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MAIN TEXT

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Biofunctionalization of surfaces to minimize undesirable effects in cardiovascular assistance devices

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Abstract

Background: The reactivity of blood with non-endothelial surface is a challenge for long-term Ventricular Assist Devices development, usually made with pure titanium, which despite of being inert, low density and high mechanical resistance it does not avoid the thrombogenic responses. Here we tested a modification on the titanium surface with Laser Induced Periodic Surface Structures followed by Diamond Like Carbon (DLC) coating in different thicknesses to customize the wettability profile by changing the surface energy of the titanium.

Methods: Four different surfaces were proposed: (1) Pure Titanium as Reference Material (RM), (2) Textured as Test Sample (TS), (3) Textured with DLC 0.3μm as (TSA) and (4) Textured with 2.4μm DLC as (TSB). A single implant was positioned in the abdominal aorta of Wistar rats and the effects of hemodynamic interaction were evaluated without anticoagulant drugs.

Results: After twelve weeks, the implants were extracted and subjected to qualitative analysis by Scanning Electron Microscopy under low vacuum and X-ray Energy Dispersion. The regions that remained in contact with the wall of the aorta showed encapsulation of the endothelial tissue. TSB implants, although superhydrophilic, have proven that the DLC coating inhibits the adhesion of biological material, prevents abrasive wear and delamination, as observed in the TS and TSA implants. Pseudo- neointimal layers were heterogeneously identified in higher concentration on Test Surfaces.

KEYWORDS
DLC coating, hemocompatibility, pseudo-neointimal and in vivo evaluation, ventricular assist devices, wettability

1 | INTRODUCTION

Heart Failure (HF) is a cardiovascular disease characterized by dysfunction of the heart muscle; the heart loses its pumping function and compromises adequate blood circulation in organs and tissues, not providing the necessary supply of oxygen and nutrients. In this case, the possible treatments are heart transplantation and mechanical circulatory assistance, when a blood pump is implanted as a ventricular assistance device (VAD).[1,2]

Hemolysis and thrombogenic response are the two main challenges in the development of a fully implantable VAD, and the influencing factors are directly related to the interaction phenomena that occur during the performance of its function.[3,4]

Medical grade II titanium is the biomaterial established in the manufacture of implants dedicated to blood because it is considered inert, low density, and high mechanical resistance; its thin layer of dioxide on the surface ensures high chemical stability and durability in severe applications, but does not impede the thrombogenic response.[4,5]

What makes clinical application possible is the mandatory introduction of sodium heparin as an anticoagulant while the device acts in parallel with the natural heart. This drug inhibits the thrombogenic response, but when used for a long period and in high concentrations, it triggers hemorrhages, renal and neurological dysfunctions.[6,7]

Since 1980, researchers and manufacturers VAD have incentive the development of new biomaterials and surface treatments for circulatory assistance applications; no doubt the surface modification processes can minimize thrombogenic effects on the blood, increasing the durability of an implant and the patient's life expectancy.[4,6–8]

The literature contains several terms that describe the hematological response to sintered titanium, such as pseudoneointima, neointimal tissue, and pannus of endothelial origin, but are not precisely defined by histological verification. In general, investigators have reported the presence of these structures as a combination of endothelial cells, fibroblasts or myofibroblasts, platelets, red blood cells, macrophages, and extracellular matrix.[9]

Since then, different modification processes have been tested, such as HeartMate® I with extruded polyurethane (PU), HeartMate II and III with sintered microspheres, Evaheart® with methacryloyphosphorylcholine (MPC) polymer, Carmeda® with heparin coating, and VentrAssist® with diamond-like carbon (DLC) coating.[8,10–14]

The properties of the DLC coating provide high mechanical resistance, high hardness, low coefficient of friction, chemical inertia, electrical insulating characteristic, and biocompatible substrate surface, among other characteristics capable of improving results of interaction with blood.[5]

