# MECHANICALLY INDUCED COLLAGEN FIBRE SYNTHESIS AND DEGRADATION IN CARDIOVASCULAR SUBSTITUTES

**Frank Baaijens, Carlijn Bouten, Niels Driessen, Ralf Boerboom**

Department of Biomedical Engineering, Eindhoven University of Technology, PO Box 513, 5600 MB Eindhoven, The Netherlands

## INTRODUCTION

*In vitro* mechanical conditioning has been demonstrated to be of critical importance in the tissue engineering of cardiovascular substitutes, i.e. vascular grafts[1] and heart valves[2]. Therefore, after static culturing, cell seeded constructs are placed in a bioreactor and subjected to pulsatile loading conditions. The objective is to stimulate cell proliferation and differentiation as well as extra cellular matrix production. In particular for aortic heart valves, the leaflets have to carry substantial hemodynamic loads, in particular during the diastolic phase. Since collagen fibers are known to provide a substantial part of the structural integrity of cardiovascular substitutes, the production of sufficient amounts of appropriately aligned collagen fibers appears mandatory. The production and alignment of collagen fibers is known to be strain sensitive, which suggests that the strain distribution, i.e. deformation modes, inside the leaflets or a graft must be controlled carefully during *in vitro* conditioning. Furthermore, at implantation the heart valves or vascular grafts may not necessarily have to be morphologically identical to the native heart valves, they, however, should be sufficiently functional.

## METHODS

Numerical analysis, using the finite element method, of the motion of the leaflets induced by the blood flow provides crucial information about the stresses and strains within the cardiovascular substitutes[3,4,5,6,7]. The numerical method is based on the so-called fictitious domain method. Fluid-structure interaction between the leaflets and the fluid is achieved via the introduction of Lagrange multipliers on non-conforming meshes, while the dispensability of the aortic wall is accounted for via the Arbitrary Lagrange Euler (ALE) formulation.

Particular emphasis is given on the modeling of the collagen fibers within the leaflets. For this purpose a structural approach is adopted that distinctively accounts for the contribution of the matrix and collagen fibers. The impact of fiber reinforcement and aortic wall flexibility on the haemodynamics of the valve is examined. Fiber reinforcement not only substantially reduces the stresses in the matrix, it also stabilizes the motion of the leaflets.

With numerical analysis the effect of mechanical stimuli on collagen remodeling is investigated. It is assumed that the change in collagen fiber content and orientation is strain modulated. A rate equation for the volume fraction of a particular fiber is formulated composed of a synthesis and degradation expression. In addition, it is assumed that collagen fibers (re)orient towards the strain field. An initially random, isotropic, fiber distribution is assumed that is allowed to remodel according to the rate equations.

## RESULTS AND DISCUSSION

Understanding the impact of mechanical loads as imposed on the tissue inside a bioreactor on the collagen fiber organization is one of the key challenges in the regeneration of the leaflet tissue. By imposing physiological loads on the leaflet and vascular graft, the collagen fibers remodel. The computed fiber directions are oriented in the circumferential direction (from commissure to commissure) and show a structure that closely resembles the fiber structure of the natural leaflet[8,9] (Fig. 1).

The remodeling theory presented describes the mechanical loading condition within the tissue and accounts for the effects of fiber remodeling on its mechanical properties. The results suggest that the collagen architecture is predominantly affected by the diastolic phase of the cardiac cycle. This is a first step towards understanding how the mechanical loading in a bioreactor should be modulated to obtain optimal mechanical tissue properties.

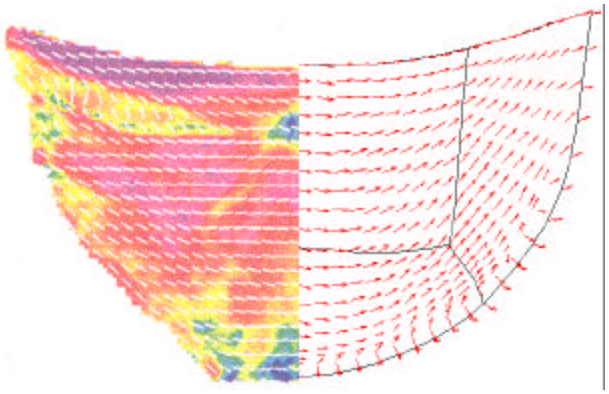

Fig. 1: Meaured collagen fibre orientation in a porcine heart valve leaflet[10] (left) compared with computed fibre directions[8,9] (right).


1 L.E. Niklason, J. Gao and W.M Abbott. *Functional arteries grown in vitro*. Science, 284, 489-493, 1999.

2 S.P. Hoerstrup, R. Sodian, S. Daebritz, J. Wang, E.A. Bacha, D.P. Martin, A.M. Moran, J. Guleresian, J.S. Sperling, S. Kaushal, J.P. Vacanti, F.J. Schoen and J.E. Mayer. *Functional living trileaflet heart valves grown in vitro.* Circulation, 102, III-44-III-49, 2000.

3 A.A.H.J. Sauren. *The mechanical behaviour of the aortic heart valve.* PhD thesis, Eindhoven University of Technology, 1981.

4 F.P.T. Baaijens. *A fictitious domain/mortar element method for fluid-structure interaction*. Int. J. Num. Meth. Fluids, 35, 743-761, 2001.

5 G. Cacciola, G.W.M. Peters, F.P.T. Baaijens. *A synthetic fiber-reinforced stentless heart valve.*, J. Biomech., 33, 653-658, 2000.

6 J. de Hart, G.W.M. Peters, P.J.G. Schreurs, F.P.T. Baaijens. *A two-dimensional fluid-structure interaction model of the aortic valve.* J. Biomech., 33, 1079-1088, 2000.

7 J. de Hart, G. Peters, P. Schreurs, F.P.T. Baaijens. *A three-dimensional computational analysis of fluid-structure interaction in the aortic heart valve.* J. Biomechanics, 36, 103-112, 2003.

8 R.A. Boerboom, N.J.B. Driessen, C.V.C. Bouten, J.M. Huyghe, F.P.T. Baaijens. *Mechanically induced collagen fibre synthesis and degradation in the aortic valve.* Submitted to Ann. Biomed. Engng, 2002.

9 N.J.B. Driessen, R.A. Boerboom, J.M. Huyghe, C.V.C. Bouten, F.P.T. Baaijens. *Computational analyses of mechanically induced collagen fibre remodeling in the aortic heart valve.* Submitted to J. Biomech. Engng, 2002.

10 M.S. Sacks, D.B. Smith, E.D., Hiester. *A small angle light scattering device for planar connective tissue microstructural analysis.* Ann. Biomed. Engng, 25, 678 – 689, 1997.