Magnetic resonance imaging of myocardial strain: A systematic review in stable ischemic heart disease and after acute ST-segment elevation myocardial infarction.

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Abstract

The purpose of this systematic review is to provide a clinically relevant, disease-based perspective on myocardial strain imaging in patients with acute myocardial infarction (MI) or stable ischemic heart disease (SIHD). Cardiac magnetic resonance (CMR) imaging uniquely integrates myocardial function with pathology. Therefore, this review focuses on strain imaging with CMR. We have specifically considered the relationships between left ventricular (LV) strain, infarct pathologies, and their associations with prognosis.

A comprehensive literature review was conducted in accordance with the PRISMA guidelines. Publications were identified that 1) described the relationship between strain and infarct pathologies, 2) assessed the relationship between strain and subsequent LV outcomes and, 3) assessed the relationship between strain and health outcomes.

In patients with acute MI, circumferential strain predicts the recovery of LV systolic function in the longer term. The prognostic value of longitudinal strain is less certain. Strain differentiates between infarcted versus non-infarcted myocardium, even in patients with SIHD with preserved LV ejection fraction. Strain recovery is impaired in infarcted segments with intra-myocardial hemorrhage or microvascular obstruction.

There are practical limitations to measuring strain with CMR in the acute setting, and knowledge gaps, including the lack of data showing incremental value in clinical practice. Critically, studies of CMR strain imaging in patients with IHD have been limited by sample size and design. Strain imaging has potential as a tool to assess for early or sub-clinical changes in LV function, and strain is now being included as a

surrogate measure of outcome in therapeutic trials.

Introduction

In recent years survival has been improving following an acute ST-segment elevation myocardial infarction (STEMI). In the United States, the mean predicted 10-year risk of death for coronary heart disease among adults aged 30–74 years decreased from 7.2% (1999–2000) to 6.5% (2009–2010)[1]. Consequently, more individuals who survive an acute STEMI have residual infarct pathology that predisposes them to the subsequent development of LV dysfunction and heart failure, which remain the major causes of death post-MI[2]. In fact, despite improvements in survival, the incidence of heart failure following acute MI has not decreased in the past several years[3,4].

Identifying individual patients who are at risk of heart failure post-MI remains problematic[5,6]. Reductions in left ventricular ejection fraction (LVEF; mild, moderate, severe) are prognostically important[7,8] and used in evidence-based guides for treatment stratification e.g. angiotensin converting enzyme inhibitor therapy[6,8], implantable defibrillator devices[6,9]. However, LVEF is a global index that reflects changes in dimensions rather than contractility and LVEF may not account for regional variations in myocardial contractility.

Strain, the change in length per unit length of tissue, reflects myocardial deformation and is more closely linked with myocyte metabolism and contractility than LVEF[10]. Strain imaging has high potential for prognostication in the setting of post-MI risk assessment[10]. Strain is a tensor that can be largely described using 3 principal strains (E_1, E_2 and E_3), or more commonly for the heart, in a cylindrical coordinate system as strains in the radial, circumferential, and longitudinal directions. Tissue shortening is reflected by a negative strain value, which is typical during systole for circumferential and longitudinal directions, whereas radial strain is typically positive since LV thickening occurs in the radial direction with contraction. Radial strain measurements are less reproducible than circumferential or longitudinal strain[11].

Cardiac Magnetic Resonance for Estimation of Myocardial Strain

There are several techniques for assessing myocardial strain with CMR (figures 1, 2). The bespoke strain methods include myocardial tagging[12], strain-encoding imaging (SENC)[13,14], phase contrast (PC) imaging[15] and displacement encoding with stimulated echoes (DENSE)[16–18] or cine-derived strain[19–23].

Bespoke strain acquisitions

Myocardial tagging measures strain based on the imaging and tracking of tissue markers (‘tags’) induced by changes to the magnetization field[12,24]. Tagging has good intra-observer agreement[25,26], moderate inter-observer agreement[27] and is considered by some as a gold standard reference method[28]. However, tagged CMR has some limitations, with the most notable being the potential fading of the tag saturation bands during diastole, prolonged breath-holds, and time-consuming analysis that typically involves manual planimetry.

