Functional and Biomechanical Performance of Stentless Extracellular Matrix Tricuspid Tube Graft: An Acute Experimental Porcine Evaluation

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Background. **Stentless porcine extracellular matrix tricuspid tubular valves have been developed for tricuspid valve reconstruction. The purpose of this study was to compare biomechanical and functional performance of native and tube graft valves in an acute porcine model.**

Methods. **Twenty-two 65-kg pigs were randomized to tube graft or control with native valve preservation. Anterior papillary muscle force was measured with a dedicated force transducer. Microtip pressure catheters were placed in the right atrium and ventricle. Leaflet motion and three-dimensional valve geometry were evaluated using 13 sonomicrometry crystals: six in the tricuspid annulus, one on each leaflet free edge, one on each papillary muscle tip, and one in the right ventricular apex.**

Results. **No regurgitation and no significant differences in intracavitary pressures, annular motion, or leaflet excursion angles were observed after tube graft implantation ($p > 0.05$). Compared with the native valve, the tricuspid annulus, leaflet orifice area, annular diameters, and the septal segment of the annulus were significantly smaller in the tube graft group ($p < 0.05$). Maximum anterior papillary muscle force was significantly lower in the tube graft group ($p < 0.005$). The implantation technique led to an annular circumferential downsizing of 20% ± 17%.**

Conclusions. **An extracellular matrix tube graft implanted in the tricuspid position produces a competent valve with physiologic performance that, despite downsizing, makes the tube graft an attractive alternative to valve replacement. The downsizing of the implantation should be considered when planning tube graft size and may be potentially beneficial by relieving tension on the repaired tissue, thereby increasing durability.**

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In recent years, attention has been drawn to the tricuspid valve as an independent cause of heart disease. Earlier assumptions that tricuspid disease is rare and irrelevant to outcome after left-sided surgical procedures [1] have been replaced by a better understanding of the tricuspid valve, to form a rational basis for tricuspid valve surgery [2–5]. Tricuspid valve repair is performed more frequently, but total tricuspid valve replacement is still a problematic procedure because of the thromboembolic risks in the low-flow–low-velocity area of the right side of the heart.

The concept of tissue engineering has led to the development of an acellular bioscaffold composed of porcine small intestinal submucosa extracellular matrix (ECM). The material possesses growth potential, low thrombogenicity, no scar tissue formation, no calcification, and the potential for integration with native tissue and repopulation with host cells [6, 7].

A tricuspid tube graft has been developed for total valve reconstruction using ECM. In previous studies, the tubular design showed favorable flow dynamics and stress distribution [8]. Successful total valve reconstruction with ECM valves has also been shown for the pulmonary valve in pigs [9], and the first human implantation has been done [10]. Total reconstruction of the tricuspid valve using this type of ECM has been described in sheep [11], with a postoperatively competent valve and normal leaflet motion. In 2014, the first early experience with total ECM tricuspid valve reconstruction in 19 patient cases of endocarditis not repairable by conventional surgery was published [12]. Follow-up was up to 18 months. The valves were competent with no more than mild regurgitation. No heart block or deaths occurred. The technique was considered suitable and promising.

The purpose of this study was to characterize the detailed hemodynamics, dynamic three-dimensional valve geometry, leaflet motion, and force development in the anterior papillary muscle (APM) of native and ECM

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tricuspid valves in an acute porcine model to compare normal and reconstructed valves biomechanically and functionally.

Material and Methods

Animals

Twenty-two Danish Landrace pigs (65 kg) were randomized to either ECM valve (intervention) or no valve replacement (control). Two pigs were excluded because of pericarditis. Two pigs could not be weaned from bypass (1 in each group), and 4 pigs died of arrhythmia before data collection (2 in each group). Fourteen animals comprised the study population, with 7 animals in each group.

The experiment complied with the guidelines of the Danish Inspectorate of Animal Experimentation.

Surgical Procedure

Premedication, transportation, and anesthesia of the animals have been described previously [13, 14].

A median sternotomy was performed and heparin (40.000 IE) given intravenously. An aortic cannula was placed in the ascending aorta followed by bicaval cannulation. Cold blood cardioplegia was administered in the aortic root (Harefield Hospital [London, United Kingdom] formulation, 1:8 ratio). The tricuspid valve was exposed on the arrested heart through a right atriotomy. The APM was divided transversely at the midportion level, and a custom-made papillary muscle force transducer was implanted in the APM by using 2-0 braided polyester suture (Ethibond, Ethicon, Inc, Somerville, NJ) with felt pledgets. The dedicated papillary force transducer used was a modification of the design by Askov and associates [15].

