Remodeling Failing Human Myocardium With Hybrid Cell/Matrix and Transmyocardial Revascularization

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Given the limited treatment options for advanced heart failure, the intrinsic regenerative properties of stem cells have been evaluated for myocardial remodeling. Previous stem cells techniques for myocardiocyte remodeling have been limited by the low cellular retention. Presented is a hybrid approach for remodeling infarcted myocardium through implantation of allogeneic human amniotic fluid–derived mesenchymal stem cells within micronized human allograft-derived liquid matrix during the performance of transmyocardial revascularization (TMR). Given the induced increase in vascular density from TMR, we hypothesize that it may serve as a therapeutic delivery system for stem cell placement into damaged myocardium. We present a patient with ischemic cardiomyopathy and refractory angina, who clinically improved after this hybrid therapy of intraoperative TMR and placement of amniotic fluid–derived mesenchymal stem cells and liquid matrix within the TMR channels. Noninvasive testing of myocardial viability biomarkers utilizing both cardiac magnetic resonance imaging and thallium imaging supported the clinical improvement in cardiac symptom may be related to ventricular remodeling in a region of infarct with subsequent functional improvement. *ASAIO Journal* 2018; 64:e130–e133.

Key Words: myocardial remodeling, stem cells, transmyocardial revascularization

Advanced heart failure (HF) continues to be a prevalent cause of morbidity and mortality. Given the limited HF treatment options, the continued search for novel therapies has made the intrinsic regenerative properties of stem cells a proposed "bridge-to-regeneration" for myocardiocytes.

Previous stem cells techniques for myocardiocyte regeneration have been limited by the low retention of stem cells during implantation.[1] To improve stem cell retention during implantation, we present a promising hybrid approach for remodeling infarcted myocardium by implanting human allogeneic amniotic fluid–derived mesenchymal stem cells (aMSC) within liquid matrix during the performance of adjunctive transmyocardial revascularization (TMR). TMR is purported to stimulate angiogenesis when multiple channels are produced on the left ventricular (LV) epicardial surface with a high-powered carbon dioxide laser. TMR has demonstrated symptomatic relief for refractory angina in patients with maximized medical therapy and coronary arteries unable to be completely revascularized.[2] Furthermore, TMR has demonstrated to decrease cardiac events and cardiac-related hospitalization time compared with medical therapy alone.[3] Given the ability of TMR to induce increased vascular density, we hypothesize that TMR may serve as a therapeutic delivery system for stem cell placement into damaged myocardium.

Clinical Summary

A 59 year old man was referred to our institution for persistent angina secondary to shortness of breath (New York Heart Association II-III) related to ischemic cardiomyopathy from chronic diabetes initially treated 14 years ago with coronary artery bypass graft (CABG) and subsequently with seven percutaneous coronary interventions. Before referral, the patient was receiving maximized medical therapy for refractory angina including, but not limited to, vasodilators (nitrates and hydralazine) and remodeling agents (beta blockers and angiotensin-converting enzyme inhibitors). The decision for referral was precipitated by the findings of a coronary angiography performed for angina in setting of the patient's risk factors. Coronary angiogram demonstrated multiple coronary artery grafts with no significant stenosis; however, the distal native vessels demonstrated severe stenosis and were determined to be poor targets for revascularization. Nuclear myocardial perfusion exam was not performed given the findings of angiography, and no recent nuclear exams were available before referral.

A cardiac magnetic resonance imaging (CMR) performed before referral demonstrated severe systolic dysfunction (LV ejection fraction [LVEF] of 27%) and a large, akinetic transmural infarct involving the inferior and inferolateral walls of the left ventricle that was highly unlikely to improve with revascularization. With the objective of LV myocardium remodeling, a hybrid therapy was performed that combined TMR and implantation of aMSC within the TMR channels in the setting of a micronized human allograft-derived liquid matrix from bank-derived amniotic membrane (AT, Phoenix). Given the evidence that aMSC demonstrate immunoprivileged qualities, these stems cells were chosen for their ability to strongly suppress immune responses, with the expectation of reversing ongoing inflammation, allowing for tissue remodeling by reduction of fibroblast-induced scarring. aMSC also have the potential to reduce the possibility of immune sensitization or inflammatory-related adverse reactions, such as acute cellular rejection.[4,5]

