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New discoveries in bioengineering applied to vascular surgery

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New discoveries in bioengineering applied to vascular surgery

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Editorial: New discoveries in bioengineering applied to vascular surgery

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vascular surgery, artificial intelligence, graft, vascular biomaterial, saphenous graft

Editorial on the Research Topic
New discoveries in bioengineering applied to vascular surgery

1. Introduction

The field of vascular medicine has witnessed the fifth cardiovascular revolution (1), thanks to the convergence and the synergistic relationship between vascular biomaterials, synthetic vascular neuronal networks, and artificial intelligence.

Healthcare has long been the beneficiary of technological advancements, with innovations consistently pushing the boundaries of what's possible in medical science. Among these remarkable developments, vascular bioengineering stands out as a beacon of hope, poised to revolutionize the treatment of cardiovascular diseases and usher in a new era of personalized medicine. This field has made substantial progress through the convergence of biology, engineering, and medical science, offering glimpses into a future where regenerative therapies, artificial organs, and minimally invasive procedures are commonplace.

These innovations have revolutionized the diagnosis and treatment of vascular diseases, paving the way for precision medicine tailored to individual patient needs (2).

1.1. The burden of cardiovascular diseases

Cardiovascular diseases (CVDs) represent a significant global health challenge, with conditions like Atherosclerosis, aneurysms, and ischemic disorders ranking among the leading causes of mortality. These diseases often necessitate invasive and high-risk interventions, such as open-heart surgeries or the implantation of synthetic materials. However, these conventional approaches are plagued by inherent issues, including the risk of rejection, limited durability, and the need for lifelong medication. Vascular bioengineering emerges as a promising solution to these long-standing problems. Vascular diseases, including atherosclerosis, aneurysms, and ischemic conditions, are among the

leading causes of mortality worldwide. Traditional treatment approaches often involve open surgeries or the implantation of synthetic materials, which present various challenges, such as the risk of rejection, limited durability, and the need for lifelong medication. Vessel characteristics vary by size, and the bioengineering of human conduits must adjust to these requirements: the primary role and, therefore, the anatomic and biochemical design of large vessels is in the efficient transport of blood while vessels of smaller diameter gradually switch to performing more exchange functions in lower pressure, slower flow environment.

Repair, graft replacement, and reconstruction are the challenges for the expected benefits of bioengineering human tissues and blood vessels because the number of patients affected by peripheral arterial disease (PAD), requiring peripheral surgery, is steadily growing. PAD and vascular injuries, including civilian and military traumatic injuries, represent another area of the critical need for replacement vessels (3).

Vascular replacements started with autologous saphenous vein graft described in 1949, and in the following years prostethic grafts have been developed (4).

1.2. The promise of vascular bioengineering

1.2.1. Regenerative therapies

One of the most exciting prospects in vascular bioengineering is the development of regenerative therapies. Stem cell research, for instance, has shown tremendous potential in growing functional blood vessels that can be tailored to individual patient needs. These regenerative approaches promise to replace damaged or diseased vessels with biologically compatible constructs, reducing the risks associated with synthetic materials.

1.2.2. Artificial organs

Vascular bioengineering also holds the key to creating artificial organs that mimic the complex functions of the human circulatory system. These bioengineered organs, like artificial hearts and blood vessels, can potentially provide patients with life-saving solutions, reducing the waiting times and complications associated with organ transplantation.

1.2.3. Minimally invasive procedures

Traditional surgical interventions often entail significant trauma and extended recovery periods. Vascular bioengineering, however, is driving the development of minimally invasive procedures. Techniques like catheter-based treatments and drug-eluting stents are becoming more sophisticated, allowing precise interventions with reduced patient discomfort and recovery times.

1.2.4. Personalized medicine

One of the most profound impacts of vascular bioengineering is the move towards personalized medicine. By leveraging advancements in genomics and biotechnology, healthcare providers can tailor treatments to each patient's unique genetic makeup, optimizing outcomes and minimizing adverse effects.

2. Vascular biomaterials

Vascular biomaterials are engineered materials designed for compatibility with the human vascular system.

They have played a pivotal role in the development of advanced vascular therapies. These biomaterials can be divided into two categories: biological and synthetic.

Biological biomaterials, such as tissue-engineered grafts and decellularized matrices, offer the advantage of biocompatibility. They can support cell growth and tissue regeneration, making them valuable for repairing damaged vessels. On the other hand, synthetic biomaterials, like biodegradable polymers, provide mechanical strength and controlled degradation rates. They are often used for stent coatings, promoting healing while preventing restenosis.

3. Synthetic vascular neuronal networks

Synthetic vascular neuronal networks, a relatively new concept, involve creating artificial neural networks that mimic the autonomic nervous system's control over vascular functions. These networks integrate with the vascular system to monitor and regulate real-time blood flow, vasodilation, and vasoconstriction. They are particularly beneficial in managing conditions like hypertension and vascular insufficiencies.

These networks are designed to adapt to individual patient needs, ensuring precise control over vascular parameters. AI algorithms play a crucial role in optimizing the performance of these synthetic networks by continuously analyzing data from digital twins and sensors and then making necessary adjustments.

4. Artificial intelligence

Artificial Intelligence (AI) has emerged as a game-changer in the field of vascular medicine. Machine learning algorithms can process vast amounts of patient data, including medical records, imaging studies, and genetic information, to identify patterns and predict disease risks. This enables early diagnosis and personalized treatment plans.

AI-driven image analysis, such as in medical imaging and pathology, enhances the accuracy of vascular disease diagnosis. Moreover, predictive analytics help forecast disease progression, allowing for proactive interventions. AI-driven robotics and surgical assistance also contribute to the precision and safety of vascular procedures.

5. Precision vascular medicine

The synergy of vascular biomaterials, synthetic neuronal networks, and AI culminates in precision vascular medicine. Tailored treatment plans are created based on individual patient

profiles, optimizing therapeutic outcomes while minimizing side effects.

Here are some key benefits:

1. Personalized Drug Delivery: Biomaterials can be used as drug carriers, releasing medications at specific locations within the vascular system, guided by synthetic networks and AI algorithms.
2. Targeted Therapies: AI analyzes patient data to identify optimal treatment strategies, considering genetic factors, lifestyle, and disease progression, resulting in targeted therapies.
3. Minimized Risks: Real-time monitoring and control by synthetic networks reduce procedural risks and enhance the safety of vascular interventions.
4. Improved Outcomes: Early diagnosis, precise treatment, and continuous monitoring lead to improved patient outcomes and quality of life.

Vascular grafts are usually made of synthetic polymers, animal and cadaveric tissues, or autologous and used with well-characterized outcomes, leaving areas of unmet need for the patients in terms of durability and long-term patency, susceptibility to infection, immunogenicity, inflammation, and mechanical failure. Vascular bioengineering aims to overcome these hurdles by leveraging cutting-edge techniques to create functional, biocompatible vascular replacements. One of the most promising areas within vascular bioengineering is tissue engineering.

One of the most significant challenges to the deployment of vascular grafts is their adoption by the host and their ability to remodel into new tissues. Several research strategies have been implemented to reduce infection rates, promote endothelialization, and inhibit inflammation. While some histological data demonstrate partial recellularization of xenografts, many clinical reports of explanted specimens provide evidence of inflammation, calcification, and neointima formation without cellularization of the implanted ECM (5).

Another facet of vascular bioengineering focuses on developing advanced prosthetics and implants.

Innovations such as bioresorbable stents that gradually dissolve after serving their purpose (6) innovative implants that monitor and respond to physiological changes, and tissue-engineered heart valves that mimic natural function are reshaping the landscape of cardiovascular interventions.

Minimally invasive procedures have become the cornerstone of modern medicine, offering reduced risks, shorter recovery times, and improved patient comfort. Vascular bioengineering contributes to this trend by creating catheters, delivery systems, and imaging techniques that enable precise interventions through small incisions. These advancements are extending the benefits of vascular treatments to a broader range of patients who may not have been candidates for invasive surgeries.

While the progress in vascular bioengineering is undeniably promising, challenges remain.

Ensuring the long-term durability and compatibility of engineered tissues and materials, addressing potential immune responses, and navigating regulatory pathways are all critical considerations. Graft failures due to loss of integrity, inflammation, and fibrosis have repeatedly been observed, often in environments experiencing mechanical stress or high pressures. Autologous grafts remain the preferred option for vessel replacement or repair, eliminating the risk of rejection presented by xenografts and allogenic vein grafts, resisting infection better than synthetic materials, and displaying mechanical properties most closely aligned with the conduit to be replaced. However, they face limitations concerning availability, risk of thrombosis due to damaged endothelium, intimal hyperplasia, and accelerated atherosclerosis. New research avenues focus on generating innovative materials that would decrease the risk of infection, thrombosis, and rejection and either undergo remodeling by the host or induce regeneration and repair of the host's tissues. Other two topics are relevant in the evolution of the vascular field: the use of robotics and endovascular devices and their relationship to the arterial wall.

The introduction of robotics represented another significant step forward for different surgical specialties, facilitating and improving the performance of minimally invasive surgery. Robot-assisted surgery has been brought into the area of vascular surgery to enhance laparoscopic vascular and endovascular skills, such as a relatively tricky manipulation of instruments and long suturing times for anastomoses and clamping of the aorta or pelvic arteries (7). It is well documented in the literature despite none of the systems described above having been employed on a widespread basis. The surgeon's movements are down-scaled into fine gestures, physiological tremor is eliminated, and the visualization is improved, thus simplifying those actions unachievable in traditional surgery. High costs and the lack of approval for use in the vascular field have contributed to their low popularity. However, concerns about addressing higher costs in favor of substantial health benefits for medical staff and patients should be considered.

The second aspect is critical of endovascular procedures. Endovascular procedures aim to create structural support to the arterial wall for a new path for the blood into the arteries, excluding aneurysms by the risk of enlargement and rupture or creating a new way in case of previous arterial occlusion.

Especially about the aneurysm treatment, the relationship between the endograft and the arterial wall can be understood in terms of the following key points: sealing and anchoring; integration and healing (it helps improve the long-term stability of the repair), minimization of blood flow (endograft alters the blood flow dynamics within the artery) and potential complications (treatment of certain vascular conditions, there can be complications related to the relationship between the graft and the arterial wall). Careful patient selection, proper sizing and positioning of the endograft, and regular follow-up are essential to minimize these risks.

The ideal design of the aortic endograft should resemble the native aorta in terms of its flexibility and hemodynamic impedance. The stent-graft polymers should be lightweight but strong, resilient, and capable of withstanding the impact of normal pulsatile high-flow arterial blood pressure. There is increasing evidence of adverse hemodynamic alteration post-TEVAR/EVAR. Interventionalists must respect the aorta as an

active organ, not a mere conduit. The best solution in the short term could be to reduce the stented length of the aorta while, in the longer term, encouraging continuous improvement in stent-graft materials and design. The relationship between a vascular endograft and the arterial wall is a complex interplay of biomechanical factors, healing processes, and medical considerations. The success of endovascular procedures relies on the proper selection and placement of the endograft, as well as careful management and monitoring to ensure optimal patient outcomes.

The intelligent endoprosthesis will adapt to prevent tissue ingrowth into its' microstructure, preventing rigidity and maintaining distensibility. Therefore, the Smart endoprosthesis will retain the ability to expand in systole and collapse in diastole. After implantation, it returns the elastic recoil to the heart, creating an almost standard aortic flow curve (8).

Vascular bioengineering represents a transformative force in cardiovascular medicine, offering solutions once confined to science fiction. As researchers push the boundaries of knowledge and technology, we can anticipate a future where vascular diseases are treated with unprecedented precision, patients experience an improved quality of life, and healthcare becomes increasingly personalized.

The potential to replace damaged vessels with bioengineered constructs, create artificial organs, and perform minimally invasive procedures heralds a brighter and healthier future for individuals affected by cardiovascular diseases. Through the intersection of biology, engineering, and medical science, vascular bioengineering is paving the way for a healthcare landscape that is more effective, patient-centered, and hopeful.

6. Conclusion

The convergence of vascular biomaterials, synthetic vascular neuronal networks, and artificial intelligence have ushered in a new era of precision vascular medicine.

Vascular bioengineering is poised to reshape the landscape of cardiovascular medicine, offering solutions that were once confined to science fiction. We anticipate a future where vascular diseases are treated with precision, patients experience improved quality of life, and healthcare becomes increasingly personalized.

This innovative approach offers personalized solutions for patients with vascular diseases, enhancing diagnostic accuracy and treatment efficacy. As these technologies continue to advance, the future of vascular healthcare promises even more remarkable breakthroughs, ultimately improving the lives of countless individuals suffering from vascular conditions.

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Endovascular Materials and Their Behavior in Peripheral Vascular Surgery

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Endovascular techniques have progressively become the first option for the treatment of stenosis and occlusions of both aorto-iliac and femoro-popliteal district. The development of new technologies and new materials has broadened the applicability of the endovascular techniques, allowing the treatment of each lesion with the most suitable material. A knowledge of the behavior of endovascular materials when treating peripheral arterial disease (PAD) is, therefore, crucial for optimization of the results. Here, we aim to review the most important technical features of the actually available endovascular materials for treating PAD.

Keywords: endovascular, peripheral arterial disease, materials, femoro-popliteal, iliac

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INTRODUCTION

Atherosclerotic peripheral arterial disease (PAD) is associated with an increased risk of limb loss (1). Therefore, it needs prompt risk factor management and optimal pharmacological treatment. Appropriate revascularization may also be required, especially in the case of progressive clinical deterioration despite optimal medical therapy or in the presence of severe limiting claudication with reduced quality of life, rest pain, and/or critical ischemia (2).

PAD may affect every segment, right from the infrarenal aorta and iliac arteries to the femoral, popliteal, and tibial arteries, extending even to the smaller foot arteries. A tailored approach is then required based on individual clinical risk and on the site of the arterial disease.

Endovascular techniques have progressively gained wide acceptance as the first option in the revascularization of short stenosis/short occlusions of both aorto-iliac and femoro-popliteal district (3), given their low invasiveness and better outcomes when compared with open surgery.

Technical improvement of the devices, along with the development of new technologies, have increased the applicability of the endovascular techniques, allowing the treatment of each lesion with the most suitable material.

A knowledge of the behavior of endovascular materials when treating PAD is, therefore, crucial for optimization of the results.

Here, we aim to review the most important technical features of the actually available endovascular materials for treating PAD.

TYPE OF ENDOVASCULAR DEVICES

A wide variety of guidewires, catheters, crossing devices, balloons, stents, and other devices are available for the endovascular treatment of PAD, but there are no clear guidelines for their application.

When planning the best endovascular strategy, the operator should consider the type and anatomic location of the target lesion, within the context of the whole vessel. Some scoring systems have also been elaborated to help in the preoperative technical stratification of femoropopliteal and infrapopliteal artery disease treatment, such as the Bollinger score, the TASC II grade, the run-off score, the calcium score, and the lesion length category (4). These scores describe the anatomical features of the index lesion and are helpful tools in predicting durability, outcomes, and response to endovascular interventions. Therefore, they should be taken into account when choosing the proper treatment.

Guidewires

Guidewires are the mainstay of endovascular treatment, since they are used basically in every procedure from the beginning to the end, to reach and cross the target lesion, and as a support for therapeutic devices such as balloons or stents.

Each guidewire has its own engineering features in terms of maneuverability, flexibility, visibility, traceability, smoothness, and support. The choice of the correct guidewire can be crucial for obtaining the optimal result, especially in the case of chronic total occlusions (CTOs).

Different guidewires are available in terms of core diameters, lengths, core material, tip design, covers, and coating. All these features may impact the strength, the flexibility, and the trackability of the wire.

The core diameter can range from 0.014 to 0.038 in., but in peripheral procedures, the most widely utilized sizes are 0.014, 0.018, and 0.035 in. The larger the diameter, the grater the rail support is. Conversely, larger diameter guidewires have reduced flexibility and trackability through the vessel (5). Usually, 0.035 in. guidewires are used for delivering sheaths and diagnostic catheters, while 0.018 in. are used for crossing more proximal lesions, and 0.014 in. are used for below knee interventions and CTOs.

The length of a guidewire can reach up to 300 cm. Usually, shorter guidewires are easier to maneuver and have a greater pushability to cross the lesion. Nevertheless, device compatibility and a knowledge of the road from the access vessel to the target lesion should be considered when choosing the proper guidewire diameter and length.

The most used guidewires are Nickel Titanium (Nitinol), which combine the columnar support of a stainless-steel guidewire with flexibility and good trackability. The tip, straight or "J"-shaped, can be made either of the same core material, giving a greater push force, or may be more delicate and soft, with a lesser probability to inadvertently damage distal vessels.

Finally, guidewires can be covered and coated by sleeves of polymer or plastic to increase lubricity, therefore, providing an enhanced lesion crossing and smooth tracking, especially in tortuous vessels. The most used are hydrophilic coatings to create a slippery surface that facilitates navigability through the vessels.

Catheters

Diagnostic and guiding catheters enable direct access to the treatment site when guidewires fail.

Depending on the case, they have specific preformed shaped tips at their distal ends that can help in intra-arterial navigation, correct orientation of the tip of the guidewire toward the lesion site, crossing of complex lesions, and opacification of the artery using a contrast agent.

The diameter unit of the catheters is measured in French (1 French = 0.3 cm). The length of the guidewire should always be greater than that of the catheter used.

Crossing Devices

CTOs are complex lesions that may deserve specific equipment with its own behavior.

Therefore, crossing devices are available for the endovascular antegrade and retrograde recanalization of peripheral CTOs, either under fluoroscopy or under intravascular sound guidance.

The aim of a crossing device is to perform microdissection and disruption of the atherosclerotic plaque while advancing the distal tip, which can have specific features (such as jaws or edges or may be connected to a generation of vibration energy) that can help penetrate through the CTO (6). While advancing through the CTO, a microguide catheter is sometimes needed to provide support to the distal end and guidewire exchange.

After having crossed the CTO, a re-entry device may be needed to reach the true distal lumen from the subintimal plane beyond the CTO. These devices usually have a hollow curved needle or a microcatheter lancet at their tip. After re-entering the true lumen, guidewire placement is needed for completion of the procedure using balloons and stent delivery.

Balloons

Balloon angioplasty can be either coated or noncoated by drugs that aim specifically at reducing the risk of restenosis caused by neointimal hyperplasia (4).

Typical features of an angioplasty balloon that can affect one's behavior during endovascular procedures include geometry, cutting ability, and the fabric material.

The geometry and the fabric material may impact the crossing profile. Balloons with a low crossing profile are for ease of entering and crossing challenging lesions and can be a useful tool to prepare the road for greater balloons. Furthermore, the geometry and the material are crucial for length and radial compliance of the balloon, which, in turn, may affect the rate of inflation and deflation.

The pressure exerted with the inflation allows the balloon to reach its nominal diameter or even a few tens of a millimeter more. However, inflation pressure cannot exceed the rated burst pressure. Usually, short balloons may need more pressure to reach their nominal diameter, but they can have a

higher radial force for short lesions. Conversely, long stenotic regions may need longer balloons that may require a longer time of application.

In highly fibrotic lesions, such as postattinic stenosis or restenosis, balloons with small cutting edges (cutting balloon) can be employed to fracture the plaque.

Stents

According to the method of deployment, stents can be premounted on a balloon (balloon-expandable) or may have their own delivery system with a self-expandable opening.

Usually, balloon-expandable stents have a greater radial force, a greater radiopacity, and a more precise delivery when compared with self-expandable stents (7). Conversely, they have lower flexibility and trackability than self-expandable stents. Therefore, balloon-expandable stents are indicated for short, calcified stenosis, while self-expandable stents perform better in long lesions and tortuous arteries.

Furthermore, each stent may have its radial force or resistance to elongation, torsion, and crushing according to the struts material and shape. The struts may have bridges that connect to each other, leading to a design with "closed-cells." Otherwise, the struts may have large uncovered gaps in a "open-cells" configuration. The number and frequency of bridges of the struts confer less flexibility and trackability to the stent.

When using balloon-expandable devices, a small risk of decrimping the stent from the balloon while crossing an occlusion or tightly calcified stenosis should be considered. Therefore, predilation with a smaller balloon is suggested. During expansion, the stent will take on the diameter of the balloon on which it is mounted. However, if needed, balloon-expandable stents may be dilated to a greater diameter by using a larger diameter balloon but that is shorter than the stent, in order to avoid dissection of the artery at the proximal and distal ends of the stent.

Differently, self-expanding stents cannot exceed their reference diameter. Therefore, when in doubt choosing between two options, it is preferable to opt for larger diameter stents. These stents open only slightly after delivery due to their low radial force, and, therefore, postdilation is needed.

Of note, self-expanding stents may act on the vessel wall in terms of chronic outward force, which is the radial force that the stent exerts at expansion, and is proportional to the amount of oversizing with respect to the vessel diameter. This amount of oversizing can induce wall shear stress, which can be responsible for in-stent restenosis; therefore, excessive oversizing should be avoided when choosing the proper stent diameter.

While the indication of stent placement in the aorto-iliac district is well recognized (7), conflicting data exist about the placement of a stent in the superficial femoral artery (SFA) and popliteal districts, since stent fatigue may occur, especially in Nitinol stents, leading to stent failure and vessel reocclusion (8).

The mechanical behavior of stents in the SFA-popliteal artery, which has been studied using the spring model and 3D finite element modeling, depends not only on the technical features of the stent, but also on the torsion and elongation of the vessel itself, to which the stent is subjected during the normal deambulation process. The type of the lesion is also an important determinant. Furthermore, overlapping regions and overexpansion of the stent beyond its nominal diameter may increase stent fatigue with the consequent risk of fracture and failure (8).

Balloon-expandable and self-expandable stents may be covered by poly-tetrafluoroethylene (covered stents) or bonded with heparin or drugs that are slowly released over time to the endothelium (drug-eluting stents, discussed below), with the aim of improving long-term vessel patency.

RECENT TECHNOLOGIES

Atherectomy Devices

Atherectomy devices represent a new way of catheter-based intervention for the treatment of PAD, based on the disruption of the plaque with different physical methods.

All of these devices have in common the presence of a catheter that is inserted inside the vessel lumen, and at the tip, there are specific devices for plaque debulking. Orbital atherectomy devices have a tip with a diamond-coated crown that rotates 360° in eccentric fashion, while rotational atherectomy uses rotating cutting blades at high speed. Directional atherectomy devices also have conical rotating blades at the tip, which has in adjunction a nose cone in which the removed debris of the plaque are captured and stored. Finally, laser atherectomy devices use the physical properties of the laser wave to debulk the lesions (5).

Atherectomy is usually performed as an adjunctive therapy with balloon angioplasty and stenting.

Lithotripsy

Intravascular lithotripsy is a novel technique for lesion preparation in calcified vessels. Lithotripsy is composed of a catheter that is connected to a generator and is enclosed in a semicompliant balloon. Electric sparks produced by the emitters create vapor bubbles in the surrounding fluid medium, resulting in acoustic pressure waves, which, in turn, create micro–macro fractures on endothelial calcium, without affecting soft tissue (5).

Drug-Coated Devices

Balloons and stents may be covered by cytotoxic drugs that aim to reduce the inflammatory response of injured endothelial cells and subsequent neointimal hyperplasia. Paclitaxel is the most used of these drugs and arrests the cells in the M phase of the mitotic cycle. Sirolimus has also been recently approved for use in PAD (9).

What makes the difference between the different kinds of available drug-coated devices is the carrier system, which ideally should both prevent the loosing of the drug while crossing the sheath and navigating the vessels and confer rapid transfer from the balloon surface to the arterial wall when the target lesion has been reached.

Focal Self-Expanding Nitinol Stents

Recently, a multiple stent system for spot stenting has been introduced for the treatment of femoro-popliteal lesions, with promising early results (10).

This device has six short (13 mm in length) self-expanding nitinol stents on a single 6F delivery system that is compatible with a 0.035 in. guidewire, and each of them can be individually implanted. The peculiarity of having multiple short stents instead of longer ones has the advantage of reducing the mechanical strain to which the stents can be subjected by bending and stretching, especially in the distal SFA or the popliteal artery.

Sigl et al. (10) described the first-in-human experience in 20 patients affected by claudication or critical limb ischemia, who underwent femoropopliteal revascularization using this device. They reported promising results with no device-related complications, no major adverse events, and a 100% patency at 6 months' follow-up.

Chocolate™ PTA Balloons

The Chocolate™ PTA balloon has a unique design. It is a semicompliant balloon that is encased in a nitinol-constraining structure (cage). When the balloon inflates, the cage expands simultaneously, causing the segmentation of the balloon in a series of pillows and grooves with controlled dilatation on the vessel wall that allows for 1:1 vessel sizing.

The over-the-wire platform is compatible with 0.014 and 0.018 in. guidewires and is available in diameters ranging from 2.5 to 6 mm, therefore, allowing treatment both below and above the knee districts, with promising early results. Sirignano et al. (11) treated 81 claudicant patients who had femoro-popliteal lesions and reported a primary patency of 98.8% at a mean follow-up of 12.3 ± 5.6 months.

Furthermore, data obtained from the Chocolate BAR multicenter postmarket registry (12) showed a 97.2% rate of freedom from major amputation at 12-months' follow-up in 262 patients.

CONCLUSION

Newer technologies are rapidly becoming available for the endovascular treatment of PAD. Endovascular operators should have a proper knowledge of the behavior of these materials in order to optimize the results.

AUTHOR CONTRIBUTIONS

DM performed data collection and was involved in manuscript preparation, critical revision, and giving final approval; MG, PR, AM, GM, and GN all did critical revision and gave final approval. All authors contributed to the article and approved the submitted version.

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Management of retroperitoneal fibrosis with endovascular aneurysm repair in patients refractory to medical management

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Background: Early diagnosis and treatment of under-recognized retroperitoneal fibrosis (RPF) are essential before reaching the poorly responsive fibrotic stage. Although most patients respond to medical therapy, relapses and unresponsiveness are common. However, open surgery in medically resistant patients is associated with major adverse clinical events.
Methods: This is a single-centre longitudinal study of optimal medical therapy (OMT) vs. endovascular aneurysm repair (EVAR) in patients presenting with RPF to our tertiary referral vascular centre. Out of 22,349 aortic referrals, we performed 1,555 aortic interventions over twenty years. Amongst them, 1,006 were EVAR, TEVAR and BEVAR. Seventeen patients (1.09%) had documented peri-aortic RPF.
Results: Out of the 17 RPF patients, 11 received OMT only, while 6 underwent EVAR after the failure of OMT. 82% ($n = 14$) were male, and the median follow-up was 62.7 months (IQR: 28.2–106). Nine (52%) had immunoglobulin G4-related disease (4 OMT vs. 5 EVAR). EVAR patients had 100% technical success without perioperative mortality. Furthermore, all the EVAR patients were symptom-free following the intervention. Pre-operative aortic RPF index (maximum peri-aortic soft tissue diameter/maximum aortic diameter) was higher in the EVAR than in OMT. However, there was a significant decrement in the aortic RPF index following EVAR ($P = 0.04$).
Conclusion: We believe that when optimal medical therapy fails in RPF, EVAR provides a promising outcome. Further studies are recommended to establish the role of endovascular repair.

KEYWORDS

retroperitoneal fibrosis, immunoglobulin G4-related disease, medical management, endovascular procedures, endovascular aneurysm repair

Introduction

Retroperitoneal fibrosis (RPF) is an uncommon disorder that causes fibrosis and scarring around the retroperitoneal space with resultant complications like ureteral obstruction and periaortitis (1–4). RPF starts as a mild inflammation around the infrarenal aorta with adventitial and periadventitial inflammation, medial thinning, and a chronic retroperitoneal inflammatory process (3–9). National Organization for Rare Diseases (NORD) (8) has stated that the exact cause of this condition is unknown in about two-thirds of cases. RPF typically develops in late middle age, i.e., 40–60 years, twice to three times more often in men than women (1–9).

Immunoglobulin G4-related disease (IgG4-RD) is a secondary RPF variant that constitutes histological predominance of lymphocytes and plasma cells (3, 4). IgG4-related RPF often has some response to glucocorticoid therapy; however, if misdiagnosed as retroperitoneal visceral malignancy, it will result in unnecessary surgical intervention (3–9). Early detection, accurate diagnosis and treatment are imperative (10–13).

Aortic antigenic targets and antibodies directed against aortic endothelial cells in RPF start as a local inflammatory response to atherosclerotic plaque antigens, leading to a local autoimmune process and cardiovascular inflammation. This results in vascular dysfunction by inducing the expression of endothelial adhesion molecules, cytokine production, and apoptosis (4, 7, 9, 13). We believe that endovascular exclusion of the infrarenal aortic wall from the circulation will cease these cascades of reactions, resulting in modulation and healing (11). Despite open surgery traditionally being the only option for patients refractory to medical management, advances in medicine have allowed us to employ endovascular repair in patients with RFP. However, we reserved it for patients who did not show a favourable response with medical management alone. Therefore, in this study, we aim to compare the outcomes of endovascular repair in RPF patients who were refractory to the optimal medical management.

Materials and methods

This is a single-centre longitudinal study of optical medical management and endovascular aneurysm repair (EVAR) in patients referred to our tertiary vascular centre with RPF from December 2002 to 2020. We included the patients with established RPF on imaging modalities. Patients with a history of tuberculosis, actinomycosis, histoplasmosis, recent trauma, illicit substance abuse, and inflammatory AAA were excluded.

The primary outcome is symptom-free survival. The secondary outcomes are all-cause mortality, perioperative mortality and technical success. Technical success is the successful deployment of the EVAR device without peri-procedural complications, like surgical conversion or death, and ELs (type I or III) or graft obstruction, kinks or twists.

Patients

All our patients were fully worked up by rheumatologists, nephrologists, urologists, and immunologists before being referred to us. They all had targeted computerized tomography (CT) and/or magnetic resonance imaging (MRI) scans, duplex ultrasound scanning (DUS), routine blood tests, renal function tests, and biopsies as necessary. Furthermore, optimal medical treatment had already been initiated before the referral.

All of our patients complained of a dull pain in the abdomen and lower back that is hard to pinpoint with swelling and discolouration of both legs and a dragging sensation in the scrotum. Patients had nausea, vomiting, loss of appetite, weight loss, and felt thirstier than usual, even in the absence of diabetes mellitus. None of our patients had a history of tuberculosis, actinomycosis, histoplasmosis, or recent trauma. All of our patients denied using cocaine and any other illegal substances.

Our overall management goal was to relieve ureteric obstruction, decrease peri-aortic fibrosis, and abolish pain. For at least three months, all our patients received optimal medical therapy (OMT) with steroids and/or mycophenolate mofetil. Patients who did not benefit from OMT and had failed medical management with anti-inflammatory medications, corticosteroids or immunosuppressants (mycophenolate mofetil) were labelled medically resistant and were offered EVAR (**Figure 1**).

All our patients had a targeted computed tomography angiography (CTA) initially and post-management, which was used to calculate the aortic RPF indices. Aortic RPF index was defined as maximum peri-aortic soft tissue diameter relative to maximum aortic diameter. These measurements were taken after defining the aortic centre-line on arterial phase images. Aortic RPF index is zero for patients without RPF or any enhancement of peri-aortic soft tissue. Furthermore, we approximate the cross-sectional area of the peri-aortic soft tissue enhancements by using the formula π (Pi) times the radius squared ($\pi * r^2$) (cross-sectional area of periaortic soft tissue enhancement = cross sectional area of the total aortic enhancement including aorta - cross sectional area surface area of aorta) (**Figure 2**).

Follow-up

The patients were regularly followed through thorough clinical evaluations, DUS, and CTA. We performed CTA

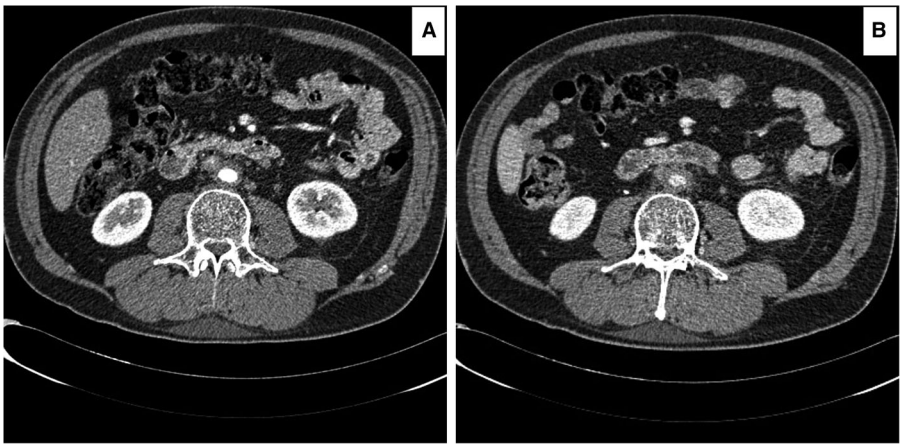

FIGURE 1
Computed tomography angiography (CTA) images showing worsening of the peri-aortic soft tissue after medical management. (A) RPF with less than 3 mm enhancements around the aorta and 21 mm aortic diameter. (B) after six months of steroid and mycophenolate, the enhancements increased to 5 mm, and the aortic diameter decreased to 18 mm. The patient had continuous abdominal and low back pain, not responding to the WHO one and two pain ladder medications.

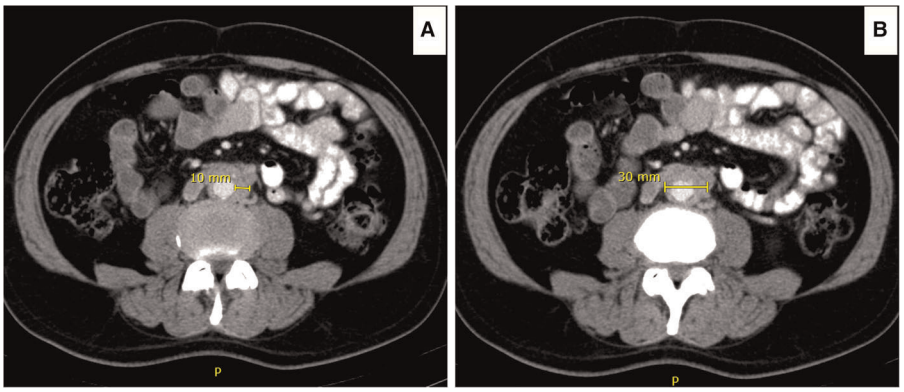

FIGURE 2
Computed tomography angiography (CTA) images illustrating the determination of the aortic retroperitoneal fibrosis index (peri-aortic soft tissue enhancement over maximum aortic diameter). (A) Peri-aortic soft tissue enhancement of 10 mm. (B) overall aortic enhancement of 30 mm, including the peri-aortic soft tissue enhancement.

initially, post-EVAR, at nine months, and annually after that. However, DUS was conducted at six weeks, six months, and every nine months.

Statistical analysis

Jamovi (the Jamovi project 2021, version 1.6) was used for statistical analyses. We summarized continuous outcomes through mean value supported with standard deviation and median value supported with interquartile range as necessary. Similarly, the categorical outcome was summarized with percentages and/or proportions. We employed Wilcoxon signed-rank test or Fisher exact test for statistical significance with $P < 0.05$ as statistically significant.

Results

Out of 22,349 aortic referrals to our tertiary referral centre, we performed 1,555 aortic interventions over twenty years. Amongst them, 910 were EVAR ± iliac branch devices (IBD), and 96 were thoracic endovascular aortic repair (TEVAR)/ branched endovascular aortic repair (BEVAR).

Over the past two decades, 17 patients (1.09%) were referred to our vascular service with RPF. Amongst them, six patients (6/

17) underwent EVAR following a deterioration despite optimal medical management. Nine patients (9/17) were IgG4-RD positive, of which five patients were medically resistant and were offered EVAR. Eight patients (8/17) were IgG4-RD negative, of which one was offered EVAR due to OMT failure (Figure 3). All medically resistant patients were referred to our services after more than a year post-RPF diagnosis. The baseline demographics of these patients are given in Table 1.

All of our patients had elevated C-reactive protein; however, none developed post-implantation inflammatory syndrome post-EVAR (Table 2). Following EVAR, all of our patients had improvements in the biochemical parameters. We had

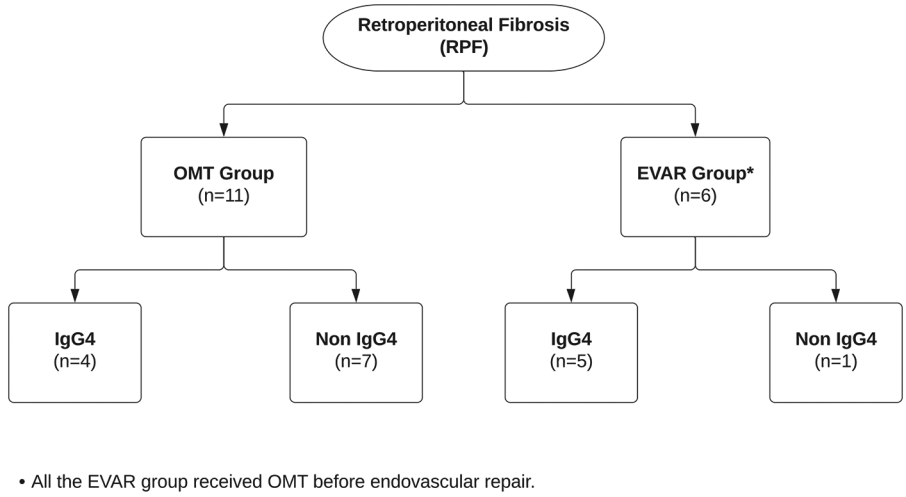

FIGURE 3
Flowchart showing patients with retroperitoneal fibrosis who were managed with optimal medical therapy vs. endovascular aneurysm repair.

TABLE 1 Baseline demographics of the patients.

	Retro-peritoneal Fibrosis ($N = 17$)		*P*-value
	Optimal Medical Therapy (OMT) Only ($n = 11$)	Endovascular Aneurysm Repair (EVAR) ($n = 6$)	
Time from diagnosis to vascular referral	6–11 months	14–22 months	0.01*
Male	9	5	1.00
Age (years), Mean ± Standard Deviations (range)	66.6 ± 12.9 (50–88)	64.0 ± 7.01 (57–76)	0.76
Smokers	4	4	0.33
Diabetes Mellitus (DM)	2	2	0.58
Chronic Obstructive Pulmonary Disease (COPD)	1	1	1.00
Hypercholesterolemia	3	3	0.60
Hypertension (HTN)	3	3	0.60
Ischemic Heart Disease (IHD)	2	3	0.28
Chronic Renal Failure (CRF)	0	3	0.02
Peripheral Vascular Disease (PVD)	1	3	0.09
Thyroid Disease	1	3	0.09
Depression	2	2	0.58
Diverticulosis	2	2	0.58
Stroke	1	0	1.00
Malignancy	5	3	1.00

**Significant.*

TABLE 2 Laboratory and biochemical parameters of the retroperitoneal fibrosis patients at the initial diagnosis, post optical medical treatment (OMT), and post endovascular aneurysm repair (EVAR).

Laboratory values	Groups	Initial (at presentation)	Post-management (at last follow-up)	*P*-value
C-Reactive Protein (CRP), mg/L mean ± SD (range)	Overall	50.90 ± 81.7 (0.60–281)	19.90 ± 28.40 (0.80–84.0)	**0.19**
	EVAR	47.10 ± 60.80 (4.50–148)	29.70 ± 34.40 (1.80–84.0)	**0.59**
	OMT	53.20 ± 96.50 (0.60–281)	14.60 ± 24.80 (0.80–84.0)	**0.26**
White cell count (WCC), 10^9/L mean ± SD (range)	Overall	11.14 ± 7.18 (5.10–32.9)	8.16 ± 3.46 (2.60–15.6)	**0.17**
	EVAR	8.28 ± 1.58 (5.10–9.10)	6.98 ± 1.03 (5.90–8.30)	**0.16**
	OMT	11.70 ± 8.64 (6.10–32.9)	8.80 ± 4.17 (2.60–15.6)	**0.37**
Neutrophils, 10^9/L mean ± SD (range)	Overall	6.72 ± 6.95 (2.20–30.2)	5.72 ± 2.74 (1.27–11.4)	**0.62**
	EVAR	4.16 ± 1.50 (2.20–6.20)	4.85 ± 1.00 (3.80–6.20)	**0.41**
	OMT	8.14 ± 8.42 (3.90–30.2)	5.00 ± 3.29 (1.27–11.4)	**0.31**
Eosinophil, 10^9/L mean ± SD (range)	Overall	0.29 ± 0.26 (0.00–1.00)	0.27 ± 0.23 (0.00–1.00)	**0.83**
	EVAR	0.28 ± 0.08 (0.20–0.40)	0.29 ± 0.11 (0.19–0.50)	**0.87**
	OMT	0.30 ± 0.33 (0.00–1.00)	0.29 ± 0.24 (0.00–1.00)	**0.94**
Estimated glomerular filtration rate (eGFR), ml/min mean ± SD (range)	Overall	69.50 ± 17.30 (20–90)	64.40 ± 22.8 (15–90)	**0.51**
	EVAR	64.40 ± 28.10 (20–90)	63.80 ± 30.60 (15–90)	**0.97**
	OMT	72.10 ± 9.65 (55–82)	64.70 ± 18.60 (32–90)	**0.27**

EVAR, endovascular aneurysm repair; OMT, optimal medical therapy; SD, standard deviation.

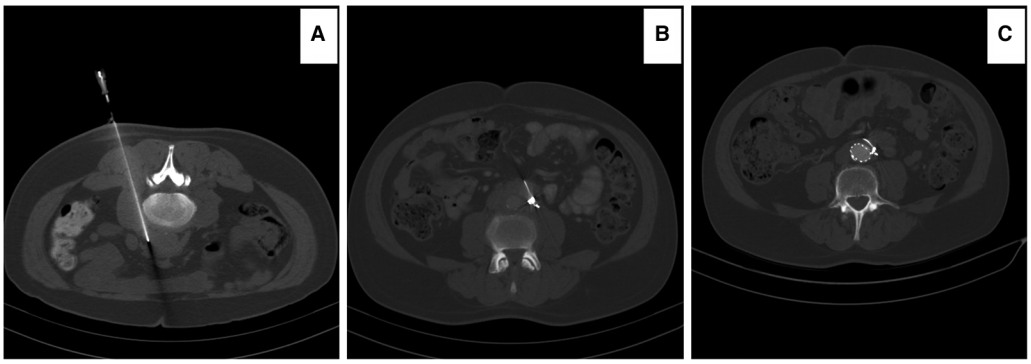

FIGURE 4
Computed tomography angiography (CTA) images illustrating: (A) percutaneous computed tomography (CT) scan guided biopsy of the retroperitoneal tissue in a prone patient. The patient developed bleeding during the biopsy. (B) the patient required three COOK coils (COOK medical LLC, Bloomington, IN) to stop the bleeding. (C) The patient was medically resistant and required EVAR 14 months post diagnosis. Note that the coils are now in the retroperitoneal space as the enhancements of the retroperitoneal fibrous tissue disappeared post-EVAR.

only one patient who was anti-nuclear antibody (ANA) positive. This patient underwent EVAR after the failure of medical management.

Most ($n = 5$) EVAR cases were performed using AFX (Endologix, Irvine, CA) and one with FORTON (Cordis, Miami Lakes, FL). We opted for AFX as it is an endoskeleton unibody with ultrathin ePTFE and depends on anatomical fixation over the aortic bifurcation rather than radial force. However, we supplemented the distal end with Bentley (Bentley InnoMed GmbH, Hechingen, Germany) covered stent graft. Also, it could be applied in narrow distal aortic diameter. Five of our six patients had distal aortic diameter <14 mm, which precludes any other bi-iliac aortic graft in the market. The patient treated with FORTON Cordis in 2003 was the only non-IgG4-RD RPF treated by EVAR. Amongst EVAR, five patients had aortic biopsies; however, three of them ended with bleeding complications that required embolization by coils to the site of biopsy (Figure 4).

Symptom-free survival

All the patients who underwent EVAR had symptom-free survival following the procedure throughout follow-up. The Kaplan-Meier plot for symptom-free survival is given in Figure 5 (log-rank test: $\chi^2 = 2.25$; $P = 0.13$). All EVAR patients went off all of the painkillers.

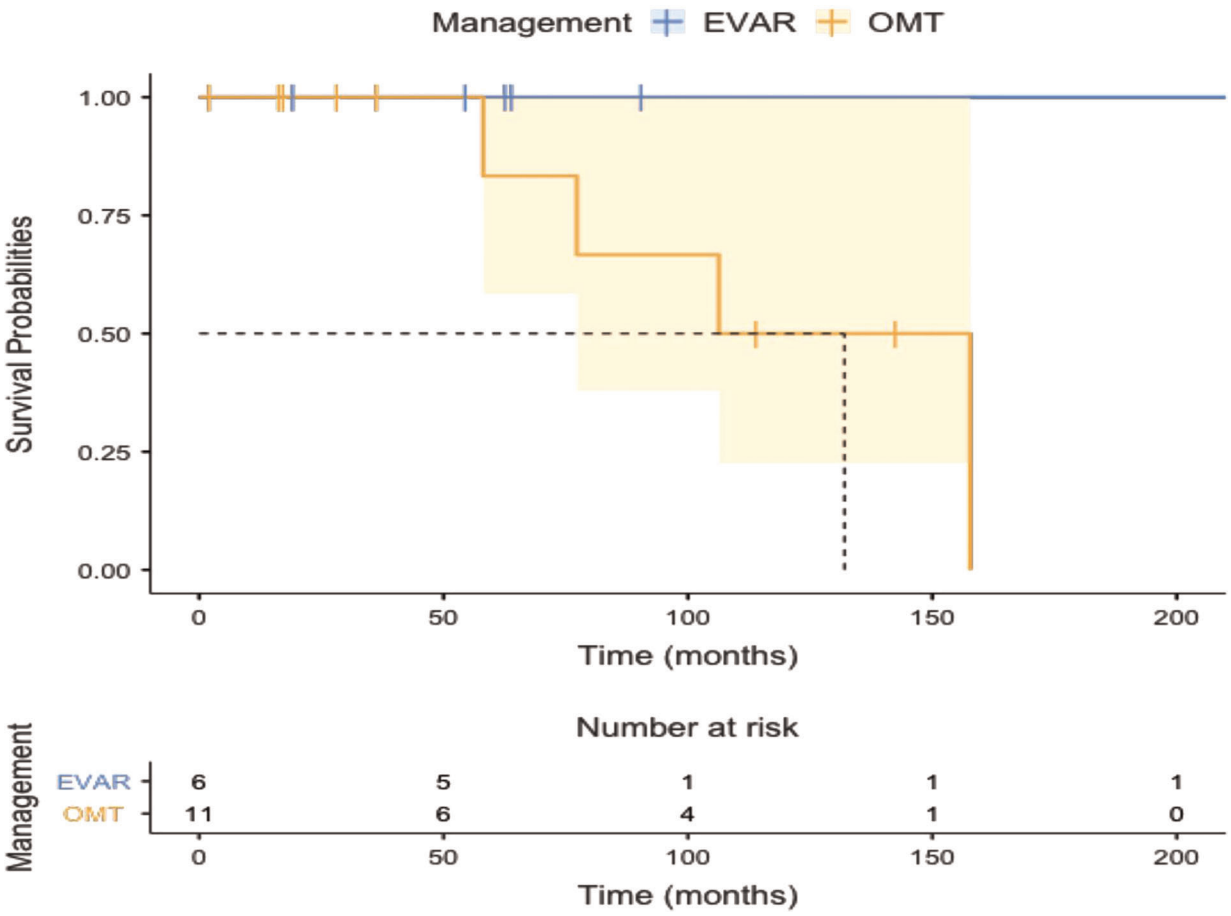

FIGURE 5
Kaplan-Meier plot showing symptom-free survival in patients with optimal medical therapy (OMT) and endovascular aneurysm repair (EVAR).

