Cellular heterogeneity of pluripotent stem cell-derived cardiomyocyte grafts is mechanistically linked to treatable arrhythmias

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Introduction

Myocardial infarction (MI), the leading cause of heart failure, results in the loss of up to 1 billion highly specialized cardiomyocytes (CMs)1. While there has been attempts to replace damaged CMs, the lack of cardiomyogenic differentiation capacity yield inconsistent results. Hence, pluripotent stem cells acts as a renewable source of CMs

Human pluripotent stem cell-derived cardiomyocytes (PSC-CMs) offer promising therapeutic potential for remuscularizing injured hearts post-myocardial infarction. However, ventricular arrhythmias is a significant complication linked to cellular heterogeneity in PSC-CM grafts.

This study investigates the mechanistic basis of engraftment arrhythmias (EAs) and its linked to cellular heterogeneity in the input PSC-CM and resultant graft and further evaluates pharmacologic and interventional strategies to mitigate their effects.

Methods

A porcine model of myocardial infarction was used to evaluate PSC-CM transplantation.

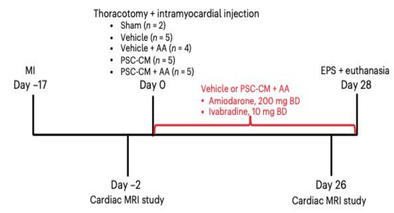

Fig. 1 | Study timeline for phase 1 large-animal experiments

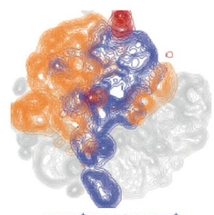

Fig. 2 |Concatenated t-SNE plot showing distribution of particularly arrhythmogenic SIRPA+CD90−CD200+ and particularly non-arrhythmogenic SIRPA+CD90−CD200− CMs.

Anti-Arrhythmic Strategies: Ivabradine and amiodarone were tested for their ability to suppress EAs.

Data Analysis: Telemetry and cardiac imaging were employed to assess arrhythmia burden and cardiac function.

Results

1. Heterogeneity and Arrhythmogenesis:
   - PSC-CM grafts exhibited diverse subpopulations, with atrial and pacemaker-like cells being major contributors to EAs.

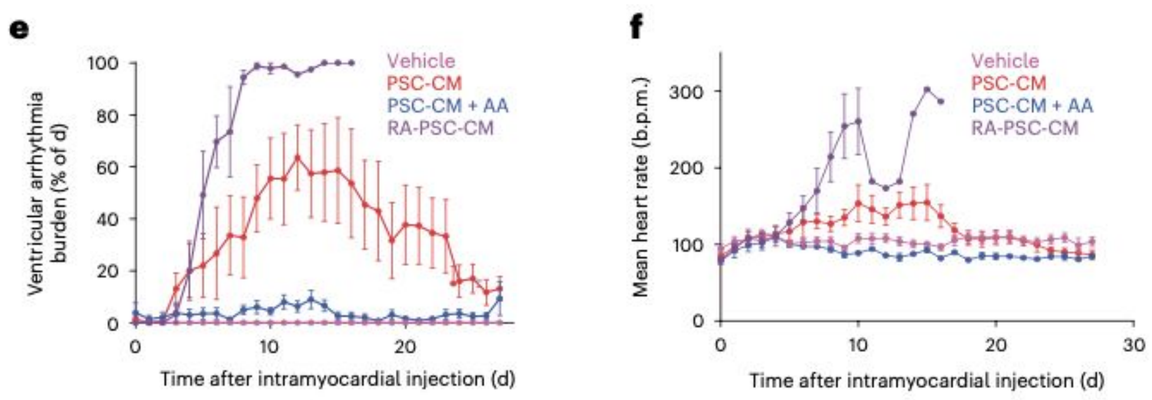

Fig. 3 | RA-PSC-CMs are enriched with atrial and pacemaker subpopulations and are highly arrhythmogenic. Percentage of time spent in ventricular arrhythmia (e) and mean heart rate per day between groups (f) (mean ± s.e.m.).

2. Pharmacologic Interventions:
   - Ivabradine and amiodarone significantly reduced arrhythmia burden, arrhythmia frequency and the heart rate in treated animals.