Harmonic phase analysis[29] provides rapid analysis of tagged images, but at the expense of reduced spatial resolution and strain accuracy[30]. Cine phase-contrast velocity-encoded imaging is another long-standing MRI method which is well-suited to the assessment of strain rate[31,32], but requires the integration of data to compute strain, which may decrease strain accuracy. This technique encodes tissue velocity directly into the phase of the signal by the application of a bipolar magnetic field gradient. SENC is effective for the quantification of through-plane strain, as the tag planes are oriented parallel to the imaging plane, but is limited in its ability to thoroughly assess radial and circumferential strains with good spatial coverage as well as measuring other parameters such as twist and torsion[13,14].

DENSE[16–18] encodes tissue displacement over a period of time that is equivalent to the T1 (ms) of the myocardium. The vector of magnetization is parallel to the static magnetic field in order to avoid signal delay due to T2* effects. DENSE has equivalent or better accuracy and reproducibility of strain as compared to tagging[33,34], while providing simple and rapid strain analysis[35–37].

Retrospective estimation of strain using cine CMR images

Feature-tracking (FT) involves retrospective motion tracking of steady-state free precession cine images. However, the method mainly derives strain by tracking the displacement of the endocardial border[19], rather than the full thickness of the myocardial tissue, with potential trade-offs on accuracy and greater measurement variability than with dedicated strain methods[22,23,38]. FT measurements will be less reliable when endocardial border definition is unclear[39] especially for segmental strain, when measurement error can be problematic[23]. Peak strain values may vary according to the technique used, with some techniques, such as FT generating higher peak strain values compared with other techniques such as tagging[27,40,41].

New techniques in how strain can be derived from cine-imaging have recently been developed. Tissue-tracking[20] incorporates strain derived from both the endo- and epicardial borders, whilst deformation-tracking is a non-commercial software utilizing an intensity based b-spline deformable image registration method[22]. Both methods have been reported to generate lower magnitudes of strain than feature-tracking.

Temporal resolution (~50 ms) is generally similar between these methods. Ideally, strain values would be consistent regardless of the method used though differences in CMR acquisition methods and analysis techniques are likely to result in inter-technique variability.

Which approach to strain imaging is preferred?

Given the contemporary drive for time-efficient imaging, short scans and patient comfort, retrospective cine-strain imaging without the need for additional breath-hold scans is appealing for routine clinical practice. For research imaging, where accuracy and precision are key considerations, a dedicated strain scan may be preferred to estimates of strain from cine scans. In this case, for patients early post-MI, a single mid-ventricular and/or longitudinal breath-hold scan may provide sufficiently meaningful data as a pragmatic trade-off against additional scans intended to gain more extensive LV coverage, especially when other components of the imaging examination may involve multiple breath-holds.

Methods

Eligibility criteria

Our aims were to:

1. Assess the relationships between strain and infarct characteristics in patients after an acute STEMI and in those with SIHD.
2. Assess the relationships between strain and LV outcomes in patients following an acute STEMI, and in those with stable ischemic heart disease.
3. Determine whether CMR-derived strain is a predictor of clinical outcome in patients following an acute MI.

We limited our search to peer-reviewed journals and human participants. Studies with less than 10 patients or those not published in English were excluded. Twenty-four publications were identified which described the relationship between myocardial strain and infarct characteristics (Supplementary Table 1).

Search Strategy

A systematic literature review was carried out according to the PRISMA[42] and MOOSE[43] guidelines by 2 independent researchers (KM and CM) (Figure 3) who independently searched PubMed and EMBASE using the following keywords and variations on them: 'myocardial infarction', 'infarct', 'coronary artery disease', 'ischemic cardiomyopathy', 'myocardial strain', 'strain rate', 'magnetic resonance imaging', 'cardiac magnetic resonance', 'outcome', 'MACE', 'mortality', 'infarct', 'infarct characteristics' (Online supplement).

Study selection

Abstracts of all potential titles were reviewed by KM and CM. References of relevant reviews and all full papers were searched to retrieve any additional papers, repeating the process until no new papers were found.

Cardiac magnetic resonance strain parameters and infarct characteristics.