Peri-operative and all-cause mortality

Kaplan-Meier survival plot for all-cause mortality is given in Figure 6 (log-rank test: $\chi^2 = 1.27$; $P = 0.26$). None of the patients had peri-operative mortality post-EVAR. The OMT group suffered two mortalities during follow-up, one with renal impairment and the other with acute pneumonia after COVID-19.

Aortic RPF index

The aortic RPF indices and cross-sectional area of the peri-aortic soft tissue are given in Table 3. Overall, the EVAR group had a higher initial aortic RPF index than the OMT group ($P = 0.01$).

Overall, there was a non-significant decrement in the aortic index from the initial diagnosis to post three to six months of the OMT in both the medical ($P = 0.14$) and EVAR ($P = 0.72$) groups (Figure 7). However, the aortic RPF index decreased significantly post-EVAR ($P = 0.04$) (mean follow-up of 84.80 ± 69.30 months) (Figures 8, 9). The pre-operative cross-sectional periaortic soft tissue area was almost double in the EVAR group compared to the OMT group. Medically resistant patients with EVAR had their cross-sectional periaortic soft tissue area decreased by nearly two-thirds within six months and reached near-normal within 24 months of follow-up.

Follow-up

Median follow-up duration was 62.7 months (IQR: 28.2–106); EVAR 63.4 months (IQR: 56.5–83.8) vs. OMT 58.1 months (IQR: 22.7–110).

Discussion

Two-thirds of RPF are idiopathic. Twelve per cent are secondary to the use of ergot alkaloid derivatives. However, ten per cent are associated with malignancies, including lymphoma,

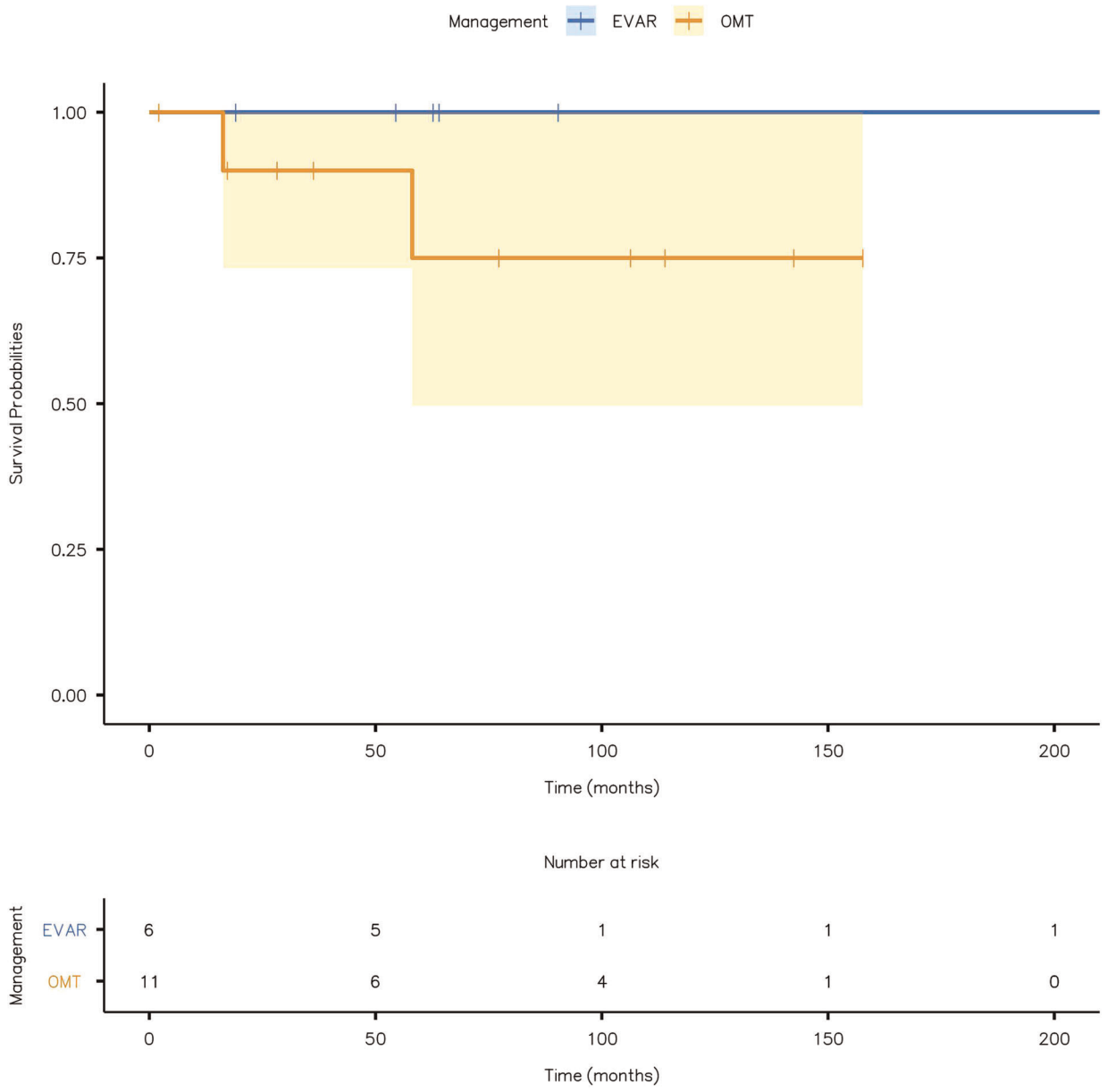

FIGURE 6
Kaplan-Meier plot showing all-cause mortality in patients with optimal medical therapy (OMT) and endovascular aneurysm repair (EVAR).

retroperitoneal sarcoma, carcinoid tumour, thyroid neoplasms, or metastatic gastrointestinal tumours (14–18).

Idiopathic and benign forms of RPF have a good outcome, whereas RPF secondary to malignancy has a poor prognosis (19). Therefore, the most crucial challenge is distinguishing benign from malignant RPF at imaging.

We have a simple algorithm that we usually follow. If aorta and inferior vena cava (IVC) is anteriorly displaced with posteriorly enlarged lymph nodes to the great vessels, in a more cephalic location in the retroperitoneum, it is usually a malignant RPF, and it often exerts mass effect on neighbouring structures (14). Benign RPF soft-tissue mass always spares the posterior aspect of the great vessels and does not cause vascular displacement. It is located mainly distal to the renal hilum (20) and has an infiltrative aspect enveloping rather than displacing adjacent structures (14). In this aspect, most physicians relied on complex surgery to relieve the obstruction caused by RPF, with an adjuvant of double J ureteric stents followed by open or laparoscopic ureterolysis. Such an approach does not address systemic symptoms, such as pain, weight loss and anaemia, or the disease's underlying causes - inflammation and fibrosis.

TABLE 3 Retro-peritoneal fibrosis (RPF) aortic index and cross-sectional area of the peri-aortic soft tissue enhancements at the initial diagnosis, post optical medical treatment (OMT) and post endovascular aneurysm repair (EVAR).

	Aortic RPF Index (Mean ± SD, range)			Cross-sectional area mm^2 (Mean ± SD, range)		
	EVAR Group ($N = 6$)	OMT Group ($N = 11$)	*P*-value	EVAR Group ($N = 6$)	OMT Group ($N = 11$)	*P*-value
Initial (at presentation)	0.36 ± 0.07 (0.27–0.49)	0.24 ± 0.08 (0.12–0.37)	0.01*	1182 ± 537 (628–2177)	650 ± 476 (207 –1627)	0.05*
Post-OMT	0.35 ± 0.06 (0.27–0.42)	0.18 ± 0.10 (0.00–0.37)	0.01*	1069 ± 638 (374–2177)	542 ± 476 (0–1627)	0.07
Post-EVAR	0.21 ± 0.14 (0.04–0.36)	–	–	803 ± 833 (111–2177)	–	–
Post-EVAR vs. Post-OMT	0.21 ± 0.14 (0.04–0.36)	0.18 ± 0.10 (0.00–0.37)	0.59	803 ± 833 (111–2177)	542 ± 476 (0–1627)	0.42

**Significant.*

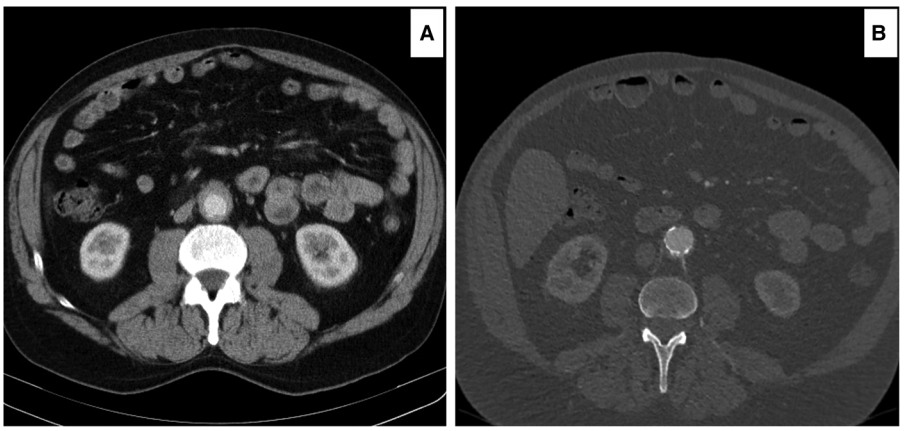

FIGURE 7
Computed tomography angiography (CTA) images showing decrement of the peri-aortic soft tissue enhancements following medical management. (**A**) Initial 4 mm peri-aortic soft tissue enhancement. (**B**) Two years post medical management, the peri-aortic soft tissue enhancement was reduced to 1 mm.

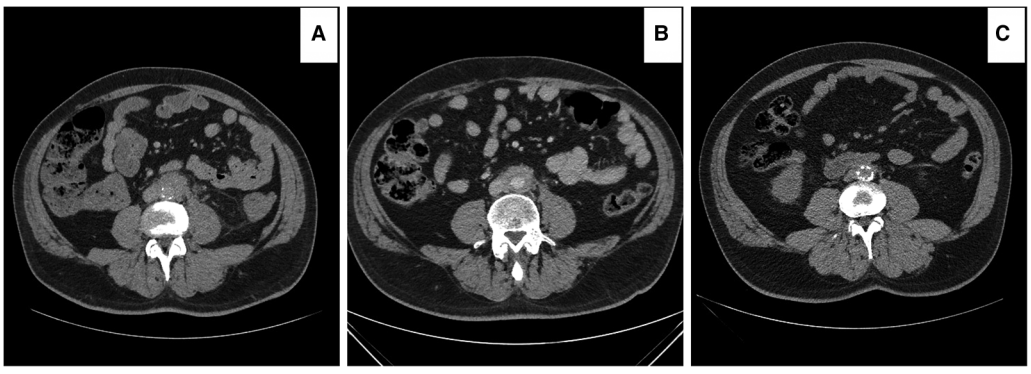

FIGURE 8
Computed tomography angiography (CTA) images showing improvement of the peri-aortic soft tissue enhancements following endovascular aneurysm repair (EVAR). (**A**) Initial peri-aortic soft tissue enhancement of 6 mm. (**B**) failure of medical treatment at 15 months with an enhancement increment to 8 mm. (**C**) Nine months post-EVAR, enhancements of 2 mm. All the symptoms and signs disappeared, and the patient is living a symptom-free life.

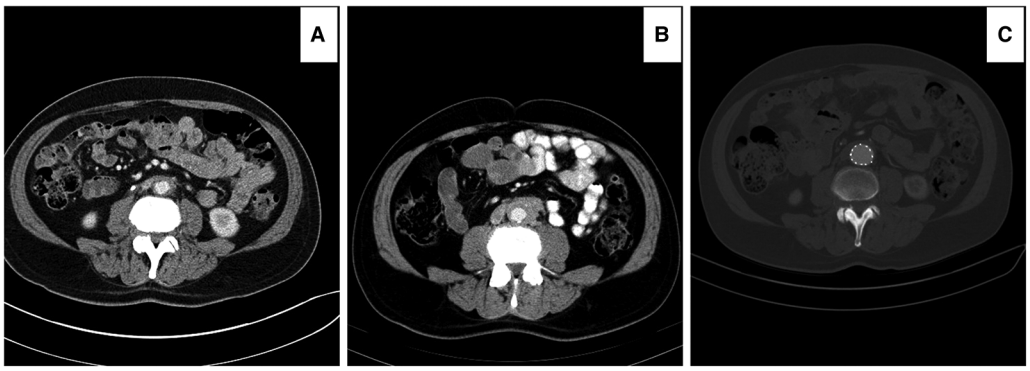

FIGURE 9
Computed tomography angiography (CTA) images showing improvement in peri-aortic soft tissue enhancement following endovascular aneurysm repair (EVAR): (A) peri-aortic enhancement of 3 mm on optimal medical therapy for three months. (B) Peri-aortic enhancements increased to 6 mm after optimal medical management for nine months. (C) peri-aortic enhancements disappeared with no evidence of RPF six months post-EVAR.

Although the pathophysiology of this process is unknown, an exaggerated local inflammatory response to oxidized low-density lipoprotein in aortic plaque has been postulated. Treatment for IgG4-RD includes high-dose steroids and Disease-Modifying Anti-Rheumatic Drugs (DMARDs); rituximab, a monoclonal antibody targeting B cells, tapering off over six months (4–7). Maintenance therapy with prednisone is recommended for up to three years. The disease recurs in 30%, and the use of mycophenolate mofetil, tamoxifen, or methotrexate should be considered for these patients.

All 17 patients were primarily managed with a minimum of three months of steroids. Symptoms and signs initially improved. But six patients became refractory to all medical therapy modalities, with flared up abdominal pain and excoriating back pain demanding an endovascular intervention by EVAR. Therefore, OMT was only successful in 11 patients in our study. The other six medically resistant patients, who required EVAR, were referred to our services more than a year after diagnosis. This may explain why their indices were higher than OMT. In those treated by EVAR, the aortic index dropped significantly after excluding the infra renal aortic wall from the circulation (**Figure 10**). Comparing post-EVAR to OMT, the aortic RPF indices indicate that EVAR was as useful as OMT in decreasing the peri-aortic soft tissue enhancements.

The aortic RPF index fell by 80% in all EVAR patients and was back to normal in 66.66% of the EVAR managed patients. In patients with IgG4-related periaortitis who were responsive to OMT, their aortic RPF index dropped in 20% of the patients.

In all EVAR patients, CTA demonstrated suppression of aortic inflammation and complete aortic remodelling within six months, and all patients went off their analgesia and immune modulations drugs. All OMT patients were kept on DMARDs lifelong.

Our management aim in RPF is to relieve clinical symptoms of the disease and abolish pain through the prevention and management of the fibrotic process. The fundamental goal is to release the encapsulated structures around the aorto-iliac, including the IVC and ureters.

IgG4-related aortic lesions are difficult to distinguish from aortitis, peri-aortitis, inflammatory AAA and RPF (21). Corticosteroid therapy's effectiveness for IgG4-related aortic lesions remains controversial as it may fail in modulating the dense periaortic fibrous tissues (9, 22). A biopsy must be done to clarify the diagnosis and rule out malignancies or infectious diseases in cases where aortitis is refractory to optimal medical therapy.

The endovascular management of complicated peri-aortic inflammation is a challenging task, and there are no fixed guidelines or algorithms to follow after medical management failure. EVAR attenuates proinflammatory T-cell changes compared with open repair. T-cell activation reduction with impaired responsiveness to superantigen (11) implies that the immunological sequelae of EVAR for IgG4 aortitis are more favourable than after the open approach, with potentially less risk of adverse outcomes.

The aortic RPF index increases with increasing peri-aortic enhancements in RPF. Monitoring with inflammatory markers and CT scan should be continued every three months while on treatment and every six months when off treatment, as RPF has recurred in some cases, even years after treatment. Ureter obstruction recurs in about half of all people who had surgery.

Our six EVAR patients had failed a nonsurgical RPF approach with two drugs - prednisone and/or mycophenolate mofetil (MMF). As their systemic symptoms did not improve, an innovative approach with EVAR was warranted. The orthodox approach in an IgG4-related inflammatory AAA is bilateral ureterolysis through an open surgical approach.

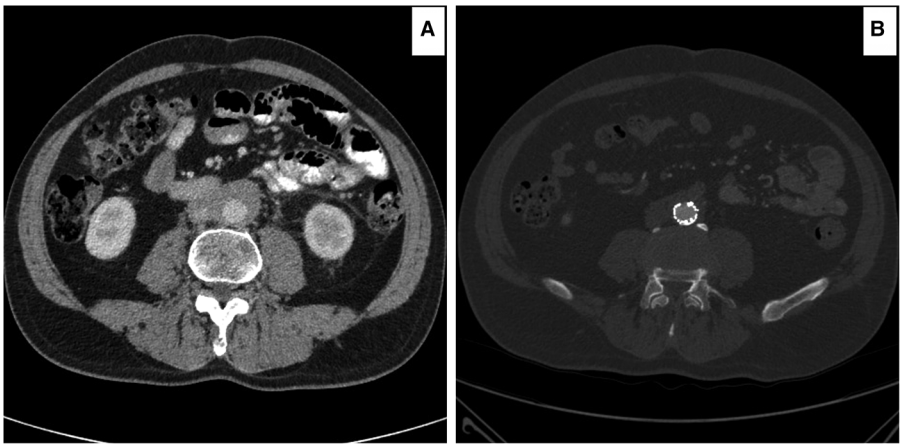

FIGURE 10
Computed tomography angiography (CTA) images showing improvement of the peri-aortic soft tissue enhancements following endovascular aneurysm repair (EVAR). (A) Post 16 months on optimal medical therapy, the peri-aortic soft tissue enhancement of 11 mm. (B) One year post-EVAR, all symptoms and signs disappeared with peri-aortic soft tissue enhancement of 3mm.

However, bilateral ureterolysis through an open surgical approach in an IgG4-related inflammatory AAA is associated with high morbidity. EVAR will avoid extensive dissection, thus minimizing the risk of morbidity and mortality.

Our results contradict the finding of Scheel (23) from John Hopkins, who used the prednisone/mycophenolate mofetil combination therapy to treat RPF patients. They reported a response rate of 95 per cent and a recurrence rate of 5 per cent. More than one-third (35%) were resistant to OMT in our study, all requiring EVAR to achieve a better clinical outcome. However, these are only the percentage of the patients who were referred or presented to us with RPF.

Our results mirror the findings of Ikeda et al. (24), who used EVAR to treat IgG4-related peri-aortitis, with a one-year follow-up that revealed complete resolution of periaortic inflammation. EVAR is best suited for an IgG4-related inflammatory AAA as the actual luminal diameter of peri-aortitis is near normal. This was depicted by the RPF aortic index, which returned to a near-normal level after EVAR. However, the thickened, diseased, disrupted aortic wall can induce a false aneurysm (25).

Our cases supplement previous publications on EVAR for complicated infrarenal peri-aortic RPF due to IgG4-related peri-aortitis in high-risk patients with ureteric compression or obstruction. In previous studies, the solution was to relieve the symptoms with ureteric stents or ureterolysis rather than treat the underlying cause (26, 27). Our results complement the finding of Hapka et al. (27), who employed EVAR when RPF was associated with hydronephrosis, common iliac artery (CIA) stenosis and saccular aneurysm.

Kawashima et al. (28) confirmed interleukin (IL) 6 upregulation in the adventitia of activated immune reactions in IgG4-aortic aneurysms (AA) patients. OMT regimens, including tocilizumab, a human monoclonal antibody that competitively inhibits IL-6 binding to its receptor for refractory disease IgG4-AA patients, are appropriate adjuvant to steroids. Furthermore, it could serve as a new effective therapy for IgG4-AAs (29). Our six patients received tocilizumab, but only three improved.

Surprisingly, expert consensus on initiating treatment in IgG4-RD active disease patients is low, considering irreversible damage to visceral organs may happen within weeks. The strategy and sole aim of management is avoidance of fibrosis and its potentially devastating impact on organs. RPF response is not sustained if glucocorticoids are decreased (30). However, remission induction and maintenance differ from country to country, depending on B-cell depletion therapy availability. Japanese rely upon glucocorticoid monotherapy. In contrast, North Americans and Europeans emphasize the early introduction of glucocorticoid-sparing agents, including B cell–depleting strategies (30).

There was no need for remission induction and maintenance following EVAR for our six patients. The physician must initiate lateral thinking, as minimally invasive infra-renal aortic exclusion by stent graft may be an ideal simple solution. Early diagnosis and treatment of the under-recognized RPF/IgG4-related disease are important before reaching the poorly responsive fibrotic stage with morbidity related to organ damage. Although most patients respond to medical therapy, relapses are still common. Inflammatory aortic aneurysms patients behave worse than patients with noninflammatory aortic aneurysms (12). Preoperative suspicion and the endovascular option offer superior results for challenging and complex aortic pathologies. However, our study is limited due to the relatively small number of patients owing to an uncommon condition and its retrospective nature. Furthermore, we compared two different management

strategies, medical vs. surgical, in medically resistant patients, which may represent a source of bias.

Conclusion

EVAR in RPF medical resistant patients is a valuable option in the armamentarium of nephrologists and rheumatologists. An endovascular intervention provides a promising outcome in RPF/IgG4-RD periaortitis, which is refractory to medical therapy. It is safe and easy to deploy and adds more options to the managing physicians. Early referral to centres experienced in managing such pathology is crucial for a superior outcome. However, the rarity of RPF precludes an RCT. Therefore, we recommend further studies to investigate and establish the long-term effectiveness of endovascular repair in RPF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Galway Clinical Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

All the authors are involved in the conception and design, data acquisition, analysis and interpretation along with the manuscript drafting and revision. All the authors have given the final approval for the publication. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Two decades of experience in explantation and graft preserving strategies following primary endovascular aneurysm repair and lessons learned

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Objectives: We aim to scrutinize our evolving re-intervention strategies following primary endovascular aortic aneurysm repair (EVAR) - EVAR GORE SalvAge Fabric Technique (ARAFAT), aortic sac double breasting with endograft preservation, and stent-graft explantation.

Methods: We performed 1,555 aortic interventions over the study period, including 910 EVARs. Factors associated with the need for reintervention and the likelihood of chronic fabric fatigue failure (CFFF) were investigated. Using conventional and innovative diagnostic modalities with Prone contrASt enHanced computed tomography Angiography (PASHA), 136 endoleaks (ELs) were identified (15 type I, 98 type II; 18 type III; 5 type IV).

Results: Forty-four (4.84%) patients underwent re-intervention post-primary EVAR; 18 ARAFATs, 12 double breastings, and 14 explantations. Choice of re-intervention was based on patient fitness and mode of failure. Mean EL detection duration following primary EVAR was 53.3 ± 6.82 months, while mean time to re-intervention was 70.20 ± 6.98 months. The mean sac size before the primary EVAR and re-intervention was 6.00 ± 1.75 cm and 7.51 ± 1.94 cm, respectively. Polyester (61.40%) was the most commonly employed stent-graft material. Use of more than three modular stent-graft components (3.42 ± 1.31, $p = 0.846$); with the proximal stent-graft diameter of 31.6 ± 3.80 cm ($p = 0.651$) and the use of iliac limbs more than 17 mm ($p = 0.364$), all added together are contributing factors. We had one peri-operative mortality following explantation due to sepsis-induced multiorgan failure.

Conclusions: Our re-intervention strategies matured from stent graft explantation to graft preservation with endovascular relining of the stent-graft. Graft preservation with aortic sacotomy and double breasting were used to manage concealed ELs due to aortic hygroma.

KEYWORDS

endovascular procedures, complications, reintervention, explantation, graft preservation

Introduction

Endovascular aneurysm repair (EVAR) has revolutionised therapeutic tactics in managing aortic pathologies over the past three decades. EVAR has shown reduced early peri-operative morbidity and mortality compared to open surgical repair (OSR) (1). However, these advantages are lost in long-term follow-up due to stent-graft complications, including fabric and material failure (2–5).

EVAR effectiveness is determined by the aortic sac segregation from systematic pressure and sac shrinkage. Complications post-EVAR need close surveillance as aortic sac dynamics influences EVAR durability, and continuous sac expansion could result in rupture (3). Endoleaks (ELs) may thrombose, but if they persist, the consequences can be detrimental, mainly if they are high-flow and associated with continued aneurysmal sac expansion (4, 5). These complications require aggressive management with re-intervention to abolish the risk of rupture. Re-intervention could be achieved through salvage of the primary endograft *via* a graft preserving strategy or explantation as necessary. In this study, we aim to analyse our three evolving strategies of re-intervention following the primary EVAR - EVAR GORE SalvAge Fabric Technique (ARAFAT), double breasting, and explantation.

Methods

This is a retrospective observational study performed in our tertiary vascular center from 2002 to 2020. The primary outcome is aortic related mortality. The secondary outcomes are technical success, perioperative morbidity and mortality, and overall survival probabilities.

Society for Vascular Surgery (SVS) reporting standards is used to define the outcomes (6). Technical success is defined as the periprocedural events from the initiation of the procedure to the first 24-hour. Primary technical success is the successful introduction and deployment without surgical conversion or death, type I or III ELs, or graft limb obstruction.

A re-intervention is classified as any procedure performed for subsequent aneurysm and/or primary procedure-related complications during follow-up of the primary EVAR. Factors associated with the need for re-intervention and the likelihood of chronic fabric fatigue failure (CFFF) were investigated amongst the re-intervention groups.

Primary EVAR and follow-up strategy

Out of 22,349 aortic referrals to our tertiary referral centre, we performed 1,555 aortic interventions over twenty years. Amongst them, 910 were EVAR ± iliac branch device (IBD), and 96 were thoracic endovascular aortic repair (TEVAR)/ branched endovascular aortic repair (BEVAR).

All our patients were followed-up with duplex ultrasonography (DUS) and plain film abdomen every six months. Patient with continuous sac expansion without detection of EL through conventional supine computed tomography angiography (CTA) underwent a Prone contrASt enHanced computed tomography Angiography (PASHA), a multiphase time-resolved four-phase positional (prone) CTA protocol for detection and classification of concealed ELs (7). The PASHA protocol enhanced the degree of contrast infiltration into the aortic sac when microleaks were present, which helped us to plan the re-intervention strategy. PASHA diagnosed all cases of type IIIb EL that were previously classified as concealed Type V EL in the context of continuous sac enlargement (7).

We identified 136 ELs (14.95%), including 15 type I ELs, 98 type II ELs, 18 type III ELs, and 5 type IV ELs. Decisions for re-interventions were formulated at the discretion of the vascular surgery multidisciplinary team, which considered factors like the rate of sac expansion, EL types, and patient's general condition (**Figure 1**). All the type I ELs were managed with proximal aortic cuff and/or distal extension or chimney endovascular aneurysm repair (ChEVAR). Four (26.70%) of these type I ELs required tertiary re-intervention at 5, 7, 8 years of post-secondary intervention. Amongst the 98 type II ELs, 12 (12.24%) that were associated with aortic sac expansion had a trial of embolisation initially; however, they all had persistent sac expansion despite embolisation. We applied PASHA diagnostic technique to them, which eventually showed aortic sac hygromas or type III ELs. Out of these 12, seven underwent double breasting for aortic sac hygromas, and the remaining five had explantations due to chronic fabric fatigue with type IIIB EL within three years of re-intervention. Our isolated type II EL had a 41.84% ($n = 41$) spontaneous resolution rate, and none of them ruptured.

Re-intervention strategies

Our practice had evolved over twenty years from diagnostics to management. Our decision-making has been influenced by several factors, including the mode of endograft failure, aneurysm sac size and patient fitness for surgery. Our ability to make informed decisions on the mode of failure evolved after we spearheaded the PASHA CTA protocol to accurately differentiate between different types of ELs and aortic sac hygromas (7). Aortic sac hygromas with the Hounsfield unit (HU) < 25 and an associated sac size greater than 7.5 cm indicate aortic aneurysm sac failure and a loss of the ability of the aortic wall to remodel (7). In cases with no defined type I, II or III ELs, and HU was less than 25, a diagnosis of expanding aortic hygroma was confirmed, and aneurysmorrhaphy was performed. In our experience, patients developing hygromas had factors, which likely contributed to

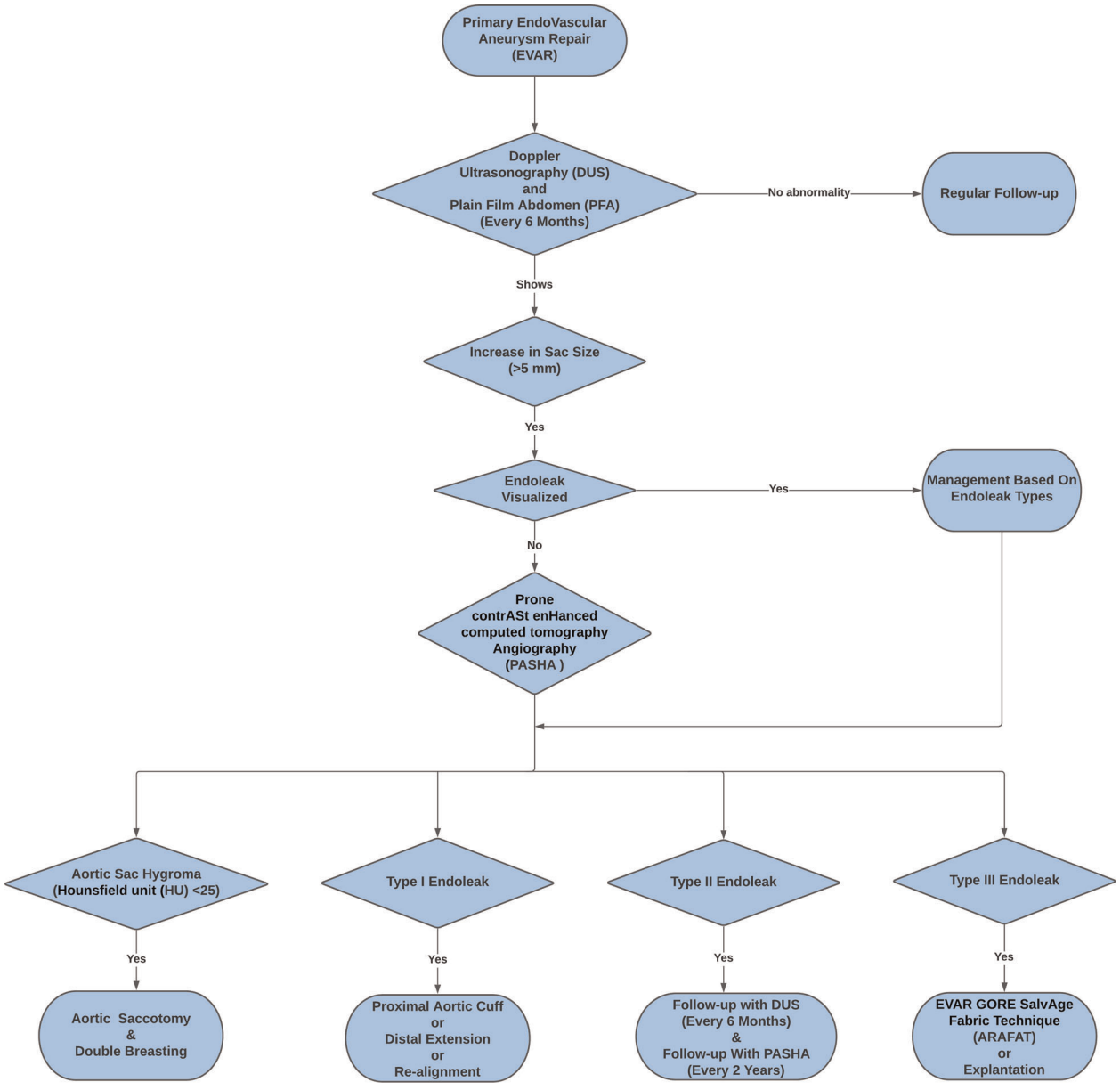

FIGURE 1
Flowchart depicting the adoption of the re-intervention strategies (EVAR GORE SalvAge FAbric Technique (ARAFAT), Double Breasting, and Explantation) following Prone ContrASt EnHanced Computed Tomography Angiography (PASHA).

the ability of fluid to exudate through the endograft material. We witnessed that the predisposing factors for aortic sac hygroma are direct oral anti-coagulant medication, administration of tissue plasminogen activator (tPA) and episodes of hypoalbuminemia (7). However, in the absence of these factors, it was considered that exudation of fluid through the endograft is likely to represent general fabric fatigue and loss of crystallinity; we considered that relining the endograft with the ARAFAT technique was more useful to exclude the failed endograft from the circulation and prevent ongoing transudation into the aortic sac. As our patients are living longer and now present 10–15 years after the index procedure, they can be late octogenarians or early nonagenarians by the time they require reintervention. This forced us to employ the ARAFAT protocol more frequently. In essence, if a patient is fit for a definitive endograft explant and open surgical repair, then this is our procedure of choice; if a patient has precedent factors that likely contributed to a hygroma and those factors are likely not to recur, then we perform an aneurysmorrhaphy; however, if the patient has an

expanding sac and is unlikely to be able to tolerate such an open surgical approach, we opt for ARAFAT physically (Figure 1).

Explantation

In our early series with type IIIB fabric failure, we performed explantation by infra-renal clamping after transfixing the left renal vein followed by partial endograft excision (Figures 2A,B). Once the fabric of an endograft has started to fray, it heralds the start of a more substantial issue and represents a more extensive reduction in fabric integrity and a loss of crystallinity. Placing a stitch in the fabric would be a temporary, and likely unsuccessful attempt to solve a chronic problem. In fact, stitching a frayed fabric would likely propagate further holes and fabric disintegration, causing more damage than good. Once the device has failed, it needs to be explanted or relined. During explantation, we routinely leave behind the suprarenal uncovered stents and their barbs and anastomosed the open surgical graft to it infra-renally after partial graft excision. However, the AFX endologix (Endologix Inc., Irvine, CA, USA) graft was totally removed as it depends on the iliac bifurcation for fixation and does not have barbs (Figure 2C). We routinely performed re-enforcement with polytetrafluoroethylene (PTFE) pledgets when anastomosing the silver Dacron graft to the old proximal failed aortic graft or the aortic wall. Pledgets were necessary for reinforcement as the aortic tissue was friable and required support.

However, many of our patients with type IIIB EL were between 4 and 9 years post-implantation and therefore, most were either septuagenarian or octogenarian. Open surgery and explantation are risky in these frail sarcopenic patients. Consequently, we developed the ARAFAT technique in patients at high risk for surgery, i.e., elderly patients with concurrent co-morbidities.

Aortic sac hygroma and double-breasting

Aortic sac hygromas are sac dilatations attributed to transudation through the stent-graft fabric. They expand slowly without evidence of EL forming a phlegmon with jelly-like consistency around the endograft. They have radio-density less than 25 Hounsfield units (HU) and are most commonly associated with polyester endografts (7–11). Diagnosis of aortic sac hygromas was neither feasible nor accurate previously; however, newer imaging techniques will identify them.

We performed aortic sacotomy after the diagnosis, with the evacuation of related hygroma and/or aortic thrombus, and all bleeding lumber vessels were transfixed. Subsequently, we filled the opened aortic sac with XenoSure® biologic patches (LeMaitre Vascular, Inc., MA, USA) to induce fibrosis. We then performed aneurysmorrhaphy by double breasting and plication of the aneurysm sac over EVAR graft to prevent contact with the bowel, thereby reducing the risk of subsequent graft infection (Figures 3A, B). Wrapping and

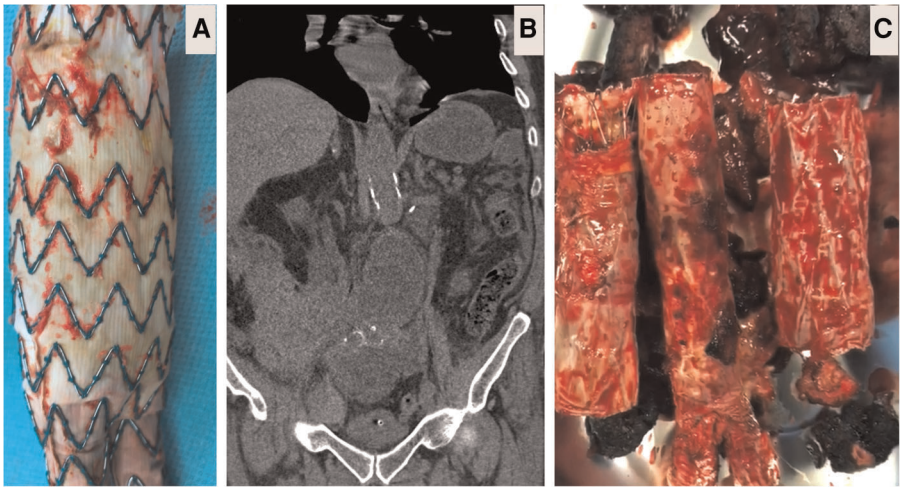

FIGURE 2
Explantation. (A) Body of partially explanted Cook (Bloomington, IN, USA) polyester-based endograft depicting micro-fabric pores due to chronic fatigue failure close to the allies of the stent. (B) Computed tomography angiography (CTA) image showing partially explanted Cook graft with the suprarenal spare springs and hooks left in-situ. (C) Here, patient underwent primary endovascular aneurysm repair (EVAR) with Endologix AFX (Endologix, Irvine, CA). However, this polytetrafluoroethylene (PTFE) based endograft failed due to the fracture of the endoskeleton, which acted as a hinge against the PTFE. Attempts to salvage the EVAR resulted in implantation of two proximal cuffs over six years follow-up. The patient presented with rapidly expanding 8 cm abdominal aortic aneurysm and abdominal pain, necessitating immediate total graft explantation and aorto-bi-iliac reconstruction by 16 × 8 mm silver Dacron graft (Maquet, Rastatt, Germany).

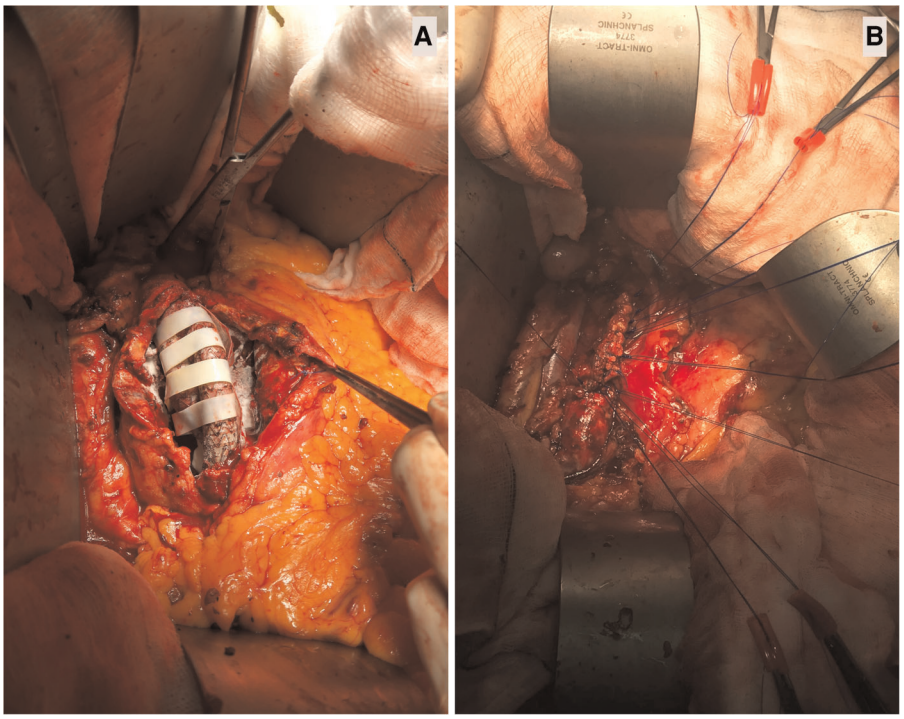

FIGURE 3
Aortic sacotomy with obliterating endo-aneurysmorrhaphy and stent-graft preservation post-EVAR. (A): Wrapping the opened aortic sac with XenoSure biological patch (LeMaitre Vascular, Inc., MA, USA) during double breasting. This 82-year-old patient had endovascular aneurysm repair (EVAR) with polytetrafluoroethylene (PTFE) GORE graft (GORE®, Flagstaff, Arizona, USA) in 2008, after which the aortic sac shrunk to 4.2 cm. However, the patient had tissue plasminogen activator (TPA) twice for acute MI in 2018, resulting in aortic sac hygroma with sac expansion to 8.9 cm. The formation of a hygroma as a consequence of ultrafiltration of blood through the stent-graft fabric led to continued sac enlargement without a detectable problem within the endograft, i.e., no structural stent-graft problem and no demonstration of EL. (B). Double breasting of the aortic sac with interrupted mattress prolene stitches to achieve hemostasis. Due to aortic sac hygroma, the patient experienced continuous sac expansion, abdominal pain, and low back pain. Computed tomography angiography (CTA) demonstrated the radiodensity of <25 Hounsfield units. The patient required aortic sacotomy, followed by wrapping the aortic ePTFE device with XenoSure biological patches and filling the post wall of the aortic sac with haemostatic powder HaemocerTM plus (Biocer Entwicklungs-Gmbh, Bayreuth, Germany), after which double breasting of the aortic sac was performed. This sealed the aortic sac and abolished the abdominal and low back pain. The aortic sac shrank to 4.5 cm during the subsequent follow-up.

cerclage of the proximal aneurysm neck were used to prevent stent-graft migration and EVAR dislodgment. Aortic sacotomy and double breasting made it possible to confirm endotension when no visible leak was seen on the preoperative CT scan. In these cases, the aortic sac hygroma presented as dark grey organised seroma with no patent back-bleeding vessels. All hygromas were sent for culture and sensitivity, and all returned sterile.

EVAR GORE SalvAge fabric technique (ARAFAT)

Over the past 5 years, we utilized ARAFAT as our protocol to seal the type IIIB EL, particularly in patients at high risk for open conversion (7). ARAFAT helped us realign stent graft to seal microleaks and improve spiral arterial flow. Here, we deployed an oversized EXCLUDER® aortic cuff (GORE®, Flagstaff, Arizona, USA) into the previously implanted stent graft, followed by the simultaneous deployment of EXCLUDER® iliac extensions as necessary in double-barrel configuration from the main cuff (**Figures 4A–C**) (7).

Ethical consideration

Ethical approval was obtained from the local Institutional Ethics Review Board (C.A. 1210). Data were collected from patients' records and anonymised. Utmost priority was given to maintain patients' confidentiality.

Statistical analysis

Continuous outcomes were summarized with mean and standard deviation (normal distribution) or median and

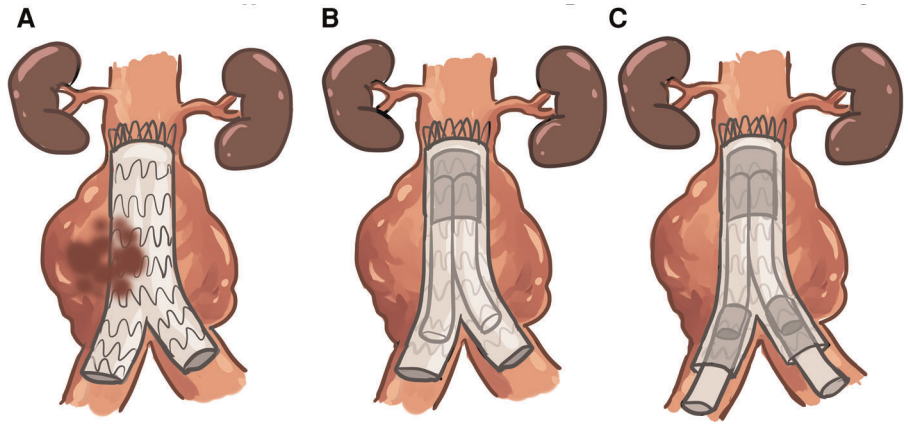

FIGURE 4
EVAR GORE SalvAge Fabric Technique (ARAFAT) is our protocol used to seal the type IIIb EL. (A) Microleaks at the endograft. (B) Oversized EXCLUDER® aortic cuff (GORE®, Flagstaff, Arizona, USA) deployed into the previously implanted stent-graft. (C) Simultaneous deployment of an EXCLUDER® iliac extension, as necessary, in double-barrel configuration from the main cuff.

interquartile range (non-normal distribution). The categorical outcomes were summarized with percentages and proportions. For statistical significance, Chi-squared and Kruskal-Wallis tests were used. $p < 0.05$ was taken as statistically significant. Statistical analyses were conducted with Minitab (Minitab® Ltd., UK).

Results

We had 44 patients who underwent reinterventions following primary EVAR, including 18 ARAFAT and 14 explantations for type IIIB ELs and 12 double breastings for aortic sac hygromas. The baseline characteristics of these patients are given in Table 1.

The average size of the aortic aneurysm sac during the primary EVAR was 6.00 ± 1.75 cm (Table 2). Twenty-seven polyester and 17 PTFE based endo-grafts were employed in these primary procedures. The average number of stent pieces used in the primary EVAR was 3.42 ± 1.31. The proximal main body diameter was 31.6 ± 3.80 mm (right limb size: 17.6 ± 4.20 mm and left limb size 17.9 ± 4.28 mm).

The mean duration of ELs identification following primary EVAR was 53.3 ± 6.82 months. The mean aortic sac expansion rate was 0.43 ± 0.25 cm per year, and the mean aortic sac size before the re-intervention was 7.51 ± 1.94 cm. Patients who underwent double breasting had the highest sac size (ARAFAT: 6.68 ± 2.13 vs. double breasting: 8.41 ± 1.72 vs. explantation: 7.52 ± 1.61 cm, $p = 0.029$). The mean duration of re-intervention following primary-EVAR was 70.2 ± 6.98 months (ARAFAT: 94.2 ± 12.5 vs. double breasting: 67.3 ± 6.78 vs. 41.8 ± 9.54 months, $p = 0.026$).

