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Extended *in-vitro* protocols for TEHV
-Implanted by Minimally Invasive Procedures-

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**Introduction**

Tissue engineering of heart valves, based on rapid degrading polymer scaffolds, and minimally invasive valve replacement procedures represent promising technologies for patients with valvular heart disease. The successful merging of these novel technologies was demonstrated in a large animal model previously [1]. However, local irregularities and thickening of the TEHV were observed after explantation (Fig. 4), of which the first may be partly due to separation of the leaflets shortly before implantation (Fig.1&2).

We hypothesized that overgrowth of the separation areas before implantation could reduce the *in-vivo* development of irregularities on the leaflets tips. Therefore, we investigated the influence of an advanced *in-vitro* methodology on valve performance.

**Methods**

Trileaflet heart valves (n=4, ØID 28mm), based on rapidly degrading polymer scaffolds and self-expandable stents, were engineered from ovine vascular derived autologous cells. Valves were grown *in-vitro* for 13 days, as described previously [1]. To overgrow the separation areas, TEHV were cultured for an additional 6 days after separation of the leaflets utilizing combined strain-flow bioreactor systems (an adaptive version of the diastolic pulse duplicator systems [2]). After crimping (Fig.1) two valves were delivered minimally invasively (mini-thoracotomy, trans-apical approach) in pulmonary position in sheep. Valves were explanted after 4 and 7 weeks.

**Results**

The advanced culture methodology indeed demonstrated the expected overgrowing of the separation areas (Fig.3).

Moreover, improved *in-vivo* performance (initial pressure gradients were 10 mmHg instead of 20 mmHg) was evident directly after implantation. However, the explant outcome was similar to the previous explants (Fig.4) and excessive remodeling was observed.

**Discussion**

The improved *in-vitro* methodology, to reduce the *in-vivo* thickening response, covered the leaflet tips with a sufficient tissue layer. Moreover, the initial *in-vivo* valve performance was promising. Nevertheless, there was no improvement regarding the excessive remodeling previously found after explantation. Although representing only a preliminary *in-vivo* study, we conclude that the local irregularities after implantation are not directly related to the separation of the leaflets and further research is necessary. Moreover, extended studies have to be initiated to clarify the *in-vivo* remodeling response.

**References**