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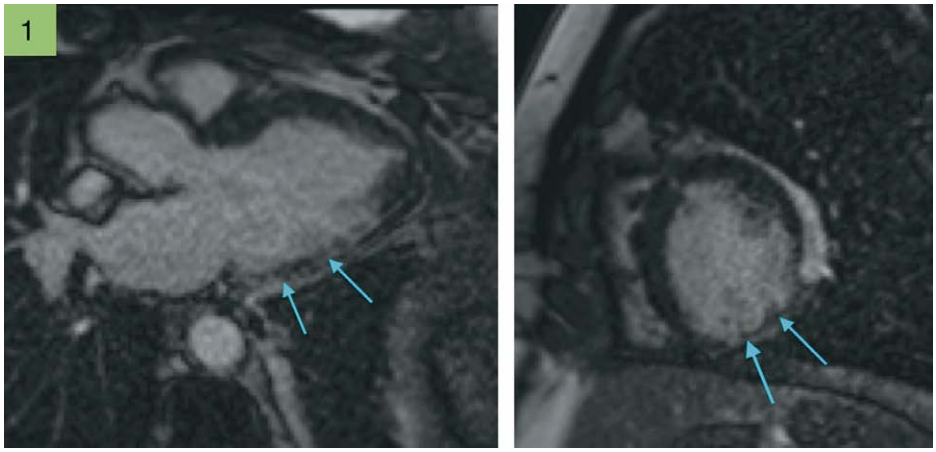

Figure 1. Postoperative day 6 late gadolinium enhancement steady-state free precession (SSFP) images in 3-chamber (left) and short-axis (right) views demonstrate transmural delayed enhancement involving the inferior and inferolateral segments of the left ventricle (arrows) diagnostic of transmural infarction.

Technique

Utilizing an institutional review board (IRB)-approved protocol, the patient underwent left mini-thoracotomy, and TMR was performed on the inferior and inferolateral LV walls with a total of 16 laser-generated myocardial channels and subsequent placement of both 1.2 million aMSC and liquid matrix around five TMR channels located in the infarct. Intraoperative transesophageal echocardiogram (TEE) demonstrated an LVEF of 35% with inferior and inferolateral wall akinesis and hypokinesis of the remainder of the LV.

The patient tolerated the procedure well with an uneventful hospital course and no complications. On postoperative day 6, the patient underwent both CMR and nuclear thallium viability exams. Delayed enhancement imaging on CMR demonstrated a stable, large, transmural infarct of the inferior and inferolateral wall (**Figure 1**), that correlated with preoperative CMR finding, and no evidence of myocardial edema on T2-weighted imaging. CMR also demonstrated persistent akinesis in the infarct region and a decreased LVEF of 27%. Thallium scan demonstrated a transmural resting perfusion defect in the inferior and inferolateral wall, with no significant thallium redistribution in the inferolateral wall on 24 hour delayed images (**Figure 2**).

On postoperative day 27, repeat CMR demonstrated multiple, new foci of hypointense signal correlating with the signal of normal myocardium located within the mid-wall of the infarct on delayed enhancement imaging. Additionally, the inferior and inferolateral LV wall demonstrated improved systolic wall thickening with an overall improved LVEF of 34%. T2-weighted imaging again demonstrated no evidence of myocardial edema, suggesting no evidence of posttreatment inflammation or rejection.

On postoperative day 91, the patient reported a clinically significant improvement in angina (New York Heart Association I), and repeat CMR and thallium viability exams were subsequently performed. Magnetic resonance imaging demonstrated confluent areas of normal hypointense signal within the mid wall of the infarct (**Figure 3**), with improved wall thickening and function in the inferior and inferolateral wall and an improved LVEF of 40%. Thallium viability scan demonstrated new confluent areas of radiotracer in the inferior and inferolateral wall on both resting perfusion and 24 hour delayed images, suggesting new, viable myocardium (**Figure 4**).

