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REVIEW ARTICLE

A Review of the Use of Decellularized, Porcine, Small-Intestinal, Submucosal, Extracellular-Matrix Patch Material in Congenital Heart Surgery

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ABSTRACT

Patch material is frequently used by pediatric cardiac surgeons during repair of congenital heart disease. The ideal patch material would be pliable, durable, promote native tissue ingrowth, and allow for somatic growth. Intraoperatively, other desirable characteristics would include the material be hemostatic (i.e. lack of bleeding at needle holes) and isotropic (i.e. stretching in all directions, allowing for complex 3-dimensional patches). Decellularized, porcine, small-intestinal, submucosal, extracellular matrix material has shown promise as a potentially ideal patch material. Proxicor (4-ply) and Tyke (2-ply) (Aziyo Biologics, Silver Spring, MD) are commercially available, extracellular matrix material products that are approved by the United States Food and Drug Administration for use in pediatric cardiac surgery. While initial studies were encouraging regarding the extracellular matrix material potential for native tissue ingrowth, subsequent studies have not reproduced the early findings. In most histological analyses, explanted extracellular matrix material has demonstrated chronic inflammatory cell migration and scarring. Despite the lack of transformation, extracellular matrix material does have the advantages of remaining pliable and resisting calcification, which are desirable in the reconstruction of congenital heart defects.

Introduction:

Patch material is often used in the surgical treatment of congenital heart disease (CHD). A variety of materials – autologous pericardium, xenograft pericardium, pulmonary allograft, and polytetrafluorethylene – have been used as patch material in the repair of CHD. Each of these materials, though, has potential drawbacks to its use (calcification, degeneration, and lack of growth potential). The ideal patch material will promote native tissue ingrowth, allowing for durability and growth. Decellularized, porcine, small-intestinal, submucosal, extracellular-matrix (SIS ECM) patch material has been shown to promote native tissue ingrowth in animal studies,[1-7] and it is approved for use in pediatric heart surgery by the Food and Drug Administration (FDA).[8] It has been successfully used in several organ systems (urologic, orthopedic, gastrointestinal, and cardiac procedures).[9-16]

There are two forms of SIS ECM patch that are commercially available and FDA-approved for pediatric cardiac surgery. Proxicor (Aziyo Biologics, Silver Spring, MD) is a 4-ply SIS ECM, while Tyke (Aziyo Biologics, Silver Spring, MD) is a 2-ply SIS ECM. These patches were originally marketed as CorMatrix (CorMatrix Cardiovascular, Roswell, GA), before being transferred to Aziyo Biologics. CorMatrix continues to develop other technologies, including ECM valves for cardiac valve replacement, which will be further expanded upon below. For the Aziyo patches, the thickness is the only differentiating characteristic; the mode of action is the same. The products' developers purport that a biologic extracellular matrix will induce a regenerative response by the body's immune and inflammatory responses (rather than a foreign body response).[8]

While animal series have suggested the potential for native tissue ingrowth, human studies evaluating explanted SIS ECM have not corroborated the animal studies' results.[15-19] Moreover, there have been human studies that suggest that the durability of SIS ECM is potentially inferior to other patch materials when subjected to systemic circuit loading parameters.[19-24] Nevertheless, SIS ECM continues to be used in repair of CHD.[25] The optimal environment (intracardiac vs extracardiac, pulmonary circuit vs systemic circuit, leaflet tissue vs annular tissue) and time *in vivo* that will promote native tissue in growth remain areas of ongoing debate.

This review aims to examine the current use and results of SIS ECM material in congenital heart surgery.

Methods/Results:

Decellularized, porcine, small-intestinal, submucosal, extracellular-matrix patch material has been utilized in several different cardiac environments. We have previously performed prospective analyses of explanted SIS ECM patches from intracardiac and extracardiac positions, as described below. Additionally, we provide a summary of the most recent series evaluating SIS ECM use in valve repair and valve replacement.

