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Decellularized Tissue-engineered Heart Valves

-as novel off-the-shelf homologous valve replacements-

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Introduction

Biological valve prostheses are created from decellularized xeno- or homografts, which are either associated with the risk of immunogenic reactions and disease transmission (xenografts) or low availability (homografts). Tissue-engineered heart valves (TEHV), based on largely available biodegradable synthetic scaffolds, have no risk for disease transmission and have shown promising results in-vivo [1,2]. Though, substantial regurgitation (fig. 1A) is observed due to cell-mediated retraction of the leaflets (fig. 2A&B).

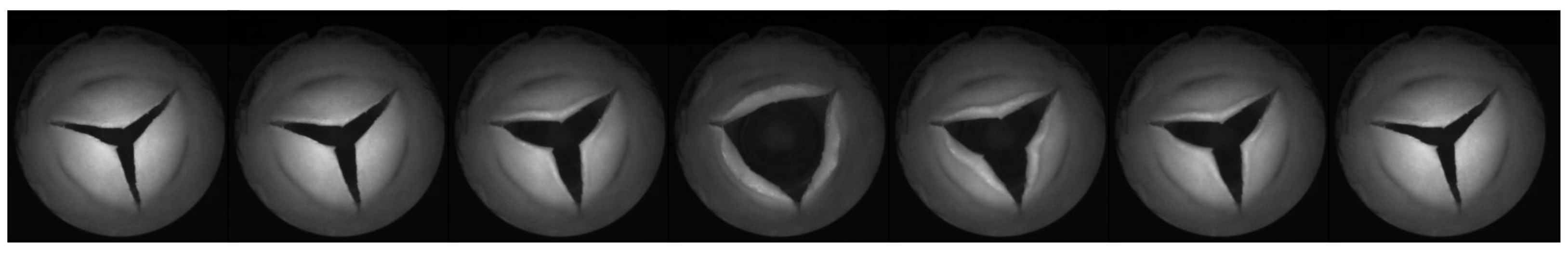

Fig. 1: in-vitro functionality of TEHV. Closure was hampered by retraction of the leaflets, resulting in substantial regurgitation.

Aim: We propose to decellularize TEHV in order to create off-the-shelf homologous valve replacements without cell-mediated retraction or graft related limitations.

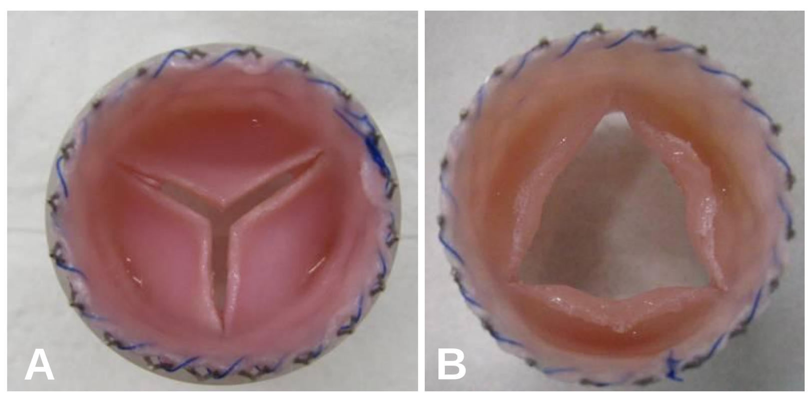

Fig. 2: Retraction of the cell-populated leaflets occurs immediately after separation of the leaflets (A) and increases after 20 minutes in-vitro functionality testing (B).

Methods & Materials

TEHV (n=11), based on rapid degrading scaffolds, were engineered from ovine vascular-derived cells. After 4 weeks in-vitro culturing, TEHV (n=8) were decellularized. Either directly (n=6) or after 18 months storage (n=2), valves were analyzed for cell removal and preservation of ECM by histology and biochemical assays. Additionally, mechanical properties and in-vitro functionality were tested and compared to their cell-populated counterparts (n=3).

