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Analysis of selected utility properties of biomaterials used in coronary stents

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Properties

ABSTRACT

Purpose: The study analysed influence of the selected functional properties of metallic biomaterials on selected functional properties of coronary stents used in invasive cardiology.
Design/methodology/approach: Pitting corrosion resistance tests were performed by means of potentiodynamic method. Corrosion resistance tests were performed on the ground of registered anodic polarisation curves and Stern method. The research also comprised galvanic corrosion resistance tests with application of Evans method. Measurements were made with VoltaLab® PGP 201 system. Tests were performed in artificial blood plasma at the temperature T = 37.0±1°C and pH = 7.0±0.2. Measurements of fluoroscopic visibility with application of cardiovascular imaging system Integris 5000 by Philips were also performed.
Findings: Application of Ta layer in composite stents made of Cr-Ni-Mo steel is an effective method used for improvement of their functional properties, and in particular of their fluoroscopic visibility, at the same time decreasing their corrosion resistance. It is of crucial meaning for increasing effectiveness and safety of low-invasive percutaneous transluminal coronary angioplasty.
Practical implications: Improvement of fluoroscopic visibility of coronary stents is possible through application of materials with increased X-ray absorptivity for their production. Within this scope you can consider certain form of implant created as a whole from one biomaterial or mixture of two biomaterials (layer implants), on the assumption that one of them features greater X-ray absorptivity.
Originality/value: Application of middle layer made of tantalum in composite stent does not influence initiation of galvanic corrosion process but it produces better fluoroscopic visibility that brings forth improved safety of coronary angioplasty
Keywords: Biomaterials; Stent; Corrosion resistance; Fluoroscopy

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1. Introduction

Since the first treatment involving widening of occluded artery lumen by means of balloon, this procedure has become routine in blood vessels disease treatment. However, restenosis was observed for ca. 30-50 % patients. Therefore, the search for ways how to prevent it started. One of the greatest achievements of medicine in the second half of the XX century was construction of miniature forms of endovascular implants - coronary stents. They have been widely used in treatment of patients suffering from coronary arteriosclerosis. PTCA treatment ending with stent implantation became a therapeutic procedure used worldwide (over 2 500 000 treatments in 2005). Application of coronary stents radically changed methods and effectiveness of blood vascular system diseases. It was possible as the result of previous experience connected with metallic materials implantation into human organism (not only into blood vascular system). Moreover, adaptation of already applied PTCA technique for stent expansion in the vessel ensures low invasiveness and safety of treatment [1-5].

Also in Poland there has been a dynamic increase of the number of cardiac catheterization labs and performed diagnostic and therapeutic treatment. At present, there are about 12 cardiac catheterization labs in Poland. According to data gathered by Polish Cardiac Society in 2003 in Poland 35 820 stent implantations were performed, which was 70% of all PCI. In 2011 those numbers increased to 98 793 and 90%, respectively.

Clinical experience gathered so far, connected with application of this form of implants shows, apart from indisputable benefits, certain limitations arising from introduction of metallic material into human blood system. Analysis of data taken from literature makes the ground for assumption that most of all they are issues connected with blood coagulation on the surface of stents and with restenosis. Thus, forming correct functional properties of stents in many biomedical engineering centres became mainly oriented for technologies of production of layers that effectively reduce unfavourable phenomena taking place on their surface [6-14].

One of crucial factors that influence proper course of low-invasive PTCA is good fluoroscopic visibility of vascular stents. It is mainly connected with applied technique of implant visualisation (with application of X-ray). Implant fluoroscopic visibility is conditioned both, by its structural form and by the type of biomaterial the stent is made of. Analysis of structural forms of currently used vascular implants proves that manufacturers of those products are trying to achieve the required fluoroscopic visibility mostly by application of special markers (distal and proximal), mounted on balloons. However, such solution does not guarantee good visibility of the implant as such, but only enables determination of its location in blood vessel [15-17].

Improvement of fluoroscopic visibility of vascular stents as such is possible through application of materials with greater X-ray absorptiveness for their production. Here, it is possible to consider a respective form of implant created as a whole from one biomaterial or mixture of two biomaterials (layer implants), on the assumption that one of them features greater X-ray absorptivity. When analysing the possibility of application of composite implants, one must take into consideration most of all the risk of corrosion process initiation arising from application of various metallic biomaterials. In addition, such solution may influence among other things flexibility and expansibility of suggested form of stent, therefore - basic factors responsible for safety and effectiveness of low-invasive angioplasty. That is why the authors of this study made an attempts to determine the impact of constructional solution and material composition of a three-layer coronary stent on its selected functional characteristics, and in particular on corrosion resistance and fluoroscopic visibility [18,19].

