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A Validation of Two-Dimensional *In Vivo* Regional Strain Computed from Displacement Encoding with Stimulated Echoes (DENSE), in Reference to Tagged Magnetic Resonance Imaging and Studies in Repeatability

Julia Kar¹, Andrew K. Knutsen², Brian P. Cupps¹, and Michael K. Pasque¹

¹Department of Surgery, School of Medicine, Washington University in St. Louis, 660 S. Euclid Ave., St Louis, MO 63110, USA

²The Center for Neuroscience and Regenerative Medicine, The Henry M. Jackson Foundation for the Advancement of Military Medicine, 6720A Rockledge Drive, Suite 100, Bethesda, MD 20817, USA

Abstract

Fast cine displacement encoding with stimulated echoes (DENSE) has comparative advantages over tagged MRI (TMRI) including higher spatial resolution and faster post-processing. This study computed regional radial and circumferential myocardial strains with DENSE displacements and validated it in reference to TMRI, according to American Heart Association (AHA) guidelines for standardized segmentation of regions in the left ventricle (LV). This study was therefore novel in examining agreement between the modalities in 16 AHA recommended LV segments. DENSE displacements were obtained with spatiotemporal phase unwrapping and TMRI displacements obtained with a conventional tag-finding algorithm. A validation study with a rotating phantom established similar shear strain between modalities prior to *in vivo* studies. A novel meshfree nearest node finite element method (NNFEM) was used for rapid computation of Lagrange strain in both phantom and *in vivo* studies in both modalities. Also novel was conducting *in vivo* repeatability studies for observing recurring strain patterns in DENSE and increase confidence in it. Comprehensive regional strain agreements *via* Bland–Altman analysis between the modalities were obtained. Results from the phantom study showed similar radial-circumferential shear strains from the two modalities. Mean differences in regional *in vivo* circumferential strains were -0.01 ± 0.09 (95% limits of agreement) from comparing the modalities and -0.01 ± 0.07 from repeatability studies. Differences and means from comparison and repeatability studies were uncorrelated ($p > 0.05$) indicating no increases in differences with increased strain magnitudes. Bland–Altman analysis and similarities in regional strain distribution within the myocardium showed good agreements between DENSE and TMRI and show their interchangeability. NNFEM was also established as a common framework for computing strain in both modalities.

Keywords

DENSE; Tagged-MRI; Lagrange strain; Nearest node finite element analysis (NNFEM); Meshfree analysis; Bland–Altman analysis

INTRODUCTION

Cardiovascular magnetic resonance (CMR) is a non-invasive magnetic resonance imaging (MRI) technique most commonly used in clinical practices and research. It is a proven accurate method for tracking and quantifying left ventricular (LV) mechanics in both normal and pathological conditions.^{5,22,25,34,44} This study was motivated by the scientific community's search for fast CMR technologies that not only have high spatiotemporal resolution but also provides accurate and rapid computation of myocardial strain. Several different CMR tissue tracking methods have been used over the past decades, including tagged magnetic resonance imaging (TMRI),^{3,5,14,32,42} harmonic phase analysis (HARP),^{1,16,35,37} velocity encoded phase contrast (PC)^{12,27,28,31} and strain encoding in MRI (SENC).^{23,36} One recently developed CMR technique is displacement encoding with stimulated echoes (DENSE) which provides higher spatial density of displacement in the myocardium. DENSE also has the advantage of short post-processing periods *via* rapid phase unwrapping and is attributed with higher temporal resolution, encoding motion over longer intervals comparable to T1 duration.^{2,17,19–21,39,40,45} Longer periods of displacement encoding are accomplished with the stimulated echoes that hold the magnetization vector along the direction of a static magnetic field, avoiding signal decay.^{39,40,45} Sufficient phase contrast can be obtained with moderate gradient strength and spatial resolution is limited only by pixel size where the pixel phase themselves are modulated by myocardial displacement. There are manifold advantages of using DENSE when compared to TMRI which has been the standard and most widely used in the past two decades. TMRI is disadvantaged by lengthy, time consuming post-processing and does not have the high spatial resolution (greater than 6 mm) found in DENSE. Among other recent developments, HARP simplifies tag analysis but does so at the expense of reduced spatial resolution.^{35,37} A disadvantage of PC is the need for multiple acquisitions for encoding in each velocity direction leading to longer scan times.^{27,40,43} DENSE is not without its disadvantages including artifacts arising from EPI readouts for which magnetization based suppression must be used.^{21,39} DENSE breath holds are also relatively longer since six data sets (magnitude and phase in three encoding directions for 3D acquisitions) must be obtained with each breath hold.²¹ Additionally, the stimulated echo in DENSE, whose phase is directly proportional to tissue displacement is characterized by relatively low signal-to-noise ratio (SNR).^{21,39}

