Design of a Novel, MRI-compatible Bioreactor for Longitudinal Monitoring of Mechanically Conditioned Engineered Cardiovascular Constructs

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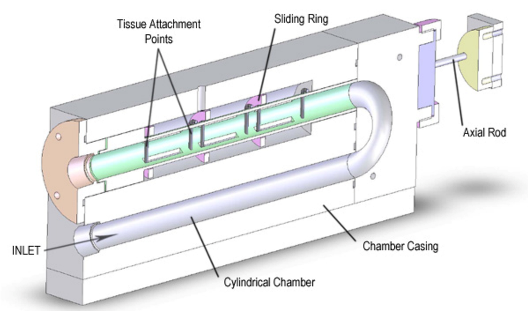
Introduction

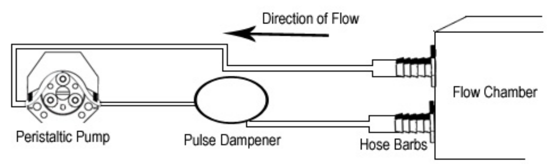
It has been demonstrated that in order for engineered tissues to be suitable for implantation and remain functional long-term, they may have to be pre-conditioned in dynamic mechanical environments [1]. While bioreactor devices have been custom built for this purpose [2], to date, no device offers the possibility of: a) the exertion of coupled/decoupled flow-stretch-flexure (FSF) stress states on tissue engineered constructs similar to that experienced by native cardiovascular tissues, such as heart valves, b) the replication of physiological hemodynamic conditions in which these stress states occur *and* c) device MRI-compatibility to permit noninvasive longitudinal monitoring of the evolving tissue. In the present study, we report on the design and development of a novel, FSF bioreactor capable of physiologically relevant scales of mechanical conditioning and intermittent noninvasive monitoring during tissue formation by MRI. This monitoring is important for tissue engineering studies because in addition to obtaining temporal and geometric information of the developing tissue, concomitant usage of cellular-based MRI techniques such as superparamagnetic iron oxide labeling will permit the tracking of the cells seeded onto the scaffold. In this manner, the effects of mechanical conditioning on the seeded cells can also be better understood and where necessary, scaffold cell-seeding protocols, critical to the ultimate quality of tissue that forms can be appropriately altered.

Materials and Methods

Design of the flow component: In order to provide fluid induced shear stresses in the physiologic range (3-80 dyne/cm^2in the case of heart valve tissue) [3], a cylindrical pipe design was implemented (Fig.1a). This offers two distinct advantages: First, it allows for a more efficient development of flow through the chamber of the device (as opposed to a rectangular channel design). Secondly, a narrow cross-section would result in higher fluid velocities at the pipe core and hence translate to higher shear stresses on the *in-situ* tissue samples, while still permitting the flow to remain laminar. To provide fluid flow through the U-shaped flow chamber, a peristaltic pump (Masterflex™, Cole Parmer, Vernon Hills, IL) was implemented. The pump is capable of generating steady flow rates of up to 2.9 LPM and can be easily converted to induce unsteady flow regimes if required. A pulse dampener was placed between the pump and flow chamber to reduce flow perturbations (Fig. 1b).



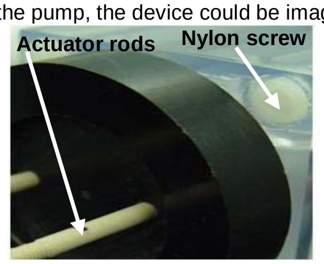
(a)



(b)

Figure 1: (a) Split, cross-section view of the bioreactor and b) illustration of connectivity of device to flow system

Design for MRI-compatibility: The main chamber of the bioreactor (Fig. 1a) was fabricated from polyetherimide (ULTEM™) which has been shown to provide excellent susceptibility matching with water [4] and excellent resistance to sterilization procedures. The role of traditional metallic components was filled by plastic equivalents, namely, as shown in Fig 2a, with Polyetheretherketone (PEEK) (McMaster-Carr, Elmhurst, IL) rods connected to a linear actuator (UltraMotion, Mattitick, NY) to permit flexure/stretch stress states of samples and Nylon socket head cap screws (SmallParts Inc, Miramar, FL) to attach/detach selected portions of the device. Sample attachment to the device was possible through the use of Titanium springs (Fig 2b) (SmallParts) which are known to present no to minimal image distortion and artifacts [5]. After simple detachment of the chamber from the actuator and the pump, the device could be imaged by MRI.



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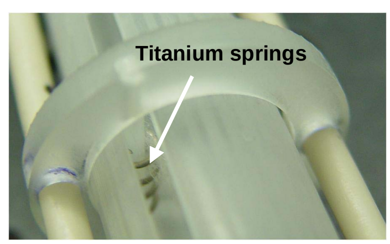

(b)

Figure 2: (a) MR compatible plastic equivalents in bioreactor design and b) MR compatible Titanium springs for sample attachment

Conclusions

In the current study, a device mimicking the dynamics and the physiological scales of stresses, native to cardiovascular tissue was developed. The device is completely MRI compatible and samples can be imaged *in situ*, in a noninvasive manner. This would allow for intermittent longitudinal MRI studies of evolving tissue engineered constructs which can be potentially used for noninvasive assessment of tissue formation induced by coupled or decoupled flow, flexure and stretch based mechanical conditioning regimes. We are currently in the process of conducting these MRI experiments with biodegradable scaffold materials seeded with bone marrow derived mesenchymal stem cells over a 3-week time frame. These results will be discussed.

References

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Acknowledgements: 1]: AHA-Scientist Development Grant; 2] Use of MR facility at Dr. Seong-Gi Kim's laboratory, McGowen Institute.