The incorporation of silver nanoparticles, for example, makes DLC bactericidal and ideal for a hospital surgical environment.[15] High wear resistance, its self-lubricating, and biocompatible principle maximize the useful life and performance of orthopedic prostheses. In cardiovascular stents, DLC can inhibit encapsulation by endothelial tissue and possible reobstruction of the artery, as observed in in vivo evaluations with the Stent Valve project.[16]

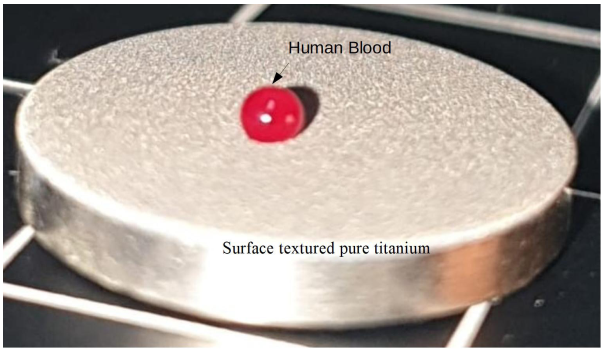

FIGURE 1 Super-plasmophobic effect attributed to textured pure titanium. [Color figure can be viewed at wileyonlinelibrary.com]

However, clinical studies published over the decades on the VAD with these last surfaces indicate variable and unpredictable interaction results[9]; the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report clarified the relationship between material properties and the biofunctional durability of VADs and stated that interfaces that do not interact with blood have better survival rates on Kaplan–Meier curves.[17]

From the polished increase, it was always possible to "prevent" the deposition of biological material on the surface and maintain hemostasis with the use of anticoagulants.[2,9] Immobilization with heparin demonstrated effectiveness for this purpose, but without sufficient durability for destination applications, only in the operative and acute postoperative periods.[18]

The production of laser-imposed periodic surface structures (LIPSS) along the pure titanium surface, followed by DLC coating in different thicknesses was able to customize the wettability profile by changing the surface energy. Figure 1 shows the super-plasmaphobic effect obtained, indicated to biofunctionalize surface of dynamic components of VAD and minimize the spontaneous effect responses with blood. For components that perform a static function, the formation of a well-adhered and thromboresistant neointimal layer is preferable.[2,4,8]

Both hypotheses are considered promising to improve the hemodynamic compatibility of a VAD under development at Dante Pazzanese Institute of Cardiology (IDPC). The surface modification able to minimize blood clotting, both by the absence of contact and through thromboresistant neointimal lining, was evaluated in vivo without the addition of anticoagulant drugs for a minimum and sufficient period to demonstrate the results of interaction hemodynamics.[19]

2 | MATERIALS AND METHODS

This experimental study followed the protocol "In vivo evaluation of hemodynamic interaction biofunctional surfaces to minimize undesirable effects in cardiovascular applications" n° 3 658 240 622 approved by the Animal Ethics Committee of the University of Sao Paulo (CEUA/USP) and ISO 10993: Evaluation Biology in Medical Devices, which determines a minimum period of in vivo experimentation of 20 weeks for the purpose of studying the biological interaction with surfaces of solid materials.

Adult Rattus norvegicus (Wistar lineage) weighing more than 300 grams were used as a living organism model; the metabolism of this species is accelerated compared with that of the human organism, each week represents three of ours, and therefore, 12 weeks of evaluation were enough to meet the specification of ISO 10993. Four groups of three animals each were considered:

- **Group 1**: Reference Material—medical grade II titanium;
- **Group 2**: Test Surface—textured Reference Material;
- **Group 3**: Test Surface A—Test Surface with 0.3 μm DLC coating;
- **Group 4**: Test Surface B—Test Surface with 2.4 μm DLC coating.

Each animal received a single implant, which was positioned in the mid-abdominal intra-aortic region.

