# PHYSICAL PROPERTIES OF BIODEGRADABLE POLYMERS EXPOSED TO ARTIFICIAL PLASMA FLOW

**Alicja Zegartowska[1]*, Mateusz Stojko[2], Kamil Joszko[1], Karolina Goldsztajn[1], Ada Orłowska[1], Janusz Szewczenko[1]**

[1] Faculty of Biomedical Engineering,
Silesian University of Technology,
Franklina Roosevelta 40,
41-800 Zabrze, Poland
[2] Centre of Polymer and Carbon Materials,
Polish Academy of Sciences,
M. Curie-Sklodowskiej 34,
41-819 Zabrze, Poland
*e-mail: aliczeg420@student.polsl.pl

## Abstract

*Despite significant advances in diagnosis and treatment, cardiovascular disease remains a major cause of premature death. Approximately 80% of cardiovascular incidents can be prevented by optimizing risk factor control and lifestyle modification, including dietary change. Treatment of cardiovascular disease, like treatment of other diseases, can be divided into conservative and curative. Conservative treatment is based on pharmacotherapy, while surgical treatment is mainly based on the use of PCI (percutaneous coronary intervention) procedures, i.e., increasing blood flow through narrowed arteries. This effect can be achieved with stents. The main limitation of metal stents is their permanent presence within the body, which can lead to complications such as thrombosis. A more advanced solution is the use of polymer or drug-coated stents, both of which are made of biodegradable materials. These stents are designed to release medications to support treatment and maintain their shape within the blood vessel before being naturally absorbed and eliminated by the body. In this study, the surface of stents made of polylactide was modified by applying a layer of PLGA using an ultrasound method. The study was carried out for uncoated and coated stents in both the initial state and after exposure to artificial plasma flow. The scope of the work included microscopic observations, weight measurements of the specimen, and examination of radial forces. The analysis of the results showed no clear effect of exposure on stent weight, but a clear effect of long--term exposure on radial forces was observed.*

***Keywords:*** *bioresorbable stents, biodegradable coating, poly(L-lactide-co-glycolide) (PLGA), splay coating, radial forces*

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## Introduction

Cardiovascular diseases are the leading cause of death worldwide. According to the WHO (World Health Organization), these diseases take the lives of approximately 17.9 million people each year. They belong to a group of cardiovascular disorders that includes diseases such as ischemic heart disease, vascular restenosis, cerebrovascular disease, and other conditions. Risk factors are social and cultural changes, including low physical activity, poor diet, stress, and smoking or consuming harmful amounts of alcohol [1].

The treatment of cardiovascular disease depends on the severity of the disease and the risk to the patient. If the cause of the disease is excessively high cholesterol levels that affect the quality of blood flow or irregular heart rhythm, pharmacological treatment is implemented. The pharmacological treatment of cardiovascular diseases depends mainly on the specific disease entity with which the patient is struggling. In the case of hypertension, hypotensive drugs are used; in the case of heart failure, multidrug therapy is used to modify the cause as much as possible. The more advanced form of the disease associated with partial or complete blockage of a blood vessel is surgically treated with coronary angioplasty or coronary artery bypass grafting. Coronary angioplasty is a procedure used to unblock the arteries of the heart using a small balloon catheter that is inserted into the blocked blood vessel to dilate it. Angioplasty is often combined with the placement of a small wire mesh tube called a stent. The use of angioplasty along with stenting has many advantages for the patient; in some cases, it can eliminate the need for arterial bypass surgery, which is a more invasive procedure and is also associated with a prolonged recovery time [2,3].