2. Materials and methods

Three-layer vascular stent Trimaxx^{TM} by AbbottVascular - Fig. 1 - that is currently in use in invasive cardiology was selected for the tests. It consists of two layers (external and internal) made of Cr-Ni-Mo steel and of middle layer made of tantalum. This implant belongs to the group of "slotted tube" type stents (cut with laser beam) and features open-cell type construction. Due to its construction, it is used for stents in blood vessels that are both, twisting and hard to access ones. Stent with wall thickness of g = 0.074 mm and length l = 13 mm was selected for the tests from dimensional range of types.

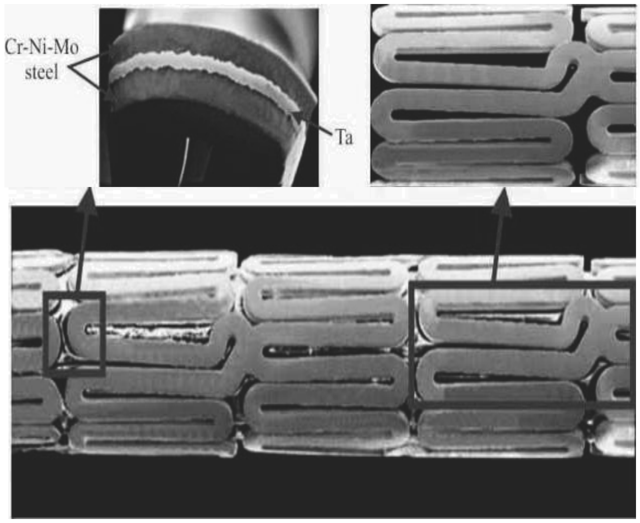

Fig. 1. Constructional form of Trimaxx^{TM} stent

In order to perform comparative measurements of corrosion and fluoroscopic visibility, testing material in the form of steel sheet with thickness of g = 2 mm made of Cr-Ni-Mo steel and strip made of Ta with thickness of g = 0.11 mm was used.

2.1. Pitting corrosion resistance tests

Pitting corrosion resistance tests of three-layer vascular stents were performed with application of potentiodynamic method, registering anodic polarisation curves. Tests performed on finished product enabled evaluation of corrosion resistance of not only the applied material composition, but also of the construction of the implant. Measurements were made in solution simulating human blood with pH = 7.0 ± 0.2 and temperature T = 37 ± 1 °C in accordance with recommendations of PN-EN ISO 10993-15:2009 Table 1.

Table 1.
Chemical composition of artificial plasma

Ingredients	Ingredients concentration, g/dm^3 distilled water
NaCl	6.8
KCl	0.4
$CaCl_2$	0.2
$MgSO_4$	0.1
$NaHCO_3$	0.2
Na_2HPO_4	0.126
NaH_2PO_4	0.026

Anodic polarisation curves for the rate of potential change of 1 mV/s, registered by means of measurement set consisting of Fig. 2:

- potentiostat PGP 201 by Radiometer,
- electrochemical cell,
- reference electrode - Saturated Calomel Electrode (SCE),
- auxiliary electrode - Platinum electrode (Pt),
- anode - tested sample,
- ultra-thermostat Medingen E5,
- PC computer with VoltaMaster 4 softare version 5.1.0.1 by Radiometer.

