the device is intended to facilitate function of the anastomosis (by e.g. providing an unobstructed flow). This can be obtained by a mere design of the device or by introducing pharmacologically active agents as such or through gene transfer to the tissues surrounding the device.

In accordance with another preferred aspect of the intervention, the device is intended to improve body’s response to the device by promoting healing and inhibiting pathological tissue growth.

Anastomotic device comprising a tubular graft connector comprising a tube, wherein the tube is expandable, it is provided with a locking device locking the tube in an unexpanded position, as well as a releasing means arranged to release the locking device after an insertion into a vessel, duct, lumen etc.

In a preferred embodiment the anastomotic device comprises an the expandable tube consists of a net mesh structure (11), where the meshes have a polygonal form having at least four corners, and which in non-expanded position are stretched.

In a preferred embodiment the anastomotic device comprises the polygonal form is quadratic, creating a rhomboidal form when expanded.

In a preferred embodiment the anastomotic device comprises the polygonal form is hexagonal.

In a preferred embodiment the anastomotic device comprises the device is further wholly or partly covered by a tightening cover.

In a preferred embodiment the anastomotic device the expansion locking device consists of a thread wound to and fro on either side of the anastomotic device outgoing from at least one releasing thread extending along the anastomotic device.

In a preferred embodiment the anastomotic device the expansion locking device consists of a helix thread forming the expandable parts of the anastomotic device and
locked in an extended position and arranged to be released/unlocked to allow the expandable part to expand by the helix reverting to an original diameter.

In a preferred embodiment the anastomotic device the cover is provided with a pharmaceutical wound healing supporting entity.

In a preferred embodiment the anastomotic device the cover with a pharmaceutical wound healing supporting entity is a low-molecular weight compound.

In a preferred embodiment the anastomotic device the compound is a superoxide dismutase mimic.

In a preferred embodiment the anastomotic device the cover with a pharmaceutical wound healing supporting entity is a nucleic acid present in a biologically compatible formulation, characterized in that said nucleic acid encodes a translation or transcription product capable of promoting wound healing.

In a preferred embodiment the anastomotic device the nucleic acid is GTU® (Gene Transport Unit).

In a preferred embodiment the anastomotic device the nucleic acid is present in the biologically compatible formulation in naked form.

In a preferred embodiment the anastomotic device the nucleic acid is present in a liposome.

In a preferred embodiment the anastomotic device the nucleic acid has been introduced in a viral vector.

In a preferred embodiment the anastomotic device the nucleic acid is has been introduced in a viral vector selected from the group consisting of retrovirus, Sendai virus, adeno associated virus, adenovirus, lentivirus, baculovirus.

In a preferred embodiment the anastomotic device the nucleic acid is an artificial chromosome.

In a preferred embodiment the anastomotic device the nucleic acid is oligonucleotide.
In a preferred embodiment the anastomotic device the nucleic acid is aptamer.

In a preferred embodiment the anastomotic device the nucleic acid encodes a superoxide scavenger molecule.

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In a preferred embodiment the anastomotic device the nucleic acid encodes extracellular superoxide dismutase.

In a preferred embodiment the anastomotic device the nucleic acid encodes endothelial mitogen.

In a preferred embodiment the anastomotic device the endothelial mitogen belongs to the platelet-derived growth factor (PDGF) superfamily.

15 In a preferred embodiment the anastomotic device the endothelial mitogen belongs to the vascular endothelial growth factor (VEGF) family.

Another aspect of the invention encompasses a method for mending a vessel or to provide a by-pass of an occlusion of a vessel or the similar in a body, whereby an anastomotic device according to the above given definitions, is provided at either end of a vessel to be mended, or is inserted into a vessel to be by-passed and is connected to an occlusion circumventing vessel, allowing the anastomotic device to expand by eliminating the releasing means thereby providing a tight seal of the vessel(-s) in question.