A stent is a medical implant that is used to maintain the normal shape of the arteries affected by atherosclerosis and prevent them from narrowing again. A stent looks like a cylinder with a diameter of approximately 3-8 mm and a thin mesh structure of 150-200 microns thick. Depending on the characteristics of the disease and the function of the vascular prosthesis, we can distinguish different types of stents. Concerning the method of implantation, stents can be divided into classic BMS (bare-metal stent) stents, also referred to as metal stent-grafts, in which it is first necessary to dilate the blood vessels using a catheter. Self-expandable stents, which are characterized by variable expansion force, thus reducing the risk of various complications such as stent thrombosis. Another classification of stents is based on the material used to manufacture them. A distinction is made between metal stents, bioresorbable stents, and the latest generation of drug-eluting stents (DES). Metal stents are usually made of alloys containing elements such as chromium or vanadium, for example, cobalt-chromium or nickel-titanium. Their negative influence related to metal-organ interaction and restenosis has prompted the development of research into bioresorbable stents, which are made of materials such as aliphatic polyesters and polyacids. These materials meet all the requirements for interaction with the human body, i.e. low toxicity, degradability under biological conditions, and adequate mechanical strength. In addition, these materials are largely amorphous, which facilitates their uniform degradation. Bioresorbable stents dissolve completely a few months after implantation. After this period, the treated vessel segment regains physiological function. Therefore, the potential benefit of bioresorbable stents is the prospect of long-term restoration of vascular endothelial reactivity and vascular reconstruction in just a few months.

Complete biodegradation eliminates the risk of late adverse coronary incidents related to the presence of foreign bodies in the vessel. The latest generation of drug-eluting DES stents is characterized by the release of specific drugs such as sirolimus and everolimus. These reduce the process of restenosis, i.e. the overgrowth of the vessel lumen [4-8].

The choice of stent type should be based on detailed clinical data and take into account: clinical indications; the presence of comorbidities, including those requiring chronic anticoagulation; the risk of bleeding associated with prolonged dual antiplatelet therapy; the risk of premature discontinuation of antiplatelet therapy (medical contraindications, patient non-cooperation). A significant advance in the field of vascular prostheses has been the use of polymer coatings as a matrix for the release of therapeutic substances. Polymer-coated stents, unlike classic metal stents, exhibit high plasticity, facilitating the transfer of the prosthesis to the target implantation site, and the polymer coating provides a good matrix for immobilization and controlled release of antiproliferative drugs. Therefore, implants of this type are an interesting alternative in the treatment of coronary artery disease. The undoubted advantage of using this type of stent is its biocompatibility (rapid and proper formation of neointima) without the need for long-term dual antiplatelet therapy [9-12].

The study aimed to determine the physical properties of biodegradable polymer stents covered with a PLGA coating. Long-term studies of exposing stents to the flow of artificial plasma were performed for stents with and without coating.

## Materials and Methods

Stents with a length of 10 mm and a diameter of 3 mm made of modified polylactide using the microinjection method (FIG. 1) were obtained from the Center of Polymer and Carbon Materials of the Polish Academy of Sciences in Zabrze. They were divided into two groups, i.e. 14 stents remained in the initial state, while 12 stents were coated with seven layers of poly(L-lactide-co-glycolide) (PLGA), each layer applied with the same parameters [7]. The application of coatings on the stents was performed using the ExtraCoat (Sono-Tech, USA) ultrasonic coating system, with the parameters shown in TABLE 1. 2% solution of PLGA in dichloromethane was used in the coating process.

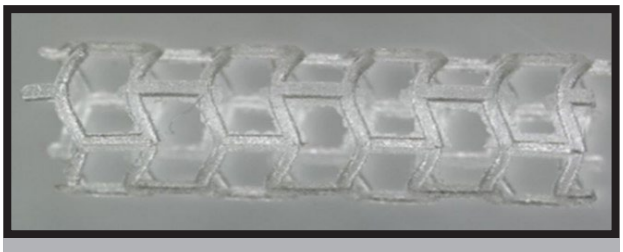

**FIG. 1. Stent in the initial state.**

**TABLE 1. Parameters of the coating system.**

| | |
|---|---|
| Ultrasound frequency | 60 kHz |
| Ultrasound power | 1.5 W |
| Solution flow rate | 0.5 $cm^3$/min |
| Sliding speed | 5 mm/s |
| Air curtain pressure | 3 Pa |
| Time between successive coats | 15 s |

After the application process was completed, the stents were dried for 48 h under ambient conditions and then for the next 24 h in a laboratory dryer at 30ºC.

The stents were exposed to artificial plasma flow for 1, 14 and 28 days. In each trial, 3 uncoated stents and 3 stents with a polymer coating were used. The tests were carried out in artificial plasma at a temperature of 36.6ºC in the range of pressure changes of 80-120 mmHg and a flow rate of 1.1 m/s. Plasma flow in a single tube was 15 ml/s. Artificial plasma with the content of: 0.14 M NaCl, 0.0027 M KCl, and 0.01 M $PO_4^{3-}$ (Chemsolve) was used in the research.

