

Results of mitral valve reconstruction using substitute extracellular matrix



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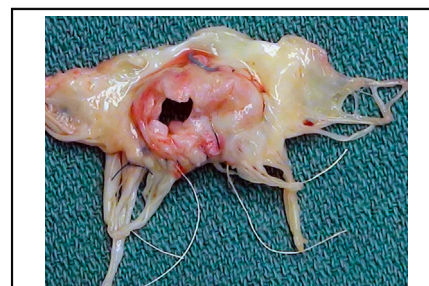
ABSTRACT

Background: During the ongoing search for an ideal patch material for reconstructive heart surgery, several versions of extracellular matrix (ECM) have been used. However, long-term performance in different cardiac positions is unknown.

Methods: We performed a retrospective review of outcomes after mitral valve surgery using ECM in 29 patients from 2011 to 2014. Clinical and echocardiographic follow-up was reviewed (mean time, 6.3 ± 2.8 years).

Results: ECM was used to reconstruct the posterior mitral annulus in 69% and to repair the mitral leaflet in 65% of the patients. The most prevalent etiology was dystrophic calcification of the annulus (80%) versus endocarditis for leaflet repair (60%). Fifty-five percent of the patients who required annular reconstruction received a mitral valve replacement (MVR). There were 2 perioperative deaths (7%). Long-term data were analyzed according to surgical technique; namely, isolated leaflet repair compared with annular reconstruction with or without MVR. There were 3 late deaths (1 per group). Overall survival was 83% at 7 years. Ninety percent of cases with mitral valve repair with or without annular reconstruction were free from more than mild mitral regurgitation, compared with 45% in the MVR and annular reconstruction group. The mechanism of failure was patch degeneration creating a severe paravalvular leak due to prosthesis dehiscence.

Conclusions: ECM used to repair the mitral valve leaflets with or without annular reconstruction offers acceptable results. However, caution should be taken with the use of ECM adjacent to prosthetic valve material because of a high rate of failure associated with patch degeneration. (*JTCVS Techniques* 2022;16:43-8)



Macroscopic view of explanted anterior mitral leaflet repaired with extracellular matrix.

CENTRAL MESSAGE

The use of extracellular matrix has been associated with early failure. We report our 5-year experience to identify modifiable causes of early failure.

PERSPECTIVE

We report one of the longest follow-ups of patients with mitral valve surgery using extracellular matrix, showing excellent results when used to repair the mitral leaflet with or without annular reconstruction. However, there is high risk of failure in the presence of adjacent prosthetic material, therefore it is not appropriate for reconstructing the mitral annulus if a valve prosthesis is required.

The surgical treatment of several cardiovascular conditions often requires the use of different conduits, patches, prostheses, or grafts to restore normal cardiac function. In the search for an ideal patch, cardiac surgeons have tried

several different materials. The ideal material should provide good mechanical properties, with low capacity to evoke immune response and calcification. Current patches used can be either synthetic material such as Dacron (Koch Industries, Inc) or biological material, but both have been shown to offer poor long-term performance because of deformation, degeneration, calcification, and thrombosis.¹⁻³ Thus, the search for a biocompatible material that provides a lifelong solution is still ongoing.

Extracellular Matrix (Aziyo Biologics) was approved by the US Food and Drug Administration in 2011. This extracellular matrix (ECM) is made from decellularized porcine small intestinal submucosa and is composed of 4 major types of molecules: structural proteins, adhesion glycoproteins, glycosaminoglycans and proteoglycans, and matricellular proteins.⁴ However, 90% of its composition is collagen type 1. This matrix serves as a bioscaffold,

