Epicardial placement of an elastic, biodegradable patch induces muscle tissue similar to embryonic myocardium in the post-infarcted wall and preserves cardiac functional reserve

Kazuro L. Fujimoto[a,e], Kimimasa Tobita[b,c,e], Jianjun Guan[a,e], Yi Hong[a,e],
Katherine E. Yutzey[d] Bradley B. Keller[b,c,e], William R. Wagner[a,b,e]
Departments of [a]Surgery, [b]Bioengineering, [c]Pediatrics University of Pittsburgh, [d]Cincinnati Children's Medical Center and
[e]McGowan Institute for Regenerative Medicine, Pittsburgh, PA 15219, USA

Introduction: The post-infarct myocardial wall is subject to progressive adverse myocardial remodeling that can lead to profound mechanical dysfunction in the absence of a recurrent ischemic event. We have recently reported that implantation of an elastomeric, biodegradable, polyester urethane urea (PEUU) [1] cardiac patch onto sub-acute left ventricular (LV) infarcts attenuates post-infarct LV dilatation and contractile function, and induces abundant smooth muscle-like bundles within the infarcted myocardium. [2] In the present study, we further characterized the induced muscle tissue and investigated the cardiac functional reserve with dobutamine stress echocardiography to evaluate the potential efficacy of this procedure.

Methods: PEUU was synthesized from polycaprolactone diol and 1,4-diisocyanatobutane with chain extension by putrescine as previously reported [1], and processed into porous scaffolds with thermally induced phase separation [3]. Two weeks after proximal left coronary ligation in Lewis rats, infarcted anterior walls were covered with PEUU cardiac patches (n=11) or sham surgery was performed (n=11). Cardiac function was assessed by standard echocardiography and at 8 weeks dobutamine stress echocardiography (15μg/kg/min) was performed to evaluate the cardiac reserve as well as the histological assessment.

Results: The majority of the PEUU patch was absorbed with putative macrophages and fibroblasts infiltrating the area of the remnant patch. Underneath the patch abundant α-SMA positive muscle bundles were apparent (**Fig. 1a-c**). Immunohistochemistry revealed that the immature muscle tissue induced by PEUU implantation co-localized with alpha-smooth muscle actin and other muscle proteins (alpha-sarcomeric actinin, actin and cardiac specific troponin-T). In situ hybridization showed expression of cardiac transcription factors Nkx-2.5 and GATA-4 was upregulated in the induced muscle tissue. We examined these multiple muscle proteins and transcription factor expression patterns in gestational day 14 embryonic myocardium, and found analogous muscle tissue as seen in the patched ventricles. For cardiac function, at baseline there was no significant difference in both groups. At 8 weeks, patch implantation significantly prevented cardiac dilatation and preserved contractile function compared with sham surgery. Under dobutamine stress, the percent fractional area change in the patch group increased, while in the sham group it decreased (34.2% vs. 16.3%, $p<0.05$, **Fig. 2**).

Conclusions: Patching post-infarct myocardium with PEUU improved cardiac function and lead to LV cellularization with phenotypic expression similar to that of the embryonic ventricular wall. This finding might provide a new methodology to achieve alternate regenerative remodeling pathways beneficial to the injured heart.

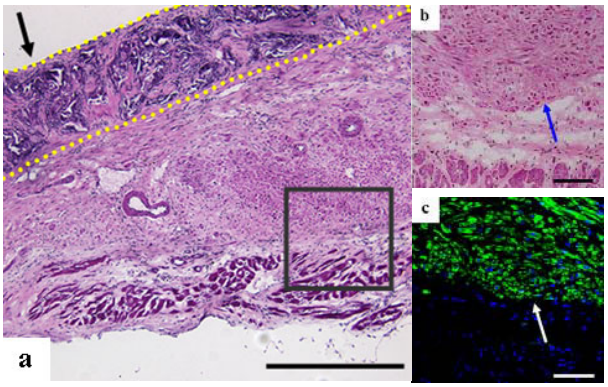

Fig. 1. Representative histological sections of PEUU patched LV wall 8 wks after implantation stained with H&E (a, b), and immunohistochemical staining (α-SMA staining appears green and nuclear staining appears blue (c)). Black arrow (yellow dotted line) indicates PEUU implanted area (a). Blue (b) and white (c) arrows indicate regenerated muscle tissue.

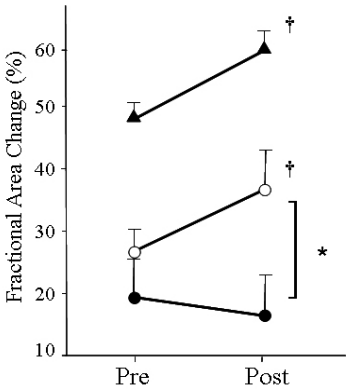

Fig. 2. Dobutamine stress echocardiographic assessment (% fractional area change) of age-matched normal controls (top), the PEUU patch group (middle) and infarction controls (bottom) at 8 wks. *$p<0.05$ between groups, †$p<0.05$ vs. 0 wk within group.

Acknowledgements & References
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