In the work, for stents without and with a polymer coating before and after exposure to the flow of artificial plasma, the following study was carried out.

The weight of the samples was determined using the analytical scale RADWAG AS 310.R2, with an accuracy of 0.0001 g. Microscopic observations of the stents were made using a Leica DVM6 digital microscope. The radial force test was carried out at the Center for Polymer and Carbon Materials of the Polish Academy of Sciences using the TTR2 with the J-Crimp Blockwise radial force testing system, which enables the testing of stents with various design features. Before measurements, the stents were conditioned at 37ºC for 30 s. The tests were performed with the parameters presented in TABLE 2.

**TABLE 2. Parameters of the radial force test.**

| | |
|---|---|
| Starting diameter | 3 mm |
| Final diameter | 1.5 mm |
| Clamping speed | 0.5 mm/s |
| Measurement temperature | 37ºC |

## Results and Discussions

The mean values and standard deviations of the weight of uncoated (U) and polymer-coated (C) stents after different times of exposure to the flow of artificial plasma are presented in TABLE 3.

**TABLE 3. Summary of weight of coated (C) and uncoated (U) stents after exposure.**

| Time of exposure [day] | Stent | Average stent weight [mg] |
|---|---|---|
| 0 | U | 4.00 ± 0.38 |
| | C | 4.60 ± 0.35 |
| 1 | U | 4.30 ± 0.60 |
| | C | 4.50 ± 0.10 |
| 14 | U | 4.30 ± 0.20 |
| | C | 4.80 ± 0.10 |
| 28 | U | 4.00 ± 0.12 |
| | C | 4.10 ± 0.50 |

