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Myocardial Viability Mapping by Magnetic Resonance-Based Multiparametric Systolic Strain Analysis

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Abstract

Background—Regional myocardial contractility can be characterized by three-dimensional (3D) left ventricular (LV) multiparametric strain maps generated from sequential magnetic resonance imaging of radiofrequency tissue tagging grid point displacements.

Methods—Normal average and standard deviation values for each of three strain indices at 15,300 LV points were determined from a normal volunteer human strain database (n = 50) by application of magnetic resonance-based 3D strain analysis. Patient-specific multiparametric strain data from each ischemic cardiomyopathy patient (n = 20) were then submitted to a point-by-point comparison (n = 15,300 LV points) to the normal strain database. The resulting 15,300 composite multiparametric Z-score values (standard deviation from normal average) were color contour mapped over patient-specific 3D LV geometry to detect the abnormal contractile patterns associated with myocardial infarction and nonviable myocardium.

Results—The average multiparametric strain composite Z-score from each LV region (n=120) was compared to the respective clinical standard viability testing result and used to construct a receiver operator characteristic curve. The area under the curve was 0.941 (P < 0.001; 95% confidence interval; 0.897–0.985). A regional average Z-score threshold of 1.525 (>1.525 being nonviable) resulted in a sensitivity of 90% and a specificity of 90%. Corresponding positive and negative predictive values were 84% and 95% respectively.

Conclusions—The clinical application of magnetic resonance-based multiparametric strain analysis allowed accurate regional characterization and visualization of LV myocardial viability.

Keywords

CABG; pathology; pharmacology; physiology; Magnetic resonance imaging (MRI); Myocardial injury; Myocardial mechanics; Ischemic heart disease

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INTRODUCTION

Catheter-based or cardiac surgical coronary revascularization procedures are the most commonly applied therapeutic interventions in patients with ischemic cardiomyopathy. Although many clinical factors are important in directing these high-risk interventions, the presence of viable myocardium in the distribution of target atherosclerotic vessels remains the foundation for intervention algorithms. Revascularizing viable myocardium improves outcomes, while high-risk revascularization procedures directed at nonviable myocardium do not improve outcomes over medical therapy alone [1–3]. Improving the accuracy of the detection and full characterization of the viable myocardium that directs the implementation of revascularization procedures is critical in our goal to improve outcomes in this high-risk patient population.

Currently utilized viability testing methodologies, such as thallium single photon emission computed tomography (SPECT) scanning, positron emission tomography (PET) scanning, delayed-enhancement magnetic resonance imaging (MRI), and dobutamine echocardiography are effective in directing clinical decision-making algorithms. These modalities, however, are limited in the accuracy of their regional and transmural characterization of myocardial viability by the *qualitative* nature of their output images. This qualitative image output predisposes to interobserver variability in the interpretation of *regional* involvement in irreversible ischemic injury. For example, multiple interpreters may variably characterize an area of nonviable myocardium that resulted from left anterior descending coronary artery occlusion and which overlaps anterior, anterolateral, and anteroseptal regions, as well as extending a variable distance from base to apex in each of these LV regions.

In a similar fashion, quantification of the degree of *transmural* injury is also limited with current modalities. Myocardial ischemia resulting from coronary artery occlusive disease is well known to affect the myocardium in a nonuniform transmural distribution, with the subendocardium being more susceptible to ischemia than the epicardial myocardium [3]. The ability to accurately differentiate isolated subendocardial infarction from transmural injury has important clinical implications in regard to prognosis, as well as the appropriate application of therapeutic intervention algorithms. Thallium SPECT scanning, PET scanning, delayed-enhancement MRI, and dobutamine echocardiography can only be expected to offer a *qualitative* characterization of transmural inhomogeneity. Once again, a lack of quantification of transmural viability predisposes to inconsistency in observer interpretation.

