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PRECLINICAL EVALUATION OF TISSUE-ENGINEERED VASCULAR GRAFTS WITH BIODEGRADABLE COMPONENTS: ASSESSING THE EFFECTIVENESS OF ANIMAL MODELS FROM RATS TO PRIMATES

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Currently, there are no highly effective small-diameter (≤4 mm) grafts on the market for cardiovascular surgery. Tissue-engineered, functionally active vascular grafts with prolonged resorption and regeneration capacity have the potential to serve as alternatives to traditional arterial grafts. These bioengineered grafts could eliminate the need for repeated surgical interventions to replace failed grafts. The accuracy of assessing the risks of failure in biodegradable small-diameter vascular grafts (SDVGs) during preclinical trials is highly dependent on the choice of animal model. This article presents the results of comprehensive preclinical trials conducted on an SDVG developed at the Research Institute for Complex Issues of Cardiovascular Diseases. Based on these findings, the study evaluates the effectiveness and feasibility of different animal models for testing biodegradable SDVGs.

Keywords: tissue engineering, small-diameter vascular graft, preclinical trials.

INTRODUCTION

At present, the field of application of artificial substitutes for some parts of organs and systems of the human body has a trend towards serious growth with the medical devices market expanding annually. However, the use of synthetic materials is associated with various complications, which the global scientific and medical community continues to address through ongoing research and innovation [1].

Despite the extensive availability of products for cardiovascular surgery, effective small-diameter (≤4 mm) vascular grafts (SDVGs) have yet to be developed [2]. Meanwhile, the annual demand for SDVGs in the Russian Federation alone is estimated at approximately 80,000, driven by the high number of surgical interventions on small-caliber arteries [3].

Tissue-engineered, functionally active vascular grafts (VGs) with prolonged resorption and regenerative potential offer a promising alternative to synthetic vascular prostheses. These grafts could eliminate the need for repeated surgeries to replace failed vascular implants. The integration of tissue engineering into the development of medical devices is increasingly relevant, as its approaches are designed to closely mimic the biocompatibility of native tissues, enhancing their long-term clinical success [4, 5].

There are two widely adopted approaches to fabricating tissue-engineered VGs [6]. The first involves creating a cell-populated prosthesis *in vitro* under simulated blood flow conditions, ideally using the patient's own cells and proteins [7–9]. The second approach focuses on *in vivo* vascular graft development, utilizing a functionally active, highly porous scaffold that guides the recruitment and differentiation of vascular cells toward the formation of fully functional vascular tissue [10–12]. Ideally, this scaffold should be completely resorbed over time [13, 14].

Various bioactive components are incorporated into VGs to enhance their functionality and promote full remodeling, with proteins exhibiting high proangiogenic activity being particularly favored [1, 15]. Understanding the synergy of interactions between these bioactive components is crucial to the success of the prosthesis.

SDVGs are classified as high-risk medical devices, falling into the third class (Class III) [16]. Consequently, they must meet the highest standards of biocompatibility and long-term effectiveness. Once *in vitro* testing demonstrates that the product meets the necessary safety and biocompatibility requirements, the next step involves preclinical testing using animal models. These preclinical trials are essential, as they provide insights into the prosthesis's performance in the complex environment of a living organism. The reliability of preclinical re-

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sults in predicting the success of a prosthesis is heavily influenced by the choice of the animal model used in these tests.

A biodegradable SDVG with a prolonged resorption period was developed at the Research Institute for Complex Issues of Cardiovascular Diseases. The prosthesis incorporates proangiogenic factors – VEGF, bFGF, and SDF-1α – layer by layer into its wall during the electrospinning process. VEGF plays a key role in vascularization by activating and supporting endothelial cell migration, proliferation, survival, and differentiation. It also enhances nitric oxide production and increases vascular permeability [17]. Basic fibroblast growth factor (bFGF) promotes endothelial and smooth muscle cell migration, proliferation, and survival, ultimately contributing to the maturation of blood vessels [18]. SDF-1α acts as a chemoattractant for endothelial cells, stimulates the formation of long and branched capillary networks, and enhances the migration of bone marrow-derived mesenchymal stem cells, which can differentiate into smooth muscle cells within the vascular wall [19, 20].

After extensive *in vitro* testing and confirmation of the' biocompatibility, functional efficacy, and acceptable physical, mechanical, and structural properties of the prostheses, we proceeded to the stage of preclinical trials on laboratory animals. Preclinical testing is crucial, as it allows for the assessment of biocompatibility and effectiveness of the developed prosthesis within a living organism.

However, highly contradictory results were observed across different animal models. This inconsistency highlighted the need to reassess not only the fabrication technology of the prosthesis but also the choice of the most appropriate animal model for final preclinical evaluations.

EFFECTIVENESS OF THE RAT MODEL IN PRECLINICAL TESTING OF SMALL-DIAMETER VASCULAR GRAFTS

The rat model is one of the most widely used and accessible options for preclinical testing of SDVGs. Implantation is typically performed in the abdominal aorta, particularly for prostheses with a diameter of 2 mm or less, making it the standard approach for evaluating SDVGs [21–23].