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Abbreviations and Acronyms

- ECM = extracellular matrix
- MR = mitral regurgitation
- MV = mitral valve
- MVr = mitral valve repair
- MVR = mitral valve replacement

enabling the body’s own stem cells to infiltrate, replace, and ultimately remodel the implanted ECM with native tissue.⁵ ECM has been used in different intra- and extracardiac structures as previously described by our group.⁶⁻⁸ The described benefits of using this material are its malleability and ease of use, remodeling properties, lack of immunogenicity, and potential promotion of native tissue growth. Since 2010 this material has been used in cardiac surgery with promising outcomes in experimental and clinical models.⁹ There are data suggesting promising results with few complications when ECM is used in a low pressure environment (ie, extracardiac veins or right side of the heart).^{8,10,11} When used at higher pressure intracardiac sites (ie, aortic or mitral positions) complications are more likely to occur probably related to varying hemodynamic loads and shear forces.^{9,12,13} Despite these reports, there is little information on the long-term performance of ECM in different cardiac positions. We decided to analyze our results with the use of this material in mitral valve (MV) surgery.

METHODS

From 2011 to 2015, approximately 200 patients underwent cardiac surgery at our institution requiring the use of ECM material for the reconstruction of different structures of the heart, as part of a clinical trial on this material. Surgeries were performed by different staff members of our department. We identified those in which ECM was used to reconstruct the MV (N = 29). ECM was mainly used for the reconstruction of 2 structures of the MV, the posterior mitral annulus (n = 20) and/or the leaflet (n = 10; Figure 1). Preoperative, intraoperative, and follow-up data were collected from our institutional medical reports and the Cardiovascular Data Management Center. Patients were also contacted via phone to complete the follow-up. Clinical and echocardiographic follow-up was reviewed after a mean duration of 6.3 ± 2.8 years. The Research Ethics Board of the University Health Network approved the study (21-5511; approved May 12, 2022) and waived the need for individual patient consent.

Operative Technique

All surgeries were performed through a median sternotomy with cardiopulmonary bypass support. Patients who underwent mitral leaflet reconstruction had patch augmentation when the coaptation was deemed to be insufficient or to correct a defect in case of vegetectomy. An appropriate segment of the ECM patch was tailored according to defect size and shape and secured with 5-0 polypropylene suture. Annular reconstruction is required when a patient presents with horseshoe type configuration of mitral annular calcification with or without penetration of the subvalvular apparatus or an annular abscess in the case of endocarditis. Our surgical technique for mitral annular reconstruction has been previously described^{14,15} and consists of debridement of the posterior mitral annulus and then reconstruction of the atrioventricular groove with a strip of ECM membrane, 2 cm wide and as long as the distance of mitral annulus to be reconstructed (range, 4-8 cm). The ECM patch is sutured to the smooth endocardium of the inflow of the left ventricle, from lateral to medial fibrous trigones and to the posterior left atrial wall. All sutures are done with continuous 3-0 polypropylene sutures. After annular reconstruction, multiple 2-0 polyester sutures with pledgets were passed through