Relationships between regional strain and infarct characteristics

Tagging[44,45] and SENC[46] discriminate patients with MI from healthy volunteers based on regional differences in myocardial contractility. Early post-MI, the infarct zone contains heterogeneous pathology including edema, inflammatory cell infiltrates, hemorrhage and viable as well as dead tissue. For these reasons infarct size by LGE is initially typically larger compared to repeat assessments months later[47]. Not surprisingly, there is only a moderate correlation between global indices of strain (circumferential or longitudinal) and infarct size when assessed early post-STEMI[27].

Reductions in global peak circumferential[11,27,46,48–55], radial[54,56] and longitudinal strain[46,51,54], as well as radial phase dispersion[57] and circumferential strain rate[58], can discriminate transmural infarction from non-transmural infarction and non-infarcted remote zones in patients with recent MI, SIHD and ischemic cardiomyopathy. Compared with longitudinal strain, circumferential strain has greater discriminative value for assessment of the transmural extent of infarction in patients with recent[27] and chronic MI[51,54].

In patients with SIHD, circumferential strain imaging with CMR[48] can reveal subtle reductions in LV contractile function that are attributable to infarct pathology, and which otherwise would not be apparent if assessed using standard measures of LV systolic function such as LVEF or fractional shortening.

Comparative analyses of strain and surrogate LV outcomes

In patients with acute STEMI, global circumferential strain[59,60], strain rate[61] and global longitudinal strain[62] are predictive of adverse remodeling in the longer term in most, but not all studies[41]. Sample size is an important consideration because only a limited proportion of patients (e.g. <10%) will experience adverse remodeling when defined in binary terms e.g. ≥20% increase in LV end-diastolic or end-systolic volume index at 6 months from baseline[41]. When FT-derived circumferential strain and longitudinal strain have been compared in prognostic studies, only circumferential strain has proven to be a multivariable associations of LV function post-MI [59]. This difference is clinically relevant since global circumferential strain predicts functional recovery after coronary revascularisation[63]. Circumferential myofibers are typically located on the epicardial aspect of the heart whereas longitudinal myofibers are typically located in the mid-endocardium, and these anatomical differences may explain the potentially superior clinical significance of circumferential strain measurements in post-MI patients[45]. Still, the available clinical evidence is limited and further research is warranted.

SENC-derived circumferential strain rate has similar prognostic value compared with the extent of late gadolinium enhancement for prediction of recovery of LV systolic function following acute MI[61]. Regional circumferential strain derived from tagging[64], rather than FT[60], has incremental prognostic utility in predicting segmental functional recovery (by wall-motion scoring) in the longer term after an acute STEMI. Compared with FT-derived strain, tagging derived strain would seem to be more robust based on reduced variance and increased predictive accuracy for identifying myocardial segments with the potential for contractile recovery post-MI[22,23].

Microvascular obstruction[61,65] and intra-myocardial hemorrhage[62,65] are associated with reduced circumferential strain, and a reduced likelihood of recovering circumferential contractile function in affected segments. On the other hand, edematous segments without infarction may generally generate less circumferential strain[66], but contractile function may recover in the longer term[67].

In patients with SIHD with or without chronic MI, the transmural extent of late gadolinium enhancement in individual myocardial segments is inversely associated with the changes in mid-ventricular circumferential strain as revealed by CMR tagging after coronary revascularisation[63], unlike LVEF which may not reflect any parameter of the segmental extent of infarct scar[63]. Therefore, compared with global LVEF, strain imaging enables more a more detailed assessment of the effects of therapeutic interventions. The threshold in the transmural extent of scar (25% or higher) varies between study populations and imaging methods[63]. Given the importance of revascularization decisions for individual patients, we think more work is needed to clarify the relevant thresholds to inform therapy.

Is myocardial strain a predictor of clinical outcome post myocardial infarction?

There is a gap in knowledge about whether or not myocardial strain assessed by CMR is independently associated with health outcomes post-MI, including major adverse cardiac events (MACE) and mortality[68]. In a group of patients referred for CMR (31% with SIHD, 13% with previous MI), lateral mitral annular plane systolic excursion (MAPSE) was a univariate and multivariate predictor of MACE. MAPSE is a surrogate for LV longitudinal function reflecting long axis LV shortening during systole[69]. In a similar all-comers group[70] (11% with coronary artery disease), tagging derived global circumferential strain was a multivariate predictor of MACE.