In our study, VGs composed of polycaprolactone and polyhydroxybutyrate/valerate, incorporating proangiogenic factors, were implanted into the abdominal aorta of rats for 12 months. The prostheses had a diameter ranging from 1.5 to 2 mm. Remarkably, the patency rate after 12 months was nearly 100%, even in the absence of postoperative antiplatelet therapy (Fig. 1) [24–26].

Cell population within the porous walls of the biodegradable prosthesis after implantation into the vascular system occurred naturally through implant remodeling, ultimately forming a three-layered vascular tissue structure resembling that of a native vessel wall [25, 26]. However, in the control group (grafts without proangiogenic factors), moderate chronic granulomatous inflammation was observed in some cases.

A well-documented characteristic of rats is their rapid endothelialization, along with the technical limitation of

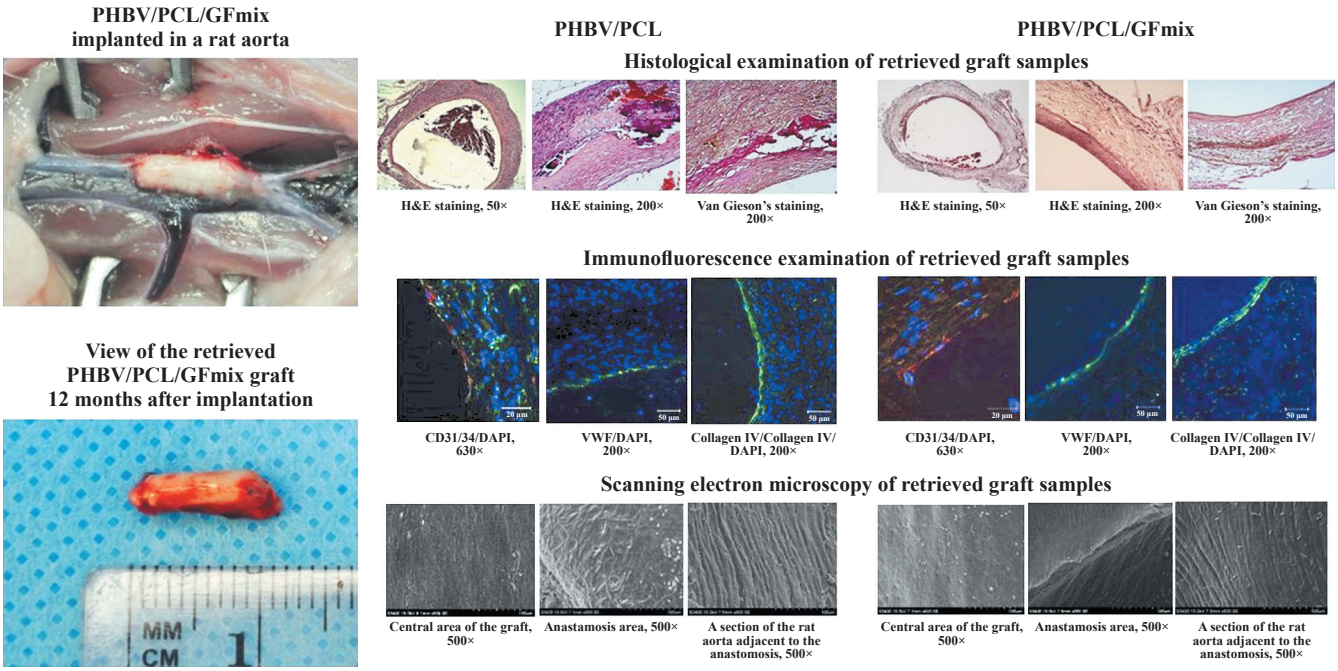

Fig. 1. Results of morphological study of PHBV|PCL vascular grafts with and without a proangiogenic factor complex (GFmix) implanted in rat aorta for 12 months [26]

implanting prostheses longer than 1 cm. This combination often results in a favorable long-term outcome regardless of the prosthesis material used [27]. Consequently, preclinical testing in a rat model has limitations – it does not fully reveal all potential risks of prosthesis failure nor reliably predict the efficacy of the device in human applications.

That said, the rat model remains a valuable tool for assessing the risk of vascular graft calcification (Fig. 2) [24].

The extent of calcification observed in VGs serves as an indirect indicator of their functional integrity. Comparative analysis of calcification in our developed grafts provided indirect evidence that incorporating a complex of proangiogenic factors helped synchronize tissue formation, prevent cell apoptosis, and significantly reduce prosthesis wall calcification. This reduction in calcification contributes to the long-term effectiveness of prostheses, provided their patency is maintained (Fig. 2).

It was also revealed that the presence and controlled release of proangiogenic factors in biodegradable VGs were found to lower the incidence of both granulomatous inflammation and prosthesis calcification [24]. In the rat model, it was discovered that in the absence of blood flow, such as in thrombosed biodegradable prostheses, no wall calcification occurred. This finding suggests that blood, as a biologically aggressive medium, and pulsatile flow play a crucial role in triggering calcification mechanisms in patent VGs [24].

These promising results encouraged further preclinical testing of the VGs on large laboratory animal models.

