First-in-man Cardiac Regeneration Using a Second-Generation Xenograft Bioscaffold: A Novel and Potentially Disruptive Treatment for Advanced Heart Failure

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INTRODUCTION

Heart disease is the leading cause of death in both the United States and the world. Current treatments range from medical therapy, such as ACE inhibitors, beta blockers, inotropes, etc, to surgical therapy such as ventricular assist device implantation and heart transplantation. Both therapeutic interventions have been demonstrated to produce only a modest benefit or have other limitations. These treatments are also focused on improving hemodynamics rather than restoring the damaged myocardium.

Proposed regenerative solutions have included various types of stem cell injections (iPSCs, fibroblasts, mesenchymal extracts, etc), exosome deliveries, and isolated growth factors (1). All of these techniques have had limited utility in clinical trials and practice, and demonstrated only modest improvements in ejection fraction (2). This first-in-man case follows the first patient (henceforth referred to as [GG]) ever treated with a second-generation xenograft cardiac patch for severe heart failure and demonstrates additional cardiac recovery beyond that expected from bypass surgery alone.

Patient Presentation

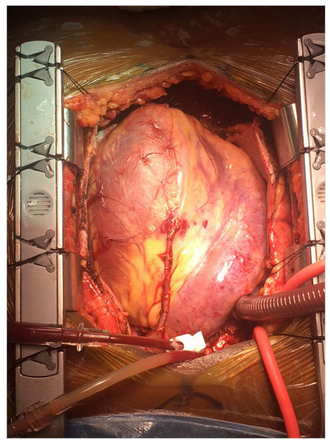
[GG] is a 29 year old male without any known medical history who experienced chest discomfort while exercising and subsequently collapsed. Upon EMS arrival, ECG showed anterior ST segment elevation. The patient then experienced pulseless electrical activity, and after three short-lived resuscitation stints experienced return of spontaneous circulation. [GG] was consistently hypoxic (spO2 < 80%) following EMS contact, and upon arrival at a community hospital was stabilized, intubated, and transferred to Vidant for emergent cardiac catheterization. Angiography demonstrated severe multivessel coronary artery disease with a completely occluded mid-LAD. Emergent mid-LAD angioplasty was performed, but due to ongoing hypotension and persistent hypoxia the patient required support with veno-arterial extracorporeal membrane oxygenation. Ejection fraction was demonstrated to be 10% by transesophageal echocardiography.

On postoperative day 4, after demonstration of neurological improvement, [GG] underwent a triple coronary artery bypass and had a novel xenograft bioscaffold patch applied to the infarcted ventricular territory. The patient was extubated the following day. On postoperative day 7, a cardiac MRI was performed showing an ejection fraction of 30%, and he was accordingly fitted with a Lifevest external defibrillator. On postoperative day 29, he was discharged to a rehabilitation facility; on day 38 he was discharged to home.

MATERIALS & METHODS

Theory

Ischemic injury following myocardial infarction is characterized by three overlapping stages: inflammation, repair, and remodeling. Immediately following insult, inflammatory cytokines, chemokines and cell adhesion molecules stimulate leukocyte digestion of necrotic cardiomyocytes. As the infarct is cleared, anti-inflammatory signals propagate, initiating the reparative and remodeling phases. The reparative phase is characterized by the expansion of surviving resident cardiac fibroblasts, and their conversion into myofibroblasts. Myofibroblasts retain some contractile activity but they lack the synchronicity of typical cardiomyocytes and thus functional improvement is limited. Concurrently, differentiated myofibroblasts deposit large amounts of extracellular matrix proteins to restore structural integrity to the infarcted ventricle. Over the first three weeks post-MI, a strong collagen network is built, which, while providing structural integrity, results in relatively electrically and mechanically inert scar tissue that does not contribute to maintaining cardiac function.

