Published in final edited form as:

Curr Cardiovasc Imaging Rep. 2012 February 1; 5(1): 53–59. doi:10.1007/s12410-011-9119-z.

Imaging Cell Therapy for Myocardial Regeneration

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Abstract

Noninvasive or minimally invasive imaging techniques are essential for developing strategies and assessing outcomes of cell-based therapies for myocardial regeneration, also referred to as cellular cardiomyoplasty. Imaging-based monitoring of cell survival is useful for selection of optimal cell type and evaluating strategies to enhance engraftment. Imaging-derived surrogate end points including global and regional contractile function, myocardial blood flow, or perfusion and bioenergetics have been used in clinical trials or in relevant large animal models to evaluate the therapeutic effect and mechanisms of action of cellular cardiomyoplasty. New techniques are emerging to assess electrical integration of donor cells with host cardiomyocytes. This review will summarize and highlight important and informative findings revealed by imaging in clinical and preclinical cellular cardiomyoplasty studies over the past 3 years.

Keywords

Cellular cardiomyoplasty; Stem cell; Molecular imaging; Contractile function; Blood flow; Bioenergetics

Introduction

Prolonged coronary artery occlusion leads to myocardial injury and varying degrees of myocardial infarction. To restore perfusion, therapies involve culprit artery intervention with percutaneously directed balloons and/or stents. Unfortunately, during both coronary occlusion and reperfusion events, damage occurs to cardiomyocytes due to a lack of blood flow and generation of reactive oxygen species. The ensuing process of left ventricular remodeling involves replacement of dead cardiomyocytes with fibrotic scar tissue, which is unable to form proper electrical coupling with neighboring cardiomyocytes, and fails to generate an adequate contractile force even after reparative processes are complete. Consequently, the formation of extensive scar in the heart following a moderate-sized or large-sized infarction frequently results in severely reduced contractile function (a hallmark of heart failure) and/or ventricular arrhythmia (a cause of sudden cardiac death).

Heart transplantation is the only way to fully reverse states of heart failure, but is limited by a severe shortage of donor organs. Cell-based myocardial regeneration, which is also referred to as *cellular cardiomyoplasty*, provides an alternative to heart transplantation. For most clinical trials of cellular cardiomyoplasty, the sample size required to detect statistical differences in mortality might be unattainable [1]. Therefore, surrogate end points are necessary and those derived from imaging are keys to gauging the therapeutic effect and determining mechanisms of action. Surrogate end points enabled by imaging include *the survival of donor cells and their electrical integration with host cardiomyocytes, global and regional myocardial contractile function, perfusion, and bioenergetics (metabolism)* of the heart. In addition, imaging techniques have been used to guide cellular delivery, and this topic has been recently reviewed [2]. This review will focus on imaging-based surrogate end points in cellular cardiomyoplasty studies, and will highlight important and informative findings revealed by these end points over the past 3 years.

Imaging Donor Cell Survival

Imaging-based tracking of transplanted cells in the heart has been integrated in numerous preclinical (animals) studies of cellular cardiomyoplasty. Pros and cons of labeling strategies (*direct labeling* versus using *reporter genes*), commonly used labeling reagents, and rationales for a multimodality approach are detailed in a review article [3], and more recent developments are summarized in other reports [4–6].

Imaging reporter gene expression allows detection of cell survival noninvasively. While not translatable to patients, firefly luciferase (Fluc) detected by bioluminescence imaging (BLI) provides a simple, sensitive, and robust method to track donor cell survival. Since the vast majority of donor cells die shortly after transplantation as shown in a recent [7] and numerous previous studies, devising and assessing anti-death strategies that enhance cell engraftment are critical [8]. One such strategy is to identify types of cells that are more resistant to death. In a recent study, Boheler et al. [9] tested a novel hypothesis that proliferative-competent, mitochondria-poor and immature cardiomyocytes derived from embryonic stem cells (ESC) are more resistant to hypoxia than their more mature counterparts. In vivo BLI to assess the time course of cell survival in the heart supports this hypothesis. Another study used BLI to compare the survival of a variety of endogenous progenitor cells and showed that bone marrow mononuclear cells have a distinct survival advantage over mesenchymal stem cells (MSC), fibroblasts, or skeletal myoblasts [10••]. Compared to Fluc, reporter genes derived from mammalian ferritin detectable by MRI [11••] and sodium iodide symporter (NIS) [12••] by PET or herpes simplex virus type 1 thymidine kinase (HSV1-tk, also detectable by PET) [13•] can be potentially applied to patients. Using NIS reporter, Higuchi et al. [14] also showed that overexpression of vascular endothelial

growth factor (VEGF) improves the survival of endothelial progenitor cells transplanted in the heart. However, ectopic expression of NIS may induce excessive sodium influx, resulting in abnormal electrophysiological behaviors in labeled cells, thus, needs more evaluation.

