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(54) Title: DEVICE AND METHOD FOR REDUCING THE RISK OF OCCLUSION AND RESTENOSIS AFTER IMPLANTATION OF A STENT

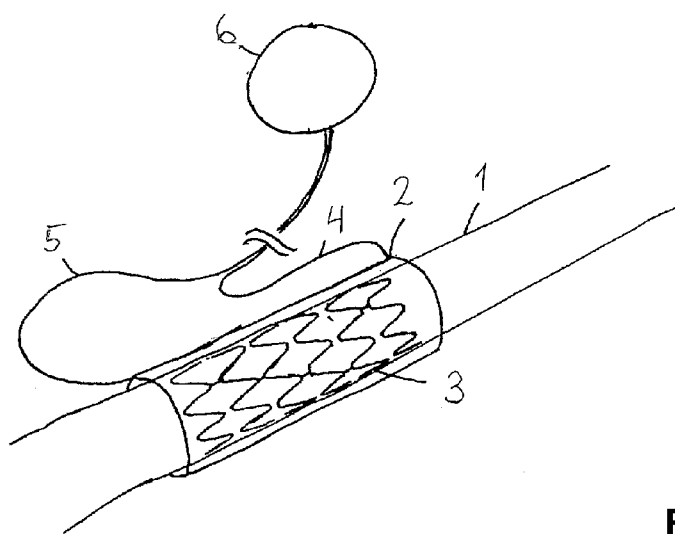


FIG. 1

(57) Abstract: A medical device for the permanent or temporal support of the wall of a blood vessel is disclosed. The device comprises an implantable tubular stent (3) having at least one electrically conducting portion, and a power source (2, 4, 5, 6) operable to supply a voltage or current to the electrically conducting portion after implantation of the stent into a blood vessel of a human or animal body. In this manner, the risk of occlusion, stenosis or restenosis of the blood vessel can be reduced. In preferred embodiments, a small surface current density into the surrounding body material in the range of 10-10000 nA/mm² is generated. Means for supplying energy to the stent both transcutaneously and through a wall of the blood vessel are also disclosed.



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TITLE

**Device and method for reducing the risk of occlusion and restenosis after
implantation of a stent**

TECHNICAL FIELD

The present invention relates to a medical device for the permanent or temporal support of the wall of a blood vessel and to a related method of reducing the risk of occlusion, stenosis and/or restenosis after implantation of such a device.

PRIOR ART

A stent is an artificial tubular structure, usually having a mesh-like configuration, that may be inserted into a blood vessel to support the wall of the blood vessel and/or prevent occlusion and restenosis. Stents are often implanted after the widening of an obstructed blood vessel by one of a variety of different methods, e.g. by balloon angioplasty. Stents may also be used in other medical contexts in the vasculature, e.g., to support an aneurysm in an artery.

A very common complication after implantation of a stent is occlusion/stenosis or restenosis. Occlusion is the narrowing or blockage of a blood vessel through thrombus formation. Stenosis is the occurrence of a narrowing of the blood vessel, leading to restricted blood flow. Restenosis is the reoccurrence of stenosis after treatment to clear a narrowing or blockage of the blood vessel.

Restenosis after implantation of a stent may be separated into two stages. In a first stage, thrombosis may occur. Administration of IIb/IIIa inhibitors immediately after surgery greatly reduces this risk. In a second stage, proliferation of cells in the intima (neointimal hyperplasia) may lead to a narrowing or blockage of the vessel. This second stage is much

more difficult to control. To tackle this problem, e.g., drug-eluting stents have been developed, which are coated with a coating containing pharmaceuticals that inhibit tissue growth and cell proliferation.

5 While there has been some success with drug-eluting stents, the drugs released by such stents may have undesired side effects. Moreover, the drug-related effect decreases over time due to the drug elution. Therefore, also with drug-eluting stents, the risk of restenosis is still substantial and a matter of time.

10 In [M. Gabi et al., "Electrically controlling cell adhesion, growth and migration", Colloids and Surfaces B: Biointerfaces 79 (2010) 365-371], the adhesion, growth and migration of C2C12 myoblasts on a specifically designed neurochip with indium-tin oxide (ITO) microelectrodes has been investigated, and it has been found that small current densities in the range of approximately 500 nA/mm² can effectively inhibit cell migration in the
15 specific setup investigated if supplied with a sufficiently high current dose. In [M. Gabi et al., "Influence of applied currents on the viability of cells close to microelectrodes"], it was shown that myoblasts directly cultured on microelectrodes undergo cell death when exposed to current densities above 570 nA/mm². These results, obtained in vitro on myoblasts, cannot be readily transferred to the conditions within a blood vessel, and
20 consequently no applications to vascular implants such as stents are suggested in these documents.

SUMMARY OF THE INVENTION

25 In a first aspect, it is an object of the present invention to provide a device for the permanent or temporal support of the wall of a blood vessel which is operable to prevent or reduce the risk of occlusion, stenosis and/or restenosis.

This object is achieved by a device as laid down in claim 1.

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In a second aspect, it is an object of the present invention to provide a method of reducing the risk of stenosis or restenosis of a blood vessel after implantation of a stent.

This object is achieved by a method as laid down in claim 20.

Further embodiments of the invention are laid down in the dependent claims.

5 Accordingly, a medical device for the permanent or temporal support of the wall of a blood vessel is proposed, comprising:

an implantable tubular stent having at least one electrically conducting portion; and
a power source operable to supply a voltage and/or current to the electrically
conducting portion after implantation of the stent into a blood vessel of a living human or
10 animal body (in the following also called the "patient body") effective to prevent or reduce
a risk of occlusion, stenosis or restenosis of said blood vessel.

The inventors have shown that cell growth and cell adhesion on vascular implants such as
stents can be reduced in vivo by supplying an electrical voltage or current to the stent,
15 which is expected to reduce the risk of occlusion, stenosis and restenosis. The voltage
and/or current may be supplied locally to the stent only, e.g. for eluting drugs or heating
the stent, as described in more detail below. However, it is preferred that the
voltage/current causes a small current flow through surrounding material of the patient
body, e.g., for electrochemically changing the environment of the stent.

20

In particular, it is preferred that the power source is operable to apply the voltage and/or
current in a manner to generate a surface current density between 10 nA/mm²
(nanoamperes per square millimeter; 1 nA/mm² = 0.001 A/m²) and 10'000 nA/mm²
between a surface of said stent and environmental body material. The term "environmental
25 body material" is to be understood broadly as encompassing any material of the patient
body in the vicinity of the implanted stent. The material may be in direct contact with the
stent or may be separated from the stent by other body material. Body materials include but
are not limited to muscle tissue, mucosa, fat tissue, blood and other body fluids etc.

30 In particular, surface current densities between 100 nA/mm² and 2'000 nA/mm² are
preferred. More preferably, the surface current density is between 200 nA/mm² and 1'000
nA/mm². If the current density is too low, its effect might not be sufficient to reduce cell
growth or cell adhesion to a degree required to be effective in preventing occlusion,

stenosis or restenosis. On the other hand, if the current density is too high, increased electrophoretic and electrolytic/electrochemical effects might lead to undesired side effects.

5 The power source is preferably operable to actively control the voltage and/or current that is supplied to the stent so as to ensure that the current density stays in the desired range. Power sources providing a well-defined current with a predetermined magnitude are well known in the field of electronics and are then usually called current sources. However, in simple embodiments, it may be sufficient to supply the voltage and/or current without
10 actively controlling its magnitude, e.g., by simply maintaining a predetermined voltage between two electrodes of which at least one is connected to the stent. The power source may be wholly or partially integrated with the stent (i.e., the stent and at least parts of the power source may together form a single implantable unit), or it may be disposed remote from the stent, being connected to the stent by surgical wires or supplying energy to the
15 stent in other ways, as further detailed below.

In preferred embodiments, the voltage and/or current may be supplied in a pulsed manner. In this case, it is preferred that, during normal operation, the intervals during which the current is switched off do not exceed 60 seconds, more preferably 30 seconds, in particular
20 10 seconds.

The pulsed voltage and/or current is preferably supplied periodically, with a period in the range of a few hundred milliseconds to about a minute. In particular, the period of the pulsed current is preferably between 0.2 seconds and 60 seconds, more preferably between
25 1 second and 30 seconds.

Whereas the voltage and/or current may be applied with alternating polarity (i.e., as an AC current, in particular as a low-frequency AC current with a frequency below 1 kHz), it is preferred to supply the current with a single polarity only. In particular, it is preferred if the
30 stent acts as the anode for the current, with a counter electrode acting as the cathode. However, it is also possible that the stent acts as the cathode, or that different portions of the stent act as the cathode and anode, respectively.