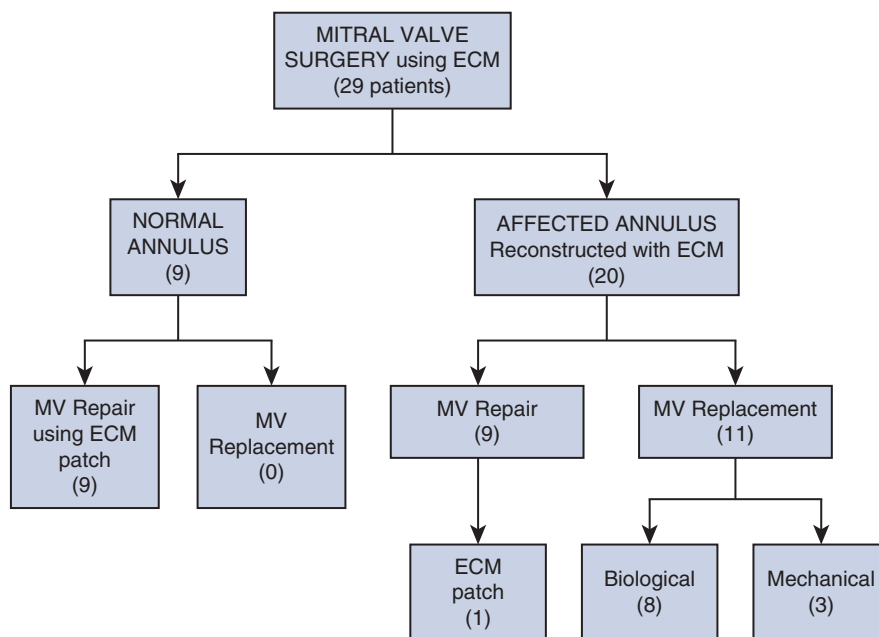


FIGURE 1. Flow chart of study cohort, indicating surgical techniques performed and the structures requiring extracellular matrix (ECM) reconstruction. MV, Mitral valve.

the ECM patch at a level that corresponded to the mitral annulus posteriorly and to the intervalvular fibrous body superiorly for valve replacement. For MV annuloplasty, the posterior leaflet is attached to the patch with running 4-0 polypropylene sutures and the annuloplasty stitches (2-0 polyester without pledgets) should incorporate part of the base of the posterior leaflet and the ECM patch.

Surgical Details

ECM was used to reconstruct the posterior mitral annulus in 69% of the patients and to repair the mitral leaflet, in 34.5%. The etiology of MV dysfunction included degenerative dystrophic calcification in 19, infective endocarditis in 7, and rheumatic disease in 3. The most prevalent etiology was dystrophic calcification in cases of mitral annular reconstruction (16/20), and infective endocarditis in cases requiring mitral leaflet repair (6/10).

Twenty-four patients required complex MV reconstructive surgery and 1 or more combined procedures. Surgical procedures performed are shown in Table 1. The MV was repaired in 18 (62%) cases. Eight cases required usual repair techniques without leaflet reconstruction, always with an annuloplasty with Simplici-T band (Medtronic). Of those requiring leaflet reconstruction with ECM (n = 10), only 3 had an annuloplasty with the Simplici-T band. The other 7 had no other structural valve abnormalities apart from the leaflet defect and no annuloplasty was performed. We replaced the valve in 11 (38%; 3 mechanical, 8 biological). All cases with isolated mitral leaflet reconstruction with ECM resulted with a successful MV repair (MVr; n = 10); when the annulus was reconstructed, the MV was successfully repaired in 9 patients (45%) and replaced in 11 (55%), usually because of extensive calcification of the leaflets (Figure 1).

Mid- and Long-Term Outcomes

Mid- and long-term follow-up data were analyzed according to group depending on the surgical technique performed on the MV. We identified 3 groups: patients with mitral leaflet repair (leaflet group; n = 10), patients with mitral annular reconstruction and MVr (annulus and MVr group;

n = 9), and patients with mitral annular reconstruction and MV replacement (MVR; annulus and MVR group; n = 11) (Table 2).

Early and Late Mortality

There were 2 perioperative deaths, located in the annular reconstruction and MVR group. Deaths were cardiogenic shock and multiple system organ failure-related. Both cases required extensive cardiac reconstruction, with 1 of them who underwent Commando surgery in combination with posterior mitral annulus reconstruction.

There have been 3 late deaths (1 per group) with only 1 cardiac-related. That patient had severe ventricular dysfunction and required extensive debridement and reconstruction of the mitral annulus and interventricular septum with ECM. A Gerbode defect was detected 2 postoperative weeks due to dehiscence of the interventricular septum patch, which was closed percutaneously with an Amplatzer atrial septal closure device (Abbott) because of the high risk of reoperation. Eight years after surgery, this patient died of congestive heart failure.

Reoperation on the MV

A total of 6 patients required reintervention during follow-up because of recurrence of severe mitral regurgitation (MR), resulting in a 78% rate of freedom from reintervention for the entire cohort. There were no cases (0/9) of recurrent MR in the annulus and MVr group. The isolated leaflet repair group had 2 recurrences of MR due to infective endocarditis, requiring both late reinterventions. One patient was initially treated with intravenous antibiotics after an episode of bacteremia, and subsequently presented with aneurysmal patch degeneration with a huge sterile perforation (Figure 2).

