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Mid-term function and remodeling potential of tissue engineered tricuspid valve: Histology and biomechanics

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ABSTRACT

Objective: Tricuspid valve reconstruction using a small intestinal submucosal porcine extracellular matrix (ECM) tube graft is hypothesized to be durable for six months and show signs of recellularization and growth potential. The purpose was to histologically and biomechanically test ECM valves before and after six months of implantation in pigs for comparison with native valves.

Methods: Ten 60 kg pigs were included, which survived tricuspid valve tube graft insertion. Anterior and septal tricuspid leaflets were explanted from all animals surviving more than one month and examined histologically (n = 9). Endothelialization, collagen content, mineralization, neovascularization, burst strength and tensile strength were determined for native valves (n = 5), ECM before implantation (n = 5), and ECM after six months (n = 5).

Results: Collagen density was significantly larger in ECM at implantation (baseline) compared to native leaflet tissue ($0.3 \pm 0.02 \text{ mg/mm}^3$ vs. $0.1 \pm 0.03 \text{ mg/mm}^3$, $p < .0001$), but collagen density decreased and reached native leaflet collagen content, six months after ECM implantation (native vs. ECM valve at six months: $0.1 \pm 0.03 \text{ mg/mm}^3$ vs. $0.2 \pm 0.05 \text{ mg/mm}^3$, $p = .8$).

Histologically, ECM valves showed endothelialization, host cell infiltration and structural collagen organization together with elastin generation after six months, indicating tissue remodeling and -engineering together with gradual development of a close-to-native leaflet structure without foreign body response. **Conclusions:** ECM tricuspid tube grafts were stronger than native leaflet tissue. Histologically, the acellular ECM tube grafts showed evidence of constructive tissue remodeling with endothelialization and connective tissue organization. These findings support the concept of tissue engineering and recellularization, which are prerequisites for growth.

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1. Introduction

Tricuspid valve replacement is still a problematic procedure due to the thromboembolic risk in the low-pressure and low-velocity area of the right side of the heart. Development of materials for both valve repair and valve reconstruction with bio-regenerative potential has been a centre of attention for many years (Yacoub and Cohn, 2004). Apart from biological tissue compatibility,

hemodynamic and functional properties comparable to native valve function are favoured as well (Sacks et al., 2009).

The concept of tissue engineering has led to the development of an acellular bioscaffold composed of porcine small intestinal submucosal extracellular matrix (ECM). The material is believed to possess growth potential, and thrombogenicity has proven low (Badyaluk, 2007). ECM has shown no scar tissue formation, no calcification, and has the potential for integration with human native tissue (Scholl et al., 2010).

A tricuspid tube graft has been developed for total valve reconstruction using ECM. In previous studies, a tubular design has shown favourable flow dynamics and stress distribution (Cox et al., 2005). Total reconstruction of the tricuspid valve using this

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type of ECM has been described in sheep (Fallon et al., 2014; Zafar et al., 2015) and pigs (Ropcke et al., 2016 Jan) with a postoperative competent valve and normal leaflet motion.

In 2014, the first early human experience with total ECM tricuspid valve reconstruction was published in 19 patient cases of endocarditis not repairable by conventional surgery (Gerdisch et al., 2014). Follow up was up to 18 months with no more than mild regurgitation. No heart block or deaths occurred.

The understanding of the biomechanical behaviour of the material in both short and long term follow-up is still very limited. Therefore, the purpose of the present study was to histologically and biomechanically evaluate and compare native and ECM tricuspid valves in a porcine model during a 6-month follow-up.

2. Material and methods

2.1. Animals

Twenty-five Danish Landrace pigs (60 kg) underwent ECM tricuspid tube graft valve implantation (Fig. 1). Two pigs were excluded due to pericarditis. Thirteen pigs died within the first 24 h; 7 from ventricular fibrillation, 4 from massive thrombosis around the ECM valve, 1 from malignant hyperthermia and 1 from laryngeal spasms at extubation. After institution of postoperative anticoagulation (Heparin i.m. 20,000 units once a day, pig 14–25), only one case of valve thrombosis was seen. The remaining 10 animals comprised the study population.

Five animals survived for six months and were euthanized according to protocol. Five weight-matched animals were used as control group.

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

2.2. Study population

Histology was performed on nine animals surviving more than one week. Biomechanical analysis was performed on the five animals surviving six months. ECM material before implantation (ECM baseline) was examined histologically and biomechanically (n = 5).