In the right ventricle, sonomicrometry crystals (Sonometrics Corp, London, Ontario, Canada) were implanted in the apex, at the tip of each of the three papillary muscles, and at the midpoint of the free edge of each leaflet by using 5-0 polypropylene suture (Prolene; Ethicon, Inc) suture (Fig 1). The wire from the force transducer and from the seven subvalvular

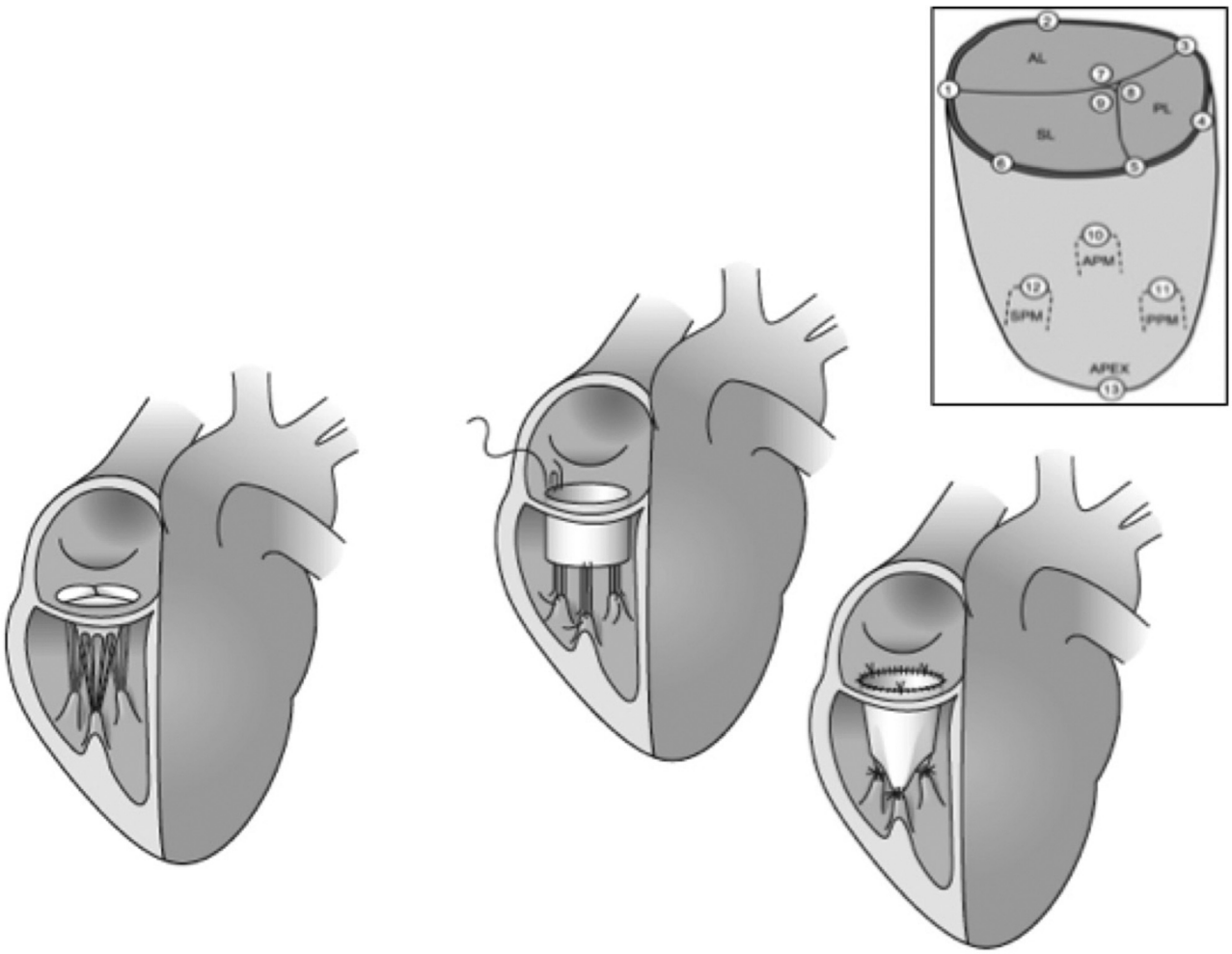

Fig 1. Implantation of the extracellular matrix tube graft. (Upper right corner) Sonomicrometry crystal implantation sites. (AL = anterior leaflet; APM = anterior papillary muscle; PL = posterior leaflet; PPM = posterior papillary muscle; SL = septal leaflet; SPM = septal papillary muscle.)

sonomicrometry crystals was exteriorized through a small incision at the right ventricular apex, which was closed after insertion of a ventricular microtip pressure catheter (SPC-350 MR, Millar Instruments, Inc, Houston, TX).

