Title: Results of Mitral Valve Reconstruction using Substitute Extracellular Matrix

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Glossary of Abbreviations:

- CVDMC - Cardiovascular Data Management Center
- ECM - Extracellular Matrix
- IVS - Interventricular Septum
- MSOF - Multiple Systems Organ Failure
- MR - Mitral Regurgitation
- MV - Mitral Valve
- MVr - Mitral Valve Repair
- MVR - Mitral Valve Replacement

Central Picture:

Central Picture Legend: 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 Statement: 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.
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±2.8y).

**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%) vs. endocarditis for leaflet repair (60%). 55% of patient who required annular reconstruction received a valve replacement (MVR). There were 2 perioperative deaths (7%). Long-term data was analyzed according to surgical technique; namely, isolated leaflet repair compared to annular reconstruction with or without MVR. There were 3 late deaths (one per group). Overall survival was 83% at 7 years. 90% of cases with mitral valve repair with or without annular reconstruction were free from more than mild MR; compared to 45% in the mitral valve replacement 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 due to a high rate of failure associated with patch degeneration.

**Keywords**: Extracellular Matrix, Mitral valve repair, Patch material
INTRODUCTION

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., Wichita, KS) or biological material, but both have shown to offer poor long-term performance due to deformation, degeneration, calcification and thrombosis. Thus, the search for a biocompatible material that provides a lifelong solution is still ongoing.

Extracellular Matrix (Aziyo Biologics; Roswell, Ga) was approved by the FDA in 2011. This extracellular matrix 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. However, 90% of its composition is collagen type 1. This matrix serves as a bioscaffold, enabling the body's own stem cells to infiltrate, replace and ultimately remodel the implanted ECM with native tissue. ECM has been used in different intra and extracardiac structures as previously described by our group. 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. There is data suggesting promising results with few complications when ECM is used in a low pressure environment (i.e. extracardiac veins or right side of the heart). When used at higher pressure intracardiac sites, (i.e – aortic or mitral positions) complications are more likely to occur probably related to varying hemodynamic loads.
and shear forces\textsuperscript{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 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 mitral valve (N=29). ECM was mainly used for the reconstruction of two structures of the mitral valve, 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 (CVDMC). Patients were also contacted by 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 (REB) of the University Health Network approved the study (REB #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 undergoing 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 MAC 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 anulus to be reconstructed (range 4 to 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 the ECM patch at a level that corresponded to the
mitral annulus posteriorly and to the intervalvular fibrous body superiorly for valve
replacement. For mitral valve 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).

24 of patients required complex mitral valve reconstructive surgery and one or more
combined procedures. Surgical procedures performed are shown in Table 1. The mitral
valve was repaired in 18 (62%) cases. 8 cases required usual repair techniques without
leaflet reconstruction, adding always an annuloplasty with Simplici-T® band. Of those requiring leaflet reconstruction with ECM (10), only 3 had an annuloplasty with 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 ended up with a successful mitral valve repair (N=10); meanwhile when the annulus was reconstructed, the mitral valve was successfully repaired in 9 patients (45%) and replaced in 11 (55%), usually due to extensive calcification of the leaflets (Figure 1).

Mid and Long-term Outcomes

Mid and long-term follow-up data was analyzed by groups depending on the surgical technique performed on the mitral valve. We identified 3 groups: patients with mitral leaflet repair (Leaflet group, N=10), patients with mitral annular reconstruction and mitral valve repair (Annulus+MVr group, N=9) and patients with mitral annular reconstruction and mitral valve replacement (Annulus+MVR group, N=11).

Early and Late Mortality

There were 2 perioperative deaths, located in the annular reconstruction and MVR group. Deaths were cardiogenic shock and MSOF related. Both cases required extensive cardiac reconstruction, with one of them undergoing commando surgery in combination with posterior mitral annulus reconstruction.

There have been 3 late deaths (one per group), only one cardiac related. That patient had severe ventricular dysfunction and required extensive debridement and reconstruction of the mitral annulus and interventricular septum (IVS) with ECM. A Gerbode defect was detected two postoperative weeks due to dehiscence of the IVS patch, which was closed.
percutaneously with an Amplatzer given 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 due to recurrence of severe 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+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, subsequently presenting 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 which 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 demonstrated 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 the dehiscences present in our study occurred when biological prosthesis were used (4 out of 8 in total), none being found with mechanical prosthesis (0 out of 3). Although we cannot draw conclusions as to whether the type of prosthesis is directly related to patch failure due to our very small sample size.

