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Engineering of highly resemblent heart valve leaflet structures fabricated from PET fibres, using 3D knitting method

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Abstract: *Knitting is a versatile technology which offers a large portfolio of products and solutions that are of interest in heart valve (HV) tissue engineering (TE). One of the main advantages of knitting is its ability to construct complex shapes and structures by precisely assembling the yarns in the desired position. Recently multiple examples of applications of knitted fabrics in HVTE were reported. One of the most frequently cited strategies was developed in Mela's group. In that case, the fibrin constituting the leaflets of valves is enforced using a warp-knitted tubular mesh, made out of polyethylene terephthalate (PET). This approach is potentially adaptable for the intelligent scaffold development, which will require replacing non-degradable yarns with bioresorbable yarns. Also, the structure of scaffold should be altered to resemble closely the original valve's shape. Our group developed a model, which reproduces the anisotropic structure characteristic for the heart valve, in particular, the 3-layered architecture of the leaflets. The biodegradable yarns used can provide oriented growth of cells in a lengthwise direction and consequently enable the deposition of extracellular matrix (ECM) proteins in an oriented manner.*

Background

The aortic heart valve (AHV) is responsible for the unidirectional flow of blood out of the left ventricle, preservation of myocardial function and control of the coronary blood flow (1). It closes and opens over 100,000 times every 24h and will function normally over the lifetime of a human being (2). During this period, it is exposed to shear stress, bending forces, as well as strain and loading forces that are a result of the hemodynamic environment in which it lies.
The ideal smart scaffold should be non-immunogenic, resorbable and capable of attracting, housing and instructing cells to produce a particular phenotype (3). It should also reproduce the performance and mechanical properties of the native valve, both in the short and long term. Using current state of the art technology, it is most reasonable to focus on combining "the best elements" of the available strategies by constructing a textile-based scaffold (4) with the required functionality and characteristics (see **Figure 1**). One major advantage of textile techniques is their utility in reproducing the anisotropic properties of the valve (5,6).

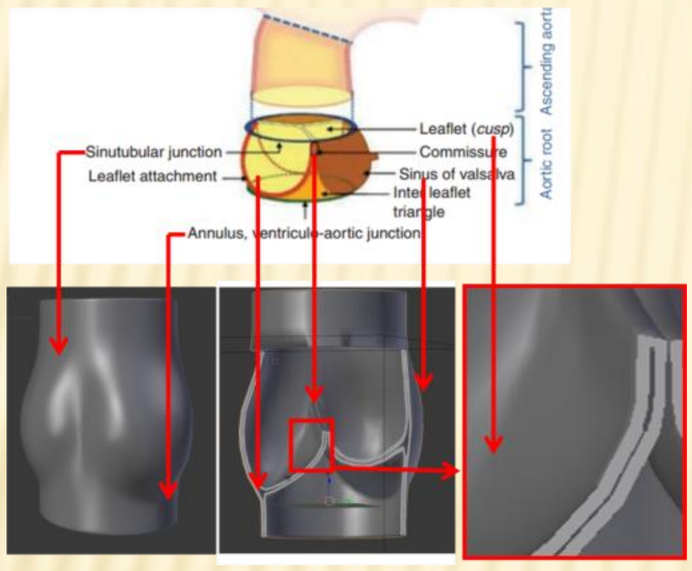

Figure 1. The geometry of the native HV (top panel) and intelligent scaffold (bottom panel). The top panel was reprinted with permission from (2).

Method

One of the most frequently cited strategies was developed in Mela's group (see **Figures 2**). The construct obtained . In that case, the fibrin constituting the leaflets of valves is enforced using a warp-knitted tubular mesh, made out of polyethylene terephthalate (PET). In all reports, the authors evaluated the biocompatibility of the construct by encapsulating the cells in the fibrin gel constituting the leaflets and quantifying the secreted ECM proteins. Other authors reported that in vivo implantation with fibrin-based tissue-engineered heart valves revealed an absence of calcification, thrombus formation, aneurysm development or stenosis. After 90 days of implantation, it was also observed that a monolayer of endothelial cells was formed, which exhibits the promise of fibrin scaffolds for HVTE.