EFFECTIVENESS OF THE SHEEP MODEL IN PRECLINICAL TESTING OF SMALL-DIAMETER VASCULAR GRAFTS

The sheep model was chosen as a large laboratory animal model for testing biodegradable SDVGs. Sheep are widely recognized as an optimal model for assessing vascular graft growth, patency, endothelialization, thromboresistance, and postimplantation imaging. One key advantage of using sheep is that they reach their maximum size relatively quickly and do not continue to grow, making them particularly suitable for long-term graft implantation. The anatomical structure of sheep provides practical benefits for surgical procedures. Their long neck and easily accessible carotid artery facilitate the implantation of longer prostheses. Furthermore, sheep are known for their increased tendency toward thrombosis and vascular calcification, making them an ideal choice for worst-case modeling [28–30]. These characteristics enable the most rigorous *in vivo* testing of VGs for assessment of their potential degeneration.

The results obtained from the two animal models (rats and sheep) were so divergent and unexpected that it became necessary to significantly modify the prosthesis manufacturing technology. In addition, a thorough investigation of the hemostasiology profile of sheep was required, comparing it with that of patients with cardiovascular pathology to optimize pre-, intra-, and postoperative anticoagulant and antiplatelet therapy.

In pilot studies using sheep, a high incidence of early postoperative thrombosis was observed in 4-mm-diameter PHBV/PCL/GFmix biodegradable VGs implanted in the carotid artery. The primary cause of thrombosis was linked to the porosity of the inner prosthesis surface, which was confirmed through ultrasound and angiographic assessments of prosthesis patency immediately after blood flow initiation. These imaging studies clearly captured the moment of thrombus formation, characterized by rapid imbibition of the prosthesis walls with blood components, thickening of the walls, and subsequent rapid narrowing of the prosthesis lumen along its entire length (Fig. 3).

This finding necessitated enhancing the thromboresistance of the prostheses, which was achieved by developing a hydrogel-based antithrombotic drug coating for PHBV/PCL/GFmix prostheses. This coating effectively protected the graft surface from thrombosis for up to 20 days post-implantation [31].

Additionally, investigations were conducted to determine the specific aspects of sheep hemostasis that contributed to their pronounced thrombogenic response [32]. It was discovered that sheep platelets exhibited an increased response to adenosine diphosphate (ADP) induction but showed minimal reactivity to adrenaline.

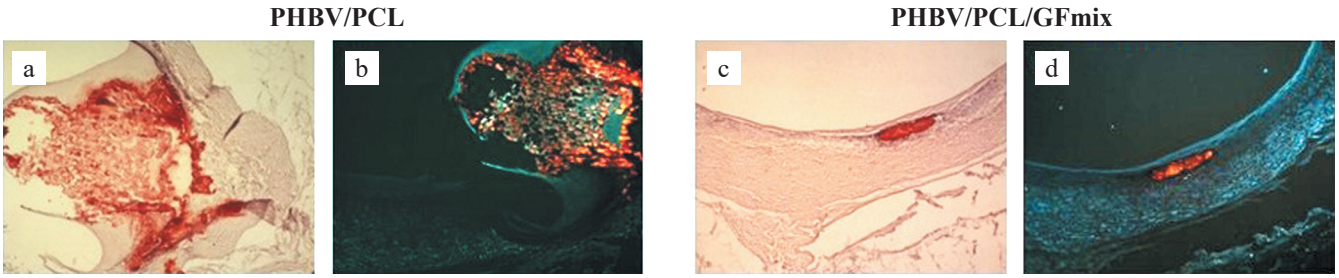

Fig. 2. Light (a) and fluorescence (b) microscopy of slices of PHBV/PCL and PHBV/PCL/GFmix vascular grafts retrieved: staining with alizarin red S (bright red color of Ca crystals) and Dapi (blue color of cell nuclei), 100×

The coagulation system of sheep was characterized by increased activity of prothrombin complex and a shortened thrombin time, while activated partial thromboplastin time (aPTT) and fibrinogen levels were comparable. Meanwhile, sheep exhibited a significant reduction in the activity of both the antiserum and fibrinolytic systems compared to coronary heart disease (CHD) patients. Evaluation of clot formation dynamics in animals revealed a faster initiation phase and higher clot density compared to patients [32]. Based on these findings, we adjusted the pre-, intra-, and postoperative antiplatelet and anticoagulant therapy as follows: preoperative phase – a single loading dose of clopidogrel administered the day before surgery; intraoperative phase – шntravenous administration of unfractionated heparin before carotid artery clamping and anastomosis, followed by an additional dose after blood flow restoration; postoperative phase (for 30 days post-implantation, provided the prostheses remained patent) – subcutaneous administration of low-molecular-weight heparin, following the manufacturer's dosage guidelines, oral administration of clopidogrel at a standard dosage, in accordance with the manufacturer's instructions. Nevertheless, the addition of an atrombogenic drug coating to the prostheses, combined with the adjusted anticoagulant therapy, improved vascular graft patency rates from 0% to 50% after 18 months of implantation in the carotid arteries of sheep [33]. However, this patency rate remains unconvincing for clinicians. A 50% thrombosis rate limits the potential clinical applicability of these prostheses, despite the fact that vascular surgery itself in sheep has been shown to induce thrombosis, as evidenced by previous studies on autoarterial implantation of the sheep carotid artery [34].

Given the high thrombotic tendency observed in sheep, it became crucial to investigate the patency outcomes of widely used synthetic VGs implanted in sheep carotid arteries.

