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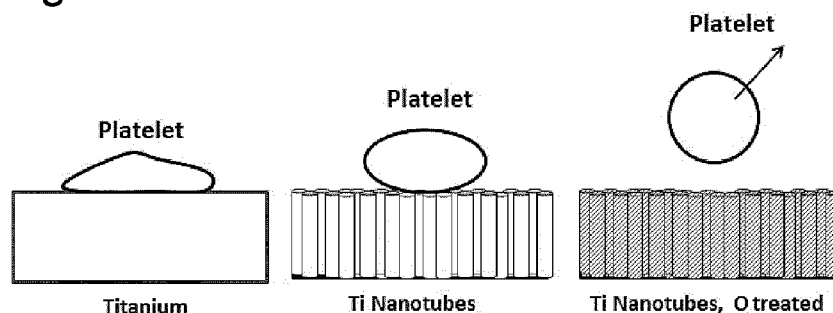
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(54) Title: METHOD FOR COATING A MEDICAL DEVICE, ESPECIALLY A VASCULAR STENT

Fig. 4



(57) Abstract: A method for producing desired morphology of a nanotubular matrix, in particular titanium dioxide containing matrix, is disclosed which reduces adhesion and activation of platelets on medical devices. Surfaces produced by the method of invention can be used for blood contacting devices, such as stents and artificial heart valves in order to reduce thrombus reactions on the implant material surface.



Method for coating a medical device, especially a vascular stent

Description

5 Background of the Invention

The present invention relates to a method for coating a vascular stent and to a vascular stent preferably produced by said method.

10 In medicine, stent is a mesh 'tube' inserted into a natural passage in the body to prevent or counteract a disease-induced, localized flow constriction and to allow open access for surgery. In blood the clumping or aggregation of platelets in the blood leads to the formation of a thrombus (clot). This thrombosis (formation of thrombus) obstructs the flow of blood through the circulatory system which leads to cardiovascular disease and increases risk of
15 heart attack and stroke as disclosed in "Coronary Artery Disease, Angina, and Heart Attacks." in Texas Heart Institute Heart Owner's Handbook. New York: JohnWiley & Sons, 1996. Sometimes, thrombosis leads to serious short-term and long-term effects. A possible short-term effect is pulmonary embolism, in which the blood clot breaks into pieces, travels to the lungs and blocks the flow of blood through the lungs. Such effects are disclosed for
20 instance in Bernardi E and Prandoni P., the post-thrombotic syndrome, Current Opinions in Pulmonary Medicine 2000, volume 6: pages 335-42. and Janssen MCH et al., The post-thrombotic syndrome: a review, Phlebology 1996;volume 1:pages 86-94.

Coronary artery disease presents the major cause of mortality in the modern world. The
25 majority of percutaneous coronary interventions involve stents, which are implemented in order to help enlarge the lumen wall and restore the blood flow through the affected vessel. Stents are made of hemocompatible and durable material such as titanium (Ti), 316L stainless steel (SS-medical grade), Nitinol (an alloy of Nickel and Titanium) and Cobalt-Chromium (CoCr). In some instances a stent can elicit allergic reactions most commonly
30 those that are containing Nickel, such as Nitinol and stainless steel as shown in "Cutaneous and Systemic Hypersensitivity Reactions to Metallic Implant", Juliana L. Basko-Piluska, Jacob P. Thyssen, Peter C. Schalock, Dermatitis, 2011; 22(2): 65-79.

Moreover during the procedure of stent implementation the vessel wall is disrupted which highly increases risk of lumen narrowing or so called stent restenosis as described in "Repeat Narrowing of a Coronary Artery Prevention and Treatment", George Dangas, MD; Frank Kuepper, MD Circulation. 2002; 105: 2586-2587. Restenosis is defined as 50% narrowing of vessels diameter and still to this day remains a major problem. In more than 33% of cases restenosis will occur, with higher possibilities in patients with high risk factors, such as diabetes. The stents can be further divided in bare metal stents (BMS) and drug-eluting stents (DES). With DES the problems of allergenic reactions as well as risks of restenosis were lowered, as DES release anti-cell-proliferative, immunosuppressive or anti-thrombogenic drugs which inhibit proliferation of smooth muscle cells and reduce thrombus formation (JACC: "Cardiovascular Interventions" Volume 2, Issue 7, July 2009, Pages 583–593 Drug-Eluting Stent Thrombosis : The Kounis Hypersensitivity-Associated Acute Coronary Syndrome Revisited, Jack P. Chen, MD , Dongming Hou, MD, PhD, Lakshmana Pendyala, MD, John A. Goudevenos, MD, PhD, Nicholas G. Kounis, MD, PhD).

Procedures and methods for coating stent surfaces are mainly accomplished by various polymeric coatings ("Polymer Coatings for Stents", Tim A. Fischell, MD, Circulation. 1996; 94: 1494-1495) or nanocrystalline powders of ceramics, such as hydroxyapatite, titanium dioxide, by plasma thermal sprays or coating of noble metal oxides (cf. US 567815, US 6099561, US 6478815) or by covering surface with bioactive coatings like heparin, chitosan, fibronectin etc. (cf. CA1257561, US3617344, WO2003070125, WO1996008149, WO2000040278).

