Reparative resynchronization in ischemic heart failure: an emerging strategy

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Cardiac dyssynchrony refers to disparity in cardiac wall motion, a serious consequence of myocardial infarction associated with poor outcome. Infarct-induced scar is refractory to device-based cardiac resynchronization therapy, which relies on viable tissue. Leveraging the prospect of structural and functional regeneration, reparative resynchronization has emerged as a potentially achievable strategy. In proof-of-concept studies, stem-cell therapy eliminates contractile deficit originating from infarcted regions and secures long-term synchronization with tissue repair. Limited clinical experience suggests benefit of cell interventions in acute and chronic ischemic heart disease as adjuvant to standard of care. A regenerative resynchronization option for dyssynchronous heart failure thus merits validation.

Keywords: biologics, cardiac resynchronization therapy, clinical trial, dyssynchrony, heart failure, myocardial infarction, regenerative medicine, stem cells

Expert Opin. Biol. Ther. (2014) 14(8):1055-1060

Cardiac dyssynchrony provoked by disparity in contractile timing is a recognized mechanism of poor outcome in patients with heart failure. Cardiac pump function relies on coordinated myocardial motion secured by ordered electromechanical activation. Even in initially healthy hearts, nonphysiological pacing triggers dyssynchrony with detrimental molecular alterations underscoring the requisite of a synchronized contractile pattern for sustained cardiac well-being. Disruption in synchronous motion impacts heart health, compromising vital parameters ranging from ejection volume and diastolic filling to valve function, wall stress and neuro-hormonal activity. Ultimately, cardiac dyssynchrony precipitates structural remodeling and worsens pump failure [1].

Cardiac resynchronization therapy (CRT) through biventricular pacing has offered a major advance in the management of dyssynchronous heart failure [2]. Growing clinical experience demonstrates that device-based CRT produces favorable effects on contractility, reverse remodeling, exercise capacity and overall survivorship. By electrically activating cardiac chambers in an attempt to correct contractile timing, CRT is particularly effective in cardiac dyssynchrony with ventricular conduction delay improving on the efficiency of the contraction–relaxation cycle and supporting hemodynamic performance [3]. Despite documented benefit, current practices that rely on pacing devices are associated with a substantial share of nonresponders among treated individuals [4].

Variance in the magnitude of the response to CRT is not fully understood but is likely due to multiple factors, including idiiosyncrasy in the disease substrate. In particular, refractory heart failure is a common outcome of massive myocardial infarction. Prompt revascularization has reduced premature death in the setting of acute myocardial infarction but has produced, in survivors, a high risk for developing chronic heart failure. Cardiac dyssynchrony develops early after successful
Cardiac resynchronization therapy relies on biventricular pacing, and is integral in managing dysynchronous heart failure. Yet, the infarction-provoked scar may impede a favorable response to pacing regimens. A nonviable myocardium is inadequately resynchronized by pacing, and dyssynchrony stands uncorrected.

Restoration of normative impact may require a tissue-reparative strategy. The notion of ‘reparative resynchronization’ was recently formulated highlighting the prospect of stem-cell-based structural and functional repair.