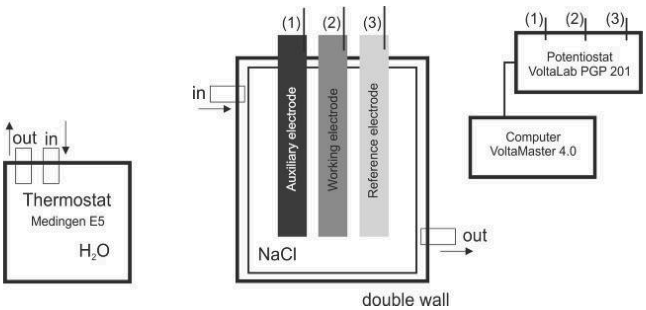

Fig. 2. Scheme of the corrosion test

Prior to the tests, implants were cleaned in 96% ethanol in ultrasonic washer Sonica 1200 M by Soltec (Italy) for 5 min. Measurements started with determination of opening potential E_{OCP}. Next, anodic polarisation curves were registered, starting the measurement with initial potential E_{start} = E_{OCP} - 100 mV. Having obtained current density of 1 mA/cm^2, polarisation direction was changed. On the ground of registered anodic polarisation curves, typical values that describe resistance to pitting corrosion were determined, namely: breakdown potential E_b, repassivation potential E_{cp}, corrosion potential E_{corr}, polarisation resistance R_p and corrosion current density i_{corr}. Stern method was used for determination of polarisation resistance value.

2.2. Galvanic corrosion resistance tests

The tests also included galvanic corrosion resistance tests with application of Evans method. In the tests, during a single measurement, samples from two different materials are used. One sample works as anode, and the other - cathode (sample made of the material with higher corrosion resistance). In the measurements, the relation between current strength in the function of potential of anode E_a and cathode E_c is registered. Samples made of Cr-Ni-Mo steel and Ta steel were used for the tests. In order to determine resistance to galvanic corrosion of the analysed composite system, the tests were performed for various values of the relation of the anode and cathode - 1:1, 2:1 and 1:2. Measurements were performed on five samples for each variant, in the solution simulating human blood environment (artificial blood plasma Table 1) with temperature of T = 37±1°C and pH = 7.0 ± 0.2 with application of measurement system used in pitting corrosion tests Fig. 2.

2.3. Fluoroscopic tests

Tests of visibility under fluoroscopy were performed with application of cardiovascular imaging system Integris 5000 by Philips equipped with digital quantitative analysis system at the Hemodynamics Laboratory of the Silesian Centre of Cardiac Diseases (Śląskie Centrum Chorób Serca) in Zabrze. The purpose of the test was determination of the degree of visibility of samples made of metallic biomaterials used for implants in invasive cardiology. In particular, samples made of Cr-Ni-Mo steel and tantalum with dimensions: 8 x 8 mm and thickness g = 0.22 ±0.01 mm were used for the tests. Final form of samples made of Cr-Ni-Mo steel was obtained by the process of abrasive waterjet cutting (with application of the device WARICUT by H.G. Ridder), and then grinding in order to obtain the required thickness. Measurements were performed for the respective types of biomaterials as well as composite systems - Cr-Ni-Mo steel - Ta for five samples for each variant of the material under conditions adequate for clinical conditions (angioplasty). Standard values, that are, respectively: l = 40 cm and 164 $mGycm^2$ (according to DAP - Dose Area Product), were applied in the measurements. Evaluation of the degree of visibility for the respective variants of sample materials as performed on the ground of the analysis of the grey level of the recorded images. For that purpose, Matlab 2007b software was used. Grey level of samples was analysed in the range from 0 - 255.

3. Results

The first stage comprised pitting corrosion resistance tests of three-layer stents Trimaxx™. Tests of that form of implants in unexpanded stents showed that mean value of corrosion potential was E_{corr} = -7 mV. Electropositive polarisation of tested samples enabled determination of perforation potential that in that case was E_{np}= +1046 mV Fig. 3a. When anodic current density exceeded i_{corr} = 1 mA/cm^2, samples polarisation direction was changed, which enabled to register return curve. Anodic polarisation curves registered in that way featured presence of hysteresis loop which proved the course of pitting corrosion. Mean value of repassivation potential was E_{cp}= +94 mV. Determined additionally mean values of polarisation resistance and corrosion current density were, respectively: R_p = 2705 kΩcm^2 and i_{corr} = 9 nA/cm^2. Process of stent expansion up to the diameter of d_1 = 3.5 mm influenced their corrosion characteristics. Decrease of mean value of corrosion potential was observed up to E_{corr} = -218 mV. Polarisation of tested samples also caused violent increase of corrosion current density with smaller values of breakdown potentials (E_b = +528 mV) Fig. 3b. Change of samples polarisation direction enabled to determine repassivation potential whose mean value was close to that of implants that were not subject to expansion and equalled E_{cp}= +100 mV. Determined mean values of polarisation resistance and anodic current density were, respectively: R_p = 1610 kΩcm^2 and i_{corr} = 15 nA/cm^2.