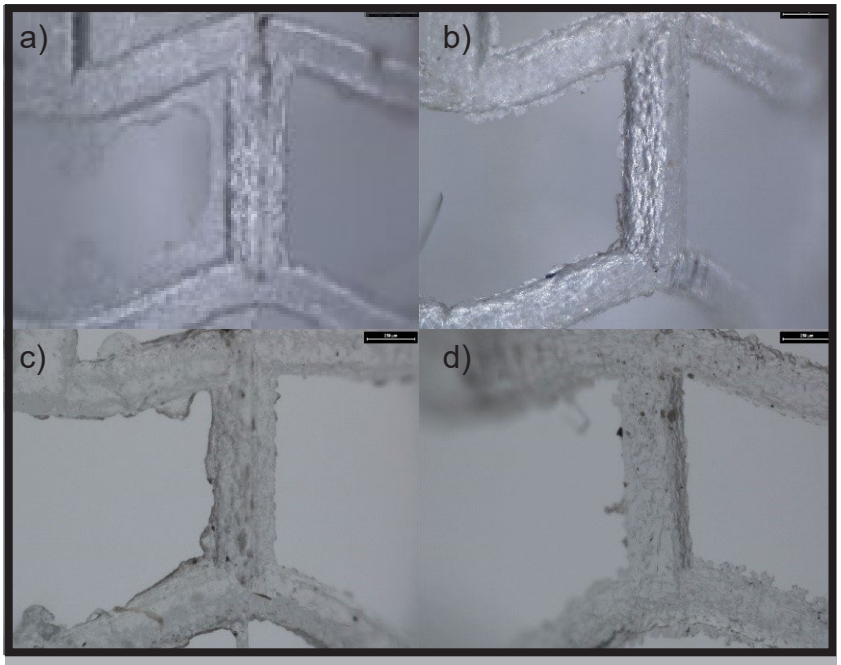


**FIG. 2. Stents in initial state: (a, b) uncoated, (c, d) polymer-coated.**

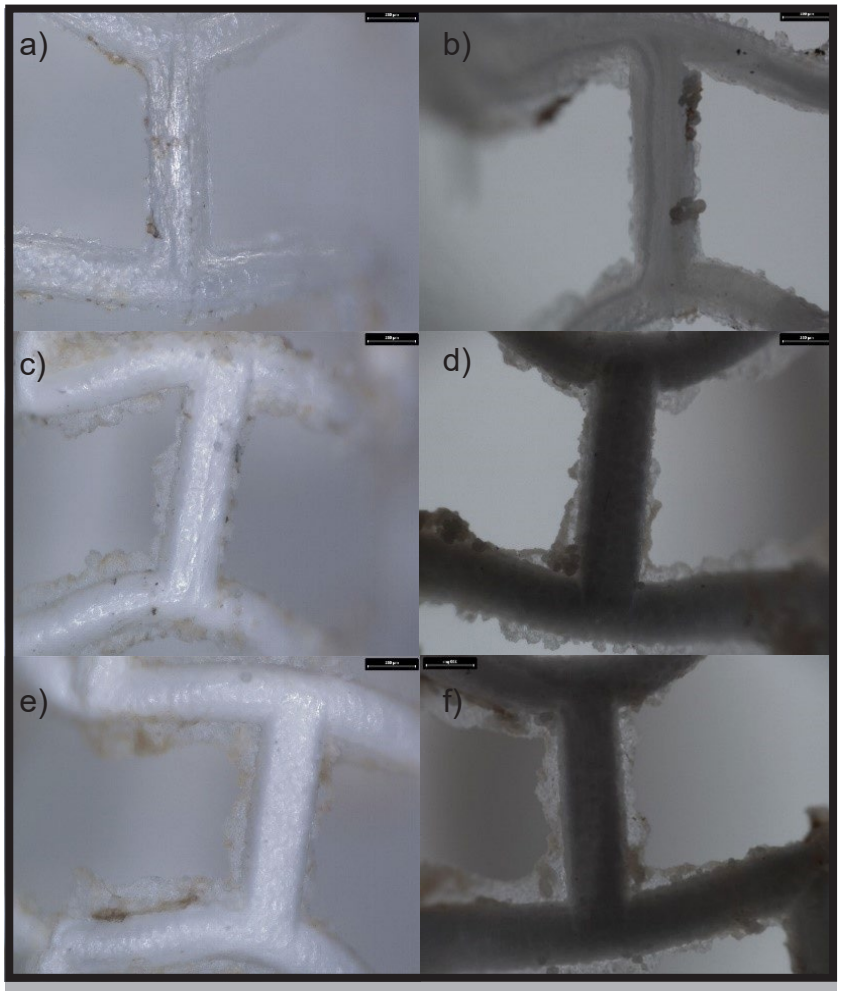


**FIG. 3. Uncoated stent exposed to artificial plasma flow for: (a, b) 1 day, (c, d) 14 days, (e, f) 28 days.**

The results of the stent weight in the initial state range from 4 mg to 5 mg. These differences result from the accuracy of the stent manufacturing process using the microinjection method, as well as the accuracy of stent trimming. The weight of the stents after exposure to plasma flow increased by an average of 0.6 mg compared to the stents before exposure. The increase in the weight of the stent after exposure is due to the deposition components of artificial plasma in the form of crystals on the stent, as well as the swelling of the polymer. Measurement of the mass of the stents in their original and coated states after exposure to plasma flow did not show significant differences.

Stents without and with coating before and after exposure to artificial flow plasma are shown in FIGs 2, 3 and 4.

The analysis of microscopic observations of the sample in the initial state revealed a smooth surface of the stent with visible sprues being the remnants of the stent manufacturing process (FIG. 2a, b). The application of the polymer coating caused the surface of the stent to become heterogeneous and characterized by greater surface development compared to the stent without the coating (FIG. 2c, d).

Microscopic observations of the stents in the initial state (FIG. 3) and with coating (FIG. 4) after different times of exposure to the plasma flow revealed additional deposits on the stent spans and sprues. The deposits in the form of crystals are the remains of the components of artificial plasma. The number of observed crystals increased with exposure time. A greater number of crystals was observed on the coated stents.

In the stents exposed to the flow of artificial plasma, after the radial forces tests (FIG. 5), changes in the shape (approach of the spans - FIG. 5b) and the places of rip stent tearing located in the zone span connections (FIG. 5a) were observed. The observations also confirmed that the presence of sprues after the stent manufacturing process and deposits in the form of crystals are the remains of the components of artificial plasma. These observations refer to both uncoated and coated stents.

