Review Article

Similarities, differences and unmet needs regarding prosthetic materials in aortic arch replacement using the frozen elephant trunk technique: a review

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Abstract: The constant improvement of operative techniques offers the possibility of treating an increasing number of patients with complex acute and chronic thoracic aortic pathologies involving the aortic arch. Reliable and durable prosthetic material forms the platform for these approaches. Besides the most important properties like impermeability for blood, infection and thrombotic resistance, there are also properties which are not seen at first glance but can nevertheless play a key role in the healing process and long-term results, such as endothelialization and immunostimulation. To ensure the best possible properties of the graft, different variables of the grafts are continuously developed. Beside the choice of material and the weaving technique, Dacron sealing with gelatin is in clinical use for many years but is still being discussed. Collecting clinical experiences with sealed and unsealed grafts in aortic arch replacement led to the conclusion that blood loss through the prosthesis, especially in the early phase after the implantation of the graft, is lowered by gelatin sealing. Furthermore, binding of antimicrobiotic and antithrombotic agents to the collagen are promising approaches to a better prevention of these dreaded complications. More research examining the healing process of the prosthesis is needed in order to find out more about the influence of the prosthesis sealing.

Keywords: Gelatin sealing; frozen elephant trunk (FET); aortic prosthesis

Submitted Apr 11, 2022. Accepted for publication Aug 23, 2022.
doi: 10.21037/cdt-22-176
View this article at: https://dx.doi.org/10.21037/cdt-22-176

A short summary of needs and demands for an alloplastic prosthesis for aortic replacement

Continuous development of surgical techniques and a resulting growing complexity in the treatment of thoracic aortic pathologies involving the aortic arch increase the demands on the vascular prostheses as well (1,2). To provide both, an optimal implantability and *in vivo* function, an aortic prosthesis has to fulfill some essential criteria such as good handling during implantation procedure, impermeability to blood, resistance to infection, low thrombogenicity, durability, low immune stimulation and resistance against kinking and compression. In order to comply with these special requirements, the leading manufacturers in the field of vascular prostheses developed different methods which need to be constantly evaluated, taking clinical results into consideration. According adaptation brings us as close to the perfect prosthesis as possible.

An important question considers the supposed benefits of a gelatin sealing of the graft. The aim of this review is to evaluate gelatin/collagen sealing and alternative methods regarding their reliability regarding impermeability and ingrowth. Therefore, we compared the clinical experiences of those different approaches with a focus on the frozen elephant trunk (FET) procedure.

Different approaches to optimize material and outcome

During the development of an ideal vascular prosthesis, it is an ongoing challenge to find the balance between ingrowth on the one hand and the greatest possible blood impermeability on the other. These two qualities can be in conflict since a higher porosity of the prosthesis supports the ingrowth of biological tissue but increases permeability to blood at the same time. A common approach addressing this challenge was either preclotting the prosthesis with blood or an impregnation with a biodegradable agent (3). During the preclotting procedure, the prosthesis is saturated with a liquid to close the pores and enhance impermeability. It has to be performed by the surgeon right before the implantation. Different techniques of preclotting were described in the past (4,5). Preclotting is difficult to manage for hybrid prosthesis as it is partly packed in the delivery system until the definite implantation. Furthermore, it stays a laborious procedure which underlies interindividual differences. This could easily be avoided by using readymade prostheses impregnated by the manufacturer. The most common agent for prosthesis impregnation is collagen or gelatin respectively.

There are four different types of hybrid prostheses used for the FET procedure (6,7). Amongst them there are elementary differences concerning impregnation. Thoraflex (Terumo Aortic), Frozenix (Japan Lifeline) and Cronus (Shanghai Microport Medical) are all gelatin sealed prostheses (8,9) manufacturer specification Terumo and JapanLifeline). Hybrid prostheses of the Evita family made by Jotec are produced without such a sealing (10). Thoraflex, Frozenix and Evita are made out of woven Dacron (8,10,11). There was no detailed information about the other manufacturers materials used for their hybrid prostheses.

Blood impermeability has been tested and validated in experimental models (2,10). Concerning the *in vivo* blood permeability, there is no prospective study available comparing those different kinds of devices.

