Injectable Poly(Vinyl Alcohol) Hydrogels for Cardiovascular Applications

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Statement of Purpose: In heart attacks, blood flow to the muscle is blocked and the muscle is damaged or dies and begins to deteriorate. Over time the heart wall remodels, displacing the papillary muscles and disrupting the normal mitral valve-ventricular spatial relationship. This is known as ischemic mitral regurgitation (IMR) and results from incomplete mitral valve closure [1]. Even moderate IMR is currently recommended for surgical intervention and most often annulopasty rings prove efficacious by reducing the annular diameter and restoring the geometry. However, the late survivability of these patients is low [2], the surgery is invasive, and the intervention does not address the underlying issue. A number of groups have considered implanting both biological and synthetic hydrogels [3], with varying success. Here we present the development and validation of a poly(vinyl alcohol) based hydrogel that uniquely utilizes phase separation and hydrogel bonding to form a permanent, stable, biologically inert hydrogel.

Methods: Poly(vinyl alcohol) (PVA) is known to gel using a freeze-thaw cycle [4] through a hydrogen bonding mediate crosslinking reaction ("cryogels"). An alternative strategy for creating PVA hydrogels uses controlled solution conditions and phase separation to drive gelation. 100 kg/mol or 200 kg/mol (both 99%+ hydrolyzed, Sigma Aldrich and Orthoplastics respectively) PVA were mixed at varying concentrations (8 to 20% by weight) with varying concentrations of poly(ethylene glycol) (PEG) (300 or 400 g/mol) (Sigma Aldrich), with the balance deionized water (Fisher). A Design of Experiment (DoE) was used to optimize the formulation and determine the range of properties accessible. All of the benchtop samples described here were unsterilized, although the animal studies used ~25 kGy e-beam radiation (Steris). This mixture is miscible at temperatures above ~60 ºC, but when the temperature is reduced the system spontaneously phase separates over a period of time to form a hydrated, viscoelastic hydrogel. The PEG then diffuses out, leaving a pure hydrogen-bonded PVA hydrogel. This system is characterized for solids content, shear modulus and gelation time (oscillatory shear rheology, Anton Paar, Physica MCR 301), creep (confined and unconfined) (TA Instruments Q800) and hardness (Shore scale), as well as chronic MR trials in an ovine model will be reported. Solvent quality of the PEG was determined by swelling of freeze-thawed hydrogels.

Results: The use of this system allows tuning of the mechanical properties, viscosity and gelation time. Water content varied from 93% down to 83% while the gels tended to swell between 1 and 1.4x their original size. The gels were in general very soft, ranging from undetectable to 55 on the Shore OO scale. The unconfined creep data indicated approximately 25% instantaneous creep with a viscous relaxation over time. Upon release, although an instantaneous recovery of 50% of the lost height is observed, generally final recovery was not complete, to only 75% of the original height. *In vivo* experiments [5] following a chronic ovine model over 8 weeks demonstrates MR reduction by 50% over controls and less LV remodeling.

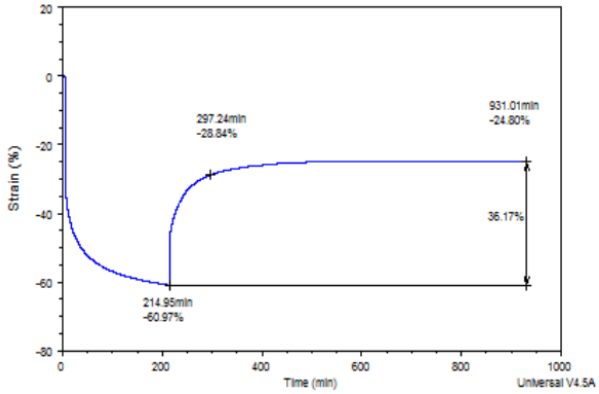

Figure 1: Unconfined creep showing approximately 61% strain. The sample recovered to approximately 75% of the original height after 12 hours.

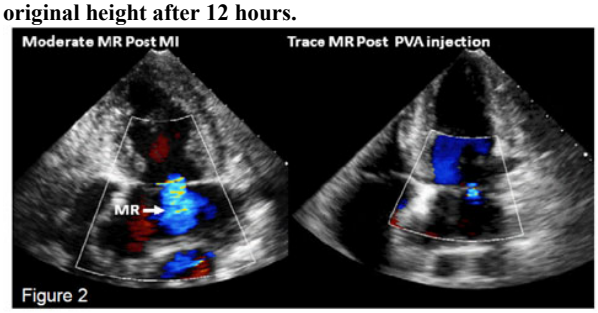

Figure 2: Ultrasound images of MR pre-and post-PVA injection (from [5]).

Conclusions: These data indicate that PVA can be manipulated to form an injectable hydrogel that uses no toxic crosslinkers and generates no bi-products. Although the mechanical properties do not look sufficient for a free-standing biomedical device, in fact the confining tissue environment is ideal for this material. The chronic animal data demonstrate that tissue augmentation restores valve function and suggests that, although not yet optimized, this material and treatment modality is very promising for this application. Because these materials rely on hydrogen bonding for crosslinking they are likely to be stable long term and therefore provide a possibly permanent solution to this tricky cardiovascular problem.

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