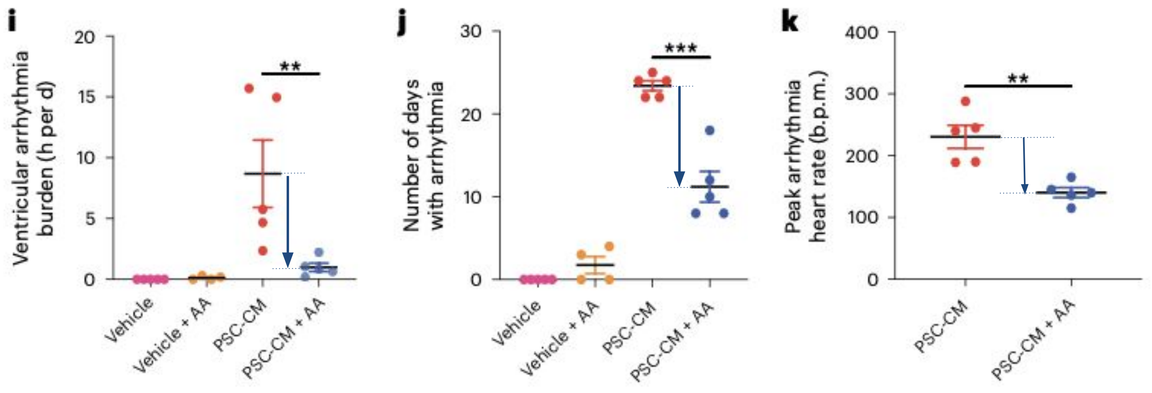

Fig. 4 | Arrhythmia parameters from day 0 to day 28 for each subject, grouped by treatment allocation (vehicle, n = 5; vehicle + AA, n = 4; PSC-CM, n = 5; PSC-CM + AA, n = 5; biologically independent animals; data are presented as mean ± s.e.m.). Significant reduction in arrhythmia burden (i) (**P = 0.008, Mann–Whitney test, two-tailed), number of days with arrhythmia (j) (***P = 0.0002, unpaired t-test, degrees of freedom (df) = 8, two-tailed) and peak arrhythmia heart rate (k) (**P = 0.002, unpaired t-test, df = 8, two-tailed) in cell recipients treated with anti-arrhythmics.

3. Cardiac Function Improvement:
   - Animals receiving PSC-CMs with anti-arrhythmic drugs showed enhanced left ventricular ejection fraction (LVEF) and stroke volume (LVSV).

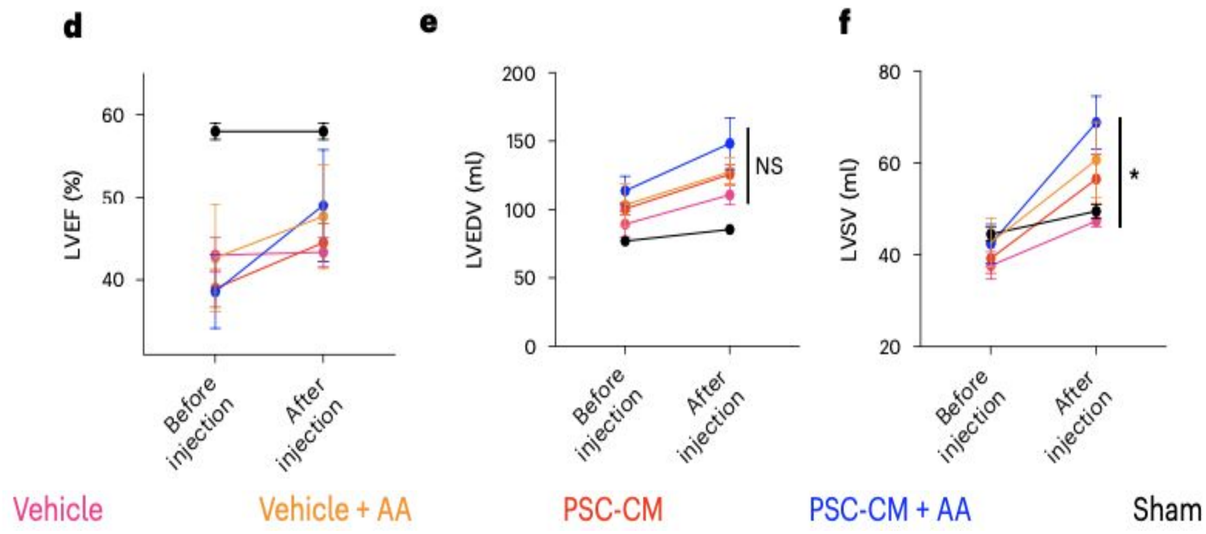

Fig. 5 | Pooled group data of left and right ventricular function at baseline (after MI, before injection) and 4 weeks after injection. The greatest improvement in LVEF (d) was noted in cell and anti-arrhythmic recipients. No significant change in LVEDV (e) was observed between groups (P = 0.76, Kruskal–Wallis test) although there was a significant improvement in LVSV (f) in cell and anti-arrhythmic recipients