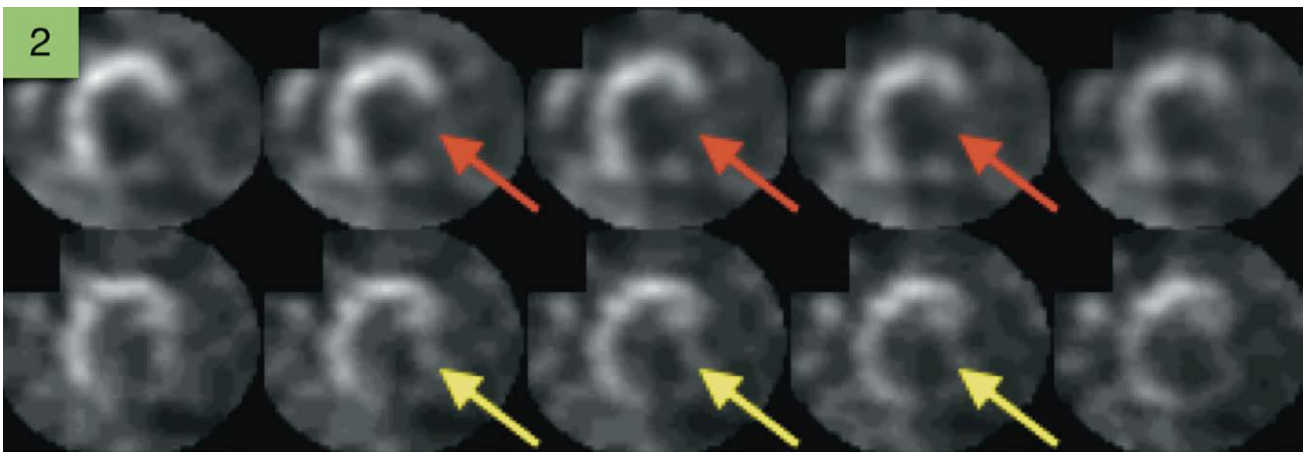

Figure 2. Postoperative day 6 short-axis tomographic views from a thallium scan demonstrate a transmural defect on both the resting perfusion images (top row, arrows) with no evidence of viable or hibernating myocardium on delayed redistribution images (bottom row, arrows).

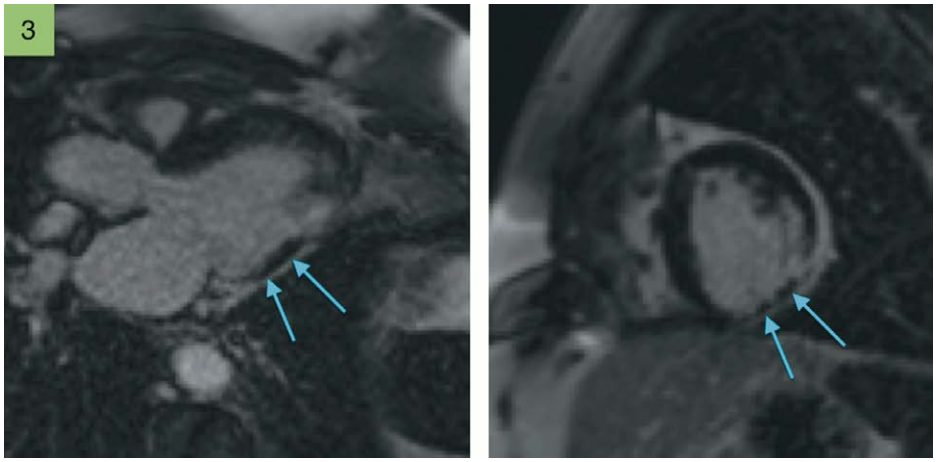

Figure 3. Postoperative day 91 from a cardiac magnetic resonance imaging (MRI) demonstrate a confluent pattern of epicardial hypointense signal in the mid wall of the previously identified region of transmural infarction. This confluent hypointense signal can be seen in both 3-chamber (left) and short-axis (right) views and demonstrates a signal intensity that matches normal myocardium.