There was no difference between stent-graft materials (27 PE vs. 17 ePTFE, $p = 0.06$) on the re-intervention rate (Table 3).

All the patients had primary technical success. However, we had one sepsis-induced peri-operative mortality following explantation in a patient who had initial re-intervention for rapidly expanding aortic sac with type I EL before being referred to us. This patient also had prior embolisation of a lumbar branch, where the coil migrated to the spine resulting in paraparesis. After being referred to our centre, we performed explantation and aorto-bi-renal-bi-iliac bypass. The patient developed multiorgan failure due to sepsis and succumbed to death on the 28th postoperative day.

The overall survival plots during an average follow-up duration of 35.6 ± 6.24 months (ARAFAT: 9.00 ± 1.36 vs. double breasting: 42.5 ± 9.51 vs. explantation: 63.8 ± 14.2) is depicted in Figure 5.

Discussion

This study aims to scrutinise our three techniques of post-EVAR re-intervention, including an EVAR graft preservation strategy and/or explantation. Significant sac expansion over a short period needs scrutiny. Stent graft explantation with subsequent replacement is the definitive management approach. Graft preservation strategies include surgical double breasting of the aortic sac or endovascular relining of the stent-graft. For patients with significant co-morbidities and an enlarged sac with a maximum diameter less than 7.5 cm, we employed ARAFAT. Our results mimic Doumenc et al. (12) finding's that explantation and endovascular management,

TABLE 1 Baseline characteristics of the patients.

Baseline characteristics	Re-intervention strategies				
	Overall	Types			
		ARAFAT ($N = 18$)	Double breasting ($N = 12$)	Explantation ($N = 14$)	p-value
Total	44	18 (40.9%)	12 (27.3%)	14 (31.8%)	–
Male, n (%)	33 (75%)	14 (42.4%)	10 (22.7%)	9 (20.5%)	**0.511**
Age (mean ± SD), years	79.7 ± 7.03	80 ± 6.86	81.4 ± 4.93	77.7 ± 8.63	**0.408**
Tissue Plasminogen Activator use	3	0	3	0	–
Ischemic Heart Disease	27	10	8	9	**0.803**
Coronary stenting	11	8	3	0	**0.251**
Hypercholesterolimia	33	13	9	11	**0.925**
Atrail fibrillation	9	0	4	5	**0.022**
Hypertension	37	15	9	13	**0.261**
Diabetes Mellitus	15	3	5	7	**0.129**
Renal disease	7	3	2	2	**0.583**

Abbreviations: EVAR, EndoVascular Aneurysm Repair; ARAFAT, EVAR GORE SalvAge FAbric Technique; SD, standard deviation.

TABLE 2 Endograft characteristics employed in the primary endovascular aneurysm repair.

Baseline characteristics	Re-intervention strategies				
	Overall	Types			
		ARAFAT ($N = 18$)	Double breasting ($N = 12$)	Explantation ($N = 14$)	p-value
AAA size (CT Scans), cm	6.00 ± 1.75	5.90 ± 1.93	6.12 ± 1.24	6.00 ± 2.05	**0.940**
Stent-graft material (PE vs PTFE)	27 (61.4%) vs 17 (38.6%)	12 vs 6	5 vs 7	10 vs 4	**0.258**
No of pieces (stents), n	3.42 ± 1.31	3.33 ± 1.37	3.58 ± 0.99	3.36 ± 1.55	**0.846**
Proximal aortic cuff size, mm	31.6 ± 3.80	32.3 ± 3.77	31.5 ± 4.03	30.9 ± 3.77	**0.651**
Right limb stent-graft size, mm	17.6 ± 4.20	15.8 ± 4.86	18.8 ± 4.37	18.0 ± 3.14	**0.306**
Left limb stent-graft size, mm	17.9 ± 4.28	16.3 ± 5.52	19.1 ± 4.29	18.1 ± 2.66	**0.422**

Abbreviations: AAA, abdominal aortic aneurysm; ARAFAT, EVAR GORE SalvAge FAbric Technique; CT, computerised tomography; PE, polyester; PTFE, polytetrafluoroethylene.

TABLE 3 Stent-graft employed during the primary endovascular aneurysm repair (EVAR) and those requiring re-intervention.

Endograft types	Fabric material	Primary EVAR (total = 910)	Re-intervention (total = 44)
Zenith (Cook, Bloomington, IN, USA)	Polyester	4 (0.44%)	3 (75.00%)
Powerlink/AFX I and II (Endologix, Irvine, CA, USA)	ePTFE	110 (12.20%)	6 (5.50%)
Talent/Endurant I and II (Medtronic, Santa Rosa, CA, USA)	Polyester	330 (36.30%)	19 (5.80%)
Excluder Generation I and II (Gore Medical, Flagstaff, AZ, USA)	ePTFE	343 (37.70%)	11 (3.21%)
Incraft (Cordis, Miami Lakes, FL, USA)	Polyester	123 (13.52%)	5 (4.10%)

Abbreviation: ePTFE, expanded polytetrafluoroethylene.

hybrid endovascular repair and ARAFAT can be achieved in high deliberate practice volume centres with satisfactory results.

All our re-interventions had aortic sac size greater than 6 cm at the time of their primary EVAR with more than three modular stent graft components. Those that underwent double breasting had the largest sac size due to aortic hygromas (more than 7.5 cm on average) (7). Polyester was the most common stent material used in the primary EVAR amongst the re-intervention groups ($p = 0.258$).

EVAR carries a higher reintervention risk than OSR, and the risk increases with time (2). Reintervention rate could range from 20% in low-risk cases to 25% in high-risk patients (13, 14). There is a minimal divergence between first, second or third-generation aortic endograft devices (15). However, there has been an acknowledged failure rate for all major commercial endografts, necessitating late aneurysmorrhaphy and double breasting (16).

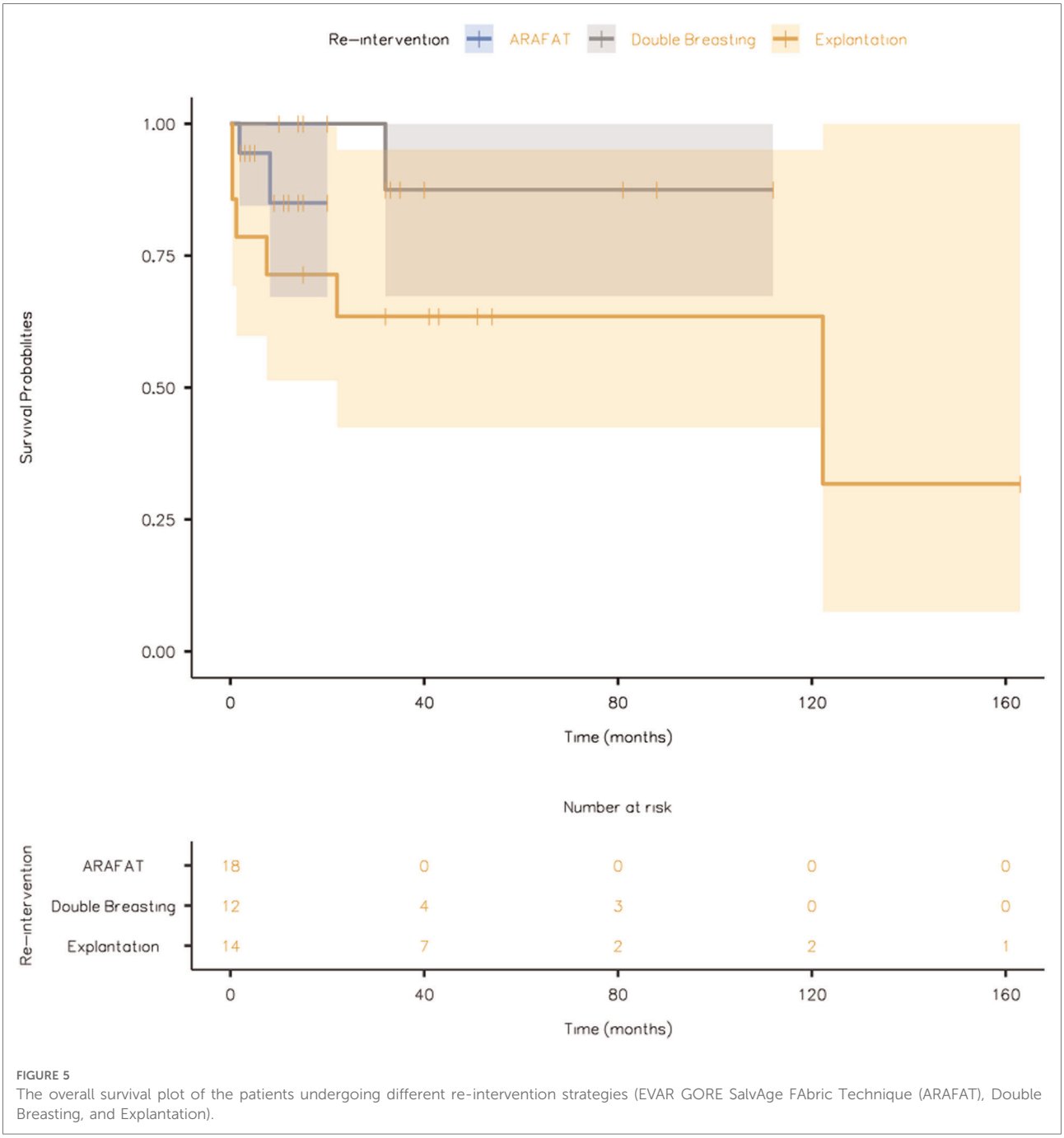

FIGURE 5
The overall survival plot of the patients undergoing different re-intervention strategies (EVAR GORE SalvAge FAbric Technique (ARAFAT), Double Breasting, and Explantation).

In our experience of 44 cases, we were surgically successful for a range of different endovascular scenarios and accomplished reasonable outcomes. There was no aneurysm-related mortality. However, amongst the nine mortalities over the mean follow-up duration, 60% were cancer-related, and 40% were cardiac-related.

Endograft twisting, dislodgment, kinking, outflow obstruction, and ELs are some of the complications encountered post-EVAR. However, the main reason for re-intervention is EL with endotension and sac expansion regardless of the EL types (17). Gambardella et al. (18) reported that EL is also the utmost reason for aortic sacotomy, aneurysmorrhaphy and double breasting. Also, our strategy mirrors their advice in favouring infrarenal clamping for partial explanation of failed supra renal fixated EVAR grafts.

Controversial views about EL and endotension are plentiful within the vascular literature. Studies have shown that persistent EL increases the risk of rupture (19). However, some advocates that type II ELs are protective against aortic rupture (20). Current guidelines recommend intervention in patients with

continuous sac expansion (21). Variable results with trans-arterial, trans-caval, direct sac access and trans-iliac-lumbar embolization for type II EL had been reported (21). Alternative approaches such as the laparoscopic approach for type II EL has been described as tricky, even by the most proficient surgeons, due to dense periaortic inflammation (22). Minimal invasive therapies for type II ELs risk repeated interventions, with poor outcomes at five years (21, 23). In our opinion, type II EL should not be accepted as the cause of aortic sac expansion until multimodal investigations with temporal information regarding perigraft blood flow have been completed.

Our type IA ELs were challenging to solve as there was no consensus. Our cases were managed by Design Reconfigure Elongate Straighten Stiffen (DRESS) technique with proximal cuff and adjuvant ChEVAR.

We agree with the recommendation of Hinchliffe et al. (24) that in frail patients who were turned down for open repair a few years earlier, less invasive approaches with a lower threshold for endograft preservation should be considered. In this context, an aortic sacotomy with ligation of patent back-bleeding vessels and preservation of the EVAR graft can be a wise alternative to a more invasive explantation to prevent rupture in an expanding aortic sac.

Almost half of the ELs seal spontaneously during the first year; however, the likelihood of spontaneous closure decreases with time (4, 25). There is no consensus regarding how long to follow up and when to re-intervene (13–15). Only 1.97% of our patients had an endovascular reintervention before aneurysmorrhaphy, as we are highly selective in offering EVAR. The mean age of our patients who underwent re-intervention was 79.7 ± 7.03 years. In frail patients, we considered open repair only if endovascular options were impractical or exhausted. However, in cases in which the aortic sac diameter was more than 75 mm with abdominal or low back pain, we performed aneurysmorrhaphy. Any prolongation of such a critical situation could have ended in aortic sac rupture. This contradicts some authors who had one-third of all their patients subjected to endovascular manipulation before sacotomy, aneurysmorrhaphy, graft preservation and double breasting (26, 27).

Complications post-EVAR could be attributed to various factors. A head to head comparison with Endurant and Excluder grafts implanted in two groups of patients having similar anatomical characteristics demonstrated that two different types of EVAR endografts implanted in similar AAAs could provoke diverse flow properties (28). The study concluded that delineation of the hemodynamic features associated with the various commercially available EVAR grafts could further promote the personalization of treatment offered to aneurysmal patients and instigate concepts for design perfection in the future.

Published data has reported several factors associated with major adverse events post-EVAR. These factors include an aortic bifurcation with 50% calcification and diameter less than 20 mm; endograft iliac limb diameters greater than 27 mm; nitinol endograft stents; and the ratio of endograft iliac limb diameters to aortic bifurcation diameter greater than 1.4 (29). Conversely, the displacement forces in tapered iliac stent-grafts with asymmetric curvatures will impact stent-graft performance. When arterial blood pressure is on a curved stent-graft, it will generate an axially oriented force. The larger the cross-section, the more significant the force. In addition, the force generated by the flow velocity in the curvature of a vessel or a stent-graft acts in the axial direction. These two drag forces are due to the flow reaction to a change in direction due to the kinetic energy of the moving blood volume. The higher this velocity, the higher the energy. When the flow rallies into the curved wall, the kinetic energy is converted into a strong force. In smaller vessels, less than 11 mm, the force-velocity is larger than the force pressure. This breeds trepidations, particularly for stent-graft designs with 11 mm contralateral gates, which necessitates 13–14 mm contralateral docking limbs as they induce mega forces that result in major adverse events. Tapered grafts increase the axial forces applied at both ends by 50% as the flow velocity increases with a smaller diameter, increasing force-velocity. These forces increase with angulation, and implantations in angulated iliacs must be avoided to minimise migration risks. These haemodynamic forces have implications for stent-graft design for both tapered and bell-bottom geometries. A tapered graft should be outsized at both ends to augment radial and frictional force with the vessel and counterbalance velocity increase (30).

Morris et al. (31) had mirrored the above findings in the abdominal aortic endografts by analysing the Zenith (Cook, Bloomington, IN) and Endurant II (Medtronic Santa Rosa, CA) devices and documented the highest radial resistive force up to 3 N/cm. The supra-renal and infrarenal compliances were 6.9–5.1×104/mmHg and 4.8–5.4×104/mmHg. In contrast, the Fortron device (Cordis Endovascular, Santa Clara, CA) had the lowest at 0.11 N/cm. The Endurant II and Excluder devices had significantly decreased infrarenal compliance by 13%–26%. All four devices increased the pulsatile arterial energy loss (PAEL) by 44%, significantly lowering aortic wall compliance after EVAR. Choosing the most compliant devices for treating AAA minimises micro and macro-ELs and graft material fatigue and failure with later explantation with avoiding long-term cardiovascular events.

Further, long term renal outcomes with proximal aortic fixation are questionable, problematic and not yet established (32). Morris et al. (31) showed a frank dissimilarity between nitinol-based endografts with Dacron and suprarenal fixation compared to nitinol-based endografts with PTFE. Zenith (Cook Medical) and Endurant II (Medtronic) had the highest aortic stiffness (radial resistive force). Moreover, significant lower infra-renal compliance was observed in Endurant II and Excluder. Similarly, the selection of the most compliant devices

will enhance aortic elastic recoil with lower post-procedural complications. The metallic endograft skeleton, whether nitinol, stainless steel or cobalt alloy, reduces aortic compliance and stiffens the aorta. This stiffness induces a mismatch in the physio-mechanical properties between the native and the stented aorta, which results in PWV intensification.

Proximal fixation devices by suprarenal barbs for wall anchoring are contemplated to lessen the risk of distal migration, perfect proximal seal, and minimise type I EL. These attributes present us with a more challenging task as the presence of suprarenal stents often leads to suprarenal or supra-visceral proximal aortic clamping. Furthermore, detachment of wall-anchoring barbs risks injury to the aortic wall and renal ostia. These challenges increase operative and aortic clamp times, explaining the high reported mortality in these patients (33, 34).

We performed a partial explantation technique by leaving the suprarenal components of stent-grafts in-situ in the absence of sepsis. This is our preferred revascularisation option to reduce the risk of intraoperative injury to the aortic wall and branch vessels. It also helps to minimise para-aortic dissection and supra visceral aortic clamp level by retaining the proximal aortic endoskeleton. We anastomose the Dacron graft enforced with pledges to the endograft components to avoid suprarenal clamping and mortality.

The incidence of late aneurysmorrhaphy and double breasting after EVAR has been reported in up to 50% of reinterventions, which is multifactorial and depends on patient selection, follow-up protocols, endograft generation and type, and expertise in both endovascular and open aortic management (35–37).

In aortic hygroma patients with aortic sac more than 8 cm with abdominal and low back pain, we perform aortic sacotomy with obliterating endo-aneurysmorrhaphy and stent-graft preservation post-EVAR.

Aortic sacotomy with obliterating endo-aneurysmorrhaphy and stent-graft preservation post-EVAR is appealing as it averts the physiologic stresses of aortic cross clamping. Our results mirror Mohapatra et al. (38) and contradict Kansal et al. (39) for their striking 43% 30-day mortality.

In our experience, we noticed no difference in patients undergoing graft preservation vs. graft explantation. However, trends indicate that the graft preservation patients' were older and a higher risk cohort.

In proceeding with graft preservation, external banding of the neck combined with ligation of all branch vessels, including inferior mesenteric artery and median sacral artery, is performed. Subsequently, the aortic sac is filled with XenoSure biological patches, and the preserved graft is wrapped with silver Dacron patches to induce fibrosis and prevent any future chance of aortic sac expansion.

Some authors advocate routine CTA follow-up post-EVAR (40, 41). However, less than 50% adhered to imaging in the EVAR-1 trial and Medicare beneficiaries after five years (42, 43). We adopted the PASHA technique over contrast-enhanced ultrasound imaging, which is operator-dependant, as PASHA is standardised, easily reproducible and can be read by everyone (7, 44, 45). We recommend lifelong follow-up every six months by DUS for both iliac arteries post explantation of aorto-bi-iliac endograft for fear of iliac degeneration and rupture, as reported by Arnaoutakis et al. (46) Postoperative CTA provides better diagnostic utility for proximal and distal neck dilatation or disconnection of the stent-graft components, which DUS could miss on regular follow-ups.

ELs are triggered by the instability of the longitudinal growth of the aorta due to the cone-shaped necks or steep angulations. The shape of the proximal portion of the stent's main body gets flattened or crushed due to the cardiovascular aortic oscillation, increasing 2–4 mm in the aortic diameter of the proximal landing zone every year. The main body migrates continuously and slowly down towards the aortic bifurcation. This creates "autologous" strut perforations with type III fabric failure and ultimately type IA that can only be salvaged by explantation or ARAFAT technique (7, 47, 48).

The ability to salvage such cases by adding FEVAR or BEVAR is deemed to fail because bridging stents are needed to provide adequate stability over time. Furthermore, new challenges have arisen concerning patency as vascular territories that are primarily unaffected are incorporated into the disease process. Moreover, devices with suprarenal fixation components preclude suitable entry to visceral and renal vessels (49). Cognisant of such findings, we strongly advocate precise and meticulous strategic primary EVAR planning.

Post-implantation syndrome (PIS) following primary procedure is also a long-term determinate of EL and micro-fabric fatigue failure. Ito et al. (50) Voûte et al. (51) and Sartipy (52) associated polyester grafts with higher postoperative pyrexia, PIS and longer in-hospital stay compared to ePTFE grafts following EVAR. Post-implantation syndrome (PIS) has been reported in up to 60% following EVAR (50, 53). Polyester triggers a higher release of inflammatory biomarkers (tumour necrosis factor-α, IL-6, IL-10, and CRP) than ePTFE *in vitro* (51, 54). However, implantation of stent-grafts made with woven polyester is not just independently associated with a stronger inflammatory response; it also results in endothelial damage. Furthermore, active fixation using penetrating hooks or barbs at the proximal aortic implantation site leads to endothelial aggression with the penetration of the foreign material. The precise balance between nickel and titanium, or even cutting and polishing the metal, will affect the antigenic properties of the nitinol (51).

It is not surprising that most of the EVAR device technology introduced over the past decade has been withdrawn from the market due to failure in sealing technology, material durability, unsupported body, stent fracture, and avulsion. Failures have also arisen when aortic device companies have

iteratively lowered the profile of their devices to make them more attracted to non-surgical interventionalists (15). It is surprising that better stents have not yet been crafted after more than three decades of EVAR.

Choosing the most compliant devices for treating AAA minimises micro and macro-ELs and graft material fatigue, thereby avoiding late failure, explantation and long-term cardiovascular events. The physician involved in the decision-making should select the most appropriate EVAR graft. In general, approximately one-third of all of our EVARs were done out of instructions-for-use (IFU) with neck less than 1.5 cm and neck angulation more than 75%, and thrombus more than 3 mm at the proximal implantation site. However, the objective going forward is to recommend open surgery if the patient is physically fit. Otherwise, EVAR can be offered but cannot be undertaken outside IFU, with rare exceptions depending on patient fitness and urgency of presentation (47).

A strong policy of obeying the indications for use or abstaining from exploiting EVAR in challenging patients will alleviate the need for late aneurysmorrhaphy and reduce the need for reintervention to exceptional cases. LOCOS-1 (55) investigators documented that the broad applicability of EVAR increased late open conversion, independent of endovascular techniques innovations or advancements in-stent and fabrics materials. However, there are limited studies on the direct comparison between endografts and long-term outcomes, which need to be interpreted with caution. The majority of the available evidence-based studies represent a retrospective single centre experience with a limited subset of patients. Also, comparison among stent-grafts is restricted to devices based on personal and/or institutional preferences.

We believe that patient choice to a less invasive option is essential in the decision-making process; however, patients must be told of their alternatives during the informed consent process. Patients need to be well informed on the advantages and disadvantages of EVAR and understand that post-EVAR complication rates are still substantial.

Study limitations

The current study is limited by its observational nature, with potential selection bias. Although the number of patients included in this study is limited, this is one of the most extensive series to date evaluating aortic sacotomy with obliterating endo-aneurysmorrhaphy and stent-graft preservation post-EVAR. We have discussed various re-intervention strategies employed in our vascular setting; however, we understand that the indications for the re-intervention are different. Furthermore, it is not feasible to make a head-on-head comparison between them. Also, most of these re-interventions were performed recently, and we lack a long-term follow-up.

Conclusion

With the increasing popularity of EVAR, we forecast high numbers of post-procedural complications in terms of graft failure, short- and long-term hemodynamic alterations, and related morbidity and mortality. These complications necessitate the development and study of re-intervention strategies to salvage existing endograft and/or address graft-related complications.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Galway Clinical Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

All the authors are involved in the conception and design with acquisition, analysis and interpretation of data, and drafting the work or revising it critically for important intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The contemporary design of endovascular aneurysm stent-graft materials: PTFE versus polyester

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Endovascular aneurysm repair of the abdominal aorta (EVAR) and of the thoracic aorta (TEVAR) have revolutionised therapeutic strategies in the management of aortic pathology, and endovascular repair is now an established and attractive alternative to open surgical repair (OSR) due to its superior short-term safety profile. However, opinions are divided regarding its long-term cost-effectiveness, which is reflected in the controversial NICE guidelines on abdominal aortic aneurysm (AAA) repair published in 2018, which advised against EVAR for elective aortic repair due to high secondary intervention rates and resultant associated costs. There is no doubt that OSR continues to have a valuable role to play in aortic repair, but it is not universally applicable, especially in older and sicker patients. Therefore, we should not dismiss EVAR and TEVAR without examining the reasons for long-term failure, and the most obvious starting point is stent graft material properties. Polytetrafluoroethylene (PTFE) and polyester are the two most common stent-graft materials; however, there has been no objective comparison of PTFE and polyester stent-graft post-procedural outcomes in EVAR and TEVAR, or even OSR. This lack of definitive data on different stent-graft materials and their configuration necessitates a comprehensive review to elucidate the post-procedural outcome in terms of endograft failure, cardiovascular events, and aortic-related mortality and morbidity.

KEYWORDS

endograft complications, aorta—remodeling, polyester, EVAR, aortic compliance/distensibility, polytetrafluoroethylene

1. Introduction

Aortic disease management, either with surgical grafts or endovascular devices, has undergone minimal development since inception over 70 years and 35 years ago, respectively. Both open and endovascular grafts are "passive", one-type-fits-all devices that do not consider anatomical location or the underlying pathology (aneurysm, dissection, trauma) and do not reinstate the aorta's regeneration, biomechanical or physiological functions, resulting in long-term major adverse cardiovascular (CV) events and high reintervention rates.

Open aortic repair (OAR), first introduced in the 1950s, has historically been the gold standard technique for treating aortic aneurysms and dissections. In OAR, a prosthetic [Polyester or Poly Tetra Fluoro Ethylene (PTFE)] surgical graft is used to **replace** the affected aortic segment. Depending on which body cavity (abdomen, thorax or mediastinum) or how many body cavities are opened, OAR can be a challenging, highly-invasive procedure unsuitable for older and those with extensive co-morbidities. The risks associated wth OAR prompted the development of endovascular procedures in the late 90s. Endovascular became the preferred choice given its lower invasiveness, shorter hospital stays and quicker recovery times. In endovascular procedures, a metal scaffold covered by fabric (endograft) is inserted inside the aorta to **exclude** the diseased wall from the circulation. However, although endovascular repair became the treatment of choice in most cases, it is not feasible in all cases due to the variety of adverse anatomical features (e.g., sufficient length of the normal aorta for an implant landing zone, vessel tortuosity, access vessel calcification etc.). Despite such exceptions, endovascular therapy was quickly disseminated into clinical practice. However, following the adoption of endovascular techniques, questions about its durability started to arise, and guidelines issued by the UK's National Institute for Health and Care Excellence (NICE) in 2020 recommend against endovascular aortic repair (EVAR) as first-line management of elective infrarenal aortic aneurysm, based on surveillance costs and high re-intervention rates (1). The NICE guidelines sent significant ripples through the clinical community. Still, they have provided an opportunity for reflection and impetus to consider if certain aspects of EVAR could be improved, such as stent-graft materials.

Polytetrafluoroethylene (PTFE) and polyester are the two most common stent-graft materials; however, there is no objective evidence comparing their relative effectiveness in abdominal aortic aneurysm (AAA) repair. In this review, we consider the influence of the contemporary stent-graft materials and their configurations on short and long-term post-procedural outcomes amongst patients undergoing EVAR for Abdominal Aortic Aneurysm (AAA). The primary aim is to compare the available contemporary stent-graft materials, PTFE versus polyester, on aneurysm-related mortality and cardiovascular outcomes. Secondary aims include graft-specific complications and reintervention rates. Subgroup analysis was planned to consider variable graft configurations on clinical outcomes.

2. Methods

This project was undertaken per the PRISMA guidelines (2) and recommendations described in the Cochrane Handbook for Systematic Reviews of Interventions (3).

2.1. Criteria for considering studies for this review

2.1.1. Types of studies

We considered randomised controlled trials (RCTs) and controlled clinical trials (CCTs) comparing patients undergoing EVAR treated with endografts made from polyester to patients treated with endografts made from PTFE for AAA for inclusion in the review. We placed no limitations on publication date, language, or status.

2.1.2. Types of participants

All participants with AAAs undergoing EVAR diagnosed using conventional methods, such as computed tomography (CT) or magnetic resonance imaging (MRI), or both, were to be included in the review. We planned to consider people with a primary AAA of any morphology (e.g. fusiform, in which the entire circumference of the aneurysmal portion of the aortic wall is dilated, as opposed to a saccular aneurysm in which there is an eccentric outpouching of the aortic wall). We did not consider aneurysm formation post-aortic dissection.

2.1.3. Types of interventions

We planned to include all studies comparing endovascular repair with a polyester-based endograft versus a PTFE-based endograft. For endovascular repair, several devices are available, and we planned to include all device types.

2.1.4. Types of outcome measures

The selection of primary and secondary outcomes was guided by the Society for Vascular Surgery (SVS) reporting standards for thoracic endovascular aortic repair (4). We planned to report outcomes on time points such as 30 days, 12 months and five years unless otherwise stated.

2.1.4.1. Primary outcomes

(1) aneurysm-related death (including rupture and death within 30-days of procedure) and (2) major adverse cardiovascular events (myocardial infarction, heart failure, arrhythmia, cardiovascular death).

2.1.4.2. Secondary outcomes

(1) endoleak, (2) aneurysm sac expansion, (3) reintervention, (4) graft infection, (5) thrombosis, (6) post-implantation syndrome, and (7) all-cause mortality.

2.2. Electronic searches

Systematic searches of the following databases for RCTs and CCTs were undertaken without language, publication year or publication status restrictions.

- Cochrane Vascular Specialised Register *via* the Cochrane Register of Studies (CRS-Web) (searched April 26, 2021)
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, issue 3) *via* the Cochrane Register of Studies Online (CRSO)
- MEDLINE (Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE) (searched April 26, 2021)
- Embase Ovid (searched April 26, 2021)
- CINAHL Ebsco (searched April 26, 2021)
- AMED (searched April 26, 2021)

The following trial registries were also searched on April 26, 2021.

- World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch)
- ClinicalTrials.gov (clinicaltrials.gov)

2.3. Searching other resources

References of relevant articles retrieved from the electronic search for additional citations were also searched.

2.4. Selection of studies

Two review authors (NH and SS) independently screened all titles and abstracts identified from the literature searches to identify those that met the inclusion criteria. We retrieved the full text of studies identified as potentially relevant by at least one author. The same review authors independently screened the full-text articles for inclusion or exclusion. We resolved any disagreements by discussion or, when necessary, we consulted a third review author (YA). The screening and selection processes are presented using the adapted PRISMA flowchart.

3. Results

The search generated 2,178 references. A total of 381 duplicates were identified and removed. The titles and abstracts of the remaining 1,797 studies were then reviewed. Of the 1,797 studies reviewed, we only carried 45 studies to full-text review and included or excluded studies based on study type and PICO (**Figure 1**). However, none of the studies met the inclusion criteria, and we did not find any RCT or CCT that compared stent-graft materials in endovascular AAA repair.

4. Discussion

We did not find any RCT or CCT that considered comparing PTFE and Polyester materials and their influence on post-procedural outcomes following EVAR. However, we did find ample evidence that endovascular repair has adverse effects, especially cardiac and aortic dysfunction. It is likely that this is a function of the overall endograft contrast rather than simply related to whether the material used is PTFE or polyester. Considering the impact of aortic disease and the expense of aortic repair, suboptimal outcomes warrant further reflection.

Aortic diseases, including aneurysms and dissections, are a leading and growing cause of death worldwide: Globally, the number of aortic aneurysm deaths increased to 172,426 in 2019, a rise of 82.1% compared with 1990 (5). The climbing death rate is even more pronounced in developing countries, with an increase in median death rate (per 100,000) of 0.71, three times higher than in the developed world, where it is 0.22 (6). Mortality is especially evident in those who present with Acute Aortic Syndromes (AAS). Despite an almost universal fall in CV deaths over the last two decades, the incidence of AAS mortality has not fallen in the past 40 years: those with AAS have more than double the mortality rate of age-matched controls at 5, 10, and 20 years post AAS (7). They have a two-to-threefold increased risk of non-aortic CV death, any first-time non-fatal CV event, and first-time heart failure (8). Even those that survive the initial acute aortic event continue to have a substantial risk of aortic death, aortic event, aortic intervention, and first-time diagnosis of aortic aneurysm (9).

The global aortic aneurysm market was valued at €2.3 billion in 2018 and is expected to register a compound annual growth rate (CAGR) of 8.6% from 2019 to 2026 (10). This translates into an increase in aortic repairs from 219,664 in 2021 to a projected >400,000 repairs in 2030. Despite perceived progress in diagnostic and therapeutic techniques, the economic burden of aortic disease is growing (11–14). In 2020, McClure et al. analysed the healthcare resource use for thoracic aortic dissections and aneurysms in Canada, which reached €430 million over a 13-year period (15). Cost expenditures to treat thoracic aortic disease escalated in an upward projection, with yearly total hospital costs significantly increasing beyond the rate of inflation over the period. The use and cost of posthospital healthcare resources were also considerable. Home care services alone were used by 40% of patients, and the one-year hospital readmission rate was 22%. Extrapolating these numbers to the European population, we could reach a tremendous yearly burden of >€1.7 billion for thoracic aortic diseases only. The abdominal aortic device market is 3.5 times bigger than the thoracic device market. (There were 169,261 Abdominal procedures versus Thoracic 46,476 procedures in 2021.) A notable percentage of these costs can be attributed to the limitations of currently used devices

4.1. Current graft materials

Synthetic grafts for OAR fail to replicate the elasto-mechanical characteristics of the native arterial tissue. The

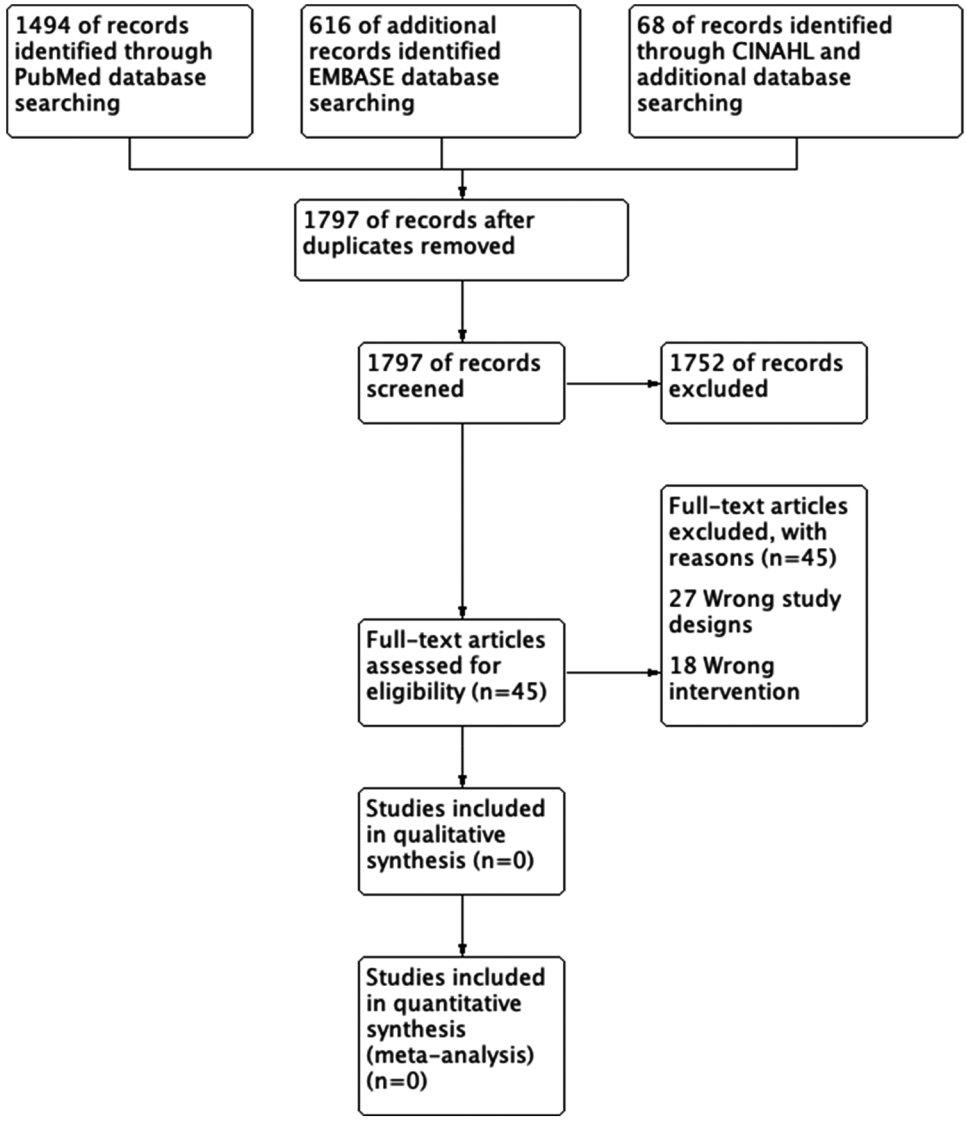

FIGURE 1
PRISMA study flow diagram.

consequent lack of adequate compliance leads to a cascade of hemodynamic and biological alterations adversely affecting cardiovascular homeostasis, especially when implanted near the heart (16). Proximal prosthetic graft replacement of the ascending aorta amplifies circumferential strain in the descending thoracic aorta, modifies energy propagation to the distal aorta and contributes to distal aortic disease manifestation (17).

These effects are even more pronounced with endovascular devices. Since the first commercially available devices were launched, aortic endografts have undergone only modest enhancements in stent material, graft fabric, fixation method, deployment mechanism, and flexibility. However, the underlying principle has not changed substantially. Both the metallic skeleton and the graft materials reduce aortic compliance, causing a mismatch in the physio-mechanical properties between the native and stented aorta (18). The materials in current endografts are designed to enhance the durability of the graft and reduce the risk of endoleaks, but endografts have biomechanical properties that are several orders of magnitude stiffer than the native aorta (19). Aortic compliance is critical to reducing the impedance and workload of cardiac ejection. Acute stiffening of the aorta following endovascular procedures results in acute elevated pulse pressure, hypertension, decreased coronary artery perfusion, and heart failure (20). The challenges of poor compliance, endovascular aortic device failure and the need for reinterventions undermine the cost-effectiveness of

endovascular repair. The endovascular approach was driven by a clinical need to treat patients unfit for open repair. Thus, the original clinical needs remain unmet.

The aortic structure and function vary considerably along its length, yet devices (open and endovascular) do not vary by anatomical location or address the variability in physiological requirements. The differences in functionality of the aorta correspond with embryological origin (21, 22). The proximal aorta arises from the cardiac neural crest as part of the left ventricular outlet tract. It has a combined need for capacitance (enhanced elasticity) and the need to propel blood forward. The distal aorta, beyond the level of the left subclavian artery, arises from the mesoderm and is associated with more muscular contraction. These differences in compliance and function alter device function relative to location. Using patient-specific FSI models (19) which used 4D MRI Dual VENC sequences (23) to quantify patient- and location-specific aortic compliances, we demonstrated that the degree of oversizing needed to prevent endoleaks in the proximal aorta was more than double that required in the distal aorta. We also found that other factors, such as ageing of the aorta, whereby the collagen transition strain and elastin content are decreased, influence the percentage oversizing. This is significant because as the percentage oversizing increases, the device compliance dramatically decreases, but clinicians or device manufacturers are not considering these factors.

In recent years, some devices have been developed, providing important learnings to the community. The Personalised external aortic root support (PEARS) device by Exostent prevents aortic enlargement and rupture by being placed around the ascending aorta and is manufactured using advanced medical imaging and computer-assisted 3D printing. Studies have shown that this biomechanical support appears to modulate tissue function and promotes recovery of the microstructure of the media. However, the PEARS device requires open surgery, and its application is limited to a small number of patients with Marfan syndrome and related genetic conditions with early dilatation (40–45 mm rather than >55 mm). The Multilayer flow modulator (MFM) device by Cardiatis is an Endovascular 3D mesh with compliance more similar to that of the native aorta. The MFM was the first device that focused on manipulating flow rather than looking at anatomy. In this way, compliance, endothelialisation, and reduction of thrombus formation are also targeted, all of which reduce peak wall stresses while simultaneously enhancing wall strength and promoting healing. However, the MFM was inappropriately disseminated and has suffered in terms of reputation. We found that this device performs well for aortic dissections but not for large chronic aneurysms, where it cannot achieve modulation beyond a certain aortic size (9, 24, 25).

Despite clear limitations, both the PEARS and MFM devices have taught us that biomechanical support and optimal compliance can positively affect tissue modulation. Biomechanical support changes gene expression of the aortic tissue to promote aortic wall modulation, which in turn improves biomechanical function. This positive feedback loop leads to tissue healing. With these passive devices, modulation was possible when the disease was in its early stages; however, since aortic disease is predominantly asymptomatic and, most patients present when their disease is beyond the early stages, more active approaches are required to achieve repair and restore tissue function.

4.2. PTFE versus polyester

There have been limited non-randomised studies which have compared PTFE and Polyester in aortic endografts. Using pulse wave velocity (PWV) as a surrogate marker to demonstrate changes in stiffness following EVAR, Kadoglou et al. (26) showed that post-EVAR with polyester endografts, there could be a threefold increase in PWV compared to PTFE. Differences have also been reported between these materials in open aortic surgery. PTFE endografts had been reported to offer significantly stronger resistance to dilatation than polyester-based endografts, albeit this advantage is lost over time (27).

There are some other effects that materials may have beyond biomechanical, such as the development of the post-implantation syndrome (PIS). PIS has been reported in up to two-thirds of the patients following EVAR (28). and can result in acute liver and/or multiple-organ failure (29–34). However, the high rate of PIS reported is likely a consequence of a robust diagnostic criteria. The symptoms and signs (high fever, leukocytosis, and elevated serum CRP and interleukin (IL)-6) are often seen as a systemic post-operative response and it can be difficult to distinguish these from PIS and some authors have used other surrogate markers to demonstrate the pathological consequences of PIS. Ito et al. (28), Voûte et al. (10), and Sartipy et al. (11) implicated polyester-based endografts in developing postoperative pyrexia, PIS, and extended hospital stay post-EVAR compared to the PTFE-based endografts. Endografts with woven polyester are thought to be associated with a more robust inflammatory response which results in endothelial damage. Ferreira et al. (12) suggested a possible link between PIS and increased cardiovascular mortality. Also, polyester implanted grafts result in an augmented inflammatory response, mainly due to IL-8 serum levels. IL-8 is a neutrophil chemoattractant that exerts different pro-tumoural functions and plays a vital role in tumour progression and metastasis. This may elucidate the probable malignant potential of polyester-based endografts (13, 14). However, there are currently no controlled studies to substantiate these findings.

4.3. Limitations

A significant limitation of our review is that we only sought to include RCTs and excluded other clinical studies. Observation studies and non-randomised trials could have been an essential source of information given the non-availability of RCTs and/or CCTs. As we could not find any RCTs based on our study objectives, we could not reach a consensus regarding the implications of the specific stent-graft materials in the post-procedural outcomes following EVAR. Of consideration is that stent-graft material alone is challenging to investigate because of confounding factors. The evidence regarding the possible post-procedural outcomes implicated in the stent-graft materials could also be attributed to the device design, shape, and the presence of an exoskeleton versus an endoskeleton.

Overall, it has been demonstrated that the currently available endografts, regardless of the stent-graft materials, are less compliant than the native aorta, and they fail to simulate the elasto-mechanical qualities of the native aorta due to insufficient compliance. Given the increasing evidence of adverse hemodynamic alteration post-EVAR, the best solution in the short term could be to reduce the stented length of the aorta. At the same time, in the longer term, encourage continuous improvement in stent-graft materials and design.

We undertook this systematic review to investigate if device materials related to adverse outcomes, i.e., PTFE vs polyester; however, not surprisingly, we did not find any RCTs or CCTs which were structured or powered to answer these specific questions. Regardless, we found experimental and observational studies that support the hypothesis that graft materials and lack of compliance adversely affect cardiac function. The paucity of RCTs is a motivation for undertaking an RCT, which owing to the variation in specialisation across aortic centres, may require us to utilise cluster-randomisation. However, the logistical difficulties of undertaking an RCT should not be underestimated. International collaboration is necessary to recruit significant enough numbers and obtain sufficient funding. Before this, the next logical step is to undertake a patient-level meta-analysis to inform specific trial outcomes. Other means of collecting evidence, such as a prospective registry—based randomised controlled trial (RRCT) is possible. RRCTs are growing in popularity, especially in Scandinavian countries where large national registries already exist, and have been applied to the assessment of cardiovascular therapies (15). Using existing data reduces cost and administrative burden, and as RRCTs do not have inclusion and exclusion criteria like RCTs, the outcomes can more readily be applied to real-world scenarios, which make them especially attractive for aortic diseases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

The Primary Author is NH, who wrote the manuscript, under took the systematic review and screened tiles, abstract and articles. YA contributed to writing the manuscript. SS screened titles and articles and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Bioengineering, augmented reality, and robotic surgery in vascular surgery: A literature review

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Biomedical engineering integrates a variety of applied sciences with life sciences to improve human health and reduce the invasiveness of surgical procedures. Technological advances, achieved through biomedical engineering, have contributed to significant improvements in the field of vascular and endovascular surgery. This paper aims to review the most cutting-edge technologies of the last decade involving the use of augmented reality devices and robotic systems in vascular surgery, highlighting benefits and limitations. Accordingly, two distinct literature surveys were conducted through the PubMed database: the first review provides a comprehensive assessment of augmented reality technologies, including the different techniques available for the visualization of virtual content (11 papers revised); the second review collects studies with bioengineering content that highlight the research trend in robotic vascular surgery, excluding works focused only on the clinical use of commercially available robotic systems (15 papers revised). Technological flow is constant and further advances in imaging techniques and hardware components will inevitably bring new tools for a clinical translation of innovative therapeutic strategies in vascular surgery.

KEYWORDS

biomedical engineering, vascular surgery, endovascular surgery, augmented reality, robotic surgery

1. Introduction: Biomedical engineering in vascular surgery

One of the definitions of biomedical engineering is *"the application of engineering principles, practices, and technologies to the fields of medicine and biology especially in solving problems and improving care (as in the design of medical devices and diagnostic equipment or the creation of biomaterials and pharmaceuticals)"* (1). This concept raises growing interest and approval thanks to the proliferation of medical implants,

such as pacemakers and artificial hips, to more futuristic technologies such as stem cell engineering and 3D printing of biological organs, with the aim of improving life quality and medical healthcare at all levels, from diagnosis to treatment assessment and subsequent recovery.

Vascular surgery is one of the medical research fields in which technological advances, achieved through biomedical engineering, have contributed to significant improvements in open and endovascular surgical techniques in all arterial districts.

The first technological breakthrough can be considered to be the discovery of X-rays in 1895, which became relevant in the vascular field only a few decades later when a tolerable contrast agent for living humans was discovered, and it was possible to perform the first arteriography in a human being by direct puncture of the carotid artery (2). Thereafter, conventional angiographic methods have been constantly refined to improve the procedure's safety and diagnostic efficiency.

The unceasing development of new surgical equipment and techniques has provided surgeons with the ability to perform more complicated procedures and successfully treat more challenging lesions in elderly and sicker patients. The innovation of endovascular aneurysm repair for patients with abdominal aortic aneurysms was a milestone in the evolution of vascular surgery into the endovascular era (3).