Intracardiac Small-Intestinal, Submucosal, Extracellular-Matrix Patch Usage

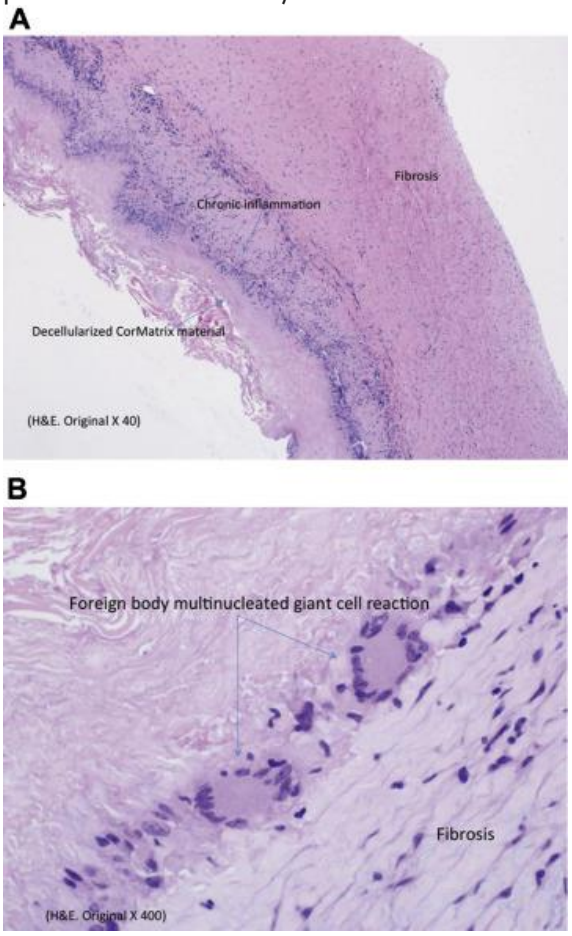
In 2016, Nelson *et al*. reported the first prospective series to date of explanted, SIS ECM (4-ply), intracardiac patches that had been placed in infants with CHD.[17] Patients who had undergone stage two palliation for single ventricle physiology with a hemi-Fontan procedure and intracardiac baffle with a SIS ECM patch over a six-month period were reviewed. During the hemi-Fontan procedure, as previously described, [26] an approximately 20mm x 20mm, SIS ECM patch was used to create an intracardiac baffle. The patch was sutured in place with poly-propylene monofilament in a running fashion and was in circumferential continuity with the right atrial wall. In its intracardiac position, the patch was exposed to a low-pressure environment (<20 mmHg).

At the time of stage three palliation (fenestrated, lateral tunnel, Fontan procedure), the intracardiac baffle patch was removed as part of the standard Fontan procedure.[27] During the Fontan procedure, the SIS ECM patches were excised and observed for aneurysmal changes, thrombus formation, gross calcification, and pliability. The patches were then sent for histopathologic examination, utilizing hematoxylin and eosin, Masson's trichrome, and Movat pentachrome stains.

Ten specimens were explanted and studied. The time spent in vivo ranged from 18-26 months (median, 21 months). At explant there was no evidence of aneurysmal degeneration, thrombosis, or calcification, and the patches remained pliable. Histopathologic analysis demonstrated acellular material, chronic inflammation, and foreign body giant cell reaction in all the specimens (**Figure 1**). Additionally, there was no evidence of native tissue

ingrowth in any of the specimens. Of note, no patches were removed for early degeneration or dehiscence. The analysis concluded that SIS ECM patch material was effective in its intracardiac position while not demonstrating evidence of native cell ingrowth.

Figure 1: (A) Low-power magnification with hematoxylin and eosin (H&E) stain showing section of the SIS ECM patch with a band of chronic inflammation and aggregates of histiocytes. (B) High-power magnification with H&E stain showing a section of the SIS ECM patch. This photomicrograph highlights the foreign body multinucleated giant cell reaction. (Reprinted from Nelson JS, Heider A, Si MS, Ohye RG. Evaluation of Explanted CorMatrix Intracardiac Patches in Children With Congenital Heart Disease. *Ann Thorac Surg*. 2016;102(4):1329-1335. doi:10.1016/j.athoracsur.2016.03.086m, with permission from Elsevier)



Extracardiac Small-Intestinal, Submucosal, Extracellular-Matrix Patch Usage

In 2021, building off of Nelson's study, Sood *et al.* reported a prospective series of explanted, SIS ECM (2-ply), extracardiac patches that had been placed in infants with CHD.[28] Patients who had undergone stage one palliation (Norwood procedure) for hypoplastic left heart syndrome and pulmonary artery patch closure with SIS ECM material over a four-year period were reviewed. During the Norwood procedure, as previously described,[29] a patch was used to close the pulmonary artery. The patch was sutured in place with a poly-propylene monofilament in a running fashion and was in circumferential continuity with native pulmonary artery endothelium. In its extracardiac position, as a pulmonary artery patch, the SIS ECM patch was exposed to pulsatile pressures through a systemic-to-pulmonary artery shunt, which was routinely placed during the Norwood procedure.