However, it was shown that DES also inhibits normal endothelium growth which potentially leads to thrombosis (cf. JACC: Cardiovascular Interventions Volume 2, Issue 7, July 2009, Pages 583–593 Drug-Eluting Stent Thrombosis : The Kounis Hypersensitivity-Associated Acute Coronary Syndrome Revisited, Jack P. Chen, MD, Dongming Hou, MD, PhD, Lakshmana Pendyala, MD, John A. Goudevenos, MD, PhD, Nicholas G. Kounis, MD, PhD). It has been shown that coated surfaces are not a satisfactory solution, as coated stents cause blood clots several years after implementation shown in Brian Vastag's, "Stents Stumble", Science News, Jun 23, 2007 vol.171, pp 394-395. Moreover patients with coated stent must receive blood thinners all their lives in order to prevent the risk for stroke or heart attack. The probability of death by cardiac infarction in the period of 6 months to 3 years after implementation of DES is 32% higher than on BMS ^{as} described by Lagerqvist B. et

al., Long term outcomes with drug eluting stents versus bare metal, New England Journal of Medicine 2007, 356, 1009-1019.

In the last few years adverse clinical data linking DES usage to arterial thrombosis had led to a large decrease in sales. Furthermore, companies are seeking to develop novel stents, while so far the improvements on DES are merely incremental. Innovations are done mostly on the polymer coatings, stent platforms and in drug components. Moreover DES are almost three times more expensive compared to BMS.

The very promising properties of titanium and titanium alloys, specifically high biocompatibility, resistance to body fluids, great tensile strength, flexibility and high corrosion resistance, have ensured their successful and extensive use as biomaterials (see Kulkarni M, Mazare A, Schmuki P and Iglič A 2013, Nanomedicine (Manchester: One Central Press) p. 111 and Roy P, Berger S and Schmuki P 2011 Angew. Chem. Int. Ed. 50 2904), e.g. material in stents. For more than 50 years, metallic materials have been used in medical applications (orthopaedics, vascular surgery and dentistry) and titanium (Ti) and Ti alloys received significant attention in stents applications (cf. M. Kulkarni, A. Flašker, M. Lokar, K. Mrak-Poljšak, A. Mazare, A. Artenjak, S. Čučnik, S. Kralj, A. Velikonja, P. Schmuki, V. Kralj-Iglič, S. Sodin-Semrl, A. Iglič, Int. J. Nanomed. 10 (2015) 1359).

Success of stents depends mainly on avoiding the aggregation of platelets in the blood vessels as well as to prevent uncontrolled proliferation of smooth muscle cells and appropriate proliferation of endothelial cells. Research in the field of nanomaterials has revealed that the topography is a crucial factor for appropriate biological response and the need to produce such surfaces for desired biological response could be the solution.

For example in WO2014087414 a method for preparing biocompatible metallic surfaces by nanostructuring is disclosed. The nanostructuring involves hydrothermal treatment in alkaline conditions at elevated temperatures by which superior endothelialization with reduced smooth muscle cell proliferation and platelet adhesion is achieved. By this method non-toxic chemicals are used at varying temperatures in order to yield distinct nanostructure, such as rods, pins, needles, pores etc. The method used to produce such nanostructures is different from our approach and the produced nanostructures differ from the ones produced by our method in size and shape. The material surface is essentially of titanium oxide (TiO₂) with

hydrophilic properties which enable improved protein interaction and enhance adhesion and proliferation of endothelial cells, while reducing adhesion of smooth muscle cells, platelets and monocytes.

- 5 In US8007674 the device and methods for fabricating nanostructures primarily on stent surface is described. Nanostructures allow adhesion and growth of one cell type, for example endothelial cells to smooth muscle cells. This is achieved by patterning the substrate to have an organized structure. The pattern is obtained by layering nanostructure material at least partially over the substrate and producing alternating layers of different
10 nanostructure material which forms a patterned layer and in the end etching the surface to form desired nanostructure.

Method for producing nanotubular array by electrochemical anodization of metal surface is disclosed in US20060229715. The surface consists of oxide metal layer which has
15 nanotubues with pore diameter between 15 to 100 nm and height of the tube between 15 to 5000 nm. The nanotubes are formed on metal containing surface by electrochemical anodization and the surface is further annealed at a temperature between 280 to about 580° C. Such surface is appropriate for bone implants, stents, drug depot and fusion cage. The main difference between the methods used in their patent is that different electrochemical
20 anodization process is employed (different electrolyte) and that nanotubular array is further annealed, while in our case after electrochemical anodization surface is treated with neutral oxygen atoms. As our nanotube formation process is different the nanotubular array produced by our method of invention is not stable at high temperatures and the surface could not be annealed. In order to preserve desired nanotopography and improve surface
25 chemical composition treatment with neutral oxygen atoms is employed and the temperatures are well below 150° C.

US20110236435 discloses the method of growing bone cells on TiO₂ nanotubular substrates treated by plasma. In this case the titanium substrate is anodized to form TiO₂
30 nanotubular array which is afterwards subjected to a radiofrequency plasma discharge to chemically modify the array and to seed bone cells for effective time to enable growth of these cells. In this patent the RF discharge is used at the pressure of 20 Pa in several gases: nitrogen, oxygen, a mixture of nitrogen and oxygen and helium. The preferred length of nanotubes to facilitate bone cells growth is 4 mm and preferred inner diameter from about

80 to 107 nm. Best results are obtained by treatment with plasma created in mixture of nitrogen and oxygen. This is primarily due to formation of nitrogen and oxygen based functional groups which promote cell growth and adhesion. The authors report increasing nitrogen concentration what is beneficial for growth of bone cells. Also, they mention that the treatment of titanium dioxide with plasma generated in a mixture of oxygen and nitrogen-containing gas introduces amino groups and enhances cell growth on biomaterial surfaces. The functional groups provide suitable surface finish for greater fibrinogen adsorption resulting in enhanced cell growth. Plasma treatment also roughened the surface as presented in US20110236435. The treatment disclosed in this document is suitable for cell growth but deteriorates the hemocompatibility due to increased fibrinogen adsorption and existence of nitrogen on the surface that enhances platelet activation.

Problem to be solved

Therefore the technical problem of the present invention is providing reduction of adhesion of platelets on implantable medical devices.

