Optimizing Gene Therapy Injection in a Simplified Heart Failure Model

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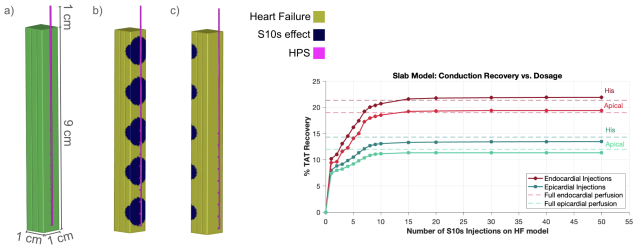
Introduction: S10s gene therapy is a novel strategy for heart failure (HF) patients non-responsive to resynchronization therapy. While upregulating sodium current (I_{Na}) shows promise, optimal spatial delivery remains unquantified. We used computational modeling to evaluate how injection patterns influence conduction restoration and His-Purkinje System (HPS) engagement.

Methods: A ventricular HF slab model with transmural heterogeneity and bidirectional HPS coupling was developed. We simulated I_{Na} upregulation (+80%) across injection densities (1–50 sites) at endocardial and epicardial surfaces. Efficacy was quantified by percentage reduction in total activation time (TAT) and bidirectional junction delays under anterograde and retrograde (apical) pacing.



Left: geometrical setups of the HF slab model and local injection patterns. Right: S10s injections vs. TAT reduction.

Results: Therapeutic efficacy followed a non-linear trend; significant gains occurred within the first 10 sites, followed by a therapeutic plateau. Endocardial targeting was superior, achieving a 21.3% TAT reduction (approximating the 21.4% uniform perfusion limit), while epicardial delivery recovered 13.5%. Endocardial delivery optimized the HPS interface by reducing retrograde entry delays by 25% (0.62 to 0.46 ms). Despite this, the absolute TAT difference between layers was only 6.5 ms, suggesting epicardial targeting remains a viable clinical alternative due to superior surgical accessibility.

Conclusion: Targeted, low-density S10s delivery effectively restores conduction in the failing heart. By facilitating earlier retrograde HPS engagement, localized injections approximate the benefits of widespread gene expression. This study highlights the necessity of incorporating specialized conduction systems to evaluate gene therapies for patients ineligible for traditional pacing.