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DETAILED DESCRIPTION OF THE PRESENT INVENTION
The invention will be described in the following more in detail with reference to the accompanying drawing wherein

30 FIG. 1 shows a side view of one preferred embodiment of the present invention;
FIG. 2 shows a side view of a further preferred embodiment of the present invention;
FIG. 3 shows a side view of another preferred embodiment of the present invention;
FIG. 4 shows the device according to FIG. 1 in an extended form;
FIG. 5 shows a detail of the locking device used;
FIG. 6 shows a device of the invention as inserted into a vessel; and
FIG. 7 shows a device of the invention as used in by-pass surgery.
The drawing shows a substantially tubular medical graft conduit 1 comprising a net structure 11 to be brought into a vessel, V, and providing a tubular body for reinforcing a vessel. The net structure 11 consisting of hexagonal cells 12, is, in a non-inserted position, extended or elongated, whereby the cells have adopted an extended form, as evident from Fig. 3. The net structure or conduit 1 is covered by a layer 2 of biocompatible expandable material. The cover may only cover a part of the tubular structure as evident from FIGs. 1-4.

The polygonal cells may be quadratic forming a rhomboidal structure when expanded, being hexagonal, which is preferred, or being octagonal, decagonal or even dodecagonal. However, they should have an even number of corners to provide for a good expanded shape.

The cover 2 may be provided with any suitable pharmaceutical composition to inhibit rejection, to inhibit bacterial growth, or to support tissue growth such as any growth factor known in the art, synthesized or extracted from a natural source. Any other wound healing supporting pharmaceutical composition or drug entity can be used as well. The cover is preferably made of an porous material providing apertures of 60 to 200 um, arranged about 60 um from each other. This facilitates in-growth of new vessel tissue into the graft.

The material of the graft can be any native graft material used, or any synthetic material used and known to the one skilled in the art. In particular a synthetic material is used when the graft is made expandable using a net structure or a helix for primarily reducing the diameter.

The net structure is made of any biocompatible material which is not rejected by the body, and which allows the walls of the vessel or duct to grow over it to provide a new biological lumen. Such materials are biocompatible polymers known in the art or a metal such as titanium, which has proved to be an efficient material in prosthetic surgery.

Preferred biomaterials are those that provide sufficient rigidity for their intended purposes in vivo. For use in forming a vascular graft and cardiovascular patch, for instance, the biomaterial will be of sufficient rigidity to allow the graft to retain graft potency in the course of its intended use. The choice of implant material will differ according to the particular circumstances and the site where the vascular or tissue implant is implanted. Vascular prostheses are made of biomaterials, selected from the group consisting of e.g. tetrafluoroethylene polymers, aromatic/aliphatic polyester
resins, polyurethanes, and silicone rubbers. However, any type of biocompatible
microporous mesh may be used. The said biomaterials can be combined with each other
or other substances, such as polyglycolic acid, polylactic acid, polydioxone and
polyglyconate. Preferred are expanded polytetrafluoroethylene and Dacron. Dacron may
be with or without velour, or modified in some other way. Dacron is usually woven,
braided or knitted and suitable yarns are between 10 and 400 deniers. The nodal
regions of ePTFE are composed of nonporous PTFE that serves to provide tear resistance
(e.g. for sutures and resistance to aneurismal dilatation). The internodal regions are
composed of fibres of PTFE, which serve to connect the nodes with the spaces between
the fibres providing the porosity referred to herein. The nodal size can be expressed as
the percentage of the tissue-contacting surface that is composed of nodal PTFE. The
distance between nodes can be expressed as the average fibril length. In turn, the
porosity is commonly expressed as the internodal distance (i.e. the average distance
from the middle of one node to the middle of the adjacent node). Preferred ePTFE
materials have nodes of sufficient size and frequency to provide adequate strength
(e.g., with respect to aneurismal dilatation) and internodal regions of sufficient
frequency and fibre length to provide adequate porosity (to allow for capillary
endothelialisation). Given the present specification, those skilled in the art will be able
to identify and fabricate devices using biomaterials having a suitable combination of
porosity and rigidity. Biomaterials are preferably porous to allow the attachment and
migration of cells, which may be followed by the formation and growth of capillaries into
the surface. Suitable pores can exist in the form of small channels or passages, which
start at an external surface and extend partially or completely through the biomaterial.
In such cases, the cross sectional dimensions of the pore capillary diameter are greater
than 5 microns and typically less than 1 mm. The upper pore size value is not critical as
long as the biomaterial retains sufficient rigidity; however it is unlikely that useful
devices would have a pore size greater than about 1 mm. Such pore dimensions can be
quantified in microscope. As will be understood by those skilled in the art, several
modifications of the graft materials and surfaces can be made, such as precoating with,
for example, proteins (see e.g. 5,037,377, 4,319,363), non-heparinised whole blood
and platelet rich plasma, glow-discharge modifications of surfaces, adding pluronic gel,
fibrin glue, fibronectin, adhesion molecules, covalent bonding, influencing surface
charges, with for example carbon (5,827,327, 4,164,045), and treating with a
surfactant or cleaning agent, without excluding any other method. Moreover, the
implant can be constructed as a hybrid of different internodal distances for the inner
and outer surfaces, such as 60 microns as an outer value and 20 microns as an inner
value, for the internodal distances (HYBRID PTFE). Also, more layers with different
internodal distances may be used. They are all intended to fall within the scope of the
present invention when not inhibiting endothelialisation. Potential biodegradable vascular implants may be used in connection with the compositions, devices and methods of this invention. For example, biodegradable and chemically defined polylactic acid, polyglycolic acid, matrices of purified proteins, semi-purified extra cellular matrix compositions and also collagen can be employed. Also, naturally occurring autogenic, allogenic and xenogenic material, such as an umbilical vein, saphenous vein, native bovine artery or intestinal sub-mucosal tissue may be used as a vascular implant material. Examples of clinically used grafts are disclosed in 4,187,390, 5,474,824 and 5,827,327. Biodegradable or bioabsorbable materials, such as homopolymers e.g. poly-paradioxanone, polyllysine or polyglycolic acid and copolymers; e.g., polylactic acid and polyglycolic acids or other bio materials, may be used either alone or in combination with other materials as the vascular graft material, as long as they provide the required rigidity. Also, other biological materials, such as intestinal submucosa, matrices of purified proteins and semi-purified extra cellular matrix compositions may be used. Appropriate vascular grafts will both deliver the gene composition and also provide a surface for new endothelium growth, i.e., will act as an in situ scaffolding through which endothelial cells may migrate. It will be understood by a person skilled in the art that any material with biocompatibility will be acceptable.

