heart valves was demonstrated to result in leaflet shrinkage, a problem commonly observed in animal studies, and resulted in regurgitation of the valve and loss of function. This symposium offers a platform to discuss the pros and cons of cell traction in valvular and vascular tissue engineering. We hope to share insights on its fundamentals and to work towards fine-tuning of this delicate balance between cell traction, extracellular matrix properties and hemodynamics towards functional valvular and vascular tissue engineering.

(9.KP) CELL TRACTION: THE PROS AND CONS IN VALVULAR AND VASCULAR TISSUE ENGINEERING

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Valvular and vascular tissue engineering rely on extracellular matrix production by cells seeded into a degrading scaffold material. The seeded cells adapt a myofibroblast phenotype, characterized by synthetic as well as contractile activity, and naturally exert traction forces to their surroundings. In nature, these surroundings are capable of withstanding these forces by the hemodynamic environment the tissue is in (e.g. pressure), the degree of constraint of the tissue (e.g. blood vessels are constrained in axial direction), and the extracellular matrix properties (both composition and mechanical behaviour). Tissue engineering has made us realize how delicate this balance in nature is. Cell traction on the one hand is shown beneficial for tissue maturation and alignment in engineered tissues, while on the other hand is causing loss of shape.

The keynote lecture will give an overview on the physiological and pathophysiological mechanisms of tissue shrinkage in general and specifically the relevance of these factors on cardiovascular tissue engineering. Furthermore the three major factors of tissue engineering (1) cells, (2) scaffolds and (3) stimuli will be analyzed with regard to their influence on tissue retraction.

(9.O1) ENDOGENOUS TISSUE CONTRACTILITY SPATIALLY REGULATES THE VEGF SIGNALING AND ANGIOGENESIS IN SELF-ORGANIZING MICROFABRICATED TISSUES

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Endogenous physical forces can drive the organization of tissues (1-2). The underlying mechanisms are currently based on cell surface mechanics (3) or mechanotransduction (4) and are thus separated from known conserved mechanisms including the formation of morphogen gradients. Here using an array of autonomously contracting and deforming, 3D, microfabricated, tissues, we show that tissue geometry and endogenous contractility spatially regulates the Vascular Endothelial Growth Factor (VEGF) signaling and the local formation of vascular patterns. The microfabricated tissues stereotypically and heterogeneously changed shape, compacted and formed robust patterns of vascular structures in regions of high deformation. This emergence correlated with the local over-expression of the receptor VEGFR2 and with the formation of a tissue-scale gradient of VEGF. We propose that endogenous tissue contractility and deformation is a morphogenetic regulator of angiogenesis, a finding which should stimulate new therapeutic strategies for vascular diseases and regenerative medicine.

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Keywords. vascular pattern, endogenous contractility, VEGF signaling

(9.O2) THE POTENTIAL OF PROLONGED TISSUE CULTURE TO REDUCE STRESS GENERATION AND RETRACTION IN ENGINEERED HEART VALVE TISSUES.

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Introduction. Tissue engineered heart valves develop a good tissue architecture, induced by traction forces, when cultured constrained. However, during culture cell traction causes tissue compaction, resulting in leaflet flattening. At time of implantation, the leaflets have to be separated and cell traction causes leaflet retraction. To get insight into these mechanisms and to develop solutions, we have developed an in vitro model system to quantify and correlate stress generation, compaction, retraction and tissue quality during a prolonged culture period of 8 weeks.

Methods. PGA/P4HB strips were seeded with vascular-derived cells and cultured for 4, 6 and 8 weeks (n=5 per time point). Compaction in width was measured during culture, while stress generation and retraction in length were measured after culture when constraints were released. Further, the amount of DNA, GAG, collagen and collagen cross-links was assessed.

Results. Compaction started after 2 weeks and continued up to 66.2±1.7% at week 4, after which width remained constant (fig 1A). Stress generation reduced from 11.8±0.9 kPa at week 4 to 2.4±0.4 kPa at respectively week 8 (fig 1B). Tissue retraction reduced from 44.0±3.7% at week 4 to 26.1±2.2% at week 8 (fig 1C). The reduced stress generation over time correlated with the reduced retraction. The amount of DNA, collagen and collagen cross-links was constant at all time points. The amount of GAGs was increased at week 6 and 8 compared to week 4 and correlated to the reduced stress generation.

Conclusion. In summary, increasing culture time resulted in decreased stress generation and retraction, likely as a result of the increased amount of GAGs. These results demonstrate the potential of prolonged tissue culture in developing functional, non-retracting, TE heart valves.

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