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Cormatrix® for vessel reconstruction in paediatric cardiac surgery—a word of caution

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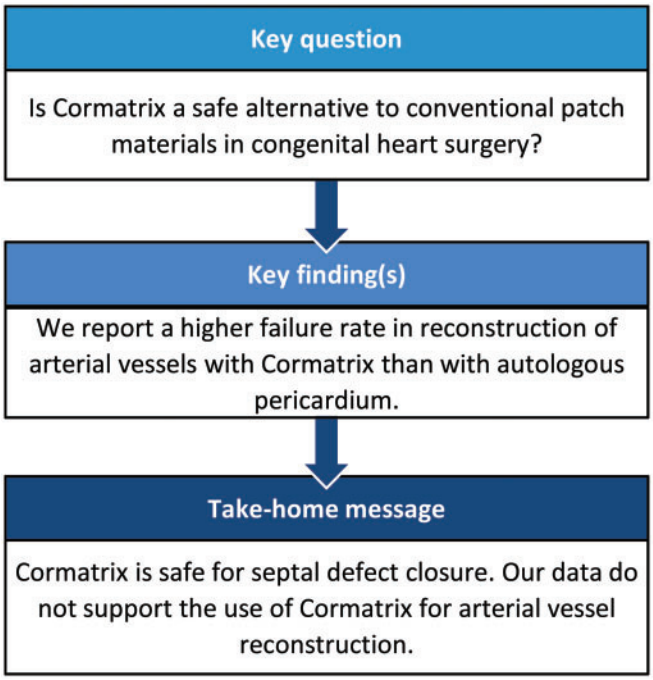

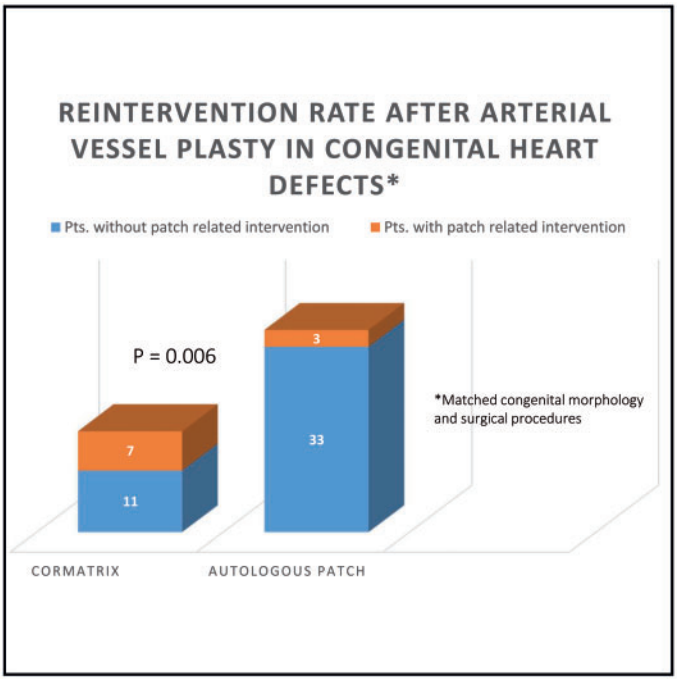

Abstract

OBJECTIVES: The aim of this retrospective study was to determine if Cormatrix® (CM) represents a safe alternative to conventional patch materials used in congenital heart surgery.

METHODS: A total of 57 paediatric patients who underwent cardiac surgery using an Extracellular Matrix Bioscaffold (CM) were categorized into 4 groups according to the patch implant location. Patch-related complications and reintervention rates were analysed. A subgroup of 18 patients was subsequently compared to a matched group of 36 patients who underwent similar surgical procedures with autologous pericardium as patch material.

RESULTS: No patient died during hospitalization. There were 2 late deaths, not related to the implanted CM patch. Fourteen (66.7%) out of 21 patients with arterial patch plasty developed progressive vessel/right ventricular outflow tract stenosis or aneurysm. All 3 patients

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with a valved CM conduit developed haemodynamically relevant valve stenosis or regurgitation. A total of 18 (31.5%) patients needed reintervention and 12 (21.1%) related to CM. Four (7%) patients needed surgical treatment with operative removal of the stenosis. Redo valve replacement was performed on 2 (3.5%) patients. Six (10.5%) patients required an interventional cardiology procedure at a median interval of 5 months from surgery. The subgroup analysis revealed a significantly lower patch-related reintervention rate in patients treated with autologous pericardium when compared to CM ($P = 0.006$).