2.1 | The configuration of medical grade II titanium implants, 99% pure

2.1.1 | Geometric profile: Wire Ø0.4 mm by 4 cm long

Only 4 mm was considered a useful surface area, which remained intra-aortic in arterial blood flow; a catheter (INTRAMEDIC Polyethylene Tubing, Clay Adams, USA) covered the remainder to aid fixation on the outer wall of the aorta and prevent possible perforation of adjacent tissues. Table 1 displays the particular properties of each type of implant developed.

In TS B, the surface micrographic profile, together with the wettability, characterizes scaffold biofunction. The Reference Material and Test Surface micrographs are shown in Figure 2. Two different thicknesses of the DLC were chosen for Test Surface A and B, which have been presented in other publications. Also, for chemical composition, as shown in Table 1, it was used a 5 kV voltage for electron beam for SEM–EDX. However, even though it was higher voltage than necessary, the best way to distinguish them should be to use lower high voltage (2 or 3 kV).

2.2 | The surgical procedure for implant placement

The animals were for 12 h as a standard preoperative procedure; the drug acepromazine (2.5 mg/kg) was previously administered as a tranquilizer and after 30 min, they were anesthetized with ketamine 100 mg/kg and xylazine 20 mg/kg. Then, with confirmation of the absence of the reflex, each animal was positioned in the stereotactic apparatus in dorsal decubitus.

Under anesthesia with isoflurane (3% for induction and 2 to 3% for maintenance), each animal underwent the surgical procedure. An incision was made in the central region of the abdomen to expose the abdominal artery; implant positioning was performed by drilling through interruption of blood flow for introduction, fixation with a polyethylene surgical mesh, and Liquiband Surgical surgical glue.

A preventive dose of pentabiotic (30 000 UI/kg), a bactericidal antibiotic, was induced together with the anti-inflammatory/analgesic ketoprofen (2 mg/kg).

TABLE 1 Properties by implant surface profile.

Surface profile	Roughness (Ra)	Modified technique	Micrograph profile	Chemical composition	Wettability with blood
RM (Reference Material)	Up to 1 μm	Does not apply	Smooth and Homogeneous	Titanium oxide (TiO_2 99%)	Θ 70° Plasmaphilic
TS (Test Surface)	10 μm$^{\pm 0.5}$	Nanosecond laser texturing	Homogeneous and porous Ø50 μm with equal depth	63.5% titanium 36.55% Oxide	Θ 162.1° Super-plasmaphobic
TS A (Test Surface A)	10 μm$^{\pm 0.3}$	Nanosecond laser texturing and DLC coating by chemical vapor deposition (0.3 μm thick)	Homogeneous and porous Ø50 μm with equal depth	34.6% titanium 12.3% Oxide 53.1% carbon	Θ 158° Super-plasmaphobic
TS B (Test Surface B)	9 μm$^{\pm 0.3}$	Nanosecond laser texturing and DLC coating by chemical vapor deposition (2.4 μm thick)	Homogeneous and porous Ø50 μm with equal depth	9.4% titanium 5.85% oxide 84.77% carbon	Θ 60° Plasmaphilic

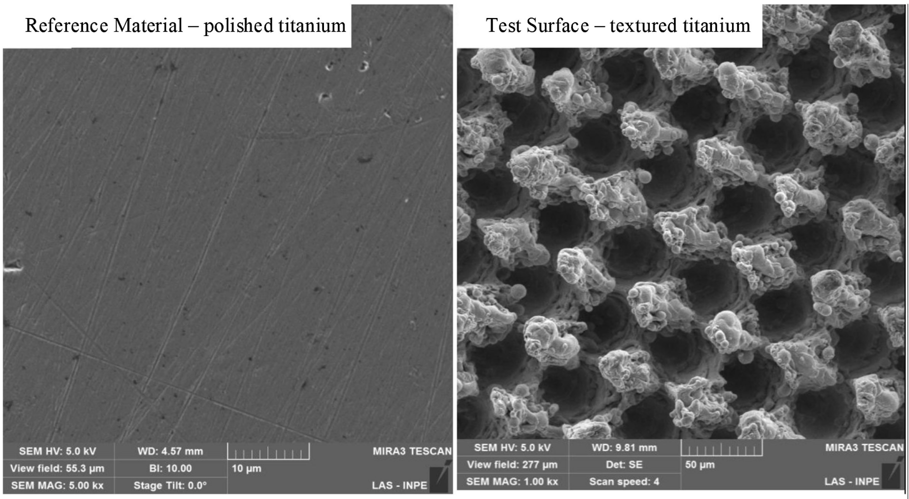

FIGURE 2 Micrographic profile of implants Reference Material and Tests Surfaces.