Our choice of tagged MRI as a modality for myocardial viability determination is based not only upon its highly accurate temporal and spatial characterization of ventricular anatomy, but most importantly upon its ability to measure displacements and strain in the myocardial wall throughout ventricular systole [4–8]. Utilizing software developed in our laboratory, the displacement of these tag lines can be utilized to generate 3D LV strain maps [6]. Application of a fitting algorithm to the point displacement information allows the interrogation of this strain map at 15,300 points in the LV, thereby characterizing all strain indices at virtually any point in the LV myocardium.

In addition to maintaining a high degree of regional and transmural discrimination, the large volume of mathematical information that describes systolic strain throughout the left ventricle also lends itself favorably to subsequent optimization of the visual display of regional viability results. Unlike most other scanning modalities whose primary output is an analogue image, the multiparametric strain tool generates a highly complex mathematical description of 3D myocardial contraction that can be post-processed to generate images that are most advantageous to clinical interpretation and inclusion in decision-making algorithms and the electronic medical record.

The hypothesis that MRI-based multiparametric systolic strain analysis can be effectively and efficiently implemented in the clinical assessment of patients with ischemic cardiomyopathy is tested in this initial clinical application. We further hypothesize that this methodology can accurately characterize *regional* myocardial viability when compared to current clinical standard viability testing methods. In reporting results, the importance of a head to head *visual* comparison of multiparametric strain 3D images to thallium SPECT and PET images is emphasized in addition to standard regional average comparisons. It is well recognized that patient-specific coronary distribution, and therefore the injury distribution following coronary occlusion, does not necessarily respect the somewhat arbitrary regional boundaries commonly utilized in the reporting of viability results.

PATIENTS AND METHODS

Patient Characteristics

Twenty patients (age 59.9 ± 9.3 years) with significant coronary artery disease, defined as $>70\%$ stenosis in at least one major coronary vessel, and at least one akinetic or severely hypokinetic LV wall segment underwent MRI-based multiparametric strain analysis. Patients with significant valvular disease or primary cardiomyopathy were excluded. A separate group of fifty healthy volunteers, who served as controls, also underwent strain analysis and contributed LV systolic strain data to our *normal subject strain database*. The control group consisted of twenty-seven females and twenty-three males with an average age of 32.8 ± 10.6 years. The racial makeup of the control group was as follows: forty-one were Caucasian, five were Asian, two were African American and one each were Native American and more than one race. The Human Research Protection Office at Washington University, St. Louis, MO, approved the study and all subjects gave informed written consent.

MR Imaging

Imaging was performed in a 1.5 Tesla MR scanner (Sonata, Siemens Medical Systems, Malvern, PA). Multiples short axis image sets were acquired in parallel planes at 8mm intervals extending from the plane of the mitral valve to the apex of the heart. Additionally, four sets of long axis images oriented radially and intersecting the centroid of the ventricle were also obtained. For each selected imaging plane, a single-slice MR tagged image was collected with a sequence consisting of a spatial modulation of magnetization radiofrequency tissue-tagging preparation [9,10] followed by a 2D balanced steady-state free precession cine image acquisition. Image acquisition was synchronized with real-time electrocardiogram at the time of the MRI scanning. Typical imaging parameters were: tag spacing 8mm; slice thickness 8mm; repetition time 30.3 ms, echo time 2.2 ms, field of view 306×350 mm and image matrix 168×256 .

Strain Calculations

The method used to compute strain in this study has been described previously [6,11], so only a summary is provided here. Manually identified wall boundaries from the tagged MR images were used to construct a finite element model of the left ventricle. Using the attachment points of the right ventricular free wall with the septum as landmarks, a consistent finite element mesh for the model was constructed consisting of six hexahedral elements for the basal and middle regions of the LV and six pentahedral elements covering the apex (Figure 1). Three-dimensional systolic displacements were computed from the deformation of the tag *surfaces* using a previously described and validated method [6]. Analysis of the displacement data was carried out in the finite element software package *StressCheck* (ESRD, Inc., St. Louis, Missouri). A continuous representation of the displacement field was obtained over the domain of the model from a least squares fitting of the MRI measured displacement data utilizing the

finite element basis functions. This fitting was done using the measurement analysis feature of the *StressCheck* program. Strain values were then computed from the results of this fitting.