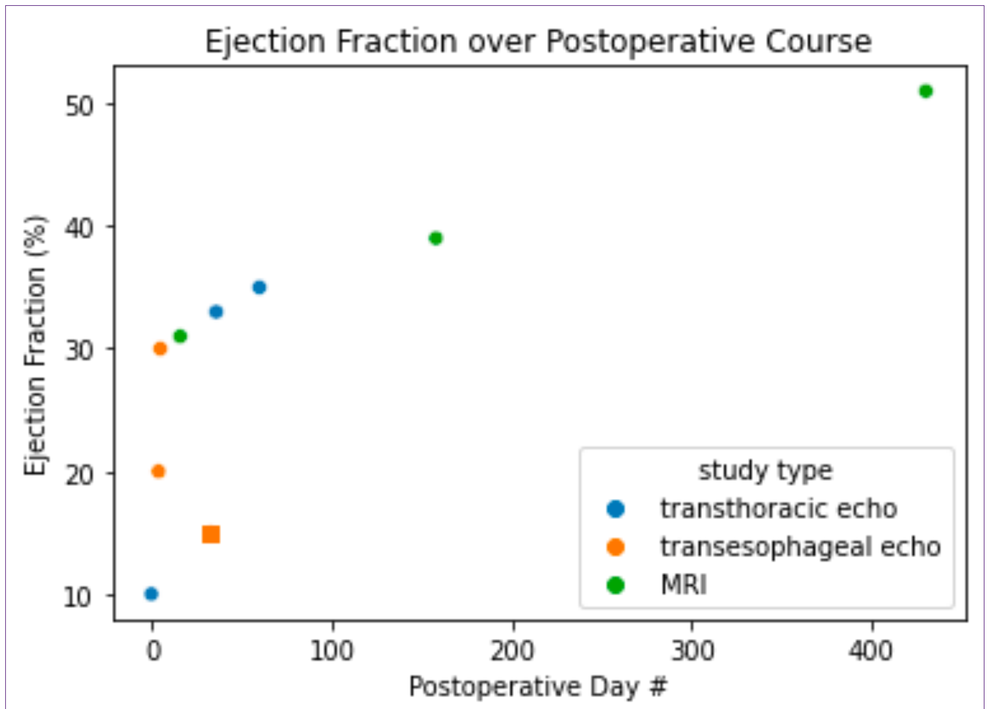


The xenograft applied to the infarcted left ventricle.

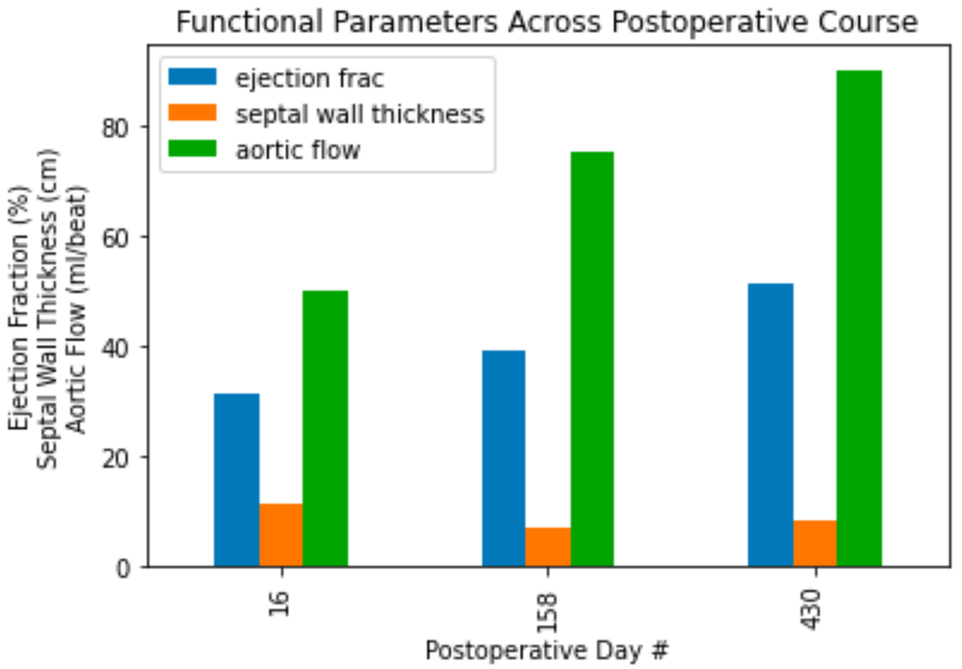
Intervention

Application of the xenograft matrix to the infarcted area helps preserve and restore the function by two mechanisms. First, mechanical constraint has been demonstrated to improve ventricular performance after infarction. This can be achieved with any number of patch materials, including synthetics, but these patches often cause secondary problems by increasing scar tissue formation. The xenograft from porcine small intestine submucosa, however, has been shown to be anti-inflammatory and prevents scarring. The second mechanism is via the delivery of paracrine factors bound within the matrix that are released into the epicardium. These factors, which include various growth factors and matrix-bound vesicles, transgress to the subepicardium and mobilize resident repair cells to enhance proliferation and produce a microenvironment conducive to angiogenesis and remodeling of the tissue (3, 4, 5).

RESULTS

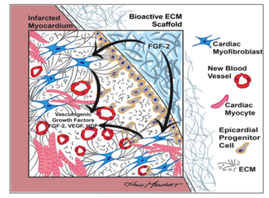


■ = arrhythmia present



DISCUSSION

The successful functional recovery of cardiomyocytes in [GG] following treatment with xenograft bioscaffold suggests this therapy holds great potential for the treatment of severe heart failure. Mr. [GG] presented with a preoperative ejection fraction of 10%, requiring full mechanical support, and progressively improved to an essentially normal ejection fraction over the course of a year. While revascularization therapy is expected to provide some functional benefits, the improvement seen is extremely variable and not expected to be of this magnitude— typically revascularization therapy results in improvements of 5-10%, and practically never all the way to the "normal" range of >50%, especially with the degree of damage seen on cardiac MRI. Future prospective studies are strongly indicated to more rigorously evaluate the impact and therapeutic benefit of such xenograft bioscaffolds in patients with severe heart failure.



Conceptual graphic of scaffold-induced proliferation mechanisms following MI.

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