CONCLUSIONS: CM is safe for atrial and ventricular defect closure. The use of CM for arterial vessel reconstruction is associated with higher reintervention rates when compared to autologous pericardium.

Keywords: Cormatrix® • Small intestinal submucosa-extracellular matrix • Congenital heart defect Bioscaffold

ABBREVIATIONS

AP	Autologous pericardium
CHD	Congenital heart defect
CM	Cormatrix®
ECM	Extracellular matrix
LPA	Left pulmonary artery
PVR	Pulmonary valve replacement
RVOT	Right ventricular outflow tract
RV–PA	Right ventricle–pulmonary artery
SIS	Small intestinal submucosa

INTRODUCTION

Corresponding to the global birth prevalence of nearly 1%, annually in Europe, ∼36 000 children are born with a heart defect [1, 2]. For most of the early corrective as well as for the palliative procedures, additional tissue is needed to reconstruct missing or defective intracardiac or extracardiac structures [3]. Commonly used materials in paediatric cardiac surgery are biological tissues, such as autologous or bovine pericardium and homografts, as well as synthetic materials, such as polyethylene terephthalate (Dacron®; Koch Industries, Inc., Wichita, KS, USA) or polytetrafluoroethylene (W. L. Gore & Associates, Inc., Newark, DE, USA) [4, 5]. Despite being of particular strength and durability, synthetical materials do have a lack of biocompatibility and a limited pliability and are suspected to induce reactive endocarditis [6, 7], whereas biological materials such as autologous and bovine pericardium are known to be affected by calcification, thickening and shrinkage over time [8]. Considering the disadvantages of these 'standard' materials, the search for the 'ideal' tissue substitute is still ongoing. Lately, the focus is on decellularized biological scaffolds, which apart from favourable properties regarding biocompatibility and mechanical characteristics should be able to prevent any form of scar tissue formation, while instead boosting the process of 'constructive remodelling' defined as the ability of the patient's own cells to repopulate the foreign tissue [9, 10].

Especially bioscaffolds obtained from small intestinal submucosa (SIS) showed encouraging results. By now, SIS-Extracellular Matrix (SIS-ECM) scaffolds have been used as patch for reconstructive surgeries in several different specialties with variable clinical outcomes. Commercially available SIS-ECM scaffold materials are predominantly obtained from pigs' small intestine. The most widely used commercially available porcine SIS-ECM bioscaffold for cardiovascular applications is Cormatrix® (CM) (Cormatrix® Cardiovascular, Inc., Roswell, GA, USA). Since 2010, CM has been used in various fields of cardiovascular surgery, from early correction of congenital heart defects (CHDs) in children to surgical treatment of acquired heart disease mainly in adults [11]. This analysis was performed to evaluate our institutional outcome with CM in paediatric cardiac surgery.

PATIENTS AND METHODS

Study design and patients

We performed a retrospective, chart review to evaluate the outcomes of 57 patients with congenital heart disease. Patients were operated at 2 centres, with the majority of reoperations being performed at centre 2. All patients underwent cardiac surgery with CM at our institution between September 2012 and March 2015. Individual patient consents were waived due to the retrospective nature of the study as determined by the institutional review board.

Based on the patch implant location, patients were categorized into 4 groups according to a previously introduced classification [4]:

- Group A, patients with septal repair ($n = 28$; 49%);
- Group B, patients with arterial vessel reconstruction ($n = 21$; 37%);
- Group C, patients with valve reconstruction ($n = 4$; 7%); and
- Group D, patients with venous vessel plasty or atrial reconstruction ($n = 4$; 7%).

When CM was implanted in >1 location, patients were adjudicated to the most appropriate group. Medical records were reviewed to extract demographic and clinical data. The follow-up documentation of each patient included echocardiographic and cardiac catheterization findings as well as surgical reports in case of redo surgery. Available information was collected and analysed regarding 2 major end points.