Multiparametric Systolic Strain Z-Score Color contour Mapping

Raw systolic myocardial strain information draws clinical meaning and utility only as it relates the individual patient's point-specific regional contractile function to "normal." To define "normal" therefore, a *normal human strain database* was developed. Utilizing MRI data from fifty normal volunteers, average and standard deviation values were computed for circumferential strain, longitudinal strain and the minimum principal strain angle [12] at 15,300 points in an evenly spaced grid over the entire human LV finite element model. Strain varies throughout the human left ventricle and is sensitive to regional and transmural position [13, 14]. The characterization of a patient-specific strain value at a discrete point in the LV myocardium must therefore be in relation to the normal average value of that parameter at that position in the left ventricle.

The normal strain database allows the "normalization" of patient-specific raw strain values by their direct correlation to normal average and standard deviation ranges for each strain parameter at each of 15,300 discrete myocardial points. Mathematically, this is expressed by calculation of a Z-score, which is a simple numerical expression of the relationship of the patient-specific raw strain value to the normal average strain value. The Z-score is computed as the difference between the measured strain value and the normal average divided by the normal standard deviation at a particular point. A Z-score of 1.87, for example, means that the raw patient value for that strain parameter at that point in the left ventricle falls 1.87 standard deviations from the *normal average* of that particular strain parameter at that point in the left ventricle.

The *normalization* of patient-specific individual strain component raw values allows the combination of multiple strain parameters, with their *variable* normal ranges, into a single multiparametric strain composite index. The patient-specific *multiparametric Z-score* for any one of the individual 15,300 points throughout the left ventricle therefore relates that patient's contractile function at that point in the myocardium to normal by relating its multiparametric strain, as expressed by a composite of three equally weighted strain components, to the "normal" multiparametric strain at that point in the left ventricle. The patient-specific multiparametric composite Z-score values for each of 15,300 LV points are then subjected to three-dimensional color contour mapping (Figures 2 and 3). To statistically compare the clinical viability standard to the MRI-based multiparametric analysis, average values of the multiparametric strain Z-score were computed for each of six standardized LV regions (anteroseptal, anterior, anterolateral, posterolateral, posterior, posteroseptal).

Clinical Standard Viability Testing

All of the patients enrolled in this trial had clinical questions of viability due to regional myocardial dysfunction. Prior viability testing had been performed in 19 of 20 (18 thallium SPECT and/or PET; one late-enhancement MRI). The 20th patient was initially referred with a clinical history of one akinetic left ventricular wall with questionable viability. After being enrolled in the study, she was later judged, by repeat echocardiography at our institution, to have normal function in all regions. She was therefore considered viable in all regions and was not subjected to further viability testing before undergoing coronary artery bypass grafting for severe three-vessel disease. Imaging sub-specialists, who were blinded to the MRI-based multiparametric strain analysis results, characterized each of six LV regions in each of the patients as either predominantly viable or predominantly nonviable. Including the six viable regions in the 20th patient, this generated a total of 120 regions for comparison to the MRI-based multiparametric strain analysis results.

Statistical Analysis

For each of 120 LV regions, the clinical standard viability testing result was assumed true. A comparison of the multiparametric strain average composite Z-score between viable and nonviable segments was done using an unpaired t-test assuming equal variances. A receiver operator characteristic (ROC) curve was generated to assess the accuracy of the regional Z-scores in distinguishing viable from nonviable myocardium and to identify a threshold value of this measurement that would optimize sensitivity and specificity. To determine the sensitivity and specificity (in regard to detection of nonviable myocardium) the results of the MRI-based multiparametric strain analysis viability testing were then compared region for region to the clinical standard viability testing result. *Sensitivity* was defined as the proportion of clinical standard *nonviable* ventricular regions that tested *nonviable* with the MRI-based multiparametric strain analysis. *Specificity* was defined as the proportion of clinical standard *viable* ventricular regions that tested *viable* with the MRI-based multiparametric strain analysis. All calculations were carried out using the SPSS statistical package (SPSS, Inc., Chicago, Illinois).

