Straining-mode dependent collagen remodeling in engineered heart valve tissue

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Introduction

Tissue engineered heart valves often lack sufficient amounts of functionally organized collagen fibers and consequently do not meet in vivo mechanical demands. To improve collagen remodeling, and hence mechanical properties, the effects of **two modes of mechanical conditioning**, being either **static or dynamic**, were quantified for several indices of collagen remodeling.

Material and methods

Rectangular strips (35x5x1 mm) of PGA/P4HB were seeded with human venous myofibroblasts and constrained at the outer ends (static strain). The effect of uniaxial dynamic straining (4%, 1Hz) (fig. A) was investigated on 1) the secretion of **collagen remodeling markers** for synthesis and degradation, differences in 2) **collagen** and 3) **cross-links** on gene expression and protein levels and 4) tissue **mechanical properties.**

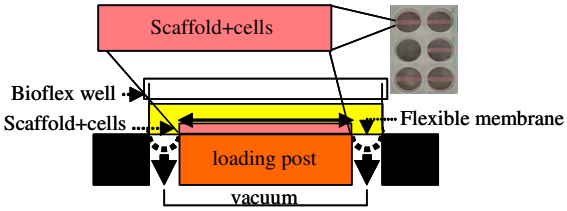

Figure A FlexCell straining device. By applying vacuum, engineered tissues are uniaxially stretched over a loading post.

Results

1) Dynamic conditioning enhanced both collagen synthesis and degradation compared to static conditioning (fig. 1).

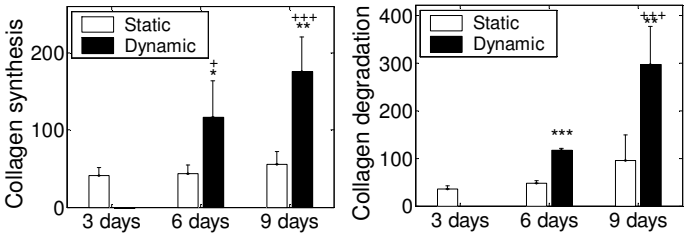

Figure 1 Markers for collagen synthesis (left) and degradation (right) of dynamically conditioned samples increased with time and were higher compared to statically conditioned samples.

2) Dynamic conditioning downregulated collagen mRNA expression and collagen content (fig. 2), but 3) enhanced both cross-link mRNA expression and content (fig. 3).

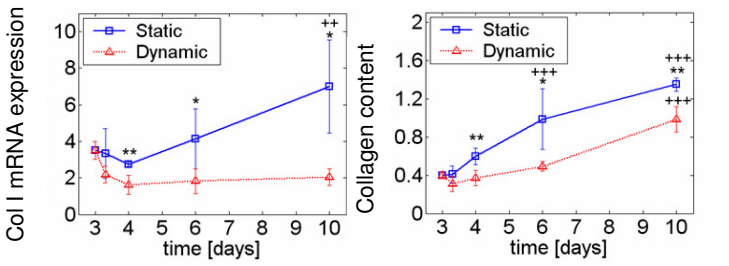

Figure 2 Collagen I mRNA expression (left) and content (right)

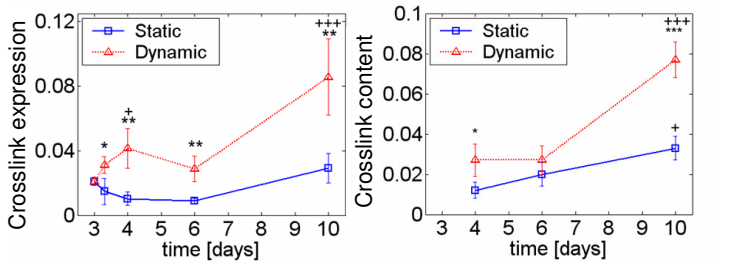

Figure 3 Cross-link mRNA expression (left) and content (right).

4) Dynamic conditioning for 4 weeks increased cross-link densities, correlated to higher moduli. No difference in the amount of collagen was found (fig. 4).

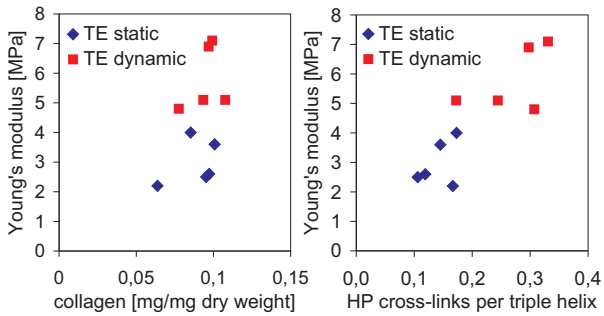

Figure 4 Dynamic conditioning did not change collagen amounts (left), but increased cross-link densities and mechanical properties (right).

Conclusions

- Gene expression results correspond to protein data.
- Compared to static conditioning, dynamic conditioning resulted in:

1) higher collagen remodeling activities, 2) lower collagen expression and content, but 3) enhanced collagen cross-link expression and density, correlated to 4) improved mechanical properties.

- Straining-mode dependent remodeling responses can be used to balance collagen and cross-link production and, thus, to fine-tune tissue mechanical properties via mechanical conditioning protocols.