Patch-related event specified for each category as follows:
Group A—Haemodynamically relevant residual shunt;
Group B—Vessel/right ventricular outflow tract (RVOT) stenosis or aneurysm;
Group C—Valve failure defined trough haemodynamically relevant valve stenosis or regurgitation; and
Group D—Any unexpected event related to the patch material.
Patch-related redo surgery or interventional cardiology procedure
Subgroup analysis: CM compared to autologous pericardium (AP).

Eighteen patients out of the study population, who underwent an arterial or RVOT reconstruction using CM (CM group), were compared to 36 patients treated with AP (AP group). The AP group consisted of patients who underwent same surgical procedure, which was either a corrective repair of tetralogy of Fallot or an Arterial Switch Procedure in patients born with transposition of the great arteries. Patients for the control group were identified in the local database (CardioDoc ©2020 HEIT GmbH) with a systematic search and underwent surgery from 1 January 2000 to 31 December 2009.

Postoperative outcomes of the CM and AP groups were compared with regard to patch-related complication and reintervention rate.

Statistical analysis

Statistical analysis examined the possible effect of CM used as biological scaffold in congenital cardiovascular surgery on the onset of specific end points mentioned above. All continuous variables were either expressed as median or mean (range), and all categorical variables as absolute numbers and percentages. The follow-up time was defined as time till last follow-up while censoring patients reaching an end point at the time of the end point. The groups were compared using the Mann–Whitney *U*-test for continuous variables and the χ^2 test for categorical variables. The analysis was carried out with IBM SPSS Statistics 25.0 for Windows (IBM Corporation, Armonk, NY, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

RESULTS

Demographic characteristics

From September 2012 until March 2015, 57 patients with CHD underwent heart surgery with CM-patch implantation. Patient demographics are given in Table 1. Twenty-six patients (45.6%) were female. The median age at the time of surgery was 11 months, range 2 days–60 years. The median weight was 6.5 kg, ranging from 2.7 to 90 kg. The study included patients with a wide range of heart defects and CM was used in various locations to account for a broad spectrum of cardiac and vascular defects.

Table 1: Demographic characteristics of Cormatrix® patients

Variables	Patients
Total patients, *n* (%)	57 (100)
Age at surgery (months), median (range)	11 (0–728)
Weight at surgery (kg), median (range)	6.5 (2.7–90)
Redo surgery, *n* (%)	15/57 (26.3)
Sex, *n* (%)	
Male	31 (54.4)
Female	26 (45.6)
Total ECM surgical procedures, *n* (%)	
Group A—septal repair	28 (49.1)
Group B—arterial plasty	21 (36.8)
Group C—valve repair	4 (7.0)
Group D—other	4 (7.0)
CM >1 location, *n* (%)	17 (29.8)
CHD diagnosis	
ASD	11 (19.3)
VSD	10 (17.5)
Tetralogy of Fallot	9 (15.8)
Transposition of the great arteries	7 (12.3)
Atrioventricular septal defect (complete/partial)	5 (8.8)
Pulmonary atresia with VSD	5 (8.8)
Single ventricle	3 (5.3)
Total anomalous pulmonary venous connection	3 (5.3)
Aorto-pulmonary window	2 (3.5)
Pulmonary stenosis	1 (1.8)
Partial anomalous pulmonary connection	1 (1.8)

ASD: atrial septal defect; CHD: congenital heart defect; ECM: extracellular matrix; VSD: ventricular septal defect.

General outcome

The median follow-up was 43 months (range 3–64 months). Major postoperative complications during hospitalization included neurological events, low cardiac output syndrome, junctional ectopic tachycardia, need for extracorporeal membrane oxygenation support (support) as well as need for mechanical ventilation for >3 postoperative days. Seventeen patients (29.8%) experienced at least 1 severe complication after surgery, although none of them was directly related to CM implantation. Postoperative outcomes are given in Table 2.

Mortality

In-hospital mortality was 0%. We observed 2 late deaths not related to the implanted CM patch. One patient died at home on postoperative day 75 after right ventricle–pulmonary artery (RV–PA) trileaflet valved conduit implantation, due to sudden respiratory failure and 1 patient with Trisomy 21 and a partial atrioventricular septal defect experienced a fatal middle cerebral artery stroke 3 years after surgery.