By combining the BLI and cardiac magnetic resonance (CMR) modalities, Zhang et al. [15•] demonstrated that despite a positive BLI signal, improper delivery of cells into the left ventricular cavity occurs at a non-negligible frequency; such a false positive can be confirmed if CMR reveals no intra-myocardial signal from cells labeled with superparamagnetic iron oxide (SPIO) particles. These data argue for using direct labeling to ensure proper transplantation of stem cells. SPIO particles are by far the most utilized cellular labeling reagent, primarily because they can be easily detected by T2 star (T2*)-weighted gradient echo (GRE) MRI, regardless of their cellular locations. The detection sensitivity increases with field strength. In contrast, sequestration inside cellular organelles or an increase in magnetic field strength reduces the relaxivity of gadolinium-based labeling molecules (e.g. gadofluorine), which have been reported to label and track transplanted cells in the mouse heart on 9.4 T MR scanner [16].

While GRE detection methods are highly sensitive, they yield a negative contrast (*dark* signal void) associated with a “*blooming artifact*” that obscures underlying tissue anatomy. A number of “positive” contrast methods have been developed (a summary of them can be found in reference [17••]). A recent development utilizes a novel MRI technique, sweep imaging with Fourier transformation (SWIFT), to detect SPIO-labeled cells in the myocardium [17••]. Compared to GRE imaging, SWIFT reduces the in vivo blooming artifact by achieving an echo time in the microsecond range (Fig. 1A–C). SWIFT technique detects the intense “pileup” of positive signal from off-resonance water in the vicinity of SPIO, thus this technique increases the cellular detection specificity (Fig. 1D–G). Finally, SWIFT magnitude images (Fig. 1B, F) retain anatomical information along with the “positive contrast,” whereas many other positive contrast methods lose tissue signal on the positive contrast image. While a minimum of 10^4 labeled cells aggregated in a gel phantom was detected by SWIFT, the threshold number of detectable cells in the heart in vivo could be greater.

The major limitation of iron oxide labeling is a rapid loss of specificity to detect viable cells, due to phagocytosis of the iron oxide particles released from dead cells. Such uptake is anticipated due to *extensive* death of transplanted cells leading to extracellular exposure of these particles, which consequently induces a host inflammatory response. Uptake of SPIO particles by macrophages has been shown with labeled MSC [18], embryonic stem cells (ESC) [19], and cardiomyocytes derived from ESC [20••]. That said, SPIO labeling provides a *robust* histological marker to identify grafted cells, which is often challenging. A recent study showed that Prussian blue staining allows high throughput screening of tissue sections to localize patches of grafted cells in the heart even months after an intra-myocardial injection; SPIO-containing macrophages were often found in the vicinity of grafted cells but can be easily separated by a macrophage-specific marker [19, 20••].

Unfortunately, the recent discontinuation of clinically usable SPIO formulations including Feridex may set back the translatability of this labeling strategy for human applications. To overcome regulatory hurdles, [F-19]fluoro-2-deoxy-D-glucose (FDG) may be a viable alternative; however, FDG rapidly effluxes from, and may cause DNA damage to, labeled cells; these issues have been examined in a recent study using FDG to label adipose-derived stem cells [21]. In contrast, SPIO labeling does not have similar limitations.

Imaging Stem Cell Integration with Host Cardiomyocytes

The ability of donor cells to electrically integrate with host cardiomyocytes is a critical criterion to gauge their regenerative potential. It was shown that fetal cardiomyocytes transplanted into adult myocardium can electrically integrate with host myocytes, and through such integration, their action potentials become characteristic of more mature cardiomyocytes [22]. In contrast, skeletal myoblasts (SKB), while able to form grafts in the infarcted myocardium, increased the rate of induced ventricular tachycardia (VT) compared to sham-injected controls. Interestingly, upon forced expression of connexin-43, a gap junction protein expressed by cardiomyocytes, SKB were no longer arrhythmogenic [23]. Electrical coupling between the graft and host myocardium is visualized by in vivo imaging of Ca^{2+} transients using a fluorescent Ca^{2+} sensor protein, GCaMP2, which is expressed in cardiomyocytes via transgenic approach. By imaging Ca^{2+} transients, it was shown that GCaMP2-expressing embryonic cardiomyocytes were able to couple with host cardiomyocytes resulting in a reduction of induced VT compared to sham-injected controls [23]. These data suggest that cardiomyocytes, which can be derived from pluripotent stem cells such as ESC and naturally express connexin-43, can potentially reduce life-threatening post-infarct arrhythmias via intercellular coupling with host cardiomyocytes, and thus, are a preferred cell type for myocardial regeneration. While GCaMP2 or similar approaches are not translatable to patients, a clinically applicable, catheter-based electro-anatomic mapping system was shown recently to characterize the electrical coupling of the myocardial scar delineated by late gadolinium-enhanced CMR in a pig myocardial infarction (MI) model [24•]. This approach can be potentially used to assess the integration of donor cells with the host myocardium if stem cell engraftment improves local myocardial electrical conduction.