RESULTS

Out of 120 total LV test regions, 41 (34%) were declared predominantly nonviable and 79 (66%) predominantly viable by the clinical standard viability testing. Multiparametric strain analysis average Z-score values were calculated for each of 120 test ventricular regions. The results of both analyses are displayed in Table 1. The average multiparametric strain Z-score in the clinical standard nonviable segments was significantly increased compared to the average in the viable segments (2.20 ± 0.69 vs. 0.89 ± 0.60 , $p < 0.001$). Average multiparametric strain Z-scores from each of the regions were used to construct a ROC curve (Figure 4). The area under the curve was found to be 0.941 ($P < 0.001$) with a 95% confidence interval having a lower bound of 0.897 and an upper bound of 0.985. Utilizing a multiparametric strain regional average Z-score of 1.525 as a cutoff value for viability (> 1.525 being nonviable) resulted in an optimized sensitivity of 90% and a specificity of 90%. The corresponding positive and negative predictive values were 84% and 95%, respectively.

The regional and transmural accuracy of MRI-based multiparametric Z-score 3D color contour mapping on patient-specific LV geometry is demonstrated by visual comparisons of representative multiparametric strain images to their respective thallium SPECT (Figure 2) and PET (Figure 3) images.

COMMENT

The tracking of the systolic deformation of radiofrequency tissue tagging grids by sequential MRI scanning uniquely allows the accurate generation of 3D LV systolic strain maps from the resulting intramyocardial point displacement information. This capability has ushered in a new era in the *quantification* of regional and transmural myocardial contractile function. Multiple strain indices can be simultaneously clinically assessed by these methods. Three of these indices (circumferential strain, longitudinal strain, and the minimum principal strain angle [12]) have demonstrated accuracy in the characterization of regional and transmural myocardial function [11,15,16].

Our ability to accurately characterize LV strain in the clinical setting has been further enhanced by the establishment of a normal human strain database ($n=50$). This strain database includes the normal average and standard deviation for all strain parameters at each of 15,300 points in the normal human left ventricle. Normalization of *patient-specific* raw strain parameters by Z-score calculation utilizing this normal strain database enables the combination of multiple strain parameters, with their widely variable raw data ranges, into a multiparametric clinical strain

tool. This strain tool can thereby characterize point-specific regional and transmural myocardial contractile function by accurately relating the patient-specific raw strain parameter information to the normal average and standard deviation. In this first clinical implementation of MRI-based multiparametric strain analysis, our results strongly suggest that its accuracy in characterizing regional myocardial contractile function has indeed resulted in accuracy in the identification and localization of post-infarction irreversible myocardial injury.

The MRI-based multiparametric strain methodology utilized in this investigation generates large volumes of numerical data describing the *patient-specific* systolic strain characteristics of the left ventricle. Since three different strain parameters are assessed at each of 15,300 points, this results in the comparison of 45,900 patient-specific strain values from each individual patient to their respective point-specific strain normal ranges. The direct relation of patient-specific data to “normal” optimizes the clinical utility of the output of this viability tool, as all medical testing results must ultimately be interpreted in relation to the expected normal human results.

The highly mathematical nature of the output from this strain analysis stands in sharp contrast to other viability testing modalities that generate images alone as primary output. They can only be taken back to numerical data with considerable difficulty. The quantitative numerical foundation for this strain viability tool allows the use of advanced computational techniques to present the results to the clinician in the most visually optimized manner. The resulting interpretation of the viability testing by the clinician is thus facilitated and optimized by the expression of the results in a 3D color-coded format that specifically relates patient-specific raw strain values directly to the normal expected values.