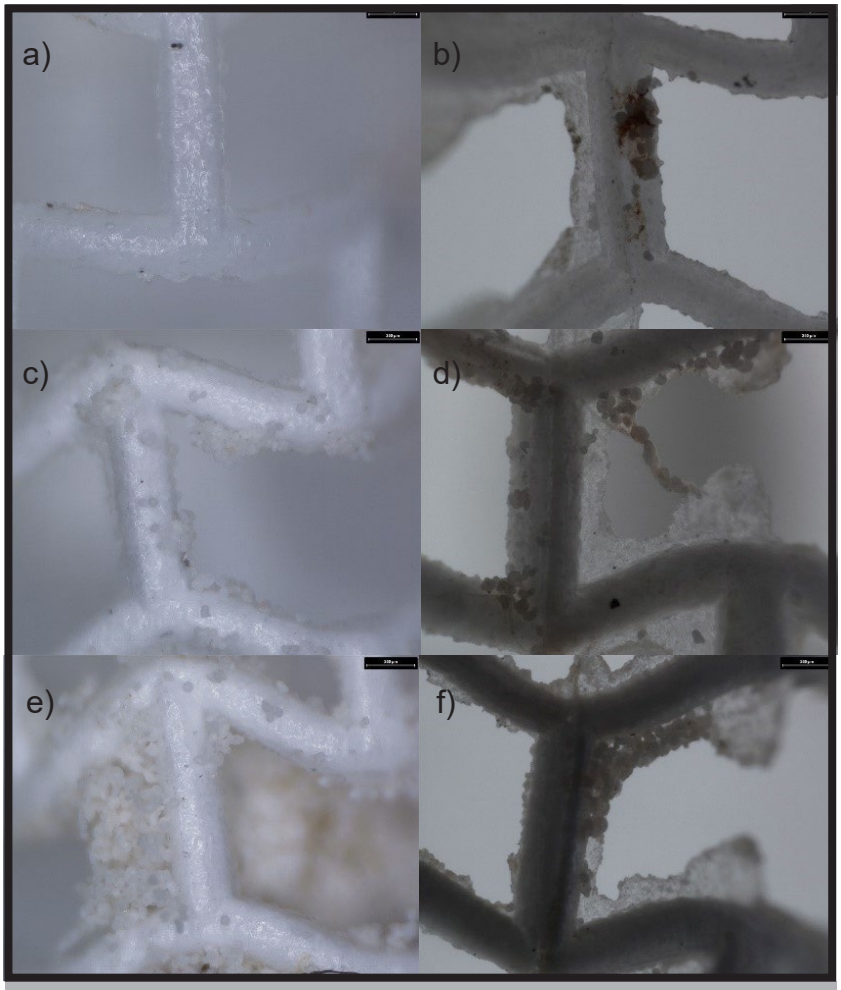


**FIG. 4. Polymer-coated stent exposed to artificial plasma flow for: (a, b) 1 day, (c, d) 14 days, (e, f) 28 days.**

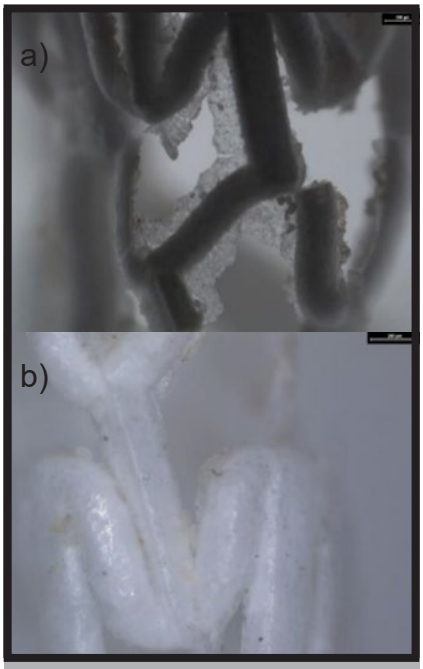


**FIG. 5. Stents exposed to artificial plasma flow and then subjected to radial force tests: a) uncoated, b) coated.**

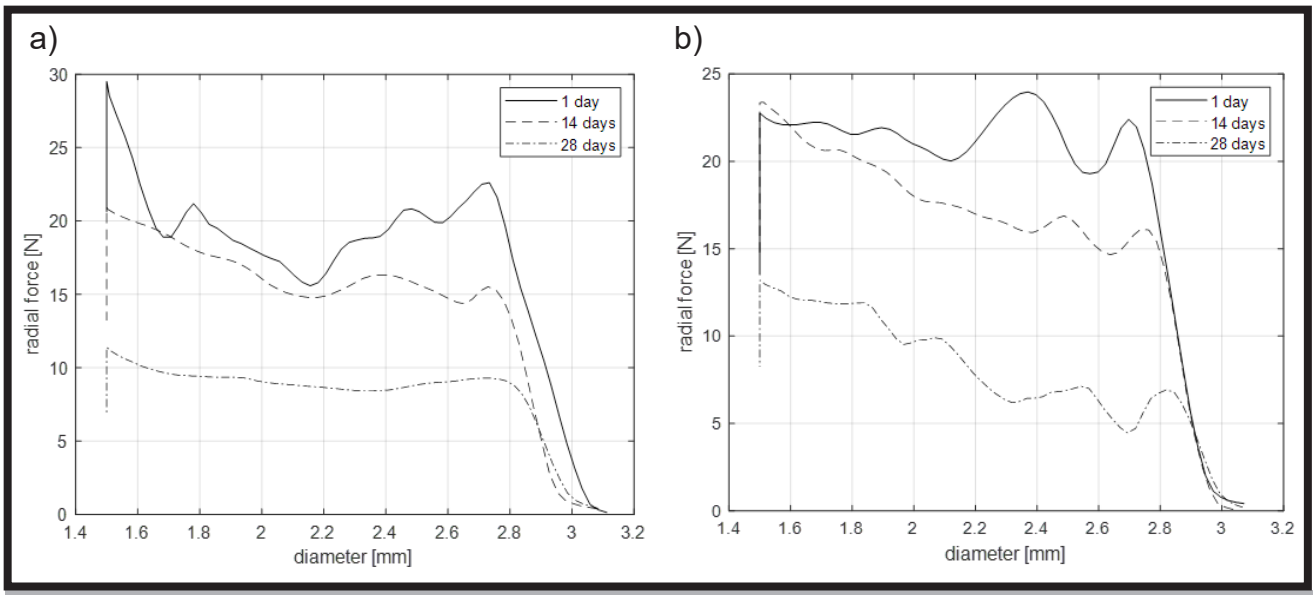


**FIG. 6. Example characteristics obtained during radial strength tests of stents after different exposure times to artificial plasma flow: a) uncoated stents, b) coated stents.**

Examples of radial force versus stent diameter curves from studies of the radial strength of the stents (without and with a polymer coating) and earlier exposure to a flow of artificial plasma are shown in FIG. 6. Curves showing the changes in radial force as a function of the stent diameter are characterized by a heterogeneous course. Along the curves, we can distinguish the elastic range, followed by plastic deformation of the material, ending with its breaking. With increasing exposure time to artificial plasma flow, a decrease in the radial force of the stents was observed. Moreover, it was observed that as the exposure time of the stents increased, the range of plastic deformations increased and the force at which the stent was destroyed decreased. For stents after 28 days of exposure, the smallest impact of changing the stent diameter on the value of its radial force was observed. A similar course of radial force curves as a function of stent diameter for different times of exposure to the flow of artificial plasma was observed for stents without and with a polymer coating.

Analysis of the test results of the radial force value at which damage occurred in stents exposed for a longer time to artificial plasma flow (14, 28 days) did not show significant differences between stents with and without a PLGA coating (TABLE 4). The higher value of the radial force was in the initial state (0) and after 1 day of exposure to plasma flow; uncoated stents (U) were compared to coated stents (C). Regardless of the type of the stent, it was observed that as the exposure time to plasma flow increased, the radial force at which the stent was damaged decreased.