Solution according to the invention

The solution of this problem is achieved by means of a method in accordance with claim 1 and a vascular stent according to claim 7.

According to the present invention a method of coating a vascular stent is provided. Said method comprises: Providing a vascular stent with at least one metal surface, in particular a titanium based surface, Forming a nanotubular matrix, wherein said nanotubular matrix comprises metal oxide, in particular titanium dioxide, said formed nanotubular matrix having predetermined dimensions formed by anodizing said metal surface in an electrochemical manner and Subjecting said formed nanotubular matrix to neutral oxygen atoms in order to remove impurities from the surface obtained during electrochemical anodization, predominantly fluorine and nitrogen, and to increase oxygen concentration on nanotubular array.

Within the scope of the present invention appropriate nanostructuring can be obtained from titanium or metal alloys of titanium on a surface. It may also be metal surfaces consisting of

titanium, titanium alloys, stainless steel alloys, cobalt based alloys, cobalt-chromium alloys or the like.

By subjecting said nanotubular matrix to neutral oxygen atoms removal of undesired chemicals that are adsorbed to the surface due to electrochemical process is provided. Moreover such treatment (that is subjecting to neutral oxygen atoms) increases oxygen content on the surfaces and a higher quality oxygen surface layer is formed, which plays an important role in biological response.

The expression "nanotubular matrix" or "array" refers to a nanotube structure which is aligned vertically to the substrate or metal surface (titanium material) and where the nanotubes are uniformly or homogenously distributed.

The method of invention enables appropriate surface conditioning, which highly reduce adhesion and activation of platelets. In particular the method involves 1.) nanostructuring the surface of titanium by electrochemical anodization and 2.) subjecting the nanostructured surface to neutral oxygen atoms to eliminate surface induced thrombotic reactions.

According to the present invention a solution for prevention of platelet adhesion and activation by combining the biomaterial properties of titanium with the nanotopography and chemical activation of the surface is provided. Electrochemical anodization represents an optimum method for obtaining nanostructures, due to its good control over nanotubular morphology and ease of application. While appropriate chemical properties can be achieved by treatment of titanium dioxide nanotubes with neutral oxygen atoms. The first event taking place immediately after stent implantation is adsorption of blood proteins at the implant-liquid interface. The amount and type of adsorbed protein further influences the success of implant. What happens with the adsorbed protein layer governs interaction of platelets and their adhesion or activation, leukocyte recruitment, activation of intrinsic coagulation and of complement; moreover, all four are capable of eliciting a thrombogenic response *in vivo*. Stepwise, firstly the adsorbed protein layer will lead to adhesion and activation of the platelets, which is fundamental in forming the fibrin clot and recruiting leukocytes (as monocytes and neutrophils). Secondly, the platelets will trigger an inflammatory immune response which would lead to either thrombosis and/ or fibrous encapsulation of the implant. Studies indicated increased blood serum protein adsorption, platelet adhesion and

activation and whole blood clotting kinetics on titanium nanotubular arrays. Furthermore, less thrombogenic effects with lower surface induced fibrin clot formation were registered on nanotubes in comparison to titanium surfaces. The latter was evident from slightly decreased levels of complement activation and slightly increased degree of free fibrinogen on nanotubular surfaces.

One aspect of the present invention is that appropriate techniques are used to produce endovascular metallic device (stent) that prevents adhesion and activation of platelets on the surface simply due to nanostructuring (appropriate size of nanotube diameter and its length) and chemical modification of the surface using only neutral oxygen atoms in the absence of plasma-generated species such as ions and electrons. The desired nanostructured array or matrix, respectively is obtained by electrochemical anodization. Chemical modification is obtained by subjecting the array to neutral oxygen atoms which remove chemical impurities induced by anodization procedure and produce denser oxygen layer which highly reduces adhesion and activation of platelets on the surface. It also causes removal of nitrogen and carbon that is typically present on the surface of titanium. By optimizing nanotopographic features as well as chemical composition of titanium surface, reduced platelet adhesion and activation on blood connecting devices (stents) from titanium is achieved.

This, titanium nanostructured surfaces produced by the present method of invention have appropriate chemical structure and topography which reduces the risk of thrombosis on blood contacting devices. To preserve desired nanotubular array morphology and surface chemistry the final sterilization step should be considered. For sterilization of nanotubular array H_2O_2 or O_2 plasma or even gamma sterilization should be employed. Other currently available sterilization techniques result in altered surface morphology and chemistry, which influences on the biological response. Especially sterilization with autoclave is not appropriate as the nanostructured morphology could be destructed and the content of carbon functional groups is undesirably increased. In case of either H_2O_2 or O_2 plasma sterilization the surface is interacting with neutral oxygen atoms, similar to the previously described treatment step by neutral oxygen atoms, thus preventing changes in surface morphology and chemistry. Gamma irradiation sterilizes the surface by high ionized energy and will not alter nanotubular array morphology nor it will significantly alter the surface chemistry.

According to an aspect of the present invention subjecting of said nanotubular matrix at fluencies, in the range of 10^{22} to 10^{25} m⁻² is provided. Due to subjecting of the nanotubular matrix or array to neutral oxygen atoms removal of impurities, such as fluorine, carbon and nitrogen is provided. Additionally the oxygen concentration on the surface is increased, which prevents adhesion and activation of platelets to the surface.

By the chosen fluencies range surprisingly the biological response of the medical device produced by the present invention could be improved.

