In vivo grafting of large, engineered heart tissue patches for cardiac repair

User review of interest 'In vivo grafting of large engineered heart tissue patches for cardiac repair' by Richard J. Jabbour et al. from the Sian E. Harding lab at Imperial College London UK published in JCI (The Journal of Clinical Investigation) Insight on 2021 Aug 9th. [https://insight.jci.org/articles/view/144068]

As the prevalence of heart failure continues to climb worldwide, most treatments that are currently available work by slowing down disease progression rather than actively reversing the disease process1. Therefore, novel therapies are urgently needed, specifically for the aging population.

In recent years, clinical trials in cardiac cell therapy have shown some promise however, only marginal benefits have been reported in patients2. This can likely be attributed to the delivery methods used which often have high levels of washout and cell death following grafting. In an effort to overcome these limitations, researchers have constructed 3D engineered heart tissue (EHT) from human induced pluripotent stem-cell derived cardiomyocytes (hPSC-CMs), recapitulating many aspects of native myocardium3.

These EHTs have shown to be effective in small animal models of heart disease showing improvements in cellular retention, vascularization and scar size, however, scale up studies involving large animal models with heart physiology more similar to humans are needed prior to being implemented in the clinic4,5.

To move this approach forward, Jabbour et al. developed a rabbit model of myocardial infarction (MI) for implanting the EHT grafting6. Compared to mice and rats, the rabbit myocardium has many similarities to the human including morphology and ionic composition of the action potential, 70% of calcium cycling through the sarcoplasmic reticulum and a positive force relationship. Importantly, the anatomy of the rabbit allows for a reproducible and cost-effective infarct model with a similar epicardial to endocardial gradient as humans.

Table 1. Comparison of different cardiac animal models

Species	Body Weight (kg)	Heart Weight (g)	Heart rate (beats/min)	Systolic pressure (mmHg)	Contractility (mN/mm)	LVEDd (cm)	Cost
Mouse	0.02 - 0.063	0.15	~600	113 - 160	23.6 ± 2.8	0.287 - 029	£
Rat	0.225 - 0.52	1	~400	84 - 184	26.7 ± 1.3	0.60 - 0.67	£
Rabbit	1 - 6	9 - 11	130 - 300	90 - 130	26.3 ± 4.4	1.37 - 1.78	££
Macaque	5 - 15	37 - 52	100 - 140	100 - 140		1.46 - 2.64	££££
Pig	30 - 70	150 - 350	70 - 120	135 - 150	19.2 ± 0.9	3.91 - 4.88	££££

Adapted from refs. 3, 11, 24, 34 - 40. More £ symbols represent higher cost. LVEDd, left ventricular end diastolic diameter

The study by Jabbour et al., is the first to demonstrate that grafting upscale EHTs is feasible and safe in a rabbit model of MI. For *in vivo* experiments, the EHT patch (2.5 cm × 1.5 cm × 1.5 mm) consisting of fibrin-based hydrogel was seeded, expanded and stimulated with up to 20 x 106 hPSC-CMs and then implanted. Retention and vascularization of EHTs in addition to electrical coupling and arrythmia burden were assessed over the four-week period. EHT grafting was found to be associated with improvements in post-MI ventricular function and reductions in scar size. Furthermore, it was not found to be linked to any significant development of arrhythmogenicity.

When compared to more conventional modalities for cell injection, tissue engineering strategies offer many benefits including improved vascularization, prolonged cell survival, structural support for the failing ventricle, and the ability to cover scarred tissue with new engineered heart muscle. While there are still many hurdles to overcome prior to clinical translation, this strategy shows tremendous promise for the effective treatment of heart failure in the near future.

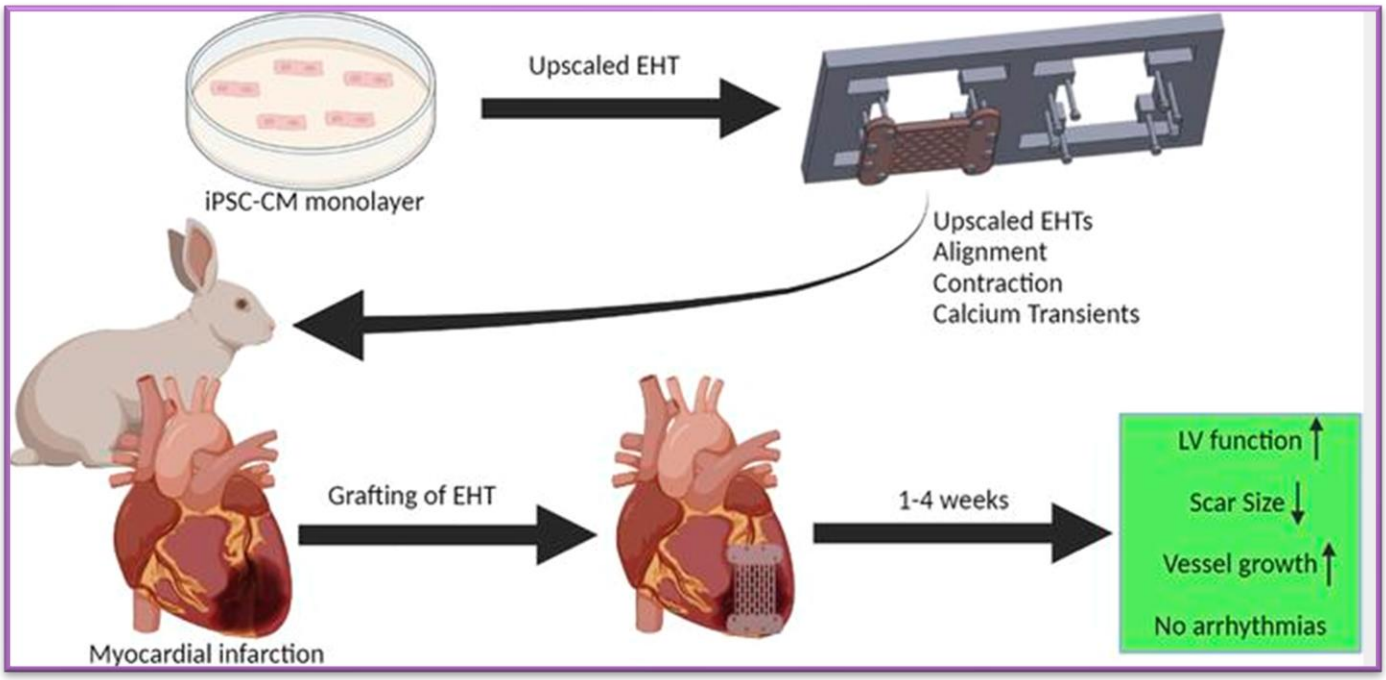

Figure: Graphical abstract as seen in *Jabbour, Richard J., et al. "In vivo grafting of large, engineered heart tissue patches for cardiac repair." JCI insight 6.15 (2021).*

If you're interested in learning more about this study, check out the full publication here: *Jabbour, Richard J., et al. "In vivo grafting of large engineered heart tissue patches for cardiac repair." JCI insight 6.15 (2021).*

References

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