For supplying the power source with energy, the power source may comprise an implantable battery. The battery may be disposed in a separate housing or, preferably, in a common housing with the rest of the power source. In some embodiments, the power source, including the battery, and the stent may form a single, self-supported implantable unit. The battery may be disposable or rechargeable. If the battery is rechargeable, the power source may comprise means for supplying recharging energy to the battery, as detailed below.

In some embodiments, energy may be supplied to the stent transcutaneously from outside the patient body, either permanently during operation of the device, as in the case where no additional implanted energy source or energy storage means are available, or intermittently, as in the case when a rechargeable battery or other implanted, rechargeable energy storage means such as a large capacitance is present. In such embodiments, the power source will generally comprise an energy transmitter to be placed outside the human or animal body, the energy transmitter being operable to transmit energy from outside the body to a location inside the body in a contact-less fashion, and an implantable energy receiver operable to receive energy from the energy transmitter in a contact-less fashion when implanted in the body. Various means for transmitting energy from outside a body to inside a body in a contact-less fashion are known, e.g., from the technical field of cardiac pacemakers or implantable medicament pumps. The most widely employed principle in such applications is inductive, i.e., an inductive coupling between the energy transmitter and the energy receiver is established, much like in a (core-less) transformer. For an example, see WO 2010/042054 and references therein. In more general terms, the energy transmitter is in such cases operable to generate an (alternating) electromagnetic field, and the energy receiver is operable to receive the electromagnetic field generated by the energy transmitter and to convert said electromagnetic field into an electrical current, as known in the art. Alternative means for energy transmission might include the transmission of light, of X-rays, of heat or of mechanical vibrations, including ultrasound vibrations.

As the stent is generally implanted in the inside of a blood vessel, an additional problem arises of how to supply energy from the outside of the blood vessel to its inside, through the wall of the blood vessel. In the simplest case, surgical wires extending through the vessel wall may be used. However, this might lead to complications, as this will imply a

permanent perforation of the vessel wall. It is therefore desirable to transmit energy from a location outside the blood vessel to the stent inside the blood vessel in a contact-less fashion.

5 In first preferred embodiments, this is achieved by inductive coupling. The stent may be inductively coupled to an inductor outside of the blood vessel, e.g. to a solenoid coil placed around the blood vessel or to a coil outside the patient body, to generate a magnetic field at the location of the stent that induces a voltage in an inductor associated with the stent. In other words, the power source then comprises a first inductor adapted to be placed outside
10 the blood vessel (inside or outside the patient body; if inside the patient body, the first inductor may be implantable at the outside of a blood vessel) and operable to generate a substantial magnetic field acting on the stent, and a voltage generator operable to supply said first inductor with a time-dependent first voltage. The stent then comprises a second inductor (which may be represented by the stent itself) which, after implantation of the
15 stent inside the blood vessel and, as the case may be, of the first inductor outside of the blood vessel, is inductively coupled with said first inductor through the vessel wall. In this manner, a second voltage may be induced in the second inductor via a time-dependent magnetic field generated by a time-dependent current in the first inductor caused by the first voltage.

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The (generally time-dependent) voltage induced in the stent-associated second inductor may cause a current in the stent and possibly in the surrounding body material in a variety of different ways.

25 In some embodiments, the stent has a first and a second electrode connected to the second inductor, and, after implantation of the stent, the first and second electrode are electrically connected with environmental body material in a manner that the second voltage causes a current to flow through the body material. In this case the first and second electrode act as anode and cathode, respectively, i.e., no separate, remote counter electrode is required.
30 Instead of a direct coupling of the second inductor to electrodes, the voltage may first be rectified by a suitable rectifier (a diode in the simplest case), and the rectified voltage may be supplied to the electrodes. A control circuit for controlling the magnitude of the resulting current may further be associated with the stent.

The present invention also provides a stent which is particularly adapted for this kind of operation. Such an implantable tubular stent will have at least two electrodes connectable to environmental body material, the electrodes acting as the terminals of an inductor
5 operable to receive a time-dependent magnetic field so as to induce a voltage between said electrodes. The stent will generally define a stent axis by its long (tube) axis. The inductor then preferably defines a substantially helicoidal current path around said stent axis.

In alternative embodiments, the second inductor may have a first and a second terminal
10 which are connected directly or indirectly, without the involvement of any environmental body material, to form a closed circuit with the second inductor. In particular, the terminals may be electrically connected by a connection having a low ohmic resistance (e.g., the terminals may essentially be shorted). The terminals may be electrically insulated from the environmental body material. The voltage generator may then be operable to supply the
15 time-dependent first voltage in a manner to induce a closed-loop current in the closed circuit. This is particularly useful if the stent comprises a drug releasable from the stent by the application of such a current, e.g., by having a drug-eluting coating whose elution rate may be controlled by current. The drug may be released electrophoretically or by electrochemical means, or by a (possibly local) heating of a portion of the stent due to the
20 current.

In second preferred embodiments, energy is supplied to the stent through the vessel wall by a capacitive coupling. In this case, the power source may comprise:

- 25 a first electrode placed in the vicinity of said stent to form a capacitance with the stent;
- a second electrode placed in environmental body tissue; and
- a voltage generator operable to supply said first electrode and said second electrode with a time-dependent first voltage so as to cause a capacitive current between the first electrode and the stent and an ionic current between the stent and the second electrode.

30

The first electrode is preferably electrically insulated from the stent and from the surrounding body material. It may partially or fully surround the stent. The second electrode may be placed remote from the first electrode and from the stent, in electrical

connection with the surrounding body material. Likewise, the stent is required in this case to have an electrical connection with the surrounding body material.

In further alternative embodiments, the power source may comprise an implantable electrical generator operable to transform mechanical energy into electrical energy. The electrical generator may then be operable to transform mechanical energy associated with blood flow, with arterial palpation or with general other body movements into electrical energy. The stent being in contact with blood, the stent could also be powered by bio-electrochemical means, e.g. via enzymatic reactions such as oxidation of glucose by glucose oxidase molecules.

As already mentioned, the stent may contain a drug, the release of the drug being controllable by a voltage and/or current applied to the stent. In particular, it is conceivable that direct electrolytic/electrochemical or electrophoretic effects might lead to a release of a drug associated with the stent. In particular, the stent may comprise a drug-releasing coating, and the device may then be operable to control release of a drug from the coating by means of said voltage and/or current. Materials that are well suited for electrically controlled drug release are disclosed in the following documents:

- P. Bawa et al, Stimuli-responsive polymers and their applications in drug delivery, Biomedical Materials 4 (2009), 022001, pp. 1-15;
- X. Luo et al, Sponge-like nanostructured conducting polymers for electrically controlled drug release, Electrochemistry Communications 11 (2009), 1956-1959;
- S. Kim, Engineered polymers for advanced drug delivery, European Journal of Pharmaceutics and Biopharmaceutics 71 (2009), 420-430;
- I. Tokarev et al, Stimuli-responsive hydrogel thin films, Soft Matter 5 (2009), 511-524;
- Y. Qiu et al, Environment-sensitive hydrogels for drug delivery, Advanced Drug Delivery Reviews 53 (2001), 321-339;
- F. Boulmedais et al., Controlled Electrodissolution of Polyelectrolyte Multilayers: A Platform Technology Towards the Surface-Initiated Delivery of Drugs, Advanced Functional Materials, 16 (1): 63-70, 2006.

It is also conceivable to control the release of the drug by (local) heating of stent material.

The stent may be fully or at least partially resorbable, and the device may then be operable to control a rate of resorption by means of the current.

5 The electrically conductive portions of the stent are preferably electrochemically inert under the conditions employed. They may be made of any of the following:

a metal or a semiconductor, in particular, Au, Ag, Ir, Ni, Cr, Co, Pt, C, Cu, Al, Ti, In, Sn, Si and any combination of thereof, in bulk form or in the form of a porous matrix;

an electrically conductive polymer, in particular, poly(acetylene)s, poly(pyrrole),
10 poly(thiophene), polyanilines, polythiophene, poly(p-phenylene sulfide), poly(p-phenylene vinylene)s, polyindole, polypyrene, polycarbazole, polyazulene, polyazepine, poly(fluorene), or polynaphthalene;

a combination of metallic particles and at least one conductive polymer; or

a polymer matrix (in particular, silicone, polyurethane or other known polymeric
15 implant materials) with an electrically conductive filler material in the form of particles, fibers, or nanotubes, wherein the filler material may e.g. be made of Au, Ag, Ir, Ni, Cr, Co, Pt, C, Cu, Fe, Al, Ti, In, Sn, Si and any combination of thereof.