Twenty-four hours after the operation, the animals were relocated to the Experimentation Vivarium of the Department of Physiology in 41X35X17 boxes, separated by group. Maintenance conditions: artificial lighting and light: dark cycle of 12:12h with free access to feed and filtered water.

In the first postoperative week, the animals underwent routine analysis to detect signs of disease and infection (redness, swelling, and/or presence of pain) and also of suffering and pain (weight loss, vocalization, stooped posture, and piloerection).

Any eventual death within the proposed period as possible causes of pulmonary embolism and/or thrombosis would be investigated.

2.3 | The explant and analyze the data

At the end of the proposed period, a new incision was made in the central region of the abdominal aorta under anesthesia to secure the implants; any friction or mechanical action that would compromise the integrity of the site and the contact surface was avoided.

Immediately after ingestion, each implant was immediately immersed in saline solution (0.9% sodium chloride) to conserve possible biological material adhered to the surfaces and to eliminate specimens suspended from them; as the investigative analyses were carried out in sequence, there was no need to use a phosphate buffer saline + formaldehyde solution.

The scanning electron microscopy (SEM) Model JSM-6460LV (Proc. FAPESP n°00/08231–1) from the Institute of Physics of the University of Sao Paulo (IFUSP) was used to demonstrate the morphological result of the interaction on the surfaces; analysis was performed under low vacuum, 130 Pa, to preserve the intended biological structures and secondary and backscattered electron detectors to assist in differentiating the chemical composition.

3 | RESULTS AND DISCUSSIONS

The fabrication of the implants' wire of medical grade ϴ 0.4 mm was considered critical for the reduction dimension, but all surface modification steps were successfully achieved and the texturing by laser-induced periodic surface structures and DLCcoating were reproduced, as seen in Figure 3.

The surgical technique and other settings arranged in the in vivo evaluation protocol were successful, as it allowed the placement and fixation of the implants without hemorrhage and post-surgery animal well-being; the animals recovered promptly and gained weight over time. There was no record of invalids, infection, visitation, presence of thrombi, or any type of intercurrence. At the end of the proposed period, the explant was performed and the investigative analyses by SEM images revealed proper morphology analyses with signs of interaction in a qualitative way, in Figure 4.

The use of the backscattered electron detectors of the SEM better identified the contained regions of biological material due to the tonification contrast between the chemical elements; the lighter regions are composed of titanium oxide and the darker ones of carbon.

The micrographs obtained through the secondary detectors better evidenced the heterogeneous coatings at certain points on the surfaces, shown in Figure 5.

Table 2 concentrates the quantitative values of the chemical composition of titanium, oxide, carbon, and nitrogen obtained by EDX in each implant, before and after in vivo; as in vivo behavior demonstrates unique effects and differs from one organism to another, results from the same group varied somewhat; so individual, mean, and standard deviation values were generated and observed to elucidate the wires textures of each tested materials.