Functional failure

Functional failure, defined as patch-related event specified for each group, occurred in 21 patients (36.8%).

- Group A—A residual shunt was detected in 2 (7.1%) out of 28 patients. None of them needed reintervention.
- Group B—Fourteen patients (66.7%) in whom CM was used to augment or remodel an arterial vessel including the RVOT, developed either vessel stenosis or aneurysm formation at follow-up.
- Group C—All 3 patients who underwent pulmonary valve replacement (PVR) with a self-constructed valved CM conduit as RV–PA connection, developed haemodynamically relevant valve stenosis or regurgitation.
- Group D—Two out of 4 patients with a superior vena cava-patch (group D) showed progressive vessel stenosis during follow-up.

Reintervention rate

During follow-up, 18 patients (31.5%) needed reinterventions. Ten patients (17.5%) needed further surgery, 6 (10.5%) due to a CM scaffold failure after a median interval of 8.5 months (1.6–28.2 months) from surgery. Eight patients (14%) required an interventional cardiology procedure. Six (10.5%) were related to CM at a median interval of 5 months (2–39 months) from surgery. Table 3 provides a detailed overview of patients requiring reintervention related to CM. Redo valve replacement for failing RV–PA conduits was performed on 2 patients. Eight (38%) out of 21 patients who underwent an arterial patch plasty with CM developed progressive vessel or RVOT stenosis related to the patch material. Four patients needed surgical treatment with operative removal of the stenosis. An interventional balloon dilatation of the affected vessel was necessary in the remaining 4 patients. Furthermore, 2 patients in whom CM was used to augment the superior vena cava showed increasing vessel stenosis requiring interventional cardiology procedure.

Table 2: General outcome after ECM (Cormatrix®) surgery

Variables	Patients
Total patients, *n* (%)	57 (100)
General outcome	
Major complication during hospitalization, *n* (%)	17 (29.8)
Major complication during hospitalization related to ECM, *n* (%)	0 (0)
ICU stay (days), median (range)	5 (1–57)
Hospital stay (days), median (range)	15 (8–133)
Hospital death (patients), *n* (%)	0 (0)
Late outcome	
Follow-up length (months), median (range)	43 (3–64)
Late death, *n* (%)	2 (3.5)
Late death related to ECM, *n* (%)	0 (0)
Reoperations after ECM surgery, *n* (%)	10 (17.5)
Reoperations related to ECM, *n* (%)	6 (10.5)
Group A—septal repair	0
Group B—arterial plasty	4
Group C—valve repair	2
Group D—other	0
Interval between ECM surgery and related reoperation (months), median (range)	8.5 (1.6–28.2)
Interventional cardiology procedures, *n* (%)	8 (14.0)
Interventional cardiology procedures related to ECM, *n* (%)	6 (10.5)
Group A—septal repair	0
Group B—arterial plasty	4
Group C—valve repair	0
Group D—other	2
Interval between ECM surgery and interventional cardiology procedure (months), median (range)	5 (2–39)
ECM functional failure at follow-up (patients),[a] *n* (%)	21 (36.8)
Group A—septal repair	2/28
Group B—arterial plasty	14/21
Group C—valve repair	3/4
Group D—other	2/4

[a]Functional failure defined for each group—refer to section Patients and Methods.

ECM: extracellular matrix, ICU: intensive care unit.

Table 3: Postoperative complications associated with Cormatrix® requiring intervention

Patient	Diagnosis	Age at surgery (months)	Patch use	Complication	Time until reintervention (months)	Reintervention
2	TAPVC	8	SVC	Stenosis	1.6	Balloon dilatation
4[a]	TOF	15	RVOT	Stenosis	28.2	Surgery
7[a]	PA/VSD	0	RV–PA conduit	Conduit failure	4.8	Surgery
8	vPS	137	RV–PA conduit	Conduit failure	12.3	Surgery
9[a]	TOF	4	RVOT/MPA	Stenosis	39.4	Balloon dilatation
27[a]	TGA	0	MPA	Stenosis	6.1	Balloon dilatation
29	HLHS	0	Aortic arch	Stenosis	3.9	Balloon dilatation
42[a]	TGA	0	MPA	Stenosis	8.1	Surgery
43[a]	TGA	0	MPA	Stenosis	19.3	Surgery
47	PA/VSD	63	LPA/RPA	Stenosis	12.1	Balloon dilatation
53	TAPVC	1	SVC	Stenosis	2.3	Stent
54[a]	SV	1	LPA/RPA	Stenosis	8.8	Surgery

[a]Patients included in the Cormatrix-comparison group—refer to section Patients and Methods.