Relevant blood permeability after implantation of the Evita open NEO, a non-sealed prosthesis has been described by different authors (12-14). In gelatin coated prostheses, no reports could be found about graft permeability during or shortly after the implantation. Only very few described cases of spontaneous leakage, which occurred years after the implantation could be found (15). Another report about two cases of bleeding from the Thoraflex prosthesis during reintervention concerning the thoracoabdominal aorta came to the conclusion, that mechanical stress can lead to permeability of the graft (16).

These observations lead to the supposition that especially in the early stage after implantation, the gelatin cover provides a higher impermeability. It was also shown *in vitro* that gelatin covered vascular prostheses have a lower permeability to liquids (2). Leakage years after the implantation does not seem to be explained through the gelatin cover, since it is usually disassembled after only a few weeks (17). A possible explanation for this late onset bleeding could be the wider pores in the sealed prostheses.

Jotec uses a special double weaving technique with the aim of ensuring the best possible impermeability without using any kind of sealing. In experimental conditions, a high impermeability was proven (10). An explanation for the described bleeding complications under clinical conditions could be a higher sensitivity of the unsealed prosthesis to mechanical stress and high doses of heparin. To avoid this complication in uncoated prostheses, priming with BioGlue before implanting the prosthesis has been discussed, but it is mentioned that this brings along the risk of other adverse effects such as tissue necrosis and thromboembolic complications (18), and it is not recommended by the manufacturer.

Also, Japan Lifeline is using a double-layered low porosity woven polyester fabric for their Frozenix prosthesis prevent leakage (personal correspondence with Japan Lifeline).

To improve the effectiveness of gelatin and collagen sealing concerning impermeability and biodegradability, the amount of crosslinking seems to play an important role. By testing different biochemical methods of crosslinking, relevant differences in their clinical outcomes could be detected (19).

Another dreaded complication after aortic replacement is graft infection, mostly by gram positive cocci. This carries a high mortality and is one of the most common reasons for redo operation after previous open and endovascular aortic repair. Mainly to avoid intraoperative infection, antibiotics

can be bound to the prosthesis [Vascutek Terumo: Instructions for use, gelatin sealed polytetrafluoroethylene (PTFE) vascular protheses]. It was shown that the amount of Rifampicin bound, as well as the duration of Rifampicin binding were higher in gelatin sealed prostheses compared to unsealed prostheses (20). At the same time, a different examination showed gelatin prostheses bound with Rifampicin were more resistant to infection with Staphylococcus aureus, one of the most common germs of aortic graft infection, compared to prostheses without antibiotic binding (21). Examinations with other antibiotical agents such as levofloxacin, teicoplanin or quinupristin have led to the same conclusion and showed higher resistance of antibiotic soaked prostheses against gram positive cocci (22,23). Concerning FET, there is no data available which allows a reliable comparison of sealed and unsealed prostheses concerning infections. Beside antibiotical binding, the graft composition seems to play an important role for bacterial adherence as well. Schmitt and colleagues found less colonialization of woven grafts compared to knitted grafts (24).

By examining aortic gelatin sealed prostheses many years ago, it was shown, that neither thrombogenic activity nor inflammatory response have been altered by gelatin sealing (25). Another approach of lowering risk of thrombogenicity is binding heparin to the gelatin before the implantation (Vascutek Terumo: Instructions for use, gelatin sealed PTFE vascular protheses). Through a quick biodegradability, the gelatin coating is not preventing the formation of a neointima (17). It is imaginable that this procedure is even faster in gelatin sealed prostheses once the gelatin is degraded, since the pores in the Dacron are wider than those in double weaved prostheses. During the implantation, gelatin covering can cause sticking of the gloves which is described as disturbing by several surgeons.

Another point which has to be discussed in connection to the use of collagen or gelatin is the risk of prion disease transmission by using xenogenic materials, which got into focus since the bovine spongiform encephalopathy (BSE) was suspected to be transmitted from bovine tissue to humans (26). So far there is no reported case of transmission of the disease by medical grafts. To minimize this risk, only gelatin from Australia, which is considered as completely BSE free, is used for prosthesis sealing by Terumo (Vascutek Terumo: Instructions for use, gelatin sealed PTFE vascular protheses). The gelatin for sealing of the Frozenix prosthesis by Japan Lifeline derives from a country with BSE controlled risk and is processed in accordance with the requirements set by the "Office International des Epizooties", so the prion risk is removed (personal correspondence with Japan Lifeline).