Brief Description of the Drawings

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

Fig. 1 shows a SEM image of nanotube arrays with 100nm in diameter- from top view (Scale bar is 500nm) according to the present invention;

Fig. 2 discloses a SEM image of nanotube arrays with 100nm in diameter- cross section view;

Fig. 3 shows the surface morphology of nanotubular array obtained by atomic force microscopy (AFM) on surfaces produced by the method of invention;

Fig. 4 Schematic representation of platelet interacting with; plain titanium foil, titanium nanotubular array surface and titanium nanotubular array surface produced by the method of invention;

Fig. 5 shows the anodization conditions for nanotubes with 100nm diameter and 3.7µm length (sample name shows: sample name, diameter, and length of nanostructures respectively), EG: Ethylene glycol, HF: Hydrogen fluoride;

Fig. 6 depicts measured values of chemical groups by ESCA (Electron Spectroscopy for Chemical Analyses) on the surface of plain titanium, nanotubular array of TiO₂ and nanotubular array of TiO₂ subjected to natural oxygen atoms;

5 **Fig. 7** shows adhesion and activation of platelets on plain titanium;

and

10 **Fig 8:** discloses adhesion and activation of platelets on nanotubular array of TiO₂ subjected to neutral oxygen atoms according to the present invention.

Detailed Description

15 It is noted that the embodiments described herein can be used individually or in any combination thereof. It should be understood that the description is only illustrative of the embodiments. Various alternatives and modifications can be devised by those skilled in the art without departing from the embodiments. Accordingly, the present embodiments are intended to embrace all such alternatives, modifications and variances that fall within the
20 scope of the appended claims.

A method according to the invention for surface finish of titanium based implants in contact with blood prevents adhesion and activation of platelets against the state of the art is disclosed.

25

The present invention comprises of a.) electrochemical anodization of titanium surface and formation of an nanotubular array of titanium dioxide with desired diameters and lengths, b.) subjecting the electrochemically anodized titanium dioxide nanotubular array to neutral oxygen atoms to remove impurities from the surface obtained during electrochemical
30 adonization, predominantly fluorine and nitrogen, and to increase oxygen concentration on nanotubular array.

In preferred embodiment the surface of titanium substrate is electrochemically anodized only in single ethylene glycol based electrolyte with specific amount of deionized water and

hydrogen fluoride as an additive for etching the titanium surface. Obtained TiO₂ nanotubular arrays are of desired diameters ranging from 15 nm to 100 nm inner diameters and lengths varying from 370 nm to 3.7 µm. The expression "nanotubular array" refers to a nanotube structure which is aligned vertically to the substrate (titanium material) and where the nanotubes are uniformly distributed as presented in Figure 1-3. Obtained nanotubular array is subjected to neutral oxygen atoms at fluencies, in the range of 10²² to 10²⁵ m⁻².

Subjecting nanotubular arrays to neutral oxygen atoms removes impurities, such as fluorine, carbon and nitrogen and increases the oxygen concentration on the surface, which prevents adhesion and activation of platelets to the surface, as schematically presented in Figure 4.

Example 1: plain titanium

In the example disclosed herein plain titanium was analysed by ESCA method in order to obtain information about chemical composition of the surface. Results of chemical composition are presented in Figure 5.

The adhesion and activation of platelets on plain titanium foil was done according to the following procedure; prior to whole blood incubation plain titanium surfaces were cleaned with ethanol, dried and incubated with whole blood taken by vein puncture from a healthy human donor. Titanium foils were incubated for 1 hour with whole blood. The blood was drawn into 9 ml tubes with tri sodium citrate anticoagulant (Sigma). Afterwards the fresh blood was incubated with titanium surfaces in 24 well plates for 1 hour at room temperature and at gentle shaking at 300 RPM. Each sample (measuring 13 mm in diameter) was incubated with 1 ml of whole blood. After 1 h of incubation, 1 ml of phosphate-buffered saline (PBS) was added to the whole blood. The blood with PBS was then removed and the titanium surface was rinsed 5 times with 2 ml PBS in order to remove weakly adherent platelets. After incubation of cells with titanium surface, the weakly adherent cells were removed from the surface by rinsing with PBS. Adherent cells were subsequently fixed with 400 µl of 1 % PFA (paraformaldehyde) solution for 15 min at room temperature. Afterwards the surfaces were rinsed with PBS and then dehydrated using a graded ethanol series (50, 70, 80, 90, 100 and again 100 vol.% ethanol) for 5 min and in the last stage in the series

(100 vol.% ethanol) for 15 min. Afterwards the samples were placed in a Critical Point Dryer, where the solvent is exchanged with liquid carbon dioxide. By rising the temperature in the drier the liquid carbon dioxide passes the critical point, at which the density of the liquid equals the density of the vapour phase. This drying process preserves the natural structure of the sample and avoids surface tension which could be caused by normal drying. The dried samples were subsequently coated with gold and examined by means of SEM (Carl Zeiss Supra 35 VP) at accelerating voltage of 1-keV. Evaluation of platelet adhesion and activation from SEM images was done according to the morphology and number of platelets. Morphological forms of platelets from the least activated to the most activated are as follows: round (R) > dendritic (D) > spread dendritic (SD) > spread (S) > fully spread (FS).

Differences in adhesion of platelets were observed from SEM images as seen in Figure 6. Platelet adhesion and activation can be determined by counting the number of attached cells as well as by observing the morphological changes of platelets on the surface. Results from SEM analysis clearly indicate that titanium surface alone is highly attractive for attachment and activation of platelets. Many platelets are observed in Figure 6 and they are mostly in FS form, which will lead to aggregation of platelets, formation of fibrinogen and undesired thrombus formation, which will reduce the life of such titanium implant.