Infarct size revealed by CMR is independently associated with health outcomes post-STEMI[71]. Renal impairment is common following acute MI[72], rendering some patients ineligible for gadolinium-contrast examinations. Further studies are required to assess whether strain imaging might serve as an alternative tool for prognostication in post-MI patients who are ineligible for contrast imaging.

Clinical Perspective

Strain provides more direct information on regional and global LV function in patients with acute MI or SIHD than LV ejection fraction or wall motion score. Initial infarct size may over-estimate the true extent of irreversibly damaged myocardium [47,73,74], which may limit its prognostic accuracy early post-MI (the time most relevant to clinicians). Accordingly, myocardial strain has emerging potential for predicting LV recovery post-MI. Strain imaging may also be useful when infarct size cannot be assessed due to intolerance of gadolinium contrast media.

Strain imaging may be useful as an early biomarker of sub-clinical impairment in systolic function before LV function may become globally impaired[75]. Strain may be measured to assess treatment efficacy in clinical trials of therapeutic interventions in IHD patients predicated on improved precision and accuracy compared with LVEF (Clinicaltrials.gov search date, February 7, 2017: Remote Ischaemic Preconditioning to Prevent Dialysis Induced Cardiac Injury (NCT02630355), Intensive Statin Therapy in Patients With Acute MI (NCT01923077)).

Strain is superior to wall motion scoring for dobutamine stress testing in patients with SIHD[76–79] (Online supplement).

Going forward, for the diagnostic value of strain imaging to be realized in the clinic, the techniques should be straightforward to learn and implement, ideally across vendors, with acceptable accuracy and precision, and short, automated post-processing.

Practical limitations to measuring strain with CMR in the acute setting

Historically, CMR vendors did not include strain analysis options within their software, and this gap may have served as a stimulus for third party software providers. When strain analysis is not possible on the CMR workstation then workflow issues may emerge as DICOM images must be transferred from the scanner to other computers. Thankfully, this circumstance is changing and commercially available strain analysis methods are becoming more accessible and integrated within imaging platforms. Post-processing times vary from minutes with feature tracking and DENSE[27,36,37] to somewhat longer with myocardial tagging[27]. Including all of the steps from image transfer to the final read-out, LV strain analysis with FT may involve half an hour per patient and more than one hour for tagging[27], which is clearly a limiting factor for the day-to-day assessment of strain in routine clinical practice.

Limitations and lack of data showing incremental value of CMR derived strain in clinical practice

Most of the CMR studies evaluating strain in patients with recent MI or SIHD have been limited by small sample size (usually 50 participants or less), and short durations of follow-up (< 1 year) (Supplementary Table). Few studies of strain imaging have described quality assurance parameters e.g. repeatability, and none have described the impact of treatment decisions based on strain values in relation to health outcomes.

Strain derived from Echocardiography

Strain by speckle tracking echocardiography is emerging as an alternative to LVEF and wall motion for the assessment of myocardial function. Most of the echocardiography literature relates to longitudinal strain because short axis acoustic windows that would be necessary for circumferential strain are commonly limited.

In patients with recent STEMI, strain derived from speckle tracking echocardiography predicts adverse remodeling[80], has the potential to assess viability [81] and correlates with infarct size[82,83]. Speckle tracking echocardiography derived global longitudinal strain has the potential to discriminate patients with obstructive CAD during stress[84–86] or even at rest[84–86], reflecting the early consequences of the ischemic cascade on myocardial contractility.

Tissue Doppler imaging (TDI) can be used to derived strain indirectly[87] based on tissue velocity measurements provided that the direction of myocardial motion is along the ultrasound probe scan lines. Speckle tracking echocardiography makes use of ‘speckle generating targets[88] which are tracked through the cardiac cycle. A variety of software options have emerged[89], leading to a lack of standardization[90]. As this technique tracks speckles from one frame to the next, the results are influenced by image quality, with reverberations and signal drop-out distally being important issues. As the speckles are generated by the interaction of reflected ultrasound off myocardial tissue, these speckles may not be stable, because contracting myocardium changes the angle at which ultrasound waves are reflected as well as moving in and out of the plane of view, with related measurement errors[89].