To investigate this further, six animals underwent implantation of synthetic Gore-Tex® VGs (4 mm in diameter) into their carotid arteries – prostheses that are widely and successfully used in clinical practice. However, all Gore-Tex® grafts thrombosed within 24 hours of implantation. Despite the immediate loss of patency, it was decided to retrieve the thrombosed prostheses after 6 months to assess the response of surrounding tissues and potential calcific formation.

It was revealed that after 6 months, the walls of the thrombosed Gore-Tex® grafts exhibited massive calcification, despite the absence of blood flow. This calcification is presumed to result from insufficient biocompatibility of the material, which may have triggered a pathological reaction in the surrounding tissues. The

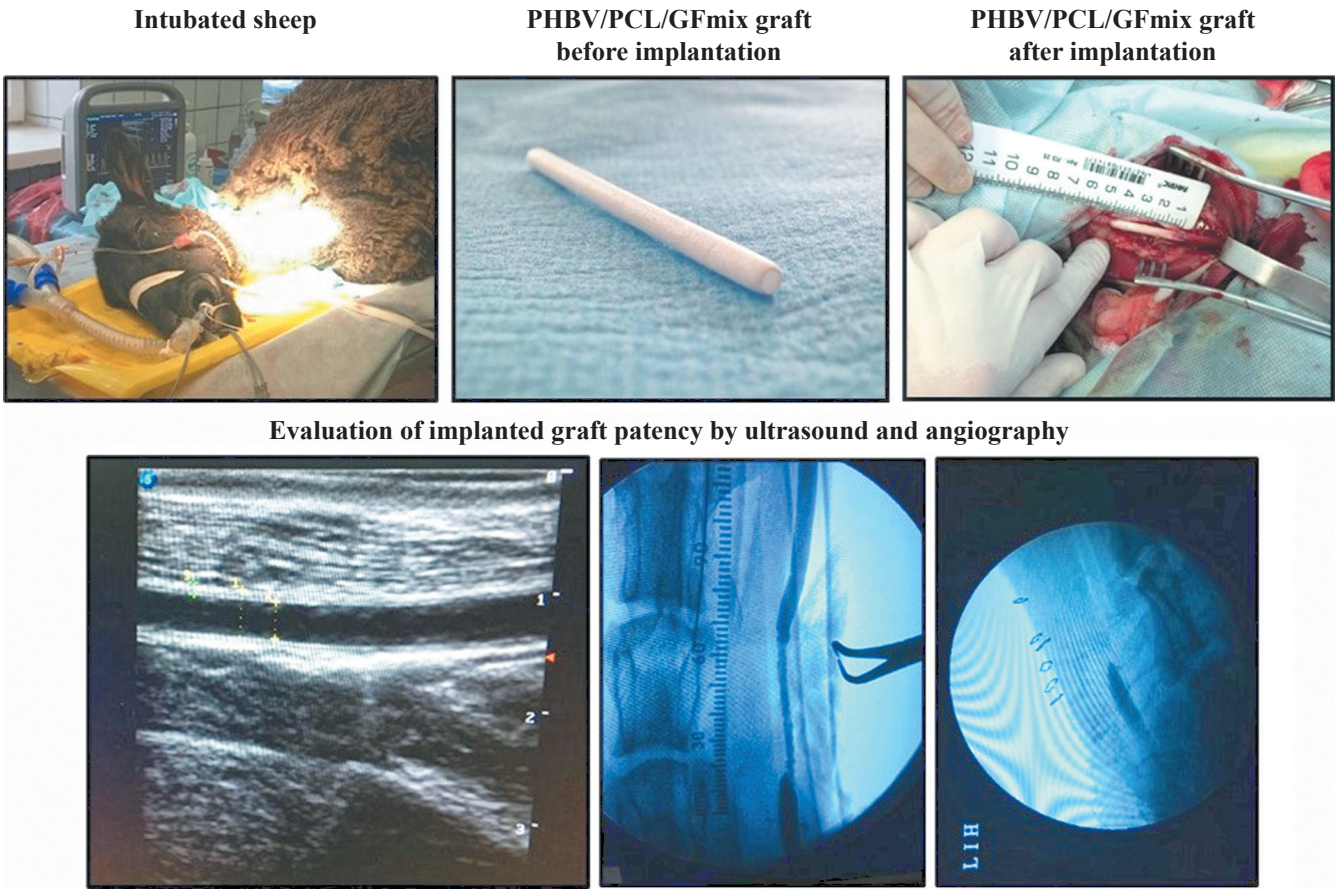

Fig. 3. Pilot preclinical trials of PHBV/PCL/GFmix vascular grafts in a sheep model

response likely involved apoptosis and the death of monocytic-macrophage and fibroblastic cells capable of penetrating the prosthesis wall from the adventitia side during the remodeling process [33, 35]. Despite the known aggressiveness of the sheep model regarding calcification, the drug-coated PHBV/PCL/GFmix grafts we developed exhibited minimal calcification. Only one retrieved patent graft showed small calcium deposits 1.5 years post-implantation, with a composition consistent with mature calcifications found in biological tissues [33, 35].

The second unexpected finding was the extremely rapid resorption of the polymeric scaffold, leading to aneurysm formation in all patent grafts. The onset of aneurysm development was observed as early as 1.5 months post-implantation, reaching its peak at 6 months, when the diameter of the VGs expanded from 4.0 mm to 2.2 cm. This dilation remained unchanged for the remainder of the 18-month implantation period [33, 35].