In contrast, 55% of the patients who required annular reconstruction and MVR had recurrent severe MR, of whom 4 underwent reoperation. The main cause of MR recurrence during echocardiographic follow-up was severe paravalvular leak due to prosthesis dehiscence, without structural valve degeneration. Echocardiograms showed a new extensive paravalvular leak extending along the posterior wall, involving one-third of the mitral annulus. At the time of reoperation, there was no recognizable ECM membrane at the level of the reconstructed mitral annulus with complete prosthetic valve detachment in all 4 patients (Figure 3). The mean time until patch degeneration was 2.4 years. Interestingly, all of the dehiscences present in our study occurred when biological prosthesis were used (4 of 8 in total), none being found with mechanical prosthesis (0 of 3). However, we cannot draw conclusions as to whether the type of prosthesis is directly related to patch failure because of our very small sample size. To conclude, the long-term durability of MVr using ECM patch to reconstruct the leaflet (80% patients with mild or less MR at 6 years) or the mitral annulus (100% at 6 years) appear to be considerably better than the long-term results of MVR onto a reconstructed annulus with ECM patch (44% at 6 years).

DISCUSSION

The present study represents one of the longest follow-ups available on the use of ECM for MV surgery. We have reviewed our results to determine if there are any predictable factors that lead to ECM failure.

Within the field of mitral surgery, most of the available information is on the use of ECM for leaflet repair. Gerdisch and colleagues¹⁶ repaired 12 MVs using a patch augmentation technique with ECM with good echocardiographic results and only 2 failures after a short mean follow-up time of 11 months. However, another report from Kelley and colleagues¹⁷ with a bigger sample (25 patients) showed a 32% failure rate at 1 year despite excellent intraoperative

TABLE 1. Operative data; mitral valve and concomitant surgical procedures performed

	n (%)
Mitral valve surgery	
Isolated	5 (17.3)
Combined	24 (82.7)
Mitral valve repair	18 (62.1)
Mitral valve replacement	11 (37.9)
Mitral annulus reconstruction	20 (68.9)
Mitral leaflet repair	10 (34.5)
Other combined procedures	
Aortic valve replacement	12 (41.4)
Aortic valve repair	1 (3.4)
Tricuspid valve repair	7 (24.1)
Replacement of the Ascending Aorta	3 (10.3)
Coronary artery bypass grafting	6 (20.7)
Maze procedure for atrial fibrillation	3 (10.3)
Others (PFO closure, myectomy, LAA closure)	6 (20.7)
Indication for reconstruction of the mitral valve	
Degenerative dystrophic calcification	19 (65.5)
Infective endocarditis	7 (24.1)
Rheumatic disease	3 (10.4)

Data are presented as n (%). PFO, Patent foramen ovale; LAA, left atrial appendage.

TABLE 2. Follow up data per group

Group	n	Perioperative death	Late death	Echo		Mean echo FU time, y	Reoperations
				≤ Mild MR	≥ Moderate MR		
Leaflet reconstruction	10	0	1 (10)	8 (80)	2 (20)	6.4	2 (20)
Annulus reconstruction and MVR	11	2 (18)	1 (11)*	4 (44)*	5 (56)*	6.1	4 (44)*
Annulus reconstruction and MVr	9	0	1 (11)	9 (100)	0	6.1	0

Data are presented as n (%). Echo, Echocardiography; FU, follow-up; MR, mitral regurgitation; MVR, mitral valve replacement; MVr, mitral valve repair. *n = 9 during follow-up because of early deaths.

echocardiographic results. The main problem during reoperation was excessive patch dilatation with an intense inflammatory response, without evidence of host integration in the histologic study. Our cohort had 10 cases of leaflet patch enlargement with ECM, with 80% freedom from more than mild MR at 6 years of follow-up. We found 2 early failures at 10 and 18 months. In both cases, an ECM patch was used to repair a mitral leaflet in the setting of infective endocarditis. One valve failed due to aneurysmal patch degeneration of the reconstructed leaflet in combination with a large perforation. This patient did have an episode of bacteremia thought to have been treated successfully with parenteral antibiotics. There was no sign of active endocarditis at reoperation. In contrast, the second failure occurred due to a new endocarditis by a different microorganism and the previous patch appeared to be intact during valve inspection. Microscopic analysis of explanted ECM showed intact patches with no evidence of reabsorption or valvular tissue in the biomaterial in both cases. More details about these findings are described in a previously published report by our group.¹³ In the absence of recurrent infection, the use of ECM for leaflet repair had acceptable long-term

outcomes in our cohort, with the limitation of the sample size.