The associated method of reducing a risk of occlusion, stenosis or restenosis of a blood
20 vessel of a human or animal body comprises:

implanting a stent into the blood vessel; and

applying a voltage and/or current to the stent during and/or after implantation into the blood vessel in a manner effective to reduce thrombus formation and/or cell growth.

25 The same consideration apply for this method as for the device discussed hereinabove, in particular, the considerations concerning current density, application in a pulsed manner, periodicity, current direction, and transmission of energy. The stent may be implanted, e.g., in a coronary artery, in a cerebral blood vessel or in a peripheral blood vessel.

30 BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the invention are described in the following with reference to the drawings, which are for the purpose of illustrating the present preferred embodiments

of the invention and not for the purpose of limiting the same. In the drawings,

- Fig. 1 is a sketch illustrating a stent implanted in a blood vessel, to which current is supplied inductively;
- 5 Fig. 2 is a sketch illustrating a stent in which a current is driven inductively;
- Fig. 3 is a sketch illustrating a stent implanted in a blood vessel, to which a capacitive current is supplied;
- Fig. 4 is a sketch illustrating how the stent can be supplied with energy transcutaneously in a contact-less manner;
- 10 Fig. 5 is a sketch illustrating an alternative embodiment of supplying the stent with energy in a contact-less manner;
- Fig. 6 illustrates the pulse generator and electrode design of an implant for in-vitro and in-vivo testing; (A) schematics of the electrode and its cross section through the active Pt* electrode; the Pt film on the lower side is not connected to the pulse generator and serves as control; (B) photograph of the working electrode connected to the Teflon-coated connected to the pulse generator; (C) photograph of the whole implant consisting of the pulse generator (electric circuit and battery), two active electrodes, and one counter electrode in comparison with a 0.05 CHF Swiss coin; (D)
- 15 schematics of the in vitro experimental setup using the two active electrodes, one counter electrode and the pulse generator submerged in cell culture medium; and
- 20 Fig. 7 is a diagram illustrating the percentage of dead cells versus time on an active Pt* surface and on a passive SiO₂ surface.

25

DESCRIPTION OF PREFERRED EMBODIMENTS

Figure 1 illustrates a first embodiment of the present invention. A stent 3 is implanted inside a blood vessel 1, e.g., of the coronary, cerebral or peripheral vasculature. An inductor 2, e.g., in the form of a solenoid coil wound around the vessel, is placed in the vicinity of the stent 3 outside the blood vessel 1. An AC voltage or, more generally, a time-dependent voltage is supplied to the inductor 2 from an implanted or extracorporeal voltage generator 6 through wires 4 and 5. The time-dependent voltage causes a time-

30

dependent current to flow through the inductor 2. This current causes a time-varying magnetic field B that permeates the stent, as illustrated in Fig. 2. The time-varying magnetic field causes a time-dependent voltage to be induced in the conducting portions of the stent.

5

In particular, the stent may act as an inductor comprising a single, meandering but generally helical conducting path, as illustrated in Fig. 2. The stent will thus act as a second solenoid coil. In this case, the induced time-dependent voltage will be available at the terminals of this conducting path. In contrast, in commercially available stents no such open-loop conducting path will generally exist.

10

This voltage may be used in a variety of ways to generate currents. In one embodiment, the conducting path is short-circuited. Current flow is then restricted to the stent in a closed current loop, and no current will flow in the environmental body material. This current flow may be used to release a drug in a controlled manner if the stent comprises a drug-eluting coating or if drugs are otherwise embedded in the stent. This can be done by the current causing electrochemical reactions in the stent for releasing the drug. The induced current will also cause some ohmic heating of the conducting path. If strong enough, this local heating may likewise be employed to release a drug from the stent.

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In other embodiments, the induced voltage may be used to cause a current i through the tissue and blood in the immediate surroundings of the stent. The current may be rectified by a diode or a bridge rectifier, if desired, and its magnitude may be electronically controlled by a control circuit (not shown).

25

Figure 3 illustrates a second embodiment. Here the blood vessel 1 containing the stent 3 is surrounded by a cylindrical electrode 7. This electrode is electrically insulated from the blood vessel and from the surrounding body tissue. A counter electrode 8 is placed in some surrounding body tissue to be in electrical contact with this tissue. An AC voltage or, more generally, a time-dependent voltage is applied by generator 6 to the electrode 7 and to the counter electrode 8. This causes a capacitive current to flow between the electrode 7 and the stent 3, and an ionic current to flow between the stent 3 and the counter electrode 8. In other words, an ionic pathway is formed between the stent 3 and the counter electrode 8.

30

The current generated by the generator 6 will be transmitted capacitively from the electrode 7 to the stent 3 and electrochemically from the stent 3 to the counter electrode 8 through the environmental body material. In reality, also non-negligible ohmic losses and stray inductances might contribute to the equivalent circuit diagram. This arrangement is particularly suited to cause currents between the stent and environmental body material such as blood and tissue.

Figures 4 and 5 illustrate two possibilities of how the stent may be supplied with energy in a contact-less fashion. A patient 13 has been implanted with a stent (not shown). An internal power supply 14 is implanted in the body. The power supply acts as a power source for the stent, either directly through surgical wires, or indirectly, e.g. through inductive or capacitive means as described above in conjunction with Figs. 1-3. A primary coil 12 is wound around the body of the patient. The primary coil 12 is connected to an external power supply 10 by a cable 11. The external power supply supplies a time-dependent electric current to coil 12, which causes a time-dependent magnetic field acting at the location of the internal power supply. By the time-dependent magnetic field, a secondary voltage is induced in a pickup coil (not shown) of the internal power supply. This secondary voltage is used either to directly power the stent, or to recharge a storage capacitor or battery in the secondary power supply. Alternatively, the internal power supply may also be omitted entirely, and the time-dependent magnetic field may act to directly induce a secondary voltage in the stent itself, as described above in conjunction with Figs. 1 and 2.

An alternative embodiment is shown in Fig. 5. Like parts are denoted with the same reference signs as in Fig. 4. Instead of a primary coil wound around the body, the primary coil 12' in this embodiment is a flat coil placed on the skin of the patient. While the direction of the magnetic field generated by this primary coil is different than in the embodiment of Fig. 4, the principle of operation is the same.

Example: In-vitro and in-vivo investigations of cell growth and cell adherence on an implant subjected to electrical currents

Using a custom-built, implantable pulse generator, the effects of small pulsed currents on

the viability of rat aortic derived cells (RAOC) were studied in vitro. The pulsed currents (370 nA/mm²) caused apoptosis within 24 h as shown by the positive staining for cleaved caspase-3 and classically apoptotic morphology. Based on these findings, the effects of such nano-currents in vivo were examined. The pulse generator was implanted subcutaneously in the rat model. The electrode/tissue interface histology revealed no difference between an active platinum surface and a neighboring control surface. However, a large difference between electrodes that were functional during the entire experiment and non-active electrodes was found. These non-active electrodes showed an increase in impedance at higher frequencies 21 days post-implantation, whereas working electrodes retained their impedance value for the entire experiment. These results indicate that applied currents can efficiently prevent cell growth on implants such as implanted stents.

A. Materials and Methods

a. Design of the pulse generator

As illustrated in Fig. 6, the electrodes were fabricated on microscopy glass slides coated with platinum and an insulating SiO₂ film. Briefly, the glass slides were consecutively cleaned in pure acetone, isopropanol, ethanol, water, blow dried with N₂ and then coated with a 10 nm layer of Ti as an adhesion promoter followed by a 40 nm layer of Pt in an electron beam evaporator (Pfeiffer Classic 500, Wetzler, Germany). One coated slide was then cut into 7 x 2 mm pieces to be used as counter electrodes. The other coated slide was partly protected with Kapton® tape (Distrelec, Switzerland), so that the following physical vapor deposition (PVD) SiO₂ coating formed an electrically insulating, 3 mm wide and 100 nm thick SiO₂ strip after removal of the tape. The slide was cut with a diamond saw into individual electrodes. Biocompatible Teflon®-coated stainless steel wires (AS632; Cooner Wire, Chatsworth, CA) were connected to the platinum region with silver epoxy glue and cured at 80 °C for 1 h. The connection was then coated with EPOTEK-320M (Epoxy Technology, Billerica MA, USA) and cured at 60 °C for 6 h to ensure full biocompatibility and electrical insulation of the connection.