Discussion

TMR for symptomatic relief of refractory angina has been demonstrated to be superior to medical management for both initial and mean 5 year long follow-up.[4,5] Although the mechanism of relief provided by TMR requires further study, a leading hypothesis is that TMR-related neovascularization is the predominant cause of clinical improvement and cardioprotection.[6] Utilizing neovascularization induced by TMR, we present a patient with ischemic cardiomyopathy and refractory angina, who clinically improved after a hybrid therapy combining intraoperative TMR and placement of aMSC in liquid matrix within the TMR channels. Although previous studies using exclusively TMR or mesenchymal stem cell have demonstrated increased myocardial perfusion and myocardiocyte transformation, respectively, to our knowledge, neither technique alone has demonstrated improved ventricular function.[7,8] Although further study is required to determine the specific mechanism of this hybrid therapy, initial research suggests that TMR delivery of aMSC to myocardium induces a paracrine-directed transition of mesenchymal tissue into viable myocardial tissue. This proposed mechanism was supported by successful detection of biomarkers of myocardial viability using both CMR and nuclear thallium imaging after hybrid therapy and improvement in the patient's angina. Furthermore, the clinical improvement in cardiac symptoms is proposed to be related to ventricular remodeling of infarct with subsequent functional improvement.

The novelty of these findings necessitates further study given the patient's specific clinical case. Although the described findings are unique to this hybrid therapy, investigation of the potential for remodeling agents to provide an adjunct role for myocardial remodeling is necessary because the patient was treated with maximized medical therapy for refractory angina, including multiple myocardial remodeling agents. Furthermore, although TMR delivery of stem cells suggests a promising approach, further study into delivery systems could provide subsequent advances in myocardiocyte regeneration. For example, the NOGA catheter could combine a noninvasive, refined delivery utilizing myocardial mapping models, and promising research using extracorporeal shockwave has demonstrated both an efficacious and noninvasive method of engraftment of aMSC into sick myocardiocytes.[9]

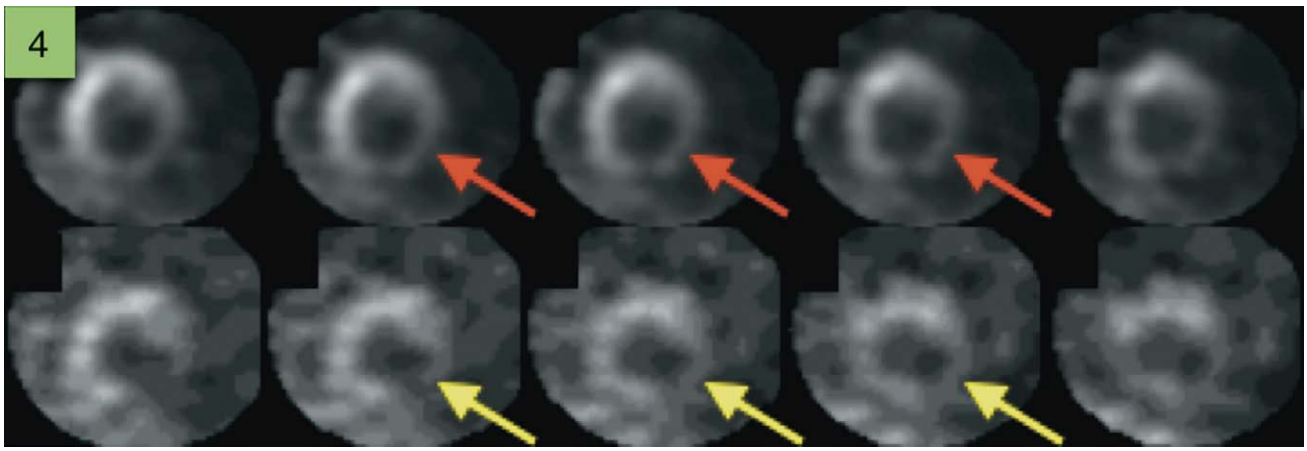

Figure 4. Short-axis tomographic views from a thallium scan performed on postoperative day 91 demonstrate improved radiotracer uptake on both resting perfusion (top row, arrows) and delayed redistribution images (bottom rows, arrows) in the inferior and inferolateral wall, suggesting viable myocardium, which is new compared with earlier images from postoperative day 6.

Conclusion

Given the improved clinical symptoms for this patient with refractory angina, we propose that a hybrid therapy utilizing a combination of human allogeneic amnion–derived mesenchymal stem cells in liquid matrix delivered by laser-generated TMR channels may provide a possible therapeutic benefit for remodeling infarcted myocardium and improving ventricular function.

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