Improving Delivery of a Biomaterial Payload in Myocardial Infarction

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Survival after an acute coronary syndrome has greatly improved because of advances in thrombolytic therapy, stabilization of the culprit lesion such as with coronary stents, and the use of pharmacological approaches to prevent recurrent thrombotic and arrhythmic events. Despite these approaches, however, myocardial injury culminating in myocardial infarction (MI) continues to be an all too common sequela. The MI region is a highly heterogeneous structure that contains several cell types, such as residual cardiac myocytes, inflammatory cells of different lineages, proliferating and transdifferentiating fibroblasts, and extracellular matrix proteins and signaling molecules. Although canonical thought was that the MI region was a rather static, fibrotic structure, it is now clear that this is a dynamic and ever-evolving entity with changes in geometry, biophysical properties, and cellular/extracellular composition. The time course and extent of these post-MI processes have been generically termed post-MI remodeling and is recognized as a milestone event for the initiation and progression to left ventricular (LV) dilation and dysfunction. One ubiquitous feature of post-MI remodeling is a progressive thinning and dyskinesia of the MI region, which is because of the summation of several factors: a loss of cardiac myocytes and thus functional myocardium, continuous turnover and instability of the extracellular matrix, and significant shifts in stress–strain patterns within this region throughout the cardiac cycle. Specifically, significant heterogeneity arises in the stress–strain patterns both within and surrounding the MI region and in turn can contribute to a feed-forward process of continuous activation of bioactive molecules and extracellular matrix instability. These biomechanical changes result in continued MI thinning and recruitment of border zone myocardium into the MI region, which is defined as MI expansion. As the MI expansion process continues in an inexorable fashion, the degree of heterogeneity in stress–strain relations are exacerbated, bulging of the MI region becomes evident by many imaging approaches, and changes in LV geometry, notably LV dilation, ensues. The evolution of this MI expansion process is dependent on the species (notably rodent versus large mammal), the size of the initial myocardial injury, transmurality, and location. Nevertheless, MI expansion eventually can lead to LV pump dysfunction and heart failure. Systemic pharmacological approaches for the management of post-MI remodeling and heart failure form the mainstay of therapeutics, notably antagonists of the sympathetic and renin–angiotensin pathway. However, strategies that specifically target the MI region and most specifically target the early MI expansion process have not been forthcoming. As such, this remains an important unmet medical therapeutic area and is of considerable research interest.

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Because the biophysical properties of the MI region, notably abnormalities in regional stress–strain patterns, likely contribute significantly to the expansion process, it would seem intuitive to alter the biomechanical properties of the MI itself. To that end, biomaterials such as alginates, hydroxyapatites, decellularized extracellular matrix, and hyaluronic acid–based gels have been injected into the MI region of animal models.[1–5] These biomaterials exhibit diverse properties, such as material stiffness, degradation rates, and associated inflammatory response. Despite the significant differences in biochemical/biophysical characteristics, the majority of past studies have identified an attenuation of the MI expansion process. Indeed, the success of these preclinical studies to favorably alter cardiovascular remodeling in general can be appreciated by the increased number of reported clinical studies using injectable/deliverable biomaterials, as shown in Figure 1. For example, the intraoperative injections of an alginate-based biomaterial (Algisyl-LVR) has been advanced to initial clinical studies.[6,7] Although this initial clinical feasibility study was performed in global ischemic cardiomyopathy patients rather than post MI, direct myocardial injections of this biomaterial was not associated with significant adverse events and improvements in certain indices of functional capacity at 1-year follow-up.[7] As such, more rigorous preclinical studies that examine the mechanisms and specific biomechanical response of these injectable biomaterials, particularly in the context of post-MI remodeling, is warranted if more effective and clinically useful strategies for the use of these biomaterials is to be realized. The study in this issue of *Circulation: Cardiovascular Interventions* by Rodell et al[8] directly addresses several of these key issues by using a relevant large animal model of post-MI remodeling and examining several key considerations about biomaterial delivery to the MI region. Specifically, this translational study advanced our understanding of biophysical thresholds of biomaterials in terms of computing material stiffness properties, degradation rates, and delivery strategies—all of which were validated in an ovine model of MI remodeling and expansion.

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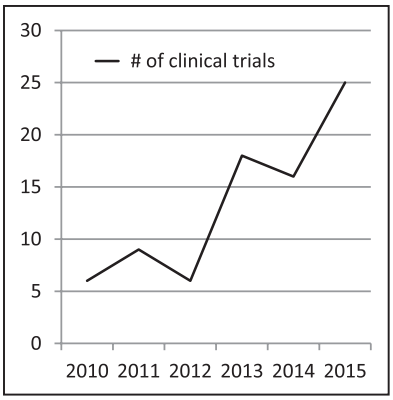

Figure 1. The number of clinical feasibility. Early clinical trials using biomaterials for cardiovascular disease has increased steadily during the past 5 y. This has been the result, in large part, to the success of biomaterials in preclinical studies and the development of biomaterial formulations, which can be used in a clinical context. (Results from PubMed Search on terms cardiovascular and biomaterials, performed September 12, 2016.)