Developments in vascular surgery are not limited to the technical part of the operative procedure. In fact, other disciplines such as radiology are also involved. Computed tomography (CT) scan, ultrasound-Doppler imaging, and magnetic resonance imaging (MRI) are a combination of physics and electrical engineering. Nowadays, imaging is a biomedical engineering discipline in its own right, integrating signal processing and computational techniques. The acquisition of trustworthy morphological and functional data on the target area is essential for deciding the feasibility of an intervention and for planning, guiding and performing a specific procedure as well (4).

Recently, augmented reality (AR) technology has been successfully helping surgeons during image-guided surgery (IGS), integrating surgical navigation with virtual planning simultaneously with the real patient anatomy (5).

The introduction of robotics represented another major step forward for different surgical specialties, facilitating and improving the performance of minimally invasive surgery. Robot-assisted surgery has been brought into the area of vascular surgery to enhance laparoscopic vascular and endovascular skills such as a relatively difficult manipulation of instruments and long suturing times for anastomoses and clamping of the aorta or pelvic arteries.

In biomedical engineering, a variety of disciplines, such as mechanical engineering, electrical engineering, chemical engineering, materials science, chemistry, mathematics, science, and computer engineering, is integrated with human biology to improve human health and reduce the invasiveness of surgical procedures. However, the efforts to explore in detail the impact of all these sub-disciplines and/or technologies could be ineffective and confusing. Considering that, this paper aims to review the most cutting-edge technologies of the last decade involving the use of augmented reality devices and robotic systems in (endo) vascular surgery.

2. Search protocol and selected studies

Based on the literature search carried out by the authors of this study, there are currently no reviews in the literature focused on the use of AR in vascular surgery, apart from the work of Lareyre et al. (6) which, however, only analyses works involving the use of Head-Mounted Displays and Smart Glasses. Therefore, a review of the current literature was carried out to allow an all-around assessment of AR technologies, including the different technologies available for the visualization of virtual content. Whereas, with respect to robotic platforms introduced to assist both laparoscopic and endovascular vascular procedures, the literature of recent years is rich in clinical reviews (7–10) focusing on robotic applications in one or both of these surgical applications. For this reason, in this manuscript, only studies with bioengineering content that highlight the trend of research in robotic vascular surgery were considered, excluding works focused only on clinical use of these systems.

The PubMed database was used to identify studies, written in English, related to the use of AR and the employment of robotic technology for vascular surgery. The search period was from January 2010 to April 2022 inclusive.

To perform the initial review process, based on paper title search, two different combination of keywords were used as follows:

- ("Augmented Reality" AND "Vascular") OR ("Augmented Reality" AND "Endovascular");
- ("Robot" AND "Vascular Surgery") OR ("Robot" AND "Endovascular Surgery").

With the exception of the keywords combination, which is different for the two investigated topics, the records selection protocol was the same. Indeed, after the collection of papers and the exclusion of duplicates, records were screened to filter out reviews, editorials, and commentary which were not under consideration for this work. Then, the remaining records were screened through abstract reading to exclude out of topic publications.

As concerns the use of AR technology in the field of vascular surgery, a total of 86 records were identified through

the studies collection from online digital library, and after removing 7 duplicates, 2 commentaries, and 6 reviews, the remaining abstracts' records were examined to exclude publications related to other surgical specialties (e.g., cerebrovascular surgical procedures, duodenopancreatectomies, etc.). The final number of publications considered relevant for the review was 11. Whereas, regarding the involvement of robotic systems in the field of vascular surgery, 63 records were identified through PubMed database searching, and after removing 5 duplicates, 1 editorial, and 14 reviews, the remaining records were screened through abstract reading to exclude out of topic publications. Eventually, 15 articles were considered relevant for the present review.

The flow chart for the selection of studies is shown **Figure 1**.

3. AR in vascular and endovascular surgery

In the following sections, the current diffusion of AR technologies in the field of vascular surgery was analyzed, examining for which specific applications these technologies have been used/proposed in both open and endovascular surgery. Furthermore, the type of AR displays adopted, the expected benefits, and the limitations of the current technology are reported, with an assessment of the maturity status of AR solutions in the vascular field. The revised records of this section are listed and described in **Tables 1**.

3.1. Visualization modalities

Available display technologies to provide the user with AR visualization include 2D monitors, hand-held displays (e.g., mobile phones and tablets), head-mounted displays (HMDs), and spatial projection-based AR displays.

Eight papers out of 11, report the use of HMDs or Smart Glasses (11–18). These displays provide the user with an egocentric viewpoint and allow operators to work hands-free, and according to recent literature (22, 23), they have been deemed the most ergonomic solution for applications including manual tasks performed by the user under direct vision, like what happens in open surgery. However, as is evident in this study, there is growing interest in the literature on the use of this type of display even for minimally invasive procedures, such as endovascular procedures.

Endovascular surgeons are traditionally forced to turn their heads away from the surgical field to view the standard fluoroscopic monitor; the use of a wearable display instead can provide surgeons with an alternative screen in front of their eyes, allowing them to keep their attention focused on the operative field. Evaluation of the potential benefits of wearable displays for performing fluoroscopically guided interventional procedures versus traditional monitor visualization is currently being explored in several surgical fields (e.g., fluoroscopically guided minimally invasive spinal instrumentation surgery (24), including endovascular surgery (16, 17). The assumption of these studies is that

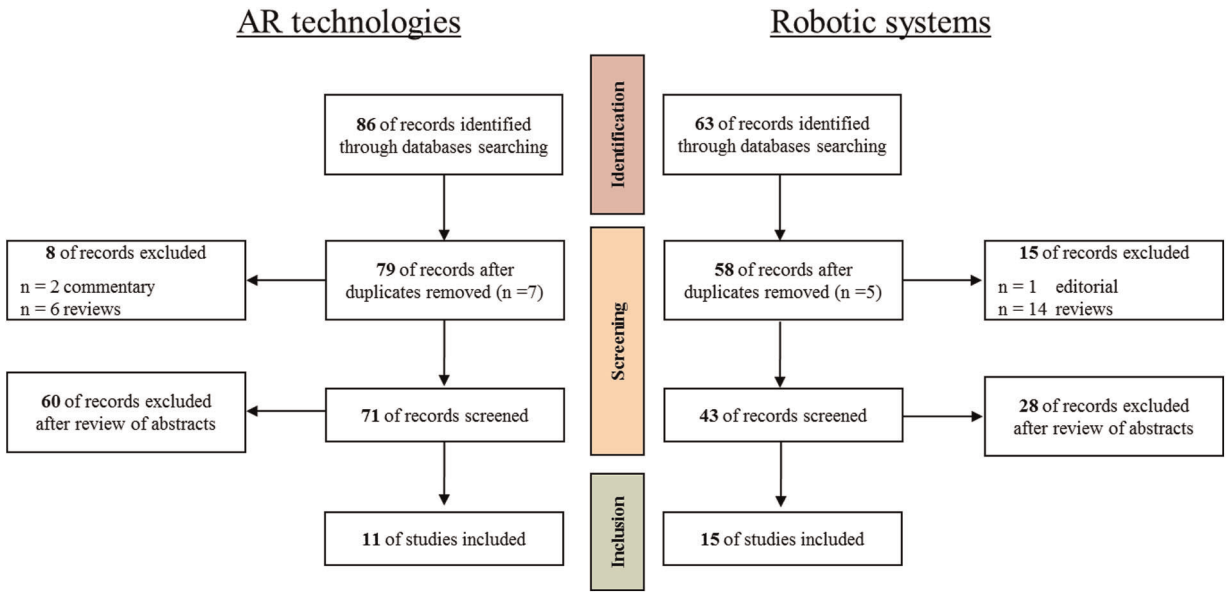

FIGURE 1
The flow chart for the selection of studies regarding the AR technologies (on the left) and the robotic systems (on the right) proposed in both vascular and endovascular surgery.

TABLE 1 AR technologies in vascular and endovascular surgery.

Author	Surgery type	Application	AR modality	Setup
Gao (11)	Endovascular	Catheter navigation	HMD	Vascular phantom
García-Vázquez (12)	Endovascular	Tools navigation in EVAR	HMD	Torso phnatom
Lu (13)	Endovascular	Retrograde peroneal access	AR glasses	Clinical
Rynio (14)	Endovascular	Planning and navigation in EVAR	HMD	Clinical
West (15)	Endovascular	Navigation and stentgraft deployment	HMD	Animal model
Mialhe (16)	Endovascular	Peripheral and carotid angioplasty, EVAR	HMD	Clinical
Mialhe (17)	Endovascular	Lower limb angioplasty	HMD	Clinical
Parrini (18)	Endovascular	Tool navigation	HMD	Vascular phantom
Cheng (19)	Endovascular	Tools navigation	2D display	*Not specified*
Aly (20)	*Not specified*	Groin incision guidance	Smartphone	Clinical/vascular phantom
Jeon (21)	*Not specified*	US-guided vascular acces	Microprojector	Vascular phantom

wearable displays have the potential to facilitate better concentration on surgical tasks by enhancing ergonomic efficiency during surgery.

Most of the studies selected in this review employ Microsoft HoloLens as HMD (12, 16, 17, 14, 15). Microsoft HoloLens is designed with an optical see-through (OST) approach: virtual reality (VR) data are projected on a semitransparent display in front of the user's eyes and the natural view of the real world is preserved, allowing the natural synchronization of visual and proprioceptive information, and complete situational awareness. This approach fits well in the surgical domain as it offers an instantaneous full-resolution view of the real world, however, in OST displays the spatial coherence between the VR content and the real scene is still suboptimal, and perceptual and technological issues still limit their employment when a high virtual to real spatial alignment (i.e., registration) is required for accurately guiding manual tasks in the peripersonal space (22). Clearly, these issues do not arise when the HMD is used solely as an alternative monitor for viewing preoperative information (e.g., 3D anatomical models extracted from preoperative computed tomography angiography (CTA) or intraoperative information (e.g., fluoroscopic images) in applications that do not require image-to-patient registration. On the contrary, video see-through (VST) systems, like the one employed by Parrini et al. (18), can offer an accurate registration of virtual content to the real scene at the cost of a camera-mediated view. In this proposed application (18), for example, the HMD is used to visualize the vessel centerlines superimposed on the patient body to guide endovascular tools.

Three papers out of 11, describe AR applications based on displays other than HMDs. More particularly: a traditional 2D display is used to display the AR scene in the application proposed by Cheng et al. (19); Aly et al. propose a low-cost handheld solution based on smartphone hardware (20); Jeon et al. employ a microprojector, attached to an ultrasound (US) probe, to project the US image over the patient skin for simplifying ultrasound-guided vascular access (21).

3.2. Surgical applications

Most of the analyzed records (9 papers out of 11) focus on the use of AR in endovascular procedures. Among them, some papers (11, 12, 18, 19) do not focus on a specific surgical procedure but describe more extensively the usefulness of AR in endovascular surgery. The rest propose the following use cases: endovascular treatment of abdominal aortic aneurysms (EVAR) (12, 16, 14, 15), peripheral angioplasty (13, 17, 16), and carotid angioplasty (16). The remaining papers concern: (1) an application useful for a wide variety of vascular and endovascular procedures, intended to guide groin incisions (20), (2) a simplified AR device for ultrasound-guided vascular access (21).

Emerging applications of AR in surgery include: preoperative systems for surgical planning and patient-specific rehearsal, intraoperative systems for navigating complex procedures and/or easing the visualization of preoperative/perioperative patient data, and simulation systems for surgical training. According to the findings of this review, in the field of vascular surgery, AR functionalities have been mainly explored for developing innovative intraoperative platforms to assist the surgeon during the navigation of endovascular tools and/or to furnish an ergonomic tool for visualizing patient data during the intervention.

Cheng et al. present an AR framework, designed to be integrated with a robotic device to navigate endovascular tools, that can also be used for surgical training/planning in ultrasound-guided endovascular procedures (19). The novelty of the system lies in the capability of allowing the surgeon to pre-plan an optimal path (which can be adjusted during operation). Moreover, the system features mixed reality functionalities fusing real-world elements (US images) with

virtual synthetic elements (3D model of the anatomy, virtual medial axis of blood vessels, planned navigation path) in a single 3D scene to enhance the surgeon's visual perception. The proposed platform employs an electromagnetic (EM) tracking module to track in real the US probe and the endovascular tools (i.e., the catheter tip) via built-in EM sensors.

EM tracking is a widely used technique that enables real-time tracking of surgical tools without line-of-sight restrictions and without ionizing radiations (25). The use of EM sensors for the tracking of endovascular instrumentation has already been proposed in the literature for the development of endovascular navigation systems based on virtual reality (26–29), and as it emerges from this study is also being evaluated for the development of AR endovascular navigation systems (19, 11, 12, 15).

The system implemented by Gao et al. (11), similarly to what has been proposed by Cheng et al. (19), provides intraoperative assistance to the surgeon for catheter navigation through AR visualization of the vasculature virtual model, the optimal catheter trajectory, and the current position of the catheter that is tracked through an EM localization system. The VR content is spatially aligned to the patient's anatomy (i.e., registered), and it is displayed via a HMD.

The navigator developed by García-Vázquez et al. (12) tackles the issues of radiation exposure and contrast agent administration during EVAR interventions by using a multidisciplinary approach to guide the endovascular tools: EM localization of endovascular tools, and AR visualization (via a HMD) of the endovascular tools' position, the 3D models of the skin and vascular structures superimposed on the patient anatomy. Additionally, the authors envision the use of 3D ultrasound, streamed from the US system to the HMD, for guiding endovascular tools and updating navigation with intraoperative imaging.

Finally, among the systems featuring EM tracking technology, there is the platform proposed by West et al. (15) for assisting in the intraprocedural deployment of endovascular stent-grafts during complex EVAR procedures. This system allows the visualization of 3D models of the patient anatomy extracted from preoperative images and offers numerical feedback for controlling the endograft landing zone and the alignment with the aorta ostia, via EM tracking of the stent-graft.

Four out of 11 papers concern an application specifically designed for intraoperative navigation, without providing EM localization of the instrumentation (20, 13, 18, 21). More particularly, the system developed by Aly et al. (20) is conceived to assist the surgeon in the localization of vascular structures via the AR visualization of a 3D model of the patient vasculature, extracted from preoperative CTA, registered to the patient body and displayed via a smartphone. Lu et al. propose an application to ease retrograde peroneal access for the endovascular treatment of critical limb ischemia (13). The application is based on the use of an AR navigation system (Xiamen Minwei Limited Company, Xiamen, China) featuring AR glasses that are employed by the authors to visualize the recommended puncture path (site, depth, and angle of puncture) to the target vessel. Parrini et al. propose using a VST HMD to visualize vessel centerline extracted from volumetric radiological images (e.g., CT, MRI, or 3D US) registered to the patient body (18). The proposed innovative application is the assistance to freehand guidance of magnetic endovascular devices. Finally, Jeon et al. propose a simplified AR device for ultrasound-guided vascular access (21): US images are transmitted to a microprojector (attached to the US probe) and projected on the patient skin. The projected images are calibrated so that the acquired anatomical structures are displayed at full scale.

The remaining 3 records concern the evaluation of the intraoperative use of AR for enhancing the ergonomic efficiency of patient data visualization. More particularly, the intraoperative use of Microsoft HoloLens to develop "screenless display" endovascular interventions has been proposed. In (16) perioperative angiography images were broadcast live in the HoloLens, with no latency, and successfully visualized by the surgeon during three interventions: peripheral angioplasty, carotid angioplasty, and EVAR procedure. In (17), during a lower limb angioplasty, up to four images originating from different sources were displayed simultaneously including: 2D angiography, operative vital signs monitoring, 3D fusion image, and 3D CT scan reconstruction. Finally, Rynio et al. used the HoloLens device during an EVAR intervention to visualize 3D models of the aneurism with its thrombus and adjacent bones, and a 2D image containing the volume rendering reconstruction with arterial diameters and planning notes (14). Moreover, they explored the manual image fusion with fluoroscopic data: for this purpose, the hologram was placed in front of the angiographic monitor, and scaling/rotation procedures were performed to manually register the 2 modalities based on bones.

3.3. Perceived advantages and current limitations

As it emerges from literature, an increasing number of surgeons perceive the potential benefits of using AR in vascular and endovascular procedures, indeed this technology may facilitate visualization and navigation during surgical procedures and could improve the surgical workflow (14).

As for intraoperative visualization of patient data, AR systems offer the opportunity to easily display many forms of 2D and 3D medical data preserving the 3D spatial relationships between the anatomical structures. According to (14) who tested the Microsoft HoloLens in the surgical room, *"until now, our workflow was to print several images of the volume rendering from different angles. We found that data useful whenever a problem arose due to difficult anatomy*

(branch takeoff angles, tortuosity, etc). However, such data always were 2D, and we could not reach for views other than those already prepared. The AR approach is far most helpful, being available all the time and enabling rotation in all angles with preservation of structural relationships." In addition, to making the information content of radiological images more intuitive and easier to use, such visualization systems could reduce the frequency of operator head-turning, and thus the risk of inattention. Moreover, HMDs such as Microsoft HoloLens can be operated by voice commands and gestures, they do not need to be handled, leaving hands free and maintaining the sterility of the environment (16). In the field of navigation, AR has the potential to lower contrast material volume and radiation exposure without interfering with the operator's routine activities (13, 15), to ease procedures and improve their accuracy (15), to decrease surgical time (15).

This review also highlights several limitations of current technologies that hinder their widespread use in clinical settings. For example, according to (14), some drawbacks of Microsoft HoloLens V1 include: non-negligible weight (579 g), which can cause some fatigue to the operator's neck, especially in case of prolonged use; restricted binocular vision field (30° diagonal) (14); limited battery life (between 2 and 3 hours of working time) meaning it may not be sufficient for long procedures. The new version of Microsoft HoloLens, partly mitigates these issues, indeed HoloLens V2 features an improved field of view (52° diagonal) and offers more comfortable wearability; however, currently available HMDs are still far from the ideal AR display, which, according to Rolland et al., should be *"conceived as a transparent interface between the user and the environment, a personal and mobile window that fully integrates real and virtual information"* (30).

Another perceived technical issue, that more broadly afflicts AR systems independently of the selected display is the difficulties in obtaining and maintaining overlapping between the AR content and the patient anatomy (20, 18, 12). None of the analyzed records employ a non-rigid image-to-patient registration technique or incorporate a method for the intraoperative update of the vascular 3D models. Moreover, they mostly employ external artificial markers or anatomical landmarks on the body surface for registration and this intrinsically limits the registration accuracy.

The registration of intra-abdominal structures that move and deform with ventilation and heart-beat is proven to be a challenge for current computer-assisted systems. As pointed out by Aly et al. (20) registration deformation is not a major issue when the vascular structures targeted by the AR application are relatively fixed and the patient is not repositioned intraoperatively. However, in this case, the effects of soft tissue deformation due to the interaction with the surgical instrumentations may reduce the system accuracy. As suggested by García-Vázquez et al. a possible solution to this problem could be the use of intraoperative data (such as intraoperative US volumes) to acquire an updated model of the patient anatomy, combined with non-rigid registration techniques (12).

3.4. Maturity of the AR technology, level of testing and certification as a medical device

Most of the AR platforms described in the selected records are based on the use of a commercial display, not specifically conceived for medicine or surgery (e.g., Microsoft HoloLens), coupled with a prototype software architecture. An exception is the CarnaLife Holo, employed by (14), a module of the telemedicine system "CarnaLife," which is certified as a medical device supporting diagnostics, class IIb. Moreover, no information has been retrieved on the internet on the "AR navigation system" (Xiamen Minwei Limited Company, Xiamen, China) used by Lu et al. (13).

Five records out of 11 (19, 11, 12, 21, 18) are feasibility studies in an in-vitro setup to qualitatively and/or quantitatively test some technical aspects of the proposed system. For example, the manuscript by García-Vázquez et al. reports a qualitative evaluation of the AR misalignment of a system based on Microsoft HoloLens and a rigid registration algorithm (12). Moreover, the same manuscript reports a quantitative evaluation in the visualization of US volumes. According to the authors, both the registration accuracy and the visualization latency should be improved before clinical applications. The latter is 259 ± 86 ms and should be at least 100 ms to display real-time 3D US volumes on HoloLens.

One record reports a feasibility study on a human volunteer to test in a qualitative way (via landmarks palpation) the registration accuracy of a system designed to assist in the intraoperative localization of vascular structures (20). Moreover, it also reports the results of an in-vitro study on a mannequin demonstrating the stability and the accuracy of the positional/rotational tracking reachable with a hybrid gyroscopic and optical tracking approach using low-cost smartphone hardware.

Four manuscripts (13, 17, 16, 14) are clinical case reports on a limited number of surgical patients (maximum 3 in (16)), showing the feasibility of using Microsoft HoloLens to develop "screenless display" endovascular interventions.

Finally, the manuscript by West et al. tests the "Three-Dimensional Holographic Guidance, Navigation, and Control (3D-GNC) prototype" for endograft positioning in porcine aorta, comparing the system performance with 2D X-Ray fluoroscopy (15). Technical success for the use of 3D-GNC (without fluoroscopy or contrast-dye administration) to orient and position the endovascular device at each renal-visceral branch ostium was 100%, and according to obtained results,

the proposed system is able to reduce procedure time (by 56%) and to improve overall orientation accuracy (by 41.5%). Positioning accuracy was comparable for both techniques.

It may be concluded that in the case of systems designed for intraoperative navigation, although in some cases the results obtained in-vitro or on animals are very promising, to date there are no clinical studies and the devices are not certified for surgical use. The use of AR technologies for intraoperative visualization of patient data is certainly a more mature application, but to date, the number of clinical studies is still limited to drawing definitive conclusions on the fascinating potential of AR.

4. Robotic surgery in vascular and endovascular surgery

Robotic technologies are increasingly being adopted in a variety of surgical disciplines to facilitate and improve the performance of minimally invasive surgery. In the following paragraphs, the main findings of existing reviews in the field of robot-assisted laparoscopic vascular surgery and endovascular surgery are first summarised. Finally, the leading bioengineering topics of current studies are reported in order to analyze the latest scientific trends in robotic vascular surgery.

4.1. Robot-assisted laparoscopic vascular surgery

The first robot-assisted vascular surgery dates back to 2002, when Wisselink et al. reported the first two cases of robotic technology being used for laparoscopic aortobifemoral bypass grafting (31). During the surgery, three robotic positioner arms were connected to the operating table rails: one for a 30-degree endoscope (Aesop Endoscope Positioner, Computer Motion) on the right, and two for surgical instruments, consisting of a needle driver and a grasper (Micro Joint Heavy Needle Driver, Micro Joint De Bakey Grasper) on the left side of the patient. The aim of using the robotic technology was to simplify endoscopic manipulation by increasing the degrees of motion and facilitating hand-eye coordination.

Since then, two advanced robotic surgical systems have been mainly used in laparoscopic vascular surgery: the da Vinci (Intuitive Surgical Inc, Mountain View, Calif) and Zeus (Computer Motion Inc, Santa Barbara, Calif) systems, which are Leader-Follower robots with similar capabilities (10). The production of the Zeus robot has been discontinued, while in the last decade, the da Vinci robotic surgical telemanipulator has been used for several vascular procedures, that, according to a recent literature review (8), include: robotically assisted repair of abdominal aortic aneurysms (AAA), thromboendarterectomy of the aorta and pelvic artery, iliofemoral and aortofemoral bypass, thoracofemoral bypass from descending thoracic aorta, splenic artery aneurysm, renal artery reconstruction, robotic treatment of type II endoleak after endovascular aneurysm repair, robotic surgery for celiac artery compression syndrome, and robotic-assisted central venous reconstruction.

Robot-assisted laparoscopic surgery offers several advantages over traditional open surgery, including less intraoperative bleeding, early restoration of gastrointestinal activity, rapid postoperative recovery, good surgical wound healing, excellent cosmetic results and healing of surgical wounds, and dramatic reduction of the occurrence of incisional hernia. In addition, the benefits of robotic technologies in terms of improved dexterity, restoration of proper hand-eye coordination and better visualisation can further enhance the surgical outcome. For example, according to (8), surgical robots can allow vascular anastomoses to be performed more quickly and easily than classic laparoscopic surgery, eliminating the difficulties of handling laparoscopic instruments. Similarly, in the field of micro- and supermicrosurgery, robotic systems are proving to successfully bridge limitations related to the precision and dexterity of the surgeon's hands, paving new options for micro-reconstruction procedures as well. Most recently, the Symani (Medical Microinstruments - MMI, Calci, Italy) robot, a teleoperated microsurgical system, has been used for the first time on humans to perform ten microanastomoses (i.e. lympho-venous and arterial anastomosis for lymphatic reconstruction) (32).

However, to date, data from the existing literature are limited to drawing a conclusion regarding the efficacy of robotic technology in vascular surgery (10), given that most studies are mainly limited to individual cases (Stadler's group, which reported on a series of 285 procedures (33), is an exception). At present, robot-assisted vascular surgery has not achieved great popularity and its use is still limited to a few centers worldwide. According to (10), one possible explanation is that the da Vinci system is not approved for this medical field, moreover, robotic surgery is generally more expensive than conventional procedures and has been associated with longer operating times for many types of procedures. However, with regard to the latter aspect, as pointed out by Soomro et al., most of the existing comparative studies may have been conducted by surgeons who were still learning the robotic technology, and therefore the results may not reflect the potential benefits of this technology (34).

4.2. Robot-assisted endovascular surgery

Research on endovascular interventional robots has been carried out since the end of the twentieth century. According

to the difference in catheter actuation, vascular robots can be classified into four categories: magnetic, pull-wire (tendon drives), smart material-actuated, and hydraulically driven (35).

Among these, the most studied systems, which have resulted in commercial solutions, are magnetic and pull-wire systems. Magnetic systems are based on the use of catheters incorporating small magnetic implants in their tip, which act as magnetic dipoles, and two or more guide magnets, placed close to the surgical table, are used to generate a magnetic field that can be controlled to deflect the catheter tip to the desired position. Pull-wire actuation is another well-studied approach for developing steerable catheters and to simplify their control in the arterial tree.

Regardless of the technology used, robotic systems allow better control of the distal tip of the catheters, so they can allow better access to difficult anatomies, as well as better catheter stability. Finally, they allow teleoperation functionalities: the patient can be treated remotely, resulting in lower exposure to X-ray irradiation for the physician (35).

Commercial robotic platforms include the Magellan and Sensei systems (both owned by Auris Health, Inc), the CorPath system (Corindus Vascular Robotics, Inc), and the Amigo (Catheter Precision, Inc). In addition, another commercial platform is the Niobe system (Stereotaxis, Inc) which is based on a magnetically guided mechanism.

The Sensei robotic catheter was approved in 2007 by the FDA for use in cardiac mapping and ablative procedures (9), followed by the Magellan system, the first purely vascular robot that received FDA approval in 2012 (10). The Sensei system is equipped with pull-wire steerable sheaths, allowing remote manipulation of catheters via a three-degree-of-freedom (3-DOF) joystick, and has been employed successfully in a range of interventions, including cardiac ablation and standard and complex endovascular aneurysm repairs (9). Furthermore, the literature reports a clinical study on the use of this technology for iliac artery and superficial femoral artery cannulation (10).

The Magellan system, specifically designed for peripheral vascular intervention, consists of a remote workstation and a robotic arm that delivers the steerable catheter. The workstation includes a controller, a 7-DOF joystick, and a control screen. The system allows the operator to remotely control the catheter insertion/withdrawal, multidirectional movement, angulation, rotation, and torque position (9). According to (10) use-cases reported in the literature include: visceral and renal vessel cannulation during FEVAR/BEVAR, catheter placement in aortic arch during TEVAR, EVAR gate cannulation, and carotid artery angioplasty.

The CorPath system, which was designed for procedures in the whole cardiovascular system, is equipped with a robotic cassette compatible with commercial devices, allowing control of all three interventional devices, i.e. guidewire, catheter and balloon/stent catheters. As reported by Cruddas et al., the use of this robotic platform for the treatment of symptomatic peripheral arterial disease has been associated with improved technical success, shorter procedural times, and reduced use of fluoroscopy and contrast (9). According to (10), use cases reported in the literature also include percutaneous angioplasty of the superficial femoral artery and carotid angioplasty. However, large studies and cost-benefit analyses on its use in daily practice are lacking in the literature (9).

The Amigo system, designed for radiofrequency ablation and cardiac mapping, allows remote 3-DOF manipulation (insertion/withdrawal, tip deflection, and rotation) of standard steerable electrophysiological catheters.

Finally, the Niobe platform is a magnetically controlled robotic system, which requires a dedicated room and magnetically compatible equipment. The system can automatically control the orientation (3-DOF) of the distal tip of the catheter. The latter is softer than the tip of cable-operated catheters, thus reducing the risk of damaging vessel walls. According to (9) use-cases reported in the literature include coronary and peripheral arterial interventions.

As concluded in (9), none of the robotic systems mentioned have been used on a large scale, nor are they employed in clinical routine, so there is limited data available about their safety, effectiveness and efficiency. The main limitations of current systems include technical complexity, high cost, and, in most cases, difficulty of use with existing endovascular devices. These barriers need to be overcome to allow for a wider diffusion of robotic technology. From a technical point of view, it is essential to ensure the compatibility of robotic systems with a wide range of off-the-shelf equipment and their easy interchangeability, and an improvement in navigation technologies.

4.3. Bioengineering research trends in robotic vascular surgery

Based on the survey conducted in this study, the main research topics addressed in the last decade in vascular robotics include: the development and testing of advanced robotic functionalities to improve robot performance and human/robot interaction, the development of simulators to be used as a training system, and the study of the learning curve of surgeons during robotic surgery.

As for the first point, research was performed to:

1. Actively monitor the safety of robotic procedures and provide force feedback to the surgeon via haptic devices (36, 37).
2. Improve the user interface (37) and provide high-fidelity human-machine interaction (e.g, in (38), a novel master controller to obtain real-time detection of surgeon's

operation without interference to the surgeon is proposed. A real catheter is used as the operating handle, thus the surgeon's feeling is similar to that in conventional endovascular interventions).

3. Design robotic systems not requiring the use of special proprietary tools, or modified catheters, to allow for wider use of the robotic technology and reduce its cost (36, 37).
4. Miniaturize endovascular devices and study magnetic propulsion methods (39).
5. Investigate the use of ultrasound imaging to navigate the endovascular tools to allow for a reduction of X-ray irradiation to the patient and contrast medium injection (39, 19).
6. Enrich the robotic platform with a framework for preoperative planning and simulation, plus advanced navigation functionalities integrating AR for improving the ergonomy of preoperative and intraoperative information visualization (19).
7. Optimise the gripping and manipulation performance of vascular interventional robots (40), modeling the hysteresis (i.e., the discrepancy between the input signals received at the proximal end of an endovascular tool and the movement that reflects at the tool's distal part) in robotic catheterization (41).
8. Enhance the autonomy of the robot to expand human capacity and capability in human-robot collaborative surgery. Zhao et al. propose a model of human-robot collaborative surgery, where the robot is controlled by both the surgeon and a trained network (38). This would, for example, allow the robot to perform repetitive, low-risk surgical tasks autonomously under the supervision of a surgeon, while the surgeon can concentrate on complex, high-risk tasks and focus the cognitive load where it is really needed.
9. Evaluate the workflow and define the telecommunication requirements for telerobotic vascular interventions. This is paramount to allow for remote interventions to distribute advanced care to hospitals where no endovascular experts are available and to provide the possibility of remote proctoring (42, 43).

An important line of research concerns the development of effective simulation systems that provide surgeons with the opportunity to train in the use of new robotic technologies within a safe and repeatable environment, while reducing risks to the patient (44–46). Research in this field aims to achieve reliable simulation of anatomical deformations and high performance in real time (46), and furnish a comprehensive training environment that combines visual cues and force sensation to assist the novice for safe procedures execution reducing collision trauma (44, 45).

Finally, some literature studies (47, 48) were addressed to the evaluation of the learning curve during robot-assisted vascular procedures (in particular with the da Vinci robotic platform). The aim is to verify the complexity of the procedures, to study the speed of the learning process of robotic surgery techniques, and to verify if and how the traditional surgical experience influences the learning curve in robotic surgery. The results of these studies can provide important guidelines about the optimal modalities for the acquisition of the necessary skills for a profitable use of the robotic technology.

5. Discussion

More and more different technologies are being developed, replaced or integrated into standard clinical practice that inevitably affect the way care is received. The purpose of this literature review was to outline the basic concepts of augmented reality and robotic technologies with regard to vascular and endovascular surgery.

This work indicates that the potential benefits of augmented reality technology extend to both surgeons and patients. These can include reducing risk to the patient and operative time, as well as optimizing contrast and radiation exposure during radiological procedures, thanks to the development of intraoperative systems for surgical planning and navigation. The use of wearable or projection-based displays would allow surgeons to maintain the concentration on the operative field, avoiding repeated movements of the head toward standard fluoroscopic monitors, and providing an ergonomic tool for patient data visualization under the user's direct vision. However, limitations such as the non-negligible weight and the restricted field of view of wearable displays, or the lack of non-rigid image-to-patient registration algorithms have to be investigated and solved to enable the AR usability in the future and to include it regularly in both clinical practice and training in vascular surgery.

The use of robotics in vascular surgery is well documented in the literature, despite none of the systems described above having been employed on a widespread basis. Aided by a robotic system, the surgeon's movements are down-scaled into fine gestures, physiological tremor is eliminated, and the visualization is improved, thus simplifying those actions unachievable in traditional surgery. Moreover, a precise and teleoperated control of endovascular instruments allows an easy access to even the most complex anatomies and a reduction of X-ray exposure for the surgeon. Further refinements are needed to fully integrate this promising technology into the clinical environment, including advances in haptic feedback and compatibility with existing devices. Unfortunately, the high costs of robotic systems, along with those related to maintenance, and the lack of approval for use in the vascular field have contributed to their low popularity. However, concerns of addressing higher costs in favor of

substantial health benefits for medical staff and patients should be considered.

The burgeoning field of biomedical engineering is the source of the most challenging technological advances in the healthcare field, affecting multiple aspects of the medical life of every patient, from the way the human body is examined for clinical conditions to the way major surgeries are ultimately performed. For this reason, there must be synergy between the different disciplines: engineers need to be aware of the many factors involved in the care and treatment process, just as clinicians need to be familiar with the engineering fundamentals behind the instrumentation they use in clinical practice and lend support in the research and development phases of new technologies. In this way, the integration of expertise derived from the medical and engineering worlds can offer patients increasingly precise, innovative, and more personalized care.

Author contributions

SC and MC contributed to conception and design of the study. SC, RP, and MC organized the database. JB, NT, MF and RB provided the clinical opinion regarding the inclusion of some papers based on their surgical target. SC and RP wrote the first draft of the manuscript. MC wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ABBREVIATIONS
GSV, great saphenous vein; RA, radial artery.

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Current intraoperative storage and handling practices of autologous bypass conduit: A survey of the royal australasian college of surgeons

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During bypass surgery for peripheral arterial occlusive disease and ischaemic heart disease, autologous graft conduit including great saphenous veins and radial arteries are frequently stored in solution. Endothelial damage adversely affects the performance and patency of autologous bypass grafts, and intraoperative graft storage solutions have been shown to influence this process. The distribution of storage solutions currently used amongst Cardiothoracic and Vascular Surgeons from Australia and New Zealand is not well defined in the literature. The aim of this study was to determine current practices regarding autologous graft storage and handling amongst this cohort of surgeons, and discuss their potential relevance in the context of early graft failure. From this survey, the most frequently used storage solutions were heparinized saline for great saphenous veins, and pH-buffered solutions for radial arteries. Duration of storage was 30–45 min for almost half of respondents, although responses to this question were limited. Further research is required to investigate whether ischaemic endothelial injury generates a prothrombotic state, whether different storage media can alter this state, and whether this is directly associated with clinical outcomes of interest such as early graft failure.

KEYWORDS
conduit, bypass, graft, intraoperative, RACS = royal australasian college of surgeons, early graft failure

Introduction

During bypass surgery for peripheral arterial occlusive disease and ischaemic heart disease, autologous graft conduit including great saphenous veins (GSV) and radial arteries (RA) are frequently stored in solution prior to anastomosis. Early graft failure (EGF), defined as occlusion within 30 days (1), remains a serious postoperative

surgical complication, with rates of 4.5% and 3% previously reported for infrainguinal and coronary bypass graft procedures, respectively (2, 3). Data reporting the most frequently used storage solutions, as well as intraoperative handling practices (i.e. use of "no touch" techniques" where the vein is harvested with a pedicle of surrounding tissue (4), and the extent to which the vein is mechanically distended) amongst Cardiothoracic and Vascular surgeons in Australia and New Zealand are lacking. Previous studies have suggested that storage media can influence conduit endothelial injury, and influence early graft patency (5). However, this is an area which is currently in need of further research (6). The aim of this study was to determine current practices regarding autologous graft storage and handling amongst surgeons in Australia and New Zealand, and discuss their potential relevance in the context of EGF.

Methods

Institutional Review Board approval was obtained (ID 69579, The Prince Charles Hospital HREC (EC00168), 22 October 2020). An electronic survey was distributed online *via* the Cardiothoracic and Vascular divisions of the Royal Australasian College of Surgeons using SurveyMonkey (San Mateo, CA, United State of America). Responses were anonymous and not identifiable. The survey questions are available in the Appendix.

Results

43 responses were received from 395 members approached (response rate = 10.9%). Response rate for Cardiothoracic and Vascular divisions was 8.3% (12/145) and 12.4% (31/250), respectively. 93% of respondents ($n = 40$) were currently practicing. All respondents (100%) routinely harvested GSV, and 33.3% routinely harvested RA. For GSV, storage solutions used were heparinized saline (76.2%), "other" (11.9%), autologous blood (7.1%), or pH-buffered solution (4.8%) (**Figure 1A**). "Other" solutions included heparinized saline and papaverine (7.1%), autologous blood and verapamil (2.4%) or no storage at all (2.4%). For RA, storage solutions used were "other" (46.1%), pH-buffered solution (23.1%), autologous blood (15.4%) and heparinized saline (15.4%) (**Figure 1B**). For "other" solutions, these included heparinized blood and verapamil (15.4%), glyceryl trinitrate and verapamil (7.7%), papaverine solution to the extraluminal vessel only (7.7%), heparinized blood with papaverine (7.7%), or heparinized blood with diltiazem and glyceryl trinitrate (7.7%). Specialty-specific responses regarding storage solution, duration, "no-touch" harvesting and extent of conduit distension are shown in **Table 1**.

Storage duration for these conduits was 30–45 min in 46.2% (6/13) (**Figure 2A**). A "no-touch" technique was used in 41.5% (17/41). Mechanical distension of the conduit was beyond twice the native vessel diameter in 2.4%, 1.5–2 times native diameter in 46.3%, filled but not distended in 48.8%, and no distension in 2.4% (**Figure 2B**).

Discussion

The present study aimed to identify current intraoperative conduit storage practices in Australia and New Zealand, and discuss their potential relevance with respect to EGF, which remains a substantial problem in cardiovascular surgery (2, 3). From this survey, for great saphenous veins, heparinized saline was clearly the predominant storage solution. For radial arteries, which are of primary relevance to cardiothoracic surgeons in Australia and New Zealand as a second arterial conduit following an internal thoracic arterial graft (7), storage solutions were more diversely spread across heparinized saline, autologous blood, buffer solutions and modified buffer solutions with vasodilators. This may potentially suggest a lack of consensus with respect to radial artery storage. Storage time was up to 45 min in almost half of respondents, although responses to this question were limited. It was also noted that the response rate to the survey was relatively low, which must be borne in mind when interpreting the findings.

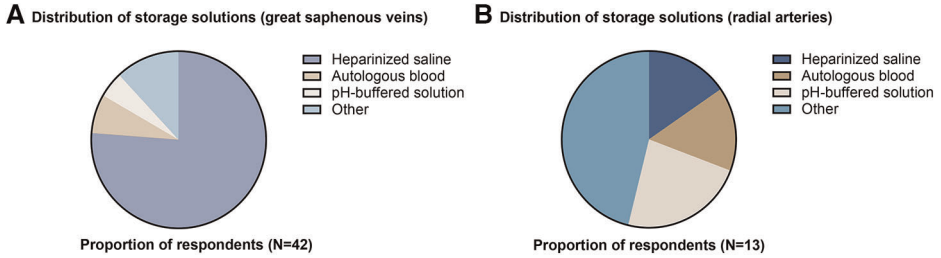

FIGURE 1
Distribution of storage solutions used for (A) great saphenous veins and (B) radial arteries.

TABLE 1 Distribution of storage solutions, storage duration, "no-touch" harvesting and degree of conduit distension by surgical specialty[a].

		Vascular Surgery	Cardiothoracic Surgery	Total
Storage solutions for harvested great saphenous veins	Heparinized saline	25	7	32
		17.99%	5.04%	
		78.13%	21.88%	
		83.33%	58.33%	
	Autologous blood	1	2	3
		0.72%	1.44%	
		33.33%	66.67%	
		3.33%	16.67%	
	pH- buffered solution	0	2	2
		0%	1.44%	
		0%	100%	
		0%	16.67%	
Storage solutions for harvested radial arteries	Heparinized saline	1	1	2
		0.72%	0.72%	
		50%	50%	
		3.33%	8.33%	
	Autologous blood	0	2	2
		0%	1.44%	
		0%	100%	
		0%	16.67%	
	pH- buffered solution	0	3	3
		0%	2.16%	
		0%	100%	
		0%	25%	
Average storage duration of harvested conduits	Less than 5 min	1	0	1
		0.72%	0%	
		100%	0%	
		3.33%	0%	
	5 to 15 min	0	2	2
		0%	1.44%	
		0%	100%	
		0%	16.67%	
	15 to 30 min	0	4	4
		0%	2.88%	
		0%	100%	
		0%	33.33%	
	30 to 45 min	0	6	6
		0%	4.32%	
		0%	100%	
		0%	50%	
"No-touch" technique used to harvest the vein or artery (i.e. the vein or artery is harvested with a pedicle of surrounding tissue)	Yes	9	8	17
		6.47%	5.76%	
		52.94%	47.06%	
		30%	66.67%	
	No	20	4	24
		14.39%	2.88%	
		83.33%	16.67%	
		66.67%	33.33%	
Extent of mechanical distension the conduit following harvest:	None	0	1	1
		0%	0.72%	
		0%	100%	
		0%	8.33%	
	Enough to fill the conduit but not expand it beyond its native (pre-dissection) diameter	12	8	20
		8.63%	5.76%	
		60%	40%	
		40%	66.67%	
	The conduit expands up to 1.5-2x its native (pre-dissection) diameter	16	3	19
		11.51%	2.16%	
		84.21%	15.79%	
		53.33%	25%	
	The conduit expands more than 2x its native (pre-dissection) diameter.	1	0	1
		0.72%	0%	
		100%	0%	
		3.33%	0%	

[a]Data reported as Count, Percent of total, Row percentage, Column percentage.

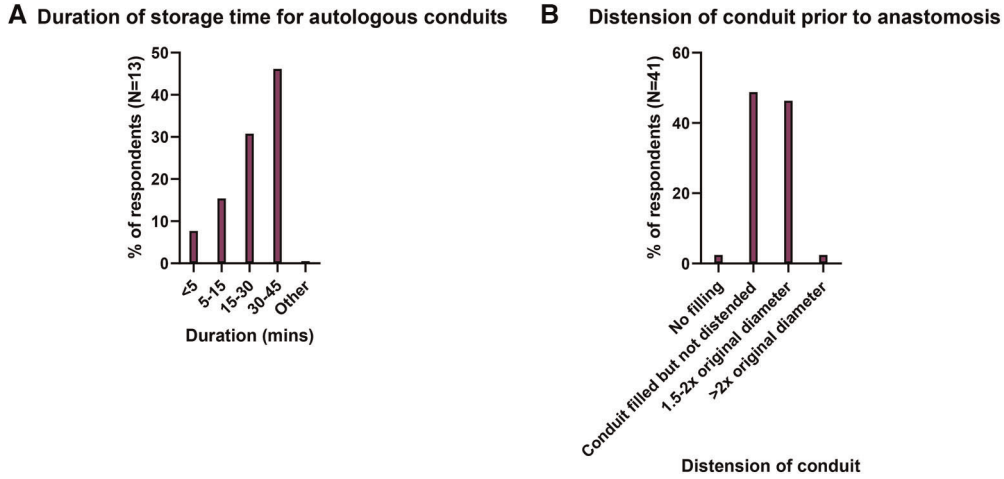

FIGURE 2
(A) Distribution of storage times for harvested autologous conduits and (B) Distension of conduit prior to anastomosis.

The effect of intraoperative graft storage solutions on endothelial damage, potential upregulated thrombogenicity, and potential subsequent graft failure is worthy of discussion. The PREVENT IV trial identified that in 2,817 patients who underwent CABG, veins stored in saline or blood-based solutions demonstrated a higher rate of failure at one year compared to buffered saline (5). Previously suggested reasons for saline being harmful to endothelium include its lack of ionic balance, and its acidic pH (5.5) (8).

Thrombosis is the major cause of early graft failure (9). Whilst thrombogenicity in this setting is highly multifactorial, endothelial injury of the conduit arguably plays an important role, and intraoperative storage solutions influence this process (5, 8, 10). Structurally, the endothelial surface layer is defined as the endothelial cellular glycocalyx, which is a layer of glycans lining all human cells, and its associated plasma proteins (11–13). The glycocalyx is a matrix consisting of various proteoglycans, glycosaminoglycans (GAGs), and plasma proteins, and it provides endothelial cellular mechano-sensation and transduction (14). Its principal GAGs include heparan sulphate (HS) and hyaluronic acid (HA), and core proteins primarily include syndecans and glypicans (11). Damage to the endothelial cell glycocalyx appears to be the earliest detectable injury to the vascular wall during the development of atherosclerosis and is associated with increased vascular permeability and adhesiveness (15). Destruction of the endothelial glycocalyx, which ranges from 200 to 2000nm in thickness, decreases vascular barrier function and leads to protein extravasation and tissue oedema, loss of substrate supply to tissues, and an increase in platelet and leucocyte adhesion (16).

During surgery, early endothelial injury begins during conduit preparation, including the harvesting technique used (e.g. open versus endoscopic), the extent to which the graft is manipulated and distended (17, 18), and surgical technique used during anastomosis. This is reflected by the teaching of "no touch" or minimal graft handling techniques, minimizing the over-distension of bypass conduits, and meticulous attention to anastomoses (19). It is worth noting that in certain circumstances, such as in-situ infrainguinal bypass surgery, storage of a free graft will be obviated, and periodic flushing is often employed in this setting once a proximal anastomosis has been completed. Endothelial damage, such as mechanical de-endothelialization, is frequently observed in free saphenous vein grafts (20) and exposes the underlying extracellular matrix. This triggers local release of tissue factors with reduced bioavailability of prostacyclin and nitric oxide (NO), which culminates in enhanced platelet activation, fibrin deposition, and ultimately thrombosis (21). During conduit harvesting, the endothelium is also rendered ischaemic due to separation from the systemic circulation and disruption of vasa vasorum of the vessel wall. Ischaemia generates oxidative stress, which may activate a procoagulant state (22). Luminal expression of prothrombotic molecules, such as thromboxane A2 and plasminogen activator inhibitor-1 upregulates the interaction between an activated endothelial surface with platelets and leucocytes. This sets in motion an accelerating process of inflammation and thrombosis, and ultimately, graft thrombosis (23).

