Illuminating the Path Forward in Cardiac Regeneration Using Strain Magnetic Resonance Imaging

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In recent years, several important studies have shown advantages of strain imaging over imaging of ejection fraction (EF) for diagnostic and prognostic applications in heart disease. For example, global longitudinal strain assessed using echocardiography has demonstrated superior performance compared with echocardiographic assessment of EF for predicting major adverse cardiac events in heart failure, myocardial infarction, and valvular heart disease.1,2 Likewise, strain is now recommended in addition to EF to identify systolic dysfunction in chemotherapy patients.3 Using accurate and reproducible magnetic resonance strain imaging methods, such as myocardial tagging and displacement encoding with stimulated echoes, strain detects subclinical systolic dysfunction in diabetics and obese children at stages where changes in EF are not seen.4,5

Using regional analysis methods, strain imaging shows high potential for detecting late activating regions and optimizing the implementation of cardiac resynchronization therapy, providing more valuable information than cine imaging.6 This recent wave of impressive strain imaging successes has led to the suggestion that strain imaging could potentially replace or supercede EF.7 Within the field of cardiac regeneration, the efficacy of emerging therapies is often assessed by measuring longitudinal changes in EF in large groups of small animals. However, such measurements do not directly interrogate contractile function localized to specific regions that were damaged and treated. In this issue of Circulation: Cardiovascular Imaging, the article by Qin et al8 from the laboratory of Dr Joseph Wu extends the successful application of strain imaging into the realm of preclinical cardiac regenerative therapies, showing that sensitive and accurate magnetic resonance imaging (MRI) strain using myocardial tagging detects subtle beneficial effects of engineered heart muscle implanted at sites of postinfarct scar, whereas imaging of EF does not.

The experiments by Qin et al8 tested the hypothesis that engineered heart muscle could preserve contractile function in regions of the heart where scar formed 28 days after induction of myocardial infarction. The experimental group consisted of rats with postinfarct scar that were treated with engineered heart tissue, whereas the control group consisted of rats with postinfarct scar that underwent a sham operation with stitching, but were not treated with engineered heart muscle. Both groups of rats were studied 4 weeks after treatment or sham surgery using an imaging protocol that included multislice cine imaging, late gadolinium–enhanced imaging, and myocardial tagging. Ultrasound imaging was also performed. Although EF did not show any difference between the control and treatment groups and end diastolic volume and scar size only showed trends toward lower values in the treated group, circumferential strain derived from myocardial tagging localized to the scar region as defined by late gadolinium–enhanced imaging showed a statistically significant benefit of engineered heart muscle.

Interestingly, ultrasound-based speckle tracking assessment of strain localized to the scar region did not show a benefit of engineered heart muscle. To resolve the apparent discrepancy between MRI-based and ultrasound-based strain results, the authors compared inter- and intraobserver variability of strain for the 2 modalities. In this regard, Bland—Altman analysis showed much larger limits of agreement for ultrasound-based strain compared with MRI-based strain. This analysis demonstrated that only the more accurate and reproducible MRI tagging method would be expected to detect the subtle benefits of engineered heart muscle with statistical significance using a sample size of 10 to 12 rats per group. An important lesson demonstrated by these data is that not all strain imaging methods are created equal—some are more accurate and reproducible than others and accordingly can support smaller sample sizes. This lesson may translate and indeed be amplified in clinical imaging, where high accuracy is needed when imaging is applied to individual patients (ie, a situation where the relevant group size has n=1).

Although conventional myocardial tagging was used by Qin et al, newer MRI strain methods such as displacement encoding with stimulated echoes9,10 have been developed that maintain or even improve on the accuracy and reproducibility of tagging for strain quantification while requiring less manual intervention and maintaining high spatial resolution.11 Thus, accurate and reproducible high-resolution MRI strain imaging with rapid analysis has been demonstrated for both preclinical and clinical applications.12,13

See Article by Qin et al

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There are also several experimental factors in Qin’s study that merit discussion. First, the engineered heart muscle was engrafted a full month after the induction of myocardial infarction, not immediately after infarction as is common in cell therapy studies. In the hearts of rodents, both dilation of the left ventricle and scar formation are highly progressed by this time. This design nicely simulates a potential clinical scenario where engraftment of engineered tissue would take place during the chronic, not acute, phase of infarct healing. Second, the engrafted tissue was composed of human embryonic stem cell–derived cardiomyocytes that typically contract at a rate of 1 Hz. At the higher in vivo frequencies of the rat heart, the surviving human cardiomyocytes were likely unable to maintain a contraction frequency synchronized to the host heart. These components of the experimental design may have attenuated the potential contribution of engineered heart tissue and may more closely resemble the potential outcome in immunocompetent adult humans where rejection of engrafted tissue will be greater than that in preclinical studies. In this context, the finding of greater preservation of circumferential shortening in the area of engrafted engineered heart muscle by Qin et al is highly significant. Given the choice to use the American Heart Association 17-segment model, it remains unclear to what degree the preservation of contractile function in the area of engrafted tissue is attributable to low-magnitude contraction of engrafted cardiomyocytes as opposed to a local paracrine effect on adjoining surviving rat cardiomyocytes that were outside the scar but located within the same segment that was classified as scar. Further, the inclusion of another control group engrafted with irradiated engineered heart muscle as was performed by Riegler et al would have revealed whether the presence of engrafted viable engineered heart muscle specifically, as opposed to a graft that resembles a biocompatible material patch on the myocardium generally, promotes the preservation of contractile function in scar tissue that was observed by Qin et al. The ability to quantify regional preservation of contractile function in the area of engrafted tissue in the absence of heightened contractile function in remote tissue is integral to differentiating local from systemic effects of cell therapy.

Ultimately, investigators developing cardiac regenerative therapies seek to discover approaches that do improve EF; however, version 1.0 of regenerative therapies will not achieve this lofty goal. Current approaches to cardiac regeneration range from direct injection of enhanced stem cells, to the application of novel prorregenerative biomaterials, to methods to promote cell cycle re-entry to repopulate infarcted tissue with functioning cardiomyocytes. Progress of any approach will likely be characterized by gradual improvements in cell survival/differentiation and restoration of contractile function that take place over many studies and through repeated technique refinement. Accurate non invasive imaging methods that can detect small improvements in regional strain will be an invaluable tool because investigators make strides toward effective therapies that improve contractile function.

There is little doubt that accurate strain imaging, applied in both preclinical and clinical settings, will help identify promising regenerative strategies and illuminate the path forward as the field evaluates various therapeutic approaches to improve contractile function in damaged regions of the heart.

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References


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