Next step of potentiodynamic tests involved measurements for tantalum samples - Fig. 4. Mean value of corrosion potential was E_{corr} = -313 mV. Determined anodic polarisation curves showed presence of passive range of values up to the value of potential E = +4000 mV. There was no observed rapid increase of anodic current density in the analysed range of measurement that would prove initiation of pitting corrosion. Values of polarisation resistance and corrosion current density, determined additionally with application of Stern method, were, respectively: R_p = 737 kΩcm^2 and i_{corr} = 35 nA/cm^2.

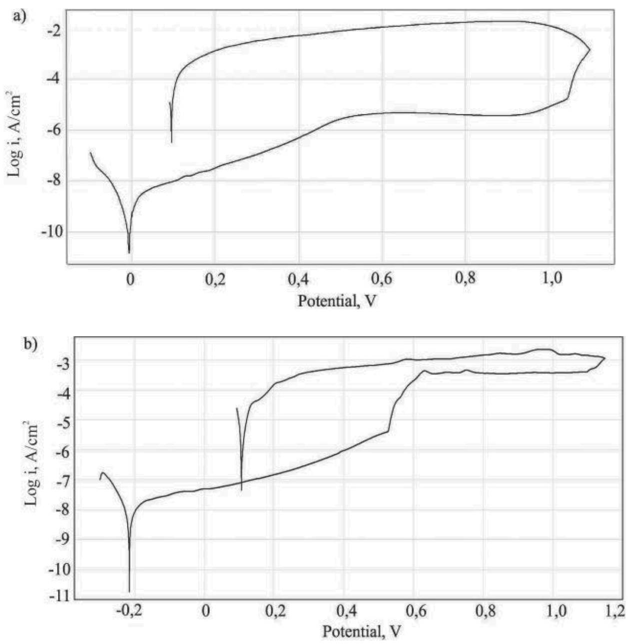

Fig. 3. Anodic polarisation curves of a three-layer stent Trimaxx^{TM}, artificial blood plasma solution: a) unexpanded, b) expanded

The last stage of pitting corrosion tests involved, for comparison, measurements performed for flat samples made of Cr-Ni-Mo steel with mechanically polished surface. Performed tests showed that mean value of corrosion potential for samples prepared that way was E_{corr} = -21 mV. Polarisation of tested samples caused rapid increase of anodic current strength with mean value of breakdown potential E_b = +1197 mV Fig. 5. When anodic current density exceeded 1 mA/cm^2 samples polarisation direction was changed. Anodic polarisation curves registered that way also in that case featured presence of hysteresis loop. The surface of samples did not undergo repassivation in the tested range of potentials. Mean values of polarisation resistance and corrosion current density,determined by means of Stern method, were, respectively R_p = 1218 kΩcm^2 and i_{corr} = 21 nA/cm^2.

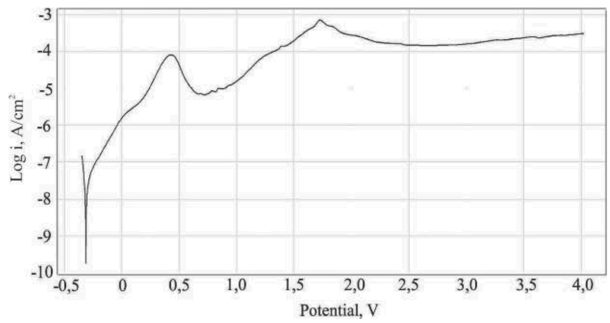

Fig. 4. Anodic polarisation curve for a sample made of pure tantalum with mechanically polished surface, artificial blood plasma solution

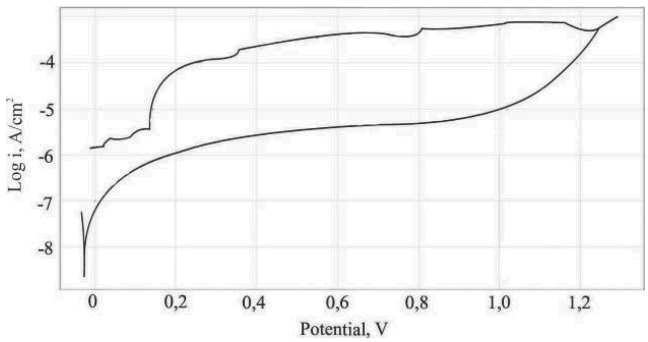

Fig. 5. Anodic polarisation curve for a sample made of Cr-Ni-Mo steel with mechanically polished surface, artificial blood plasma solution