The endothelial expression of thromboprotective proteins, such as thrombomodulin, plays a vital role in early graft patency (9). Thrombomodulin is a surface glycoprotein which modulates the activity of thrombin from a procoagulant to an anticoagulant protease (24), and its expression is vital in graft thromboresistance. When bound to thrombomodulin on the endothelial surface, thrombin is unable to generate fibrin or activate platelets but instead becomes a potent activator of

protein C. The activated form of protein C (APC) is an anticoagulant protease that selectively inactivates coagulation factors Va and VIIIa, providing an essential feedback mechanism to prevent excessive coagulation. Although activation of protein C *in vivo* is completely dependent on thrombomodulin, the efficiency of protein C activation is enhanced by another endothelial cofactor, the endothelial protein C receptor (EPCR) (25). Furthermore, ischaemic injury has been shown to downregulate thrombomodulin expression (26). Kim *et al* demonstrated, in a rodent model, that early loss of TM expression significantly impairs vein graft thromboresistance and results in enhanced local thrombin generation (9). Immunohistochemical staining of autologous rabbit vein graft sections revealed that the expression of TM, but not EPCR, was reduced significantly early after graft implantation. Western blot analysis revealed that TM expression was reduced by >95% during the first 2 weeks after implantation, with gradual but incomplete recovery by 42 days (9).

Despite the clinical burden of acute conduit occlusion, whilst some studies have previously investigated the influence of different storage solutions on endothelial integrity, few have investigated their effect on thrombogenesis (27). In order to mitigate endothelial shedding secondary to ischaemic injury, as well as the prothrombotic and proinflammatory state which accompanies it, a small number of novel treatment solutions have been studied *in vitro* and *in vivo*. Normal saline, whilst extensively used as a graft storage solution, has been shown to be damaging to autologous grafts, demonstrated both histologically as well as functionally, with impaired endothelial-dependent vasoreactivity (28, 29). Cardioplegia is used for myocardial protection during cardiac surgery. Generally, they may be classified as blood or crystalloid forms, such as St Thomas', del Nido, and Bretschneider solutions. Crystalloid cardioplegia was initially used to achieve myocardial protection until Buckberg introduced the concept of blood-based cardioplegia, which subsequently became increasingly popular (30). With respect to graft conduit storage, a recent prospective trial by Papakonstantinou *et al* reported that cardioplegia may better protect endothelial cells compared to heparin enriched solutions, however the association with clinical outcomes remains to be proven (31).

Furthermore, a new chloride-poor, iron-chelator-enhanced cardioplegic solution (Custodiol-N) has demonstrated improved liver, lung and heart preservation in different experimental studies (32–34). In a large animal study by Veres *et* al., this novel (Custodiol-N) conferred greater coronary endothelial protection compared to Custodiol after hypothermic cardiac arrest (35). TiProtec, a chloride-depleted, iron chelator-fortified modified HTK solution and Duragraft, an endothelial damage inhibitor, have shown promising results in preclinical studies involving both in murine aortic tissue and human saphenous veins. In a recent study in 2016, Veres *et al.* reported that in a murine model where aortic arches were harvested, stored in a novel TiProtec preservation solution, and grafted to the abdominal aorta, endothelial function was better preserved in the TiProtec group when compared with the saline and Custodiol groups (35). In a study of human saphenous vein segments and isolated pig mammary veins by Pachuk *et al*., normal saline caused damage to vascular endothelium, loss of graft cell viability, and mediated cell damage, whereas no evidence of damage or reactivity was observed in DuraGraft-exposed cells (29).

It is justifiable that the conduit endothelium should be protected as much as possible from ischaemic injury from the moment it is harvested. Intraoperative storage solutions may influence this pathophysiological process. Further research is required, however, regarding the effect of intraoperative storage media on expression of thromboprotective proteins, such as thrombomodulin (27), and clinical outcomes, such as angiographic evidence of graft failure, and rates of readmission and reintervention for graft occlusion, limb salvage (peripheral bypass), and mortality.

Conclusion

The distribution of storage solutions used in Cardiothoracic and Vascular Surgery in Australia and New Zealand is not well documented in the literature. From this survey, for great saphenous veins, heparinized saline was clearly the predominant storage solution. For radial arteries, storage solutions were more diversely spread across heparinized saline, autologous blood, buffer solutions and modified buffer solutions with vasodilators. This may potentially suggest a lack of consensus with respect to radial artery storage, although responses were limited. Storage time was up to 45 min in almost half of respondents, although responses to this question were limited. Data in the literature suggests that storage with neither saline nor autologous blood is able to protect the endothelium against cold ischaemia and warm reperfusion injury. Further research is required to investigate whether ischaemic endothelial injury generates a prothrombotic state, whether different storage media can alter this state, and whether this is directly associated with clinical outcomes of interest such as early graft failure.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by ID 69579, The Prince Charles Hospital HREC

(EC00168), 22 October 2020. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ABH - study conceptualization and design, conduct of survey, collation and interpretation of results, preparation of manuscript. NP, TC, MPV - study design, analysis of results, critical review of manuscript SP, DM, RN, JJ, JYS, JFF - critical review of manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TEVAR and EVAR, the unknown knowns of the cardiovascular hemodynamics; and the immediate and long-term consequences of fabric material on major adverse clinical outcome

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This review discusses the impact of endovascular aneurysm repair on cardiovascular (CV) hemodynamics and the role of stent-graft material, i.e., polytetrafluoroethylene (PTFE) vs. polyester in post-procedural outcomes. Endovascular aneurysm repair has been widely employed in the last decades for thoracic and abdominal aneurysm repair. However, aortic endografts are stiff and alter the native flow hemodynamics. This failure to simulate the native aorta could lead to added strain on the heart, manifesting as increased left ventricular strain, higher pulse pressure, and congestive heart failure later. This could result in adverse CV outcomes. Also, evidence is mounting to support the implication of stent-graft materials, i.e., PTFE vs. polyester, in adverse post-procedural outcomes. However, there is an absence of level one evidence. Therefore, the only way forward is to plan and perform a randomised controlled trial to demonstrate the alterations in the CV hemodynamics in the short and long run and compare the available stent-graft materials regarding procedural and clinical outcomes. We believe the best solution, for now, would be to reduce the stented length of the aorta. At the same time, in the longer term, encourage continuous improvement in stent-graft materials and design.

KEYWORDS
abdominal aortic aneurysm (AAA), endovascular aneurysm repair (EVAR), thoracic endovascular aneurysm repair (TEVAR), stent-Graft material, cardiovascular outcome

Introduction

Compared to open surgical repair, endovascular repair of the thoracic and abdominal aorta has been shown to reduce early perioperative morbidity and mortality (1, 2). However, this advantage is not maintained later due to an increment in cardiovascular (CV) complications secondary to arterial stiffening by

endograft (3). It is, therefore, essential to be aware of the impact of endograft design, their relative configuration, and stiffness compared to the native aorta (3–5). Also, the role of the endograft composition and structural design (i.e., endograft materials—polyester vs. polytetrafluoroethylene (PTFE), stent wires—nitinol vs. stainless-steel stent vs. cobalt-chromium) on the post-procedural outcomes needs to be acknowledged (3–9).

This review discusses the impact of endograft on CV hemodynamics in the first half and, subsequently, in the second half, the impact of stent-graft material, i.e., PTFE vs. polyester, in post-procedural outcomes, including post-implantation syndrome.

Materials and methods

This study was conducted through a non-structured online literature search (PubMed, Google Scholar and EMBASE) using the keywords—"Cardiovascular Hemodynamics," "Cardiovascular Complications," "Cardiovascular Outcomes," "Abdominal Aortic Aneurysm," "AAA," "Endovascular Repair," "TEVAR," "Thoracic Endovascular Aneurysm Repair," "EVAR," "Endovascular Aneurysm Repair," "Endograft," "Stent-graft material," "PTFE," "Polytetrafluoroethylene," "Polyester," and "Outcome." No selective restrictions were made on the type of studies, publication year and language. A secondary reference search was used to obtain further studies.

Impact of EVAR and TEVAR on cardiovascular haemodynamics

Aortic endografts are stiffer than the native aorta, and even the best available contemporary endograft design could potentially alter the flow haemodynamics (3–5). Studies have shown that aortic endografts could significantly reduce coronary perfusion by elevating systolic blood and pulse pressure (5–7, 10). These patients suffer on and off chest pain and systolic hypertension from early postoperative days. However, the broader CV community lack insight regarding cardiac remodelling post-aortic stents as interventionalists primarily focus on endo-graft adaptation rather than hemodynamic alterations. Furthermore, our follow-up protocols are based only on close supervision for endograft migration, detecting endoleak and aortic sac regression, for which we are not afraid of further stenting and coiling, thereby creating a stiffer aortic wall, which could further compromise cerebral, cardiac, renal, and mesenteric perfusion (3–7).

Pathophysiology

The aorta receives the left ventricle (LV) stroke volume in systole, which is distributed peripherally through the stored aortic elastic forces gained during diastole. This aortic compliance and blood flow through the aorta is best represented by the "Windkessel effect" (**Figure 1**) (10).

Windkessel effect impact both the heart and the peripheral circulation. Aortic compliance decreases the LV afterload. Furthermore, blood collected within the distended aorta helps to enhance coronary perfusion.

A mismatch between the native aortic to endograft compliance could manifest as adverse CV outcomes. Any change in the Windkessel effect could significantly increase the LV burden, resulting in adaptative LV hypertrophy and loss of ventricular-arterial coupling (11, 12).

As aortic endografts are less compliant than the native aorta, insufficient compliance results in a surge in hemodynamic shifts that impair CV homeostasis (3, 5, 8). Arterial stiffening results in elevated systolic blood pressure but lowers diastolic blood pressure, further exacerbating LV afterload, resulting in mal-perfusion of the coronaries. These changes contribute to LV hypertrophy, coronary ischemia, and arterial wall tissue fatigue, which are independent risk factors for CV morbidity and mortality (10–14).

Rong et al. (15) demonstrated amplification of circumferential strain in the descending thoracic aorta, paralleling distensibility by using intra-operative transoesophageal echocardiography to study the effect of endograft on the haemodynamic alteration. They showed that prosthetic replacement of the ascending aorta could interfere with the propagation of energy to the distal aorta resulting in adverse aortic remodelling. These results explain the development of resistant systolic hypertension post-TEVAR/EVAR with shortness of breath (SOB) and intermittent chest pain.

The impact of aortic flow dynamics on the LV function has been studied in experimental models (16), animals (17) and clinical studies (18). These studies support the Windkessel theory to establish the role of aortic capacitance in resultant ventricular size and function. However, the stented aorta loses its elasticity following simple and/or complex endovascular procedures, like TEVAR, FEVAR, BEVAR, and ChEVAR, failing the Windkessel effect. This failure of the Windkessel effect and change in pulse wave propagation multiplies a substantial workload for the LV putting an extra strain on the aortic valve's functioning. The resultant adaptative LV hypertrophy will manifest as CV complications (10–12).

The negative impedance due to endograft and LV strain will cause a decrease in diastolic systemic BP and reduces coronary blood flow and myocardial ischemia without coronary artery stenosis (10, 13). Sultan et al. (3, 5, 8, 10, 14–18) documented

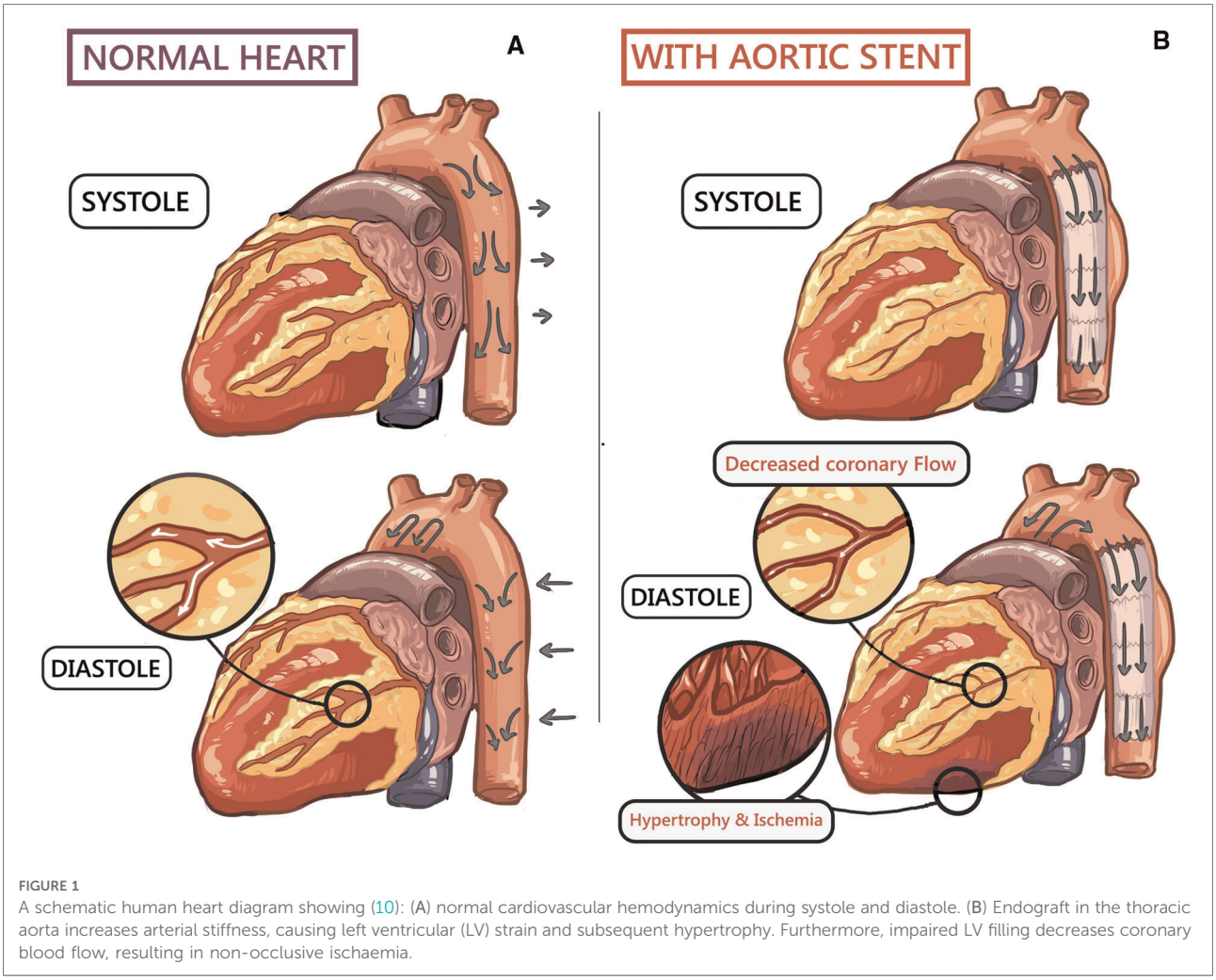

FIGURE 1
A schematic human heart diagram showing (10): (A) normal cardiovascular hemodynamics during systole and diastole. (B) Endograft in the thoracic aorta increases arterial stiffness, causing left ventricular (LV) strain and subsequent hypertrophy. Furthermore, impaired LV filling decreases coronary blood flow, resulting in non-occlusive ischaemia.

cardiac dysfunction on the postoperative echocardiograms of TEVAR/EVAR cases, with moderate LV hypertrophy and diastolic dysfunction. This is manifested by an increase in proBNP, which supports myocyte stretching and ventricular strain. Moreover, there was a significant troponin rise without coronary artery stenosis. Furthermore, the coronary angiography confirmed the absence of the coronary blockage, which supports the alternative explanation of coronary hypoperfusion following reduced diastolic pressure (**Figure 2**) (10).

Aortic compliance mismatch and hemodynamic alterations will be more evident after increasing the length of the stented aorta, for example, following combined TEVAR and EVAR. As such, endograft tend to adapt to these increments in shear stress. Studies have shown gradual endograft dilation after open surgical repair (3.2% per year post repair) (19–22). This could sometime result in excessive strain on the fabric architecture and the development of new aneurysms (10, 13).

Aortic integrity affects CV outcomes. This is evident in acute aortic syndrome, where CV complications are the main culprit for the late rehospitalisation after discharge (23, 24). Weiss et al. (24) showed nonfatal CV events and heart failure in patients with aortic dissection, intramural hematoma and penetrating aortic ulcer. These outcomes strengthen the need for long-term CV follow-up following endovascular aortic repair.

Pulse wave velocity

One of the ways to measure the impact of endograft stiffness on aortic impedance is to measure PWV.

PWV represents arterial stiffness, as higher arterial stiffness is seen with higher PWV. Subsequent increment in PWV increases the CV morbidity and mortality. Interesting, PWV could increase within a few hours of TEVAR and/or EVAR (21, 22, 25). TEVAR and EVAR increase the PWV by 2–5 and 1–3 m/s; however, a combined TEVAR/EVAR will result in an increment of 3–8 m/s (21, 22, 25). Blacher et al. (21) acknowledged that 1 m/s of PWV increment would double the all-cause mortality.

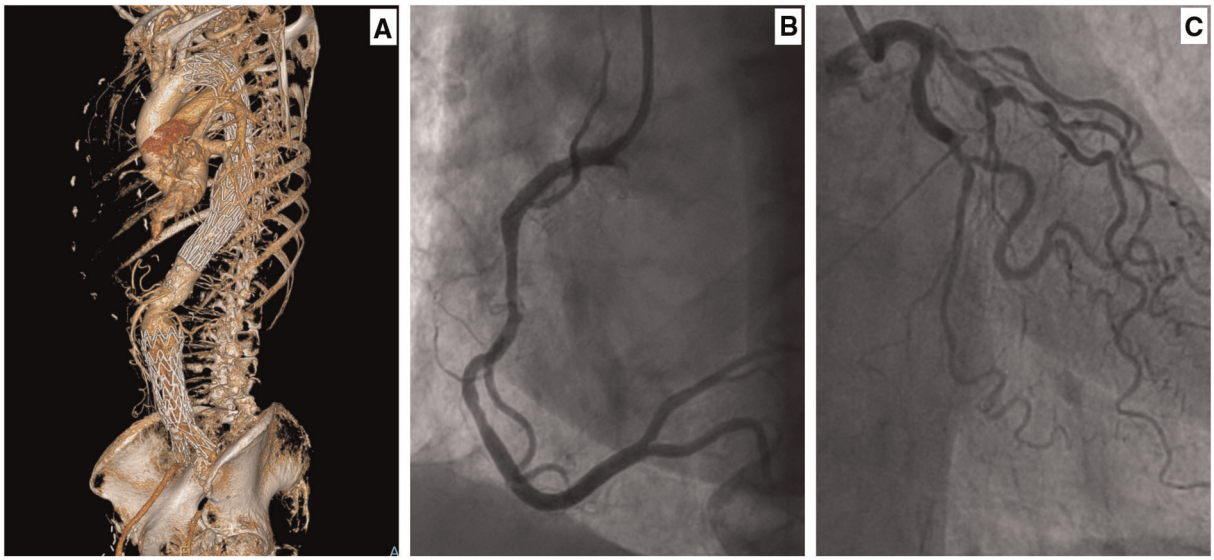

FIGURE 2
A female in her seventies with a saccular aneurysm in the descending thoracic aorta (10). She had thoracic endovascular aortic repair (TEVAR) in 2015 and subsequently underwent endovascular repair of her infrarenal aortic aneurysm in 2018. Her background history included ex-smoker, hypertension, lipid disorder, and right femoral-popliteal percutaneous transluminal angioplasty. (A) A 3D-CTA reconstruction, showing thoracic endograft. Following the TEVAR, the patient complained of intermittent chest pain and shortness of breath. A coronary angiogram was performed after her symptoms worsened. (B) Coronary angiogram (right main coronary artery) with no evidence of occlusive coronary disease. (C) Coronary angiogram (left main coronary artery) with no evidence of occlusive coronary disease.

TEVAR has been shown to increase LV stroke work by 26% (26). Van-Bakel et al. (16) showed that structural stiffness increased from 10.2 to 154.6 MPa/mm post-TEVAR. This is a 15-fold increase in workload for the heart within minutes of deployment of a TEVAR; as the heart was not preconditioned, the CV haemodynamic changes accelerate over time. Furthermore, increment in vascular stiffness with endograft results in ventricular diastolic dysfunction, thereby negatively impairing exercise tolerance amongst patients with lower LV distensibility (11, 12, 27).

We contemplated that PWV could be utilised in risk assessment in the peri-operative period post-TEVAR/EVAR. Risk stratification provides an opportunity to address hemodynamic alterations and modulate the CV risk (21, 22, 25).

Impact of stent-graft materials on post-procedural outcomes and post-implantation syndrome

A 4-dimensional strategy (14) is necessary to manage complex aortic pathologies as altered haemodynamic forces increase wall shear stress and impair blood flow, causing flow turbulence, pressure gradients, and blood viscosity increment. It involves the morphological adjustment and hemodynamic milieu of natural body forces since the resultant flow disturbance affects the management outcome (14).

Sultan et al. (10) documented that patients with combined TEVAR and EVAR can develop adaptive LV hypertrophy and diastolic dysfunction. This could result in a clinical picture like lower limb oedema, SOB, and chest pain with a normal coronary angiogram (**Figure 2**) (10).

The increase in aortic stiffness post-TEVAR could be seen earlier than EVAR due to proximity to the heart (28). However, the length of the stented aorta also matters. Combined TEVAR and EVAR in this regard have earlier and more pronounced impacts (10). Nonetheless, it is prudent that all the available endograft are less compliant than the native aorta (16, 29).

In terms of the endograft material, the Liapis group (30) showed that endograft made with polyester results in a threefold increment in PWV than PTFE.

We witnessed that TEVAR patients developed the abdominal aortic disease after endograft implantation (10). In these patients, worsening hypertension and late CV complications were potentiated by having a stiff tube in the aorta. This necessitates studies that specifically focus on CV complications post-aortic endograft. Also, it is possible that careful analysis of the endograft based registry could answer that question at present.

Patients with connective tissue disorder, like Marfan's syndrome, have a defect in the aortic wall, which could further complicate the compliance mismatch and result in aneurysmal dilatation.

Suppose this is explained to young trauma patients post aortic transection who underwent emergency TEVAR. This will result in unexplained congestive cardiac failure and dilated cardiomyopathy post-TEVAR in many young patients following aortic trauma.

Modified and complex endovascular techniques (BEVAR, FEVAR, PETTICOAT (31), STABILISE (32), FLIRT (33), Candy Plug (34), Knickerbocker (35), and Kinetic Elephant trunk (36) could provoke additional aortic wall stress. The risk of these CV complications increases more when stents are deployed closer to the heart and aortic valve (7, 36–39).

We acknowledged in our previous publications that the best solution is to reduce the length of the stented aorta through a "Staged hybrid single lumen reconstruction (TIGER)" protocol (3, 4, 26, 40, 41). TIGER protocol combines open abdominal aortic repair with thoracic aortic stenting. For this, we first create a single lumen from supra celiac, infra-diaphragmatic aorta to bilateral common iliac arteries through visceral arteries open surgical patching and subsequently perform TEVAR after that (4). With the reduction in the stented length of the aorta, the TIGER technique has shown that fewer aortic stents and grafts have superior long-term CV outcomes (3, 4, 14, 41).

Cardiac dysfunction following TEVAR/EVAR is a complex challenging scenario for CV interventionalist (10, 29). Therefore, it is essential to contemplate the compliance mismatch and long-term adverse CV outcomes. The nearer to the heart the endograft is deployed, the worse is the effect. The way to the future is to respect the aorta as an active organ, not a mere conduit.

The ideal design of the aortic endograft should resemble the native aorta in terms of its flexibility and hemodynamic impedance. The stent-graft polymers should be lightweight but strong and resilient and capable of withstanding the impact of normal pulsatile high flow arterial blood pressure. However, ePTFE and polyester are synthetic polymers that are relatively stiff and rigid compared to the native aorta (42–47).

There are no RCTs or CCTs to validate post-procedural outcomes following EVAR/TEVAR with specific stent-graft materials. Although not powered to demonstrate the difference in outcomes based on endografts, the EVAR I trial showed reduced major adverse clinical events (MACEs) with the PTFE based GORE Excluder graft (48, 49). Furthermore, direct comparisons are further complicated by the heterogeneity of individual manufacturers' differences in endograft design and procedural deployment techniques (50–53).

Consequently, it is difficult to accurately predict the impact of the stent-graft materials on hemodynamic alteration. PWV is a surrogate marker that demonstrates changes in stiffness following EVAR. Liapis et al. (30) showed that post-EVAR with polyester endografts, there could be a threefold increase in PWV compared to PTFE. PTFE endografts have been reported to offer significantly stronger resistance to dilatation than polyester-based endografts initially, albeit this advantage is lost over time (54). Similarly, there were lower complications with PTFE grafts (55). However, there are no reports of apparent long-term advantages.

PTFE-based endografts, compared to polyester, are associated with a lower incidence of post-implantation syndrome (PIS). PIS has been reported in up to two-thirds of the patients following TEVAR/EVAR (56), resulting in acute liver and/or multiple-organ failure (57–62). Ito et al. (56), Voûte et al. (63), and Sartipy et al. (64) implicated polyester-based endografts in the development of postoperative pyrexia, PIS, and more extended hospital stay post-EVAR compared to the PTFE-based endografts.

Ferreira et al. (65) suggested a probable interlink between PIS and increased CV mortality as polyester-based endografts increased inflammatory responses that caused endothelial damage. Higher serum IL-8 levels support this as IL-8 has pro-inflammatory and pro-tumoural functions. Also, IL-8 implicates the potential of polyester-based endografts; however, it is yet to be established (66–68).

Similarly, the use of polymers in EVAR within PTFE fabric has been controversial, and the polymer-based endografts, like Nellix (Endologix Inc., Irvine, CA, USA) and Ovation iX (Endologix Inc., Irvine, CA, USA) abdominal stent graft system device, were subsequently removed from the market (69, 70). They failed in short and mid-term follow-ups because of an inadequate proximal fixation with continuous pressure necrosis on the aortic sac for Nellix and aortic neck wall for the Ovation (69, 70). Any technology that uses embedded high inflation rings (Ovation iX) or balloons/endobags (Nellix) must be contraindicated, as the aorta is an organ that must be respected. Any attempt to manage it as a mere conduit is destined to fail.

The Alto device is a newer generation of the Ovation Xi platform, which combines PTFE limbs with the main body with polymer-filled rings to assist with sealing the proximal aortic neck (69). The technology is evolving, and there is limited long-term data on performance.

There have been studies looking at the effect of Ovation on PWV, which found no increment, but they did not compare it to other devices (71). However, PIS with polymer-based EVAR has the equivalent outcome as PTFE-based endografts with the added complications of aggravated PIS due to activation of TNF and monocytes at the site of high inflation balloons and/or rings (63–65).

The future

We must innovate in creating intelligent, compliant, durable endoprostheses that do not require any maintenance or follow up. It will be manufactured by a "Bio-inspired Smart Self-Healing Material with Autonomous and Non-Autonomous

Nanoparticles" as a nano-carrier for self-healing, self-repairing and self-assembly systems. These elements are vital components for durable smart endoprostheses.

The intelligent endoprosthesis will adapt itself to prevent tissue ingrowth into its' microstructure, preventing rigidity and maintaining distensibility. Therefore, the Smart endoprosthesis will retain the ability to expand in systole and collapse in diastole. After implantation, it gives back the elastic recoil to the heart, creating an almost standard aortic flow curve.

Bio-active-bio-inspired scaffolds will allow the smart endoprosthesis to be more robust and fault-tolerant. Transverse and longitudinal crimping that expands in systole and contracts in diastole will mimic the elastic recoil of the aorta. Hence it will abolish CV hemodynamic consequences of adaptive LV hypertrophy, the wide pulse pressure, the congestive heart failure and the renal impairment.

This paradigm shift towards utilising bio-inspired smart self-healing materials to build smart endoprosthesis capable of advanced self-healing during the functional lifetime of the endograft is a disruptive technology and will augment bio-convergence (72).

Intelligent bio-inspired endoprosthesis will lengthen product lifetime and abolish the need for follow-up or re-interventions. It is an intelligent green environmental friendly endoprosthesis that requires no service—a "TESLA like scenario".

Conclusion

There is increasing evidence of adverse hemodynamic alteration post-TEVAR/EVAR. Furthermore, evidence to support the implication of specific stent-graft materials, i.e., PTFE vs. polyester, in adverse post-procedural outcomes following endovascular repair of AAA is mounting. Interventionalists must respect the aorta as an active organ, not a mere conduit. The best solution in the short term could be to reduce the stented length of the aorta while in the longer-term encouraging continuous improvement in stent-graft materials and design. In the absence of level one evidence, the only way forward is to plan and perform an RCT or CCT to compare the available stent-graft materials regarding procedural and clinical outcomes.

Author contributions

Concept and design: SS, YA, OS, JCP, NH. Data collection: N/A. Analysis and interpretation: SS, YA, OS, JCP, NH. Writing the article: SS, YA, OS, JCP, NH. Critical revision of the article: SS, YA, OS, JCP, NH. Final approval of the article: SS, YA, OS, JCP, NH. Overall responsibility: SS, YA, OS, JCP, NH. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The web of clinical data, bioengineering, augmented reality and robotic in vascular surgery

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The new protocol for information distribution amongst scientists within the CERN, once slightly refined and publicly announced as the Worldwide Web in the August of 1991, has led to impressive achievements beyond the starting plan.

Let's imagine a similar story: we replace the scientists who study particle physics at CERN with scientists and professionals in medicine and healthcare to create the Web of Clinical Data (WCD). Like at CERN, only persons with proper authentication credentials could access the WCD, which would become a huge repository of personal health records (PHR) and clinical data from medical centers worldwide. Scientists and professionals in medicine could gain access to the repository by applying to an international scientific committee that supervises the WCD.

Doctors could access anonymous PHR located in any corner of the world employing software tools similar to those we daily experience on the Web. The WCD would become a paradigm shift (1) in the way students and experts in medicine access clinical data, and it could open the doors to the grand challenge of building decision support systems for medical decisions. These software agents could exploit the content of the health records and their similarities, so successful treatments buried in remote corners of the planet could be retrieved based on automatic induction from similar patterns of clinical data. In addition to the direct access to word, WCD offered to scientists and medical professionals, the progressive growth of the WCD would also catalyze emerging technologies in the broad field of artificial intelligence, with an enormous impact on medicine.

While this colorful story, which crosses fiction, makes us dream of fantastic progress in medicine and a massive diffusion of successful health care protocols, especially in third world countries, one might be overwhelmed by anxiety and fears of violating our privacy. Although in good faith, you may be tempted to dampen down these terrible Orwellian distortions and switch them off vigorously before they can unleash their contaminant force. However, the history of science teaches us that everything imaginable, sooner or later, will be the object of attention and study and that no proclamation can extinguish such a curiosity. History teaches us not to evoke stale

forms of luddism, that freedom has a high price, and that man is called to govern the application of nuclear physics to produce energy rather than to construct nuclear weapons. Interestingly, this story of the WCD is only partially new, and those privacy issues have already been carefully considered. In the United Kingdom, a few years ago, the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) jointly funded the Clinical Practice Research Datalink (CPRD). It is a new English NHS observational data and interventional research service designed to maximize the link of anonymous clinical data to originating research activities. It aims to generate outputs that are beneficial to improving and safeguarding public health.

Since the earliest work on Artificial Intelligence (AI) in medicine in the 1970s, advances in Technology and computational methods have led to a growing interest in potential applications in both Medical Research and Clinical practice. According to Vuong et al., the use of AI in medicine can be categorized into two main branches: the physical branch, which includes the development of assistive robots for care, surgery, or drug delivery, and the virtual branch, including the development of the informatics approach and expert systems (2, 3).

About augmented reality, recently, this technology has been successfully helping surgeons during image-guided integration of surgical navigation with virtual planning simultaneously with the real patient anatomy.

In open surgery augmented reality is important in surgical planning and patient specific study to navigate before complex operations and in simulation systems for training.

On the other side, in endovascular surgery evaluation of the potential benefits of wearable displays for performing fluoroscopically guided interventional procedures is currently being explored for developing innovative intraoperative platforms to assist the surgeon during the navigation (4, 5).

To date, despite the reported series by a few pioneers, laparoscopic aortic surgery has not been widely embraced by the majority of vascular surgeons.

This lack of interest can probably be explained by the technical difficulties experienced by surgeons with endoscopic techniques, especially during the performance ho aortic anastomosis (6–10).

This technical difficulty in suturing vascular anastomoses with laparoscopic instruments, as the main limitation, has stimulated the development of hybrid procedures whereby laparoscopic dissection is followed by hand-sewn anastomosis through a mini-laparotomy incision or and to hand-assisted laparoscopic surgery (HALS). However, laparoscopy's maximal benefit is achieved by avoiding mini-incisions altogether.

The application of robotic techniques in vascular surgery can be considered a great innovation and an actual revolution in the surgical field. This technique provides certain advantages for some surgical interventions, especially during specific tasks of the procedure, in light of its endo-effectors linked to mechanical arms that enable incredibly precise movements, considered practically impossible by direct human manipulation (11).

The slow adoption of robotic vascular surgery can also be attributed to the perceived risk associated with the telemanipulation of vessels. However, several published series of partial and total robotic aortoiliac operations have demonstrated low mortality and acceptable conversion rate (12–14).

Aortoiliac surgery, more aneurysmal disease than the occlusive, is undoubtedly a good indication to perform mini-invasively aortoiliac reconstructions with the robot, offering better clinical outcomes for patients than open surgery. There is still a place for conventional repair besides endovascular techniques, and life expectancy will benefit most from robotic surgical repair of abdominal aortic aneurysm repair.

A close collaboration between Doctors and Data scientists plays a crucial role in developing fitting tools and guiding engineers to answer the right medical question with the correct data (15).

Author contributions

All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effect of anesthetics on postoperative nausea and vomiting after peripheral vascular surgery in end-stage renal disease patients: A retrospective observational study

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Background: Propofol-based total intravenous anesthesia (TIVA) is considered a prophylactic approach to decrease postoperative nausea and vomiting (PONV). Despite general anesthesia commonly being performed in end-stage renal disease (ESRD) patients, PONV in ESRD patients has not been well-described. We investigated PONV in peripheral vascular surgery under general anesthesia in ESRD patients.

Methods: To compare PONV between propofol-based TIVA and anesthesia with volatile anesthetics, we collected retrospective data from patients who underwent peripheral vascular surgery under general anesthesia from July 2018 to April 2020. We performed univariable and multivariable analyses, including factors that could be associated with PONV and those previously shown to affect PONV.

Result: A total of 1,699 peripheral vascular surgeries under general anesthesia in ESRD patients were eligible for analysis. Based on the multivariable analysis, TIVA (odds ratio [OR], 0.45; 95% confidence interval [CI], 0.35–0.60; $P < 0.001$) significantly decreased PONV. Female sex (OR, 1.85; 95% CI, 1.44–2.38; $P < 0.001$) and anesthetic duration (OR, 1.01; 95% CI, 1.00–1.01; $P < 0.001$) were associated with increased PONV.

Conclusion: Propofol-based TIVA is the most influential factor decreasing PONV after peripheral vascular surgery in ESRD patients. Anesthesiologists can apply propofol-based TIVA as an alternative to anesthesia with volatile anesthetics.

KEYWORDS

ESRD, PONV, peripheral vascular surgery, propofol, TIVA

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common adverse effects of general anesthesia (1). Generally, the importance of PONV has been devalued, although it has a significant impact on postoperative care. PONV can delay discharge, disrupt oral intake, and lead to serious complications such as wound dehiscence and anatomic leaks. Therefore, it can increase treatment costs (2). Furthermore, PONV is a more common cause of patient discomfort than postoperative pain (3). Numerous factors affect the incidence of PONV, including patient characteristics, anesthetic factors, and surgical procedures (4). Among the prophylactic options for PONV, propofol-based total intravenous anesthesia (TIVA) is considered an excellent anesthetic strategy (5).

The incidence of end-stage renal disease (ESRD), the final stage of chronic kidney disease (CKD), is increasing globally. In the year 2000, approximately 1.1 million patients worldwide were being treated for CKD, showing an increase of 6%–7%, which is greater than the global population growth rate. The number of hemodialysis patients is estimated to reach 3,500,000 by 2020 (6). For these patients, hemodialysis is the most common treatment, which has increased the survival rate and improved patient quality of life (7). To achieve vascular access for chronic hemodialysis, peripheral vascular surgeries are performed in ESRD patients (8).

Although vascular access surgery (arteriovenous fistula formation) for hemodialysis can be performed under local anesthesia alone, many patients require general anesthesia for complicated peripheral vascular surgeries (e.g., graft interposition or aneurysm removal) due to the complexity of the procedures. For this reason, general anesthesia is commonly performed in ESRD patients.

Maintenance of general anesthesia should be achieved using short-acting drugs with minimal renal metabolism. Generally, short-acting volatile anesthetics such as desflurane or sevoflurane are preferred and the opiate remifentanil and the hypnotic propofol can be administered through continuous intravenous infusion as an alternative (9, 10). However, volatile agents are commonly considered the main cause of PONV, whereas TIVA with propofol is thought to decrease PONV (5, 11). Furthermore, there is a relatively high incidence of nausea and vomiting in hemodialysis patients (6). Nevertheless, PONV in peripheral vascular surgery for ESRD patients has not been well-described.

The aims of this study were to investigate PONV in peripheral vascular surgery under general anesthesia in ESRD patients and to compare the incidence between propofol-based TIVA and anesthesia with volatile anesthetics.

Materials and methods

To compare PONV after general anesthesia in ESRD patients with propofol-based TIVA or anesthesia with volatile anesthetics, retrospective data collection was performed from July 2018 to April 2020 at Soonchunhyang University Hospital, Seoul, Republic of Korea. This retrospective observational study was approved by Soonchunhyang University Hospital's institutional review board (IRB number: SCHUH2020-06-004). Written informed consent was waived because of the retrospective case-control nature of the study. Our findings are presented following the format recommended by the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (12). All methods were carried out in accordance with relevant guidelines and regulations.

Study population

We retrospectively enrolled 1,923 consecutive cases: all were ESRD patients who underwent peripheral vascular surgery under general anesthesia at age 30–90 years. Among them, emergency surgeries and cases without postoperative visit records for managing PONV were excluded.

Data collection

Medical records were reviewed retrospectively for patient characteristics, laboratory data, medical treatments, and clinical outcomes. We defined PONV as any nausea, retching, or vomiting according to the postoperative visit records. Demand for antiemetics and medical records indicating PONV in the post-anesthesia care unit (PACU) on postoperative day (POD) 1 were analyzed.

Anesthetic management

When departing for the operating theater, all patients were premedicated with 0.1 mg of glycopyrrolate intramuscularly, except when contraindicated. Upon arrival in the operating theater, standard monitoring devices were applied, including electrocardiography, pulse oximetry, and an oscillometric noninvasive blood-pressure cuff. Bispectral index monitoring (BIS System; Aspect Medical Systems, Newton, MA, United States) was performed for all participants.

In the TIVA group, general anesthesia was induced and maintained with propofol and remifentanil *via* effect site targeting using a target-controlled infusion system (Orchestra Primea; Fresenius Kabi AG, Bad Homburg, Germany) after

intravenous lidocaine (40 mg) administration. Propofol was administered using the Schnider pharmacokinetic model and remifentanil using the Minto model. The target concentrations of propofol and remifentanil were maintained at 2–5 μg/ml and 0–6 ng/ml, respectively, according to a BIS of 40–60.

In the volatile-anesthetics group, induction was performed using intravenous lidocaine (40 mg), propofol (1–1.5 mg/kg), and rocuronium (0.6 mg/kg) for neuromuscular blockade. Anesthesia was maintained with oxygen, medical air, and volatile anesthetics, including desflurane ($n = 170$, 29.1%) or sevoflurane ($n = 415$, 70.9%). Patients were administered intravenous remifentanil as required in the same way as the TIVA group. The volatile anesthetic and remifentanil dose were adjusted to achieve target BIS values of 40–60.

Patients received intravenous ephedrine (4 mg), phenylephrine (50 μg), or an inotropic infusion as required for blood pressure values below 20% of baseline during the operation. At skin closure in both groups, patients received intravenous fentanyl (0.3–0.5 μg/kg). At the end of the surgical procedure, the neuromuscular blockade was reversed with intravenous pyridostigmine (0.2 mg/kg) and glycopyrrolate (5 μg/kg) or with sugammadex (1–2 mg/kg) as needed. Tracheal extubation was performed under a monitoring train-of-four ratio >0.9.

The agents used for anesthesia depended on the discretion of the anesthesiologist assigned to each case. In the PACU and ward, patients received opioid or anti-emetics on demand.

Statistical analysis

The Kolmogorov-Smirnov test was used to test the hypothesis of a normal distribution for continuous variables. All continuous variables were reported as means ± standard deviations and all categorical variables were reported as n values (proportion, %). Categorical variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using the *t*-test or Mann-Whitney *U* test for intergroup comparisons of PONV and other clinical variables. To explore the relationships between PONV and other clinical variables, we performed univariable and multivariable analyses, including factors that could be associated with PONV and those previously known to have an effect on PONV. R software (version 4.0.0; April 24, 2020, R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses; a *P*-value <0.05 was considered significant.

Results

Among 1,923 cases, 224 were excluded because of a lack of postoperative visit records or emergency surgery. A total of 1,699 peripheral vascular surgeries under general anesthesia in ESRD patients were identified during the study period and all were included in the analysis.

Patient characteristics

The clinical characteristics of the patients are presented in **Table 1**. Age ($P < 0.001$), hypertension ($P < 0.001$), and diabetes mellitus ($P < 0.001$) were higher in the TIVA group than in the volatile group. The proportion of female sex ($P < 0.001$) and previous cerebrovascular accidents were higher in the volatile group ($P = 0.02$) than in the TIVA group. There were no significant differences in atrial fibrillation, current angina, previous myocardial infarction, asthma, chronic obstructive lung disease, or obesity between the two groups.

Anesthetic management and PONV

Table 2 shows anesthetic management and PONV. The incidence of PONV was significantly higher in the volatile group in total ($P < 0.001$) and in the PACU ($P < 0.001$) than in the TIVA group (**Figure 1**). Anesthetic duration ($P < 0.001$) and the volume of intraoperative crystalloid infusion ($P < 0.001$) were higher in the volatile group than in the TIVA group. PONV at POD 1, use of intraoperative vasoactive agents, use of postoperative inotropic agents, laryngeal mask airway, patient-controlled analgesia (PCA), fentanyl dosage in PCA, and dosage of administered antiemetics (palonosetron hydrochloride and ramosetron hydrochloride) did not differ significantly between the two groups.

Univariable and multivariable analyses of factors associated with PONV

Based on our univariable analysis, TIVA ($P < 0.001$), female sex ($P < 0.001$), age ($P = 0.001$), anesthetic duration ($P < 0.001$), fentanyl dosage in PCA ($P < 0.001$), and volume of intraoperative crystalloid infusion ($P = 0.01$) were significant factors affecting PONV (**Table 3**). Among these factors, TIVA (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.43–0.65) and age (OR: 0.99; 95% CI, 0.98–1.00) were associated with decreased PONV. Female sex (OR, 1.85; 95% CI, 1.78–2.69) and anesthetic duration (OR, 1.01; 95% CI, 1.01–1.01) were associated with increased PONV.

Based on our multivariable analysis, TIVA ($P < 0.001$), female sex ($P < 0.001$), anesthetic duration ($P < 0.001$), and fentanyl dosage in PCA ($P < 0.001$) were significant factors affecting PONV. Multivariable analysis showed that TIVA (OR, 0.45; 95% CI, 0.35–0.60) decreased PONV. Female sex (OR, 1.85; 95% CI, 1.44–2.38) and anesthetic duration

TABLE 1 Clinical patient characteristics.

Characteristics	Total ($n = 1,699$)	TIVA group ($n = 1,114$)	Volatile group ($n = 585$)	*P*-value*
Sex (M: F)	860 (50.62%): 839 (49.38%)	613 (55.03%): 501 (44.97%)	247 (42.22%): 338 (57.78%)	<0.001
Age (years)	63.89 ± 13.62	65.1 ± 13.08	61.59 ± 14.35	<0.001†
Hypertension	1,405 (82.7%)	952 (85.46%)	453 (77.44%)	<0.001
Atrial fibrillation	90 (5.3%)	54 (4.85%)	36 (6.15%)	0.30
Current angina	99 (5.83%)	61 (5.48%)	38 (6.5%)	0.46
Previous MI	51 (3%)	29 (2.6%)	22 (3.76%)	0.24
Diabetes mellitus	845 (49.74%)	597 (53.59%)	248 (42.39%)	<0.001
Previous CVA	236 (13.89%)	139 (12.48%)	97 (16.58%)	0.02
Asthma	31 (1.82%)	19 (1.71%)	12 (2.05%)	0.75
COPD	15 (0.88%)	11 (0.99%)	4 (0.68%)	0.72
Obesity	6 (0.35%)	4 (0.36%)	2 (0.34%)	>0.99‡

COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; MI, myocardial infarction.
All continuous variables are reported as the mean ± SD and all categorical variables as *n* (proportion, %). Data were analyzed using the †*t*-test, χ^2 test, and ‡Fisher's exact test.
Obesity defined as BMI > 25 ($kg \cdot m^{-2}$).
**P*-value for an analysis between the TIVA group and volatile group.

TABLE 2 Anesthetic management and PONV.

	Total ($n = 1,699$)	TIVA group ($n = 1,114$)	Volatile group ($n = 585$)	*P*-value*
Anesthetic duration (min)	116.83 ± 49.39	106.15 ± 43.08	137.17 ± 54.08	<0.001†
Intraoperative vasoactive agents				
Ephedrine	644 (37.9%)	417 (37.4%)	228 (38.9%)	0.746
Phenylephrine	411 (24.1%)	253 (22.7%)	158 (27.0%)	0.333
Dopamine infusion	19 (1.1%)	15 (1.4%)	4 (0.7%)	0.495
Norepinephrine infusion	19 (1.1%)	10 (0.9%)	9 (1.5%)	0.556
Crystalloid	172.66 ± 195.1	164.61 ± 194.6	187.99 ± 195.3	<0.001†
LMA	435 (25.6%)	285 (25.58%)	150 (25.64%)	>0.99
PCA	273 (14.20%)	189 (16.97%)	84 (14.36%)	0.13
Fentanyl dosage in PCA	1,071.79 ± 291.25	1,053.44 ± 307.10	1,113.10 ± 248.75	0.21†
Palonosetron HCl	0.15 ± 0.03	0.14 ± 0.05	0.15 ± 0	0.41ᴷ
Ramosetron HCl	0.71 ± 18	0.72 ± 0.17	0.7 ± 0.18	0.82†
PONV total	587 (34.55%)	329 (29.53%)	258 (44.1%)	<0.001
PONV in PACU	539 (31.72%)	296 (26.57%)	243 (41.54%)	<0.001
PONV at POD 1	96 (7.80%)	61 (6.86%)	35 (10.26%)	0.06

HCl, hydrochloride; LMA, laryngeal mask airway; PACU, post-anesthesia care unit; PCA, patient-controlled analgesia; POD, postoperative day; PONV, postoperative nausea and vomiting.
All continuous variables are reported as mean ± SD and all categorical variables as *n* (proportion, %). Data were analyzed using the †*t*-test, ᴷMann–Whitney *U* test, and χ^2 test.
**P*-value for an analysis between the TIVA group and volatile group.