Example 2: growth of nanotubes and platelet adhesion and activation

Titanium dioxide nanotubular array titanium with 100 nm in diameter was obtained by electrochemical anodization of titanium foils (Advent, 0.1 mm thickness, 99.6% purity). Prior to anodization, titanium foils were degreased by successive ultrasonication in acetone, ethanol and deionized (DI) water for 5 min each and then dried in nitrogen stream. Nanotubes with diameter 100nm and 3.7 μ m lengths were obtained in ethylene glycol based electrolyte containing 8M water and 0.2M hydrogen fluoride. Anodization voltage was set to 58V for 2.5h to get desired diameters and lengths of nanotubes. Anodization experiments were carried out at room temperature ($\sim 20^{\circ}\text{C}$) in a two-electrode system with titanium foil as the working electrode and platinum gauze as the counter electrode, with a working distance of 15 mm.

The TiO₂ nanotubular arrays were analyzed by ESCA method in order to obtain information about chemical composition of the surface. Results of chemical composition are presented in Figure 5.

- 5 The studies on adhesion and activation of platelets were done on TiO₂ nanotubular arrays were conducted by the same procedure as described in Example 1. Attached and activated platelets can be seen in Figure 8.

SEM analysis clearly showed that less platelet adhere on TiO₂ nanotubular array and those
10 that are adhering are mainly in less active form; round and dendritic as seen in Figure 7. Such surfaces will to lesser extent elicit undesired thrombus formation in comparison to the samples prepared in Example 1.

15 **Example 3: growth of nanotubes by the method of invention and platelet adhesion and activation**

Titanium dioxide nanotubular array with 100 nm in diameter was obtained by electrochemical anodization of titanium foils according to the procedure described in
20 Example 2.

Dried TiO₂ nanotubular arrays were mounted into the treatment chamber and were treated only by neutral oxygen atoms in the absence of plasma-generated species such as ions and electrons. The fluence of natural oxygen atoms was about $2 \times 10^{22} \text{ m}^{-2}$.

25 Surface chemical composition was measured by ESCA method. Results are presented in Figure 5.

The studies on adhesion and activation of platelets were done on TiO₂ nanotubular arrays
30 immediately after exposure to neutral oxygen atoms. The studies were done by the same procedure as described in Example 1.

According to SEM analysis on samples done by the method of invention it can be seen that platelet adhesion is prevented, as practically no platelets were observed on the surfaces

prepared by this method. In cases where platelets were observed on the surface they were in round form, which is a sign that platelets are not activated and will not lead to thrombotic reactions. Surfaces produced by the method of present innovation could be used in blood connecting devices, such as stents.

5

Although specific embodiments have been illustrated and described herein, it will be appreciated by those of ordinary skill in the art that a variety of alternate and/or equivalent implementations may be substituted for the specific embodiments illustrated and described without departing from the scope of the present invention. This application is intended to
10 cover any adaptations or variations of the specific embodiments discussed herein. Therefore, it is intended that this invention be limited only by the claims and the equivalents thereof.

CLAIMS

1. A method of coating a vascular stent, comprising:
 - Providing a vascular stent with at least one metal surface, in particular a titanium based surface;
 - Forming a nanotubular matrix, wherein said nanotubular matrix comprises metal oxide, in particular titanium dioxide, said formed nanotubular matrix having predetermined dimensions formed by anodizing said metal surface in an electrochemical manner; and
 - Subjecting said formed nanotubular matrix to neutral oxygen atoms in order to remove impurities.
2. Method according to claim 1, where the nanotubular matrix is further sterilized by H_2O_2 or O_2 plasma in order to treat the surface with neutral oxygen atoms.
3. Method according to claim 1, where the nanotubular array is sterilized by gamma sterilization.
4. Method according to claim 1, wherein said anodizing step is an electrochemical anodization of said metal surface, in particular said titanium based surface.
5. Method according to claim 4, wherein said electrochemical anodization comprises ethylene glycol electrolytes and a specific amount of water and hydrogen fluoride, and/or other similar electrolytes or only single ethylene glycol based electrolytes with specific amount of deionized water and hydrogen fluoride as an additive for etching the titanium surface.
6. Method according to any of the preceding claims, wherein the nanotubular matrix dimensions are ranging from 15 nm to 300 nm inner diameters and lengths from 370 nm to 4 μm .
7. Method according to any of the preceding claims, wherein subjecting of said nanotubular matrix to neutral oxygen atoms is provided at fluencies, in the range of 10^{22} to 10^{25} m^{-2} .

8. Method according to any of the preceding claims, wherein said subjecting with neutral oxygen atoms is provided between 0 and 150 °C, preferably between 50 and 100 °C.
- 5
9. A metallic vascular stent in particular coated with titanium dioxid nanotubes provided by means of a method according to at least one of the preceding claims.
10. A metallic vascular stent according to claim 9, wherein said nanotube-length of said matrix is up to 6 micrometers with reference to the metal surface, in particular the titanium based surface of said vascular stent.
- 10
11. A metallic vascular stent according to claim 9 or 10, wherein said dioxide nanotubes, in particular said titanium dioxide nanotubes, are of inner diameter in the range of 15 to 110 nm and in diameter preferably in the range of 50 nm to 100 nm.
- 15
12. A metallic vascular stent according to at least one of claims 9 to 11, wherein the titanium dioxide nanotubes are of length in the range of 1 µm to 4 µm, preferably in the range of 3.4 µm to 3.8 µm with reference to the metal surface, especially the titanium based surface of said vascular stent.
- 20