3D speckle tracking echocardiography is now available[91], however measurement accuracy and precision are uncertain[92]. Disadvantages include a longer acquisition time, over multiple heartbeats and a bulkier hand held probe making it reliant on good echo windows. The main advantage of 3D speckle tracking is that through-plane motion is discounted.

Echocardiography and CMR derived strain

In an all-comers study of 106 patients, strain values estimated with speckle-tracking echocardiography and CMR-FT were moderately well correlated[93]. In patients with SIHD, regional circumferential strain revealed by tagging and speckle-tracking are at best moderately correlated[52], but small sample size (n=23) limits firm conclusions. In a study of layer-specific myocardial deformation in 29 patients with ischemic cardiomyopathy, Altiok et al.,[49] noted that endocardial strain (the inner half of the myocardium) by SENC was only weakly correlated (r=0.50, standard error of the estimate=5.2%) with the magnitude of endocardial strain by 2D speckle-tracking echocardiography, and the magnitude of strain was under-estimated by SENC as compared with echocardiography. The prognostic value of global longitudinal strain[94–97], and global circumferential strain[98] as revealed by echocardiography in STEMI survivors is fairly well established.

Echocardiography is the standard of care in clinical practice because of its portability, lower cost, safety, and higher temporal resolution, when compared to CMR. Strain can also be retrospectively estimated from routinely acquired echocardiograms, provided image quality is sufficient. On the other hand, CMR has higher precision and accuracy than echocardiography[99], is not limited by acoustic windows, and permits spatial registration of strain with infarct pathology.

Conclusions

We have conducted a systematic review of the literature on imaging myocardial strain in patients with coronary heart disease. For practical applications in the clinic, strain imaging with echocardiography and CMR are emerging options for the detection of early impairment in myocardial contractility prior to a reduction in global LVEF in patients with SIHD. In patients with borderline LVEF values, strain imaging may also be clinically useful to examine contractility in greater detail.

Multiple factors influence the decision to use echocardiography or CMR, not least cost and logistics. CMR offers the additional advantage of integrating myocardial function with pathology. Based on the available evidence, global circumferential strain has superior prognostic value compared to global longitudinal strain in post-MI patients.

Critically, strain imaging studies have been limited by design i.e. cross-sectional, small sample size, short duration of follow-up, lack of blinding, and in prognostic studies use of surrogate outcomes rather than 'hard' health outcomes. Looking to the future, further studies should involve larger numbers of participants to increase precision. More information is needed on whether parameters of myocardial strain have incremental prognostic value for prediction of LV surrogate and health outcomes in post-MI patients, compared with standard imaging parameters. Should this be the case then strain imaging early post-MI may emerge as a new tool in the clinic and for measurement of surrogate outcomes in clinical trials.

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Figure 1. Feature tracking derived strain.

A 48-year-old male patient presented with acute anterior STEMI. He underwent CMR 2 days after primary percutaneous angioplasty to his proximal left anterior descending artery, with restoration of normal antegrade coronary flow (TIMI flow grade 3).

(A) depicts an end-diastole mid-left ventricular short axis cine acquisition. ‘I’ denotes infarct region and ‘R’ denotes remote. (B) depicts an end-systole cine acquisition, with noticible thickening in the remote ‘R’ region, but not in the infarcted region ‘I’. (C) matched mid-diastolic late gadolinium enhancement depicting a transmural septal scar with microvascular obstruction. (D) peak radial and circumferential strain, with ‘I’ being over the antero-septal segment, which shows reduced radial and circumferential strain and ‘R’ being within normal ranges.