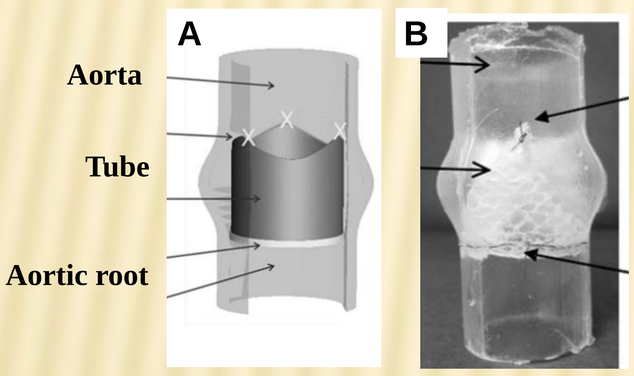

Figure 2. Tube-in-tube valve and its biocompatibility test. The principle of the tube-in-tube valve (A). The black arrow indicates the textile structure. Sutured in a silicone tube featuring the sinuses of Valsalva (B). Reprinted with permission from (7).

This approach is potentially adaptable for the intelligent scaffold development, which will require replacing non-degradable yarns with bioresorbable yarns. It would be necessary since in the smart solutions the synthetic yarns need to be finally absorbed and replaced by extracellular matrix proteins, deposited by in situ recruited cells. PET is not a bioresorbable material, and thus alternative strategies need to be proposed to enable growth of valve tissue within the patient.

Figure 3. Three-dimensional weft-knitted spacer fabric made out of PET yarn originally made for sport-garment. 1,2,3 are three layers of fabric (A). The fabric was used to construct leaflets which provide a closer structural match to three layer architecture of leaflet than examples reported before (7). Ventricular (B) and aortic (C) sides of the valve construct.

Inspired by these reports, we fabricated valve leaflets using spatial PET knitted fabric (see **Figures 3-5**). The construct obtained closely matched the histological structure of leaflets with three layer architecture (see **Figures 4**). The construct obtained . It is already significant accomplishment towards scaffold closely matching the architecture of native valves. The future steps will involve replacing PET with polycaprolactone yarns to enhance construct biocompatibility.

Figure 4. Structure of a 3D knitted fabric

Figure 5. Prototypes of obtained 3D-knitted leaflet structure.

Figure 6. The impregnating process of the leaflet with alginate hydrogel. Three leaflets in PDMS holder, view from the aortic site (A). Agarose gel containing CaCl2 (B), the same loaded into PDMS holder from the ventricular side (C). Valve root filled with sodium alginate dyed in red (D). The leaflets consisting cross-linked alginate in their inner part (E, F).

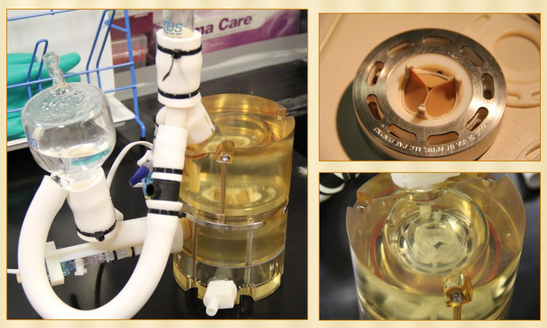

Figure 7. Obtained heart valve scaffolds impregnated with hydrogel were subjected to artificial flood (25% glycerol/0,9% saline solution) flow with the pressure of 30 mmHg and heart rate 70 bpm in 10h, using pulse replicator APTUS. The results were compared with ones obtained from commercially available Edwards 2800 valve.

Measurement	Our groups prototype	Edwards 2800
stock volume	19 ml	35 ml
flow rate	1,35 L/h	2,46 L/h
diastolic pressure	16,9 mmHg	14,8 mmHg

Conclusions

The results indicate that our groups valve parametres are inferior to commercially available one and need improvement (see **Figures 7**). However, the overall performance parametres were stable during the tests which clearly shows that the valve undergoes no changes during the process, for example, the alginate (see **Figures 6**) is not being washed out. Our plan is to use finer PET or PCL yarns to create an even thinner fabric that will perform in the desired manner.

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