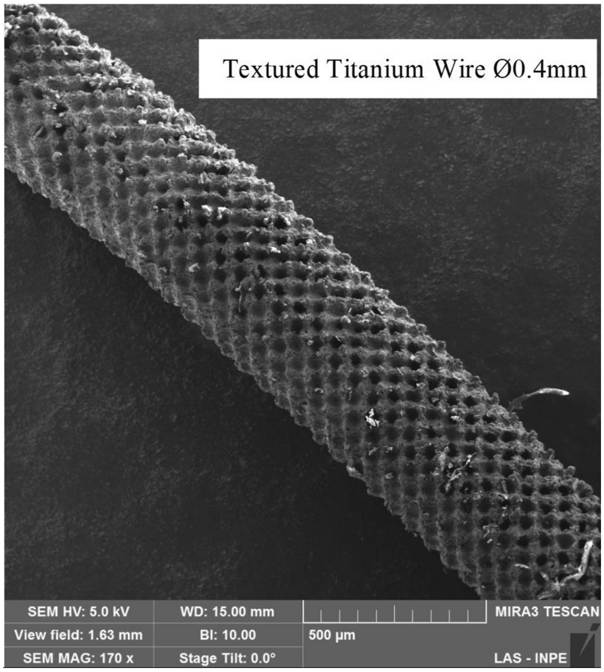

FIGURE 3 Scanning electron microscopy (SEM) image of the implanted surface: 0.4 mm textured titanium wire.

Based on the quantification performed on each group of implants, the interaction results, before and after the in vivo experimental period, were compared; for the Reference Material group, the substantial values remained stable, the implant of the first animal presented 10% less titanium concentration compared with that obtained with the other two animals, which reproduced a standard deviation next to 5.6.

The Test Sample and TS A implants also showed stability in the results with low standard deviation values; however, it was extrapolation the TS B implant, standard deviation of 12 for the carbon concentration. As follows, Table 3 compares the mean chemical quantification values of each group of implants and displays the related difference.

The SEM/EDX analyses allowed the detection of carbon/nitrogen contents on the samples submitted to in vivo evaluation. In Reference Material implants, there was a reduction in titanium greater than 60 at.% and an increase of carbon by approximately 50 at.% In Test Sample, carbon predominated by replacing the titanium oxide portion, a fact that also occurred in TS A, but half intensity. The values observed in TS B indicated low alteration of the chemical composition; however, the standard deviation values were relevant.