Results of electrochemical tests of galvanic corrosion resistance of the analysed composite system Ta -Cr-Ni-Mo steel as the function of differentiated area of the respective materials is presented in Fig. 6. Measurements made for samples with the same area showed that mean value of short-circuit current strength and its respective value of short-circuit potential were, respectively I = 0.025 µA and E = -190 mV. The fact that area of sample made of Cr-Ni-Mo steel was doubled brought about favourable decrease of short-circuit current strength up to the value of I = 0.013 µA and slight increase of short-circuit potential up to the value of E = -182 mV. Whereas, when the area of sample made of Cr-Ni-Mo steel was reduced by half in relations to the sample made of Ta, it was proved that values of short-circuit current strength and short-circuit potential were, respectively I = 0.023 µA and E = -202 mV.

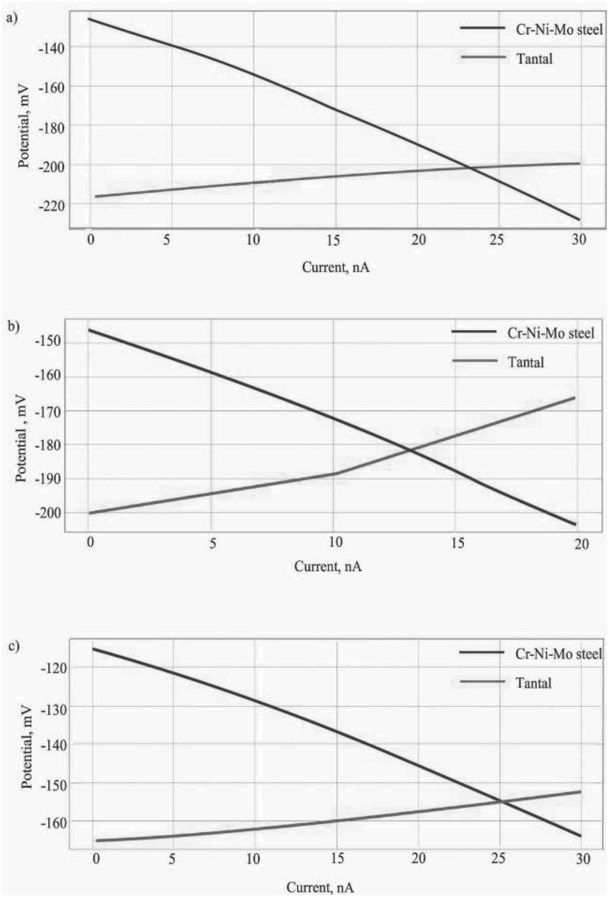

Fig. 6. Change of the value of short-circuit potential of the system Ta - Cr-Ni-Mo steel as the function of short-circuit current, artificial blood plasma solution, relation of the area: a) 1 : 1, b) 1 : 2, c) 2 : 1

a) b)

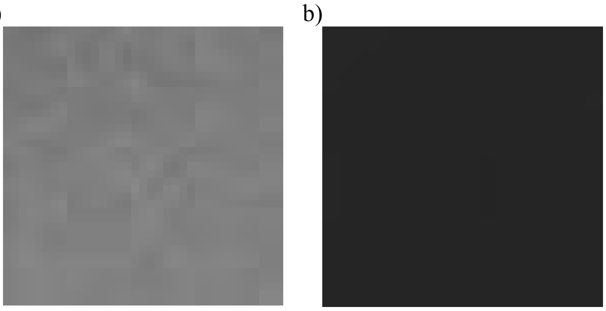

Fig. 7. Radiographs registered for samples: a) made of Cr-Ni-Mo steel, b) made of tantalum

The results of performed measurements of fluoroscopic visibility are presented in Figs. 7-10. Greyness of the middle part of registered radiographs that corresponds to the area of samples with dimensions: 5 x 5 mm was subject to analysis - Figs. 7, 9. Results obtained from that analysis show differentiation of the degree of image blackening for the respective metallic biomaterials. The smallest value of grey level was obtained for tantalum, and the biggest for Cr-Ni-Mo steel. Mean values of grey level for those biomaterials were, respectively: 2.4 and 126.9.