Results

After decellularization, in-vitro valve functionality was improved (fig. 3) due to reduced retraction of the leaflets (fig. 4A&B). Histology demonstrated the removal of all cells and

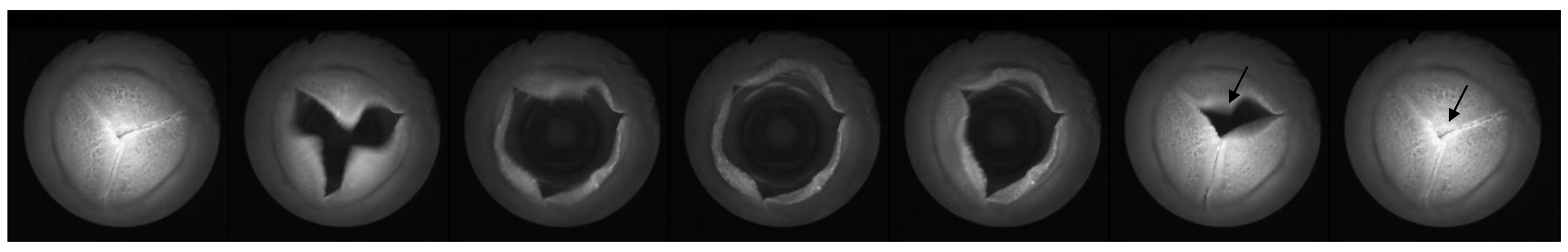

Fig. 3: Decellularized TEHV showed proper opening and closing behavior during in-vitro functionality testing. Only subtle prolapse was observed (black arrows).

F-actin after decellularization (fig. 5A vs E & 5B vs F) without altering the collagen structure (fig. 5C&D vs 5G&H), which was confirmed by biochemical analysis (fig. 6A). GAG content decreased by decellularization. Although leaflet stiffness increased, the tissue strength was not affected by decellularization (fig. 6B). Storage of the decellularized TEHV for 18 months did not affect the biochemical contents or bio-mechanical properties (fig. 6A&B, respectively).

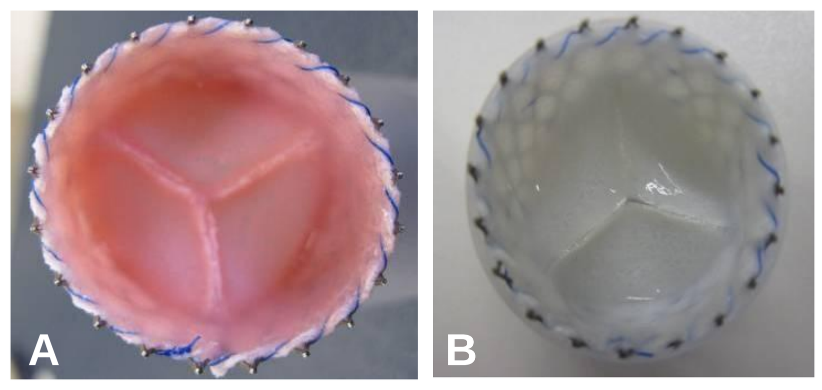

Fig. 4: Retraction of the leaflets was absent in the decellularized TEHV (A) even after 24 hours in-vitro functionality testing (B).

