Designing Temporary Mechanical Supports to Alter Adverse Remodeling in Ischemic Cardiomyopathy: A Biomaterial-Based Approach to Cardiac Failure

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Statement of Purpose: The process of tissue remodeling in response to disease and trauma often yields results that are dysfunctional and which may ultimately progress towards tissue failure. In the case of mechanically active soft tissues, it is increasingly appreciated that the mechanical environment in which the damaged tissue heals impacts the direction and outcome of the remodeling process. To develop biomaterial-based approaches to improve outcomes in soft tissue repair we have designed a variety of degradable supports that act as scaffolds for new tissue generation or as temporary load bearing elements during the remodeling process. A primary effort has been aimed at the adverse remodeling process that occurs in the ventricular wall following myocardial infarction and which results in dilated ischemic cardiomyopathy (heart failure).

Methods: Two general approaches to developing temporary mechanical supports have been pursued, beginning with candidate material design, synthesis and characterization, and proceeding through efficacy testing in animal models of ischemic cardiomyopathy. In the first approach a variety of thermoplastic elastomers based on polyurethane chemistry have been synthesized and solvent processed to form microporous elastic patches that can be placed upon the infarcted heart in the period following acute remodeling. This approach has been examined in both the rat and porcine models with temporal assessment by echocardiography and immunohistochemical and tissue mechanical analysis following the implant period.

A second approach has focused on the development of injectable thermoresponsive polymers based on N-isopropylacrylamide (NIPAAm) copolymerized with monomers designed to provide tunable degradation behavior, drug delivery capacity and variable mechanical properties. These hydrogels are designed to exhibit a lower critical solution temperature between room and body temperature to allow gelation upon injection into the infarcted ventricular wall. Over time pendant groups are cleaved from the polymer backbone, raising the lower critical solution temperature above body temperature and resulting in polymer removal from the injection site. As with the patch approach, in vivo studies have been performed in a rat model of ischemic cardiomyopathy with functional assessments.

Results: Both approaches have demonstrated positive effects on echocardiographic function over the assessment period with altered tissue remodeling patterns characterized by increased muscle mass in the treated ventricular wall. Ventricular dilatation was interrupted with both therapies and fractional area change (a two dimensional analog of ejection fraction) was maintained or increased. Patch placement resulted in a ventricular wall that was significantly thicker and softer than control infarcted specimens, with passive mechanical behavior approaching that of the healthy ventricular wall.

Conclusions: Myocardial infarction takes a tremendous personal and economic toll in modern society. Revascularization technologies have had a major impact in both limiting the damage from a recent myocardial infarction and reducing the likelihood of future events, yet a substantial population is beyond the point at which they would derive benefit from revascularization. These patients face progression to end-stage heart failure, where cardiac transplantation, ventricular assist device support, or hospice care are the remaining clinical options.

The adverse tissue remodeling process that is associated with the progression from myocardial infarction to end-stage heart failure might be altered by a variety of interventions resulting in preserved and extended cardiac function. The biomaterial-based approaches of degradable elastic patch placement or thermoresponsive hydrogel injection therapy have shown promise in animal models and may provide a minimally invasive strategy to alter the mechanical environment associated with ventricular wall thinning and dysfunction.