Six crystals were placed around the tricuspid annulus by using 2-0 Ethibond, with three crystals at each commissure and three halfway between two commissures (Fig 1). The wires were exteriorized through the atriotomy, which was closed after insertion of an atrial microtip pressure catheter (SPC-350 MR, Millar Instruments, Inc). In the ECM group, the native tricuspid valve was excised after implantation of the APM force transducer and the three crystals in the papillary muscles.

Competence of each valve was confirmed by using water testing and digital imaging before atrial closure. After 40 minutes of reperfusion, the pig was weaned from cardiopulmonary bypass.

After data collection, the animals were euthanized. The heart was explanted, and proper position of crystals and force transducer was confirmed visually.

Extracellular Matrix Valve Design and Implantation

ECM valves (CorMatrix Cardiovascular, Inc, Alpharetta, GA) were provided as tube grafts (height, 3.5 cm; circumference, 10.0 cm [11]) and were designed to replicate weight-adjusted dimensions of the native valve in humans [16–18] and animals [19]. The valves were constructed by the company from a flat sheet of ECM, which was folded into a tubular shape by suturing the two edges together with 6-0 Prolene, which hereafter was implanted as a cylinder valve (Fig 1).

First, the distal end of the tube graft was sutured to the three papillary muscles by using 5-0 Prolene. The three tube graft leaflets were sized with 40% of the circumference for the anterior leaflet and 30% for the two remaining leaflets, on the basis of a personal communication with Matheny regarding the experience with ovine ECM tricuspid reconstruction [11]. The proximal circumference of the tube graft was sutured to the tricuspid annulus by using three 5-0 Prolene running sutures, one for each of the three leaflet segments (Fig 1).

Data Acquisition

Measurements of APM force, right ventricular and atrial pressures, heart rate, and sonomicrometry data were acquired after hemodynamic stabilization, consisting of 40 minutes of reperfusion and weaning from bypass. No inotropic therapy or pacing was needed. The pressure catheters and the APM force transducer were calibrated before and after implantation. The force transducer was connected to data acquisition hardware (cDAQ 9172 and NI-9237, National Instruments Corp, Austin, TX). Sonomicrometry data was recorded with a digital circuit board (Digital Sonomicrometer (Sonometrics Corp). The electrocardiogram was monitored with the CardioMed data acquisition system (Model 4008; CardioMed A/S, Oslo, Norway). Papillary muscle force and hemodynamic data were recorded with virtual instrumentation software (LabVIEW version 10.0, National Instruments Corp).

Two recordings for 30 seconds each were performed. Echocardiography was performed before opening the pericardium (baseline) and after weaning off bypass to assess valvular competence.

Data Analysis

For offline analysis, all signals were ensemble averaged over ten heart cycles.

On the basis of sonomicrometry data, multidimensional scaling (MDS, CardioSOFT, and SonoXYZ, Sonometrics Corp) techniques were used [20]. Analog signals were converted to digital data by using dedicated software developed in LabVIEW (National Instruments Corp). Data were obtained from all 14 pigs, although papillary muscle sonomicrometry data were missing from 1 pig in the ECM group.

Annular segmental lengths were calculated by adding the distances between the relevant annular crystals. Each segment corresponds to the base of one leaflet (septal, anterior, and posterior segment) where it attaches to the annulus.

The ratio of the annular height to the commissural width was calculated as the ratio of the three most deviating crystals in systole (annular height from least square plane of all annular crystals) and from the distance between anteroseptal and anteroposterior commissures (commissural width) as described for the mitral valve [21].

The surface area of each leaflet was reconstructed from the leaflet edge crystal and three adjacent annular crystals. The four crystals divided each leaflet into two triangles, and the surface area was calculated by adding these triangular areas.

Mobility excursion angles were defined as the difference between the maximum and the minimum opening angle of each leaflet. The angle was determined as the angle between a line from one leaflet's midannular segment crystal, to the free edge leaflet crystal, and the annular plane.