Background for cardiovascular patches is well described in for example 5,104,400, 4,164,045, 5,037,377. In the case of vascular patches, one side of the patch engages the blood while the other side engages other surrounding tissues to promote transgraft growth of the endothelial cells. In the case of intracardiac patches, blood engages both sides of the patch. Preferred biomaterials are those that provide sufficient rigidity in vivo. A vascular patch biomaterial will be of sufficient rigidity to allow the patch to retain its form and pore-structure in the course of its intended use. The choice of patch material will differ according to the particular circumstances and site where the vascular patch is implanted. Vascular patch is made of synthetic biomaterial, such materials include, but are not limited to, tetrafluoroethylene polymers, aromatic/aliphatic polyester resins, polyurethanes, and silicone rubbers, however, any type of biocompatible microporous mesh may be used. The said biomaterials can be combined with each other or other substances such as polyglycolic acid. Preferred are expanded polytetrafluoroethylene and Dacron. Dacron is usually woven, braided or knitted, and with or without valour, and suitable yarns are between 10 and 400 deniers. The nodal regions of ePTFE are composed of nonporous PTFE that serves to provide tear resistance (e.g. for sutures and resistance to aneurismal dilatation). The internodal regions are composed of fibres of PTFE which serve to connect the nodes, with the spaces between the fibres providing the porosity referred to herein. The nodal size can be expressed as
the percentage of the tissue-contacting surface that is composed of nodal PTFE. The distance between nodes can be expressed as the average fibril length. In turn the porosity is commonly expressed as the internodal distance (i.e. the average distance from the middle of one node to the middle of adjacent node). Preferred ePTFE materials have nodes of sufficient size and frequency to provide adequate strength (e.g., with respect to aneurismal dilatation) and internodal regions of sufficient frequency and fibre length to provide adequate porosity (to allow for capillary endothelialisation). Such materials will provide fewer though thicker nodes, which will in turn confer significantly greater strength \textit{in vivo}. Given the present specification, those skilled in the art will be able to identify and fabricate devices using biomaterials having a suitable combination of porosity and rigidity. Biomaterials are preferably porous to allow the attachment and migration of cells, which may be followed by the formation and growth of capillaries into the luminal surface. Suitable pores can exist in the form of small channels or passages, which start at an external surface and extend through the biomaterial. In such cases, the cross sectional dimensions of the pores are larger than the diameter of a capillary 5 microns and are typically less than 1 mm. Upper pore size value is not critical as long as the biomaterial retains sufficient rigidity. However, it is unlikely that useful devices would have pore size greater than about 1mm. Such pore dimensions can be quantified in microscope. As will be understood by a person skilled in the art, several modifications of graft materials and surfaces can be made, such as precoating with for example proteins (for example, 5,037,377, 4,319,363), non-heparinised whole blood and platelet rich plasma, glow-discharge modifications of surfaces, adding pluronic gel, fibrin glue, adhesion molecules, covalent bonding, Influencing surface charges with for example carbon (5,827,327, 4,164,045), treating with a surfactant or cleaning agent, without excluding any other method. Also the implant can be constructed as a hybrid of different internodal distances in inner and outer surface, such as outer 60 microns and inner 20 microns in internodal distance (HYBRID PTFE). Even more layers with different internodal distances may be used. They all are intended to fall in the scope of present invention when not inhibiting endothelialisation. Potential biodegradable materials may be used in connection with the compositions, devices and methods of this invention, for example homopolymers e.g. poly-paradoxanone, polylysine or polyglycolic acid and copolymers e.g., polyactic acid and polyglycolic acids or other bio materials, such as matrices of purified proteins and semi-purified extra cellular matrix compositions may be used either alone or in combination with other materials as cardiovascular patch material, as long as they provide the required rigidity. Naturally occuring autogenic, allogenic and xenogenic material such as an umbilical vein, saphenous vein, native bovine artery, pericardium or intestinal submucosal tissue may also be used as cardiovascular patch material. Examples of clinically used vascular patches are disclosed
in 5,037,377, 5,456,711, 5,104,400, 4,164,045. Appropriate vascular patches will both deliver the gene composition and also provide a surface for new endothelium growth, i.e., will act as an in situ scaffolding on which and through which endothelial cells may migrate. Preferably, nucleic acids are attached to the side engaging the tissues surrounding the vessel. Appropriate intracardiac patches will both deliver the gene composition to the surrounding tissues and provide a surface for new endothelium growth, i.e., will act as an in situ scaffolding on which and through which endothelial cells may migrate. Preferably, nucleic acids are attached to both intracardiac patch surfaces. Alternatively, nucleic acids may be attached to one of the intracardiac patch surfaces. It will be understood by a person skilled in the art that any material with biocompatibility, rigidity and porosity to allow endothelialisation will be acceptable.