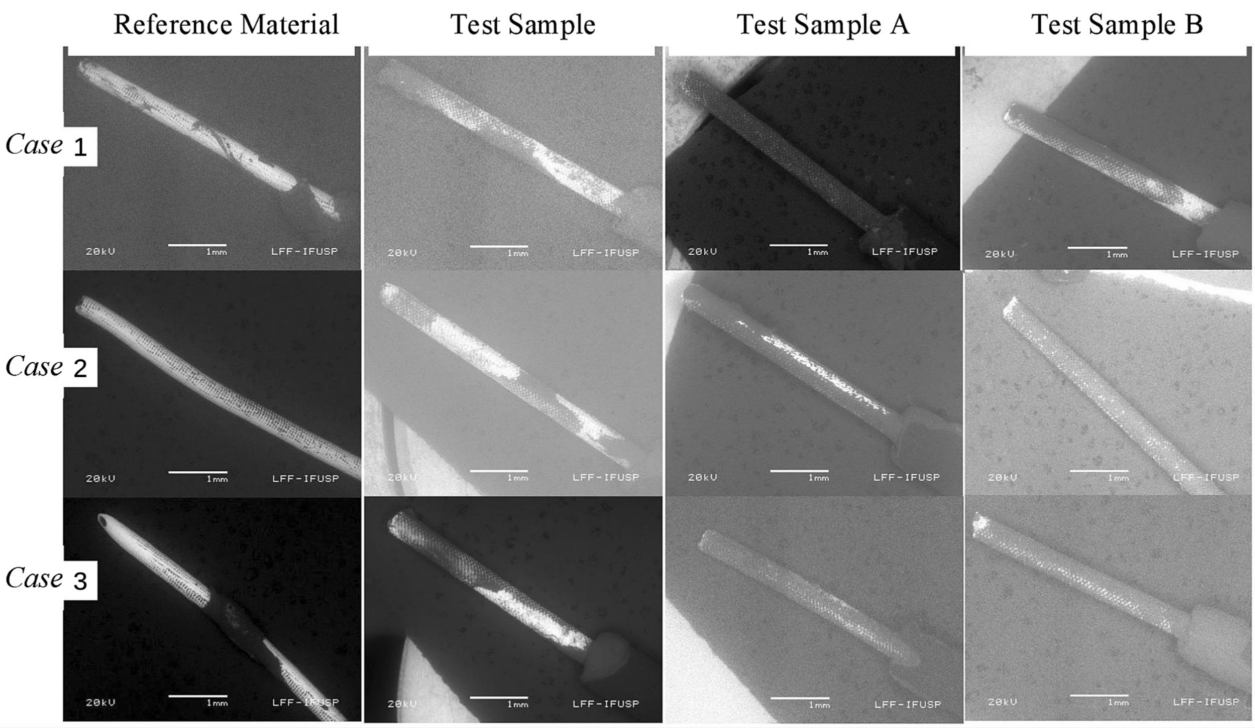

FIGURE 4 Implants after in vivo; groups in X-axis (horizontal) and number of case in Y-axis (vertical).

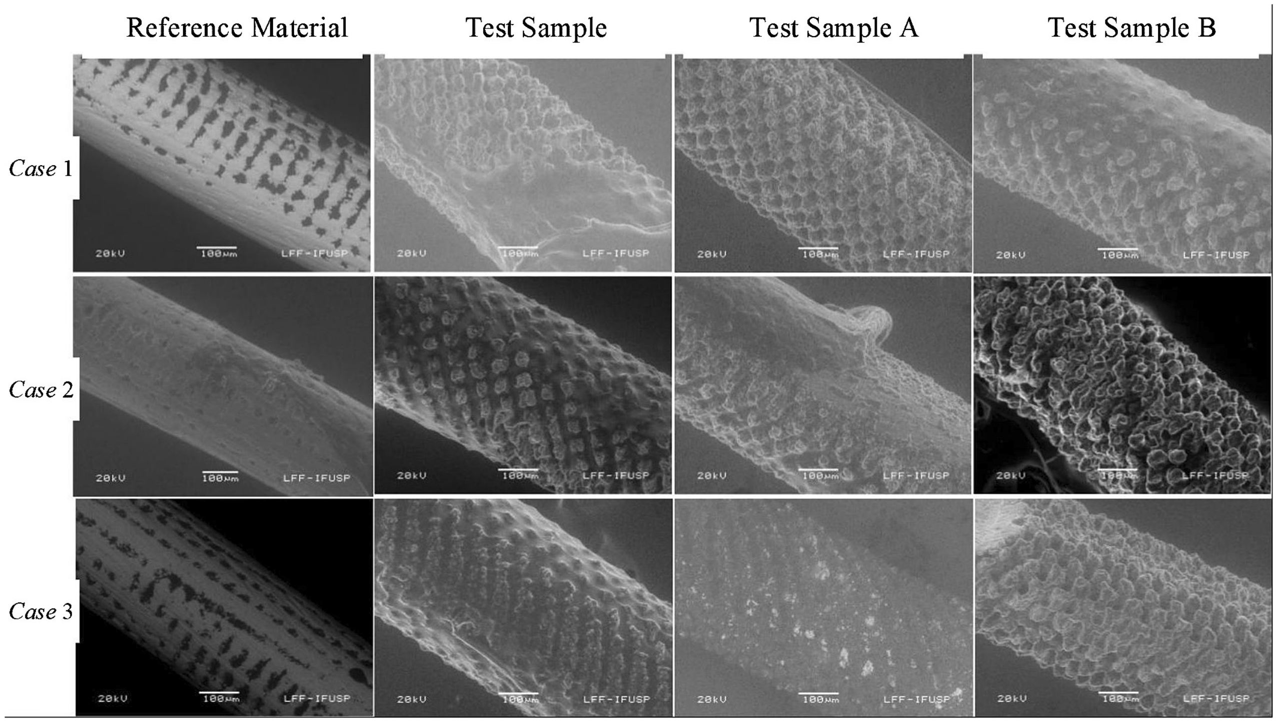

FIGURE 5 Scanning electron microscopy (SEM) images of the Implants after in vivo; groups in X-axis (horizontal) and number of case in Y-axis (vertical).

