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Review

Ventricular wall biomaterial injection therapy after myocardial infarction: Advances in material design, mechanistic insight and early clinical experiences

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ABSTRACT

Intramyocardial biomaterial injection therapy for myocardial infarction has made significant progress since concept initiation more than 10 years ago. The interim successes and progress in the first 5 years have been extensively reviewed. During the last 5 years, two phase II clinical trials have reported their long term follow up results and many additional biomaterial candidates have reached preclinical and clinical testing. Also in recent years deeper investigations into the mechanisms behind the beneficial effects associated with biomaterial injection therapy have been pursued, and a variety of process and material parameters have been evaluated for their impact on therapeutic outcomes. This review explores the advances made in this biomaterial-centered approach to ischemic cardiomyopathy and discusses potential future research directions as this therapy seeks to positively impact patients suffering from one of the world's most common sources of mortality.

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Introduction

Cardiovascular diseases (CVD) are one of the leading causes of mortality worldwide. In 2012 CVD accounted for 17.5 million deaths around the world [1]. Among CVD, myocardial infarction (MI) and other types of ischemic heart diseases (IHD) are a principal source of mortality [2]. The concept of intramyocardial biomaterial injection therapy was introduced and has been widely investigated during the past decade as a mechanical strategy to reduce left ventricular (LV) wall stress by mechanical load shielding, increasing LV wall thickness and decreasing the ventricle radius, thereby moderating the pathological LV remodeling process (Fig. 1). In 2004, Christman et al. reported that direct injection of fibrin glue into the infarcted myocardium preserved cardiac function, decreased infarct size and increased neovasculature formation [3,4]. Two years later, Wall et al. described the mechanical contribution of injectates in reducing LV wall stress and improving ejection fraction using finite element modeling. The injection of biomaterials into a thinned ventricular wall increases the wall thickness, thus reducing the myofiber stress, and if the injectate is properly distributed, normalizes the stress in the LV [5]. The early experimental data and the computational model laid the foundation for many subsequent investigations into cardiac wall injection therapy as a potential means for improving functional outcomes in post-MI patients.

The concept of intramyocardial biomaterial injection therapy began to capture the attention of the broader biomaterials community in the first five years after solidification of the concept, with early progress being well-summarized and highlighted by several groups in 2011 [6–8]. A variety of biomaterials including naturally-derived hydrogels, synthetic hydrogels, self-assembling peptides and microparticles have been shown to have therapeutic effects in animal models [6–8]. Among all candidate injectate materials, alginate hydrogel was the first to reach phase I clinical trials beginning in 2008 [9]. In the past five years, research and developments in the field have built momentum and significant progress has been made in virtually all aspects of the therapy, bringing this approach closer to the bedside. More biomaterials have entered pre-clinical and clinical trials. More sophisticated models for the mechanical and biological effects of biomaterial

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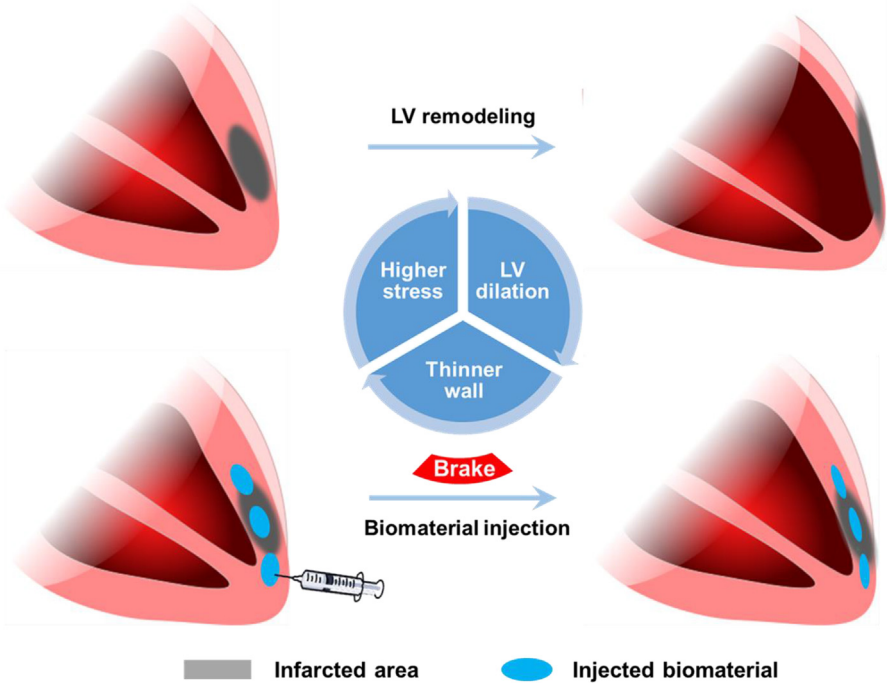

