PROMETHEUS and POSEIDON
Harnessing the Power of Advanced Cardiac Imaging

Atul R. Chugh, Joao A.C. Lima

Imaging has played a central role in gauging the potential therapeutic effects of cellular therapies in cardiovascular medicine. In earlier studies, left ventriculography was used as the means of evaluation of the global myocardial function. Although this modality had its benefits with convenience and availability, the method does not allow for sufficient global ventricular cavity reconstruction because it only allows one to measure the ventricle in 2 planes. Some earlier transition to 2-dimensional echocardiography was made in clinical trials; however, cardiac MRI soon became the gold standard modality to image patients undergoing cellular therapy in clinical trials. The fact that the modality not only allows for very precise global and regional function but also very effectively measures what we consider fibrotic or scar burden made it the obvious front-runner. Subsequent studies bore this point out well. In fact, therapies that had a great deal of promise in earlier stages of application had lesser salutary signals with later studies. For instance, changes in ejection fraction (EF) that were noted in earlier bone marrow cell studies in the setting of acute myocardial infarction, such as Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction (REPAIR-AMI, where EF was measured by ventriculography), were not noted in the Swiss Multicenter Intra coronary Stem Cells Study in Acute Myocardial Infarction (SWISS-AMI, where EF was measured by cardiac MRI). One potential contributing factor to this change is the difference in the imaging modality in the earlier versus later studies, which highlights the importance of imaging methodology in clinical stem cell trials. This observation was confirmed in a recent meta-analysis in that positive outcomes in EF were noted more in bone marrow cell studies when echocardiography or ventriculography was used as the imaging modality over cardiac MRI. In this issue of Circulation Research, we are fortunate to have 2 studies from a group that would help define and expand the role of advanced cardiac imaging modalities in the field of cardiac regenerative therapies.

The use of cardiac MRI in cardiovascular cellular therapy trials has been somewhat to the point in examining select indices of global function (with global EF now being the de facto gold standard end point), regional myocardial function, and scar regression as indirect measures of myocardial regeneration. More specifically, most cardiac MRI–driven stem cell studies have focused on the global function, the regional scar, and changes in the regional scar functional changes without delving into the entire myocardium as a potential therapeutic target. However, these phenotypic changes to the myocardium secondary to cell therapy may reflect transformations occurring globally outside of the infarct zone. This point is made in light of the fact that mechanisms of injury in the setting of ischemic heart failure include inflammatory changes that may not be tethered to the infarcted region. Moreover, if analyses are exclusively focused on these parameters, we simply assume that the mechanistic action of cellular therapy is limited to the treatment area and exerts no effect on the myocardium as a whole. This negates the possibility of phenomena such as remote paracrine effects, stem cell migration, as well as adjacent or remote endogenous (host) stem cell recruitment. Lastly, in trials in which cell treatment is used in conjunction with revascularization, this somewhat focused imaging approach disallows the possibility of parsing out results attributable to revascularization versus cell treatment. Hence, to fully appreciate the effects and potential mechanistic values of this promising therapeutic combination, a more global approach must be taken.

Here we commend the work by Karantalis et al, which highlights this point. In the PROMETHEUS study, we are offered the unique opportunity to potentially isolate the effects of cell therapy versus those of revascularization. In the study, cell treatment was delivered transepicardially to areas deemed nonrevascularizable, whereas surgical revascularization was performed to myocardial segments that were not directly treated. Scar tissue, perfusion, wall thickness, wall thickening, and systolic strain were all quantified using accepted methods. Variations in the intensity of change from the target area, adjacent/remote revascularized regions, and untreated segments give us, for the first time, imaging-based evidence that synergistic mechanisms may be at play when using cell treatment and treatment in conjunction with revascularization. The results suggest that treatment area cells were able to exert some action onto adjacent revascularized segments. The parameter that may illustrate this best is the systolic wall thickening, which increased in graduated fashion with the greatest improvement in the cell-treated area and the least effect on the remote revascularized area. Such information is critical to the future development of cell therapy, particularly when considering cell delivery strategies and...
combination therapies. It must be appreciated, however, that the study does not account for the fact that cells may have been delivered to a single segment twice, which may make the data difficult to interpret in terms of magnitude of improvement as merely a function of cell dose. This inherently remains a limitation in a segmental versus global analysis. In this study that includes only 6 patients, however, a segmental analysis is almost necessary. Nonetheless, the study demonstrates important treatment-targeted differences from region to region. Another creative concept introduced by the study is the concordance index scale, which attempts to use multiple imaging parameters and condense them down to 1 metric as a measure of congruity of effect. This, in itself, is an important first step toward deviating away from the global EF as the lone gold standard end point for stem cell studies. Geometric remodeling, fluctuant loading conditions, and changes in valvular regurgitant volumes, among other reasons, can influence this parameter to a greater extent compared with the regional measures of myocardial mechanical behavior. Hence, the dependence on EF alone or in a vacuum may be neglecting important signals when examined in concert with a multitude of phenotypic changes. Therefore, the concordance index scale, although limited because score indices are a pragmatic reduction of complex phenomena into simplistic formulae, represents a good initial step in the direction of accounting for multiple influences in regional mechanical performance.