Tenting area enclosed between two opposing leaflets (anterior-posterior, posterior-septal, anterior-septal leaflets) and the annular plane was determined in systole.

Table 1. Baseline Data for Native and Extracellular Matrix Animals

Baseline Measurements	Native (Mean ± SD)	ECM (Mean ± SD)	*p* Value
Weight (kg)	65 ± 1	64 ± 2	0.6
Mean arterial pressure (mm Hg)	62 ± 10	54 ± 14	0.2
Systolic blood pressure (mm Hg)	77 ± 9	80 ± 3	0.4
Diastolic blood pressure (mm Hg)	45 ± 7	49 ± 8	0.3
Heart rate (beats/min)	92 ± 7	94 ± 13	0.7
Clamp time (min)	66 ± 19	69 ± 8	0.8

ECM = extracellular matrix.

Statistical Analysis

Data are presented as mean ± standard deviation. Data did not follow a gaussian distribution and were therefore analyzed using the Mann-Whitney U test; $p < 0.05$ is considered statistically significant.

Results

Baseline data for native (control) and ECM (intervention) groups are shown in Table 1. All equipment was ex vivo found to be in correct position, except for one loose annular crystal in the native group, which was excluded. Valve competence was confirmed with epicardial echocardiography with no more than trace regurgitation (mild central jet in two native and two ECM valves). No animals needed pacing or inotropes at the time of data collection.

Hemodynamics and Anterior Papillary Muscle Force

No significant difference was observed between native and ECM groups in right ventricular pressures (32 ± 11 mm Hg vs 33 ± 11 mm Hg, $p > 0.1$) or transvalvular pressure gradient (22 ± 10 mm Hg vs 19 ± 12 mm Hg, $p > 0.1$). Peak systolic force measurement in the APM was significantly higher in the native valves (0.9 ± 0.6 N) compared with the ECM valves (0.3 ± 0.08 N, $p = 0.001$) (Fig 2).