On the ground of analysis of registered radiographs for composite systems it was discovered that the system Cr-Ni-Mo steel - Ta features relatively high value of grey level. Mean grey level value for that system of materials is 31.0 - Fig. 10.

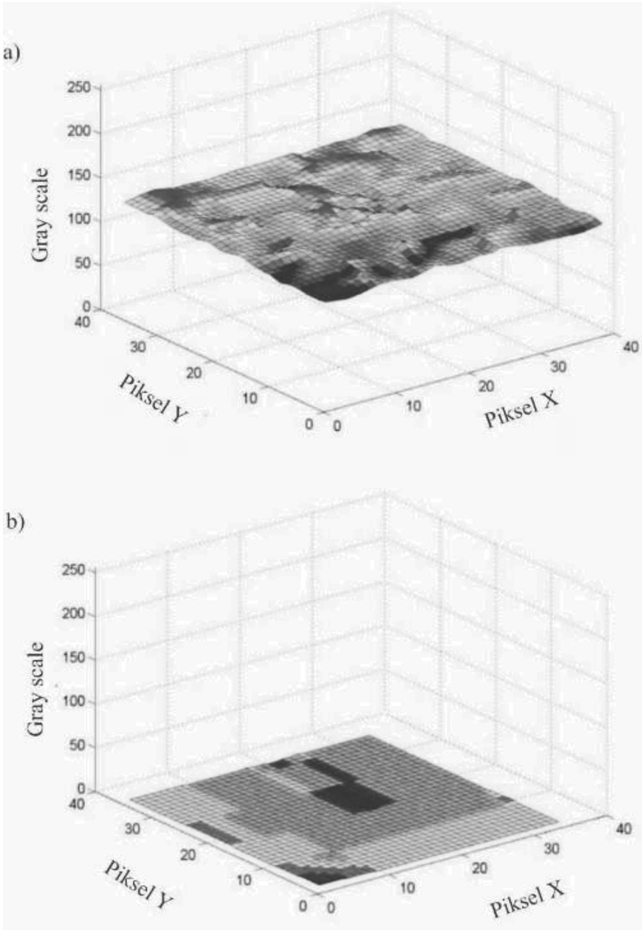

Fig. 8. Distribution of grey level in samples made of: a) Cr-Ni-Mo, b) tantalum

Fig. 9. Radiographs registered for composite system of Cr-Ni-Mo steel - Ta

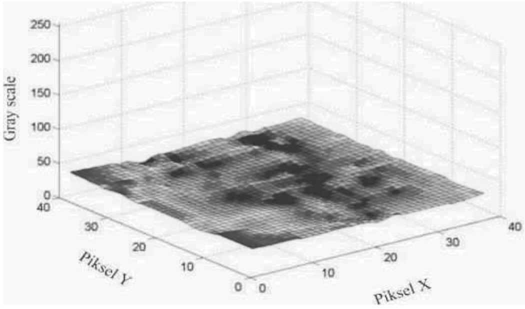

Fig. 10. Distribution of grey level in composite system: Cr-Ni-Mo steel - Ta

4. Conclusions

Utilisation of endovascular implants in order to maintain blood circulation in blood vessels characterised by lesion was started by Dotter in 1969 [20]. That treatment consisted in implantation of a metal pipe into dogs peripheral artery. After over two years 2 out of 3 implanted stents were still patent. In 1982 D. Maass, and in 1985 Julio Palmaz performed next tests on animals. The beginning of their clinical application was implantation of stents into human coronary artery made in 1986 by Sigwart [21]. Stents implanted then (Wallstent) were self-expanding implants. Coronary stents expanded by means of catheter with balloon were put into use in 1987 (Richard Schatz, Gary Rubin) [22]. The concept of stent application was presented as a way of vessel scaffolding that prevented collapse of tunica intima and tunica media, and consequently prevents the change of vessel diameter and protects from the phenomenon of elastic recoil [23]. In Poland the first stent implantation was performed in 1992 by prof. Witold Rużyłło at the Institute of Cardiology in Warsaw.