TABLE 2 Quantitative results of chemical composition, mean, and standard deviation of implants in vivo after.

%	Case 1	Case 2	Case 3	Mean	Standard deviation	In vivo before
Reference material						
Titanium	26.53	36.62	35.7	35.7	5.58	99.73
Oxide	7.59	5.21	4.78	5.21	1.51	0.14
Carbon	52.7	49.91	55.3	52.7	2.7	0
Nitrogen	10	7.35	2.9	6.39	3.59	0
Test surface						
Titanium	17.26	21.01	15.01	17.26	3.03	63.5
Oxide	10.2	10.36	10.1	10.02	0.84	36.55
Carbon	70.27	64.5	72.11	70.27	3.97	0
Nitrogen	2.27	4.13	2.76	2.76	0.96	0
Test surface A						
Titanium	7.65	9.76	8.07	8.07	1.12	34.61
Oxide	5.59	5.98	6.32	5.98	0.37	12.25
Carbon	84.96	79.95	82.05	82.05	2.52	53.14
Nitrogen	1.8	4.31	3.56	3.9	1.29	0
Test surface B						
Titanium	18.41	1.48	1.64	1.64	9.72	9.4
Oxide	10.19	3.8	3.92	3.92	3.65	5.85
Carbon	67.75	93.04	82.55	82.55	12.71	84.77
Nitrogen	3.65	1.68	11.89	3.65	5.42	0

To conclude, the biofunctionalization of surfaces dedicated to blood revealed that the hematological response does not always remain stable and can promote thrombus or pannus; thus, a deep understanding of the cell/blood/biomaterial interaction dynamics, platelet deposition, hemodynamics, and inflammatory mediators will be fundamental to guarantee consistent, reliable advances for integration of confluent and stable neointimal endothelial

TABLE 3 Comparative analysis of chemical quantification before and after in vivo.

%	In vivo before	In vivo after	Difference
Reference material			
Titanium	99.73	35.7	−64.03
Oxide	0.14	5.21	5.07
Carbon	0	52.7	52.7
Nitrogen	0	6.39	6.39
Test surface			
Titanium	63.5	17.26	−46.24
Oxide	36.55	10.02	−26.53
Carbon	0	70.27	70.27
Nitrogen	0	2.76	0
Test surface A			
Titanium	34.61	8.07	−26.54
Oxide	12.25	5.98	−6.27
Carbon	53.14	82.05	28.91
Nitrogen	0	3.9	3.9
Test surface B			
Titanium	9.4	1.64	−7.76
Oxide	5.85	3.92	−1.93
Carbon	84.77	82.55	−2.22
Nitrogen	0	3,65	3.65

lining capable of improving the hemocompatibility of implants dedicated to the blood and consequently the quality of life of patients. This study clarifies that the biofunctional surface composed of DLC inhibits the adhesion and proliferation of any biological material; this principle added to the super-plasmaphobic effect was able to preserve balanced blood conditions by attributing minimal contact interaction between the implant and blood constituents.

4 | CONCLUSIONS

The method developed to biofunctionalize surfaces dedicated to blood and constituents of VAD proved reproducibility even in pieces with reduced dimensions, such as 0.4 mm titanium wire implants.

The dimensional definition of the surface (micrometric) was essential to prevent the destruction of hematological cells by mechanical action in order to promote their anchoring and metabolic maintenance and enable the endothelialization process. On surfaces containing DLC, with low contact energy, it was not possible to observe deposition of biological material. With these results, the plasmaphobic surface attenuated the two undesirable effects, hemolysis, and platelet aggregation.

As the animals carrying the implants remained healthy and, based on the quantitative and qualitative results, it can be concluded that the biofunctional surfaces showed great potential to achieve the proposed goal.