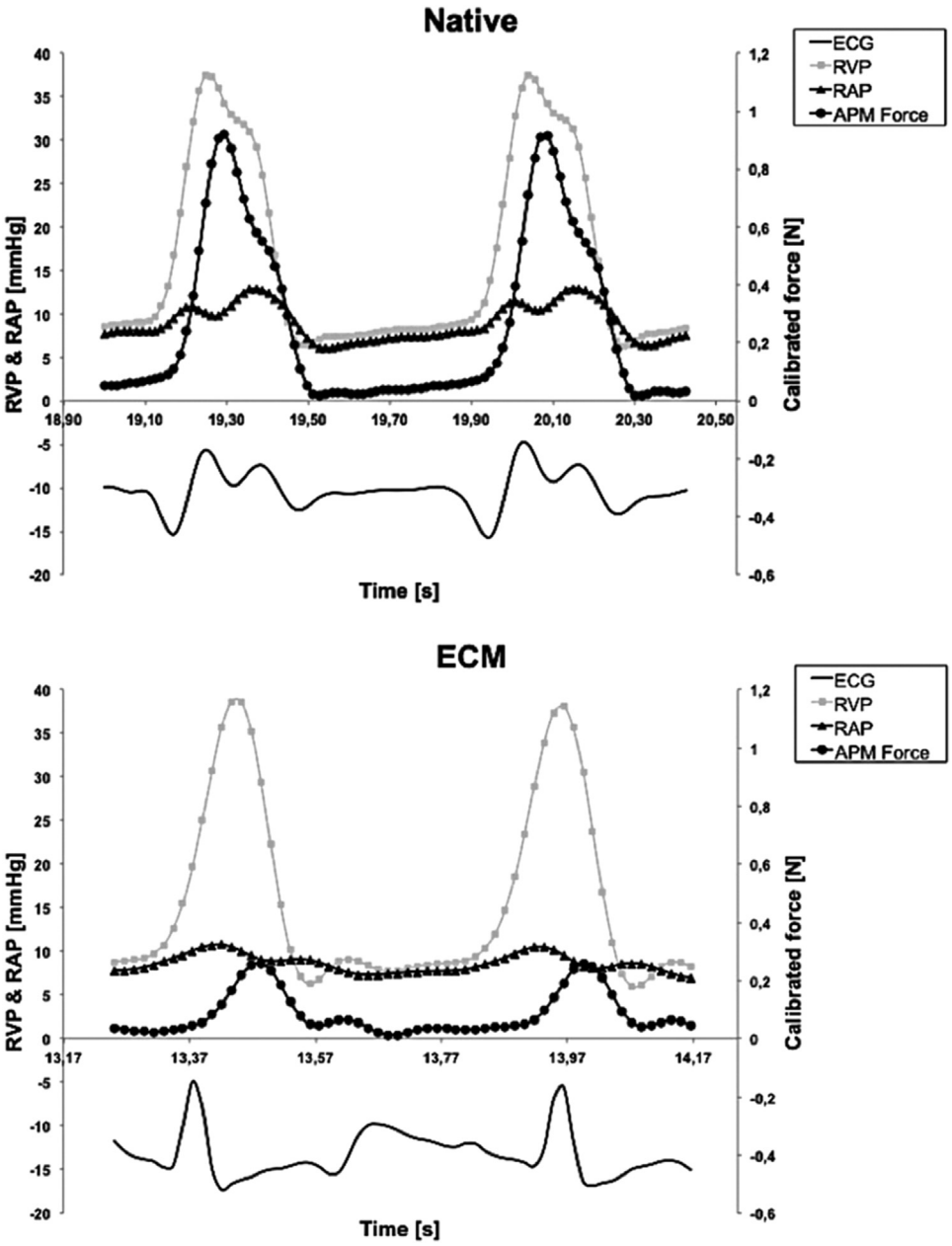

Fig 2. Representative curves illustrating right ventricular pressure (RVP), right atrial pressure (RAP), and anterior papillary muscle force (APM force) in one native and one extracellular matrix (ECM) valve.

Table 2. Comparison of Length of Annular Measurements and Relative Changes in Native and Extracellular Matrix Tricuspid Valves

Measurement	Native Max length (mm)	Native Min length (mm)	Native Change (%)	ECM Max length (mm)	ECM Min length (mm)	ECM Change (%)
Anterior segment	35 ± 9	27 ± 6	21 ± 6	30 ± 4	24 ± 4	20 ± 15
Posterior segment	34 ± 7	27 ± 5	20 ± 6	26 ± 12	22 ± 9	14 ± 10
Septal segment	47 ± 7	34 ± 5	28 ± 11	30 ± 5*	26 ± 4*	14 ± 9*
Annular circumference	99 ± 29	86 ± 26	13 ± 10	84 ± 15	76 ± 13	10 ± 13
Septal-lateral diameter	32 ± 4	27 ± 5	18 ± 9	20 ± 4*	17 ± 3*	13 ± 7
Septal-posterior diameter	29 ± 7	23 ± 6	21 ± 7	22 ± 3*	18 ± 5*	20 ± 21
Anterior-posterior diameter	36 ± 4	32 ± 4	13 ± 5	24 ± 5*	22 ± 5*	10 ± 7

* $p < 0.05$.

ECM = extracellular matrix; Max = maximum; Min = minimum.

Annulus and Saddle Height

The diastolic tricuspid annular circumference and -area appeared smaller in the ECM valves compared to native valves (84 ± 15 mm vs 99 ± 29 mm, $p = 0.1$; 391 ± 71 mm^2 vs 710 ± 154 mm^2, $p < 0.001$).

The length and shrinkage of the anterior annular segment and the posterior segment were similar. However, length and shrinkage of the septal segment were significantly smaller in the ECM valves (Table 2).

The three annular diameters in the tricuspid valve (septal-lateral, septal-posterior, and anterior-posterior diameters) were all significantly shorter in the ECM valves. The relative change in diameters from maximum to minimum during heart cycle was not different between valve types (Table 2).

The diastolic and systolic out-of-plane tricuspid annular deformation is shown in Figure 3, depicting each annular crystal's distance to the least square plane (LSP; mean plane from all six crystals). In native valves, the anteroposterior commissure, the anterior segment of the annulus, and the anteroseptal commissure were located higher above the LSP in midsystole compared with middiastole (approximately 1 mm). In ECM valves, the two-dimensional shape of the tricuspid annulus was similar in systole and diastole. The ratio of the annular height to the commissural width was similar in ECM and native valves, with the greatest difference in midsystole (11% ± 9% /10% ± 5%, $p = 0.8$, respectively).