Stent herein means a medical implant in the form of a hollow cylinder, which will provide support for the body lumen when it is implanted in contact with a site in the wall of a lumen to be treated. They can be of several different designs such as tubular, conical or bifurcated. The configuration can be such as a coiled spring, braided filament, perforated tube, slit tube, and zigzag, or any other variant. Preferably, it is adapted for use in blood vessels in a way that the stent has an outer, lumen-contacting surface, and an inner, blood-contacting surface. Many stents of the art are formed of individual member(s), such as wire, plastic, metal strips, or mesh, which are bent, woven, interlaced or otherwise fabricated into a generally cylindrical configuration. The stent can also have underlying polymeric or metallic structural elements, onto which elements; a film is applied (5,951,586). Stents have been classified into either self-expanding or pressure expandable. The terms expand, expanding, and expandable are used herein to refer to diametrically adjustable intraluminal stents. When the self expanding stents are positioned at the treatment site with a delivery catheter, they are supposed to radially expand to a larger diameter after being released from a constraining force, which force restricts them to a smaller diameter and conform a surface contact with a blood vessel wall or other tissue without exertion of outwardly directed radial force upon stent. Stents of this type include stents of braided or formed wire. The pressure-expandable stents are fabricated of malleable or plastically deformable material, typically formed of metal wire or metal strips. The collapsed stent is taken to the treatment site with a delivery catheter, and is then radially expanded with a balloon or other stent-expansion apparatus to its intended operative diameter. Thread elements or strands formed of metal are generally favoured, for applications requiring flexibility and effective resistance to radial compression after implantation. The favourable combination of strength and flexibility is largely due to the properties of the strands after they have been age hardened, or otherwise thermally treated in the case
of polymeric strands. The braiding angle of the helical strands and the axial spacing between adjacent strands also contributes to strength and flexibility.

