A novel experimental/numerical method to assess BHV biomaterial fatigue response *in-vivo*

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Statement of Purpose: Approximately 200,000 valve replacements are performed each year with the number of patients opting for bioprothetic valve (BHV) replacements now at nearly 80% [1, 2]. The most frequently used BHV biomaterials include glutaraldehyde (GLUT) treated bovine pericardium and porcine aortic valve (PAV). GLUT was originally chosen for its immunosuppression capabilities. However, as a cross-linking agent it is shown to be mechanically unstable under long term cyclic loading and play a role in BHV calcification and valve failure [3]. Importantly, there does not currently exist a means to evaluate and predict *in vivo* bioprosthetic valve response to long-term cyclic loading and blood contact interactions. Herein, we present a novel, integrated numerical/experimental technique to assess BHV biomaterial response *in vivo* in a completely device independent manner. This will allow for the development of a predictive model to develop durable BHV designs.

Methods: GLUT treated porcine aortic valve leaflets are cut into shape and implanted in the anterior mitral valve leaflet of Dorset sheep. To better explore the stress induced change in configuration, we implant the PAV patch in 2 different orientations: with the circumferential direction of the patch aligned to the circumferential direction of the mitral valve (C-C aligned), and with the circumferential direction of the patch aligned to the radial of the mitral valve (C-R aligned) thus interchanging the loading boundary condition in the circumferential and radial direction of the patch. To quantify the *in vivo* deformation and subsequently determine the *in vivo* stress, 4 sonocrystals are placed at the corners of the implanted patch, with an additional one at the center. An inverse finite element model is applied to the implanted patch using shell elements. The mechanical properties are then optimized to induce the necessary deformation matching the central marker [4]. This model incorporates variations in fiber architecture measured pre-implant. After four weeks *in vivo*, the valve is explanted and further evaluated for mechanics and microstructure.

Results: Preliminary results demonstrate that when compared with the original cross-linked material, the patch implanted in the C-C orientation exhibited a nearly identical stress-strain response when subjected to biaxial mechanical testing. However, the patch implanted in the rotated C-R orientation appears to drastically increase in stiffness and exhibit significant permanent creep along the radial direction of the patch. This result is evident in Figure 1, which shows the applied force versus displacement for both configurations. The predicted *in vivo* temporal stress response and average stress generated from 5-sonocrystal data and the finite element model is estimated and presented in Figure 2.

Conclusions: We conclude that the observed changes in mechanical properties for the rotated orientation patch may be caused by a permanent set phenomenon. It is proposed that the aldehyde group in GLUT reacts with the amino groups on proteins in part via a Schiff base cross-linking reaction; however, Schiff base chemistry between aldehydes and amines are typically not stable enough to create permanent bonds. It appears that the cyclic loading is combined with the potential reversibility of the Schiff based cross-linking reaction causes the fibers to reorganize to be aligned with the direction of maximum stress and thus take on the mechanical properties of the surrounding valve tissue. Future *in vivo* studies are to verify our result and increase statistical relevance, as well as to evaluate other more permanent fixation chemistries. These future studies will incorporate the use of five sonocrystals with readings taken at three different time points to obtain *in vivo* strain data, including principal stresses and principal directions, to reveal the temporal evolution of what is believed to be a permanent set phenomenon. This data will be combined with microstructural geometry obtained from imaging to generate a predictive model of *in vivo* BHV biomaterial response.

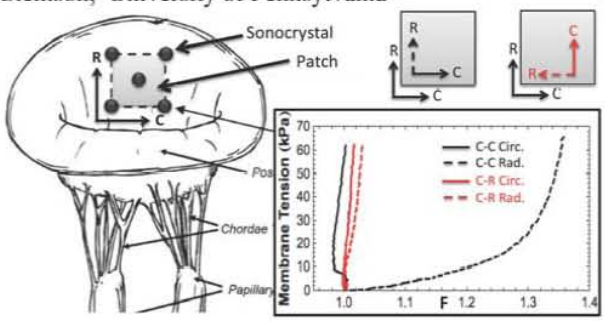

Figure 1. Implant geometry w.r.t. mitral valve. Inset – current results showing major changes in anisotropy after 4 weeks implant: membrane tension vs. deformation gradient for C-C and C-R aligned mitral valve patches along circumferential and radial patch directions.

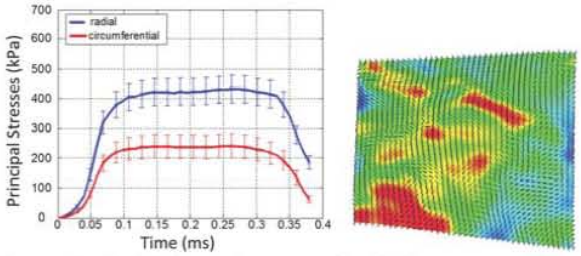

Figure 2. (a) Estimated mean principal stresses ±SD as function of time; (b) FE predicted principal stresses and directions of the MVAL at the fully-loaded state.

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References: [1] Chikwe et al. Nat Rev. Card. 2010. [2] Starr A. Nat Med. 2007;13:1160-1164. [3] Schoen FJ et al. Am J Pathol. 1986;123(1):134-145. [4] Lee C.H. et al. J Biomech. 2013; In Press.