In the native valve, the APM tip was 20 ± 5 mm from the anteroposterior commissure in middiastole, and it was 20 ± 7 mm in the ECM valve; in midsystole, this value was 24 ± 5 mm in the native valve and 24 ± 6 mm in the ECM valve. The same measurements were 18 ± 6 mm in the native valve and 16 ± 6 mm in the ECM valve (middiastole) and 25 ± 8 mm in the native valve and 20 ± 7 mm in the ECM valve (midsystole) between the posterior papillary muscle and the posteroseptal commissure. From the septal papillary muscle (SPM) to the anteroseptal commissure, the distance in middiastole was 24 ± 7 mm in the native valve and 16 ± 3 mm in the ECM valve, and in midsystole it was 30 ± 7 mm in the native valve and 20 ± 4 mm in the ECM valve. Only the distance from the SPM tip to the anteroseptal commissure was significantly different in the ECM valve ($p < 0.01$).

Leaflets and Subvalvular Structures

Leaflet surface areas of native and ECM valves were as follows: in the anterior leaflet, 340 ± 176 mm^2 in the native valves and 495 ± 211 mm^2 in the ECM valves ($p < 0.05$); in the septal leaflet, 410 ± 183 mm^2 in the native valves and 422 ± 249 mm^2 in the ECM valves ($p < 0.05$); and in the posterior leaflet, 257 ± 208 mm^2 in the native valves and 458 ± 219 mm^2 in the ECM valves ($p > 0.05$).

Mobility excursion angles of native and ECM valves were as follows: in the anterior leaflet, 21 ± 25 degrees for the native valves and 20 ± 20 degrees for the ECM valves; in the septal leaflet, 4 ± 57 degrees for the native valves and 13 ± 21 degrees for the ECM valves; and in the posterior leaflet, 19 ± 31 degrees for the native valves and/ 26 ± 29 degrees for the ECM valves ($p > 0.05$ for all angles).

Maximum and minimum tenting areas were not significantly different ($p > 0.05$).

Comment

The objectives of this study were to implant an ECM tube graft in the tricuspid position of pigs and to evaluate early biomechanical and physiologic performance in comparison with native tricuspid porcine valves.

The annulus of ECM valves was smaller in area and circumference. The size of the tube grafts was designed to replicate the native tricuspid annulus and was in accordance with the measurements of the maximum annulus circumference of the native tricuspid valve (Table 2). As seen in Table 2, implantation of the ECM valve resulted in segmental downsizing to 65% to 87% of native segment lengths. This suggests that the implantation technique resulted in circumferential shrinking and downsizing of the ECM tissue, mostly in the septal segment. On average, the ECM valve annulus was 20% ± 17% smaller. This can be explained by design and surgical technique because 30% of the circumference of the tube graft was