Stent wires may be of metal, inorganic fibres or organic polymers. They should be elastic, strong, biocompatible, and fatigue and corrosion resistant. For example, core wires made of metals, such as stainless steel or gold or other relatively pliable non-toxic metals and alloys that do not degrade during the time of implantation or are not subject to severe degradation (corrosion) under the influence of an electric current, are usually chosen. Such metals include, but are not limited to, platinum, platinum-iridium alloys, copper alloys, with tin or titanium, nickel-chrome-cobalt alloys, cobalt based alloys, molybdenum alloys, nickel-titanium alloys. The strands need not be of metal and may for example be of a polymeric material such as PET, polypropylene, PEEK, HDPE, polysulfone, acetyl, PTFE, FEP, and polyurethane without excluding any other substance (other variants: polytetrafluoroethylene, fluorinated ethylene propylene, polytetrafluoroethylene-perfluoroalkyl vinyl ether copolymer, polyvinyl chloride, polypropylene, polyethylene terephthalate, broad fluoride and other biocompatible plastics). Also, a biodegradable or bioabsorbable material, such as homopolymers e.g. poly-paradoxanone, polylysine or polyglycolic acid and copolymers, e.g. polyactic acid and polyglycolic acids, polyurethane, or other biomaterials, may be used either alone or in combination with other materials as the stent material. Such monofilament strands range from 0.002 to 0.015 inches in diameter but of course the diameter could vary depending on the lumen size and the degree of support needed. To stents may also antithrombotic, anti-platelet, vasodilators, antiproliferative, antimigratory, antiinflammatory agents and more specifically, heparin, hirudin, hirulog, etritinate, freskolin and the like, be attached. Examples of clinically used stents are disclosed in 4,733,665, 4,800,882, 4,886,062 incorporated here by reference.

Stent grafts, also called covered stents, for transluminal implantations include a resilient tubular interbraided latticework of metal or polymeric monofilaments, a tubular interbraided sleeve formed of a plurality of interwoven textile strands, and an attachment component that fixes the latticework and the sleeve together, in a selected axial alignment with one another, engaged with one another and with a selected one of the latticework and the sleeve surrounding the other, whereby the latticework structurally supports the sleeve. It is ensured that the latticework and the sleeve behave according to substantially the same relationship governing the amount of radial reduction that accompanies a given axial elongation. The sleeve may be exterior or interior to the latticework, or the latticework may be integrated in the sleeve, and it can be continuous or discontinuous. Several prosthesis constructions have been suggested.
for composite braided structures that combine different types of strands, e.g. multifilament yarns, monofilaments, fusible, materials and collagens. Examples are found in WO91/10766. Textile strands are preferably multifilament yarns, even though they can be monofilaments. In either case the textile strands are much finer than the structural strands, ranging from about 10 denier to 400 denier. Individual filaments of the multifilament yarns can range from about 0.25 to about 10 denier. Multifilament yarns can be composed of various materials, such as PET, polypropylene, polyethylene, polyurethane, HDPE, silicone, PTFE, polyolefins and ePTFE. By modifying the yarns it is possible to modify sleeve qualities, for example untwisted flat filaments provide thinner walls, smaller interstices between yarns so achieving lower permeability, and higher yarn cross-section porosity for capillary transgraft growth. Porous expanded PTFE film has a microstructure of nodes interconnected by fibrils and may be made as taught by for example U.S. Pat. Nos. 3,953,566, 4,187,390 and 4,482,516. Suitable pores can exist in the form of small channels or passages starting at an external surface and extending through the biomaterial. In such cases the cross-sectional dimensions of the pores are larger than the diameter of a capillary 5 microns, and are typically less than 1 mm. Upper pore size value is not critical so long as the biomaterial retains sufficient rigidity, however it is unlikely that useful devices would have pore size greater than about 1 mm. Such pore dimensions can be quantified in microscope. As will be understood by those in the art several modifications of stent graft materials and surfaces can be made such as precoating with proteins, non-heparinised whole blood and platelet rich plasma, glow-discharge modifications of surfaces, adding pluronic gel, fibronectin, fibrin glue, adhesion molecules, covalent bonding, influencing surface charges with for example carbon (5,827,327, 4,164,045), treating with a surfactant or cleaning agent, mechanically changing the characteristics, such as adding grooves and changing the end angles without excluding any other method. Also the implant can be constructed as a hybrid of different internodal distances in inner and outer surface such as outer 60 microns and inner 20 microns in internodal distance (HYBRID PTFE). Even more layers with different internodal distances can be used. They all are intended to fall in the scope of present invention when not inhibiting endothelialisation. The fibrils can be uni-axially oriented, that is oriented in primarily one direction, or multiaxially oriented, that is, oriented in more than one direction. The term expanded is used herein to refer to porous expanded PTFE. It will be understood by a person skilled in the art, that any material with biocompatibility and porosity to allow transgraft growth will be acceptable. Examples of clinically used stent grafts are disclosed in 5,957,974, 5,928,279, 5,925,075, 5,916,264.
Also, naturally occurring autologous, allogenic or xenogenic materials, such as arteries, veins and intestinal submucosal can be used in stent grafts, such as an umbilical vein, saphenous vein, or native bovine artery. Potential biodegradable vascular implants may be used as stent grafts in connection with the compositions, devices and methods of this invention, for example biodegradable and chemically defined polylactic acid, polyglycolic acid, matrices of purified proteins, semi-purified extra cellular matrix compositions. Appropriate vascular grafts and stent grafts will both deliver the gene composition and also provide a surface for new endothelium growth, i.e., will act as an in situ scaffolding through which endothelial cells may migrate. The particular design of the implants that are implanted using the methods and compositions of the invention are not important, as long as they act as scaffolds through which endothelium can migrate, in the context of in vivo embodiments, and ultimately give rise to endothelialisation of the implant.