First experiments with stents application were not very promising, and early observation showed problems arising from their application. Despite intensive anticoagulant treatment, early thrombosis in stent was observed. It resulted in prolonged stay of patient in hospital and complications in the form of haemorrhage [24].

The first scientist who described the reasons for unsatisfactory results of stent implantation and determined ways how to avoid complications was A. Colombo. His research that was made with application of intracoronary ultrasound showed that stents implanted in accordance with traditional methods featured insufficient implant pressure deployment, despite good effects in angiographic image (so called hanging stents). Application of stent expansion with a balloon under high pressure (p = 16-20 atm) in order to ensure optimum adhesion of stent to vessel walls and proper pharmacological therapy reduced substantially frequency of restenosis and thrombosis in stents [25]. Results of those tests started the era of planned stent implantation. In 2003, the results of meta-analysis of published 29 random tests made on 9 918 patients were presented, which compared balloon angioplasty with implantation of coronary stents. They confirmed that stenting reduced frequency of restenosis appearance and re-interventions, but it does not reduce mortality or frequency of myocardial infraction [26].

One of basic criteria that decide about applicability of certain constructional and material solutions of vascular implant is its hemocompatibility [28-30]. Instead, corrosion resistance of implants in blood environment is one of its crucial elements. Being a liquid part of connective tissue, blood forms corrosive environment characterised by specific and stable pH. Its stable value, that guarantees proper homeostasis process, ensures presence of among other things sodium bicarbonate ($NaHCO_3$), sodium dihydrogen phosphate and disodium hydrogen phosphate (NaH_2PO_4 and Na_2HPO_4) in blood plasma [31-34]. Therefore, a crucial factor determining the conditions of performed corrosion resistance tests was selection of temperature and corrosion environment, taking into consideration the aforementioned features of human blood plasma. Therefore, measurements of pitting corrosion resistance with application of potentiodynamic method were performed the solution simulating chemical environment of blood plasma (according to PN-EN ISO 10993-15) at the temperature of $T = 37 \pm 1\ ^{\circ}C$ and $pH = 7.0 \pm 0.2$.

Pitting corrosion resistance tests were performed with application of final form of coronary vascular stent of Trimaxx™ type and in addition of flat samples made of Cr-Ni-Mo steel and tantalum. In order to determine the influence of low-invasive technique of implantation, used in angioplasty, measurements were made for unexpanded as well as expanded stents. One part of performed corrosion test was also devoted to analysis of possibility of galvanic corrosion initiation due to the applied material composition in the tested form of three-layer stent (Cr-Ni-Mo steel - Ta - Cr-Ni-Mo steel). Here, electrochemical measurements with application of Evans method were made. In addition, that type of tests becomes particularly important due to the fact that in clinical practice there are cases of vascular stent implantation (frequently made of a different metallic biomaterial) into implants that are already placed in the vessel.

On the ground of performed measurement it was discovered that a tested composite system showed the lowest susceptibility to galvanic corrosion in the situation when the area of a sample made of Cr-Ni-Mo steel is twice the size as tantalum. Therefore, application in construction of composite stents with middle layer made of tantalum does not influence significantly initiation of galvanic corrosion process. It can be additionally justified by the fact that the relation of total area of internal and external layers (made of Cr-Ni-Mo steel) that come into contact with blood environment to the area of the middle layer is much bigger than that considered in performed measurements (2:1).

In order to determine applicability of used material composition of three-layer implant, fluoroscopic visibility measurements were also made. Possibility of application of proper apparatus (angiograph Integris 5000 by Philips), as well as standard values of image registration parameters (distance between the lamp and the surface of samples, the amount of X-radiation dose) enabled to perform measurements under conditions adequate to those applied in angioplasty. Performed analysis of image grey level with application of Matlab 2007b software, for samples made of particular biomaterials showed its smallest value for tantalum equal 2,4 (the biggest level of image blackening). It is connected to a great extent to atomic number Z of that element. Therefore, application of the middle layer made of Ta in three-layer stents contributes to improvement of their fluoroscopic visibility.

To sum up, it can be stated that, undoubtedly, stents with three-layer construction made of Cr-Ni-Mo steel (external and internal layer) and tantalum (middle layer) feature better fluoroscopic visibility. Such form of stents enables precise determination of their position in vessel, which consequently improves effectiveness and safety of performed angioplasty.

Acknowledgements

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