Imaging Contractile Function Improvement

Echocardiography is a routine clinical tool to evaluate cardiac function because of its low cost, easy access, and compatibility with implanted cardiac devices which have relative contraindications in the CMR scanning environment. Nonetheless, the versatility of CMR to assess infarct size, function, perfusion, and metabolism in a single examination has been well recognized [1, 15•, 20••, 25, 26•, 27••, 28], and its high reproducibility has made it a popular method for quantifying cardiac function in many recent cellular cardiomyoplasty studies [20••, 25, 29–33].

LVEF, a global functional parameter measurable by echocardiography or CMR, is the most widely used index to assess the effect of cellular cardiomyoplasty in patients and animals. A recent study showed that while cardiac resident stem cells (CSC) potentially provide an autologous cell source for myocardial regeneration, transplantation of CSC into the infarcted mouse heart led to poor survival at 8 weeks and no long-term improvement in LVEF [34•]. In comparison, *endogenous* CSC activated by intracoronary administration of growth factors were shown to increase LVEF as well as reduce fibrosis and reactive hypertrophy in a pig model of acute MI [29]. In this study, the number of activated CSC was not known, therefore it is uncertain to what extent the improvement in cardiac function can be attributed to CSC activation alone. CSC can be obtained from endomyocardial biopsy samples and can be expanded in culture by forming cardiospheres. Johnston et al. [30] infused cardiosphere-derived cells (CDC) into a pig MI model; they found that CDC infusion led to a significant reduction in infarct size and improvement in hemodynamics (dP/dt), but no change in LVEF compared to placebo controls; however, the survival status of CDC was not monitored.

As a global functional parameter, LVEF is *insensitive* to detect regional contractile function changes after stem cell engraftment. To measure 2-dimensional and 3-dimensional wall motion, CMR techniques are the gold standard [35], while ultrasound-based strain and strain

rate imaging are relatively new additions to conventional echocardiography [36]. In a recent study of patients with ST-elevation MI receiving bone marrow progenitor cells, strain rate imaging revealed an increase in regional cardiac function, whereas LVEF failed to demonstrate improvement [37]. These results suggest that regional functional recovery may precede global function improvement and is more sensitive to gauge the local effects of cell engraftment. Strain rate imaging combined with dobutamine stress echocardiography also revealed an improved *diastolic* function 6 weeks after injection of bone marrow stem cells into the infarcted pig heart [38].

However, echocardiography-based regional wall motion analysis must be used carefully. Two-dimensional strains estimated by speckle tracking and tissue velocity imaging were compared with those by harmonic-phase (HARP) tagged MRI. Only modest correlations were demonstrated, suggesting that greater care is required to understand the limitations and technical challenges associated with these two ultrasound-based techniques [39]. In a clinical trial where eight patients were subjected to intramyocardial injection of autologous bone marrow mononuclear cells or MSCs, and evaluated by CMR for 1 year, Williams et al. [27••] showed a significant improvement in circumferential strain in the treated infarct zone that occurred before the improvement of global functional parameters. Qiao et al. [20••] engrafted ESC-derived cardiomyocytes into a rat model of 1-week-old MI, and found that circumferential strains in the infarcted and border region improved substantially in the cell-treated group versus vehicle-treated controls at 8 weeks post-injection. Improvements in regional wall motion likely contributed to improved global functional parameters including LVEF observed in Williams' and Qiao's studies. Recognizing that the infarct size in surgery-induced rodent MI models varies considerably, Qiao et al. [20••] measured the infarct size before treatment to exclude animals with very small or very large infarctions; such procedures enhanced the rigor of the study.

Imaging Myocardial Perfusion and Bioenergetics in Response to Cell Transplantation

Quantification of myocardial blood flow (MBF) is important when evaluating cell-based therapy for MI. Regional MBF is a key factor which determines the grafted cell survival, and MBF improvement is a specific index for restored microvascular function, which is an underlying mechanism of cell-based therapies. By comparing the upslope of signal intensity time courses obtained from first-pass gadolinium contrast-enhanced CMR images, an early (1 week post-injection) increase in perfusion in the infarcted region was found to precede the improvement in global function, the reduction in apoptosis and infarct size in MSC-treated hearts in pig MI models [26•, 40], again suggesting the restoration of microvascular function as the mechanism of MSC-mediated cardiac repair. However, the semi-quantitative approach used in these studies might not be adequate to evaluate the extent of regional MBF recovery.