In another embodiment, FIG. 2, an expansion means is shaped as a helix 11, the diameter of which is reduced by stretching the helix and locking it prior to insertion, and unlocking the helix after insertion allowing the biocompatible cover to expand.

The locking of the expandable material prior to insertion is by using a locking thread 3 wound to and fro around the tubular conduit in conjunction and cooperation with a releasing, removable thread 4 arranged to be withdrawn from its locking position. Thus the locking thread is wound around the releasing thread to and fro. Thus the releasing thread 4 is drawn along the tubular conduit, and then the locking thread 3 is drawn to and fro said releasing thread 4, as shown in detail in FIG. 5.

The locking thread 3 may be removed from the site, i.e., from the site where the conduit 1 is inserted or may be made of any biocompatible resorbable material known in the art of suturing, such as a polylactic material.

An insertion device 6 may used for stabilizing and holding the conduit 1 during insertion into two vessel parts V, as shown in FIG. 6. The insertion device simultaneously is a counterpart for the withdrawal of the releasing thread 4. The insertion device comprises guiding part 7 forming an enclosing grip of the conduit 1, and a handle 8 comprising a pair of eyes 9 to be used by the surgeon's fingers or the endoscope robotic arms for guiding the conduit 1 and acting as a counterpart when removing the thread 4. The eyes 9 of the handle 8 are also connected to the guiding enclosing part 7 and is arranged to release said enclosing grip of the conduit.
When using the stent graft of the invention any invasive method can be used to enter the site of preparing a shunt or other type of by-pass that is needed. Thus, general surgery can be used as well as endoscopy where an endoscope is introduced through a blood vessel or the similar and is guided to the site. The vessel to be provided with the anastomotic device is then closed up-stream the damaged site, a surgical incision is made to cut away any damaged tissue of the vessel, and the anastomotic device of the invention is brought into one end of the vessel and is then inserted into the other end of the vessel to be repaired. The releasing thread is then removed from the anastomotic device by drawing it away. Normally, two releasing threads are used starting from the middle of the conduit part and extending to either end of the conduit. See FIG. 5. By allowing the expandable tube parts to expand no suturing is needed but the force of the expansion will keep the connection tight. At the expansion the two ends of the vessel or duct will also be drawn closer to each other and they will rapidly grow together forming a tissue tight seal. The expansion of the net structure is due to its original net polygonal structure to which it strives to revert to. The vessel repaired is then opened after insertion of the conduit and removal of the releasing thread and the blood is allowed to flow through the anastomotic device of the invention.