An electric pulse generator was built with prospect for implantation by using a low power stable multivibrator HEF4047BT from Philips (Distrelec, Switzerland) powered by a 3 V,

25 mAh coin cell lithium ion battery (Energizer CR1216, France). Ohmic resistor (10 M Ω) and capacitor (220 nF) were used to set the period of the current pulses. This way the pulse generator delivers two differently pulsed DC square wave signals at different ports (2.5 s current, 2.5 s pause - referred to hereafter as electrode 1; 5 s current, 5 s pause - electrode 2). The electrically active Pt coated working electrode surface is labeled hereafter as Pt*. The third electrode served as the counter electrode to close the circuit.

Another ohmic resistor (2 M Ω) was connected in series to each output as a voltage/current converter according to Ohm's law, so that the resulting current was set to $I = 1.5 \mu\text{A}$ per electrode (0.37 A/m²), whereas the ohmic resistance of the culture media is negligible. The electronic circuit and battery were mounted on a printed circuit board (11 x 11 x 0.8 mm). Inside custom built Teflon® molds, the whole circuit was embedded in EPOTEK-320M and cured at 60°C for 6 h. The dimensions of the pulse generator implant without electrodes were 19 x 19 x 7 mm (Fig. 5 C).

b. Cell culture

RAOC were proliferated under standard incubator conditions (37°C, 5% CO₂) in endothelial basal medium (EBMTM-2; Cambrex, Walkersville, MD) containing growth factors and supplement: vascular endothelial growth factor (VEGF), human fibroblasts growth factor (hFGF), human recombinant long-insulin-like growth factor-1 (R-3-IGF-1), human epidermal growth factor (hEGF), gentamycin and amphotericin (GA-1000), hydrocortisone, heparin, ascorbic acid, and 2% fetal bovine serum (FBS).

c. Cell viability

The electrodes were again sterilized with 70% ethanol and irradiated for 30 minutes with UV light. The cells were detached using 0.25% trypsin/EDTA solution (PAN Biotech GmbH, Aidenbach, Germany) and seeded directly onto the implant lying in a Petri dish (Fig. 5 D). The systems were then incubated for 1, 6, 12 and 24 h at 37 °C and 5% CO₂. The number of dead cells on the electrodes was visualized by propidium iodide staining (Molecular Probes Inc., Eugene, OR). Hoechst 33342 (Molecular Probes) was used to count the total number of cells as it stains the condensed chromatin of all cells irrespective

of membrane integrity. To ensure that the different coatings (SiO_2 , Pt) had no influence on cell behavior and viability, a control experiment was performed over 24 h with the same method as above, however without the application of current (data not shown).

5

d. Cell death

The type of cell death and the cell adhesion contact size was investigated with
10 immunochemical staining: after exposing the RAOs to electric current for 24 h, the electrodes were washed in phosphate buffered saline (PBS, pH 7.4) solution, then blocked with 0.1 M glycine in PBS for 5 min and permeated for 10 min in PBS containing 0.2% Triton X-100. After blocking with 5% normal (pre-immune) goat serum and 1% bovine serum albumin in PBS for 30 min, primary antibodies - rabbit polyclonal cleaved caspase-3
15 (Asp175), (Cell Signalling Technology, MA) or anti-human vinculin-1 (Sigma, Switzerland) - were added and incubated for 1 h at room temperature then washed in PBS. Fluorescence-labeled secondary antibodies - Cy3 anti-mouse or Cy2 anti-rabbit IgG (both from Jackson Immunochemicals, PA) - were diluted in 1% bovine serum albumin (BSA) containing Tris-buffered saline (TBS; 20 mM Tris base, 155 mM NaCl, 2mM ethylene
20 glycol tetra acetic acid, 2 mM magnesium chloride) and incubated for 1 h at room temperature. All samples were counter stained with DAPI (Sigma, Switzerland) for nuclear localization. Actin filaments were visualized by Alexa488 and Alexa546 labeled phalloidin (Molecular Probes, Invitrogen, Switzerland). Finally, the cells were washed in PBS and mounted in 0.1 M Tris-HCl, pH 9.5, a 3:7 mixture of 0.1 M Tris-HCl (pH 9.5) and glycerol
25 supplemented with 50 mg/ml n-propyl gallate as an anti-fading reagent. Immunofluorescence images were taken using a Leica AF6000 system equipped with a DMI 6000B microscope and a DFC350 FX digital camera (Leica Microsystems, Switzerland).

30 e. Implantation

A single implant consisting of the pulse generator and three electrodes was implanted in each of 20 Sprague-Dawley rats obtained from Harlan Laboratories (Horst, Netherlands).

All procedures were performed in a laminar flow cabinet under sterile conditions using sterile equipment and standard surgical techniques. Anesthesia was induced by 2.5-5% isofluorane inhalation with 1 L/min oxygen in an enclosed induction box. Once the rat was sufficiently anesthetized, it was laid in a prone position. Sterile ophthalmic ointment was applied to the eyes of all animals. A custom-made mask was applied to supply continuous oxygen (1 L/min) and isofluorane (2.5-5%) as necessary to maintain adequate anesthesia throughout the procedure. The level of anesthesia was monitored by observing breathing rate, heart rate and color of mucous membranes. The dorsal implantation area was prepared for surgery by shaving off all fur from the nape of the neck to the mid back, and the skin disinfected with Kodan® (Schulke & Mayr, Switzerland). A dorsal, midline, transcutaneous incision was then made to allow implantation of the electrodes. The three electrodes were placed approximately 5 mm apart in distended pockets in the fascial plane created by blunt dissection and individually secured with a single stay suture 6/0. The counter electrode in each system was implanted between the two working anodes, and the pulse generator was placed a minimum of 5 cm away from the electrodes. The incision was then closed with non-absorbable sutures (4.0 gauge polyamide, Braun®). 0.05 mg / kg Buprenorphine for post-operative analgesia was routinely given subcutaneously at the end of each procedure. A second dose was administered 12 h later as clinically needed. The rats were then placed individually in clean cages with a heat pad for post-operative monitoring and allowed to recover. All rats tolerated the surgery well and were monitored daily until the study endpoint.

f. Impedance measurement

The impedance spectra of the implanted electrodes were measured right before explantation with an Autolab PGSTAT302N potentiostat with the Frequency Response Analyzer Software v.4.9.007 from Eco Chemie (Utrecht, Netherlands). The spectra were measured with an amplitude of 50 mV between 0.2 Hz - 1 MHz. The pulse generator was therefore taken out of the anaesthetized rat, the wires were cut and dismantled, while the electrodes remained in their position under the skin. The free ends of the cables were then connected to the potentiostat with Kleps clamps. The impedance was measured between the active Pt* electrode and counter electrode. After a lethal dose of carbon dioxide inhalation the rats were decapitated to keep the electrodes in their position in the tissue.

The implant's operational capability was then tested ex situ with a voltmeter and implants with no signal were categorized as "non working".

Impedance measurement control experiments were performed in culture medium and in a
5 freshly sacrificed mouse. After removing the coat, two incisions were made in the hind
limb muscles and the electrodes were placed in the pockets to measure the resistance of
muscle tissue. Filling the incisions with culture medium simulated the liquid gap between
electrode and tissue. The impedance was also measured across fascia|muscle|fascia or
fascia|fatty tissue|fascia by adding a small amount of culture medium between electrode the
10 fascia and mechanically attaching the electrode on the surface.

g. Histology and staining of the implants

The rat heads with the implanted electrodes were put in 4% formaldehyde for fixation at 4
15 °C. The solution was exchanged daily during one week. After x-ray imaging to assure the
position of the electrodes, the skull was separated from the neck with the electrodes to
minimize the tissue amount for embedding. The neck was then rinsed with H₂O 3 x for 30
min. The tissue was dehydrated in a watery solution with increasing ethanol content 50%
90min, 70% 24h, 80% 24h, 90% 12h, 96% 12h, 100% 96h, then the sample was stored in
20 Xylene for 4 days. Next, the tissue was embedded in PMMA (Polymethylmethacrylate) by
placing the sample into a small Tupperware® container and filled with the PMMA
precursor mixture 89.5% methyl methacrylate MMA (Fluka Chemie, Switzerland), 10%
dibutyl phthalate DBP (Merck, Germany) and 0.5% di(4-tert-butylcyclohexyl)
peroxydicarbonate Perkadox 16 (Dr. Grogg Chemie, Switzerland). The polymerization in a
25 vacuum at 4 °C to avoid any bubble formation was finished after 7 days. The block was
then cut into 0.6 mm slices with a saw microtome Leica SP1600 (Leica Microsystems) and
glued on acrylic glass carrier for polished on a Planopol V (Struers, Denmark) with
decreasing grain size. The polished slice was then 4 min etched in 0.7% formic acid and
blow dried before staining for 20 min in 1% toluidine blue solution.