Morphological analysis of the retrieved prosthesis samples confirmed complete endothelialization of the inner surface, formation of new vascular tissue (neointima and adventitia) replacing the resorbed tubular scaffold, and minimal wall calcification. However, a critical limitation was identified – the absence of elastic fibers and true smooth muscle cells within the remodeled prosthesis walls (Fig. 4) [33, 35].

It should be noted that major publications on the testing of biodegradable SDVGs in sheep models have emerged since 2020. These studies have also reported early aneurysm formation in the walls of prostheses made from biodegradable polymers such as polycaprolactone, polylactide, and thermoplastic polyurethane [36, 37].

However, some authors have presented very impressive results, demonstrating the successful implantation of 4-mm biodegradable vascular grafts reinforced with a nitinol microframework into the coronary arteries of sheep. The incorporation of this microframework effectively prevented aneurysm formation [38].

Thus, the sheep model revealed an additional risk of prosthesis failure – early aneurysm formation – caused by accelerated resorption of biodegradable prosthetic frameworks. This resorption rate was significantly higher than that observed in the rat model. Moreover, the absence of elastin and true smooth muscle cells, combined with the rapid degradation of the polymeric framework, underscored the urgent need to modify the vascular graft fabrication process to incorporate aneurysmal protection.

To address this challenge, we explored three distinct approaches to prevent aneurysmal expansion of biodegradable vascular prosthesis walls:

1. Reinforcement of the outer contour of the prosthesis with extruded polymer spiral.
2. Creation of a reinforcing layer of polymer – synthetic elastomer with a low rate of bioresorption – on the outer surface of the prosthesis by electrospinning.
3. Introduction of synthetic elastomer with low biosorption rate into the tubular biodegradable framework

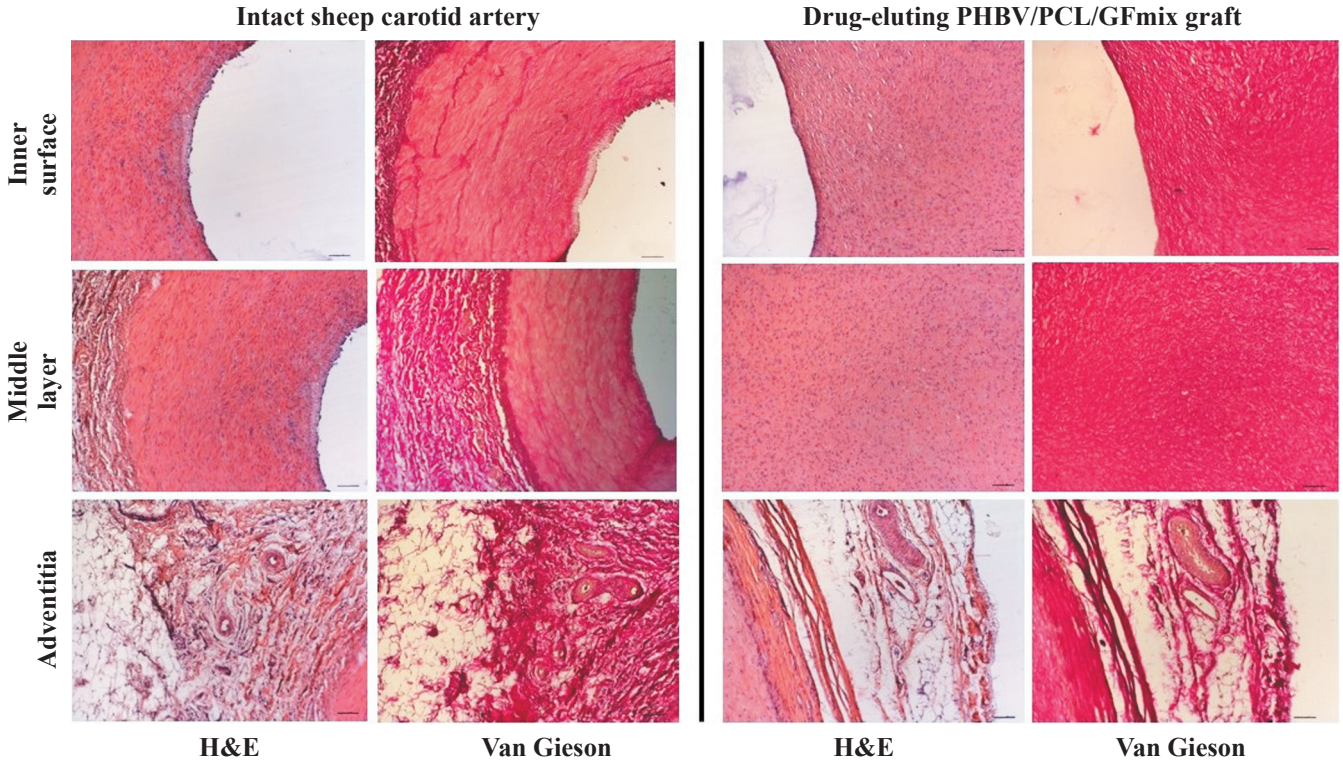

Fig. 4. Comparative histological picture of sheep carotid artery and drug-eluting PHBV/PCL/GFmix vascular graft at 18 months of implantation into a sheep carotid artery. Scale bar 100 μm

in the process of vascular prosthesis fabrication by electrospinning.