Normal native tricuspid valves from weight-matched pigs were examined as a control group both histologically and biomechanically (n = 5).

Blinding was not possible due to quite distinct visual differences between groups.

2.3. ECM tube graft

The tube graft ECM material was an acellular, non-cross linked, 4-ply sheet of small intestinal submucosal extracellular matrix from pigs (CorMatrix® Cardiovascular Inc., Alpharetta, GA, USA). The ECM valves were provided as fixed-sized tube grafts (height = 3.5 cm, circumference = 10.0 cm) (Fallon et al., 2014) and designed to replicate weight-adjusted dimensions of the native valve in humans (Silver et al., 1971; Tei et al., 1982), and animals (Hiro et al., 2004). The valves were constructed from a flat sheet of ECM, which were folded into a tubular shape by suturing the two edges together. Hereafter the tube was implanted as a cylinder valve (Fig. 2) with three distal fixation points in the ventricle (one on each papillary muscle) and a circular fixation in the annulus, using 5–0 Prolene.

The three leaflet parts were sized with 40% of the tube circumference for the anterior leaflet and 30% for the two remaining leaflets each. This distribution was based on experience with ovine ECM tricuspid reconstruction (Fallon et al., 2014).

2.4. Surgery

Premedication, transportation, anaesthesia and porcine tricuspid surgery through the right atrium have been described in details previously (Fallon et al., 2014; Ropcke et al., 2016 Jan). All animals were operated through a median sternotomy. Cold blood cardioplegia was used for cardiac arrest, and extracorporeal circulation (ECC) was established using bicaval cannulation and arterial cannulation in the ascending aorta.

2.5. Valve explantation

At study termination, a re-sternotomy was performed, and the heart was eviscerated. The tricuspid valve including annulus and papillary muscles was excised and photographed (Fig. 3). The anterior leaflet was rinsed in saline and cut vertically in two, one for histology and one for biomechanical analysis. Specimens for histology were stored in formalin, while specimens for biomechanical analysis were stored in a freezer between two layers of thin plastic sheets. Testing was performed within two weeks after explantation.

2.6. Stress strain analysis

From the anterior tricuspid leaflet, three 3 mm wide strips were cut in circumferential direction (parallel to the annulus) with a multicutter. The thickness of the central part of each strip was

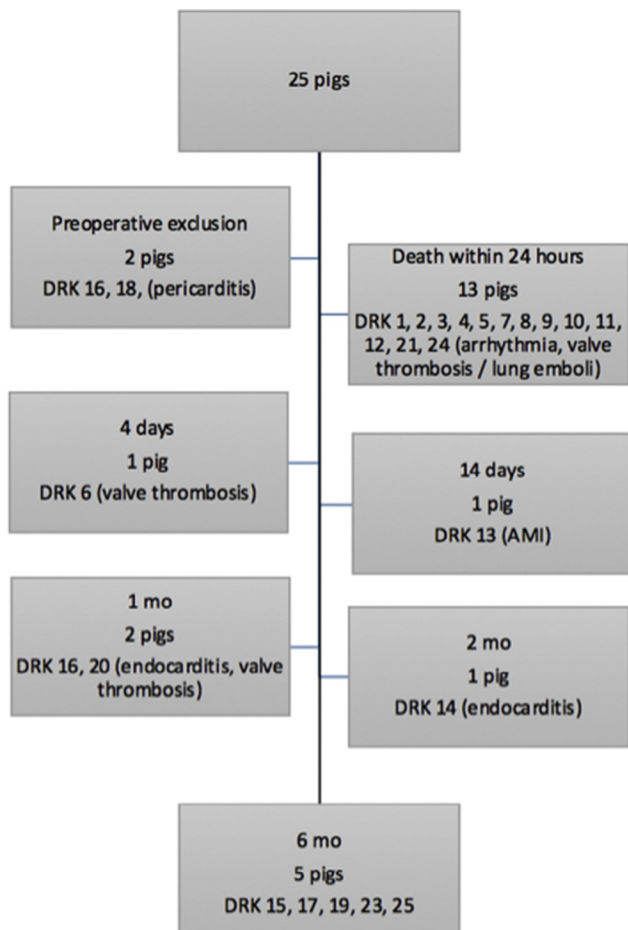


Fig. 1. Flow chart showing inclusion and exclusion/dropout during the study. "DRK x" is the name of each animal. AMI = acute myocardial infarction, mo = month(s).

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