30

B. Results

a. In vitro

i. Cell viability under applied pulses

The implant and the electrodes were placed in a Petri dish before adding the RAOC
5 suspension. Exposed to the pulsed current densities of 0.37 A/m^2 , the RAOCs displayed an
increase in cell death with time (Fig. 7). The cell mortality was higher on electrode 2 (5 s
current, 5 s pause) for the first hour. After 24 h, cell death was $96 \pm 3\%$ on electrode 1 (2.5
s current, 2.5 s pause) and $96 \pm 5.0\%$ on electrode 2. In contrast, cells grown on the SiO_2
control on the same electrode had a mortality of 3-8% throughout the experimental time.
10 The cell death was highly localized to the active Pt^* surface, with a well defined boundary
limited to the active Pt^* electrode surface.

ii. Type of cell death

15 The presence of apoptotic cell death was determined by staining with anti-cleaved caspase
3 antibody which detects the large fragment (17/19kDa) of activated caspase-3; a
determinant protease of apoptosis. The cells on the SiO_2 control surface showed minimal
cleaved caspase-3 activity, while $95 \pm 4 \%$ of RAOCs on the active Pt^* surface, were
stained positive for this apoptotic marker.

20

C. In vivo

i. Histology

25 The electrodes used for histology worked for up to 21 days in the animal and were fully
functional at the time of explantation. The toluidine blue stained cross section of a
representative selected electrode (21 days) allowed direct comparison between working
and control areas on the same electrode. No significant difference were found in the
morphology of the surrounding connective tissue between the working platinum electrode
30 Pt^* , control platinum electrode Pt without the current and SiO_2 bulk material. No signs of
cell necrosis or apoptosis were noted in the cells sheets bordering the electrode surface.
Additionally, the images show the absence of the monocyte/macrophage recruitment to the
site of implant site, indicating the absence of a stronger foreign body response either to the

control or the active sides of the electrodes.

ii. Impedance measurement

5 The electrode impedance was measured in vivo from seven electrodes that remained functional for the entire experimental time and from 17 electrodes of implants that stopped working during the experiment. The impedance spectrum of all electrodes was measured with an amplitude of 50 mV between 0.2 Hz and 1 MHz. For working implants the impedance value remains on a more or less constant level during the entire experiment,
10 whereas the non working implants showed an increase in impedance at the selected frequencies.

D. Discussion

15 a. In vitro experiments

Currents applied during cell attachment clearly induced apoptosis of cells on the active electrodes as indicated by their globular shape. In addition, staining of the cells after 24 h of current application revealed that most cells died by activation of apoptotic pathways.
20 The activation of caspase-3 is a central event in apoptosis and is an early marker of apoptosis. It has previously been reported to display either weak or no cytoplasmic staining in later stages of apoptosis, or staining to be localized to the nucleus. Therefore, the few cells which stained negative on the active electrodes may represent later stages of apoptosis not longer expressing cleaved caspase 3. In addition, as the anti-cleaved caspase-
25 3 antibody does not recognize full length caspase-3 or other cleaved caspases, its detection indicates apoptosis only via the caspase-3 pathway. As a result, although caspase-3 is considered the hallmark key executioners of apoptosis, the presence of other apoptotic pathways cannot be excluded. In this study cells were exposed to pulsed currents throughout the experiment, i.e. including some time preceding cell attachment, in order to
30 simulate the conditions during in vivo implantation of clinically used electrodes. Although the generated electrochemical products diffuses into the culture medium, the space between cells and electrode becomes a small gap of around 100 nm, when a cell attaches to the electrode surface. The products are accumulated within this gap and might reach toxic

concentration levels depending on the current applied, adhesion size and the diffusion coefficient of the toxic products. The cells in suspension have a round shape. Cells must therefore attach to the electrode before a significantly large area of their membrane gets exposed to the "dangerous zone" causing cell death. This is a possible explanation of why we observed cell death after increased time in comparison to other studies that exposed cells to electric currents only after they had formed a confluent layer on the electrode.

The adhesion size was optically determined by vinculin (focal contacts) staining. Vinculin represents a key element in the transmembrane linkage of the extracellular matrix to the cytoplasmic microfilament system and is associated with a large number of cytoskeletal and focal adhesion proteins. These multi-protein complexes are further associated with cell adhesion signaling molecules important to rendering cells susceptible or resistant to apoptosis. The apoptotic RAOC adhesion size was $26 \mu\text{m}^2$, radius $r = 2.8 \mu\text{m}$ if we assume a circular cell adhesion spot after 24 h of applying currents. The observed adhesion area was independent of the applied current pulses (1, 2), further supporting the hypothesis that a critical adhesion area over the electrode is required for inducing apoptosis.

Modeling the expected pH in the gap, it was found that the short pulsed electrode 1 reaches lower mean pH values during the initial phase of cellular attachment but almost the same asymptotic pH. This might explain the observed higher ratio of dead cells on electrode 1 after 1 h. On the other hand, the simulated asymptotic pH vs. cell radius curve shows no special reason for the observed critical adhesion radius of $r = 2.8 \mu\text{m}$.

Another electrochemically generated product is chlorine, which reacts with water to HOCl (hypochloric acid). HOCl has been reported to cause apoptotic cell death due to the formation of chloramines in the culture medium. In addition, a minute amount of chlorine induced de-spreading of adherent cells.

As such, if the electrochemical products suppress cell adhesion this itself might induce apoptosis. The disruption of focal adhesion complexes weakens the interaction between the cells and the extracellular matrix, rendering them more susceptible to apoptosis, even in the presence of sufficient growth factors.

Another possible mechanism is related to the corrosion of the electrode itself: e.g. platinum chloride compounds from electrode corrosion dissolve at higher potentials and can inhibit cell growth, however at lower potentials and in the presence of serum albumin no platinum dissolution was observed. On the other hand, the platinum corrosion can probably be ruled out in this case, since a similar growth inhibiting effect at low currents was also observed on indium tin oxide electrodes.

b. In vivo

In vitro, the implantable custom built pulse generators have shown a full workability during repeated, short term experiments. There was no leakage or malfunction observed. In vivo in contrast, the electronic circuit and battery, embedded in EPOTEK-320M, were compromised by the inflammatory foreign body reactions and some implants stopped producing electric pulses in vivo. In these failed implants, a weak point was found in the epoxy casing due to non-uniform embedding, where body fluids could enter and caused failure of the electric circuit while implanted.

Seven electrodes remained functional for the entire time and 17 electrodes stopped working during the experiment. The impedance of all functional electrodes but one remained low at all three measured frequencies. The impedance of electrodes connected to a pulse generator that stopped working at a certain time point was higher. This indicates that applied currents reduce the impedance of implanted electrodes. At low frequencies (0.2 Hz), changes in the electric double layer at the interface boundary were measured. The formation of a biological film here could lead to increased impedance as observed on the electrodes that stopped working or their electrical contact was broken. The tissue conductivity was measured at higher frequencies. Current is transported by the motion of free ions according to the applied electric field. The initial inflammatory tissue response increased the amount of exudate around the implants and kept impedance low for all electrodes for the first 15 days. After 21 days, the histology samples no longer showed a liquid gap between the electrode surface and the tissue. The impedance of the non working electrodes showed the expected increase due to the diminished fluid gap and the presence of densely packed cells on the platinum electrode surface. In the control experiments, the impedance was decreased by -40% adding culture media to the electrode interface.

In contrast, the electrodes with applied pulsed current showed no increase in impedance at 1 kHz and 0.5 MHz even though histological data did not reveal any changes comparing the tissue surrounding the active electrode surface Pt* with the platinum control surface Pt and the SiO₂ control surface.

E. Conclusions

In vitro, small pulsed currents induce apoptosis within 24 h in almost all cells attached to the electrode surface. Apoptosis is induced either directly by toxic concentrations of electrochemically generated products in the gap between the cell and the surface or indirectly by inhibiting cell adhesion, which induces then apoptosis.

In vivo, application of pulsed currents to the electrodes kept the impedance lower compared to electrodes that stopped working during implantation. However, major histological differences were not observed. It is believed that integrating all electrodes on a single chip would allow for a better comparison of the impedance and histological data. This would, in addition, enable a more thorough investigation of the nearest cell layer by immunohistochemical staining.

In summary, the experiments have shown that growth and adhesion of cells of the type found in the vicinity of implanted stents can be effectively inhibited by the use of small electric currents.