Fig. 1. Left ventricular (LV) remodeling and intramyocardial biomaterial injection therapy. The LV wall thickness is better maintained by biomaterial injection, and lower wall stress is believed to contribute to the preservation of LV geometry.

injection have been introduced. An array of designed, injectable biomaterials that incorporate specific functionalities have been reported. Optimization of parameters in the injection procedure has been stressed, and more options in minimally invasive injection procedures have been explored.

The collective effort of the community could be assembled at this point into a long-term vision for the implementation of this promising biomaterial-based intervention: (1) imaging of the patient's heart provides data for personalized finite element model construction, emphasizing the spatial distribution of the infarct; (2) a bioactive, bulking material capable of positively influencing post-MI remodeling events is selected; (3) an injection plan with parameters guided by personalized cardiac modeling to achieve optimized mechanical and biological effects is developed; and (4) the patient undergoes the procedure to precisely deliver the biomaterial and is treated with a complementary pharmaceutical regimen to further facilitate an optimal chronic outcome. In this review, we summarize the progress in the field in the past five years that would contribute to meeting the elements that comprise this vision.

Clinical trials and large animal studies

PRESERVATION-1 clinical trial

As noted above, alginate was the first biomaterial evaluated in clinical trials. IK-5001, an alginate hydrogel (1% sodium alginate plus 0.3% calcium gluconate) developed by Leor et al. and BioLineRX (Jerusalem, Israel) was shown to have therapeutic benefit in terms of reduced LV enlargement and increased scar thickness in a preclinical (porcine) infarction/reperfusion model in 2009 and soon entered a phase I clinical trial (NCT00557531) [9,10]. In the first-in-man study, 27 patients with moderate-to-large ST-segment-elevation MI and successful revascularization were enrolled and had IK-5001 injected within 7 d after infarction through the infarct-related coronary artery using an infusion catheter with percutaneous radial artery access [11]. In the earlier porcine model, IK-5001 was shown to diffuse through the vasculature and gel in the infarcted myocardium [10]. Six months follow up in patients showed the safety of the intracoronary hydrogel injection approach [11].

Following the phase I trial, a larger scale PRESERVATION-1 trial (NCT01226563) investigating the effectiveness of IK-5001 for prevention of ventricular remodeling and congestive heart failure was initiated [12–14]. The long-term results were recently reported with the conclusion that intracoronary injection of IK-5001 prevented neither LV remodeling compared to saline control nor the occurrence of heart failure [15]. 303 patients with large ST-elevation myocardial infarction (STEMI) were enrolled and randomized 2:1 to receive a 4 mL injection of alginate or saline in the infarct artery 2–5 d following MI. At 6 and 12 months, LV end-diastolic volume index increased for both groups without statistical differences. In addition, no differential improvements were observed in secondary endpoints for the hydrogel group [15]. The lack of clinical efficacy following encouraging porcine model data might be attributable to larger infarction sizes in patients, which would decrease the likelihood of delivery across the entire infarction region. It would be interesting to know how the delivered hydrogel was distributed with respect to the varied infarcts in the patient group and whether LV wall thickening was observed. Additionally, the degradation rate of the injected material was unknown. There are also conceptual concerns associated with the intracoronary delivery method. Infusion of the hydrogel precursor into the coronary arteries might be expected to be accompanied by the risks of hydrogel occluding smaller vessels and remote embolization. Such effects may be sub-clinical and obviate mechanical benefits provided by the hydrogel myocardial placement.

AUGMENT-HF clinical trial

An alternative alginate-based strategy has been pursued by Lee et al. and LoneStar Heart (Laguna Hills, USA). Unlike the IK-5001

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