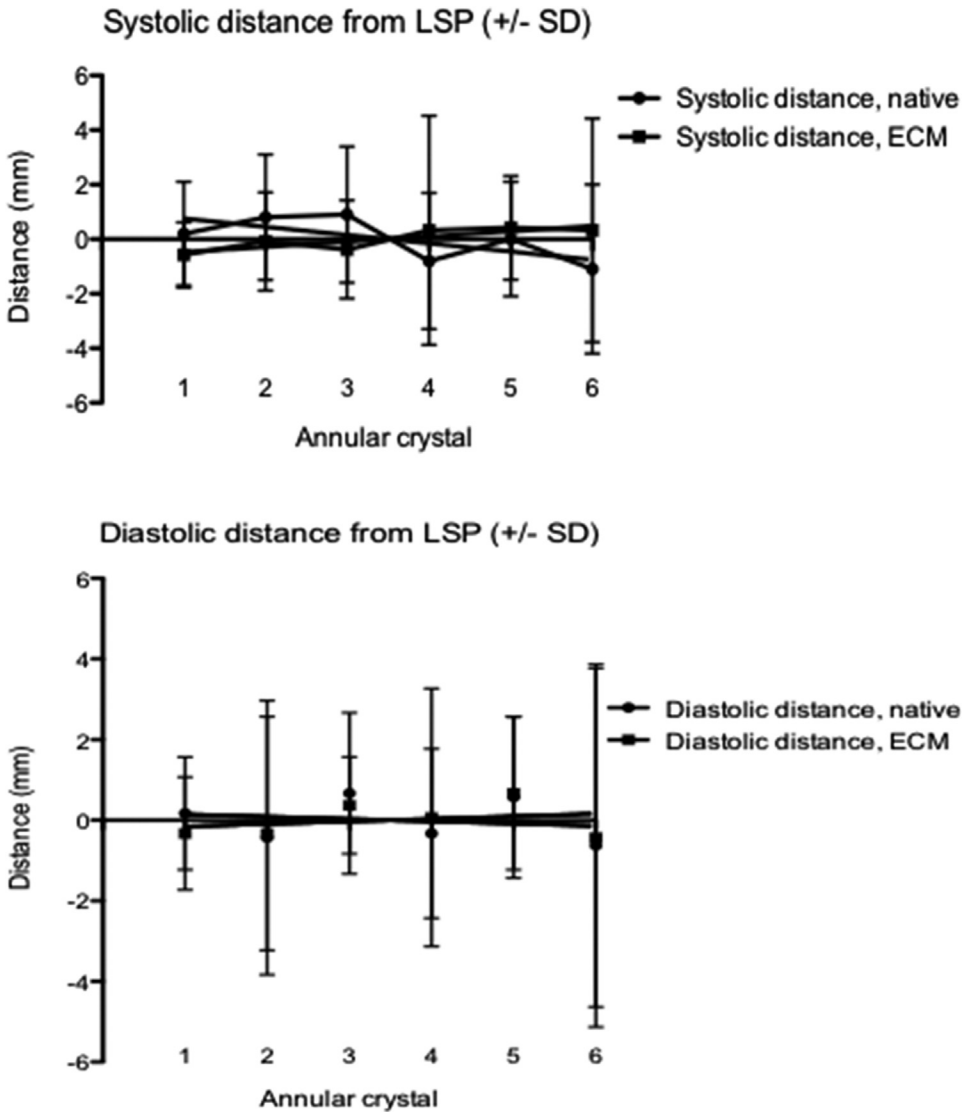

Fig 3. Average annular crystal distance to least square plane (LSP). Numbers relate to the crystals in Figure 1. $p > 0.05$. (ECM = extracellular matrix.)

chosen for the septal annulus, and the septal segment was the last to be sutured. Despite the mainly downsized septal segment and the significantly shorter annular ECM diameters, the relative change in length of the diameters was equal between ECM and native valves, a finding suggesting normal annular contraction during the heart cycle in the ECM valve. The downsizing effect may explain the smaller distance from the SPM to the anteroseptal commissure seen in ECM valves.

The septal annulus should probably receive relatively more of the ECM tube graft circumference compared with the posterior annular segment, to reach a more physiologic distribution of segment lengths. We suggest choosing 40% of the circumference for the anterior and septal segments each and 20% for the posterior segment. Another possibility is a systematic oversizing of tube grafts, although adjustment of the tube length in that case is necessary. Worthy of consideration is using locked or interrupted sutures to avoid the plication and downsizing seen in this study, although continuous approximation ensuring tissue-to-ECM contact is favored.

Fawzy and colleagues [22] performed complete mapping of the tricuspid valve in 5 40-kg pigs by using sonomicrometry. In that study, the anterior, posterior, and septal segments changed 16%, 13%, and 10% in length, respectively. In this study, these changes were 21%, 20%, and 28%, respectively, in native valves (Table 2). In both studies, the septal segment was the longest and the anterior segment the shortest.

The three-dimensional shape and motion of the annulus in relation to the LSP are not significantly different between valve types, and especially the diastolic distances from the annular crystals to the LSP show similar patterns. In systole, it seems that the out-of-plane annular deflection is greater in the native valves compared with the ECM valve, a finding suggesting additional annular fixation by the ECM valve (Fig 3). This finding may be explained by the shortening of the septal

segment and commissure resulting from the inherent septal downsizing. It is plausible that choosing an oversized tube graft would cause less annular fixation.

The maximum APM force was significantly lower in the ECM valve compared with the native valve. This difference could reflect the significant downsizing of the tricuspid annulus, thus resulting in smaller leaflet orifice areas exposed for the transvalvular pressure difference. Another explanation could be the length of the tube graft. The distance between the papillary muscle tips and the commissures tended to be larger in the ECM valve compared with the native valve, although not significantly. Changing the subvalvular attachment could also affect the papillary muscle tethering forces and thereby affect the APM force measurements.

The present analysis of the native tricuspid annulus geometry is in accord with previous observations [19, 22], suggesting that the annulus conforms into a multiplanar shape in systole. In this study, implantation of the ECM valves resulted in a universal downsizing of the tricuspid annulus circumference. However, leaflet function in terms of tenting areas, mobility excursion angles, and leaflet areas was similar in native and ECM valves. The anterior leaflet area is the only parameter significantly different between valves. This is probably because of the design, with 40% of the tube graft dedicated to the anterior leaflet.