CLAIMS

1. A medical device for the permanent or temporal support of the wall of a blood vessel, comprising:
 - an implantable tubular stent having at least one electrically conducting portion; and
 - a power source operable to supply a voltage and/or current to the electrically conducting portion after implantation of the stent into a blood vessel of a human or animal body effective to prevent or reduce a risk of occlusion, stenosis and/or restenosis of said blood vessel.
2. The device of claim 1, wherein the power source is operable to supply said voltage and/or current in a manner to generate a surface current density between 10 nA/mm^2 and $10\,000 \text{ nA/mm}^2$ between a surface of said stent and environmental body material.
3. The device of claim 1 or 2, wherein the power source is operable to supply said voltage and/or current in a pulsed manner.
4. The device of claim 3, wherein the power source is operable to supply said voltage and/or current periodically in a pulsed manner with a period between 1 s and 60 s.
5. The device of any of the preceding claims, wherein the power source is operable to supply the voltage and/or current with a predetermined single polarity.
6. The device of any of the preceding claims, wherein the power source comprises an implantable battery.
7. The device of any of the preceding claims wherein the power source comprises:
 - an energy transmitter to be placed outside the human or animal body, the energy transmitter being operable to transmit energy from outside the body to a

location inside the body in a contact-less fashion;

an implantable energy receiver operable to receive energy from the energy transmitter in a contact-less fashion when implanted in the body.

8. The device of claim 7, wherein the energy transmitter is operable to generate an electromagnetic field, and wherein the energy receiver is operable to receive the electromagnetic field generated by the energy transmitter and to convert said electromagnetic field into an electrical current.
9. The device of any of the preceding claims comprising:
 - a first inductor operable to generate a substantial magnetic field acting on the stent; and
 - a voltage generator operable to supply said first inductor with a time-dependent first voltage,
 - wherein the stent represents a second inductor which, after implantation of the stent, is inductively coupled with said first inductor to induce a second voltage in said stent via a time-dependent magnetic field generated by a time-dependent current in said first inductor caused by said first voltage.
10. The device of claim 9, wherein the stent has a first and a second electrode connected with the second inductor, and wherein, after implantation of the stent, the first and second electrode are electrically connected with environmental body material in a manner that the second voltage causes a current to flow through the body material.
11. The device of claim 9, wherein the second inductor has a first and a second terminal, wherein the first and second terminal are electrically connected to form a closed circuit with the second inductor, and wherein the voltage generator is operable to supply the time-dependent first voltage in a manner to induce a closed-loop current in said closed circuit.
12. The device of any of the preceding claims wherein the power source comprises:
 - a first electrode placed in the vicinity of said stent to form a capacitance

with the stent;

a second electrode placed in environmental body tissue;

and a voltage generator operable to supply said first electrode and said second electrode with a time-dependent first voltage so as to cause a capacitive current between the first electrode and the stent and an ionic current between the stent and the second electrode.

13. The device of any of the preceding claims, wherein the power source comprises an implantable electrical generator operable to transform mechanical energy into electrical energy.
14. The device of any of the preceding claims, wherein the power source is operable to generate a voltage and/or current by bio-electrochemical means.
15. The device of any of the preceding claims where the stent comprises a drug releasable from the stent, and wherein the device is operable to control release of a drug from the stent by means of said voltage and/or current.
16. The device of any of the preceding claims wherein the stent is at least partially resorbable, and wherein the device is operable to control a rate of resorption by means of said voltage and/or current.
17. The device of any of the preceding claims wherein the stent comprises:
 - an electrically conductive polymer; or
 - a polymer matrix with an electrically conductive filler material in the form of particles, fibers, or nanotubes.
18. An implantable tubular stent for use in a device according to any of the preceding claims, the stent having at least two electrodes connectable to environmental body material, the electrodes being connected by an inductor operable to receive a time-dependent magnetic field so as to induce a voltage between said electrodes.
19. The stent of claim 18, wherein the stent defines a stent axis, and wherein the

inductor defines a current path that is substantially helicoidal around said stent axis.

20. A method of reducing a risk of occlusion, stenosis and/or restenosis of a blood vessel of a human or animal body, the method comprising:
 - implanting a stent in said blood vessel; and
 - applying a voltage and/or current to the stent during or after implantation into the blood vessel in a manner effective to prevent thrombus formation and/or to reduce cell growth.
21. The method of claim 20, wherein a current having a surface current density between 10 nA/mm^2 and $10\,000 \text{ nA/mm}^2$ is generated between a surface of said stent and environmental body material.
22. The method of claim 20 or 21, wherein the voltage and/or current is applied in a pulsed manner.
23. The method of claim 22, wherein the voltage and/or current is applied periodically in a pulsed manner with a period between 1 ms and 60 s.
24. The method of any of claims 20-23, wherein the voltage and/or current is applied only in a predetermined direction.
25. The method of any of claims 20-24, wherein the current flows through the stent in a closed loop essentially without current flow in environmental body material.
26. The method of any of claims 20-25, wherein the voltage and/or current causes release of a drug from the stent.

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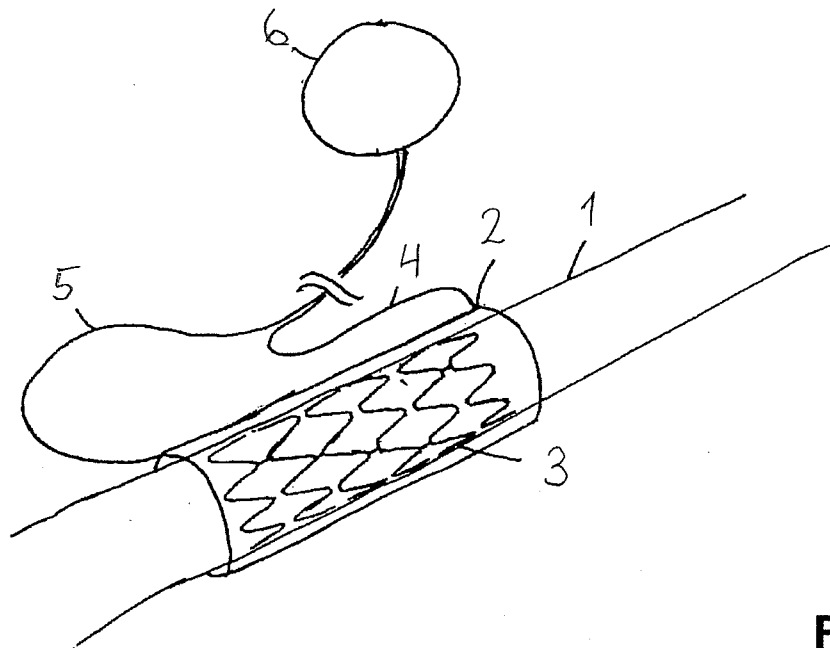