What should the perfect prosthesis of the future look like?

Aortic prostheses have reached a high standard over many years of development, but development continues. The prosthesis remains a foreign body in the human organism so the objective in the next year's development must be to come as close to the natural properties as possible.

Gelatin sealing has contributed to an improvement of quality in aortic prostheses and so it does in the hybrid prostheses used for aortic arch replacement. Especially bleeding complications during and soon after implantation seem to be rare in gelatin sealed grafts. Despite the impression we gained from the available literature, also unsealed prostheses are widely used with good results. It is possible that these prostheses are more sensitive to mechanical stress such as aortic clamping and higher doses of Heparin during the implantation procedure, whereas gelatin sealed prostheses seem to be more robust and less sensitive to such influences. Therefore, more prostheses specific experience seems to be needed for the use of unsealed prostheses.

Differences concerning further aspects such as thrombosis or graft infection remain more unclear and require further investigation to find out specific advantages of the different materials.

Furthermore, little is known about the prosthetical healing by ingrowth of autologous cells. This could influence resistance against infection and could also increase tightness of the prosthesis, but also influence mechanical properties such as reduced dilatation over time, and probably play a key role especially in long term results. Besides binding of antimicrobial and antithrombotic agents to the gelatin cover of the prosthesis, an addition of cell and vascular invasion stimulating factors should be tested to improve the healing process and higher the quality of the graft.

Ongoing development is mainly focusing on the technical aspects of hybrid prostheses to ease and speed up the implant procedure of the prosthesis (27). A new hybrid prosthesis, called Ascyrus, is designed for replacement of the ascending aorta and the aortic arch with one single hybrid graft (28). This prosthesis on the stent portion however, relies merely on the radial force of a Nitinol matrix without

a fabric at that level.

Concluding, it can be said that the collagen sealing brings along certain advantages reflecting its broad application in thoracic aortic hybrid prostheses. Since there are no disadvantages seen in gelatin sealed prostheses, it seems to be the least common denominator with regards to blood impermeability. When implanted with diligence and with awareness regarding the risk of graft oozing, unsealed prostheses show very good results as well. Therefore, the prosthesis to choose remains a question of the surgeon's personal preference. But it seems to be definitely worthwhile to examine differences regarding the sealing which concern more subtle factors such as healing and inflammatory properties, which can probably have an impact on long term results of prostheses for the FET procedure.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Mohamad Bashir, Edward P. Chen and Mohammed Idhrees) for the series "Frozen Elephant Trunk" published in *Cardiovascular Diagnosis and Therapy*. The article has undergone external peer review.

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-176/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-176/coif). The series "Frozen Elephant Trunk" was commissioned by the editorial office without any funding or sponsorship. MK received speaking honoraria from Terumo Aortic. SK has received speaking honoraria from Terumo Aortic. RG is shareholder of TEVAR Ltd. and Ascense Medical GmbH. BR is consultant to and received support and speaker honoraria from Terumo Aortic, a shareholder of Ascension Medical, and holds patent on Single Device for Transcatheter Aortic Valve Replacement and Ascending Aortic Repair, 5860/Z6551, University of Pennsylvania, USA, 2013. MC is a consultant for Terumo aortic, Medtronic, Endospan and NEOS, received speaking honoraria from Bentley and Cryolife-Jotec and is shareholder of TEVAR Ltd. and Ascense Medical GmbH. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Discher P, Kreibich M, Berger T, Kondov S, Walter T, Benk J, Beyersdorf F, Gottardi R, Siepe M, Rylski B, Czerny M. Similarities, differences and unmet needs regarding prosthetic materials in aortic arch replacement using the frozen elephant trunk technique: a review. Cardiovasc Diagn Ther 2022;12(5):722-726. doi: 10.21037/cdt-22-176