The performance of ECM when used to reconstruct the atrioventricular continuity is less known. The only information available is from Gerdisch and colleagues¹⁶ with 7 patients in whom the mitral annulus was reconstructed with ECM patch after extensive decalcification, with 5 mitral repairs and 2 replacements. Again, the main limitation of that study was the short follow-up. We had a cohort of 20 patients who underwent mitral annular reconstruction with ECM patch. Dystrophic degenerative disease was the most prevalent etiology in line with previously published reports.¹⁷ We found excellent echocardiographic results at 6 years of follow-up when the annular reconstruction was associated with MVr, with 100% freedom from more than mild MR. In contrast, the combination of mitral annular reconstruction and MVR had the worst outcomes, with recurrence of severe MR in half of these cases and a high rate of reoperation. ECM acts as a substrate to activate, mobilize, and integrate host tissue-specific cells, promoting a regenerative remodeling; but not all anatomic sites are as equally receptive to ECM implantation.

The company has specifically advised against sewing prosthetic material such as Dacron or Gore-Tex patches (W. L. Gore & Associates) to ECM. It is also inadvisable to sew ECM adjacent to the sewing cuff of prosthetic valves. The material requires circulating progenitor cells to infiltrate the scaffold and regenerate the adjacent tissue. Theoretically, the presence of foreign material between ECM and host tissue can prevent the migration of circulating cells and thereby prevent beneficial remodeling. When both techniques—annulus reconstruction and MVR—are combined, no biological tissue remains and both prosthetic materials are in close contact. This might be the reason that MVR performs worse than MVr. If the MV is repaired, the leaflet is reattached to the patch and the band is placed on top, which allows tissue growth to be promoted.

Macroscopic findings during reoperations showed an intact valve prosthesis detached from the posterior annulus that had been reconstructed with ECM, with no recognizable membrane. If any strip of ECM was found during reoperation, it was sent to pathology and it is remarkable that the analyzed

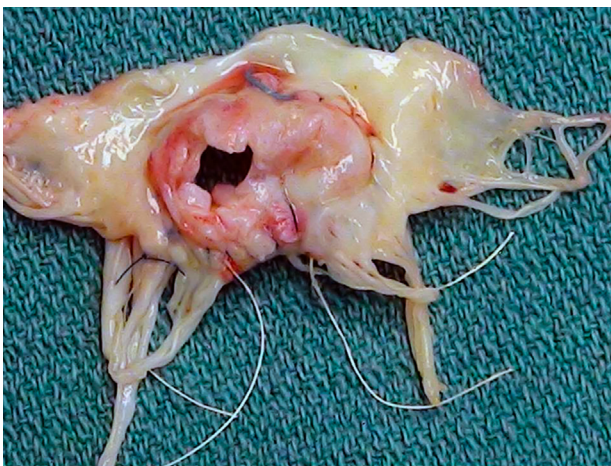


FIGURE 2. Macroscopic image of an explanted anterior mitral leaflet previously repaired with an extracellular matrix patch. The failure of the repair was related to aneurysmal degeneration of the patch with a huge sterile perforation after an episode of bacteremia despite being treated with intravenous antibiotics.

