In Vivo Assessment of Engineered Cardiac Patches for Repairs of Congenital Heart Defects

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Introduction: Congenital heart defects generally require surgical placement of a patch across the right ventricular outflow tract (RVOT) in an area that normally consists of contractile myocardial tissue. Current materials for RVOT repair induce an inflammatory foreign-body response, resulting in the material encased by a fibrous scar-like tissue that does not degrade, grow with the child's heart, nor provide contractile force. These patch materials also disrupt electrical conduction, and serve as a nexus for calcification. As a result, patients with heart patches have an increased risk of heart failure, arrhythmias, infection and aneurysm.[1] The objective of this study was to investigate a cardiovascular tissue engineered device using *in vivo* methodological approaches and to develop novel therapies to treat cardiac defects by reducing the drawbacks associated with current cardiac patches.

Materials and Methods: Three different patches, each 6 mm in diameter, were prepared: (1) gelatin (type-A)-chitosan composite hydrogel,[2] (2) decellularized porcine myocardium (referred as heart matrix)-chitosan coated on polycaproactone core[3] and (3) SJM™ Pericardial patch for the control. Full thickness RVOT repair surgery on the Sprague-Dawley rat (200-300g) model was performed. Briefly, the purse-string was applied to the surface of RVOT and right ventricle (RV), then the RV wall was resected. The patch was sutured along the margin of the purse-string suture to cover the resected region in the RV. Cardiac MRI imaging was performed for detailed assessment of cardiac function of all hearts treated with the three different patches at three time points (2, 4, and 8 weeks post-surgery) and images were compared with those taken from a native heart. Images were taken from the LV and RV throughout systole and diastole. Cardiac function was assessed by calculation of the ejection fraction and end diastolic volume adjacent to the implanted graft using Amira Imaging software. Rats were sacrificed after 8 weeks and hearts were fixed and sectioned. Immunohistochemistry analysis was also performed to evaluate cell immigration from the native tissue and tissue regeneration using haematoxylin and eosin, Masson's Trichrome, CD31 (endothelial cells), Cx43 (gap junction), and α-smooth muscle actin (α-SMA).

Results and Discussion: MRI results showed that there was no RVOT obstruction due to the surgery. Left ventricular ejection fractions (LVEF) of patched hearts were reduced significantly after 2 weeks post surgery. LVEF of both gelatin and heart matrix patched hearts were normalized after 8 weeks while Pericardial patch samples maintained reduced LVEF (Fig. G). Newly grown tissue covered the patched area, and no significant areas of clotting or fibrosis were observed on the patch (Fig. A-C). The connective tissue surrounding the heart matrix patch had a continuous endothelial layer on the surface. Both engineered patches promoted aligned cardiac smooth muscle cell formation though the patched area (Fig. E&F) whereas the pericardial patch had no cell immigration (Fig. D). Further, engineered patches promoted neovascularization through the patched region and localized in the same area (Fig. H&I). Furthermore, positive staining for cTnT was observed through the patch and connective tissue. However, gap junction formation (cx-43) was observed in only connective tissue area.

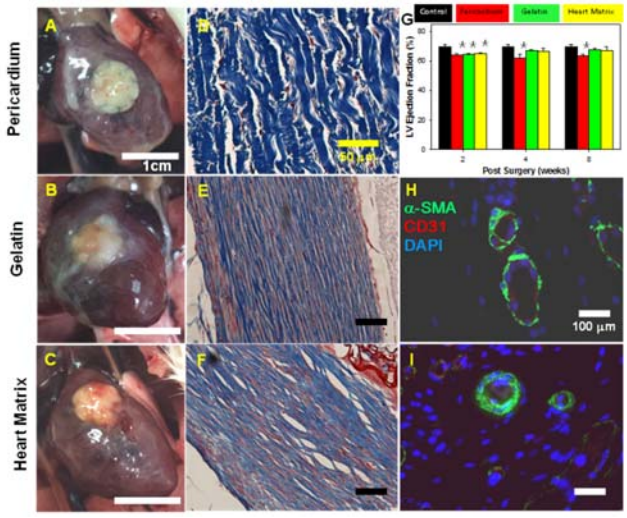

Figure. (A-C) Representative patched heart images, (D-F) Masson's Trichrome stained patches, (G) left ventricular ejection fraction after 2, 4 and 8 weeks and (H-I) antibody stained patches. (*; $p<0.05$)

Conclusions: These results demonstrate that an engineered patch promotes cell immigration and neo-endothelialization though the patched area and regenerates along the native tissue, demonstrating improved function as a full-thickness cardiac patch in RVOT repair for cardiac defects. Future research will involve testing cellularized patches to improve cardiomyocytes maturation through the patched area.

References:

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