HLHS: hypoplastic left heart syndrome; LPA: left pulmonary artery; MPA: main pulmonary artery; PA/VSD: pulmonary atresia with ventricular septal defect; RPA: right pulmonary artery; RVOT: right ventricular outflow tract; RV–PA: right ventricle–pulmonary artery; SV: single ventricle; SVC: superior vena cava; TAPVC: total anomalous pulmonary venous connection; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; vPS: valvular pulmonary stenosis.

Cormatrix® versus autologous pericardium

Eighteen patients from the CM collective (CM group) were compared to a group of 36 patients in whom AP was used as patch material (AP group). The AP group consisted of patients who underwent an identical surgical procedure at our institution between 2000 and 2009.

The groups were comparable with regard to patients' age, weight and surgical procedure (Table 4). In 3 patients within the CM group, tetralogy of Fallot repair included PVR due to severe

Table 4: Demographic characteristics of comparison groups

Variables	Cormatrix® patients	Autologous pericardium patients	*P*-value
Total patients	18	36	
Age at surgery (months), mean (range)	6 (0–42)	6.4 (0–72)	0.637
Weight at surgery (kg), mean (range)	5.4 (2.7–10.9)	5.9 (2.4–16.7)	0.588
Sex, *n* (%)			0.690
Male	12 (66.7)	22 (61.1)	
Female	6 (33.3)	14 (38.9)	
Diagnosis, *n* (%)			0.01
TOF	7 (38.9)	23 (63.9)	
TGA	6 (33.3)	13 (36.1)	
SV	1 (5.6)	0	
PA/VSD	4 (22.2)	0	
Surgical procedure, *n* (%)			0.125
TOF repair	10 (55.6)	23 (63.9)	
PVR	3	1	
Transannular patch	0	6	
Arterial switch OP	6 (33.3)	13 (36.1)	
Other	2 (11.1)	0	

OP: operation; PA/VSD: pulmonary atresia with ventricular septal defect; PVR: pulmonary valve replacement; SV: single ventricle; TGA: transposition of the great arteries; TOF: tetralogy of Fallot.

pulmonary stenosis. Two out of 3 were treated using an RV–PA valved conduit made of CM, whereas 1 patient got a pulmonary homograft. In the AP group, only one patient needed a PVR with homograft implantation. A transannular patch was used in 6 out of 23 AP patients. The groups were predominantly compared regarding postoperative outcome and reintervention rate. General postoperative outcomes comparing both groups are given in Table 5.

Functional failure and reintervention rate

In the CM group, 10 patients (55.5%) required reinterventions, 7 of them (38.8%) due to a CM scaffold failure at a median follow-up of 8.5 months (4.8–39.5 months). Five patients underwent reoperations and 2 patients an interventional cardiology procedure (Table 3). The reintervention rate related to the patch material was significantly lower in the AP group. Eleven patients (30.6%) needed further interventions. Three patients (8.3%) needed redo surgery due to an AP patch failure at a median follow-up of 118.8 months (Table 6). All 6 patients in the AP group with tetralogy of Fallot in whom a transannular patch was used to repair pulmonary stenosis needed PVR after a median follow-up duration of 9 years (0–126 months).

Individual mode of failure

In the 2 patients with reconstruction of the superior vena cava, obstruction in the patched region was first diagnosed 4 and 6 weeks postoperatively and was progressive. In the 2 patients who had insertion of an RV–PA valved CM conduit failure of the valve with high-grade PI was demonstrable already on echo on postoperative days 1 and 3 after an initially satisfactory intraoperative result. In addition, both patients additionally developed progressive stenosis necessitating RV–PA conduit replacement later on. In patients where CM was used for reconstruction of the main PA ($n = 3$), pulmonary bifurcation or branched pulmonary arteries ($n = 2$) stenosis in the patched region developed after 4–5 weeks postoperatively. In 1 patient with a transannular patch, the CM showed aneurysmal degeneration, the indication for reoperation, however, most probably was due to residual muscular hypertrophy in the RVOT. In the 2 patients with hypoplastic left heart syndrome and hypoplastic left heart complex in whom CM was applied for reconstruction of the aortic arch and the pulmonary bifurcation (pt. 54), progressive stenosis developed after 4 and 5 weeks, respectively, as demonstrated on Doppler echocardiography.