The first approach led to excessive weight gain and impaired surgical handling, making anastomosis more challenging. The second approach failed to establish a strong bond between the biodegradable prosthesis framework and the synthetic polymer outer layer, resulting in prosthesis delamination both before and during implantation, which triggered thrombosis. Therefore, the third approach – integrating a synthetic elastomer into the main polymer framework during electrospinning – proved to be the most effective. This method produced a cohesive, structurally stable prosthesis while preserving functional activity through controlled release of incorporated proangiogenic factors, and complete remodeling potential via the porous structure and partial biodegradation of the polymeric framework.

EFFECTIVENESS OF A PRIMATE MODEL IN PRECLINICAL TRIALS OF SMALL-DIAMETER VASCULAR GRAFTS

A primate model was selected for the final preclinical trials, as it closely resembles humans and provides the most reliable assessment of potential risks associated with biodegradable vascular grafts. Baboons were chosen as the largest primates available for experimental use from Russian research nurseries.

The similarities between baboons and humans in terms of metabolism, diet, body structure, and blood coagulation function were expected to minimize the species-specific limitations encountered in the sheep model. A thorough review of literature on vascular anatomy and structure of baboons was conducted [39, 40].

As a result, the femoral artery was identified as the optimal implantation site for <4 mm grafts. This selection minimized the risk of global limb ischemia in the event of graft thrombosis.

It is important to note that in adult male baboons aged 9 to 17 years and weighing 18 to 38 kg, femoral artery diameters do not exceed 3.2 mm. To ensure optimal graft performance, baboons were preselected, and ultrasound measurements were conducted to determine the diameter of each femoral artery.

To minimize the risk of thrombosis due to graft/artery diameter mismatch, custom-fabricated VGs were designed for each baboon, ensuring an exact fit with the native artery during implantation.

VGs with diameters of 3.0–3.5 mm and lengths of 3.0–4.5 cm were implanted into the femoral arteries of 6 adult male baboons for a period of 6 months (Fig. 5). The pre-, intra-, and postoperative antiplatelet therapy regimen mirrored that used in the sheep model.

No delamination of the prosthetic walls was observed during implantation or after 6 months. Ultrasound assessments confirmed a final prosthesis patency rate of 83.3%. Early thrombosis occurred in one case, attributed to concomitant pathology (excessive body weight twice the age norm, respiratory insufficiency, and arrhythmia).

Histological and immunofluorescence analyses of retrieved graft samples demonstrated complete endothelization of the internal surface, a neointima without signs of hyperplasia, and a neoadventitia containing all typical structural elements. Additionally, cell migration into the prosthesis walls was observed (Fig. 6). There were no signs of inflammation or calcification.

A significant advantage was the interchangeability of staining with human fluorescent antibodies for im-

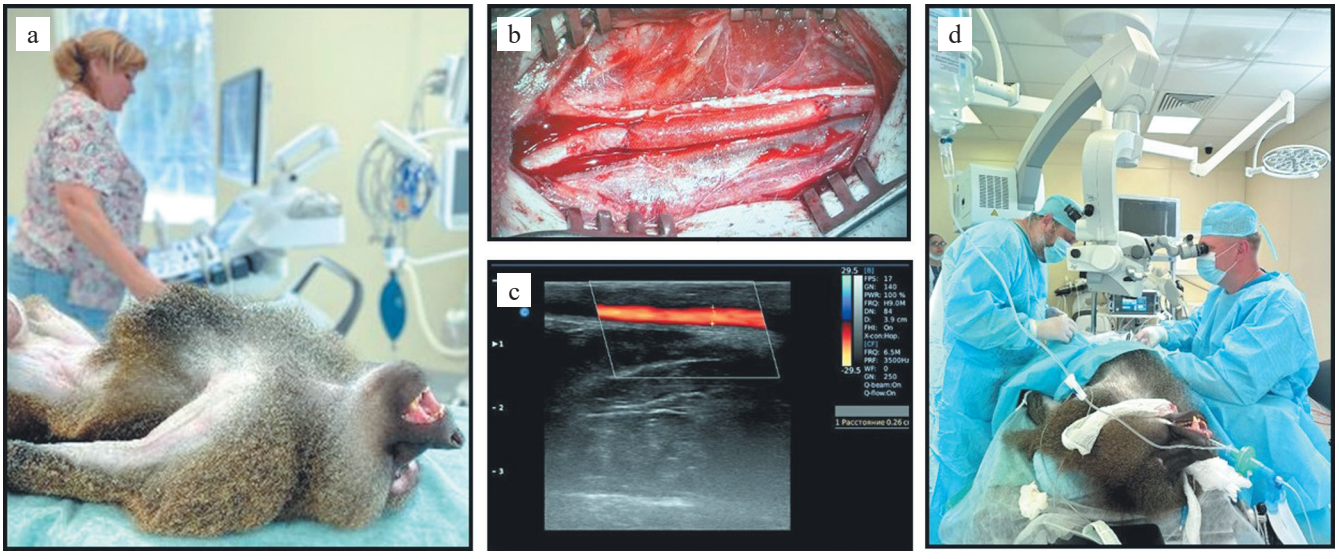

Fig. 5. Preclinical trials of small-diameter vascular grafts on a primate model: a, ultrasound assessment of femoral artery diameter; b, view of the implanted vascular graft in the femoral artery of a baboon; c, ultrasound confirmation of implanted graft patency; d, vascular graft implantation procedure

munofluorescence studies of retrieved prosthetic specimens. This proved highly convenient, as primate-specific primary antibodies are scarcely available on the market. The compatibility of human-specific antibodies with primate antibodies allowed for a more comprehensive morphological analysis, leveraging the broader range of available human antibody panels compared to those for other animal models.