1/4

Fig. 1

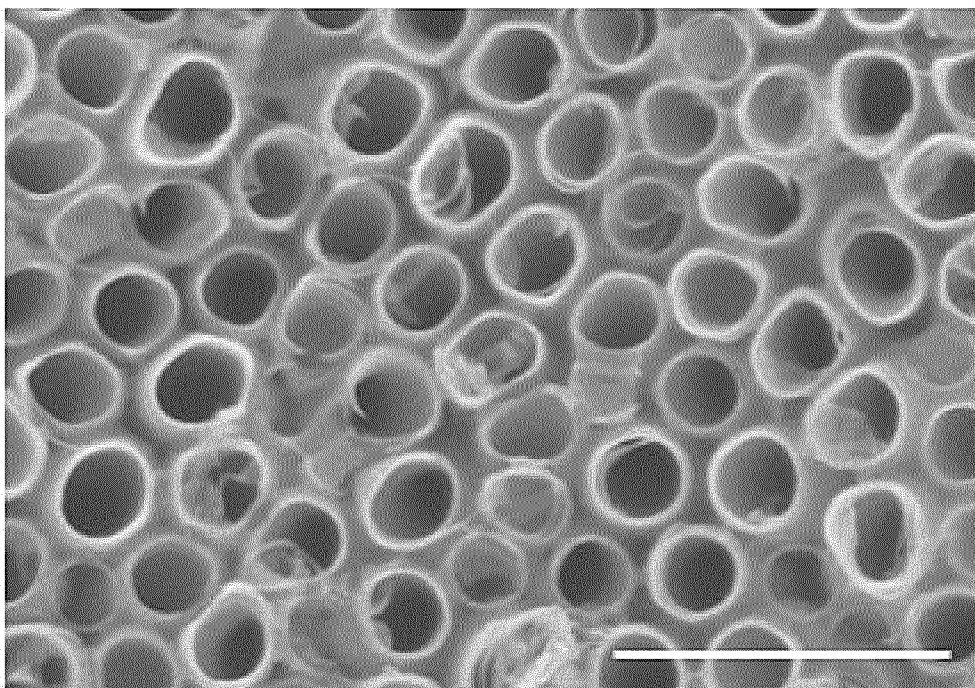
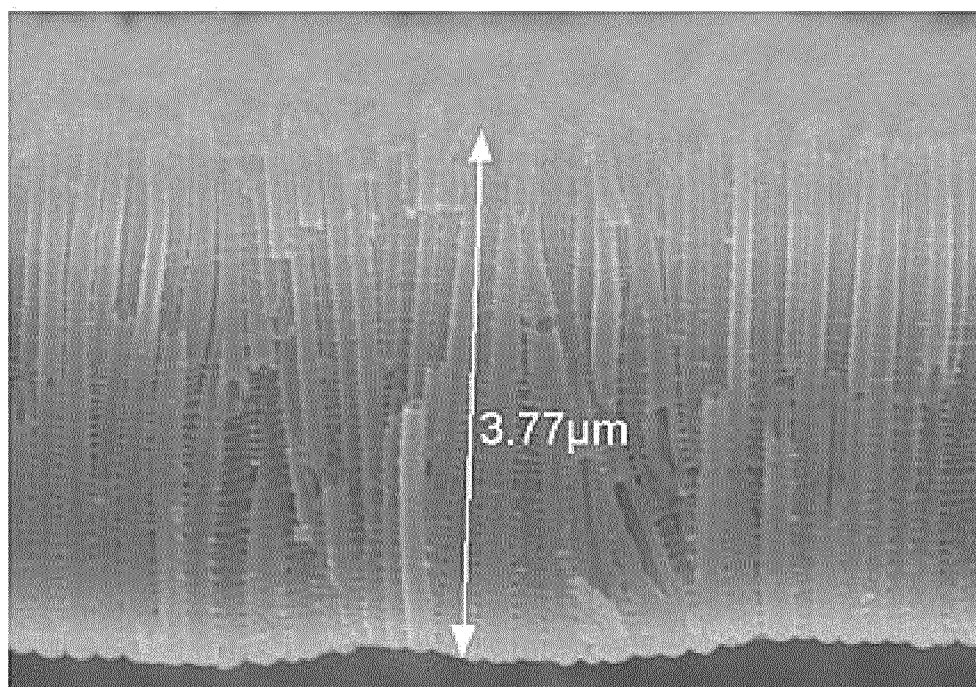