The anastomotic device of the invention can also be used for by-pass surgery where one end of the anastomotic device is introduced into a vessel down-stream or upstream an occlusion, OS, and the vessel circumventing the occlusion is added to the other end of the device. See FIG. 7. In the figure the vessel, CV, circumventing the occlusion is seen up the left, whereby the releasing thread 4 has been removed from this part and the conduit has been allowed to expand, and whereby to the right the non-expanded part of the conduit 1 has just been entered into the vessel, V.
CLAIMS

1. Anastomotic device comprising a tubular graft connector comprising a tube, wherein the tube is expandable, it is provided with a locking device locking the tube in an unexpanded position, as well as a releasing means arranged to release the locking device after an insertion into a vessel, duct, lumen etc.

2. Anastomotic device according to claim 1, wherein the expandable tube consists of a net mesh structure (11), where the meshes have a polygonal form having at least four corners, and which in non-expanded position are stretched.

3. Anastomotic device according to claim 2, wherein the polygonal form is quadratic, creating a rhomboidal form when expanded.

4. Anastomotic device according to claim 2, wherein the polygonal form is hexagonal.

5. Anastomotic device according to claim 1, wherein the device is further wholly or partly covered by a tightening cover (2).

6. Anastomotic device according to claim 1, wherein the expansion locking device consists of a thread (3) wound to and fro on either side of the anastomotic device outgoing from at least one releasing thread (4) extending along the anastomotic device.

7. Anastomotic device according to claim 4, wherein the expansion locking device consists of a helix thread (11) forming the expandable parts of the anastomotic device and locked in an extended position and arranged to be released/unlocked to allow the expandable part to expand by the helix reverting to an original diameter.

8. Anastomotic device according to one or more of the preceding claims, wherein the cover (2) is provided with a pharmaceutical wound healing supporting entity.

9. Anastomotic device according to one or more of the preceding claims, wherein the cover with a pharmaceutical wound healing supporting entity is a low-molecular weight compound.
10. Anastomotic device according to one or more of the preceding claims, wherein the compound is a superoxide dismutase mimic.

11. Anastomotic device according to one or more of the preceding claims, wherein the cover with a pharmaceutical wound healing supporting entity is a nucleic acid present in a biologically compatible formulation, characterized in that said nucleic acid encodes a translation or transcription product capable of promoting wound healing.

12. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid is GTU® (Gene Transport Unit).

13. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid is present in the biologically compatible formulation in naked form.

14. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid is present in a liposome.

15. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid has been introduced in a viral vector.

16. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid is has been introduced in a viral vector selected from the group consisting of retrovirus, Sendai virus, adeno associated virus, adenovirus, lentivirus, baculovirus.

17. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid is an artificial chromosome.

18. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid is oligonucleotide.

19. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid is aptamer.

20. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid encodes a superoxide scavenger molecule.
21. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid encodes extracellular superoxide dismutase.

22. Anastomotic device according to one or more of the preceding claims, wherein the nucleic acid encodes endothelial mitogen.

23. Anastomotic device according to one or more of the preceding claims, wherein the endothelial mitogen belongs to the platelet-derived growth factor (PDGF) superfamily.

24. Anastomotic device according to one or more of the preceding claims, wherein the endothelial mitogen belongs to the vascular endothelial growth factor (VEGF) family.

25. Method for mending a vessel or to provide a by-pass of an occlusion of a vessel or the similar in a body, whereby an anastomotic device according to claims 1-24, is provided at either end of a vessel to be mended, or is inserted into a vessel to be by-passed and is connected to an occlusion circumventing vessel, allowing the anastomotic device to expand by eliminating the releasing means thereby providing a tight seal of the vessel(s) in question.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC7:** A61B 17/11

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)

**IPC7:** A61B

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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☐ Further documents are listed in the continuation of Box C. ❌ See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search: 10 October 2003

Date of mailing of the international search report: 15-10-2003

Name and mailing address of the ISA/Swedish Patent Office
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Hélène Erikson/Els
Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)
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INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☒ Claims Nos.: 25
   because they relate to subject matter not required to be searched by this Authority, namely:

   See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

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

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

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant’s protest.

☐ No protest accompanied the payment of additional search fees.