Since an increase in capillary density (by histology) does not necessarily lead to an increase of blood flow *in vivo*, a noninvasive quantification of MBF is desirable. At present, positron emission tomography (PET) is the clinical standard for MBF measurement [41]. First-pass contrast-enhanced CMR can be used to *quantify* MBF only after extensive modeling of the kinetic data [42]. In contrast, spin labeling-based CMR (SL-CMR) utilizes endogenous water molecules, hence eliminating the need to inject any exogenous tracers and has been extensively applied in animal models [43, 44] and in humans [45, 46]. Recently, Zhang et al. compared an SL-MRI based noninvasive MBF measurement with the standard fluorescent microsphere method (Fig. 2A–D). Importantly, MBF improvement in the infarcted region was detected 2 weeks after injection of human umbilical vein endothelial cells and was accompanied by an increase in capillary density estimated by histology (Fig. 2E–J).

A recovery of myocardial perfusion in the infarcted heart likely leads to improved bioenergetics of the heart. Phosphorus-31 magnetic resonance spectroscopy (³¹P MRS) can noninvasively quantify the concentrations of cardiac high-energy phosphates, ATP, and creatine phosphate (PCr), which are rapidly and reversibly converted by the creatine kinase (CK) reaction. The ratio of phosphocreatine PCr/ATP based on the area of PCr and beta-ATP resonance peaks is widely taken as an index of myocardial creatine kinase reserve. Zhang and his coworkers showed an improvement of PCr/ATP ratio in the endocardium of the infarcted border zone after transplantation of bone marrow stem cells [28]. Compared to the PCr/ATP ratio, measurement of ATP production rate [47] appears more sensitive to detect the “energy starvation” in the failing heart [48]. The potential utility of ³¹P, ¹H, and ¹³C hyperpolarization MRS techniques in the studies of heart failure has been reviewed most recently [49••]. These spectroscopic techniques combined with MRI such as blood oxygenation level dependent (BOLD), which allows estimation of myocardial oxygen extraction [50], could more reliably reveal the degree of metabolic improvement mediated by cellular cardiomyoplasty in a failing heart.

Conclusions

For assessing the effect of cellular cardiomyoplasty, regional and global contractile function, perfusion and bioenergetics of the heart have been used as surrogate end points in clinical trials and large animal models; CMR imaging combined with spectroscopy represents a versatile modality for obtaining all these indices in one session. With the discontinuation of clinical SPIO formulations, alternative labeling strategy, and multimodality approach such as labeling with FDG detectable by PET, perfluorocarbon or perfluorooctyl bromide nanoparticles detectable by MRI and CT [5] might be the relevant clinical molecular imaging strategies in the next 3–5 years for cardiovascular stem cell applications. On the biological side, lack of transplanted cell survival and integration with host myocardium are considered as major hurdles to advance the field of cellular cardiomyoplasty, and imaging can play a unique role in developing strategies to enhance cell survival and integration.

Acknowledgments

The research was supported by NIH grants R01-HL081185A1 and R01-HL081185S1 (RZ).

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Fig. 1.

SWIFT detection of SPIO-labeled stem cells in the heart. ECG-gated in vivo SWIFT and GRE images of a rat receiving 5 million SPIO-labeled embryonic stem cells (A–C). SPIO-associated signals are marked by a *yellow circle*. In vivo GRE image (D), ex vivo SWIFT imaginary (E), magnitude (F), and ex vivo GRE magnitude (G) images obtained from a heart receiving 0.5 million labeled stem cells. *Arrows* indicate location of cells. The off-resonance signal is displaced over a few voxels and “piles up” in magnitude and imaginary mode images. As shown in E–G, the positive and negative signal in the imaginary component of the SWIFT image facilitates to distinguish SPIO particles from signal void at tissue boundary, whereas GRE cannot discriminate the two.

(From Zhou et al. [17••]; reprinted with permission)

Fig. 2.

Spin labeling-MRI to evaluate the myocardial blood flow changes in response to endothelial cell (EC) engraftment. Nonslice-selective T1 map ($T1_{ns}$, **A**), slice-selective T1 map ($T1_{ss}$, **B**), and MBF map (**C**) calculated from **A** and **B**. Distribution of fluorescent microspheres in a left ventricle tissue section (**D**). The late gadolinium-enhanced image, the corresponding MBF map, and immunostaining of von Willebrand Factor (vWF) for estimation of capillary density are shown for a representative heart from EC-treated group (**E–G**) and vehicle group (**H–J**). DAPI stains for nuclei. Scale bars = 100 μ m. *Arrowheads* point to a gel phantom in the CMR image as a reference for quality control for estimation of $T1_{ns}$ and $T1_{ss}$.