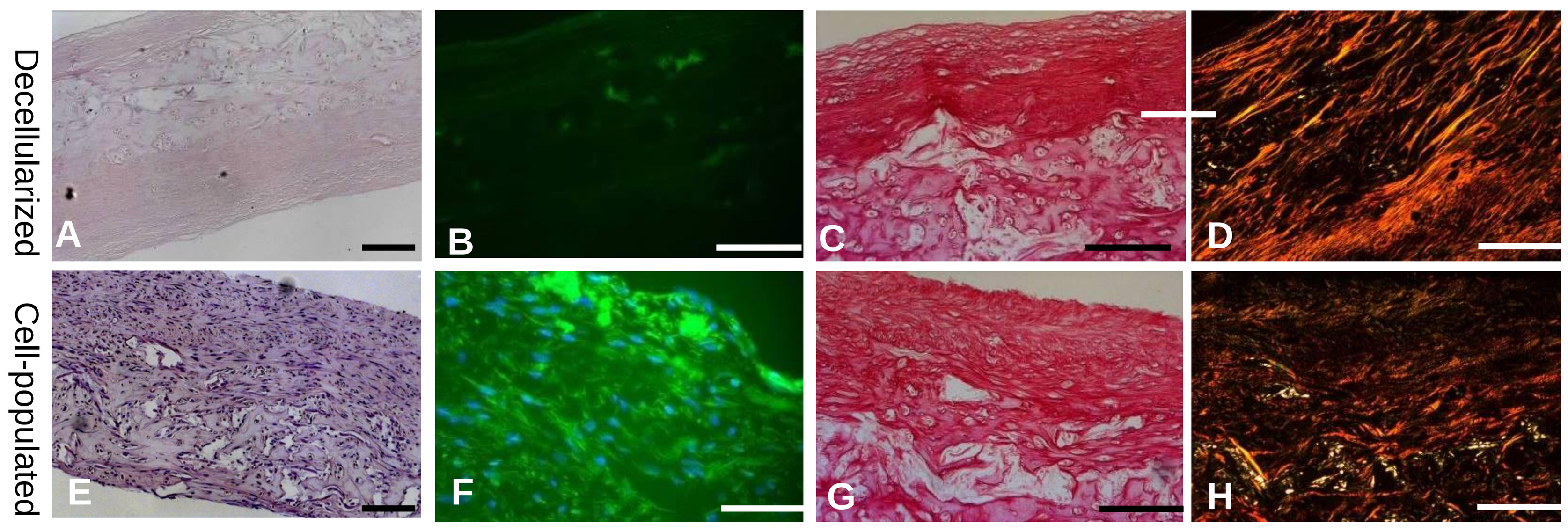

Fig. 5: Representative images of H&E staining (A,E), Phalloidin and DAPI staining (B,F), Picrosirius red staining visualized by transmitted light (C,G), and Picrosirius red staining visualized by polarized light (D,H) of the leaflets. Scale bars represent 200µm.

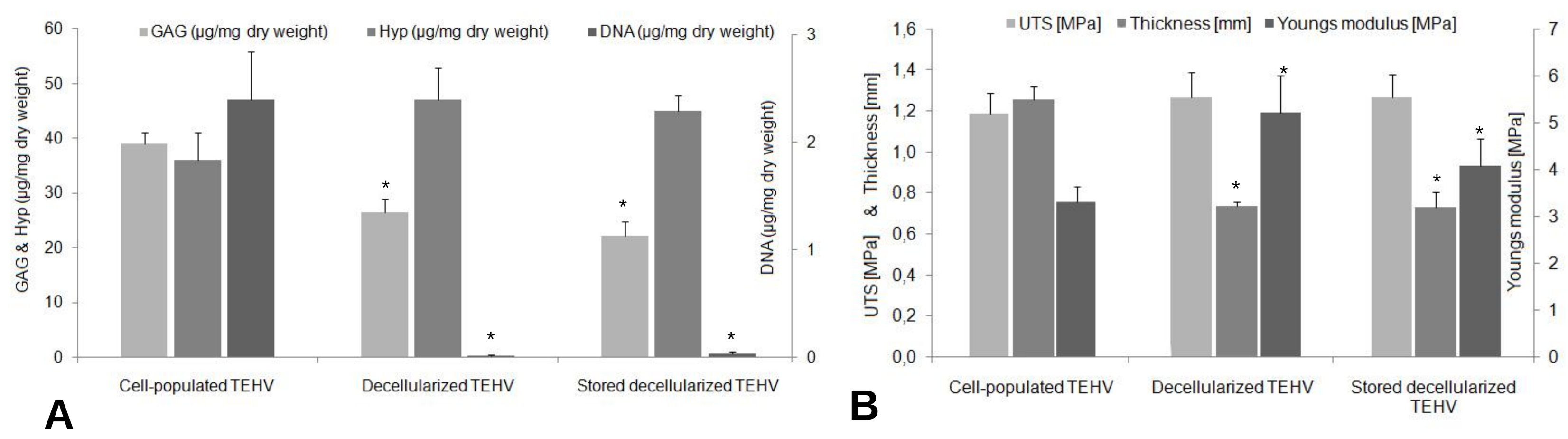

Fig. 6: (A) Biochemical and (B) biomechanical analyses of the cell-populated, decellularized, and stored decellularized TEHV leaflets. (*significant difference compared to the cell-populated TEHV, $p<0.05$)

Conclusions

Decellularization of TEHV is feasible with efficient cell removal and preservation of collagen structure and tissue strength. Reduced retraction improved valve functionality. No changes upon storage enables off-the-shelf availability. We hereby provide largely available homologous valve replacements, which can serve as alternative starter matrices to homo- and xenografts.

References
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SEVENTH FRAMEWORK PROGRAMME
LifeValve
dpte Dutch Program for Tissue Engineering