Fig. 2



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Fig. 3

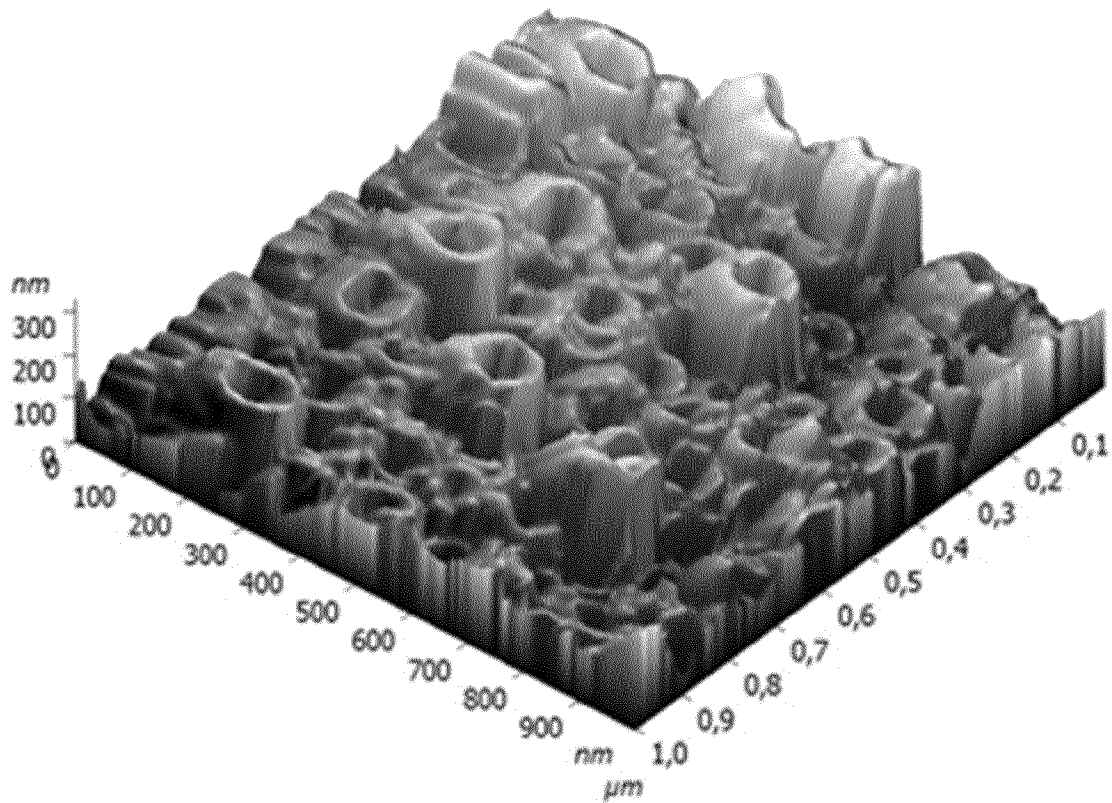


Fig. 4

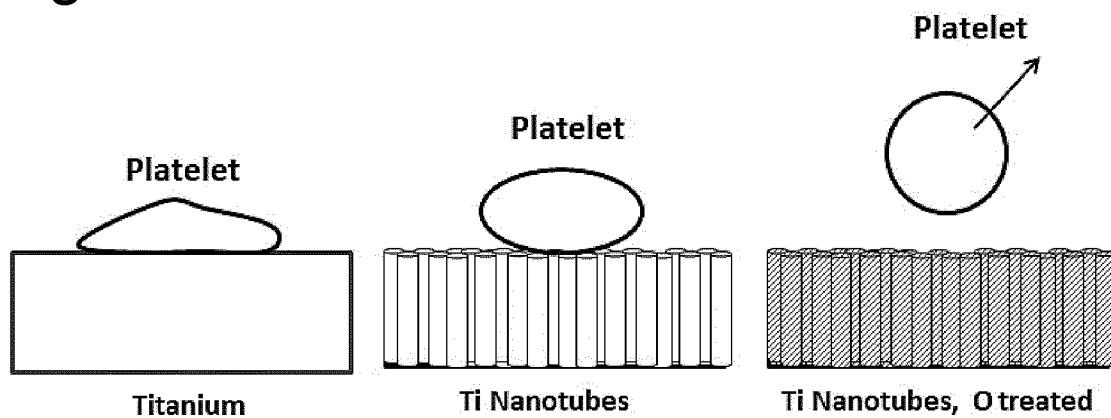
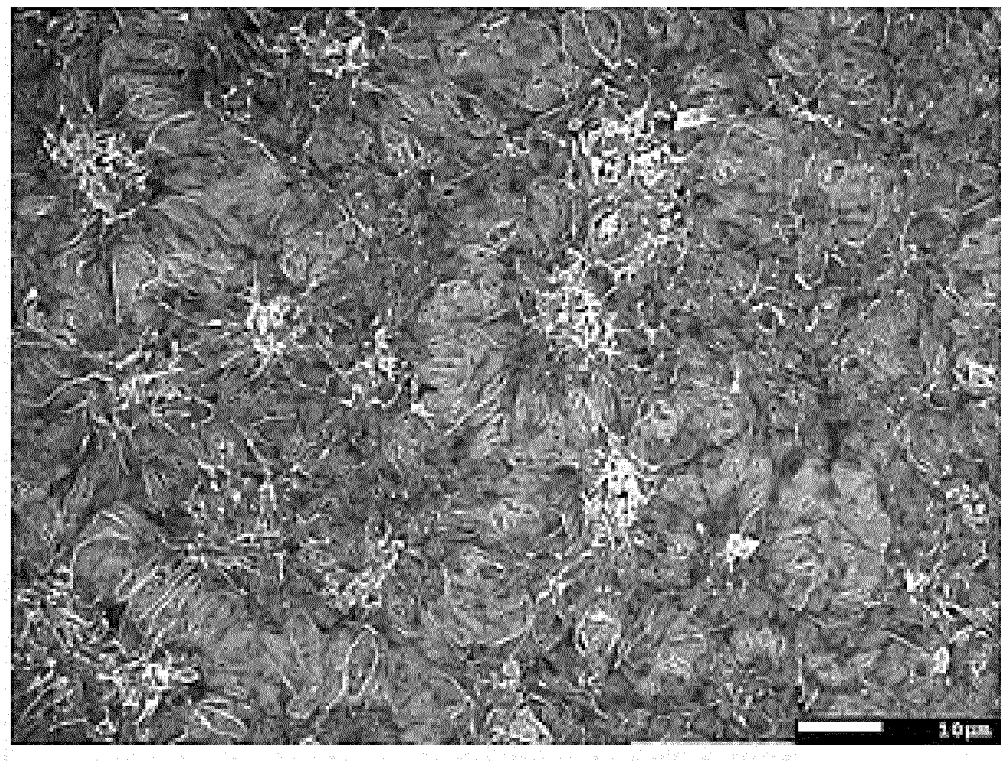


Fig. 5

Atomic percentage	C	O	Ti	N	F
Plain titanium	41.2	38.3	18	2.5	0
Nanotubes	24.3	48	19.9	1.2	6.6
Nanotubes treated	20.2	55.6	22.7	0	1.5