FIG. 1

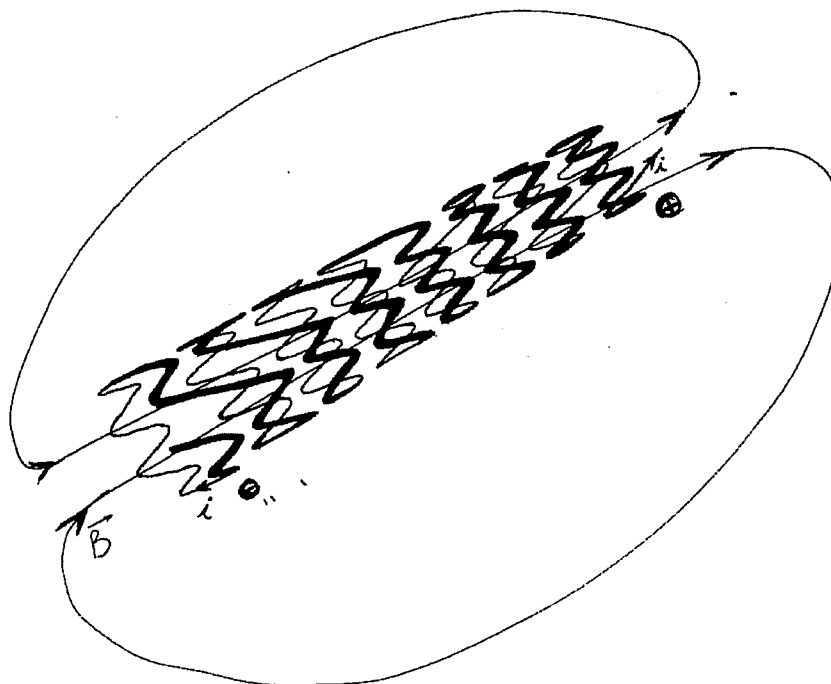


FIG. 2

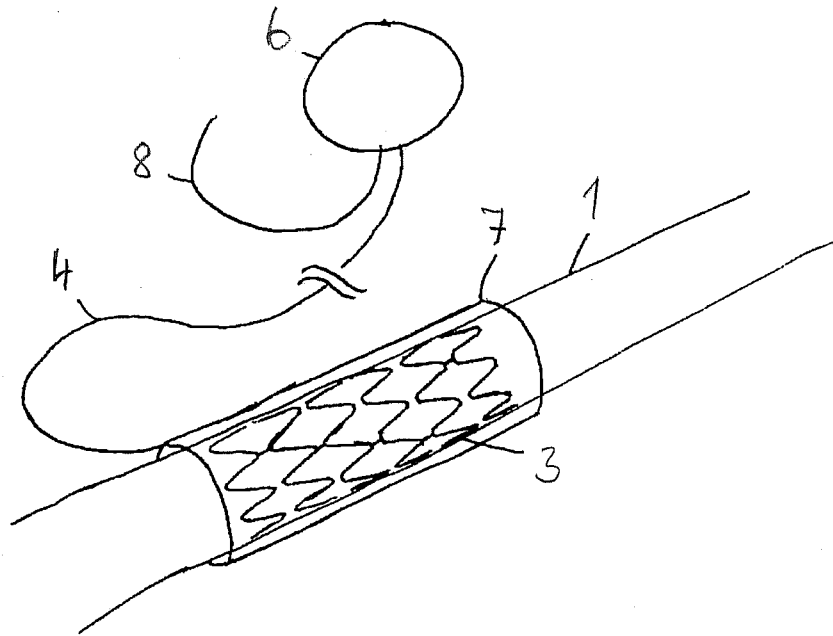


FIG. 3

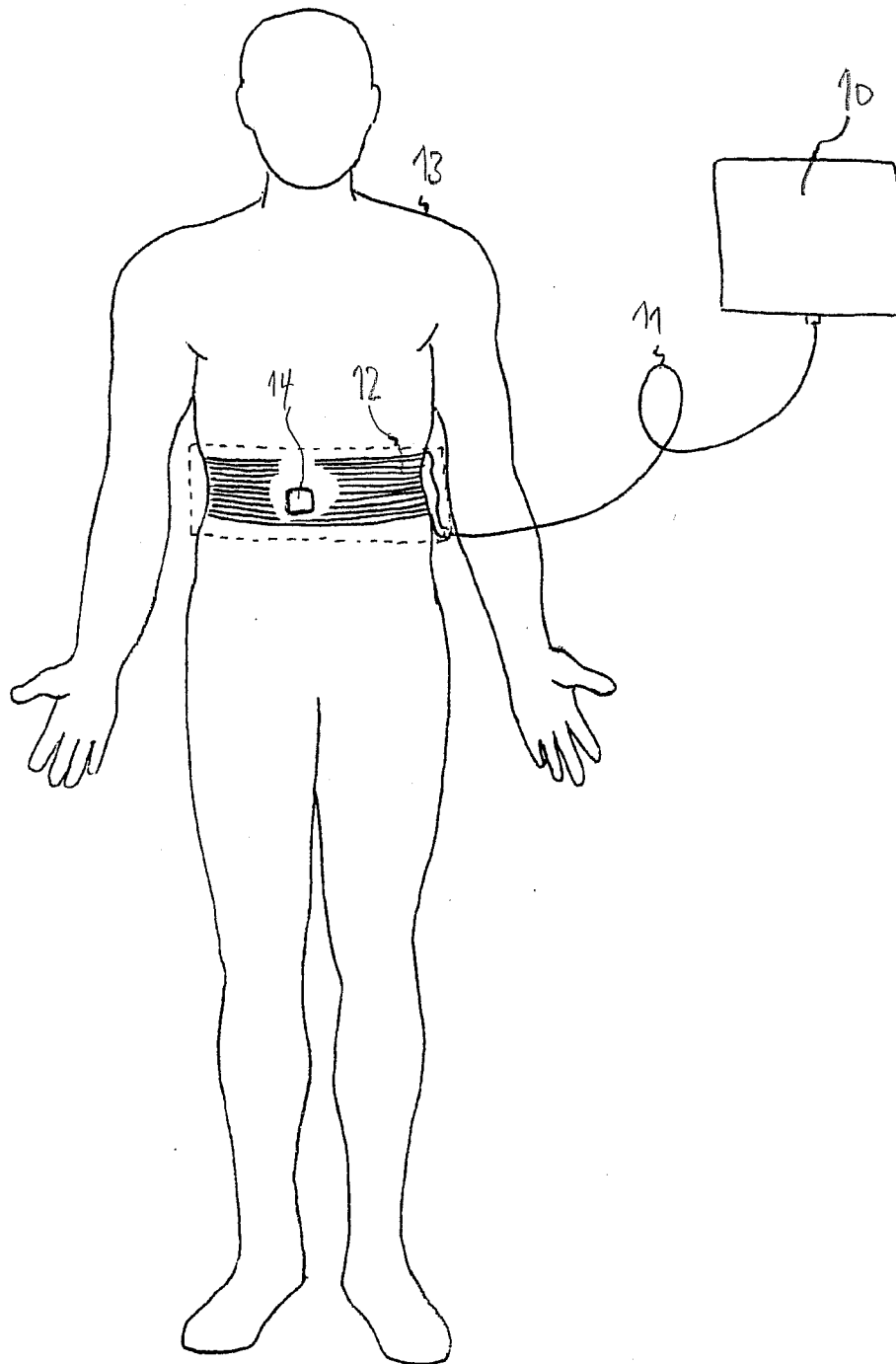


FIG. 4

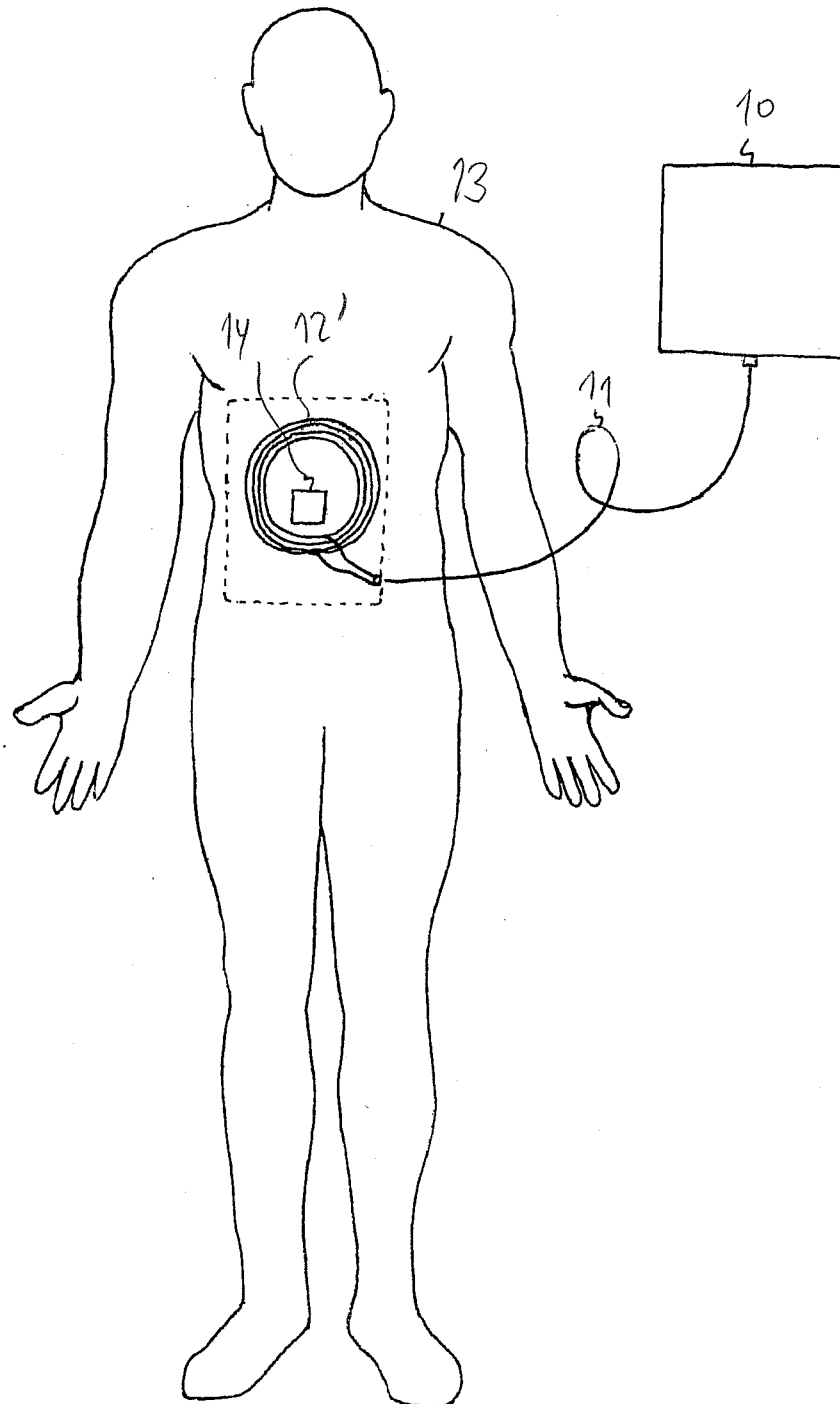


FIG. 5

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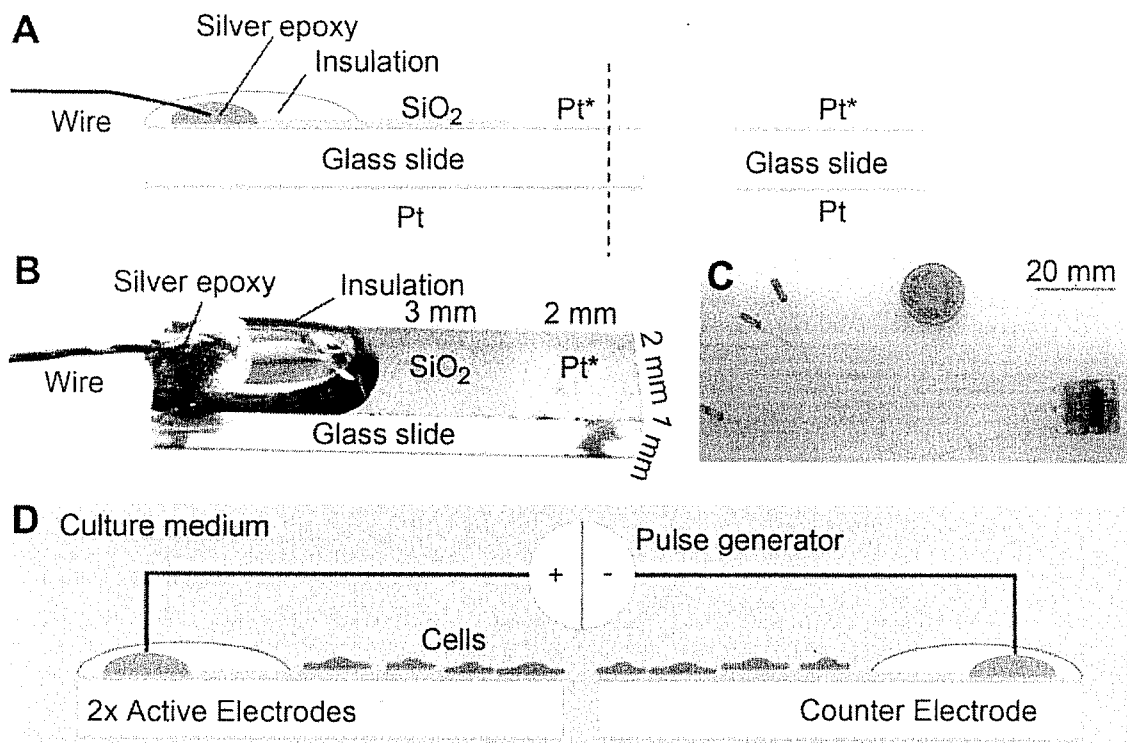


FIG. 6

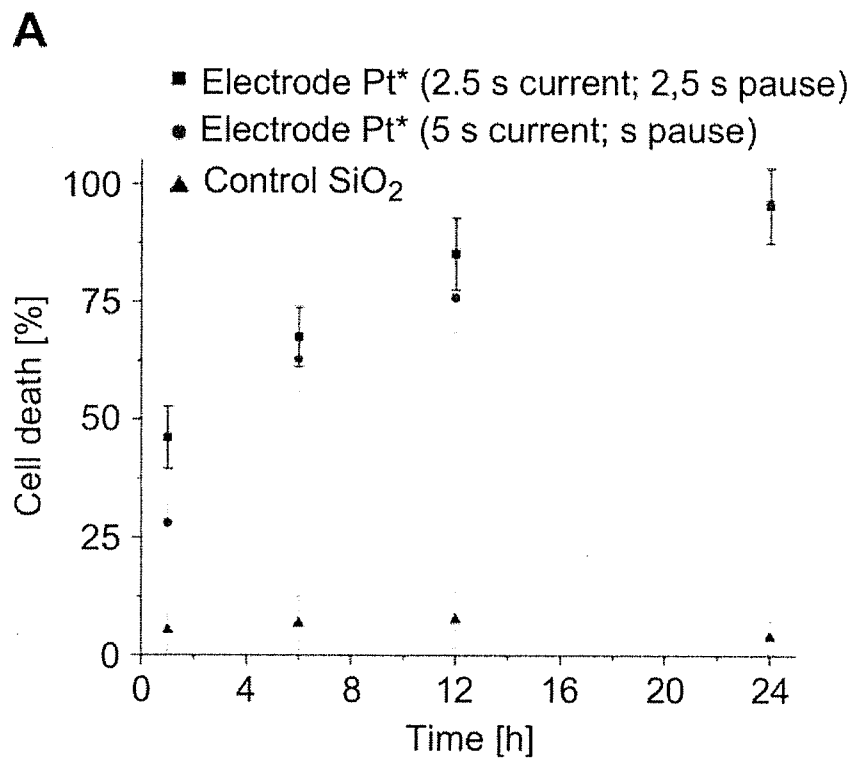


FIG. 7

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061397

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61F2/Q6 A61N1/18 A61N1/40 A61F7/12 A61F7/00
A61N2/Q2 A61M5/00

ADD.

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)

A61F A61N A61M

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/158584 AI (CATES ADAM W [US] ET AL) 21 August 2003 (2003-08-21) abstract paragraph [0047] - paragraph [0066] paragraph [0078] - paragraph [0107] paragraph [0127] - paragraph [0134] paragraph [0145] - paragraph [0156] -----	1-11, 13-15 , 18, 19
X	W0 2007/120742 A2 (SEARETE LLC [US] ; WOOD LOWELL L [US] ; SWEENEY ELIZABETH A [US] ; WOOD V) 25 October 2007 (2007-10-25) abstract page 3, paragraph 3 - paragraph 4 page 6, paragraph 2 - page 8, paragraph 2 page 12, paragraph 2 - page 21, paragraph 1 ----- - / - -	1,6-8, 13-15



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 document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

29 September 2011

Date of mailing of the international search report

10/10/2011

Name and mailing address of the ISA/

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Authorized officer

Beck, Ewa

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/061397

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 808 535 B1 (JORDAN ANDREAS [DE]) 26 October 2004 (2004-10-26) abstract column 2, line 3 - column 3, line 54 -----	1, 9