To conclude, the long-term durability of mitral valve repair 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 mitral valve replacement 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 mitral valve 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 et al.\(^{16}\), repaired 12 mitral valves using patch augmentation technique with ECM with good echocardiographic results and only two failures after a short mean follow up time of 11 months. However, another report from Kelley et al.\(^{17}\) with a bigger sample (25 patients) showed a 32% failure rate at 1 year despite excellent intraoperative echocardiographic results. The main problem found during reoperation was excessive patch dilatation with an intense inflammatory response, without evidence of host integration on the histologic study. Our cohort has 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, a 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 paper by our group. 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 atrio-ventricular continuity is less known. The only information available is from Gerdisch et al with 7 patients where 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 have a cohort of 20 patients that underwent mitral annular reconstruction with ECM patch. Dystrophic degenerative disease was the most prevalent etiology in line with previously published reports. We found excellent echocardiographic results at 6 years of follow up when the annular reconstruction was associated with mitral valve repair, with 100% freedom from more than mild MR. In contrast, the combination of mitral annular reconstruction and mitral valve replacement had the worst outcomes, with recurrence of severe MR in half of these cases and a high rate of reoperations. ECM acts as a substrate to active, 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 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 mitral valve replacement, are combined, no biological tissue remains and both prosthetic materials are in closed contact. This may be the reason why MVR performs worse than
MVR. If the mitral valve 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 tissue showed no evidence of any significant tissue growth or inflammation on its surface. Only the junctional areas showed some granulation tissue for very short distance.

It is unclear why 50% of the patients with annular reconstruction and MVR had successful outcomes. Success may 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.

Limitations

This study has several limitations and the conclusions may 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 is to provide information on how ECM performs used in the different techniques of mitral valve surgery and provides 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 mitral valve surgery. Despite widespread concern about failure rates with this material, we found satisfactory results when ECM was used to facilitate mitral repair by 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.

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Table Legend

Table 1. Operative Data. Mitral valve and concomitant surgical procedures performed.

Table 2. Follow up data per groups.

Figure Legend
Figure 1: Flowchart of study cohort, indicating surgical techniques performed and the structures requiring ECM reconstruction.

Figure 2: Macroscopic image of an explanted anterior mitral leaflet previously repaired with an ECM 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 ECM patch. A and B show 3-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, demonstrating a 5x7 mm posterior paravalvular leak. C shows the presence of the same paravalvular leak in a zoomed transesophageal 2-chamber view.
Table 1. Operative Data

<table>
<thead>
<tr>
<th>Mitral Valve Surgery</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated</td>
<td>5 (17.3)</td>
</tr>
<tr>
<td>Combined</td>
<td>24 (82.7)</td>
</tr>
<tr>
<td>Mitral Valve Repair</td>
<td>18 (62.1)</td>
</tr>
<tr>
<td>Mitral Valve Replacement</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Mitral Annulus Reconstruction</td>
<td>20 (68.9)</td>
</tr>
<tr>
<td>Mitral Leaflet Repair</td>
<td>10 (34.5)</td>
</tr>
<tr>
<td><strong>Other combined procedures</strong></td>
<td></td>
</tr>
<tr>
<td>Aortic Valve Replacement</td>
<td>12 (41.4)</td>
</tr>
<tr>
<td>Aortic Valve Repair</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Tricuspid Valve Repair</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Replacement of the Ascending Aorta</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Coronary Artery Bypass Grafting</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Maze Procedure for Atrial Fibrillation</td>
<td>3 (10.3)</td>
</tr>
<tr>
<td>Others (PFO closure, Myectomy, LAA closure)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td><strong>Indication for reconstruction of the mitral valve</strong></td>
<td></td>
</tr>
<tr>
<td>Degenerative Dystrophic Calcification</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>Infective Endocarditis</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Rheumatic Disease</td>
<td>3 (10.4)</td>
</tr>
</tbody>
</table>

Data are presented as n (%).
Table 2. Follow up data per groups

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Peri-operative deaths</th>
<th>Late deaths</th>
<th>Echo ≤ Mild MR</th>
<th>Echo ≥ Moderate MR</th>
<th>Mean Echo FU time</th>
<th>Reoperations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaflet reconstruction</td>
<td>10</td>
<td>0</td>
<td>1 (10)</td>
<td>8 (80)</td>
<td>2 (20)</td>
<td>6.4 y</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Annulus reconstruction + MVR</td>
<td>11</td>
<td>2 (18)</td>
<td>1 (11)*</td>
<td>4 (44)*</td>
<td>5 (56)*</td>
<td>6.1 y</td>
<td>4 (44)*</td>
</tr>
<tr>
<td>Annulus reconstruction + MVr</td>
<td>9</td>
<td>0</td>
<td>1 (11)</td>
<td>9 (100)</td>
<td>0</td>
<td>6.1 y</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are presented as n (%).

*N=9 during follow up due to early deaths.

Abbreviations: MR, mitral regurgitation; MVR, Mitral Valve Replacement; MVr, Mitral Valve Repair; FU, follow up.
MITRAL VALVE SURGERY using ECM (29 patients)

NORMAL ANNULUS (9)
- MV Repair using EMC patch (9)
- MV Replacement

AFFECTED ANNULUS Reconstructed with ECM (20)
- MV Repair (9)
- MV Replacement (11)
  - EMC patch (1)
  - Biological (8)
  - Mechanical (3)