The foundation of the characterization of regional viability by multiparametric strain analysis is the accurate quantification of regional and transmural myocardial *contractile function*. The fact that regional multiparametric strain Z-scores greater than 1.52 accurately identify nonviable myocardium (as determined by clinical standard viability testing) is a reassuring additional attribute of a modality whose primary mission is to *quantify regional myocardial contractile function*. MRI-based multiparametric strain analysis is the first viability testing modality that utilizes highly quantified, observer-independent regional contractile function information to provide the viability characterization rather than relying upon surrogate markers for contractile function, such as perfusion or substrate metabolism. The foundational obligatory mission of the heart is to pump blood and improving this contractile capability is the whole point of determining viability in the setting of ischemic cardiomyopathy. In addition to identifying *nonviable* regions, MRI-based multiparametric Z-score mapping is the first clinically applicable methodology to also render a complete regional and transmural *quantification* of myocardial contractile function in the *viable* regions of the heart. A full characterization of contractile function for all regions of the heart is made available to the clinician to, among other things, allow the quantification of *remote* ventricular wall remodeling effects that occur secondary to the localized primary infarction injury.

Limitations

Despite the fact that MRI-based multiparametric strain analysis is based upon far more clinically *measured transmural* wall displacement information than any other currently utilized clinical modality, concerns have arisen regarding the number of measured data points relative to those extrapolated by the fitting algorithm employed in this methodology. When applied to hearts with normal wall thickness, currently utilized tissue tagging grid dimensions limit the number of tag lines that can fit transmurally and therefore contribute to the density of measured displacement information in the radial direction. Our experience with *radial* strain analysis has in fact confirmed this limitation, with radial strain consistency and uniformity lagging behind that of circumferential and longitudinal strain measurements. This is, however, precisely where

the strengths of a *multiparametric* strain analysis are demonstrated. The ability to “normalize” raw patient-specific strain component data by comparison to a normal human strain database uniquely allows the combination of parameters such that the analysis can be focused upon the strengths of the MRI tissue tagging grid density. Specifically, it allows the three strain parameters that are based on the highest density of tag line data (circumferential, longitudinal, and minimum principal strain directions) to be combined into a single multiparametric strain index. This ability to focus the strain analysis on these directions—which in fact represent the directions of maximal fiber contraction—almost certainly contributed to the demonstrated accuracy of this methodology in the clinical detection of the abnormal contractile patterns that are associated with nonviable myocardium.

The lack of a pathological “gold standard” to directly quantify regional and transmural nonviable myocardium in each of the 20 enrolled patients is a limitation that has been encountered during the initial clinical implementation of all of the currently available viability detection methodologies. Since no pathological specimens were available, the results obtained by multiparametric strain testing were instead compared to the clinical standard viability testing results obtained in the course of each patient’s clinical management at a large, university-based teaching hospital. The qualitative nature of the regional viability discrimination of the clinical standard testing modality (primarily thallium SPECT and PET) compounded this limitation since areas of infarction often partially overlie multiple LV regions. The actual images obtained in six different patients whose infarcts extended over more than one region are therefore included in the results section of this manuscript. These images clearly demonstrate the need to move away from the qualitative regional descriptions utilized in the report rendered by the imaging subspecialist to the clinicians involved in patient management. In contrast, the true regional extension and transmural extension of the discrete areas of injury are all accurately displayed to the clinician by MRI-based multiparametric strain Z-score color contour mapping.

Conclusions

MRI-based multiparametric strain Z-score color contour mapping allows quantification and direct visualization of patient-specific regional contractile function in a format that specifically relates it to the expected norm. The accuracy of this regional quantification of myocardial contractile function appears to be such that it can very reasonably duplicate the results obtained with current clinical standard myocardial viability testing.

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Figure 1. Region-based Left Ventricular Finite Element Model

The attachment points of the right ventricular free wall to the septum serve as fiducial landmarks to consistently and uniformly divide the left ventricle into six clinical standard regions. Each region is then divided into basal, middle, and apical segments. The standardized finite element mesh for the LV model therefore consists of six hexahedral elements each for the basal and middle regions of the left ventricle and six pentahedral elements covering the apex.