Type of Material
• Degradable / Stable
• Mechanical Properties
Type of Injection
• Volume
• Pattern
• Timing
Type of Delivery
• Epicardial / Endocardial
• Intramyocardial
• Intracoronary
• Endoscopic/ Minimally Invasive Surgery
Type of Therapeutic
• Biomaterial Alone
• Adjunct with Cell Therapy
• Adjunct with Drug Delivery

Figure 2. Critical considerations for the advancement of injectable biomaterials in the context of post–myocardial infarction remodeling and expansion. Although not intended to be comprehensive, generalized categories of issues to be addressed in terms of thematic areas for both preclinical and clinical research have been identified.

The first important finding from the study by Rodell et al[8] is that different biomaterials, hydrogels, were constructed with different biomechanical properties (compressive moduli) and stability (degradation rates). Specifically, hyaluronic-based hydrogels (HA gels) with or without dual cross-linking were used in compression studies, which demonstrated that the dual cross-linked HA gels exhibited nearly a 40-fold higher material stiffness with only an ≈5% degradation after 8-week incubation. Through the use of finite element analysis and modeling, it was determined that the dual cross-linked HA gel reduced predicted myocardial fiber stress by ≈50%. These studies provided in vitro and in silico demonstration that specific biophysical characteristics of injectable biomaterials can be evaluated and potentially optimized. This is an important set of studies in that it provides a platform for discovery of basic properties of injectable biomaterials that may have optimal effects on LV mechanics in the post-MI context.

The second important finding from the study by Rodell et al[8] is that the different HA gel formulations developed and initially subjected to finite element modeling were then examined and validated in the intact ovine MI model. Both histological and serial magnetic resonance imaging demonstrated that when the HA gels were injected at the time of MI induction, increased MI thickness was observed at both 4 and 8 weeks post MI. However, the relative magnitude of these MI thickness measurements were greater in the cross-linked HA gel formulation. By extension, this would imply that the regional wall stress within the MI region with this cross-linked HA gel formulation would be lower and thus attenuate a driving stimulus for MI expansion and eventual LV dilation. Indeed, this study demonstrated a modest but significant reduction in LV dilation with HA gel injections. These findings would suggest that a hydrogel formulation with higher stiffness (compression moduli) reduced degradation kinetics would provide optimal characteristics in terms of counteracting the adverse stress–strain relations that exist in the post-MI region. However, this interpretation may be oversimplistic in that HA gels, as with most biomaterials, are not biologically inert. For example, alterations in inflammatory cascades and cellular proliferation (ie, macrophage polarization, fibroblast proliferation/transdifferentiation) are likely induced by HA gel injections. As such, although most certainly contributory, the effects of these gel injections are unlikely to be solely because of physical bulking of the MI region. The findings of Rodell et al, which suggest multiple mechanisms of action for the injection of the HA gels, is that in silico modeling predicted a 50% greater myocardial fiber stress reduction with the cross-linked HA gel, but in vivo assessment of LV dilation (the key response variable for MI expansion) was only modestly and not significantly different between HA gel formulations. These findings underscore the importance of using both computational and animal models in examining the effects of injectable biomaterials. There were some shortcomings from the study by Rodell et al,[8] which are worthy of mention in that these should serve as a catalyst for future studies and research directions. First, the biomaterials were injected at the time of MI induction, which is unlikely to be a relevant clinical time point. The authors recognize this limitation and indeed advanced an injectable formulation that could be deployed at later post-MI time points. Second, the study used a 16-injection pattern for a total HA gel injection volume of ≈5 mL, which may be a highly complex injection strategy and volume of biogel to delivery clinically. This raises the issue that research into optimal injection patterns and volumes must also be considered in addition to the type of injectable biomaterial.

The final important step by Rodell et al[8] was the development and deployment of a newly designed sheer-thinning and self-healing HA gel. The sheer-thinning characteristics of the HA gel allowed for injection through a steerable 4F injection system directly into the midmyocardium. The self-healing characteristics of the HA gel allows for polymerization and stabilization of the injected material at the target site. Although there are several devices under preclinical/early clinical evaluation for directed myocardial delivery using minimally

invasive methods,[9,10] these have been primarily for delivery of cell-based/small molecule–based therapeutics. The use of an injectable HA gel that potentially can be used in these delivery systems most certainly moves this exciting field forward. These HA gel catheter delivery studies outlined by Rodell et al[8] were intended to be initial proof of concept. Thus, more careful assessment and use of the HA gel formulation in relevant large animal post-MI models and refinement of the delivery devices are most certainly exciting areas for future research.

The use of injectable biomaterials most certainly holds promise for attenuating and potentially reversing adverse post-MI remodeling, but many issues and considerations remain. Although not intended to be comprehensive, a summary of the considerations for the use of injectable biomaterials is shown in Figure 2. Briefly, the type of biomaterial to be used in terms of stability and biophysical characteristics and the type of injection strategies in terms of injection volumes, patterning, and timing are important areas for further research. The route and target for biomaterial injection and to what degree these biomaterials can provide efficacy as a stand-alone treatment or harnessed as an adjunctive delivery platform for cell-based/small molecule–based therapeutics remains to be established. One of the perhaps unrecognized and important outcomes from the study by Rodell et al[8] is that this was performed by a collaborative team of biochemists, computational/mechanical engineers, and cardiothoracic surgeons. It is through these translational and collaborative research efforts that the full potential of injectable biomaterials for the treatment of major cardiovascular disease will be realized.

Disclosures

None.

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