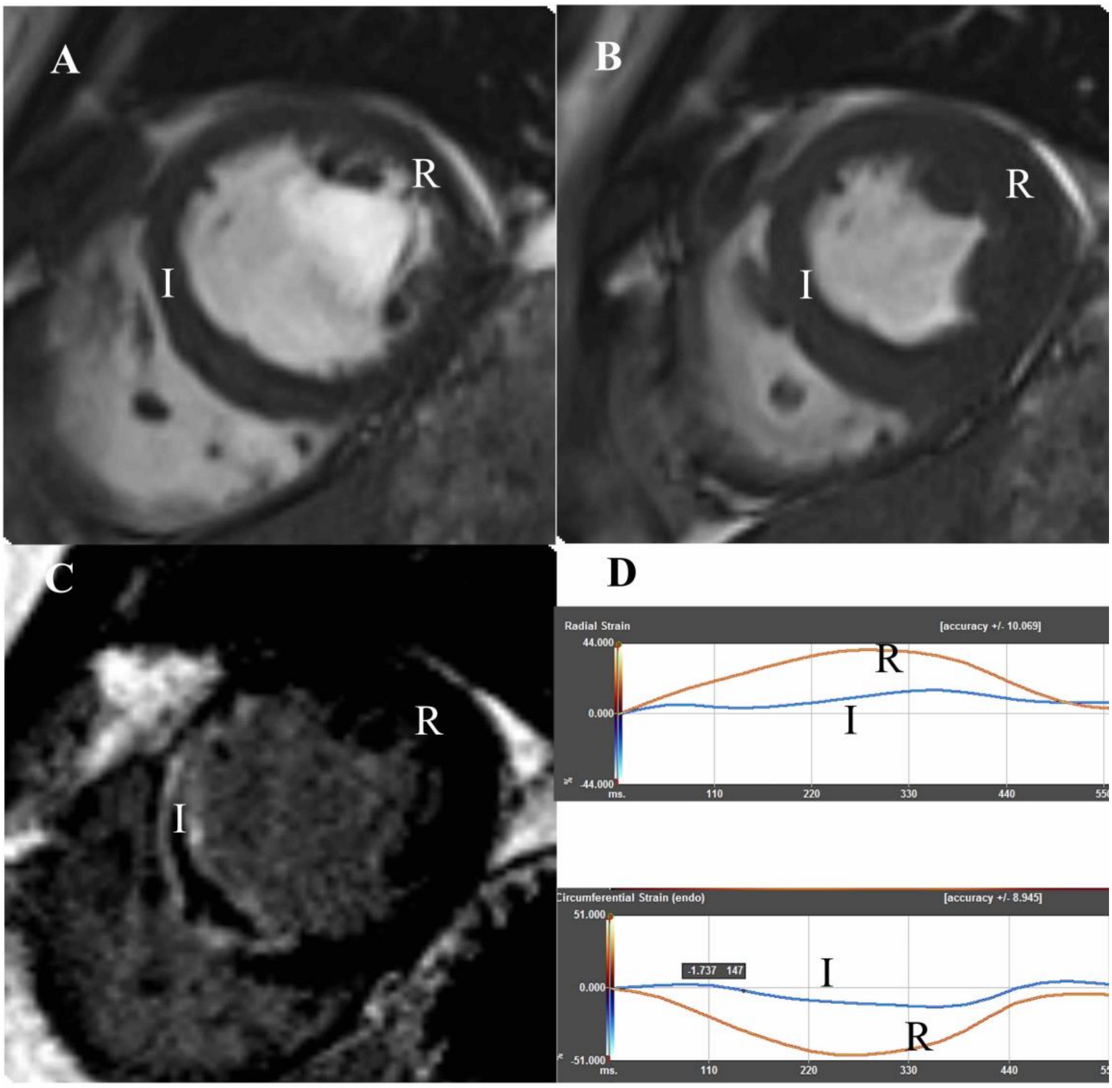
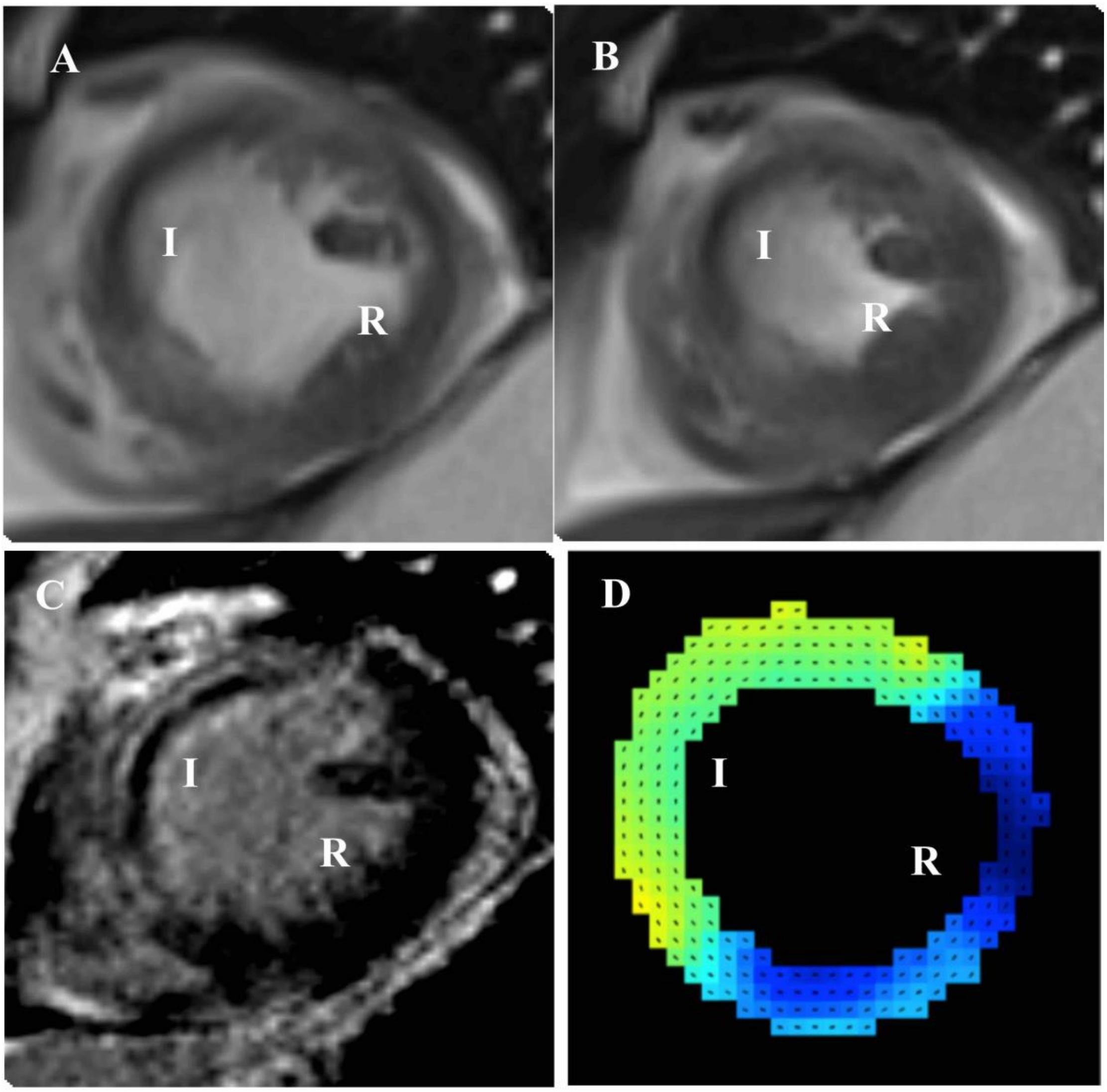

A
R
I
B
R
I
C
R
I
D
Radial Strain
[accuracy +/- 10.069]
44.000
0.000
-44.000
R
I
ms.
110
220
330
440
Circumferential Strain (endo)
[accuracy +/- 8.945]
51.000
0.000
-51.000
-1.737 147
I
R
ms.
110
220
330
440

Figure 2. Displacement ENcoding with Stimulate Echoes (DENSE) derived strain.

A 52-year-old male patient presented with anterior STEMI. CMR scan was performed 2 days after primary percutaneous angioplasty to his proximal left anterior descending artery.

(A) depicts an end-diastole mid-left ventricular short axis cine acquisition. ‘I’ denotes infarct region and ‘R’ denotes remote. (B) end-systole cine acquisition. (C) matched mid-diastolic late gadolinium enhancement depicting a transmural septal scar. (D) DENSE-derived circumferential strain map, with lower magnitudes of strain depicted as green pixels (infarct region 'I'), and higher magnitudes depicted as blue pixels (remote region 'R').


A
I
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