All baboons in the experiment were adult, age-matched males. Given that the average lifespan of baboons in the wild is around 30 years – but significantly lower in captivity – the experimental group already exhibited a premorbid background typical for age-matched individuals.

For instance, thrombosis of one prosthesis occurred in a 15-year-old male with obesity, arrhythmia, and respiratory failure. In addition, the oldest baboon (17 years old) exhibited hypertrophy of the femoral artery wall throughout and a discontinuous endothelial layer.

When comparing the quality of endothelization in the vascular graft implanted in this baboon with that of its intact contralateral femoral artery, it was found that the graft exhibited superior endothelization. This finding indirectly confirmed the efficacy and activity of the proangiogenic factors incorporated into the prosthesis (Fig. 7).

CONCLUSION

1. The accuracy of identifying failure risks in biodegradable SDVGs during preclinical testing is highly dependent on the choice of the animal model.
2. The rat model does not accurately predict long-term patency of VGs due to its rapid endothelialization, inability to implant long prostheses into the rat aorta, and its incompatibility with human physiology. However, it remains useful for evaluating the calcification potential of VGs.
3. The sheep model exhibits an excessively high susceptibility to thrombosis, necessitating modifications in the manufacturing process to enhance the thromboresistance of the medical device. Consequently, the hemocompatibility of the device may be tailored more to the hemostasiologic profile of a laboratory animal rather than humans. However, a significant advantage of this model is its ability to reveal the accelerated biodegradation of polymers, which led to aneurysm formation throughout the entire length of the prosthesis. Moreover, according to various literature sources, polymers used in VGs should not undergo resorption before three years. In addition, the sheep model is highly prone to calcification, making the low calcification rates observed in the developed prostheses an indicator of their biocompatibility.