4. Interventional Strategies:
   - Catheter ablation (CA) is a feasible therapeutic strategy for EAs. However, treatment success, particularly with highly arrhythmogenic cell doses, may require complete ablation of all engrafted regions if arrhythmogenic cell populations are not removed before transplantation.

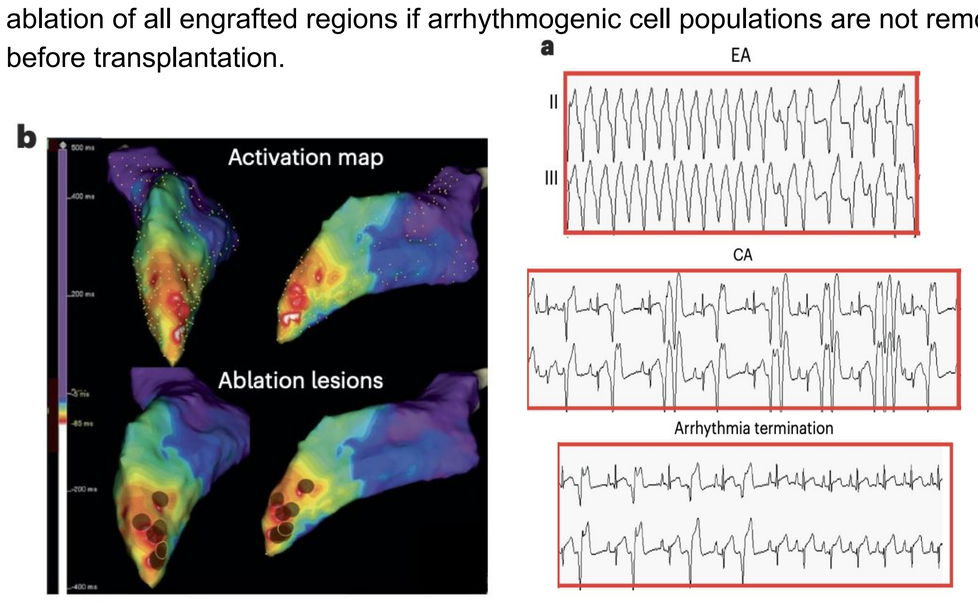

Fig. 6 | CA is a feasible and effective EA treatment strategy. (a) Representative rhythm strip showing termination of EA during CA. (b) Electroanatomic maps from a representative CA-treated subject. Top, activation map of EA showing anatomic origin of arrhythmia (early activation, white; late activation, purple). Bottom, activation map overlaid with ablation lesions (brown circles) that were delivered at sites of earliest activation, resulting in termination of arrhythmia.

Conclusion

The presence of specific cell subpopulations (eg. SIRPA+ CD90− CD200) is associated with increased arrhythmogenic risk. Arrhythmias occurring after pluripotent stem cell-derived cardiomyocytes (PSC-CMs) transplant have been found to be linked to presence of atrial and pacemaker-like cardiomyocytes.

Enhancing PSC-CM production protocols by refining the differentiation and selection processes will produce a purer and safer population of cells for transplantation, further decreasing the risk of engraftment arrhythmias.

First-line pharmacological treatment using ivabradine and amiodarone has also been shown to be effective in lessening the burden of engraftment arrhythmias. For refractory arrhythmias, catheter ablation has been proven to be a feasible fallback strategy as well.

Overall, the paper findings addresses how to reduce the risk of arrhythmias when using PSC-CMs, allowing for more effective and safer uses in repairing damaged hearts. By ensuring the benefits of revascularization and improved cardiac function outweigh the potential risks, it helps push for PSC-CMs as a viable clinical treatment option.

References

1. Laflamme, M. A. & Murry, C. E. Heart regeneration. Nature 473, 326–335 (2011).
2. 1.Dinesh Selvakumar et al. Cellular heterogeneity of pluripotent stem cell-derived cardiomyocyte grafts is mechanistically linked to treatable arrhythmias. Nature Cardiovascular Research 3, 145–165 (2024).