At the time of the stage two palliation (hemi-Fontan procedure), the pulmonary artery patch was removed as a part of the standard hemi-Fontan procedure.[26] During the explant, the SIS ECM patches were observed for aneurysmal changes, thrombus formation, gross calcification, and pliability. Similar to the study by Nelson et al, the explanted patches were then sent for histopathologic examination, utilizing hematoxylin and eosin, Masson's trichrome, and Movat pentachrome stains.

Nine specimens were explanted and studied. The time spent in vivo ranged from 4-10 months (median, 4.9 months). At explant, consistent with Nelson et al, there was no gross evidence of aneurysmal degeneration, thrombus, or calcification, and the patches remained flexible. Again, histopathologic analysis revealed acellular material, chronic inflammation, fibrosis, and foreign body giant cell reaction in all the specimens (**Figure 2**). Furthermore, no explanted SIS ECM patches demonstrated evidence of native endothelial tissue at a median of 4.9 months in vivo. Again, no patches were removed for early degeneration or dehiscence. The analysis concluded that SIS ECM patch material was effective in its extracardiac position while not demonstrating evidence of native cell ingrowth.

Figure 2: (A) Low-power (10x) magnification with hematoxylin and eosin (H&E) stain showing marked foreign body giant cell reaction. (B) High-power (20x) magnification with H&E stain showing foreign body giant cell reaction and eosinophil reaction. (Reprinted from Sood V, Heider A, Rabah R, Si MS, Ohye RG. Evaluation of Explanted CorMatrix Tyke Extracardiac Patches in Infants With Congenital Heart Disease. *Ann Thorac Surg*. 2021;112(5):1518-1522. doi:10.1016/j.athoracsur.2020.06.151, with permission from Elsevier)

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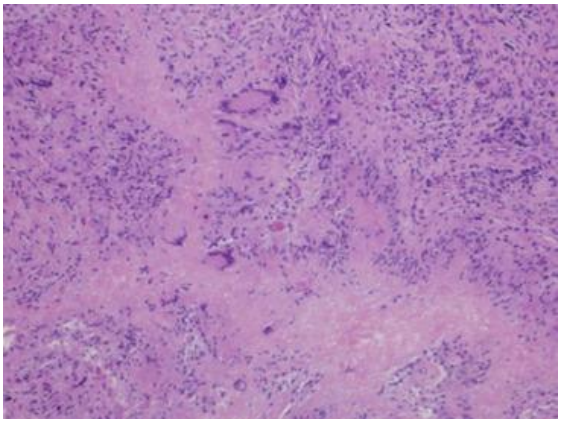

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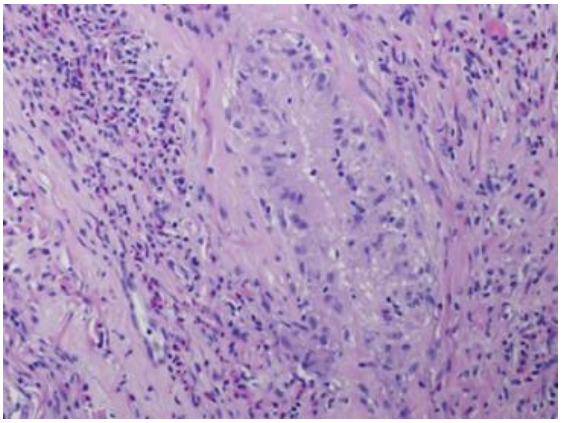

Small-Intestinal, Submucosal, Extracellular-Matrix Usage for Valve Repair

In addition to usage as an intracardiac or extracardiac patch, SIS ECM has been utilized as patch material for cardiac valve repair.

Hoffmann *et al*. reported a retrospective, single-center review of 6 pediatric patients who had undergone aortic valve repair (leaflet augmentation or leaflet replacement) with SIS ECM material.[22] Early follow up of their cohort revealed well-functioning aortic valves following repair; however, significant aortic valve insufficiency developed in 5 of the 6 patients at mid-term follow up. Histologic examination of the explanted SIS ECM material demonstrated chronic inflammatory response without evidence of native cell migration.

Nezhad *et al*. reported a single case in which SIS ECM was utilized in complex aortic valve leaflet augmentation.[30] In this analysis, SIS ECM material functioned well (stable aortic valve function) at early follow up but went on to develop early failure (severe aortic insufficiency requiring reintervention). The explanted SIS ECM material was analyzed and found to have extensive calcification, inflammatory cell infiltrate, fibrosis, and no evidence of native leaflet ingrowth. When used to augment the aortic valve cusps, SIS ECM has been demonstrated in several series to degenerate quickly and require early reintervention. While few histopathologic studies exist, when it has been studied, explanted SIS ECM has demonstrated a chronic inflammatory response without any evidence of native tissue ingrowth.[30]

Zaidi *et al*. reported a retrospective, single-center review comparing explanted SIS ECM to explanted autologous pericardium in patients who had undergone aortic valvuloplasty and/or mitral valvuloplasty.[19] In their study, SIS ECM was associated with an intense inflammatory response, involving macrophages, giant cells, and prolific eosinophils. Interestingly, in one explanted patch – that had the longest implant duration (9 months) – there was evidence of a neo-intima and significant resorption of the patch material.