Figure 2. Thallium SPECT Viability Imaging vs. MRI-based Multiparametric Strain Z-Score Color Contour Modeling

Similarity is demonstrated between the blue areas of irreversible abnormal perfusion in the left-sided thallium SPECT image and the yellow (Z-Score >1.5) and red (Z-Score >2.25) areas of the corresponding MRI-based multiparametric strain Z-Score color contour images on the right. For each of three representative patients, a thallium SPECT scan on the left is compared to its corresponding multiparametric strain Z-score 3D color contour model on the right. Each 3D multiparametric strain image was rotated to obtain the anatomically analogous view of the myocardial region of interest. The common finding of extension of infarction boundaries across multiple regions of the left ventricle is well demonstrated.

Figure 3. MRI-based Multiparametric Strain Z-Score Color Contour Modeling vs. PET Viability Imaging

PET scan results from three representative patients are presented in 2D cross-sectional format. A corresponding 2D slice was obtained for comparison by subjecting the MRI-based multiparametric strain Z-score 3D color contour model to a post-processing cutting tool. In each comparison, the PET scan is found on the left with a comparable slice through our model in the same patient being found immediately to the right. Nonviable areas on the PET images are represented by a *gap* in the red, yellow, or green circular contour of the ventricular cross-section. Once again, similarities are demonstrated between the PET nonviable regions on the left and the yellow (Z-Score >1.5) and red (Z-Score >2.25) areas of the corresponding MRI-based multiparametric strain Z-Score color contour images on the right. The propensity of irreversible injury from myocardial infarction to extend across multiple regional boundaries of the heart is again apparent.

Figure 4. ROC Curve Generated from Multiparametric Z-Score Data

The average multiparametric strain composite Z-score from each LV region (n=120) was compared to the respective clinical standard viability testing result and used to construct a ROC curve. The area under the curve was found to be 0.941 ($P < 0.001$) with a 95% confidence interval having a lower bound of 0.897 and an upper bound of 0.985.

Table 1

Regional Average Multiparametric Strain Z-scores

Patient	Region					
	AS	A	AL	PL	P	PS
1	1.99	1.25	1.37	1.05	0.91	1.16
2	2.88	1.88	1.42	1.78	1.85	2.06
3	1.95	1.47	1.31	1.51	0.71	1.26
4	1.38	1.38	1.58	2.37	1.44	1.25
5	1.60	0.55	0.30	0.39	0.94	2.47
6	1.21	1.29	1.04	1.02	1.70	1.77
7	0.67	0.68	1.58	3.25	2.30	1.39
8	0.11	0.04	0.02	0.20	-0.18	0.22
9	2.24	1.69	2.05	4.23	2.64	2.57
10	0.65	0.34	0.56	1.22	1.29	0.80
11	0.33	0.81	1.12	1.10	0.83	0.61
12	1.68	1.01	0.98	2.27	2.82	1.72
13	1.23	0.68	0.05	0.69	1.03	0.90
14	-0.35	-0.30	-0.10	0.05	-0.37	-0.44
15	3.53	2.08	1.93	2.22	2.23	2.56
16	2.01	1.53	1.01	1.21	2.07	2.02
17	1.27	1.17	1.01	1.19	1.61	1.52
18	2.36	0.94	0.28	0.39	0.80	2.18
19	3.89	2.95	1.22	0.71	0.70	2.06
20	1.40	0.68	1.01	2.27	2.28	1.86

Regional comparison of clinical standard viability testing and MRI-based multiparametric strain analysis. Regional average MRI-based multiparametric strain Z-Score values (standard deviation from normal average) are shown for each of six LV regions for each study patient (n=20). Shaded regions were determined to be predominantly nonviable by imaging subspecialist interpretation of clinical standard viability testing. A = anterior; AL = anterolateral; AS = anteroseptal; P = posterior; PL = posterolateral; PS = posteroseptal.