**TABLE 4. Radial destructive force for the uncoated (U) and coated (C) stents, exposed for different times to the flow of artificial plasma.**

| Time of exposure [days] | Stent | Radial destructive force value [N] |
|---|---|---|
| 0 | U | 17.4 ± 4.6 |
| | C | 19.5 ± 4.9 |
| 1 | U | 20.9 ± 5.5 |
| | C | 19.1 ± 5.7 |
| 14 | U | 17.7 ± 5.3 |
| | C | 17.5 ± 5.2 |
| 28 | U | 8.6 ± 2.2 |
| | C | 8.3 ± 3.2 |

## Conclusions

To summarize:

- the surface of the PLGA spray-coated stent is heterogeneous and characterized by a greater surface development as compared to the stent without the coating;
- no effect of PLGA coating on the change in weight of the stent exposed to the flow of artificial plasma was observed, for both coated and uncoated stents, the observed temporal weight changes were similar and unambiguous;
- the PLGA coating does not affect the radial strength of the stent, both in the case of the stents with and without the coating, the decrease in the radial force with increasing exposure time to the flow of artificial plasma was noted;
- the weight of the stents after exposure to plasma flow increased by an average of 0.6 mg compared to the stents before exposure. The increase in the weight of the stent after exposure is due to the deposition components of artificial plasma in the form of crystals on the stent, as well as the swelling of the polymer;
- measurement of the mass of stents in their original and coated states after exposure to plasma flow did not show significant differences.

The analysis of the study results shows the suitability of the ultrasound method for the application of polymer coatings on biodegradable vascular stents. The produced PLGA coating does not change the mechanical properties of the stent in its initial state or after exposure to artificial plasma flow. This indicates the possibility of using such a coating as a matrix for locally released active substances.

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**ORCID iD**

A. Zegartowska: https://orcid.org/0009-0000-7552-8617
M. Stojko: https://orcid.org/0000-0001-8868-9495
K. Joszko: https://orcid.org/0000-0002-8229-3032
K. Goldsztajn: https://orcid.org/0000-0003-2545-9339
A. Orłowska: https://orcid.org/0000-0002-0168-7508
J. Szewczenko: https://orcid.org/0000-0001-9718-8617

## References

[1] https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1
[2] F. Otsuka, M. Nakano, F.D. Kolodgie, R. Virmani: Evaluation of Vulnerable Atherosclerotic Plaques. In: Coronary Artery Disease; Eds. T.J. Willerson, J.R.D. Holmes; Springer, London 2015.
[3] B.J. Bachar, B. Manna: Coronary Artery Bypass Graft, National Library of Medicine, In: StatPearls. Treasure Island (FL): StatPearls Publishing 2023.
[4] A. Guildford, M. Santin, G.J. Phillips: Cardiovascular stents. In: Biomaterials and Devices for the Circulatory System, University of Brighton, Woodhead Publishing Series in Biomaterials (2010) 173-216.
[5] J. Marciniak: Stenty w chirurgii małoinwazyjnej, wyd. Politechniki Śląskiej, Gliwice 2006
[6] M. Latos, A. Masek: Biodegradowalne poliestry. Instytut Technologii Polimerów i Barwników, Łódź 2017
[7] I. Vroman, L. Tighzert: Biodegradable Polymers. Materials 2(2) (2009) 307-344.
[8] H. Ding, Y. Zhang, Y. Liu, C. Shi, Z. Nie, H. Liu, Y. Gu: Analysis of Vascular Mechanical Characteristics after Coronary Degradable Stent Implantation. BioMed Research Interational (2019) 8265374.
[9] R.C. Eberhart, S.-H. Su, K.T. Nguyen, M. Zilberman, L. Tang, K.D. Nelson, P. Frenkel: Bioresorbable polymeric stents: current status and future promise. Journal of Biomaterials Science, Polymer Edition 14(4) (2003) 299-312.
[10] A. Foerster, M. Duda, H. Kraśkiewicz, M. Wawrzyńska, H. Podbielska, M. Kopaczyńska: Physico-chemical stent surface modifications. In: Functionalised Cardiovascular Stents, Eds. J.G. Wall, H. Podbielska, M. Wawrzyńska, Woodhead Publishing (2018) 137-148.
[11] M.A. Sayed Patwary, S.M. Surid, M.A. Gafur: Properties and Applications of Biodegradable Polymers. Journal of Research Updates in Polymer Science 9 (2020) 32-41.
[12] E. Vassallo, M. Pedroni, M. Aloisio, S.M. Pietralunga, R. Donnini, F. Saitta, D. Fessas: Plasma Treatment of Different Biodegradable Polymers: A Method to Enhanc Wettability and Adhesion Properties for Use in Industrial Packaging. Plasma 7(1) (2024) 91-105.