Small-intestinal, submucosal, extracellular-matrix usage for mitral valve repair in patients with CHD has had similar results: early degeneration and early reintervention.[23-24]

Small-Intestinal, Submucosal, Extracellular-Matrix Usage for Valve Replacement

In addition to its use as a material for valve repair, SIS ECM has been utilized for novel valve replacement techniques.

Cylinder valve replacement, as described elsewhere,[31] is a novel valve replacement technique for adults and children. Particularly for children, who are too small to receive a commercially available tricuspid and mitral valve replacement, handmade SIS ECM cylinder valves have been successfully employed. There is currently an ongoing

pivotal trial for the use of a commercially produced CorMatrix (CorMatrix, Roswell, GA) tricuspid cylinder valve for both adults and children.

The ability to replace damaged or absent heart structures with material that will incorporate with native tissue during pediatric cardiac surgery remains one of the ultimate, but as of yet, unachieved goals of pediatric cardiac surgeons. In the majority of reported series, SIS ECM has not demonstrated evidence of native tissue ingrowth. Rather, in most histological analyses, explanted SIS ECM has demonstrated chronic inflammatory cell migration and scarring.

Small-intestinal, submucosal, extracellular-matrix is FDA approved and marketed as a patch material for intracardiac, extracardiac, and valvar uses. It's developers purport native tissue ingrowth as a result of the decellularized SIS-ECM scaffolding. While animal studies, and a minority of human studies, have suggested tissue ingrowth on SIS ECM patches, the majority of published studies has not reproduced this trait of SIS ECM material.

In prior studies, the loading stress on the patch, time in vivo, and proximity to native tissue have been hypothesized as areas for further investigation in order to promote the ideal conditions for native tissue ingrowth on implanted SIS ECM. As described in this review, though, SIS ECM has been utilized in intracardiac positions, extracardiac positions, as part of complex valve repair, and for variable lengths of in vivo duration. To date, no study has demonstrated consistent tissue ingrowth on SIS ECM patch material.

Both studies described from this authorship have suggested that SIS ECM patches, while having no histopathologic evidence of native tissue ingrowth, are reasonable choices for patch material because of its pliability, durability, and freedom from calcification. There are, however, a number of studies that have pointed to early degeneration of SIS ECM – particularly when it is under the strain of the systemic circuit (aorta, aortic valve, LVOT, and mitral valve). Aziyo currently recommends against the use of their ECM products for leaflet free-edge reconstruction.

Independent of whether there is native tissue ingrowth or transformation, case reports have demonstrated the successful use of ECM as both mitral and tricuspid cylinder valves. A commercial version of a tricuspid cylinder valve (CorMatrix Cardiovascular, Roswell, GA) is undergoing a pivotal trial. Work also continues on the use in the mitral position, where it would be particularly useful in the pediatric population, where current options for valve replacement are limited (Frank Scholl, MD, e-mail communication, January 2023).

The single explant from the Zaidi manuscript[19] that demonstrated resorption of the ECM and neointimal proliferation is intriguing. While the argument can be made that native scar is living tissue, it is not optimal. Work continues to better understand the optimal conditions whereby a consistent transformation of ECM to native tissue other than scar, as in the one explant reported by Zaidi.[19] Bibevski *et al.*[32] provide a review of the biological basis of this potential to have ECM transform into native tissue. The Bibevski lab is attempting to seed ECM patches with autologous induced pluripotent stem cells to provide the factors necessary to promote native tissue ingrowth (Steve Bibevski, MD/PhD, e-mail communication, January 2023).

Conclusion:

Small-intestinal, submucosal, extracellular-matrix has shown the potential to transform to native host tissue in animal models and, rarely, in human beings. Regardless of its ability to support native tissue ingrowth, it has many positive qualities of the material make it a good choice for the standard repair of congenital heart defects. Additional important uses, including as a replacement for the tricuspid and mitral valve are currently undergoing evaluation. In the pediatric population, successful deployment in these setting would be potentially game changing for this challenging cohort of patients who do not have other options. Ongoing research is focused on optimizing the SIS ECM itself, as well as the environment, to promote true transformation into living, functional native tissue.

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