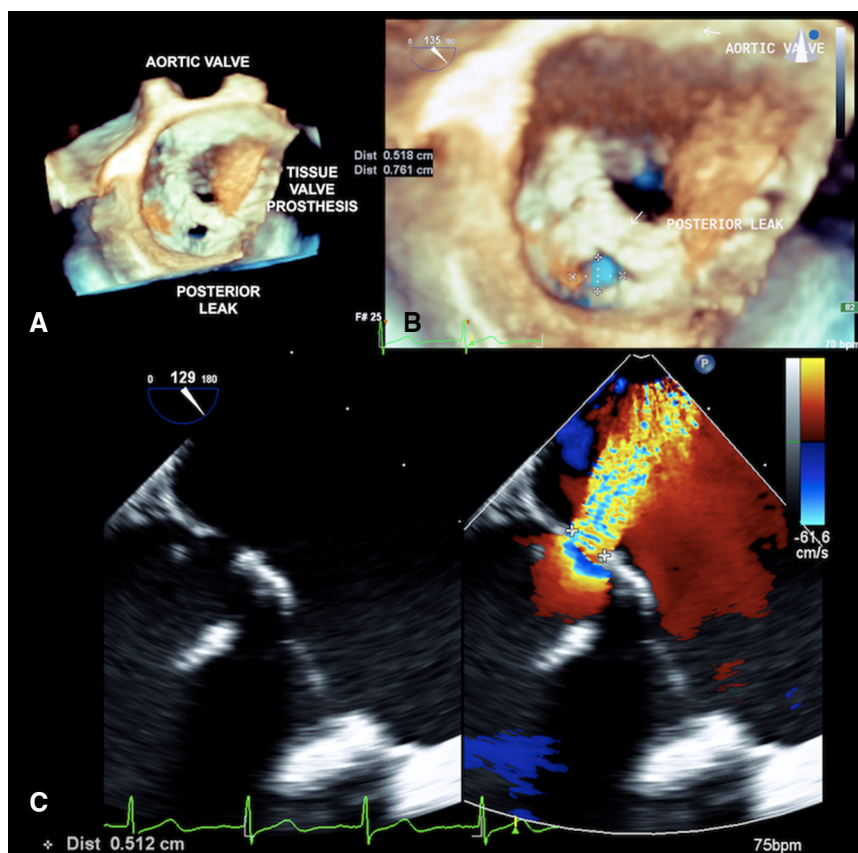


FIGURE 3. Echocardiographic views of the mitral valve of a patient with previous mitral replacement with tissue prosthesis Hancock 29 mm and posterior mitral annulus reconstruction with extracellular matrix patch. A and B, Three-dimensional transesophageal echocardiographic images of the mitral valve, as seen from the left atrium with the aortic valve located at the 12 o'clock position, showing a 5 × 7 mm posterior paravalvular leak. C, Shown is the presence of the same paravalvular leak in a zoomed transesophageal 2-chamber view.

tissue showed no evidence of any significant tissue growth or inflammation on its surface. Only the junctional areas showed some granulation tissue for a very short distance.

It is unclear why 50% of the patients with annular reconstruction and MVR had successful outcomes. Success might be dependent on the tissue quality on the contralateral side of the patch (away from the valve). However, the unpredictable outcomes lead us to avoid using ECM in these situations.

Limitation

This study has several limitations and the conclusions might not be generalizable. It is a retrospective review of a small cohort of patients with heterogeneous surgical techniques performed by different surgeons. The complexity of the cases varies greatly from case to case, from simple mitral repairs to complex intervalvular fibrous body reconstructions, creating interpatient and intergroup variability that makes long-term data analysis difficult. Our aim was to provide information on how ECM performs as used in the different techniques of MV surgery and our results provide important information that should be considered when selecting ECM as a repair material.

CONCLUSIONS

This report represents one of the longest clinical follow-ups in patients who received ECM during MV surgery. Despite widespread concern about failure rates with this material, we found satisfactory results when ECM was used to facilitate mitral repair with either patch augmentation of the leaflet or annular reconstruction. However, as cautioned by the manufacturer, the use of ECM adjacent to prosthetic material is associated with a high rate of failure and should be avoided. Interestingly, in explanted specimens from this series, we did not observe any tissue regeneration. Pathologic analysis of functional ECM patches is needed to determine if there is truly a regenerative capability of this material.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: extracellular matrix, mitral valve repair, patch material