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Myocardial Repair with SIS

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Small intestinal submucosa (SIS) has been shown to promote accelerated wound healing, cause connective tissue differentiation, and to serve as a scaffold for remodeling of large and small diameter blood vessels. The combination of these properties suggest that SIS may be useful as a biomaterial for repair of cardiac defects. This premise was tested in four dogs as part of a preliminary study.

A single 1.8 cm-diameter circular atrial septal defect was created in two dogs (average weight 22 kg). Each defect was repaired in a single thickness layer of SIS. One of these dogs was sacrificed three and the other dog at five months following surgery.

Likewise, in two separate dogs, a single 3.5 cm-diameter circular defect was created in the right ventricular free wall near the base. These defects were repaired with a single thickness layer of SIS. Again, one dog was sacrificed three and the other at five months after surgery. Microscopic and macroscopic tissue appearance at the time of sacrifice was the primary endpoint and remodeled tissue excitability compared to normal myocardium excitability was our secondary endpoint. At the time of sacrifice, the remodeled graft sites were dissected free of the myocardium, sectioned such that half of the remodeled tissue was placed in neutral buffered formalin, and the other half placed immediately in oxygenated tissue containing Krebs solution at 37 C. Specimens for histopathological analysis were sectioned and stained with both hematoxylin and eosin and with Masson's trichrome stain. Tissue collected for *in vitro* stimulation studies was connected to a myograph and stimulated with various intensities of current in order to generate strength duration curves.

Results: Electrical stimulation studies conducted *in-vitro* demonstrated that the remodeled myocardium contracted in response to a single electrical stimulus (50 msec, 160 mA). Chronaxie was then established at 1.32 msec and 1.06 msec for dogs number 1 and 2 respectively. The chronaxie for normal myocardium is typically 1.63 msec. No spontaneous contractions in the remodeled atrial tissue were observed but the ventricular specimens exhibited contractions at a low rate.

Histopathologic examination of tissues showed distinct findings for the remodeled atrial septal defects vs the right ventricular wall defect areas. The SIS which had been used to replace the atrial septal defects was no longer visible at either the three months or five months following surgery. The tissue was replaced with a mixture of connective tissues including differentiated cartilage, fibrous connective tissue, and adipose connective tissue. The surface of the atrium (both right and left sides) was lined by an intact confluent layer of endothelial cells. There was no evidence for an inflammatory reaction. There were wisps of striated spindle cells with central nuclei indistinguishable from cardiomyocytes.

The remodeled tissues from the right ventricular wall showed replacement by organized collagenous connective tissue and bundles of striated spindle cells indistinguishable from cardiomyocytes. These cells represented approximately 40 to 50% of the remodeled area in the dog sacrificed at three months and approximately 60% of the area in the dog which survived for five months. The tissues from both animals showed increased vascularity. There was no evidence for an inflammatory reaction. The endocardial surface was lined by a layer of endothelial cells with a subjacent layer of connective tissue consistent with endocardium. The overlying epicardial surface in both dogs was adherent to the pericardium and showed confluency between the two tissues.

Conclusion: Feasibility studies conducted in four animals suggest that a single layer of SIS supports remodeling in the right ventricular free wall and the interatrial septum. There is an accumulation of multiple types of connective tissue in the interatrial septum and there is an accumulation of fibrous connective tissue and contractile tissue in the right ventricular free wall. The origin of these connective tissues remains undetermined. Additional studies are in progress.

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Related Publications:

Lantz G, Badylak SF, Coffey A, et al. Small intestinal submucosa as a small diameter arterial autograft in the dog. *J Invest Surg* 1990; 3:217-227.

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