(OR, 1.01; 95% CI, 1.00–1.01) were associated with increased PONV.

Discussion

In this retrospective observational study, TIVA was the most influential factor decreasing PONV after peripheral vascular surgery in ESRD patients. Female sex and anesthetic duration were factors that increasing PONV. The total incidence of PONV was 34.55%. Our study shows that propofol-based TIVA could be considered an alternative anesthetic method to reduce PONV in peripheral vascular surgery for ESRD patients.

Several independent factors are thought to be associated with PONV. These factors can be divided into multiple categories, including patient-specific (age, sex, smoking status,

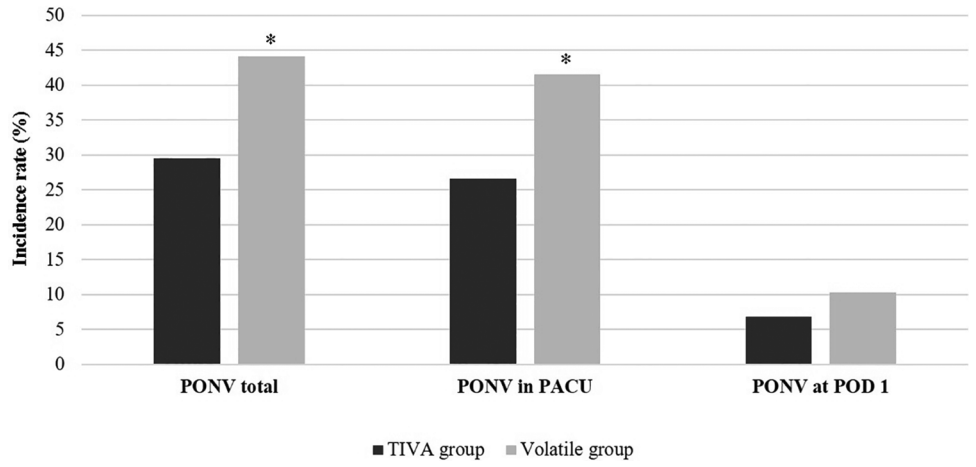

FIGURE 1
Incidence rate of postoperative nausea and vomiting (PONV) between total intravenous anesthesia (TIVA) group and volatile anesthesia group. *P value <0.05 between two groups.

TABLE 3 Univariable and multivariable analysis of factors associated with PONV.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
TIVA	0.53 (0.43–0.65)	<0.001	0.45 (0.35–0.60)	<0.001
Sex (F)	2.19 (1.78–2.69)	<0.001	1.85 (1.44–2.38)	<0.001
Age (years)	0.99 (0.98–1.00)	0.001	1.00 (0.9–1.01)	0.42
Hypertension	1.07 (0.82–1.39)	0.63	1.41 (0.98–2.03)	0.07
Previous MI	1.23 (0.69–2.18)	0.48	1.22 (0.61–2.42)	0.58
Diabetes mellitus	0.84 (0.69–1.02)	0.08	0.95 (0.73–1.25)	0.74
Previous CVA	1.17 (0.88–1.56)	0.27	1.04 (0.72–1.51)	0.82
Anesthetic duration (min)	1.01 (1.01–1.01)	<0.001	1.01 (1.00–1.01)	<0.001
Fentanyl dosage in PCA	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	<0.001
Crystalloid	1.00 (1.00–1.00)	0.01	1.00 (1.00–1.00)	0.94

CI, confidence interval; CVA, cerebrovascular accident; MI, myocardial infarction; OR, odds ratio; PCA, patient-controlled analgesia; TIVA, total-intravenous anesthesia.
Wald confidence intervals were calculated.

history of motion sickness or previous PONV), anesthetic (volatile anesthetics, intraoperative use of opioids, hydration, anesthetic duration), surgical (type and postoperative use of opioid), and other (mask ventilation, body mass index, pain) (4, 13). Among these, the most reliable risk factors of PONV were female sex, history of PONV or motion sickness, non-smoker, younger age, volatile anesthetics and postoperative opioids (14).

In ESRD patients, previous studies reported a higher prevalence of upper gastrointestinal (GI) symptoms such as nausea (74%), vomiting (68%), and anorexia (64%) (15). The reason for the high prevalence of GI symptoms in ESRD patients is unclear. Nevertheless, multiple etiologies such as treatments for the digestive system, the patient's diet, medication regimen, and developed disabilities are considered major causes of nausea and vomiting (16, 17).

Among the available anesthetics, propofol is commonly used for the induction and maintenance of general anesthesia because it is a rapid-onset and short-acting hypnotic agent. Moreover, propofol is known to have an antiemetic effect and TIVA with propofol is effective to reduce the incidence of PONV (11). General anesthesia with volatile anesthetics is largely responsible for PONV and avoidance of volatile anesthetics alone reduced the incidence of PONV by 19% (5). In our study, propofol-based TIVA reduced the incidence of PONV, even in ESRD patients.

For patient characteristics, female sex was considered the most important risk factor for PONV in several previous reports (3, 18–20). In these articles, female patients suffered from PONV three times more often than male patients. This may be due to hormone status, since this difference between the sexes begins at puberty. Nevertheless, the menstrual cycle does not have an impact on the occurrence of PONV (21). Although the mechanism of high PONV incidence in females remains unclear, our study showed the same results with female sex increasing the incidence of PONV.

Anesthetic duration is believed to increase PONV (18, 22). Correlation between anesthetic duration and PONV was same in our study. Some studies demonstrated that sufficient intravenous fluid administration might effectively prevent PONV (23, 24). But, there was no difference according to the amount of crystalloid infusion in our study.

There are some limitations to our study. First, similar to other retrospective studies, the data were incomplete so it may have introduced unrecognized bias into the results. In addition, some baseline characteristics of the two groups were significantly different. It might cause selection bias. Second, we did not evaluate patient-specific risk factors such as smoking status, history of motion sickness, and previous PONV. Despite these factors being strongly associated with PONV, our study did not reveal a correlation. Third, we analysed the data only up to POD 1 because of most patients were discharged at POD 2; therefore, we did not compare subsequent days. Finally, nausea is a subjective symptom so the collected data relied on patient answers.

In conclusion, propofol-based TIVA is the most influential factor in decreasing PONV after peripheral vascular surgery in ESRD patients. Additionally, female sex and anesthetic duration might be increasing factors of PONV. Considering the strong prevalence of PONV in ESRD patients, anesthesiologists can apply propofol-based TIVA as an alternative to anesthesia with volatile anesthetics.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Soonchunhyang University Hospital's institutional review board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HBC and SYP: Writing original draft; NK and SJC: Data analysis; SS and JHY: Writing review & editing; MGK: Data curation; JWC: Supervision and conceptualization. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Oscillatory shear stress promotes vein graft intimal hyperplasia *via* NADPH oxidase-related pathways

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Background: Uncontrolled intimal hyperplasia (IH) after autologous saphenous vein grafting triggers a high restenosis rate; however, its association with the activation of NADPH oxidase (NOX)-related pathways is unclear. Here, we investigated the effects and mechanism of oscillatory shear stress (OSS) on grafted vein IH.

Methods: Thirty male New Zealand rabbits were randomly divided into control, high-OSS (HOSS), and low-OSS (LOSS) groups, and the vein grafts were harvested after 4 weeks. Hematoxylin and eosin staining and Masson staining assays were used to observe morphological and structural changes. Immunohistochemical staining was used to detect α-SMA, PCNA, MMP-2, and MMP-9 expression. Immunofluorescence staining was used to observe reactive oxygen species (ROS) production in the tissues. Western blotting was used to determine the expression levels of pathway-related proteins (NOX1, NOX2, AKT, *p*-AKT, and BIRC5), PCNA, BCL-2, BAX, and caspase-3/cleaved caspase-3 in tissues.

Results: Blood flow velocity was lower in the LOSS group than in the HOSS group, while vessel diameter did not change significantly. Shear rate was elevated in both HOSS and LOSS groups but was higher in the HOSS group. Additionally, vessel diameter increased with time in the HOSS and LOSS groups, whereas flow velocity did not. Intimal hyperplasia was significantly lower in the LOSS group than in the HOSS group. IH was dominated by smooth muscle fibers in the grafted veins and collagen fibers in the media. OSS restriction significantly reduced the α-SMA, PCNA, MMP-2, and MMP-9 levels. Moreover, ROS production and the expression of NOX1, NOX2, *p*-AKT, BIRC5, PCNA, BCL-2, BAX, and cleaved caspase-3 were phase-reduced in LOSS compared to the levels in the HOSS group. Total AKT was not differentially expressed among the three groups.

Conclusion: OSS promotes the proliferation, migration, and survival of subendothelial vascular smooth muscle cells in grafted veins, which may be related to the regulation of downstream *p*-AKT/BIRC5 levels through the increased production of ROS by NOX. Drugs inhibiting this pathway might be used to prolong vein graft survival time.

KEYWORDS

oscillating shear stress, endothelial proliferation, NOX, reactive oxygen species, revascularization

Abbreviations

NADPH, nicotinamide adenine dinucleotide phosphate; NOX, NADPH oxidase; OSS, oscillatory shear stress; HOSS, high-OSS; LOSS, low-OSS; VSMCs, vascular smooth muscle cells; IH, intimal hyperplasia; VECs, vascular endothelial cells; WSS, wall shear stress; BIRC5, baculoviral inhibitor of the apoptosis repeat-containing protein 5; H&E, hematoxylin and eosin; Masson, Masson's trichrome; IOD, integrated optical density; α-SMA, α-Smooth muscle actin

Introduction

Coronary artery bypass grafting and peripheral revascularization are the most common treatments for arterial occlusion, with autologous saphenous vein grafts being the most popular grafts (1). After venous grafting, the graft undergoes a process of "arterialization," which causes complex changes by hemodynamic factors in the lumen of the grafted vein owing to different graft characteristics (2–4). These include proliferation of subendothelial vascular smooth muscle cells (VSMCs) and deposition of the extracellular matrix, both of which accelerate intimal hyperplasia (IH) in the grafted vein. Uncontrolled IH leads to vein graft failure and serious clinical complications.

There is growing evidence that hemodynamic changes initiate the development of many vascular diseases (5, 6). In the pathogenesis of vascular disease, vascular endothelial cells (VECs) can convert mechanical stimuli, such as wall shear stress (WSS), into biological signals that promote the proliferation, migration, and survival of VSMCs. Such pathological events ultimately lead to IH and vascular stenosis. WSS is a stress exerted on the inner wall of the lumen by the passage of liquid. The WSS of blood flow is a stress composed of magnitude and vector, while the oscillatory shear stress (OSS) is a regular stress that is inconsistent with the overall direction of blood flow (7). In the physiological state, a certain degree of high flow shear stress has a protective effect on VECs (8). However, recent studies have shown that fluctuating WSS, particularly oscillatory shear stress (OSS), can significantly accelerate the development of IH (9–11). Furthermore, OSS-derived vein graft IH involves multiple signaling pathways, which activate oxidative stress factors and cause an imbalance between endogenous oxidants and antioxidants in VSMCs.

Oxidative stress results from the sustained production of reactive oxygen species (ROS), most of which are produced by mitochondrial enzymes, such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) and xanthine oxidase (12). The NOX family consists of seven members, including NOX 1–5, dual-function oxidase 1 (DUOX1), and DUOX2. NOX1, 2, 4, and 5 are mainly expressed in VSMCs and VECs (13). NOX1 and NOX2 are generally considered promote the proliferation and migration of VSMCs under pathological conditions (14, 15). NOX4 is essential for the maintenance of the differentiation of VSMCs, regulating troponin and serum response factors to support the expression of differentiation genes under non-stimulatory conditions, while antagonizing the proliferative effect of NOX1 (16). Rabbit NOX5 is abundantly expressed and generates ROS in a calcium and PMA-dependent manner at rest (17). Moreover, NOX5 has a protective effect on rabbit arteries, and knocking out NOX5 will aggravate rabbit atherosclerosis (18). VSMCs sense mechanical stimuli conveyed by VECs, which continuously promote NOX production (19, 20). NOX-generated ROS activate many downstream molecules and channels, including MAPK, ERK, and AKT signaling, as a means of regulating downstream targets (21). The baculoviral inhibitor of the apoptosis repeat-containing protein 5 (BIRC5) gene (also known as survivin), a well-known target gene for cancer therapy, is involved in controlling multiple signaling pathways in tumor cells and has the dual function of inhibiting apoptosis and promoting cell proliferation (22). Although BIRC5 is closely associated with tumor development, it is not tumor-specific (22, 23). In previous studies, BIRC5 was found to be a key factor in the AKT pathway, which regulates the proliferation, migration, and survival of VSMCs in the arterial intima (9). Prevention of vascular occlusion triggered by excessive intimal proliferation in the grafted veins is an important therapeutic measure after revascularization. However, most previous studies only discussed the mechanisms of arterial IH with respect to the influence of hemodynamic-related factors, and few have examined the pathway-related factors affecting graft vein IH. Therefore, for graft vein IH, it is unclear whether OSS also regulates BIRC5 through oxidative stress to promote the proliferation, migration, and survival of VSMCs in vein grafts.

In this study, we used a rabbit external jugular vein graft model with increasing stenosis in the venous graft inflow tract artery. The flow rate was decreased to produce different levels of OSS and to study its association with graft vein IH. Our findings provide new ideas for the prevention of excessive IH in venous grafts and vascular remodeling.

Materials and methods

Experimental design

Animals were provided by the Animal Center of Chongqing Medical University. The experiments were performed in accordance with the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guidelines. Thirty male New Zealand rabbits (Yuda Experimental Rabbit Farm, Chongqing, China), weighing 2.0–2.5 kg, were randomly divided into three groups of 10 rabbits (**Figure 1**). Given the minimum reproducibility of the experiment, we considered this amount to be acceptable. In the control group, only the external jugular vein and common carotid artery were freed without grafting. In the high-OSS group (HOSS), the right external jugular vein was reversed and grafted to the ipsilateral common carotid artery. In the low-OSS group (LOSS), the inflow into the tract artery was restricted after receiving the venous graft.

Surgical methodology

The rabbits were anesthetized by ear margin intravenous injection (0.5 ml/kg) and intraperitoneal injection (1 ml/kg) of 3% sodium pentobarbital. The animals' vital signs were closely observed during the operation, and if the rabbits developed temporary respiratory arrest owing to an excessive anesthetic dose, then mechanical ventilation was performed to assist respiration (Reward Life Sciences Co., Ltd., Shenzhen, China, cat. no. R407). Blood was then heparinized by intravenous injection of heparin solution (200 IU/kg) through the ear margins. After skin preparation, the surgical site was disinfected with iodophor disinfectant (5 g/l) for 5 min. Local anesthesia was administered to the surgical area by subcutaneous injection of 2.5 ml of 2% lidocaine. The skin was incised along the midline of the neck under aseptic conditions, and the right external jugular vein in the

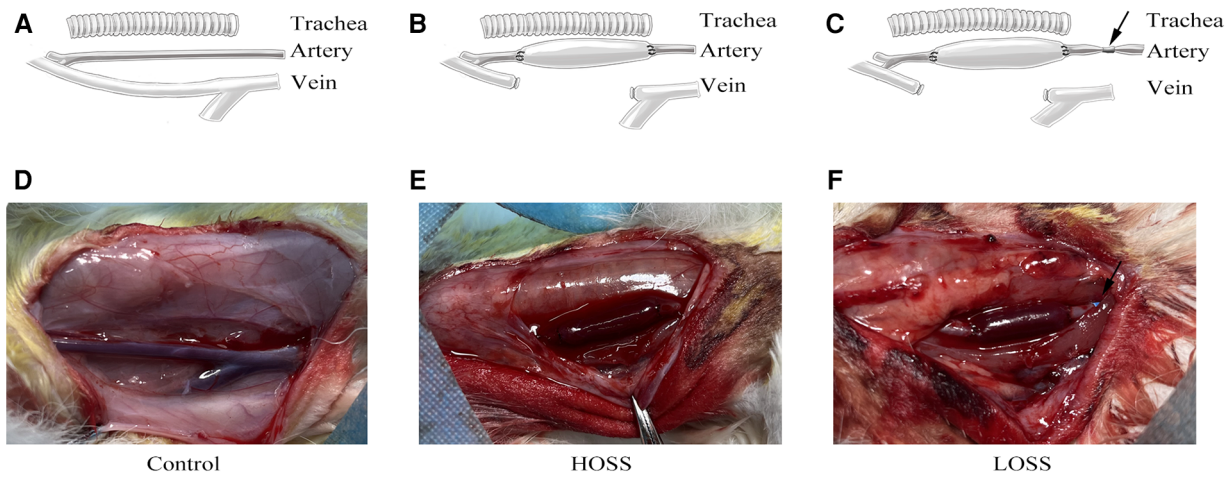

FIGURE 1
Surgical grouping and model construction. Rabbits were randomly divided into three groups: (A,D) control group (exposed vessels only), (B,E) high-oscillatory-shear-stress (OSS; HOSS) group (external jugular vein grafted to the ipsilateral common carotid artery), and (C,F) low-OSS (LOSS) group (vessels ligated to 50%–70% lumen area using a sheath at 5 mm of the inflow tract artery after vein grafting). $N = 10$ per group. Black arrow: 5F vascular sheath ligation.

superficial fascia and ipsilateral paratracheal common carotid artery were completely separated using a non-contact approach. Non-invasive microscopic hemostatic clips were placed proximal and distal to the artery, the external jugular vein (2.0–3.0 cm) was harvested by ligating both ends of the vein, and a section of the common carotid artery (1.0–2.0 cm) was excised. The free vein was inverted after being flushed with heparin solution (6,000 IU/l), and end-to-end anastomosis of the free vein and artery was performed using an 8-0 non-invasive suture with an eight-stitch interrupted suture. After the sutures were completed and the hemostatic clips were opened to ensure that the graft vein was patent and there was no bleeding at either end, the suture incision was closed layer by layer. In the LOSS group, after successful grafting of the vein, an arterial sheath with appropriate shearing was placed in the arterial inflow tract, 5 mm proximal to the anastomosis. The arterial lumen diameter at this site was limited to 50%–70% of the normal lumen area by circumferential constriction sutures. Penicillin (800,000 IU) was administered intramuscularly for five days, and aspirin (50 mg) was administered orally for three days. New Zealand rabbits were placed in a 12 h light/dark cycle and fed with adequate food and water.

The procedure was repeated 4 weeks after surgery. After applying the same anesthesia, the original incision was reopened, the venous graft was cut. The harvested graft was approximately 2.5 cm in length. In order to ensure that the harvested graft would not be disturbed by the fused vessels at the suture, we selected the grafted vein 1−2 mm close to the suture and resected it. And the 4% paraformaldehyde-fixed tissue was embedded in paraffin for hematoxylin and eosin (H&E), Masson's trichrome (Masson), and immunohistochemical staining. Fresh tissue was used for immunofluorescence staining after frozen sectioning and western blotting. After the experiments, New Zealand rabbits were deeply anesthetized with a 3% pentobarbital aqueous solution with a high concentration of carbon dioxide ventricular rest, sacrificed, and the carcasses were placed in a special storage freezer in the animal center.

Vascular ultrasonography

Successful venous graft model establishment was determined using vascular ultrasound (Figure 2). The blood flow velocity and vessel diameter of the venous grafts were measured both intraoperatively and 28 days postoperatively using an animal color ultrasound machine (Kyle Medical Instruments Ltd., cat. no. KR-S80). OSS was calculated according to the formula $OSS = 8\eta v^{mean}/d$ to determine the difference in OSS between the different experimental groups.

Histological examination

Graft vein tissues were fixed in 4% paraformaldehyde for 24 h, embedded in paraffin wax, and cross-sectioned into 4 μm sections. Tissue sections were placed on an electric heating plate at 60–70 °C for 3–4 h, followed by dewaxing using xylene for 15 min at room temperature (20–25 °C). Dewaxing was completed after two repetitions. The sections were subsequently hydrated in a gradient of decreasing ethanol and washed with tap water for 5 min to remove excess ethanol. Sections were then H&E and Masson stained to examine the structural changes and degree of hyperplasia of the graft vein. The stained sections were observed under a light microscope (magnification, ×100; Leica, Wetzlar, Germany). The thickness of the intima and media was measured using ImageJ, and the intima/media ratio was calculated simultaneously. Three different parts of each sample were randomly selected for measurement, and the average value was calculated.

For H&E staining (Shanghai Biyuntian Biotechnology Co., Ltd., cat. no. C0105S), the sections were stained with hematoxylin for 4–5 min and washed with tap water for 5 min. The sections were placed in a hydrochloric acid-ethanol fast differentiation solution (Shanghai Biyuntian Biotechnology Co.,

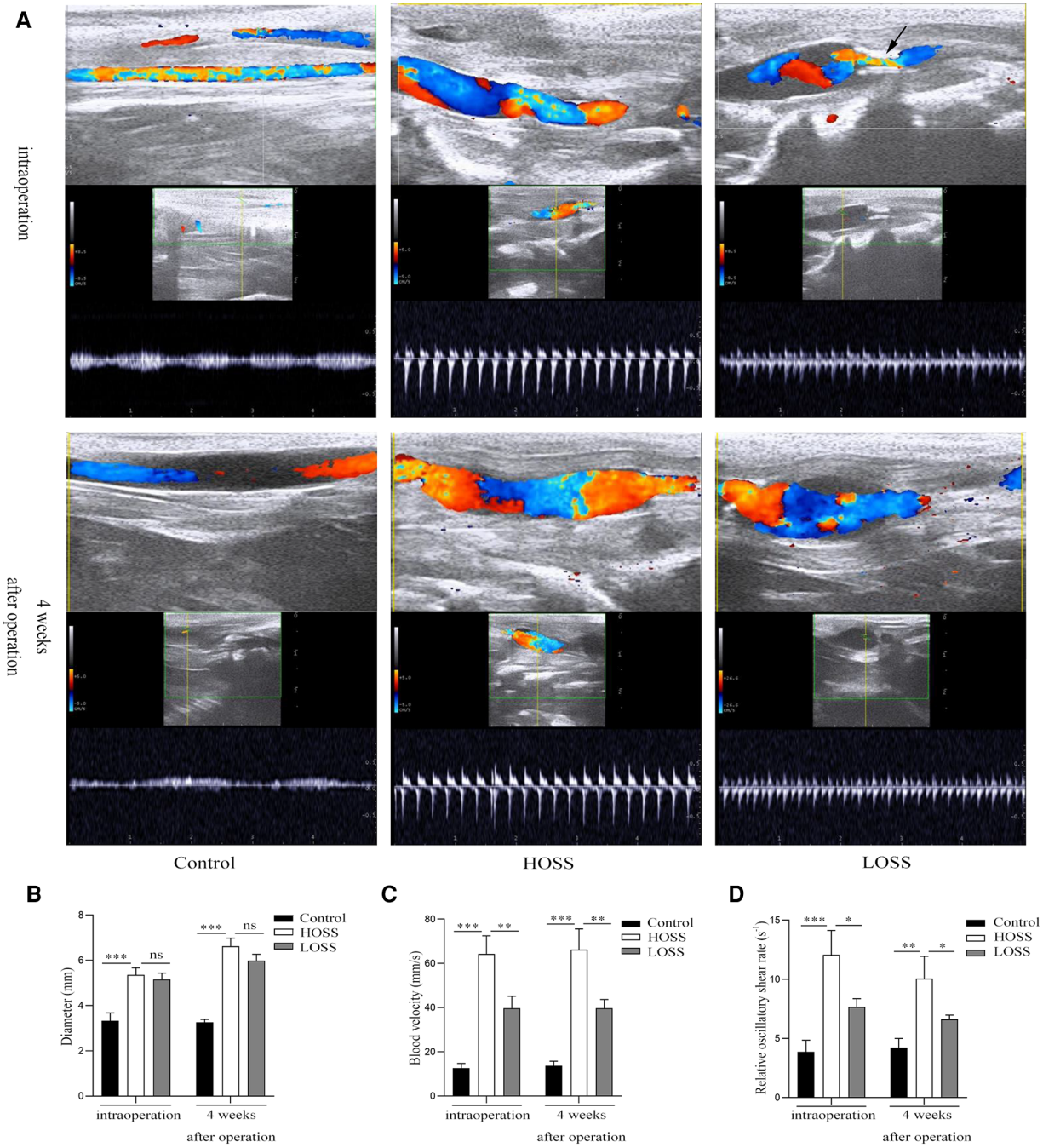

FIGURE 2
Vascular ultrasound shows changes of oscillatory shear stress (OSS) in grafted veins. (**A**) Vein graft morphology under ultrasound. (**B**,**C**) Columnar diagrams show the diameters and blood velocity. (**D**) Statistical results indicate that oscillatory shear rate differed among the three groups. Experiments were repeated in triplicate. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ns: no significant difference. Black arrow: inflow into the tract stenosis.

Ltd., cat. no. C0163S) for 10 s and washed with water for 5 min. The hydrated tissue sections were again immersed in an eosin staining solution for 3 min. The sections were subsequently dehydrated using graded increments of ethanol and coverslips were fixed with neutral gum.

For Masson staining (Beijing Solarbio Technology Co., Ltd., cat. no. G1340), sections were stained with Ponceau S dye for 5 min and washed with tap water for 5 min. The sections were incubated with 1% phosphotungstic acid solution for 5 min and then stained with aniline blue dye for 5 min. Subsequently, they were incubated with 1% glacial acetic acid in water for 1 min, dehydrated with graded increments of ethanol, and fixed with neutral gum.

Immunohistochemical staining

A mouse SP kit (Beijing Zhongsugi Jinqiao Biological Co., Ltd., cat. no. SP-9002) was used for antigen detection. The hydrated complete paraffin sections were restored using sodium citrate

antigen repair solution and boiled for 20 min in a microwave oven. Subsequently, they were washed in phosphate-buffered saline (PBS) buffer for 5 min. This process was repeated three times. The sections were dried on filter paper and incubated in an appropriate amount of endogenous peroxidase blocking agent for 10 min at room temperature (20–25 °C). The sections were incubated with normal goat serum working solution for 30 min at room temperature. Sections were incubated overnight at 4 °C with primary antibodies against α-SMA (1:200; Proteintech, cat. no. 55135-1-AP), PCNA (1:200; Bioss Antibody, cat. no. bsm-2006M), MMP-2 (1:100; Bioss Antibody, cat. no. bs-20705R), and MMP-9 (1:100; Bioss Antibody, cat. no. bs-20705R). Afterward, the sections were incubated with a biotin-labeled goat anti-mouse IgG for 50 min, followed by dropwise incubation with horseradish enzyme-labeled streptavidin working solution for 15 min. The sections were stained with hematoxylin staining solution for 3 min after 30 s of incubation by adding freshly prepared DAB chromogenic solution (Beijing Zhongsugi Jinqiao Biological Co., Ltd., cat. no. ZLI-9018). The sections were dehydrated in graded increments of ethanol and fixed in neutral gum. Images were observed using a light microscope (magnification, ×200; Leica) and analyzed using ImageJ (version 1.8.0; National Institute of Health, Bethesda, MD, USA) software (https://imagej.nih.gov/ij/). The cumulative optical density value and area of each image were measured and used to calculate the average integrated optical density value at the site (IOD/area).

Immunofluorescence staining

Briefly, freshly isolated graft veins were embedded in tissue frozen OCT compound (Sakura Fintek, CA, USA), cut into 4 μm thick sections, and placed on slides. Dihydroethidium dissolved in dimethyl sulfoxide (40 μmol/l) was added to tissue sections and incubated at 37 °C for 45 min in the dark (9). After washing three times with PBS, a blocker containing DAPI was added dropwise. Sections were placed under an orthomosaic fluorescence microscope (magnification,×100; Leica) and analyzed for fluorescence intensity using ImageJ.

Western blotting

The isolated fresh tissues were ground using a tissue mill, and the tissue lysates were extracted from the tissues by adding the appropriate amount of lysis buffer (pH 7.4, RIPA:PMSF: phosphatase inhibitor = 100:1:2), followed by low-temperature high-speed centrifugation (4 °C, 12,000 *g*). The supernatant was aspirated and the bicinchoninic acid method was used to determine the protein concentration. Equal amounts of total protein from different samples were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to nitrocellulose membranes. Then, 5% skim milk powder was used to block the nitrocellulose membranes for 90 min, and then they were washed with TBST buffer for 10 min. The membranes were then incubated with targeting NOX1 (1:1,000; Novus, cat. no. NBP1-31546), NOX2 (1:1,000; Proteintech, cat. no. 19013-1-AP), AKT (1:500; Wanlei Bio, cat. no. WL0003b), *p*-AKT (1:500; Wanlei Bio, cat. no. WL0003b), BIRC5 (1:500; Wanlei Bio, cat. no. WL03492), PCNA (1:2,000; Bioss Antibody, cat. no. bsm-2006M), BCL-2 (1:1,000; Abcam, cat. no. ab16904), BAX (1:500; Wanlei Bio, cat. no. WL01637), caspase-3/cleaved caspase-3 (1:500; Wanlei Bio, cat. no. WL02117), and β-actin (1:5,000; Bioss Antibody, cat. no. bsm-33036M) primary antibodies at 4 °C overnight (12–16 h). The membranes were washed three times with TBST buffer for 10 min each. After incubation with horseradish peroxidase-conjugated secondary antibody (1:2,000; Cell Signaling Technology, cat. no. 91196S) for 90 min at room temperature, the signal intensity was observed using chemiluminescence (Bio-Rad, CA, USA) according to the manufacturer's instructions. Image grayscale values were analyzed using ImageJ.

Statistical analysis

All data are expressed as mean ± standard deviation of at least three independent experiments. One-way analysis of variance (t-test with least significant difference) was performed using SPSS (version 24.0; IBM, Armonk, NY, USA) to determine significant differences between the groups. Statistical significance was set at $P < 0.05$.

Results

Differences of OSS in grafted veins

All rabbits survived and both immediate and 28-day postoperative vascular ultrasound revealed the patency of venous grafts (**Figure 2A**). The diameters in the HOSS group were similar to those in the LOSS group both postoperatively and 28 days after surgery, and both groups had increased diameters relative to the control group (**Figure 2B**). Moreover, the diameter 28 days after surgery was significantly larger than that in the immediate period in both experimental groups ($P < 0.05$), and the change in diameter was the same in both groups postoperatively, whereas there was no significant change in the control group. The flow rate in the HOSS group was significantly greater than that in the LOSS group, and both were significantly greater than that in the control group ($P < 0.05$, **Figure 2C**). Contrary to the above results, there was no significant change in vascular flow velocity in any of the three groups in the immediate postoperative period and at 28 days. In addition, the shear rate (v/d) of the HOSS group was significantly higher than that of the LOSS group, and both were significantly higher than that of the control group ($P < 0.05$, **Figure 2D**). The difference in the OSS was derived from the formula $OSS = 8\eta v^{mean}/d$, and the shear rate was proportional to OSS. Therefore, the postoperative OSS went from high to low in the HOSS, LOSS, and control groups, confirming the validity of the animal model.

Wall remodeling characteristics in grafted veins

Hyperplastic graft veins were isolated 28 days postoperatively and analyzed using H&E and Masson staining (**Figures 3A,B**). The

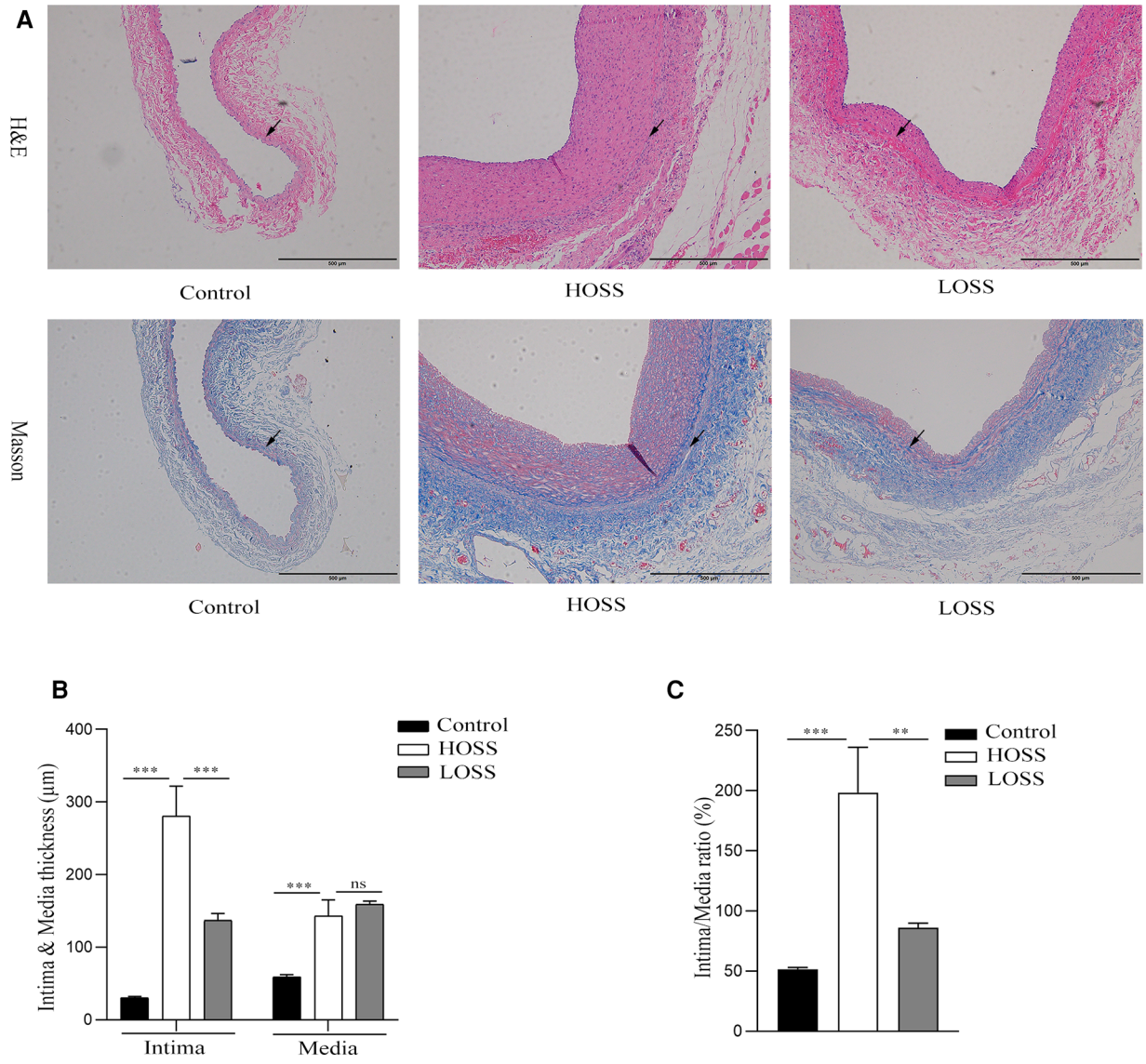

FIGURE 3
The extent of graft vein proliferation and structural changes. (A,B) Hematoxylin and Eosin (H&E) staining and Masson's Trichrome staining (magnification,×100). (C,D) Changes in intima and media thickness and intima/media ratio in the three groups. Visible deposition of collagen fibers (blue) in the graft vein to the media and muscle fibers (red) to the endothelium in Masson stain. Oscillatory shear stress (OSS) promoted vascular proliferation and accelerated graft vein remodeling. Experiments were repeated in triplicate. $^{**}P < 0.01$; $^{***}P < 0.001$; ns: no significant difference. Black arrow: boundary between intima and media.

intima and media were significantly thicker in the HOSS and LOSS groups than in the control group ($P < 0.05$, Figure 3C). Moreover, the intima/media ratio showed that the HOSS group was larger than the LOSS group, and both were larger than the control group ($P < 0.05$, Figure 3D). Masson staining showed that the main component of the intima was myofibrils, whereas collagen fibers were expressed more in the media. Compared to the control group, the HOSS and LOSS groups had relatively more disorganized collagen fibers. In addition, immunohistochemical staining was performed to observe protein expression sites and relative expression levels (Figure 4A). Statistical analyses (Figure 4B) revealed that OSS significantly induced the expression of α-SMA, PCNA, MMP-2, and MMP-9 in the hyperplastic intima and media of the venous grafts, and decreased OSS levels resulted in decreased expression ($P < 0.05$). We also found that PCNA, MMP-2, and MMP-9 were abundantly expressed in the media and adventitia membranes of grafted veins, while the expression was progressively diminished in the location near the sub-endothelium. These results suggested that the thickening of the grafted veins was due to OSS, which promoted the migration and proliferation of their subendothelial smooth muscle cells.

OSS-induced changes in ROS

Twenty-eight days after model establishment, ROS immunofluorescence staining was performed on the grafted veins to assess ROS levels in the different experimental groups

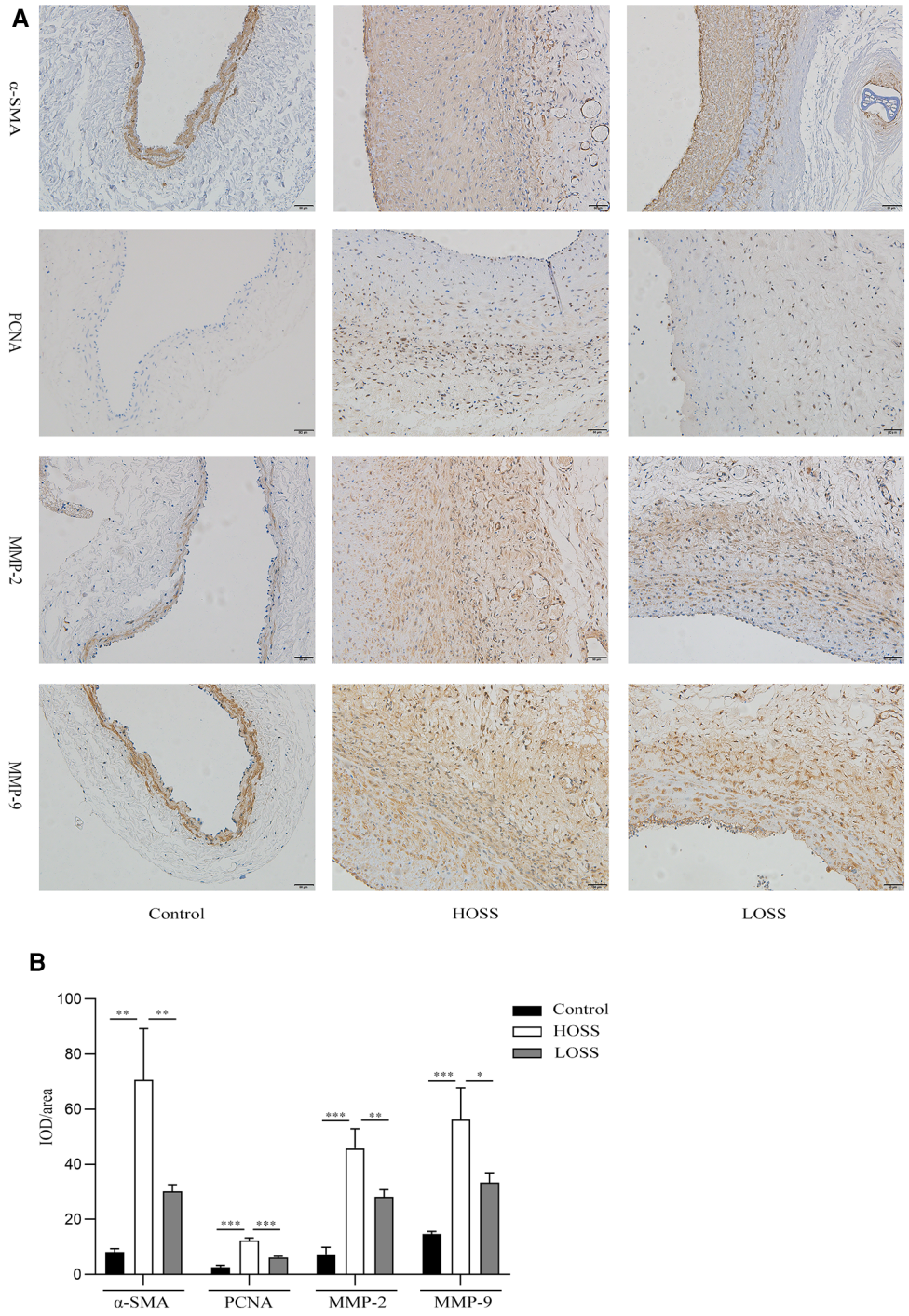

FIGURE 4
Effects of oscillatory shear stress (OSS) on proliferation and migration on vein grafts. (A) Immunohistochemical staining was performed to assess the expression of α-SMA, PCNA, MMP-2, and MMP-9 in vascular tissue (magnification,×200). (B) OSS promotes the expression of the above proteins, while its reduction slows down the proliferation and migration of vascular smooth muscle cells (VSMCs). Experiments were repeated in triplicate. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

(Figure 5A). The results showed that the basal ROS production in the control group was located in the subendothelial VSMC layer. ROS production was significantly increased in both grafted veins relative to that in the control group and was greater in the HOSS group than in the LOSS group ($P < 0.05$, Figure 5B); that is, high levels of OSS significantly promoted ROS expression through transduction of mechanical signals.

OSS alters NOX-related signaling, cell proliferation, and apoptosis-related factor expression

Next, protein lysates purified from grafted veins with different OSS were subjected to western blotting 4 weeks postoperatively (Figure 6). The expression of the pathway-related proteins NOX1,

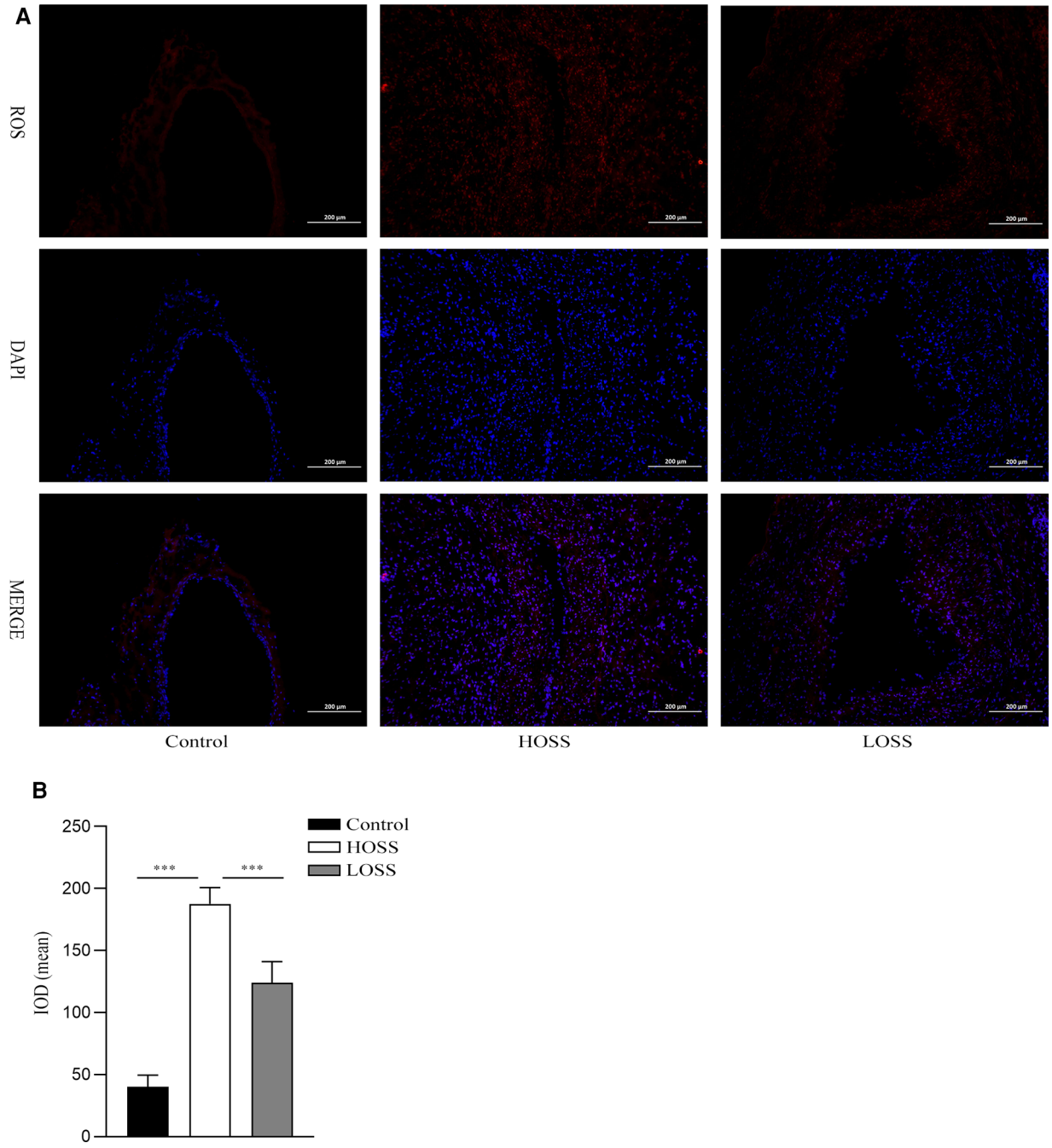

FIGURE 5
Oscillatory shear stress (OSS) upregulated reactive oxygen species (ROS) expression. (**A**) Immunofluorescence staining was used to measure the expression of ROS in the grafted veins. ROS (red) expression in grafted veins of different experimental groups was determined by immunofluorescence staining (magnification,x100). DAPI (blue) was used for nuclear staining. (**B**) Statistical analysis showed that the ROS fluorescence intensity was significantly increased in the high-OSS (HOSS) group and relatively diminished in the low-OSS (LOSS) group compared to that in the control group. Experiments were repeated in triplicate. ***$P < 0.001$.