DISCUSSION

The main finding of this study is that the performance of CM in paediatric cardiac surgery primarily depends on the intended use. CM performs well when used for atrial and ventricular defect closure. However, the use of CM for arterial vessel reconstruction and valve reconstructions is associated with higher reintervention rates when compared to standard AP.

Corrective surgeries often require additional prosthetic tissue to reconstruct proper cardiac structure and function [3]. To fulfil these expectations an ideal patch material has to maintain its initial form, which means not being affected by tissue calcification, thickening or degradation. Following surgery, no signs of severe inflammation, fibrosis or infection should arise. The patch must be long lasting and resistant to mechanical failure. During the surgical procedure itself, the patch should be pliable, haemostatic and easy to model [11]. On top of these basic requirements, the material should also have the ability to adapt for patient somatic growth and, therefore, there is great interest in materials that have the ability to remodel into growing tissue, which could significantly reduce the number of reoperations in patients with CHD [12]. Especially decellularized bioscaffolds obtained from SIS such as CM showed very promising general outcome as vascular and myocardial patches in preclinical animal studies. As expected of bioscaffolds made of ECM, long-term inflammatory reaction was rare, especially regarding xenogeneic

Table 5: General outcome after ECM surgery comparing between Cormatrix® and autologous pericardium

Variables	Cormatrix® patients	Autologous pericardium patients	*P*-value
Total patients	18	36	
Early outcome			
Median ICU stay (days), median (range)	14 (3–56)	14 (3–129)	0.956
Median hospital stay (days), median (range)	28 (10–133)	28 (4–140)	0.949
Major complication during hospitalization, *n* (%)	12[a] (66.7)	15[a] (41.7)	0.083
Hospital death	0	1[b]	
Late outcome			
Follow-up length (months), median (range)	47 (3–64)	121 (0–203)	<0.001
Late death	1[b]	0	
Reintervention rate, *n* (%)	10 (55.5)	11 (30.6)	0.076
Interval between surgery and reintervention (months), median (range)	8.5 (1.5–39.5)	110.7 (0–127.9)	0.029
Reinterventions related to patch, *n* (%)	7 (38.8)	3 (8.3)	0.006
Interval between surgery and related reintervention (months), median (range)	8.5 (4.8–39.5)	118.8 (18.6–120.2)	0.087
Reintervention type, *n* (%)			0.301
Redo surgery rate	5 (27.7)	3 (8.3)	
Interventional cardiology procedure	2 (11.1)	0	

[a]None of them related to patch.
[b]Not related to surgery.
ECM: extracellular matrix; ICU: intensive care unit.

Table 6: Postoperative complications associated with autologous pericardium patches requiring reintervention

Patient	Diagnosis	Age at surgery (months)	Patch use	Complication	Time until reintervention (months)	Reintervention
68	TGA	0	MPA	Stenosis	18.6	Surgery
69	TGA	0	MPA	Stenosis	120.2	Surgery
88	TOF	8	RVOT/MPA	RVOT-aneurysm	118.8	Surgery

MPA: main pulmonary artery; RVOT: right ventricular outflow tract; TGA: transposition of the great arteries; TOF: tetralogy of Fallot.

implantations. Histopathological examination of explanted tissue regularly revealed repopulation of the matrix with native cell populations as well as clues for neo-angiogenesis and formation of new endothelial tissue [13–15]. While the vast majority of currently available patches works perfect when septal defects are closed, a patch that has growth potential and has the potential of re-endothelialization is highly desirable for vessel and valve reconstructions. Given the experimental findings and the potential properties of an ECM, CM was advertised to provide the latter.