X	EP 1 036 574 A1 (DIAMANTOPOULOS LEONIDAS [GR]) 20 September 2000 (2000-09-20) abstract paragraph [0004] - paragraph [0010] -----	1, 9
X	US 2003/187340 A1 (KENKNIGHT BRUCE H [US] ET AL) 2 October 2003 (2003-10-02) abstract; claims 1,50-65 paragraph [0031] - paragraph [0039] -----	1,2, 12
X	US 2010/010640 A1 (GEROLD BODO [DE] ET AL) 14 January 2010 (2010-01-14) abstract; claims 1,2 paragraph [0039] - paragraph [0041] -----	1,2, 12, 16
X	US 2003/100865 A1 (SANTINI JOHN T [US] ET AL SANTINI JR JOHN T [US] ET AL) 29 May 2003 (2003-05-29) abstract paragraph [0025] paragraph [0037] - paragraph [0038] paragraph [0049] - paragraph [0050] paragraph [0061] - paragraph [0063] paragraph [0072] paragraph [0094] - paragraph [0096] -----	1, 15-17
X	WO 2007/013065 A2 (GROSS YOSSEI [IL]) 1 February 2007 (2007-02-01) abstract page 13, line 28 - page 15, line 10 page 17, line 14 - line 29 -----	1,2, 6-10, 18, 19
X	WO 2007/078770 A2 (BOSTON SCIENT SCIMED INC [US] ; KVEEN CRAIG L [US] ; HASTINGS ROGER N [U]) 12 July 2007 (2007-07-12) page 17, line 10 - page 20, line 19 -----	1,2,9 , 10, 18, 19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/061397

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☒ Claims Nos.: 20-26
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery and therapy.
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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/061397

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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wo 2007120742	A2	25-10-2007	NONE
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EP 1036574	AI	20-09--2000	GR 1003340 BI 09--03--2000
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