NOX2, *p*-AKT, and BIRC5 was significantly increased in the grafted veins of the HOSS group relative to that in the control veins, whereas reducing the OSS levels decreased the expression of several of these proteins ($P < 0.05$). That is, Alterations of ROS-producing NOX and ATK-BIRC5 in grafted vein VSMCs were associated with OSS, which promoted their proliferation, leading to IH. In addition, the expression trend of PCNA, a protein associated with cell proliferation, BCL-2, BAX, and cleaved caspase-3, a protein associated with apoptosis, was consistent with the above findings ($P < 0.05$). However, no statistically significant changes in total AKT protein expression were observed among the three groups.

Discussion

The prevention of long-term patency decline due to excessive IH of the grafted vein has historically been the most important follow-up factor after autologous saphenous vein grafting (24, 25). Fluctuating

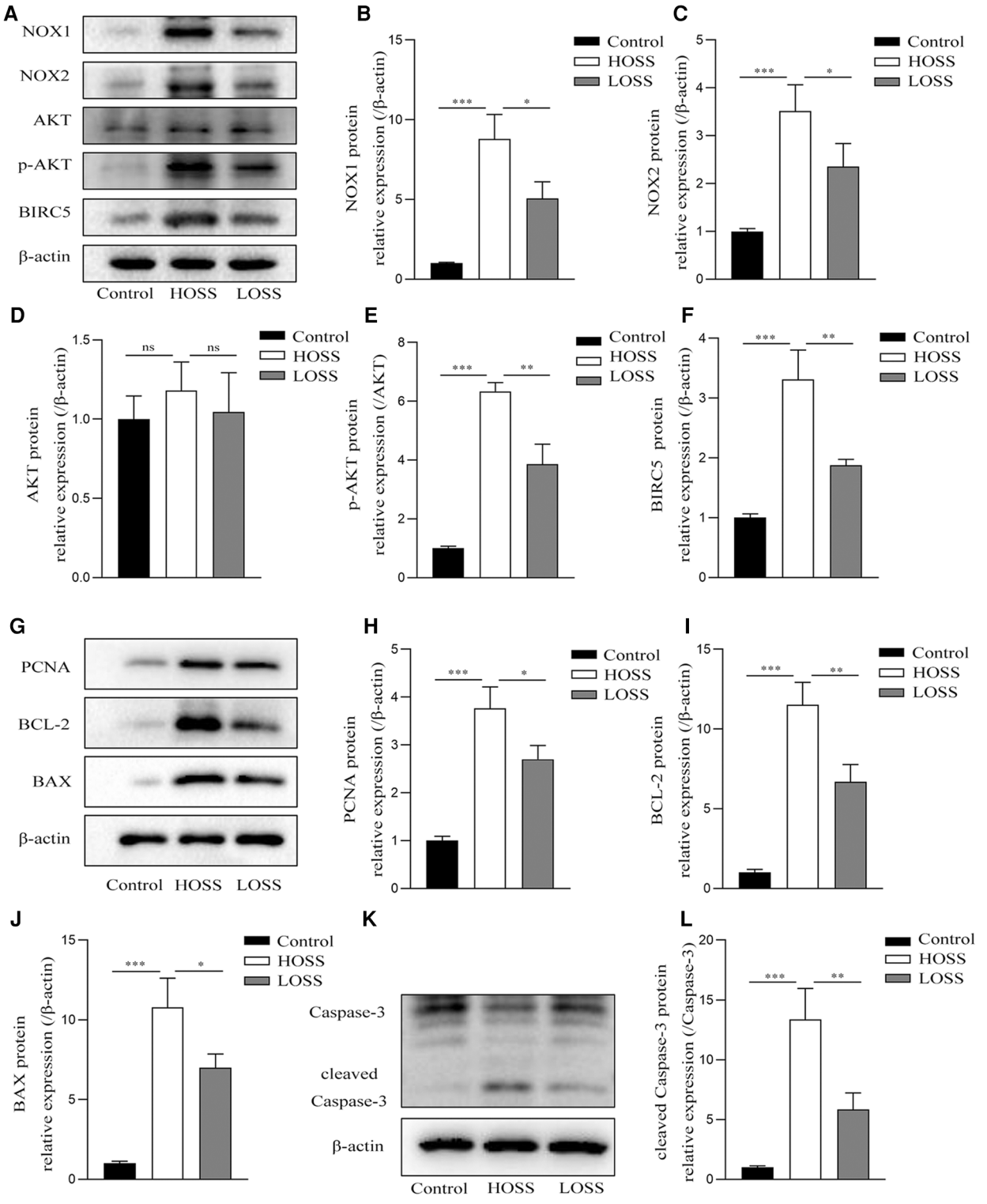

FIGURE 6
Oscillatory shear stress (OSS) is involved in altering NOX-AKT-BIRC5 signaling, cell proliferation, and apoptotic factor expression. Western blotting of purified protein lysates from grafted veins was used to detect protein expression. (A–F) OSS was positively correlated with the expression of NADPH oxidase-related proteins in grafted veins. (G–L) High OSS (HOSS) promoted the expression of proliferative, apoptotic, and anti-apoptotic related proteins, whereas decreasing the shear level attenuated their expression. Experiments were repeated in triplicate. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ns: no significant difference.

OSS can significantly accelerate the development of IH through multiple signaling pathways, in which oxidative stress factors are implicated (10, 11). NOX-generated ROS activate MAPK, ERK, and AKT signaling, and BIRC5 is a key factor in the AKT pathway, which regulates the proliferation, migration, and increased survival of VSMCs in the arterial intima (21). To date, it

remains unclear whether OSS regulates BIRC5 through oxidative stress to promote the proliferation, migration, and increased survival of VSMCs in vein grafts. Here, we sought to study the association of OSS with graft vein IH. To that aim, we used a rabbit external jugular vein graft model with increasing stenosis in the venous graft inflow tract artery, and the flow rate was decreased to produce different levels of OSS. Our results suggest that a certain degree of high OSS is an important factor causing IH and fibrosis in venous grafts. Arterial blood flow to the graft vein produced a higher OSS relative to the venous environment owing to mismatched diameters and fast flow rates, which was sufficient to induce oxidative stress in the graft vein. This was accompanied by an increase in ROS levels in the graft vein and the increased expression of ROS-producing NOX1 and NOX2 proteins and the downstream AKT-BIRC5, which ultimately lead to irreversible IH and tissue fibrosis.

Owing to their physiological structure, veins are much thinner than arteries (26). When transplanted into an arterial environment, several factors accelerate the remodeling of the grafted vein to "arterialize" to this rapidly changing environment, with OSS being one of the most important hemodynamic factors (25, 27–29). The graft vein undergoes both positive remodeling in the form of lumen enlargement and negative remodeling in the form of IH during the vascular remodeling process (3). Ultrasound results showed that significantly increased blood flow per unit time when grafted into the arterial circulation led to an early increase in the lumen diameter of the grafted vein. Rapid turbulent flow produces a higher OSS, causing injury and exfoliation of the endothelium, which induces vein graft reendothelialization. However, the nascent endothelium responds to the over-enhanced OSS by releasing various intracellular signaling molecules such as ROS, thus triggering the proliferation and migration of VSMCs and causing IH (30). α-Smooth muscle actin (α-SMA), a myofibroblast marker protein, is abundantly expressed in VSMCs. Masson and α-SMA immunohistochemical staining revealed the presence of a layer of annular endothelial VSMCs in normal veins, and α-SMA was expressed only in subendothelial SMC. In contrast, α-SMA was abundantly expressed in the intima and media layers in both grafted veins. Therefore, it is reasonable to speculate that the OSS in the arterial environment promotes the continuous proliferation of VSMCs in the grafted veins, while the proliferating SMCs migrate from the media to the intima, causing a large accumulation of subendothelial SMCs and resulting in IH.

Our results also confirmed that the expression of proteins associated with proliferation, survival, apoptosis, and migration (PCNA, BCL-2, BAX, caspase-3, MMP-2, and MMP-9) was increased in the grafted veins. In contrast, reducing OSS by narrowing the inflow tract diameter of the graft vein and slowing its flow velocity slowed the remodeling of the graft vein and decreased the expression of related proteins. This is consistent with the above reasoning that, although proliferation, increased survival, injury, and apoptosis are present simultaneously in the process of vein remodeling, a certain degree of high OSS in the arterial environment still accelerates the proliferation of VSMCs, leading to more severe IH after 4 weeks.

In the peripheral vascular system, ROS are mainly produced by NOX, which is a downstream mediator of the OSS-triggered cellular events (31). Among the NOX family, NOX2 was the first NADPH oxidase identified, whereas NOX1 was its first homolog (also called MOX1), and both were shown to be mainly expressed in VECs and SMCs (13, 32). Animal experiments have confirmed that NOX1 and NOX2 are involved in vascular growth and remodeling and play important roles in vascular diseases such as hypertension and atherosclerosis (14, 33, 34). ROS, as a central link in oxidative stress, are similar to second messenger signaling molecules that activate many redox-sensitive signaling pathways and are important signaling molecules that regulate the structural and functional status of blood vessels (12). ROS are produced by VECs, SMCs, and arterial outer membranes. Excessive ROS production is strongly associated with inflammatory responses, atherosclerosis, diabetes, hypertension, and tumorigenesis (35). In a normal venous environment, basal expression of ROS occurs mainly in the intimal layer of the vein. We found that OSS enhanced the production of ROS in the venous vessel wall of *in vivo* grafts, which was positively correlated with the expression of NOX1 and NOX2. Although ROS are not exclusively generated by NOX, ROS generation in this experiment was closely associated with the increased expression of NOX1 and NOX2.

In VSMC dysfunction, NOX-derived ROS seem to play a central role in coordinating different initiation-altering factors (hemodynamic factors, cytokines, and growth factors), signaling mediators (PKC, integrins, AKT, ERK1/2, and NF-κB), and other regulatory systems (systemic and local renin-angiotensin system and reactive nitrogen species) (35). When the expression of NOX-derived ROS in and around cells increases, the downstream AKT-BIRC5 axis is activated and the proliferation of VSMCs is promoted (36). BIRC5, also known as the survivin gene, is a member of the apoptosis inhibitory protein family that has received attention because of its unique role in regulating the proliferation of VSMCs. BIRC5 is regulated by upstream AKT (37). When intracellular ROS increases, it activates downstream AKT and accelerates its phosphorylation, thus promoting an increase in the activated form of *p*-AKT, which in turn regulates BIRC5 protein expression. BIRC5 promotes graft vein IH and is mainly associated with the promotion of VSMC proliferation and the migration of the macrophage system to cells (38, 39). In our experiments, although there was no difference in total AKT protein expression, the trend of change in *p*-AKT and BIRC5 expression was consistent with that of ROS production, which ultimately led to the proliferation of VSMCs in grafted veins and increased the expression of anti-apoptotic and migratory proteins. Therefore, we hypothesized that when veins are transplanted into the arterial setting, it is possible that subendothelial VSMCs are influenced by OSS to promote increased intracellular NOX expression, which positively regulates downstream *p*-AKT/BIRC5, leading to irreversible IH in transplanted veins.

Although the results of our study confirm that OSS promotes IH of vein grafts in rabbits, more research is required for its application in clinical settings. Human grafted veins experience higher blood flow and stronger OSS than in animals. Due to their thicker media and adventitia, when compared with rabbits, localized IH is already

present before transplantation, which would accelerate the failure of grafted veins (40). Studies have pointed out that transplanting venous external stents can effectively delay venous remodeling and prolong survival time (41). This may be related to improving the compliance of grafted veins and restoring laminar flow in the blood vessels. To a certain extent, higher laminar shear stress can inhibit the proliferation of VSMCs, thereby delaying IH (8, 42). However, OSS is a stress that varies based on the overall blood flow direction, considering a vector, which can be considered as a low laminar shear stress (7). Moreover, in a long-term follow-up (>1 year) of human saphenous vein grafts, some factors, such as inflammatory cell infiltration, will accelerate atherosclerosis occurrence (43). Reducing OSS and prolonging the survival time of vein grafts are challenges that need to be resolved urgently in clinical settings. Although we have provided novel insights on the effect of OSS on IH, the present study had some limitations that should be addressed. The NOX-related pathways that promote vein graft IH are discussed in this paper; however, whether these pathways are specifically dominated by NOX1 or NOX2 remains unclear. To overcome this limitation, in future studies, we will inhibit NOX1 and NOX2 based on the present study model to further observe potential mechanisms and improve our understanding.

Conclusion

We found that OSS promotes the proliferation, migration, and survival of subendothelial VSMCs in grafted veins, thereby promoting IH. This may be related to the regulation of downstream *p*-AKT/BIRC5 levels *via* the increase in ROS generation by NADPH oxidase. Therefore, drugs inhibiting this pathway might be used to prolong graft vein survival time after vein grafting. Furthermore, the pathway may be required for the remodeling of vein to arterial circulation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The animal study was reviewed and approved by Ethics Committee of the First Hospital of Chongqing Medical University (ID: 2021-620).

Author contributions

GQY, YZ, and XHW conceived and designed the experiments; GQY, HHL, XYZ, CKW, and YLX performed the experiments; GQY wrote the manuscript; GQY and HHL conducted the data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Abdominal aortic aneurysm volume and relative intraluminal thrombus volume might be auxiliary predictors of rupture—an observational cross-sectional study

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Objectives: The study aimed to identify differences and compare anatomical and biomechanical features between elective and ruptured abdominal aortic aneurysms (AAAs).

Methods: Data (clinical, anatomical, and biomechanical) of 98 patients with AAA, 75 (76.53%) asymptomatic (Group aAAA) and 23 (23.46%) ruptured AAA (Group rAAA), were prospectively collected and analyzed. Anatomical, morphological, and biomechanical imaging markers like peak wall stress (PWS) and rupture risk equivalent diameter (RRED), comorbid conditions, and demographics were compared between the groups. Biomechanical features were assessed by analysis of Digital Imaging and Communication in Medicine images by A4clinics (Vascops), and anatomical features were assessed by 3Surgery (Trimensio). Binary and multiple logistic regression analysis were used and adjusted for confounders. Accuracy was assessed using receiving operative characteristic (ROC) curve analysis.

Results: In a multivariable model, including gender and age as confounder variables, maximal aneurysm diameter [MAD, odds ratio (OR) = 1.063], relative intraluminal thrombus (rILT, OR = 1.039), and total aneurysm volume (TAV, OR = 1.006) continued to be significant predictors of AAA rupture with PWS (OR = 1.010) and RRED (OR = 1.031). Area under the ROC curve values and correct classification (cc) for the same parameters and the model that combines MAD, TAV, and rILT were measured: MAD (0.790, cc = 75%), PWS (0.713, cc = 73%), RRED (0.717, cc = 55%), TAV (0.756, cc = 79%), rILT (0.656, cc = 60%), and MAD + TAV + rILT (0.797, cc = 82%).

Conclusion: Based on our results, in addition to MAD, other important predictors of rupture that might be used during aneurysm surveillance are TAV and rILT. Biomechanical parameters (PWS, RRED) as valuable predictors should be assessed in prospective clinical trials. Similar studies on AAA smaller than 55 mm in diameter, even difficult to organize, would be of even greater clinical value.

KEYWORDS

AAA, volume, risk prediction, ILT, RRED, PWS

Introduction

Natural history of abdominal aortic aneurysms (AAAs) is progressive dilation until eventual rupture. The asymptomatic and insidious nature of this disease frequently prevents timely diagnosis, which is nowadays accomplished through national screening programs organized in certain countries. Open or endovascular repair of AAA has been substantially improved, providing low-risk preventive procedures to patients. However, early mortality of up to 2% for endovascular repair, 5% after open repair, and 20% rate of late reintervention after endovascular repair are precluding liberal use of AAA repair, and the threshold for repair is based on maximal aneurysm diameter (MAD) (1, 2). To optimize the risk–benefit ratio, it is useful to assess the risk of rupture. There are concerns about the validity of measuring the sensitivity to reveal disease progression by only MAD assessment (3). Aneurysm volume and thrombus thickness are associated with aneurysm growth or rupture; however, contrary to MAD, they are not widely accepted as parameters for clinical decision-making (4–6).

Finite-element analysis (FEA) may be used to more accurately estimate forces, like peak wall stress (PWS), acting on the aneurysm wall (7–10). Rupture risk equivalent diameter (RRED) may be used to compare biomechanical estimates among the patient groups (10). This parameter reflects the average aneurysm size that experiences the same estimates as the individual case. Subtracting the MAD from RRED can be used to compare among patient groups independently of the actual diameter (size). Such a biomechanical test is still not accepted in clinical practice even though PWS, as calculated with FEA, was significantly higher in ruptured AAAs than in intact AAAs across multiple studies and in one meta-analysis (11). Another systematic review concluded that although FEA is frequently applied in research, the methodology has not been standardized for AAA, and its technical limitations have only marginally improved. In addition, for using such a method, at least basic education of physicians in biomechanics and FEA is necessary (11, 12).

The aim of this study was to assess rupture risk prediction of comorbid conditions, patients' demographics, maximal aneurysm diameters, and other morphological characteristics and to compare them with biomechanical imaging markers (PWS, RRED).

Methods

The study was designed and presented in this paper according to Strobe's recommendations (13). It was performed at the university clinic from January 01, 2015, to January 01, 2016, and it was approved by the local ethical committee.

The observed outcome was the rupture of AAA. The rupture was defined if multidetector computed tomography (MDCT) examination showed AAA with visible loss of wall integrity and/or surrounding hematoma.

Two hundred and eighty-eight consecutive patients with AAA greater than 40 mm in diameter, both asymptomatic and ruptured, were included in the observational cross-sectional study. These patients underwent MDCT (slice thickness 0.625 mm). In our institution, MDCT is indicated in patients with more complex aneurysms (short neck, peripheral occlusive disease) or in those that are candidates for endovascular repair due to advanced age, comorbid conditions, or hostile abdomen. Operative treatment was indicated according to contemporary clinical practice guidelines, and treatment results were not part of this study.

Patients were excluded from the study in case of an inflammatory aneurysm (thickening of the aortic wall with a well-defined halo and an irregular external margin between the aneurysm and surrounding tissue) or low-quality images due to the low contrast volume in aortic lumen precluding biomechanical or morphological analysis. Also, patients operated on only according to ultrasonography examination were excluded. Two hundred and eighty-eight consecutive patients with AAAs of maximum diameters ≥40 mm were admitted to our institution during the study period. Out of them, 180 patients were excluded from the study due to the following reasons: lack of MDCT examination (133), presented with symptoms and no sign of rupture on MDCT (35), presented with inflammatory aneurysms (3), and low-quality images because of low contrast volume in the aortic lumen (9) that were difficult or impossible to analyze. Out of 288 patients considered for the study, 98 (34.02%) patients fulfilled the inclusion criteria and were included in the study.

Included patients were divided into two groups: patients with asymptomatic AAA (aAAA) and patients with ruptured AAA (rAAA).

Diagnostic criteria are as follows: AAA was considered asymptomatic if diagnosed in an elective setting, with no sudden and severe pain, and if ultrasound and MDCT did not show any irregularities in the aneurysm wall morphology. Ruptured AAA was considered any aneurysm revealed in an emergency setting, with sudden abdominal or back pain with MDCT signs of retroperitoneal hematoma. As explained above, patients with symptoms and no signs of rupture were excluded since they did not belong to any of the two groups.

Data regarding patients' comorbidities and demographics were collected prospectively by a previously determined questionnaire.

Images of MDCT delivered in a DICOM (Digital Imaging and Communication in Medicine) file were analyzed by a single operator using available software—3Surgery (Trimensio) for morphological analysis and A4clinics (VASCOPS GmbH, Graz, Austria) for the morphological and biomechanical assessment.

Morphological data obtained by standard center lumen line analysis in the 3Surgery working station (Trimensio, Unites States) were MAD, neck diameter and length, aneurysm and iliac length, aneurysm diameter, and angulations. Angulations were calculated through angle measurements and by using the shape index—the ratio between the two different diameter measurements (shortest and longest ones) on the axial cross section (14). These measurements were made by common techniques also used in seizing and planning for endovascular procedures. *Morphological data* derived from the analysis in A4Clinics software were total AAA volume (TAV in cm^3), ILT volume (in cm^3), and maximal ILT thickness (in mm). These parameters were automatically calculated by the software. Since

the ILT volume could depend on the total aneurysm volume, the relative intraluminal thrombus (rILT) volume was calculated, expressing the ILT volume in percentages: ILT volume × 100/ total aneurysm volume. *Biomechanical data* obtained from A4Clinics were PWS (in kPa) and RRED (in mm).

RRED was introduced by Gasser et al. to translate biomechanical rupture risk values into equivalent diameters of the average aneurysm patient with the same risk of rupture (based on epidemiologic and biomechanical data) (9, 10). Both parameters, PWS and RRED, are automatically calculated by A4Clinics software. To exclude the influence of pressure on RRED, values of boundary condition were the same for all patients. The FEA model was pressurized by the mean arterial pressure (MAP; 1/3 systolic pressure 2/3 diastolic pressure), which predicted the mechanical stress (force per area) in the wall of the aneurysm. This pressure was predefined as 120/80 (mean 92.3 mmHg).

As previously published, apart from geometry and arterial pressure, an FEA model requires constitutive descriptions of the wall and the ILT (10, 15). A constitutive description is a mathematical model of biomechanical properties, which relates stress and strain (deformation) and/or describes the strength of the tissue. The FEA models used in the present analysis considered isotropic constitutive descriptions for the ILT and the aneurysm wall. An isotropic constitutive model is a common approximation for aneurysm tissue and assumes that the tissue's mechanical properties do not depend on the orientation; i.e., the stress–strain responses of circumferential and longitudinal strips of tissue are identical.

To reduce selection bias, all subsequent AAAs were included in the analysis. However, a substantial number of AAA patients did not undergo an MDCT examination, which was the reason for their exclusion. The decision to perform or not MDCT was exclusively clinically driven, and the authors of this study had no influence on it.

Statistical analysis

Data were entered into a customized database and analyzed using IBM SPSS Statistics, Version 20.0 (IBM Corp. 2011). We considered P values <0.05 as statistically significant.

Differences in continuous variables between the groups were analyzed by Student's t-test for normally distributed variables and by the Mann–Whitney U test for variables with the non-Gaussian distribution. Group differences for categorical variables were examined by the chi-square test, and univariate associations were evaluated by Spearman's correlation analysis.

Odds ratios (ORs) were calculated using binary logistic regression analysis to determine whether anatomical, morphological, and biomechanical parameters had any potential for predicting aneurysm rupture. Independent association of examined parameters (with high practical importance and availability) with aneurysm rupture was tested using multiple logistic regression analysis. Adjustments were made to correct the influence of confounder variables (gender and age). Age was entered as continuous and gender as a categorical (1, female; 0, male) variable.

The accuracy of the examined parameters was assessed using receiving operative characteristic (ROC) curve analysis. Statistically significant parameters were combined based on their practical importance and availability, the curve for this model was plotted, and the area under the ROC curve (AUC) was presented as C statistics from the analysis. By using the Hosmer and Lemeshow rule for logistic models, the discriminative abilities of the model were classified according to their AUC values as poor ($0.5 \leq AUC < 0.7$), acceptable ($0.7 \leq AUC < 0.8$), excellent ($0.8 \leq AUC < 0.9$), or outstanding ($AUC \geq 0.9$) (16).The optimal cut-off (cut-off with the highest Youden index – sensitivity + specificity) and correct patient classifications were calculated for examined parameters.

Data are shown as mean ± SD for normally distributed continuous variables, as median and quartile values for non-normally distributed variables, and as absolute and relative frequencies for categorical variables.

Results

There were 75 (76.53%) asymptomatic (Group aAAA) and 23 (23.46%) ruptured AAAs (Group rAAA) with an average age of 70.6 ± 8.22 years. Comorbid conditions and demographic characteristics of patients in both groups are compared and presented in Table 1.

The differences in anatomical, morphological, and biomechanical parameters between the two groups are presented in Table 2 (only statistically significant parameters are presented).

Regression analysis was performed to explore the association between rILT volume with other examined parameters. Values of rILT correlated with MAD in both groups, slightly higher in the rAAA group ($\rho = 0.462$; $p = \mathbf{0.035}$) compared to the aAAA group ($\rho = 0.245$; $p = \mathbf{0.041}$) (Bold significance are $p < 0.05$). On the other side, rILT correlated with total aneurysm volume ($\rho = 0.296$; $p = \mathbf{0.011}$), neck diameter ($\rho = 0.309$; $p = \mathbf{0.009}$), and neck length ($\rho = 0.294$; $p = \mathbf{0.012}$) in the aAAA group but not in the rAAA group for TAV ($\rho = 0.390$; $p = 0.081$), aneurysm neck diameter ($\rho = -0.168$; $p = 0.493$), and aneurysm neck length ($\rho = -0.071$; $p = 0.771$) (Bold significance are $p < 0.05$).

We used binary logistic regression to determine whether anatomical, morphological, and biomechanical parameters had any potential for the prediction of AAA rupture. Unadjusted analysis showed that low values of the shape index in the neck zone (OR = 0.560, $p = 0.046$) were associated with AAA rupture. In contrast, high values of RRED, MAD, PWS, mean wall stress, TAV, ILT volume, rILT volume, lowest renal to aortic bifurcation distance, and maximal ILT thickness increased AAA rupture probability. Data are presented in Table 3.

Adjusted logistic regression analysis was performed to explore rILT volume, TAV, and MAD predictive abilities for AAA rupture. In a multivariable model, including gender and age as confounder variables, all previously mentioned parameters continued to be significant predictors of AAA rupture (MAD: OR = 1.063; TAV: OR = 1.006; rILT: OR = 1.039; PWS: OR = 1.010; and RRED: OR = 1.031). Data are presented in Table 4.

TABLE 1 Cardiovascular risk factors in asymptomatic and ruptured AAAs.

Comorbid condition	aAAA group, *N*=75 (%)	rAAA group, *N*=23 (%)	*p*
Mean age (years)	70 ± 7.9	71.4 ± 8.74	0.20
Male/female	63/12 (84/16)	18/5 (78.37/21.73)	0.524
Hypertension	60 (80)	15 (65.2)	0.564
Hyperlipoproteinemia	15 (20)	3 (13.04)	0.424
Statin therapy	9 (12)	2 (8.69)	0.217
Diabetes	6 (8)	2 (8.69)	0.230
Coronary artery disease	37 (49.33)	8 (18.4)	0.053
Previous PCI or CABG	21 (28)	16 (15.53)	0.111
Atrial fibrillation	9 (12)	7 (6.79)	0.176
COPD	15 (20)	5 (20.73)	0.229
Renal insufficiency	9 (12)	8 (7.76)	0.775
PAOD	8 (10.66)	7 (6.79)	0.855
Previous vascular operation	3 (4)	2 (1.94)	0.472
Carotid disease	15 (20)	6 (5.82)	0.153
Aneurysm in other arterial segments	3 (4)	1 (0.97)	0.198

Comorbid condition	Study group, *N*=98 (%)	Non-study group, *N*=241 (%)	*p*
Mean age (years)	70.6 ± 8.2	71.4 ± 8.74	0.433
Male/female	81/17 (84/16)	214/27 (88.8/11.2)	0.048
Hypertension	75 (76.5)	206 (85.5)	0.498
Diabetes	8 (8.16)	25 (10.4)	0.300
Coronary artery disease	45 (45.91)	57 (23.7)	0.000
Atrial fibrillation	9 (12)	7 (6.79)	0.176
COPD	20 (20.4)	36 (14.9)	0.014
Renal insufficiency	9 (12)	8 (7.76)	0.775
PAOD	8 (10.66)	7 (6.79)	0.855
Previous vascular operation	3 (4)	2 (1.94)	0.472
Carotid disease	15 (20)	6 (5.82)	0.153
Aneurysm in other arterial segments	3 (4)	1 (0.97)	0.198

AAAs, abdominal aortic aneurysms; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; PAOD, peripheral arterial occlusive disease.
Variables were compared by the chi-square test.

TABLE 3 Logistic univariate regression analysis for anatomical, morphological, and biomechanical predictors of AAA rupture.

Parameters	OR (95% CI)	*p*
RRED	1,031 (1,009–1,054)	0.007
MAD	1.062 (1.041–1.082)	<0.001
PWS	1.011 (1.004–1.018)	0.003
Mean wall stress	1.027 (1.003–1.051)	0.028
Total aneurysm volume	1.006 (1.003–1.010)	<0.001
Lumen volume	1.010 (1.003–1.016)	0.004
ILT volume	1.011 (1.005–1.018)	<0.001
rILT volume	1.041 (1.003–1.079)	0.032
Neck length	0.976 (0.932–1.021)	0.293
Neck diameter	1.020 (0.944–1.102)	0.620
Shape index in the neck zone	0.56 (0.003–0.950)	0.046
Shape index in the aneurysm zone	0.031 (0.01–4.416)	0.170
Shape index in the iliac zone	0.380 (0.041–3.552)	0.396
Lowest renal to aortic bifurcation distance	1.030 (1.003–1.059)	0.032
Maximal ILT thickness	1.084 (1.029–1.141)	0.002

AAAs, abdominal aortic aneurysms; rAAA, ruptured abdominal aortic aneurysms; OR, odds ratio; CI, confidence interval; MAD, maximal aneurysm diameter; PWS, peak wall stress; RRED, rupture risk equivalent diameter; TAV, total aneurysm volume; rILT, relative intraluminal thrombus volume.
All variables are continuous.

Finally, we explored the diagnostic abilities of RRED, MAD, PWS, rILT volume, and TAV for AAA rupture (Table 5). Although the AUC corresponding to MAD (AUC = 0.790) was the highest among the obtained AUC values, the correct classification at the optimal cut-off value of 68 mm was 75%. TAV showed acceptable diagnostic accuracy with 79% correct classification, but the accuracy for rILT was poor. At the optimal cut-off value of 41.3 derived from the curve, only 60% of subjects were correctly classified based on rILT. Correct classification by PWS and RRED was 73% and 55%, respectively, at optimal cut-off values of 249.8 kPa for PWS and 46 mm for RRED. Furthermore, we explored whether the combination of MAD, TAV, and rILT improves the prediction of AAA rupture

TABLE 2 Significantly different anatomical, morphological, and biomechanical parameters between asymptomatic and ruptured AAAs.

Parameter	Total	aAAA	rAAA	*p*
MAD (mm)	66.59 ± 18.76	60.82 ± 15.49	79.30 ± 19.3	<0.001[a]
Total aneurysm volume (cm^3)	201.0 (146.9–201.0)	187.4 (134.7–238.7)	337.4 (203.8–482.1)	<0.001[b]
Lumen volume (cm^3)	91.8 (66.7–128.0)	87.4 (61.3–117.4)	130.7 (87.5–211.0)	<0.001[b]
ILT volume (cm^3)	77.0 (39.7–138.3)	67.4 (36.8–111.0)	149.2 (84.4–297.0)	<0.001[b]
rILT volume (%)	39.68 (29.38–50.37)	37.12 (28.00–45.40)	45.31 (37.70–54.40)	0.027[b]
PWS (kPa)	224.1 ± 69.6	212.9 ± 64.5	269.7 ± 72.27	0.001[b]
RRED (mm)	56.99 ± 22.23	53.52 ± 18.90	71.41 ± 29.60	0.002[a]
Mean wall stress (kPa)	110.90 ± 24.06	108.44 ± 22.34	124.78 ± 29.18	0.020[a]
Mean stress in ILT (kPa)	7.15 ± 1.25	7.00 ± 1.28	7.86 ± 0.96	0.016[a]
Shape index in the neck zone[c]	0.75 ± 0.17	0.77 ± 0.16	0.68 ± 0.21	0.040[a]
Distance from lower renal to aortic bifurcation (mm)	116.38 ± 21.65	113.62 ± 19.19	126.20 ± 27.18	0.022[a]
Maximal ILT thickness (mm)	20.58 ± 11.04	18.61 ± 9.69	28.10 ± 13.07	<0.001[a]

AAAs, abdominal aortic aneurysms; rAAA, ruptured abdominal aortic aneurysms; ILT, intraluminal thrombus; MAD, maximal aneurysm diameter; PWS, peak wall stress; RRED, rupture risk equivalent diameter; rILT, relative intraluminal thrombus volume: ILT volume × 100/total aneurysm volume.
[a]Data are expressed as mean ± SD and compared by Student's *t*-test.
[b]Values are expressed as medians and quartile values and compared by the Mann–Whitney *U* test.
[c]Shape index demonstrates the level of angulation.

TABLE 4 Multivariable logistic regression analysis for anatomical, morphological, and biomechanical predictors of AAA rupture.

	OR (95% CI)	*p*
Adjusted for gender and age		
MAD	1.063 (1.042–1.085)	<0.001
TAV	1.006 (1.003–1.010)	0.001
rILT volume	1.039 (1.002–1.078)	0.038
PWS	1.010 (1.003–1.018)	0.009
RRED	1.031 (1.008–1.054)	0.006

AAAs, abdominal aortic aneurysms; OR, odds ratio; CI, confidence interval; MAD, maximal aneurysm diameter; PWS, peak wall stress; RRED, rupture risk equivalent diameter; TAV, total aneurysm volume; rILT, relative intraluminal thrombus volume.
Gender is a categorical variable. All variables are continuous.

TABLE 5 Results of ROC and C analyses for discriminating asymptomatic from ruptured AAAs.

	AUC 95% CI	Cut-off values	Correct classification, %
MAD, mm	0.790 (0.726–0.854)	68	75
PWS, kPa	0.713 (0.593–0.832)	249.8	73
RRED, mm	0.717 (0.590–0.844)	0.46	55
TAV, cm^3	0.756 (0.626–0.886)	310.4	79
rILT volume %	0.656 (0.529–0.783)	41.3	60
MAD + TAV + rILT	0.797 (0.687–0.908)	0.05[a]	82

[a]Probability cut-off for AAA rupture.
AAAs, abdominal aortic aneurysms; ROC, receiving operative characteristic; AUC, area under the ROC curve; CI, confidence interval; MAD, maximal aneurysm diameter; PWS, peak wall stress; RRED, rupture risk equivalent diameter; TAV, total aneurysm volume; rILT, relative intraluminal thrombus volume.

on existing parameters. The AUC for the model with combined parameters indicated an acceptable ability for AAA rupture prediction (Table 4). The combination of three parameters increased the correct patient classification to 82%. The results of ROC and C analyses for discriminating asymptomatic from ruptured AAA are presented in Table 5.

Discussion

Our study has shown that biomechanical parameters (PWS and RRED) are greater in rAAA and some morphological aneurysm features like TAV, rILT, and MAD. Combined into logistic models, MAD, rILT, and TAV might have good rupture risk prediction values, better than MAD, PWS, or RRED alone.

The rationale for AAA repair is based on the ratio between the procedure and rupture risk. Contrary to procedure risk, rupture risk is difficult to assess accurately. MAD as a common criterion has been challenged in the last two decades. Important progress was made using FEA with PWS as the main outcome variable (8). Further improvement potentiated analysis of aortic tissue strength and its computed estimation that enabled calculating the ratio between the wall stress and wall strength expressed through the potential rupture index (17). Gasser et al. went even further with their RRED and translated biomechanical information into our surgical language of maximal diameter (9).

A recent systematic review identified 1,503 potentially relevant articles that assessed biomechanical imaging markers and their potential association with AAA growth or rupture (12). The authors concluded that published studies had confounding bias between groups due to baseline differences in aneurysm diameter, did not report basic characteristics (demographics, comorbidity) of the included patients, and FEA methodology has not been standardized (12). PWS was significantly higher in ruptured than in intact AAAs across multiple studies, as shown in the previous meta-analysis.

In addition, nowadays, it is still difficult to include biomechanical analysis of AAA rupture risk in common clinical practice. It requires not only dedicated software but also educated personnel capable of performing and translating information into clinical practice, standardized research studies to determine thresholds for intervention, education of vascular surgeons in FEA and biomechanics, the inclusion of bioengineers as a part of the multidisciplinary aortic team, etc.

Previous studies rarely described the demographics of included patients (12). None of the comorbid conditions in our study could be used for the rupture prediction model since there were no differences in this regard between the groups. Smoking habit is still very present in Serbia, so both groups had a very high rate of smokers. MAD, PWS, and RRED as predictors of rupture were adjusted for gender and age.

MAD is used in our clinical practice to present aneurysm size and consequently rupture risk. Basically, if centerline analysis is used, such a measure is gained from one cross section of the aneurysm sac with improved accuracy. However, such a measure does not provide sufficient information about the aneurysm magnitude. For these purposes, aneurysm volume might better represent its real magnitude and consequently its growth. In our study, TAV was a predictor of aneurysm rupture independent of aneurysm diameter. Previous papers showed that an aneurysm is not always growing at the level of the longest diameter (4, 5).

ILT has its role in aneurysm evolution and rupture development. It was shown that ILT influences the histology of the aneurysm wall and promotes rupture by inducing hypoxia or weakening the aneurysm wall (6, 18). Since ILT volume might depend on aneurysm size, we expressed the volume of ILT as a percentage of total aneurysm volume through rILT volume. In this manner, we avoided the influence of MAD on ILT volume, and rILT volume was an independent predictor of aneurysm rupture.

Finally, we combined MAD as the main parameter (as we are used to it), TAV (as a better measure of aneurysm magnitude), and rILT (as a better expression of ILT extent) in the logistic model that showed its predictive value of AAA rupture under the ROC curve, which is comparable to parameters gained from biomechanical analysis. RRED has an advantage since it calculates wall stress and tissue properties, while the three parameters included in the model only represent anatomy and morphology. On the other side, MAD, TAV, and rILT volume can be measured easily in everyday practice and could also be used in the follow-up. Further analysis, publication, and education of surgeons should be organized to make biomechanical testing available in everyday practice.

The concept of biomechanical rupture risk assessment was proposed more than 20 years ago and is still under investigation. It was not accepted in common clinical practice due to probably different reasons. Measuring the MAD is very simple and familiar to all vascular physicians. No matter that such a measurement is also not standardized and very simplified, underestimating the complexity of the pathology of the aneurysm may lead to AAA growth and rupture. Measuring biomechanical features of a particular aneurysm is neither complicated nor time-consuming (it takes less than 30 min); however, it requires dedicated software and an understanding of the concept that rupture occurs when biomechanical forces overcome wall strength. Finally, we need more convincing data that this concept works. In the recent systematic review, only 300 patients were included in seven comparative studies with moderate to high risk of bias (21). The present study might support clinicians to measure aneurysm volume and even rILT volume during follow-up of small aneurysms or those of longer diameters unsuitable for treatment and use it in decision-making together with MAD as additional information.

Limitations

Even though data were collected prospectively, this is a cross-sectional study. Also, a significant number of patients were excluded from the study due to the lack of MDCT images or their inadequate quality. The majority of excluded patients were from the 4A group, and no differences in demographic and comorbid parameters were noticed between the excluded and included patients (this analysis was not included in the Results section due to limited space). There were significantly fewer patients with rAAA in this study. The reasons are multiple. rAAA is a rare condition, patients with rAAA are not always undergoing MDCT, or the examination has been done in another institution and patients were sent without the electronic version of the examination. Contrast timing is not perfect in unstable or bleeding patients with low image quality and potential to perform analysis. Patients with ruptured AAA had greater values of MAD; however, this was included in multivariate analysis. No sensitivity analysis has been performed in our study. All measurements in the study were made by one, although a very experienced, person. For the measurement of anatomical and morphological parameters, the author has more than 1,000 planned endovascular aneurysm repair (EVAR) cases, while for performing measurements of biomechanical variables, a dedicated understanding and validation were performed with authors of A4Clinic software. Previous papers showed good inter- and intraobserver variability (22) when using A4Clinics software. FEA models introduce numerous modeling assumptions and cannot completely reflect the biomechanics of the real aneurysm in a particular patient, considering calcifications or other morphological irregularities of the aneurysm wall (19). Likewise, 10 patients with ruptured aneurysms were excluded from the study since it was not possible to differentiate the aortic wall from the surrounding hematoma. Also, the presented biomechanical data in this study must always be seen in relation to the specific modeling assumptions. In our study, we focused on boundary conditions of arterial pressure of 120/80 mm Hg; however, exposing aneurysm morphology and geometry to different boundary conditions might show different results. This assumption should be included in future studies (20). Finally, there were few patients with aneurysms smaller than 55 mm in diameter. Future studies should focus more on these patients since these aneurysms are also prone to rupture, and identification of those at higher risk would support clinical decision-making and prevent eventual unexpected rupture.

Conclusion

Based on our results, in addition to maximal aneurysm diameter, other important predictors of rupture are total aneurysm volume and relative volume of intraluminal thrombus, which might be used during aneurysm surveillance. Biomechanical parameters (PWS, RRED) as valuable predictors should be used in clinical practice for patients included in clinical trials where their estimation will be standardized. Future studies on small aneurysms are needed to improve clinical decision-making and prevent unexpected rupture.

What this paper adds

This paper shows that when assessing the risk of abdominal aortic aneurysm (AAA) rupture, in addition to diameter, the magnitude of the aneurysm should be presented with the total aneurysm volume. In addition, the volume of intraluminal thrombus expressed relatively to the total aneurysm volume should be considered. These aneurysm characteristics are possible to measure routinely nowadays and could be used during surveillance, especially in patients at risk of intervention. On the other side, biomechanical parameters are important and should be systematically incorporated into clinical studies and common practice in the future. The results of this study could apply to aneurysms with diameters longer than 55 mm since there were a low number of aneurysms with shorter diameters.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the University Clinical Center of Serbia. Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements.

Author contributions

IK designed the study, analyzed the data, and drafted the manuscript. ND, ZM, and NF performed the measurements. NB-S performed the statistical analysis. NI, MD, and MM revised the article. MS and IK were involved in data acquisition. AV helped in drafting the manuscript. LD supervised the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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In-vivo evaluation of silk fibroin small-diameter vascular grafts: state of art of preclinical studies and animal models

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Autologous vein and artery remains the first choice for vascular grafting procedures in small-diameter vessels such as coronary and lower limb districts. Unfortunately, these vessels are often found to be unsuitable in atherosclerotic patients due to the presence of calcifications or to insufficient size. Synthetic grafts composed of materials such as expanded polytetrafluoroethylene (ePTFE) are frequently employed as second choice, because of their widespread availability and success in the reconstruction of larger arteries. However, ePTFE grafts with small diameter are plagued by poor patency rates due to surface thrombogenicity and intimal hyperplasia, caused by the bioinertness of the synthetic material and aggravated by low flow conditions. Several bioresorbable and biodegradable polymers have been developed and tested to exploit such issues for their potential stimulation to endothelialization and cell infiltration. Among these, silk fibroin (SF) has shown promising pre-clinical results as material for small-diameter vascular grafts (SDVGs) because of its favorable mechanical and biological properties. A putative advantage in graft infection in comparison with synthetic materials is plausible, although it remains to be demonstrated. Our literature review will focus on the performance of SF-SDVGs *in vivo*, as evaluated by studies performing vascular anastomosis and interposition procedures, within small and large animal models and different arterial districts. Efficiency under conditions that more accurately mime the human body will provide encouraging evidence towards future clinical applications.

KEYWORDS
silk fibroin, vascular graft, animal models, biological graft, preclinical *in vivo* studies

1. Introduction

Bioengineering is becoming a crucial aid to cardiovascular surgery, especially with the introduction of endovascular means. Therefore, knowledge of the behavior of surgical or endovascular grafts and their long-term impacts onto large and small vessels is vital to the cardiovascular specialist.

This scientific approach improved the management of vascular pathologies through different techniques and materials. A constant dialogue between clinicians and bioengineers is essential for the development new effective graft materials, with desirable characteristics over the aforementioned issues.

Cardiovascular diseases are projected to grow in the following years to an estimated overall mortality of 23.4 million in 2030 (1). Moreover, the age of patients who require treatment has been increasing. Vascular and cardiac surgery are the eminent fields for surgical or endovascular treatment of both large and small vessels. Most cardiovascular diseases are caused by the occlusion or narrowing of arteries of medium or small diameters and in this scenario, autologous grafts are currently the gold standard for the revascularization of coronary and lower limb arteries (2).

However, the use of these conduits is often limited because atherosclerosis is a systemic disease that can involve all arterial districts, including arterial conduits most harvested for revascularization. Another issue arises in patients who underwent a prior harvesting of an arterial or venous conduit, limiting the availability of a possible graft for further interventions.

Synthetic grafts provide a viable solution for large vascular replacement, but their performance with low flow conditions in smaller vessels is disappointing. For this reason, vascular tissue engineering aims to find a solution to have a functional and infection-resistant graft to replace the diseased artery. We consider the need for endovascular but also open revascularization and look for available and safe alternative materials applicable to all the small vessels requiring intervention.

Indeed, the most critical problem is to obtain suitable materials for small grafts assuring a long-term patency and infection resistance.

About the first aspect, vascular and cardiac surgeons are skilled in the harvest of autologous vessels, proven to maintain patency with low thrombogenicity. The most employed vessels for open surgical revascularization include mammary or radial arteries, or different veins of the superficial system of the upper and lower limbs, (cephalic, basilic, great and small saphenous veins). In surgery of peripheral arterial disease, revascularization by means of in-situ venous conduits is also used to bypass occlusions of the distal arteries of the limbs.

Secondly, to prevent infection, autologous grafts should be preferred over synthetic ones, particularly in case of revascularization of wet gangrene of the lower limbs.

Different authors are reporting experiences of using silk fibroin (SF) *in vivo* in anima (for the most small) models in a preclinical phase as an arterial substitute and its further development, in terms of patency, endotelialization, low restenosis, surrounding tissues involvement, and resistance to infections.

Silk is a natural, versatile protein biopolymer which is produced by various insects (silkworms, spiders, scorpions, mites, and flies). This ancient textile material has long been used to prepare sutures in surgery thanks to its biocompatibility and remarkable tensile strength (3). Among the variants, a regenerated silk fibroin obtained from Bombyx mori silkworm cocoons is widely explored for regenerative medicine.

Silk fibroin shows suitable properties allowing its use for vascular applications: biocompatibility, tunable biodegradation, low immunogenicity, ability to adapt to different geometries and preparations (4, 5), mechanical strength, easy accessibility, cost-effectiveness, and easy green processing (6). As a biodegradable the starting material can be easily purified and processed in different 2D/3D shapes. It is not immunogenic in humans and favors angiogenesis, an essential feature for tissue repair and regeneration (7, 8).

These results are possible because electrospinning has the ability to mimic the nanoscale properties of fibrous components (collagen and elastin fibrils) of the extracellular matrix and to realize a range of biochemical, topographical, and mechanical properties conducive to improved cell interactions (9) (**Figures 1**, **2**).