As one-third of qualified candidates who fulfill clinical guidelines for cell-based resynchronization that reported absence of either arrhythmogenicity or uncontrolled cell growth [13-15]. Clinical trials have thus established safety and feasibility; however, patient age or comorbidities may compromise the regenerative capacity of utilized stem-cell types, mandating further investigation and optimization [16]. Clinical trials have thus established safety and feasibility; however, patient age or comorbidities may compromise the regenerative capacity of utilized stem-cell types, mandating further investigation and optimization [16]. Clinical trials have thus established safety and feasibility; however, patient age or comorbidities may compromise the regenerative capacity of utilized stem-cell types, mandating further investigation and optimization [16]. 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are increasingly tested in experimental settings (Table 1). Case in point, cardiosphere-derived stem cells, isolated directly from heart tissue, are composed of cell subpopulations with markers of cardiac progenitors, mesenchymal stem cells and endothelial cells that collectively promote cardiac regeneration. Transplantation of cardiosphere-derived stem cells, as a monotherapy, into an infarction model (2 million cells per rat heart) shows improved regional and global contractility with decreased dyssynchrony within infarcted/peri-infarcted regions [17]. Beyond adult stem-cell sources, nuclear reprogramming has provided more recently an unprecedented means to reset cell fate and engineer from somatic tissue, such as a fibroblast, induced pluripotent stem (iPS) cells, which can serve as an unlimited autologous source of new tissue [18]. In vitro, iPS cells can differentiate into functional beating syncyta expressing cardiac contractile proteins and ion channel sets responsive to excitation inputs. In vivo, iPS cell transplantation achieves, post-injury, multilineage tissue reconstruction [19]. High-fidelity speckle-based imaging has been used to map the transition from the initial focal insult to global dysynchrony, and assess the responsiveness to therapeutic interventions [20]. Prospective speckle-tracking echocardiography documents the aptitude of targeted iPS cell implantation to rescue contractility and correct discoordination in infarcted regions, a recognized epicenter of dysynchrony [10]. Initial preclinical experience suggests that dysynchronous motion characterized by early stretch followed by delayed contraction in the infarcted heart is correctable by iPS cell therapy (200,000 undifferentiated iPS cells per mouse heart; Figure 1). Regional benefit of iPS cell intervention translates into improved left ventricular conduction and contractility, reduced scar and reversal of structural remodeling, protecting against organ decompensation [10]. iPS cells rely on glycolytic metabolism, providing a possible survival advantage within the low-oxygen–containing environment of the ischemic myocardium [21]. In situ imaging and ex vivo histological validation have implicated iPS cell engraftment and lineage differentiation, pointing to endogenous cell-cycle activation in the diseased heart associated with reduction in fibrotic burden post-infarction [10,19]. Reestablishment of myocardial mechanical properties and correction of coordinated cardiac wall motion offer thereby an integrated readout of myocardial function achieved by tissue repair. Multiple mechanisms of action possibly underlie the benefit of an iPS cell-based intervention, including putative differentiation into cardiomyocytes, vasculature and/or paracrine effects, culminating into induction of an innate regenerative response.

Translation and adoption of the cell-based cardiac resynchronization principle into practice will require establishment of scalable and standardized stem-cell platforms with robust safety and efficacy profiles, optimized for delivery and tissue implantation in patient populations stratified for maximal benefit. Potential applications of stem-cell–based resynchronization include nonresponders to current management strategies, and prophylactic use as an early intervention for high-risk groups (Figure 2). To this end, establishing validated quality-control procedures through standard operating practices for harvesting, isolation and expansion of cell populations is an essential component in securing desired outcome. Evidence-based and cost-effective procedures will ultimately define an evolving model of regenerative care likely to be implemented.

### Table 1. Stem-cell–based cardiac resynchronization studies.

| Study | Myocardial infarction (MI) | Combination therapy | Cells Type | Dose/heart Route of delivery | Outcome Follow-up period Echocardiographic readout Efficacy on LV synchrony |
|-------|-----------------------------|---------------------|------------|----------------------------|-----------------------------------------------|
| **Clinical** | | | | | |
| Chang et al. (2008) [13] | Acute MI Drug-eluting stent (+) | CD34+ 90 × 10^6 Intra-coronary | | 6 months Tissue Doppler | Favorable |
| van Ramshorst et al. (2009) [14] | Chronic MI CRT (-) | BMNC 93 × 10^6 Intra-myocardial | | 3 months Speckle tracking | Favorable |
| Pokushalov et al. (2011) [15] | Chronic MI CRT (+) | BMNC 43 × 10^6 Intra-myocardial | | 12 months Tissue Doppler | Favorable |
| **Experimental** | | | | | |
| Bonios et al. (2011) [17] | Acute MI model (rat) Stem-cell monotherapy | CDC 2 × 10^6 Intra-myocardial | | 1 month Speckle tracking | Favorable |
| Yamada et al. (2013) [10] | Acute MI model (mouse) Stem-cell monotherapy | iP 200 × 10^4 Intra-myocardial | | 3 months Speckle tracking | Favorable |