In the present study, CM did not have any influence on long-term survival with no in-hospital mortality and 2 late deaths, which were clearly not related to the patch material. When analysing the reintervention rates after defect repairs with CM, we found a strong dependence on the intended use. CM performed as intended for atrial and ventricular defect closure with no patch-related complications and a negligible incidence of residual shunts. This is in line with previous studies that report excellent outcomes with CM for septal defect closures/separation of atrial and ventricular chambers [3, 4]. In light of our own experience and when compared to other reports, septal defect patches are probably the most promising application for CM in terms of safety and durability [3, 4]. From our data, we cannot answer if any re-seeding with autologous cells takes place when the patch is used for atrial septal defect/ventricular septal defect closure. However, we observed high reintervention rates in patients when CM was applied to augment or remodel arterial vessels. These patients showed an increased risk of patch-related complications. Eight out of 21 patients needed reintervention due to progressive vessel stenosis after a median follow-up duration of 10.4 months. Again, a similar outcome regarding PA reconstruction using CM was attained by Padalino *et al.* [4]. At a median follow-up time of 12.6 months, 8 out of 71 patients with an arterial vessel augmentation, mainly PA plasty, required an interventional cardiology procedure for restenosis. The median age at surgery was 19.7 months (1 day to 62 years). The high complication rate with CM as patch for hypoplastic vessels might best be explained by a previously described [12, 16, 17, 18] early response of the innate immune system, which leads to an increased thickness of the vascular wall at the implant location. Especially in young children with very small pulmonary arteries, this kind of inflammatory reaction could easily lead to a relevant vessel stenosis.

When comparing patch plasties with CM and AP we found significantly lower reintervention rates in the AP group. In the CM group, 7 patients (38.8%) needed patch-related reinterventions after a median follow-up time of 8.5 months. Among patients treated with AP, only 3 patients (8.3%) needed patch-related redo surgery at a median follow-up time of 118.8 months. This might best be explained by major differences in histological findings of explanted CM and AP specimens used for valvuloplasty in children with CHD [12]. CM explants revealed an intense

inflammatory reaction of the adjacent native tissue spreading onto the bioscaffold with no sign of remodelling. On the contrary, AP explants appeared almost free from inflammation, showing even more signs of constructive remodelling. In addition, when comparing CM and AP, handling and fitting is far better with AP. Given our experience and also in light of reports by other groups that mirror our findings, it has been suggested that several precautions and modifications to the CM patch could improve outcomes with CM. In particular, oversizing and thinning of the patch (using only 1 or 2 layers of the three-layered material) have been described. This is certainly reasonable, however, only predictable to a certain point.

The worst performance of CM was observed when implanted as a trileaflet valved conduit in 3 patients with pulmonary atresia. Two out of 3 conduits needed replacement with a bioprosthetic valve within 1 year after surgery. In view of the small number of cases, it is difficult to draw clear conclusions about the leading cause of graft failure. As suggested elsewhere [19], the translation of mechanical host signals, critical for a favourable remodelling process of dynamic cardiac structures as valves and vascular walls, is highly sophisticated. The incorporation of biochemical host signals, of major significance in the application of SIS-ECM bioscaffolds as septal defect patches with relatively mild physical motion patterns, is more easily achievable.

Limitations

This work has several limitations, which are important to consider. The major limitation of the study is the small sample size and the fact that the results relate to a small study population with a broad range of different CHDs. The small sample size can introduce bias when comparing groups. In particular, the sample size limits the ability to account and control for population differences. All patients included in the study were treated at the same institution and the results were reviewed retrospectively. The longest follow-up time within the CM group did not exceed 5 years, whereas the patients in the AP group have been observed much longer. The patients in the CM group were treated by a different surgical team than the patients in the AP group.

CONCLUSION

CM is safe for atrial and ventricular defect closure. The use of CM for arterial vessel reconstruction is associated with higher reintervention rates when compared to AP.

Conflict of interest: none declared.

Author contributions

Johanna Weis: Data curation; Investigation; Methodology; Software; Visualization; Writing—original draft; Writing—review & editing. **Ralf Geiger:** Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Software; Supervision; Writing—review & editing. **Juliane Kilo:** Data curation; Investigation; Methodology; Writing—review & editing. **Daniel Zimpfer:** Methodology; Validation; Writing—review & editing.