However, limitations with the MRI modality itself cannot be ignored. One of the issues we continue to grapple with is the value of delayed gadolinium enhancement. Gadolinium is an inert molecule that simply diffuses into areas with decreased space occupation (ie, decreased cellularity). Hence, delayed gadolinium may very well define scar or infarct tissue but may also be seen in conditions where pericellular space is enlarged, which can be secondary to replacement or interstitial fibrosis. Therefore, in-depth investigation using newer technologies such as T1 mapping and viability studies (eg, manganese-enhanced imaging) may add greater detail to the signals one could recognize with delayed gadolinium enhancement (Figure 1). These additive methods should enhance mechanistic information, which could differ with cell types.

Of particular interest is whether the phenotypic changes seen post-treatment would lend themselves toward greater paracrine effect or direct angio- or myocardiogenesis in patients. Furthermore, understanding this fundamental mechanism could result in more efficient delivery systems or the identification of complementary coagents.

A limitation from a trialist’s point of view is the issue that the patient pool that requires cellular therapy with greatest urgency is often precluded from MR studies because of a pre-existing implantable cardiac defibrillator. The lack of our ability to adequately image these patients may be significantly slowing down the pace of our discovery process. Of note, at current adherence rates, $\approx50\%$ of eligible patients were implanted with an implantable cardiac defibrillator, thereby impairing the inclusion of up to half of the patients who could be potentially enrolled in heart failure trials for cardiac MR studies. However, the paradigm is rapidly shifting with the reporting of safety data from multiple high-volume centers, which suggest that cardiac MRI is safe and feasible with no discernable adverse short- or long-term clinical events. Another approach to this problem is the use of other tomographic imaging modalities that have different safety profiles than that of cardiac MR. The POSEIDON study does this by using cardiac CT, an emerging tool in clinical stem cell studies, to examine scar size and function in the form of global and segmental EF after injection of mesenchymal stem cells transendocardially in patients with ischemic cardiomyopathy. The study confirms that the greatest effect in regional functional improvement is close to the site of injection, whereas the magnitude of difference is seen greatest in regions where dysfunction was worst. The latter concept has been well demonstrated in previous trials with other cell types. However, the novelty of the study lies in the fact that cardiac CT technology is sensitive enough to show evidence of regional function improvement in this relatively small study.

In relation to cardiac MR, although some ambiguity exists regarding the significance of delayed gadolinium enhancement, even greater ambiguity exists with segmental early enhancement defect because there are only limited studies proposing its use beyond those performed in patients with ischemic cardiomyopathy. Moreover, histopathologic confirmation of these changes is not yet available in a widespread manner as it is for cardiac MRI. Although the study shows changes in the segmental early enhancement defect quantities, the significance of this may remain ill-defined for some time until more studies are done to establish this modality’s use in myocardial characterization. As the modality’s popularity grows in this context, the imaging community will need to address the issue of radiation exposure, which is a well-documented safety concern. Promisingly, newer multidetector systems and efficient protocols continue to attenuate this exposure with the evolution of this technology. Overall, the 2 studies break new grounds in the field of stem cell research imaging. The PROMETHEUS study accomplishes this by analyzing the entire myocardium of a treated heart and then examining regional effect differences based on proximity to treatment. The study’s findings bring us one step closer to understanding how stem cell therapy works in producing improvements of left ventricular architecture and function. The POSIEDON study uses cardiac CT and, therefore, bypasses the barriers of cardiac MR to demonstrate that this tool may indeed have the sensitivity and bandwidth to measure phenotypic changes in cardiac stem cell studies. In conclusion, what the studies illustrate is that advanced cardiac imaging will play a key central role in the clinical development of regenerative therapies both for end point anchoring and for gauging important mechanistic information, which may lead to groundbreaking improvements in cell therapies.

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