Our review aims to provide a comprehensive overview of the principal fields of preclinical use of silk fibroin as a vascular substitute in different animal models evaluating silk fibroin (SF)

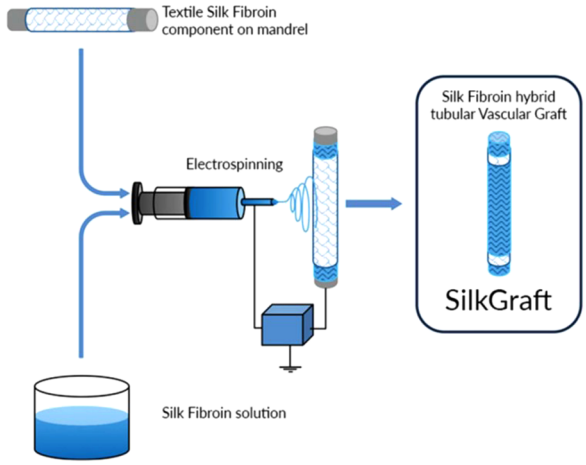

FIGURE 1
Description of creation process of silk fibroing vascular graft through hybrid-textile electrospun architecture.

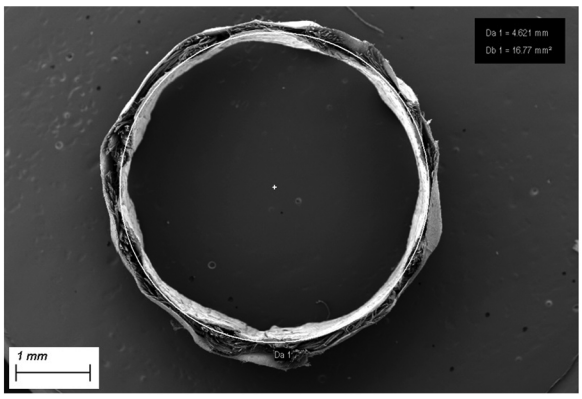

FIGURE 2
Cross section of SF-SDVG showing the tri-layered wall with the two electrospun layers encasing the intermediate textile layer.

behaviour in term of endothelialization, biocompatibility and short and long term patency.

2. Aim, search protocol and selected studies

Although other reviews on tissue-engineered vascular grafts have been previously published (10), including regarding specific applications of silk biomaterials (11), the aim of the present research is to collect and report the studies in which SF-based small-diameter vascular grafts were evaluated *in vivo* by performing vascular anastomosis and interposition procedures within small and large animal models and different arterial districts.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement was used to obtain a strict paper selection (12).The PubMed, Scopus and Embase databases were questioned to identify studies, without specifying an interval of publication years. All types of articles were initially included, whereas review articles were then manually discarded following the selection algorithm.

To perform the initial review process, based on paper and abstract title search, the combination of keywords used, connecting Boolean operators, was:

> ((silk fibroin) AND (vascular)) AND (*in vivo*)

The Rayyan QCRI [Qatar Computing Research, Doha, Qatar (available at https://rayyan.qcri.org/)] was chosen to manage and screen selected papers. After the collection of all search results, duplicates were automatically excluded before the screening process.

A series of exclusion criteria were considered to select the articles that best applied to our objectives. Articles and abstracts not containing the selected keywords in their title were excluded. Subsequently, the remaining articles were screened for relevance of topics according to the aims of our review, as well as pertinence of the experimental model in which SF was evaluated. Indeed, studies exclusively including *in vitro* analysis of the biological response to silk-based biomaterials were not applicable to our review process. Furthermore, out of the studies where SF was applied *in vivo*, those where the grafting biomaterial was not inserted by vascular anastomosis (e.g., in case of subcutaneous implantation) were also excluded. Finally, remaining articles utilizing vascular grafts developed from materials not including SF were discarded.

As a result of this selection process, a total of 31 articles concerning *in vivo* assessment of SF-based vascular grafts were reviewed, with experimental models ranging from small to large animals: murine, leporine, canine, porcine and ovine. Henceforth, the included studies are presented according to the respective animal model. Because the results were not fit for a meta-analytic investigation due to the heterogeneity of the *in vivo* animal models and graft materials, they were discussed in a narrative way.

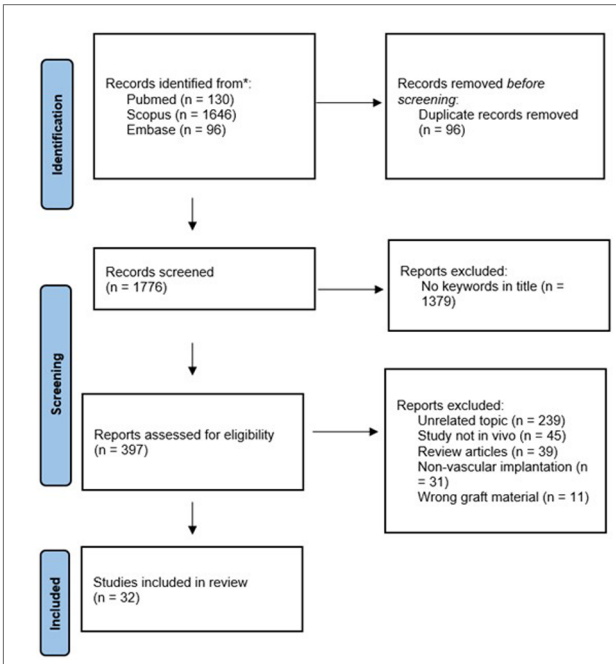

FIGURE 3
The flow chart for the identification and selection of studies for the review via databases and registers.

The flow chart for the selection of studies is shown Figure 3.

3. SF in small animal models

Compared to larger animals, small animals are easier to handle and less expensive. However, the technical difficulty of their size makes the surgical insertion of vascular conduits difficult. Rats and rabbits are the most employed, and both can often receive conduits with very small (2 to 5 mm) and small (2 mm) diameters (13). Accordingly, most of the published experimentation of SF grafts *in vivo* was performed on murine and leporine models.

3.1. SF in murine models

Some authors discourage the use of murine models to test the patency of short graft portions, especially in the absence of a clinically relevant control (13). Although size-mismatched grafts up to 4 mm in diameter have been employed, the small size of murine arterial conduits often restricts their utility for the assessment of grafts to the aortic (1 to 2 mm diameter) or femoral (1 mm diameter) sites. The main issue with using rats to simulate human biocompatibility to very small conduits is that these animals typically have high patency rates for ePTFE grafts, unreflective of the clinical outcomes of such material.

Some authors report that the surgical interposition of completely silk-based vascular grafts in mice is often coupled with *in vitro* demonstration of rapid endothelial cell attachment

and excellent resistance to blood clot and fibrin network formation suggesting that silk fibroin might be a promising material to develop vascular prostheses for smaller arteries (14). Electrospun silk conduits have been shown to enhance biocompatibility (15). *In vitro*, they enhanced endothelial cell proliferation 5-fold, from day 1 to 6, significantly greater than ePTFE controls. Moreover, they demonstrated comparable elasticity to rat aorta and were significantly more elastic than ePTFE. When implanted into the abdominal aorta of rats, silk conduits were well tolerated up to 24 weeks, showing only low levels of inflammatory cells and neointimal hyperplasia, and demonstrated complete patency at all time points when compared to control animals implanted with commercial ePTFE of similar diameter (15). Overall survival over 24 weeks was 95% for the silk grafts, while ePTFE failure occurred at 27%, with graft failures relating to deaths occurring post-operatively or, alternatively, due to complete occlusion. These results demonstrate a high degree of variability in ePTFE survival, which is consistent in observations in humans, and were related to rapid coverage of endothelial cells upon the electrospun silk graft lumen, contrary to ePTFE, which remained largely uncovered, even at 24 weeks (15).

Other studies produced small caliber fibroin matrices with electrospinning techniques with the aim to replace small arterial segments. A study evaluating electrospun fibroin scaffolds implanted into the rat abdominal aorta concluded that formation of vascular tissue containing elastin occur already at 7 days after implantation on fibroin scaffold without prior *in vitro* cellularization (16). Indeed, fibroin matrices not only allowed host cell infiltration and extracellular matrix remodeling, but also the formation of vasa-vasorum in the outer layer of the fibroin material.

A different study evaluated the impact of porosity of gel-spun silk tubes upon their biological features *in vivo*, including degradation of the biomaterial, cellularity, and host integration over time (13). Tubes with higher porosities showed early improvements in cell colonization that progressively increased over time. However, none of the highly porous tubes remained patent at 6 months, likely because the remodeling can induce bulk mechanical failure or a compromised blood-material interface (5).

The introduction of functional peptides is useful for improving the mechanical properties of SF. In the last decade, germ line transformation of silkworms was developed using transposons to obtain fusion of exogenous proteins with fibroin. Genes encoding the exogenous protein of interest may be injected into the eggs of silkworm so that the transgenic silk product will be produced in the worm's silk gland and expelled in the cocoon silk.

A study evaluated the performance of SDVGs obtained by four kinds of recombinant SFs derived from the fusion of peptide sequences from laminin B1 and fibronectin (17). Despite a slight decrease in tensile strength, compared with native SF, the adhesive activities of mouse endothelial and smooth muscle cells have been shown to increase significantly with recombinant SF films. When implanted into the rat abdominal aorta *in vivo*, grafts coated with recombinant SF allowed longer migration distance of the endothelial cells from the anastomotic margin. In view of these results, recombinant SF incorporating laminin peptide sequence can be potentially used as a vascular graft material.

In a different study, vascular endothelial growth factor (VEGF) introduced into the SF heavy chain to improve its properties showed greater enhancement of cellularization behavior compared to wild type (WT)-SF (18). VEGF-SF also showed lower platelet adhesion than the RGD SF and WT-SF. *In vivo*, early endothelialization was observed for VEGF transgenic SF, including the occurrence of native tissue organization at three months after implantation in rat abdominal aorta.

Moreover, VEGF-SF has been shown to support significantly higher and earlier endothelialization in the central part of aortic grafts in mice compared to WT-SF (19). However, complete endothelialization was not confirmed after 3 months of implantation in neither of the fibroin grafts.

In vivo substitution of arterial segments with SF grafts has also been attempted with carotid arteries in murine models. In one of such models, a small-sized graft of 0.9 mm inner diameter was braided from a SF thread and interposed to carotid arteries in mice using a cuff technique (20). Upon histological analysis after graft harvesting, endothelial cells had already started to proliferate at 2 weeks after implantation while, after 4 weeks, the luminal surface was found to be covered with a neointimal layer. Graft patency was confirmed at up to 6 months after implantation.

In a different model employing patches of SF with a gelatin hydrogel incorporating simvastatin micelles for sustained release of simvastatin was investigated for its promotional effects on endothelial progenitor cell mobilization from bone marrow and recruitment to sites of vascular injury, exhibiting acceleration of re-endothelialization (21). *In vivo* implantation of the patches incorporating simvastatin significantly increased the recruitment of circulating endothelial progenitor cells (EPCs) and allowed complete re-endothelialization on the SF patches at 2 weeks after implantation in rat carotid arteries.

A significant number of studies employing SF *in vivo* into small animal models do so by combining it with other synthetic graft materials to obtain different mechanical and physiological outcomes, especially by developing a SF coating of the inner lumen. Indeed, coating is an important factor to maintain the strength of the anastomotic region of vascular grafts, and to prevent the blood leak from the vascular grafts after implantation.

A study evaluating electrospun poly (L-lactic caprolactone) /SF small-diameter grafts, loaded with VEGF and heparin, found that such artificial blood vessels have good cytocompatibility and histocompatibility, but the patency and degradability need to be improved (22). Indeed, laser Doppler perfusion imaging showed that the blood flow velocity decreased at 1 day after implantation of the artificial blood vessel, and then gradually decreased, until the third week. Moreover, despite new angiogenesis and uniform endodermis were formed on the inner wall of the sample, scanning electron microscopy showed that the fibers were basically broken at the 6th week of implantation of the artificial blood vessel, and the fibers became thinner.

In an alternative combination, a tri-layered nano-fiber scaffold of SF and poly-caprolactone (PCL), fabricated using a sequential

electrospinning method and containing Spirulina extract in its inner SF layer, was implanted into rat carotid artery and evaluated for histological analysis after 3 weeks (23). Besides excellent mechanical properties *in vivo* (longitudinal and circumferential tensile strength, burst pressure strength, and suture retention strength), vessel patency was maintained, and the inner lumen of the scaffold showed regenerated endothelial cells. Platelet adhesion was supposedly countered by the presence of Spirulina extract in the inner SF layer.

A different research group developed a SF-coated poly(ethylene terephthalate) (PET) graft of diameter <6 mm. The tubular PET graft was produced through the double-raschel knitting technology and then coated with porous SF prepared using glycerin (Glyc) as porogen. *In vivo* outcomes of SF(Glyc)-PET graft were compared with a widely used commercial gelatin-coated PET graft (24). In implantation experiments in rats, the SF (Glyc)-coated PET graft was rapidly degraded *in vivo* and remodeling to self-tissues was promoted compared with the gelatin-coated PET graft. Importantly, unlike the gelatin-coated PET graft, side reactions such as thrombus formation and intimal hyperplasia were not observed in the SF(Glyc)-coated PET graft.

In a parallel study SF and PET tubular grafts of 1.5 mm diameter, produced with a double-raschel knitting machine, were coated with aqueous SF or gelatin (G) to make four types of vascular grafts (SF/SF, SF/G, PET/SF, and PET/G, shown as "base/coating material," respectively) (25). The four types of grafts were implanted into rat abdominal aortae ($n = 6$, respectively) and explanted 2 weeks or 3 months later. Two weeks after implantation, no significant differences were found among the kinds of grafts in biological reactions evaluated by histopathologic examination. However, a remarkable difference was observed after 3 months in terms of area of tissue infiltration into the graft wall, 2.5 times larger in SF/SF than that in PET/G. The endothelialization was achieved almost 100% in SF/SF, despite only 50% was achieved in PET/G. Therefore, SF delivered promising results both as base and as coating materials for small-diameter vascular prostheses.

Another study of the same group focused on the coating of 1.5 mm diameter SF grafts produced by double-raschel knitting with SF solutions at different concentrations (1%, 2.5%. 5%, and 7.5%) containing polyethylene glycol diglycidyl ether (PGDE) as cross-linker. The effect the different coatings on tissue infiltration and remodeling was investigated (26). The grafts were implanted in the rat abdominal aorta and removed after 3 weeks or 3 months. While SF concentration had no significant effects on the patency rate, 2.5% SF coating was found to be the most suitable concentration, based on the characteristics of less stenosis, early tissue infiltration, and less neointimal hyperplasia.

In the work reported in a distinct study, small-diameter vascular grafts 1.5 mm in diameter were prepared by coating a double-raschel knitted silk fiber graft with SF aqueous solution containing PGDE as a cross-linking agent (27). Eight weeks after implantation of the grafts in rat abdominal aorta, early formation of thrombosis was avoided possibly as an effect of the SF coating, providing also protection against leakage of blood from the graft, and elasticity to the graft.

As an alternative application, a blend of SF and thermoplastic polyurethane (PU, Pellethane®) was employed in order to produce by electrospinning a cardiovascular patch with appropriate elastomeric characteristics without sacrificing the excellent tissue affinity and biocompatibility of silk (28). Upon implantation into rat abdominal aorta, histological evaluation revealed that with increasing SF content the tensile strength and elasticity of the patch decreased, while tissue infiltration, elastogenesis and endothelialization were shown to improve. Indeed, the authors propose the blended patch as an attractive alternative material that could induce the growth of a neo-artery composed of tissue present in native artery.

SF has also been applied as substrate for cylinder stents of small diameter (29). In a single study, a solution of native SF directly taken from the silk gland was used to prepare a cylindrical stents of 1 mm diameter and 5 mm length. The stents were inserted *in vivo* into the abdominal aorta of 22 rats and fixed using methylmethacrylate. Such technique of stent anastomosis produced significantly shorter ischemia time during implantation compared to conventional sutures and, after 4 months, the anastomosis was shown to be functionally patent in all cases. However, thrombus formation, frequent and severe abdominal infections, and heavy host rejection remain critical issues.

3.2. SF in leporine models

Rabbits are the small animal of choice for conduits 1 to 4 mm in diameter, enabling bilateral implantation of longer conduits and having a greater similarity than rats to humans in coagulation, endothelialization, and patency. Carotid artery grafting is convenient in the rabbit due to technical feasibility, similar longitudinal tension to humans, as well as comparable endothelial response to prosthetic conduits. In fact, patency rate over time closely simulates the clinical response to chronic ePTFE grafts seen in humans.

A study employed a 3 mm diameter tubular scaffold, produced by braiding SF yarns and coating with a SF-PGDE aqueous solution, to evaluate endothelialization and steady-state blood flow *in vivo* by implanting and replacing a common carotid artery in rabbits (30). Doppler ultrasound and angiography demonstrated graft patency without aneurysmal dilations or significant stenoses at any time point, with waveforms comparable to the native contralateral artery. In addition, immunohistochemistry results showed that a clear and discontinuous endodermis appeared after one month of implantation, while a full endothelial layer covered the inner surface of the graft after three months. This finding was backed by the RT-PCR results indicating that the gene expression level of CD31 of cells populating the SF graft was 45.8% and 75.3% by that of the contralateral carotid artery at 3 months and 12 months respectively, while the VEGF gene showed a high expression level that continued to increase after implantation.

For what concerns SF blends with other polymers as vascular grafts in leporine models, a study implemented electrospun bi-layered scaffolds made of an outer layer of SF-poly(L-lactide-

co-ϵ-caprolactone) (SF/PLCL) and an inner layer obtained by shell-core electrospinning, in which the shell was SF/PLCL or PLCL alone and the core was a 15% aqueous heparin (Hep) solution, yielding SF/PLCL/Hep or PLCL/Hep grafts (31). A rabbit carotid artery replacement model was used to evaluate the vascular scaffolds *in vivo* (1.5 cm in length, 2 mm in diameter). Compared to the graft with PLCL/Hep as inner membrane, the hydrophilicity of the graft including SF (SF/PLCL/Hep) was significantly improved, with optimal biocompatibility and maintained lumen patency for 3 months after carotid artery transplantation at ultrasound examination.

SF has also been utilized to enhance the biocompatibility and hemocompatibility of commercially available 4 mm ePTFE grafts (32). A film of SF has been formed onto the inner surface of the ePTFE graft and then it has been exposed to sulfur dioxide plasma to obtain sulfonated SF. The study compared the patency rate between 12 of such SF-modified grafts and 10 unmodified ePTFE grafts used to replace a section of the lower abdominal aortic artery in rabbits. The patency rates of SF-modified ePTFE grafts were found to be higher than those for the unmodified grafts at all timepoints (on day 3, from day 4 to 3 months, and at 3 months the patency rates were 100% vs. 60.0%, 91.7% vs. 33.3%, and 91.7% vs. 20.0%, respectively). Moreover, grafts harvested 3 months postoperatively showed that approximately 84% of the inner surface of the SF-modified grafts were covered by endothelial cells, compared to 11% of the inner lumen of the unmodified grafts, also harboring an inflammatory and thrombogenic substrate of activated platelets, erythrocytes, and newly formed extracellular matrix.

4. SF small diameter vascular grafts in large animal models

4.1. SF in canine models

Most of the published research performing arterial anastomosis of SF-SDVGs *in vivo* involved murine models, in which patency and remodeling potential were generally evaluated upon arterial grafting of the abdominal aorta. For this reason, the transition of such *in vivo* experiments towards larger animal models might be able to provide more ideal empirical conditions. According to the retrieved literature, canine models were the second-most employed animal for experimental purposes involving SF after the abovementioned murine models. However, some authors have shown that dogs are more susceptible to blood clotting than other animal species, thereby introducing a possible bias on the long-term patency rates of the implanted SF-SDVG in some settings (13). Furthermore, research contradicting the assumptions of low patency and absence of spontaneous endothelialization attributed to prosthetic vascular conduits implanted in dogs no longer support the use of canine models in the preclinical assessment of arterial grafts (33). Although originally advised, compared to other animals, the canine model has more differences and variability in hemostatic processes, as well as a proclivity for quick endothelialization of vascular prostheses.

Some studies have tested the features of hybrid combinations of SF and different synthetic graft materials to achieve improvements in mechanical and biological characteristics. SF has been used as biological sealant to counter thrombogenesis and foreign body or inflammatory reactions of textile arterial prosthesis (25). Six SF-coated polyester (PET) velour vascular grafts were implanted in the abdominal aorta of dogs for scheduled periods and outcomes were compared with commercial collagen-impregnated grafts and untreated external velour grafts. Besides rendering the graft impermeable to blood, the SF coating was shown to improve endothelialization of the synthetic graft material by favoring the outgrowth of a neointimal layer (34).

A different application in a canine model evaluated the mechanical properties and tissue biocompatibility of a surgical patch made by electrospinning a blend of SF and thermoplastic polyurethane by replacing part of the wall of the canine descending aorta (35). After 3 months the histological examination revealed excellent intimal tissue coverage of the intraluminal surface, absence of calcium deposition, and minimal inflammatory reaction, without signs of degradation.

Regarding the application of SF grafts in canine carotid arteries, a study monitored the patency of knitted SF grafts, double-coated with 5% SF and 10% PGDE, by means of Doppler sonography and histological analysis (36). Of five implanted grafts, 3 mm in diameter and 3 cm length, four were observed over four weeks and one graft was observed over one year. Indeed, while no significant changes were observed on the short term, hemodynamic alterations were observed after one year, suggesting intimal plaque or stenosis formation on behalf of the middle and proximal portion of the vascular prosthesis despite its patency. Moreover, albeit SF was almost degraded and replaced by fibrous tissue without any sign of necrosis, calcification, or infection, endothelialization of the graft appeared as incomplete.

In another study the same group compared the outcomes of thirty-five SF-coated SF grafts and five ePTFE grafts implanted via end-to-end anastomosis into the carotid arteries of dogs, determining a non-significant difference in patency rates at six months of 7.8% and 0%, respectively (37). However, the SF grafts were found to induce unique histological responses, such as maintaining the thickness of the luminal layers despite SF fiber degradation, due to fibrin accumulation and collagen fiber replacement with endothelialization at three months post-implantation.

Canine femoral arteries were also subjected to surgical replacement with SF grafts. A study aiming to investigate the biocompatibility and function of chitosan-sulfated SF prostheses randomly allotted eight dogs towards an experimental group in which the graft was implanted and a control group which received no intervention (38). Six months after implantation, the architecture of endothelial and smooth muscle cells and coagulation function were found to be comparable between the two groups.

In a recent study, knitted SF grafts coated with SF-Glycerin were implanted in the femoral artery of six dogs and patency

was assessed periodically with Doppler sonography and histologically analyzed (39). Five of the six grafts exhibited a high patency rate, with evidence of endothelialization in the central part of the graft as as three months post-implantation, with no luminal narrowing. In the remaining case, occlusion was secondary to progressive graft bending and consequent thrombosis. For this reason, the authors suggest that enhancing biodegradation and early endothelialization of the graft may counter the onset of thrombosis due to mechanical factors.

4.2. SF in porcine vs. ovine models

Sheep are indicated as the large animal model of choice for vascular conduits with diameters of 4 to 6 mm (13) (**Figure 4**). Porcine models are also frequently employed for assessing vascular conduits, with platelet activity and coagulation like humans, as well as a proclivity for biomaterial implant calcification. However, complete endothelialization was shown to occur within three months post-implantation in all polyester conduits in pigs, whereas only peri-anastomotic endothelialization was observed in sheep, which more closely matches human physiology.

The performance of SF in a pig model was evaluated by employing a multilayered silk protein coating for drug-eluting stent systems (40). In this study, the SF layer was intended as a drug carrier and delivery system of molecules such as heparin, paclitaxel, and clopidogrel to modulate vascular cell responses to stent placement. The preliminary short term (2.5 h) *in vivo* study in a porcine aorta showed integrity of the silk coatings after implantation and the reduction of platelet adhesion on the heparin-loaded silk coatings.

In a more recent study, a hybrid vascular using SF and polyurethane (Silkothane), manufactured by electrospinning, was employed to evaluate patency and short-term remodeling in a sheep model of arteriovenous shunt (41). Nine Silkothane grafts were implanted between the common carotid artery and the external jugular vein of sheep and assessed at 30, 60, and 90 days. Eight of nine sheep (89%) showed complete primary unassisted patency of the graft at the respective time of sacrifice (one case of surgery-related thrombosis excluded), while microscopic analysis found coverage by endothelial and inflammatory cells and pseudointimal formation inside the graft lumen, especially at the venous anastomosis, with no impairment of the functionality of the shunt.

Some authors initiated pilot studies to assess whether the porcine or the ovine animal model would be better to use for future trials regarding the suitability of the surgical model and the long-term biological outcomes of interposed SF-SDVGs. In a single study, the carotid arteries of 1 minipig and 1 sheep were replaced with novel a tri-layered SF graft, monitored with Doppler sonography and angiography, and histopathology of explants was examined after four weeks (42) (**Figure 5**). Carotid implantation was preferred over femoral arteries to mimic clinical use and to avoid anatomical limitations. In both animal models the grafts were found to be patent, without any evidence of aneurysm, dilation, dissection, blood collection or signs of infection (**Figure 6**).

While in the mini-pig endothelial-like cells were found along the whole surface of the graft neointimal layer, endothelialization within the grafted sheep carotids was restricted to peri-anastomotic sites. This reflects a slower rate of endothelialization in the ovine model, closer to what occurs in humans. Microscopic evidence of an ongoing foreign body inflammatory reaction was observed in both animals, but only in the ovine model no concurring subendothelial hyperplasia and no damage to neighboring tissues had occurred. Therefore, in light of the

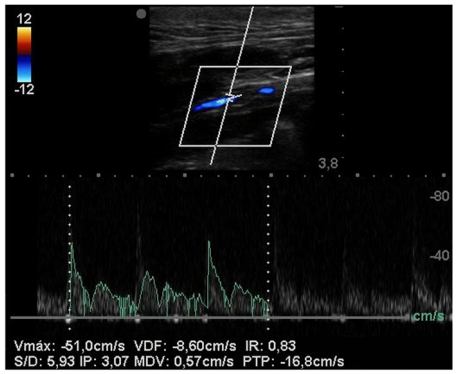

FIGURE 5
Duplex ultrasound of SF-SDVG in the carotid of a minipig after 1 month shows regular patency without any turbulence or velocity acceleration.

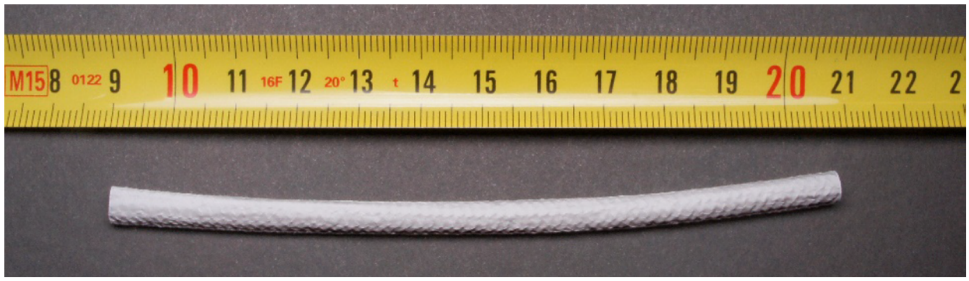

FIGURE 4
Silk fibroin-based small diameter vascular graft (SF-SDVG) of 12 cm length and 4.5 mm inner diameter ready for the implantation.

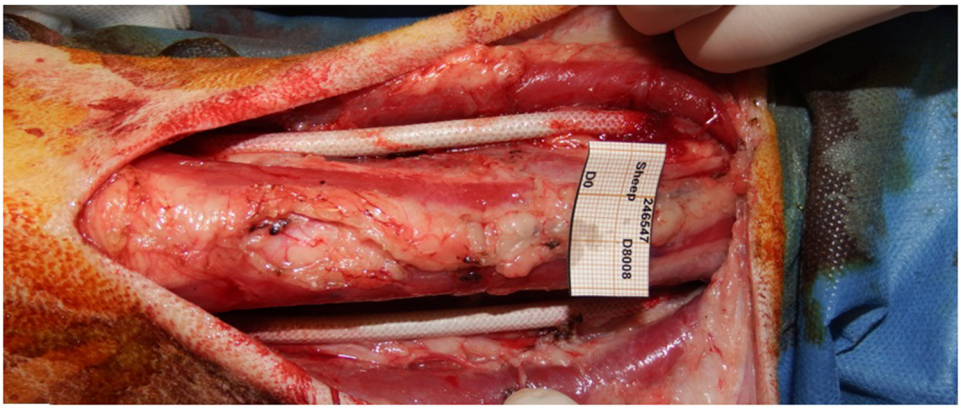

FIGURE 6
SF-SDVGs correctly implanted as vascular substitute of common carotid artery of both sides.

biological outcomes observed, as well as several technical and practical advantages, the ovine model was deemed more suitable than the minipig for long-term studies aimed at assessing the performance of SF grafts. According to the findings of such pilot study in large animals, the use of a small caliber vascular graft entirely made of pure SF has been validated by favorable biologic outcomes coupled to its simplicity in handling and surgical feasibility and, as a result, can be designed as an "off-the-shelf" device meant for preliminary clinical trials on humans.

Table 1 summarizes all the studies in literature about the SF animal models.

5. Discussion

While synthetic grafts (including PET or ePTFE) are a viable option in the replacement of large vessels, these have been shown to perform poorly when replacing small diameter vessels. Consequently, the need for an effective non-autologous vascular graft material for districts such as coronary and peripheral arteries appear to be still an open task for surgeons and bioengineers.

The optimal vascular graft should have scaffolds that mold the graft with an adhesive matrix primarily made of fibrin and vascular cells. Such biomaterials should also be capable of replacing the host's tissue, have a composition that is strong enough to prevent rupture, and have a sufficient size for clinical use.

The benefit of employing natural polymers is their built-in bioactivity, which results in favorable characteristics for graft regeneration.

Silk shows some properties that make it suitable to be a substrate for the creation of vascular grafts or in general vascular scaffolds for the healing of endothelial cells. They could be considered in two different groups: mechanical property and on the other hand biological properties as immune response and its interaction with vascular cells, biodegradation and haemocompatibility.

Multidisciplinary scientific efforts have converged to pinpoint the advantageous characteristics of vascular scaffolds in the quest to increase the clinical viability of vascular grafts. Indeed, the physical and chemical characteristics of the vascular scaffolds pragmatically dictate their therapeutic outcomes. Additionally, by adjusting the graft's characteristics, it is possible to calibrate the remodeling and formation of a neo-intimal layer in an implanted vessel. The ability to attract and recruit host cells while also providing them with a favorable microenvironment for growth, hemocompatibility, and minimal immunogenicity are just a few of the desirable features from an ideal vascular biomaterial.

Recruiting and attracting host cells is the base of endothelialization and it is a critical point in such a research especiallyfacing potentially biologic scaffolds. Endothelialization might be defined as cells and smooth muscle cells migrated into the fibroin graft early after implantation becoming organized into an endothelium and a media-like smooth muscle layer14. More specifically a transanastomotic endothelialization consists in the growth of the host intimal layer across the anastomosis because of a migration of native endothelial cells (43).

Other expectations include *in situ* biodegradation that facilitates constructive graft remodeling, mechanical resilience, and stability throughout the process of graft remodeling, the ability to attract and recruit host cells, and minimal immunogenicity (Figure 7).

Silk has a long history of being used as suturing material, largely due to its exceptional mechanical qualities. Various silk varieties have different amino acid contents, which results in native silk fibers having different mechanical strengths. As reported, native and regenerated forms of silk fibroin are both well used but they have different characteristics for different patterns. Native silk fibers confer better elasticity and slower time of degradation than regenerated, a crucial aspect to allow neo-tissue formation. The process of scaffolding as a silk vascular graft is dynamic and it is important to have a material with slower biodegradation time with higher strength and mechanical resistance. Regenerated forms are more managed to have a scaffold with quicker time of degradation as hydrogels, skin films or others not grafting use (44).

TABLE 1 Summary of the studies of *in vivo* use of silk fibroin grafts in the different animal models.

Graft composition	Graft inner diameter	Animal model	Implantation site	Implantation time	Author, year
Braided SF	1.5 mm	Sprague-Dawley Rats	Aorta	18 months	Enomoto et al., 2010
Electrospun SF	1.5 mm	Sprague-Dawley Rats	Aorta	3, 6, 12, 24 weeks	Filipe et al., 2018
Electrospun SF	1.5 mm	Lewis Rats	Aorta	1 week	Cattaneo et al., 2013
Gel-spun SF	1.0–1.5 mm	Sprague-Dawley Rats	Aorta	1, 3, 6 months	Rodriguez et al., 2019
Double Raschel-knitted TG-SF	1.5 mm	Sprague-Dawley Rats	Aorta	2 weeks	Asakura et al., 2014
Double Raschel-knitted TG-SF	1.5 mm	Sprague-Dawley Rats	Aorta	2, 4, 8 weeks	Saotome et al., 2015
Computer-controlled braided TG-SF	1.5 mm	Sprague-Dawley Rats	Aorta	2 weeks; 3 months	Fukuyama et al., 2017
Braided SF	0.9 mm	C57BL/6 Mice	Carotid Artery	1, 2, 4 weeks; 3, 6 months	Tanaka et al., 2020
Dip-coated SF/gelatin patches + Simvastatin micelles	N/A	F344 Rats	Carotid Artery	2 weeks	Thitiwuthikiat et al., 2015
Electrospun PCL/SF + VEGF + Heparin	1 mm	Rats	Carotid Artery	3, 4, 6 weeks	Yue et al., 2022
Electrospun PCL/SF + Spirulina	*	Rats	Carotid Artery	3 weeks	Kim et al., 2015
Double Raschel-knitted PET + SF(Glyc) Coating	1.5 mm	Sprague-Dawley Rats	Aorta	2 weeks; 3 months	Tanaka et al., 2020
Double Raschel-knitted SF + SF Coating	1.5 mm	Sprague-Dawley Rats	Aorta	2 weeks; 3 months	Fukuyama et al., 2015
Double Raschel-knitted SF + SF/PDGE Coating	1.5 mm	Sprague-Dawley Rats	Aorta	3 weeks; 3 months	Fukuyama et al., 2015
Double Raschel-knitted SF + SF Coating	1.5 mm	Sprague-Dawley Rats	Aorta	2, 8 weeks	Yagi et al., 2011
Electrospun SF/PU Patches	N/A	Sprague-Dawley Rats	Aorta	1, 3, 6 months	Chantawong et al., 2017
Dip-coated SF Stents	1 mm	Sprague-Dawley Rats	Aorta	16 weeks	Smeets et al., 2016
Braided SF + SF Coating	3 mm	NZ White Rabbits	Carotid Artery	2 weeks; 2, 3, 6, 12 months	Li et al., 2019
Electrospun PLCL/SF + Heparin	2 mm	NZ White Rabbits	Carotid Artery	2 weeks; 1, 2, 3 months	Jin et al., 2019
SF-coated ePTFE	4 mm	NZ White Rabbits	Aorta	3 months	Zhang et al., 2017
SF-impregnated Dacron	8 mm	Mongrel Dogs	Aorta	4 h; 3 days; 2 weeks; 1, 3, 6 months	Huang et al., 2008
Electrospun SF/TPU Patches	N/A	Beagle Dogs	Aorta	3 months	Shimada et al., 2017
Double Raschel-knitted SF + SF Coating	3 mm	Beagle Dogs	Carotid Artery	4 weeks; 12 months	Aytemitz et al., 2013
Double Raschel-knitted SF + SF Coating	3.5 mm	Beagle Dogs	Carotid Artery	1, 2, 3 days; 1, 2, 3 weeks; 1–7 months	Haga et al., 2017
Chitosan-sulfated SF	*	Beagle Dogs	Femoral Artery	6 months	Ma et al., 2017
Double Raschel-knitted SF + SF Coating	3.5 mm	Beagle Dogs	Femoral Artery	3, 5, 12 months	Tanaka et al., 2021
SF/Heparin/Clopidrogrel-coated Metallic Stents	6 mm	Yorkshire Swine	Aorta	2.5 h	Wang et al., 2008
Electrospun SF/PCU	6 mm	Sheep	Carotid-Jugular AV Shunt	1, 2, 3 months	Riboldi et al., 2020
Electrospun SF/TEX	5 mm	Sheep and Minipig	Carotid Artery	1 month	Alessandrino et al., 2019

*Not present in the paper.

The spinning procedure and other industrial alterations that could be made to the biomaterial are additional influential aspects that impact mechanical qualities.

SF-based vascular grafts are excellent candidates for the engineering of products intended as "off-the-shelf" devices due to their promising biological responses. Since pre-seeding with cells is no longer necessary, this eliminates associated time delays and costs and minimizes the steps for graft preparation before implantation. Fibroin is a biodegradable protein derived from silk that provides an antithrombotic surface and serves as an ideal scaffold for various cell types in tissue engineering (45).

Modern technologies have demonstrated the capacity to logically implement the clinical viability of various SDVGs by providing results that are convincing and attest to the blooming nature of this subject. Despite these developments, none of the SDVGs have yet been commercialized, and only a small number of prospective

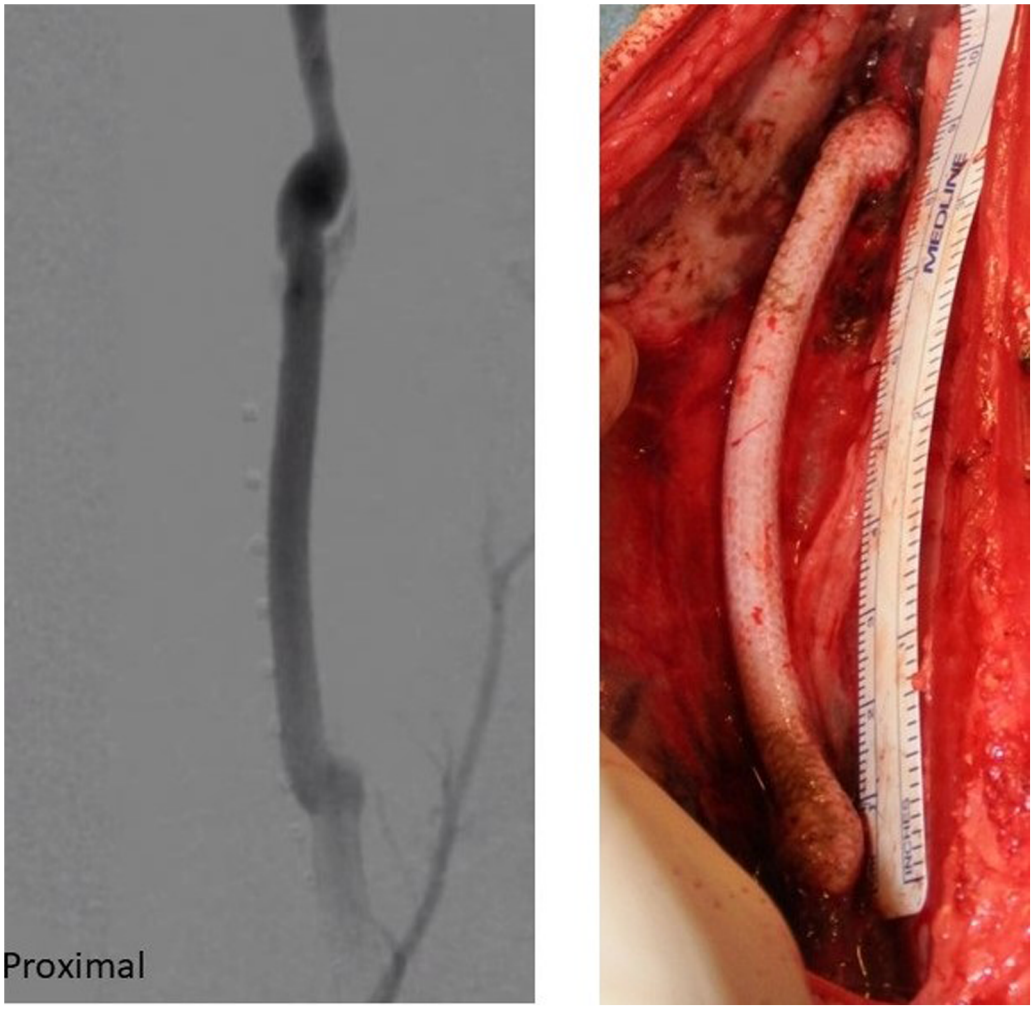

FIGURE 7
SF-SDVGs implanted in carotid artery of a sheep (**right**) and angiographic control revealing regular patency without dilatation or stenosis.

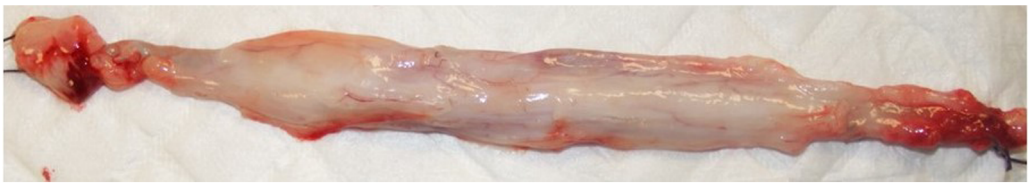

FIGURE 8
Anatomo-pathological sample of explanted SF-SDVG shows a complete healing of the graft and surrounding tissues.

targets are close to being translated into clinical practice. Existing research points to a few essential prerequisites for the clinical feasibility of SDVGs. The optimal solution would be widely available SDVGs, which would also need to be economically feasible and have sufficient mechanical and biological qualities.

Numerous healthcare items with silk as their substrate have been developed thanks to significant advancements in silk biomaterial research. Adipose, cartilage, bone, and wound dressing are just a few of the important non-vascular tissues that can be regenerated using products based on silk fibroin. Additionally, silk's prospective applications have been studied in the fields of medication delivery systems, medical implants, and occasionally evidenced by clinical proof. Its use has also been expanded to include the treatment of several dermatological disorders as well as breast and abdominal wall reconstruction.

In the vascular system an important topic for the evaluation of a new graft is the biocompatibility and haemocompatibility (44).

Usually, SF graft works as a scaffold for the progression of endothelial cells and progressive endothelialization of the substitute which could be the key point of its application. It is also reported the relationship between silk and human cells. Silk grafts showed to favor the adhesion, growth and survival of isolated human cells of three cell types of human peripheral arteries (endothelial cells, smooth-muscle cells and adventitial fibroblasts) respect to a polystyrene surface (46).

All the cell types, once cultured on either SilkGraft or polystyrene, exhibited similarly low basal levels of TIMP-2, a metalloprotease blocker which regulates extracellular matrix (ECM) remodeling processes and interactions between cells and ECM. It is interesting to note that no significant pro-inflammatory cytokines (Tumor Necrosis Factor-α (TNF-α), or of profibrotic cytokines (Transforming growth factor-b (TGF-b) were secreted by the three cell types grown on either substrate. The patterns of cytokines and chemokines secreted suggest a proliferative attitude while neatly excluding a pro-inflammatory and/or profibrogenic proclivity.

The biological haemocompatibility of SF is corroborate by lack complement activation and hemolysis meanwhile the cell adhesion, intense metabolic activities and the expansion of the cell populations cultured with no secretion of pro-inflammatory or pro-fibrotic cytokines show the high level of compatibility of SF rather than a synthetic graft (47) and this hemocompatibility of silk-based TEVGs has been validated in animal studies (48).

An important tool of Silk fibroin is the possibility to seed it with different cells. It has been reported that silk fibroin is a good scaffold for the cells of the endothelial wall but also bone marrow seeding or other cells type useful for the different use of the graft to reduce the thrombogenicity (49). The difference between seeded and not-seeded grafts is related to the use. Especially as vascular substitute, for the most, a not seeded graft is indicated, possibly made with multiple layers to reach more resistance and strength.

Although silk grafts have demonstrated extraordinary long-term regeneration capability in trials on small animals, their effectiveness in larger animals remains underdeveloped and field for future studies.

The development of other silk variants is still in its infancy and requires further attention. A couple of silk-based products that have been validated for clinical use belong to the tissue regeneration (41). While FDA permission has been obtained for the use of regenerated silk-based scaffolds in the reconstruction of non-vascular tissues, at the present, none of the silk-based SDVGs have reached the stage of human clinical trials yet.

Natural materials offer a solid blueprint to reinterpret, reengineer, and simplify modern manufacturing while preserving sustainability.

SF is minimally immunogenic and avoid fibrous capsule encapsulation by chronic immune response. The factors which are determining the bio response of SF-based tissue-engineered grafts include the format of the material, implantation site and degradation rate and time. Hard tissue implantation and shorter degradation time would result in minimal immunogenicity, while SF matrices having longer degradation time and implanted at soft tissue sites would elicit comparatively elevated immunogenic response (50). This reaction could be considered as an advantage because the tissue is involved in constructive graft remodeling (51) (**Figure 8**).

A crucial aspect is the mechanic reaction and strength of the biodegradable materials to maintain a structure without degradation before a good vessel healing and organization avoiding rupture or aneurysm formation causing hemorrhagic complications. Gradual proteolytic degradation takes longer in silk: silk fibers generally lose most of their tensile strength less or equal to 1 year *in vivo* and become unrecognized at the site less or equal to 2 years (52).

Last important topic for SF is the innovative formats of 3D printing for biological research and engineering technology. The capacity of SF to be processed into a variety of configurations for various applications provides as an additional benefit over other polymers. Its use in many applications is made possible by a tunable degradation pattern and exceptional physical and chemical characteristics. Due to the existence of additional desirable qualities, composite materials of SF and blends have emerged as a superior alternative option for many clinical and biological applications. There are no reports about the joining of SF and 3D prints in vascular tissues (in other fields this technique is already developed), but considering the opportunities of both, in the next future an increase of the possibilities of revascularization could be really evaluated (53).

In our review all preclinical studies were analyzed. If a new material for vascular grafts should be studied, the way to the clinical phase is surely longer than other districts especially if it is a scaffold for the cellular growing. Literature reports some good results of pre-clinical phase and good efficacy of the graft as vascular scaffold for arterial, venous and artero-venous reimplantation. Clinical phase requires a particular assurance of the strength and resistance of the graft especially in the anastomotic sites. Results from different experiences are encouraging but we need more data from *in vivo* in large animal models before trying the silk fibroin grafts in humans (54, 55).

6. Conclusions

Our review showed how vascular grafts encompassing silk fibroin are promising for further biological development in animals and humans. Biodegradability and biocompatibility of this natural polymer will likely foster the development as biomaterial of choice for vascular reconstruction.

The key point remains that future studies should investigate silk-based vascular grafts in preclinical large animal models, focusing on the optimization of graft design parameters. Since the exact mechanism of graft remodeling and neo-tissue formation is not clear considering the heterogeneity of studies involving SF vascular grafts, further insight into the endothelialization of the grafts must be provided, along with long term outcomes on thrombogenicity and patency rates. Inevitably, the coming of age of SF as predilected biomaterial for vascular reconstruction will be sanctioned by the first clinical trial in humans.

Author contributions

AS and GB writing, data analysis and final revision. PS and EM final revision. AA, GF, and GV writing and final revision. AA is a stock owner and employee of Silk Biomaterials Srl. GF is a stock owner and consultant of the same organization. All authors contributed to the article and approved the submitted version.

Conflict of interest

AA is a stock owner and employee of Silk Biomaterials Srl; GF is a stock owner and consultant of the same organization.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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