Fig. 6



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Fig. 7

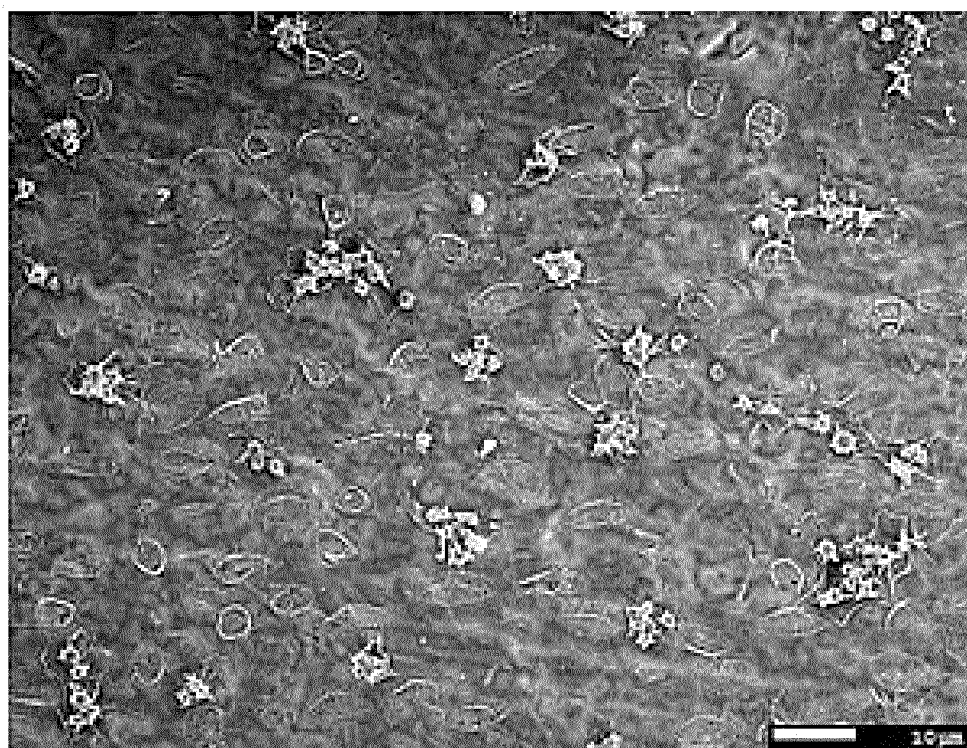
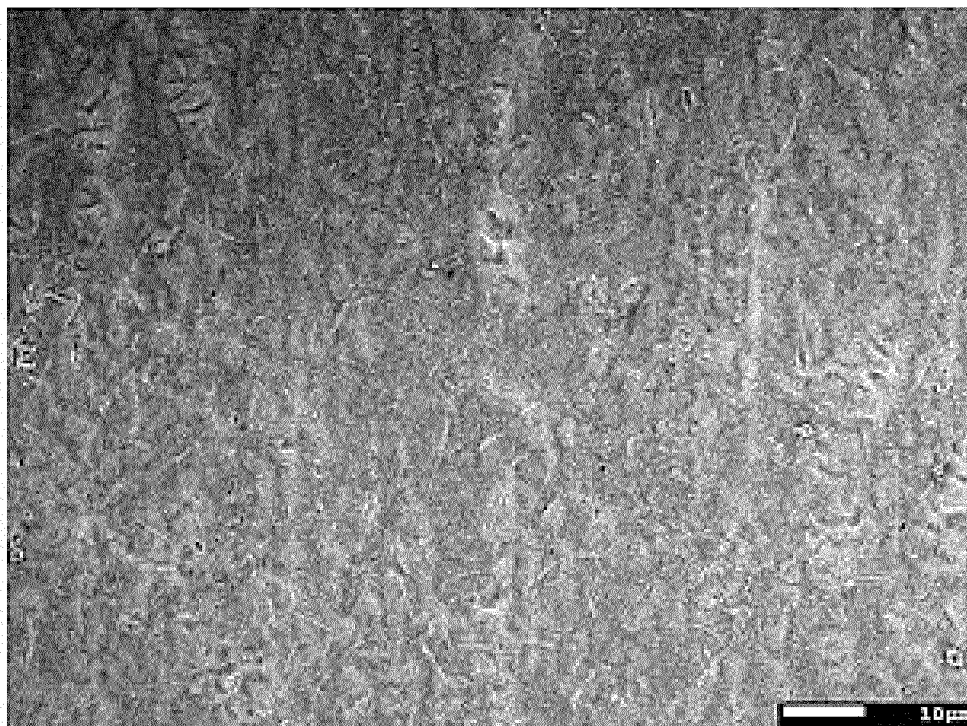


Fig. 8



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/070007

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L31/08
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)
A61L

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AJDA FLASKER ET AL: "Binding of human coronary artery endothelial cells to plasma-treated titanium dioxide nanotubes of different diameters :", JOURNAL OF BIOMEDICAL MATERIALS RESEARCH. PART A, vol. 104, no. 5, 30 January 2016 (2016-01-30), pages 1113-1120, XP055422450, HOBOKEN, NY, US ISSN: 1549-3296, DOI: 10.1002/jbm.a.35646 abstract; page 1113 Growth of TiO₂ NTs by electrochemical anodization; page 1114 Gaseous plasma treatment of NTs; page 1114 Discussion and conclusions; -/--	1-12



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

7 November 2017

Date of mailing of the international search report

14/11/2017

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Authorized officer

Dudás, Eszter

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/070007

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	page 1119 - page 1120 ----- US 2006/229715 A1 (ISTEPHANOUS NAIM [US] ET AL) 12 October 2006 (2006-10-12) page 1, paragraphs 0001,0009,0010 page 2, paragraphs 00213,0024,0025,0027 page 3, paragraph 0033 page 4, paragraphs 0041,0043 page 6, paragraphs 0052,0053 -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2017/070007

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			CN 101166549 A 23-04-2008
			EP 1863544 A2 12-12-2007
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