Previous in vitro studies of ECM and native tricuspid valves suggested that function and biomechanical behavior were similar in the two valve types regarding coaptation geometry and force development in the papillary muscles [23]. It was found in vitro that systolic force in the APM was lower, although not significantly, in the ECM valve compared with the native valve (0.7 ± 0.4 N vs 1.1 ± 0.2 N, $p = 0.07$). In the present in vivo study, this difference was significant. We measured forces only in the APM in this study because pilot studies demonstrated that three force transducers compromised right ventricular function.

Study Limitations

The major limitations of this study are those of an acute animal model. Biomechanical changes of the ECM and potential compensatory changes in the right ventricle and subvalvular attachment were not considered. The animals were anesthetized and studied in open-chest conditions. Furthermore, the implanted crystals and force transducer may have compromised tricuspid valve motion. The downsizing effect of the ECM implantation produced a limitation when aiming to compare ECM and native tricuspid valve geometry.

Conclusions

In conclusion, an ECM tricuspid tube graft can be implanted in pigs and immediately function with hemodynamics, three-dimensional annular and leaflet motion, coaptation geometry, and subvalvular function comparable to those of native porcine valves. We anticipate that the restrictive annulus remodeling effect after tube graft implantation may be potentially beneficial by relieving tension on the repaired tissue and protecting repair durability. Alternatively, oversizing of the tube graft to compensate for the downsizing of ECM valve implantation should be considered when aiming for physiologic valve performance. Currently, animal survival studies are in progress with varying observational periods, aiming to characterize the long-term behavior and durability of the ECM tricuspid tube graft.

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INVITED COMMENTARY

Several years ago, I was shown a video made in the laboratory of Dr James Cox, from 1993. A cylinder of intestinal submucosa was implanted as a tricuspid valve in a pig. We and others had since begun using Cormatrix decellularized extracellular matrix (ECM) for cardiac reconstruction. Ovine studies revealed positive histologic remodeling for tricuspid ECM cylinder valves. Dr Rao performed the first in-human implant in November 2011, and it continues to function normally today. Last year, we published the retrospective clinical experience of 12 surgeons implanting 19 valves. Most recently, the Food and Drug Administration approved a clinical trial to prospectively evaluate the performance of CorMatrix ECM tricuspid valves. Refinement of technique and design is expected, and that makes the present study by Ropcke and colleagues [1] particularly timely.

This acute porcine study examines the immediate function of a tubular, stentless ECM tricuspid valve and analyzes its mechanics. The authors performed three-dimensional measurements of the functioning valve leaflets, annulus, and subvalvular apparatus with sonomicrometry and intracavitary pressure transducers and compared the test article with native tricuspid valves in 26 animals. No difference in intracavitary pressures, leaflet excursion, or annular motion was found between groups. However, the annular size was smaller in the test group, with an average reduction of 20%. That may be due to suturing technique. Whether that can or should be avoided in the future is undetermined. Addressing pathology involving the tricuspid valve often requires some annular reduction. The annulus, however, does retain much of the normal movement during the cardiac cycle, a characteristic exclusive to this dynamic device. The maximum anterior papillary muscle force is less in the ECM valve. Identification of force variability may prove important to design, as ECM cellularization is dependent on force transduction through the ECM. That may also apply to the effect of annular downsizing. The current device includes a seam, which is typically placed at the septal papillary muscle and may play a role in the papillary tip to commissure distance discrepancy identified.

No current valve prosthesis provides the requirements for a perfectly functioning heart valve. The traditional ex-vivo tissue engineering approach of combining cells with a three-dimensional scaffold and conditioning in a bioreactor before insertion has failed to produce a valve that is cost effective, readily available, and capable of growth. Although an in-vivo regenerating valve is an exciting prospect, it comes with inherent obstacles. It must function immediately and perfectly. Unlike those conditioned in a bioreactor, it must continue to function during the remodeling period and result in normal cellularity. The final result must not be a valve that resembles a normal valve, but a truly regrown functioning valve that no longer contains any foreign material. This study by Ropcke and colleagues [1] provides insight into the first component: immediate function. Furthermore, it identifies opportunities for optimizing early performance, which may translate into better long-term function. Of course, detailed long-term follow-up will be needed to determine whether normal histologic and mechanical valve characteristics can be realized.

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Dr Gerdisch discloses a financial relationship with Cormatrix.

Reference

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