BMMC: Bone marrow-derived mononuclear cells; CDC: Cardiosphere-derived stem cells; CD34+: Granulocyte colony-stimulating-factor-mobilized CD34+ cells from peripheral blood; CRT: Device-based cardiac resynchronization therapy; iPS: Induced pluripotent stem cells; LV: Left ventricle.
Figure 1. Stem-cell intervention rescues disparity in ventricular wall motion post-infarction. Impact of stem-cell biotherapy on cardiac dyssynchrony deconvoluted in a murine infarction model. A total dose of 200,000 undifferentiated induced pluripotent stem (iPS) cells per heart (40,000 cells/site × 5 sites) was delivered by epicardial route into the peri-infarcted anterior wall of the left ventricle within 30 min following coronary ligation. Pre-infarction, all segments of the left ventricle demonstrate harmonious contraction during systole (left top) and relaxation during diastole (left middle) documented by in vivo speckle-tracking echocardiography. At 1 month, infarction precipitated dysynchronous motion characterized by early stretch followed by delayed contraction (middle) with correction afforded by iPS cell therapy (right). Bottom row depicts fitted strain patterns reflecting normokinesis pre-infarction (left), dyssynchrony post-infarction without treatment (middle), and resynchronization following cell therapy (right). See also Ref. [10].

Figure 2. Stem-cell–based resynchronization complements standard of care. Dyssynchronous heart failure is a malignant disorder commonly refractory to the existing therapeutic armamentarium that currently combines pharmacotherapy with device-based resynchronization. Responsiveness to pacing devices is impeded by the scar burden post-infarction, mandating approaches capable to promote tissue repair. Potential applications of stem-cell–based reparative resynchronization include cardioprotection in acute/subacute phases of disease to prevent disease progression, and normative restitution to restore structure and function in the setting of chronic dyssynchronous heart failure.

Guidelines-directed standard-of-care

Dyssynchronous heart failure

Stem cell-based resynchronization

Onset

Medical therapy

Progression

Device-based resynchronization

Advanced disease

Protective biotherapy

Restorative biotherapy

Harmonization

Velocity

Area of interest

Systole/Diastole

Early stretch

Delayed contraction

Early stretch

Delayed and reduced contraction

Organized and timed wall motion

Strain pattern

Fitted

Velocity

Pre-infarction

Systole

Diastole

Normokinesis with normal geometry

Dyssynchrony with parenchymal loss

Resynchronization with tissue repair
Mechanical dyssynchrony after myocardial infarction is a predictor of poor outcome in the setting of myocardial infarction. However, infarction-induced scar burden impedes an adequate response to device-based CRT. Delivery of stem cells in the acute phase of infarction or with progression of chronic heart failure shows significant potential in reducing the extent of dysfunctional substrates, and prospectively achieving synchronization at the whole organ level. Stem-cell-based resynchronization thus emerges as a promising biotherapeutic strategy equipped to address the primary defects in myocardial pathodynamics that underlie dyssynchronous heart failure post-infarction.

**Expert opinion**

By harnessing the potential of regenerative medicine, stem-cell biotherapy emerges as a potential means to reconstitute collapsed mechanics in the failing myocardium as a complement to standard of care.

**Declaration of interest**

The authors are supported by the American Heart Association, National Institutes of Health, Hitachi, Fondation Leducq, Florida Heart Research Institute, Marriott Heart Disease Research Program and Center for Regenerative Medicine at Mayo Clinic. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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