Reviewer information

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REFERENCES

[1] Dolk H, Loane M, Garne E; European Surveillance of Congenital Anomalies (EUROCAT) Working Group. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005. Circulation 2011;123:841–9.
[2] Van Der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ *et al.* Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241–7.
[3] Witt RG, Raff G, Van Gundy J, Rodgers-Ohlau M, Si MS. Short-term experience of porcine small intestinal submucosa patches in paediatric cardiovascular surgery. Eur J Cardiothorac Surg 2013;44:72–6.
[4] Padalino MA, Quarti A, Angeli E, Frigo AC, Vida VL, Pozzi M *et al.* Early and mid-term clinical experience with extracellular matrix scaffold for congenital cardiac and vascular reconstructive surgery: a multicentric Italian study. Interact CardioVasc Thorac Surg 2015;21:40–9.
[5] Holubec T, Caliskan E, Sündermann SH, Starck CT, Plass A, Bettex D *et al.* The use of extracellular matrix patches in cardiac surgery. J Card Surg 2015;30:145–8.
[6] Vaideeswar P, Mishra P, Nimbalkar M. Infective endocarditis of the Dacron patch—a report of 13 cases at autopsy. Cardiovasc Pathol 2011;20:e169–75.
[7] Robinson KA, Li J, Mathison M, Redkar A, Cui J, Chronos NA *et al.* Extracellular matrix scaffold for cardiac repair. Circulation 2005;112:I135–43.
[8] van den Heever JJ, Neethling WM, Smit FE, Litthauer D, Joubert G. The effect of different treatment modalities on the calcification potential and cross-linking stability of bovine pericardium. Cell Tissue Bank 2013;14:53–63.
[9] Badylak SF. The extracellular matrix as a scaffold for tissue reconstruction. Semin Cell Dev Biol 2002;13:377–83.
[10] Londono R, Badylak SF. Biologic scaffolds for regenerative medicine: mechanisms of *in vivo* remodeling. Ann Biomed Eng 2015;43:577–92.
[11] Mosala Nezhad Z, Poncelet A, De Kerchove L, Gianello P, Fervaille C, El Khoury G. Small intestinal submucosa extracellular matrix (Cormatrix®) in cardiovascular surgery: a systematic review. Interact CardioVasc Thorac Surg 2016;22:839–50.
[12] Zaidi AH, Nathan M, Emani S, Baird C, Del Nido PJ, Gauvreau K *et al.* Preliminary experience with porcine intestinal submucosa (Cormatrix) for valve reconstruction in congenital heart disease: histologic evaluation of explanted valves. J Thorac Cardiovasc Surg 2014;148:2216–25.
[13] Padalino MA, Castellani C, Dedja A, Fedrigo M, Vida VL, Thiene G *et al.* Extracellular matrix graft for vascular reconstructive surgery: evidence of autologous regeneration of the neoaorta in a murine model. Eur J Cardiothorac Surg 2012;42:e128–35.
[14] Badylak S, Obermiller J, Geddes L, Matheny R. Extracellular matrix for myocardial repair. Heart Surg Forum 2003;6:E20–6.
[15] Boni L, Chalajour F, Sasaki T, Snyder RL, Boyd WD, Riemer RK *et al.* Reconstruction of pulmonary artery with porcine small intestinal submucosa in a lamb surgical model: viability and growth potential. J Thorac Cardiovasc Surg 2012;144:963–9.
[16] Rosario-Quinones F, Magid MS, Yau J, Pawale A, Nguyen K. Tissue reaction to porcine intestinal submucosa (Cormatrix) implants in pediatric cardiac patients: a single-center experience. Ann Thorac Surg 2015;99:1373–7.
[17] Woo JS, Fishbein MC, Reemtsen B. Histologic examination of decellularized porcine intestinal submucosa extracellular matrix (Cormatrix) in pediatric congenital heart surgery. Cardiovasc Pathol 2016;25:12–17.
[18] Quarti A, Nardone S, Colaneri M, Santoro G, Pozzi M. Preliminary experience in the use of an extracellular matrix to repair congenital heart diseases. Interact CardioVasc Thorac Surg 2011;13:569–72.
[19] Kislitsina ON, Revishvili AS, Cox JL. Unlocking the secrets to regenerating cardiac tissue: an update. Interact CardioVasc Thorac Surg 2018;26:146–53.