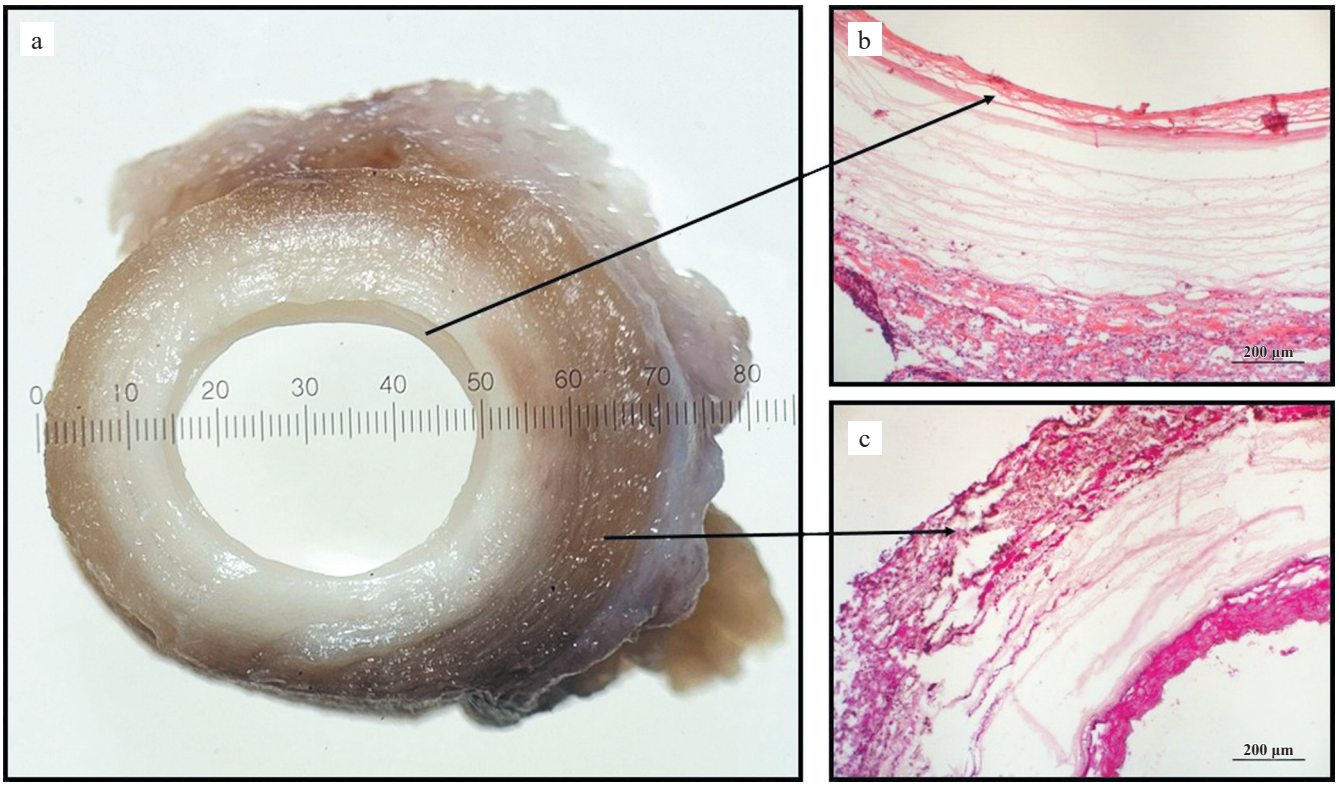

Fig. 6. Results of morphological analysis of small-diameter vascular grafts at 6 months post-implantation in the femoral arteries of baboons: a, spectroscopy of a cross-section of the retrieved graft (10×); b, hematoxylin-eosin staining (100×); c, Van Gieson's staining (100×)

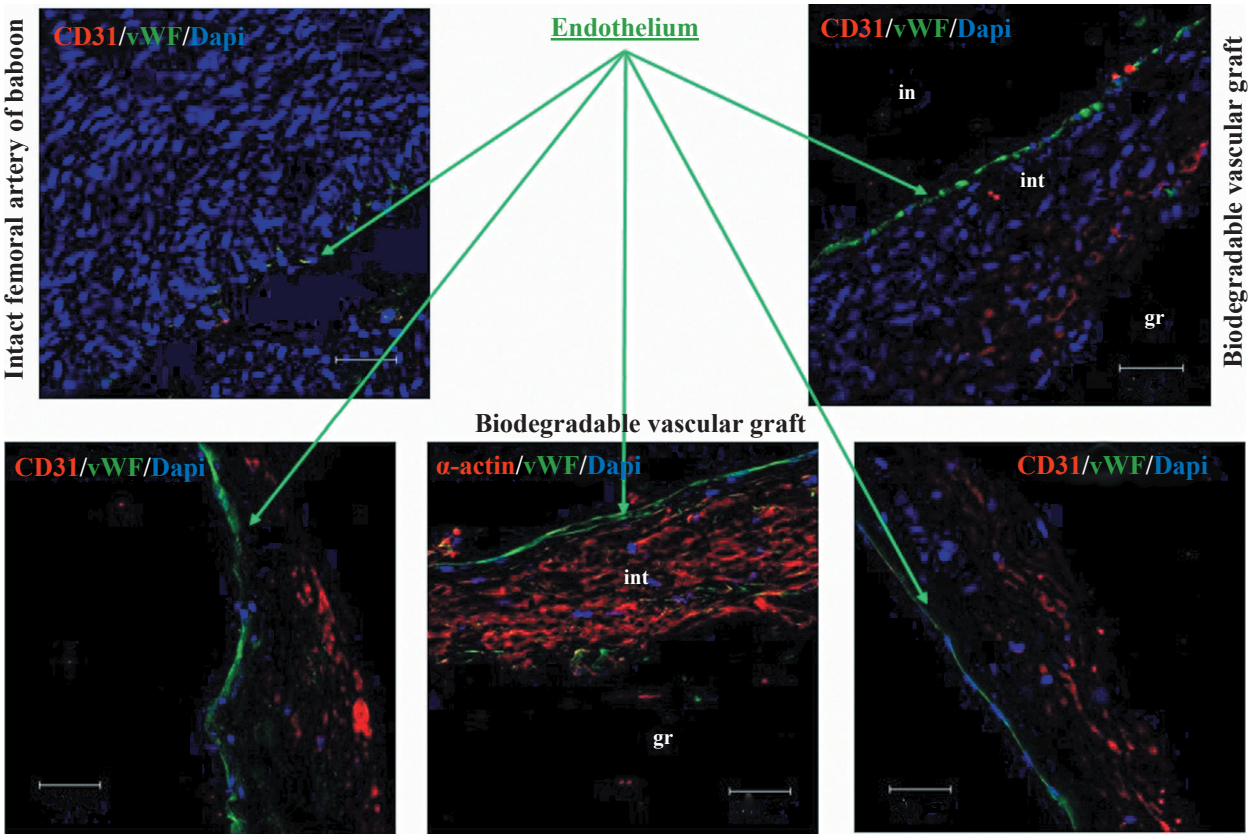

Fig. 7. Immunofluorescence results of a retrieved small-diameter vascular graft and a contralateral intact femoral artery of a baboon. Scale bar 50 μm

4. The primate model proved to be the most balanced for preclinical testing, providing an accurate assessment of both long-term patency and graft remodeling. It also demonstrated appropriate sensitivity to intra- and postoperative antiplatelet therapy. When using age-matched animals with a premorbid background similar to that of elderly patients with cardiovascular pathology, the evaluation of VGs occurs under conditions that closely resemble future human clinical trials. The identity of specific human antibodies with primate antibodies significantly enhances the depth of morphological analysis of retrieved prosthesis samples.

This research was conducted as part of the fundamental theme of the Research Institute for Complex Issues of Cardiovascular Diseases, No. 0419-2022-0001: "Molecular, cellular, and biomechanical mechanisms of the pathogenesis of cardiovascular diseases in the development of new treatment methods for cardiovascular diseases, based on personalized pharmacotherapy, introduction of minimally invasive medical devices, biomaterials, and tissue-engineered implants".

The authors declare no conflict of interest.

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