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The role of collagen cross-links in biomechanical behavior of human aortic heart valve leaflets - *Relevance for tissue engineering.*

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Introduction

In native heart valves, the anisotropic matrix architecture assures sustained and adequate functioning under high pressure conditions. Collagen, being the main load bearing matrix component, contributes significantly to the biomechanical strength of the tissue. In tissue engineering (TE) the collagen amount is commonly taken as a measure for tissue development. This study investigates the relation between collagen content, collagen cross-links, and biomechanical behavior in human aortic heart valve leaflets, as a benchmark for cardiovascular TE.

Materials and Methods

Analysis - Function

The mechanical properties (modulus of elasticity (E), ultimate tensile stress (UTS) and strain at break (ε_{max})) of human aortic valve leaflets (n = 9) were assessed by uniaxial tensile experiments in two directions.

Analysis - Structure

Corresponding collagen amounts and collagen cross-link concentration was determined using an amino acid analysis.

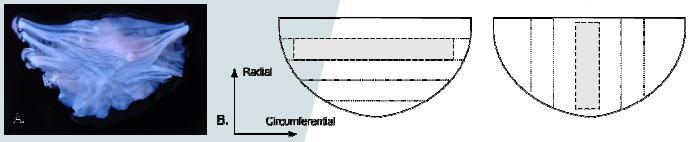
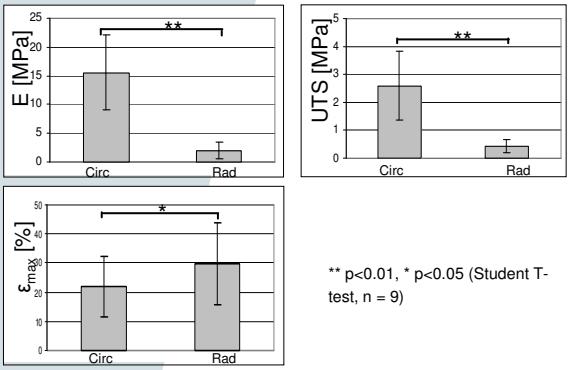


Figure 1. A. Aortic valve leaflet. B. Local orientation of tensile test strips in circumferential and radial direction.

Results and Discussion

Function



** p<0.01, * p<0.05 (Student T-test, n = 9)

Figure 2. Biomechanical properties of human aortic valve leaflets

The data above were consistent with recently published values [1], and clearly show anisotropic behavior. A high diversity was observed among and within the heart valve leaflets, possibly related to the large biological variations in gross fiber architecture.

Structure–function relation

Figure 3 suggest that the number of cross-links, rather than the amount of collagen, is correlated to the tissue's modulus in circumferential direction. In radial direction, however, this correlation was not observed.

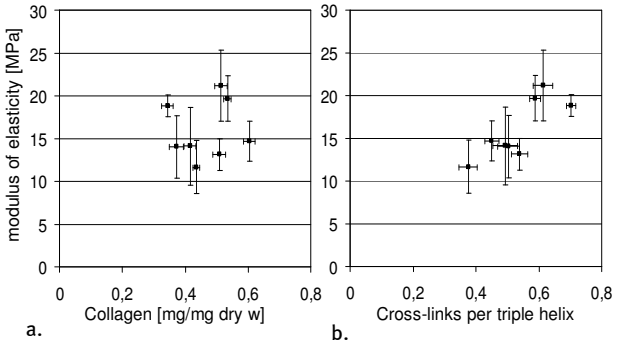


Figure 3. Data of heart valve leaflets in circumferential direction (n = 9). a. No correlation between modulus and amount of collagen (r = 0.05, p = 0.80). b. Positive linear correlation between modulus and cross-links per triple helix (r = 0.58, p < 0.005). Each marker represents one valve (n = 4).

This directional difference may imply that collagen cross-links act in conjunction with collagen fiber orientation in providing strength.

Comparison Native – TE constructs

The collagen content and the number of cross-links in TE constructs (2 groups: static/dynamic straining), are lower compared to native tissue (fig. 4a). The dynamically strained group had similar values of collagen content as the static group, while the number of cross-links and the modulus are higher (fig. 4a,b.). A linear trend is observed in the cross-link-modulus correlation of TE constructs towards that of native valves, suggesting a dominant role of cross-links in tissues mechanical properties.

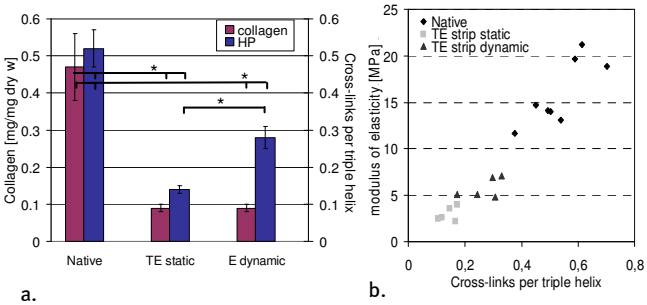


*Figure 4.a. Collagen and cross-link data for native tissue and TE constructs (Rubbens, 2006). * p < 0.01 b. Linear trend in modulus versus cross-links of native valve leaflets and TE constructs.*

Conclusion

Native valve and tissue engineering data have shown that collagen cross-links are stronger predictor of tissue strength than collagen amount itself. This new insight broadens the focus in TE to follow the development in time of the collagen architecture as a whole, and specifically collagen cross-links.

References

[1]. Stradins, Eur J Cardiothorac Surg. 2004 Sep;26(3):634-9.