The first group of Reference Material implants showed an increase of approximately 50% of carbon, which indicates the presence of biological material; however, the SEM images did not register anything of the kind in the region that remained in contact with the blood flow, only in the implant of the third animal that there was pannus formation in a slightly angled region and that probably must have remained in contact with the inner wall of the abdominal aorta.

In the second group of animals, with Test Surface implants, carbon predominated in 70% and the images revealed the presence of non-homogeneous and random coating in a large part of the surface area; this event was consistent with that described by Menconi, Zapanta, and team, high variation in the number of "white islands of irregular shape" with Ø0.1 to 3.0 cm in "random" location and unrelated to the flow field.

In Test Surface A implant, the carbon increase was approx. 30%, half of what happened in Test Surface; however, there was no visible coating, except in the explant of animal 2, in which shear and delamination wear marks were recorded, as well as the presence of neointimal lining in this region.

According to the results of chemical quantification, the Test Surface B implants were the ones that showed the least alterations before and after the in vivo evaluation, but with high values of standard deviation due to what was observed in the implant of the first animal; where the 50% increase in titanium oxide concentration and the SEM images indicated the effect of wear and delamination by flow, as well as the presence of pseudoneointima in these uncovered regions of DLC.

Based on the evidence, it can be stated that the DLC coating inhibits the adhesion and proliferation of biological material, also composed of carbon in greater concentration.

The neointima that developed on surfaces containing titanium oxide in a higher concentration was compatible with what was reported in related studies; a laminated, thin, and transparent microstructure composed of collagen and fibrin. A "microthrombus" is considered to be initial stage coating infiltrated on the surface of the Test Surface implant, composed of erythrocytes, macrophages, platelets, fibrin, and fibroblasts; thereafter, this "thrombus" was gradually replaced by fibrotic or thrombosis-resistant neointima. This mature fibrotic neointima has a minimal concentration of inflammatory cells and meets proposal to minimize responses received from interaction.[16]

In future and advanced studies, the durability of the surface characteristic attributed to the modification method and its wettability effects should be evaluated in a flow condition compatible with that of the arterial system, but in larger dimension, capable of providing a greater contact area with blood flow.

The amount of biological tissue detected in this study was too small to proceed with tissue analysis; therefore, this research will continue with the introduction of this technology to Biofunctionalize Surfaces of fully implantable Circulatory Assist Devices. So, the contact area between the implant and the blood flow must be larger to promote the formation of biological tissue and the activation of the endothelialization process, in the short period of these experiments, capable of safely guaranteeing statistical analysis.

It is very important to say that, the titanium surface will be potentially improved with DLC coating. The DLC coating with low friction coefficient and with very high adhesion on titanium will increase the wear resistance and also, the DLC as a very hard coating with very good adhesion will improve the mechanical proprieties of the titanium surface by increasing the crack threshold allowing liquid flow for long time. Finally, the texture process, in case of DLC coating, the wear resistance will be kept.

AUTHOR CONTRIBUTIONS

Rosa Correa Leoncio de Sa assumes primary responsibility for the proposal, content, methods, data and analysis of this study. Aron Jose Pazin de Andrade, Eduardo Guy Perpetuo Bock, Vladimir Jesus Trava-Airoldi and Vagner Roberto Antunes had significant contributions to the study design. Eduardo Guy Perpetuo Bock and Vladimir Jesus Trava-Airoldi had full access to the data and assumed responsibility for the definition and integrity of the data. Vagner Roberto Antunes provided substantial contributions to determine the sample number and statistical treatment in conducting the experimental study with animals. Joao Roberto Moro, Cecilia Salvadori, Fernanda de Sa Teixeira, and Evaldo Jose Corat contributed to the characterization and data interpretation analyses. Rosa Correa Leoncio de Sa wrote the article, and Aron Jose Pazin de Andrade, Eduardo Guy Perpetuo Bock and Vladimir Jesus Trava-Airoldi provided reviews of the article.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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