The primary goal of this study was to investigate whether a fast-track modality like DENSE was interchangeable with lower resolution TMRI sequences and associated lengthy strain analysis procedures.^{5,13,33} The main purpose was obtaining agreements between DENSE and TMRI in radial and circumferential Lagrange strain, computed from functional data acquired from the same 12 healthy subjects. The underlying requirement was to establish a method for tracking discrete points in the LV, determine their 2D displacements, investigate regional circumferential and radial strains, generate strain contour maps, and validate DENSE as an appropriate alternative to TMRI. Equally important, in addition and prior to *in vivo* agreement between modalities, was asserting the occurrence of similar radial-circumferential shear strain ($\varepsilon_{r\theta}$) between the modalities using a phantom rotating device. A novel meshfree nearest node finite element method (NNFEM) approach for strain computation was used to establish similar $\varepsilon_{r\theta}$ from the two modalities in the phantom and determine whether regional strains from DENSE displacement encoding and TMRI tag-finding agreed favorably. A novel part of this study, which has not been presented previously, was to examine agreement between DENSE and TMRI with the LV divided into regions according to standardized American Heart Association (AHA) segmentation guidelines.¹¹ Using a common strain simulation framework for both DENSE and TMRI was an important part of this goal for ensuring the accuracy of agreements between the modalities. A second goal, which is also unprecedented in previous studies, was to

investigate the repeatability of strains computed with DENSE in ten normal subjects. The objective of the second goal was increasing confidence in DENSE as an accurate MRI tool for functional cardiac imaging and also to increase confidence in NNFEM as a novel strain simulation technique in the myocardium.

MATERIALS AND METHODS

Overview of Cardiac Strain Computation with DENSE and TMRI

Offline segmentation of the myocardium, phase unwrapping, tagged tissue tracking, and calculation of specific mechanical parameters were accomplished with a custom C++ utility developed within this laboratory. The myocardium was segmented using a semi-automated method where manual delineation of the endocardial and epicardial contours were performed at the initial cardiac phase, followed by propagation of these contours to all other cardiac phases.^{13,33} This segmentation process generated 16 regions for strain measurements within the LV in accordance with AHA guidelines on standardized myocardial segmentation for clinical and research purposes.¹¹ The remaining displacement and strain analyses were automated for both DENSE and TMRI. An automated spatiotemporal phase unwrapping scheme (Fig. 1a) guided by a flood-fill algorithm developed for 2D cine DENSE plus time was applied to the pixels of the segmented myocardium to compute displacements in DENSE.^{39,40} TMRI displacements were computed by first identifying sets of tag lines at end-diastolic, followed by an automated tag-finding algorithm based on pixel intensity (Fig. 1b) to identify tag lines in successive phases and finishing at end-systolic.^{13,33} Computation of myocardial strain, with both DENSE and TMRI, was performed offline in MATLAB (Mathworks Inc., Natick, MA, USA) using a novel simulation approach in the myocardium called NNFEM.^{4,6,26} The simulation accuracy of NNFEM was first compared to results from a more conventional finite element method (FEA) known as measurement analysis (MEA) which is a numerical analysis technique based on piecewise polynomial approximations that employ elements of variable sizes.^{7,33,41} Comparison between the two simulation techniques was conducted using TMRI data from a phantom rotating device. This phantom was also instrumental in establishing similar shear strains between the two imaging modalities. Finally, experiments with healthy human subjects were conducted to establish *in vivo* agreement in regional myocardial strain between the two modalities and in DENSE repeatability studies.

Phase Unwrapping Algorithm

Phase unwrapping consists of computing and averaging phase angles of a series of Fourier transforms in an image by a method of suppressing unwanted environmental effects imposed on the image resolution.^{17,19,20,39,40} An important aspect of phase unwrapping is that computed phase angles inherently contain ambiguities of integral multiples of 2π where it is important to obtain continuous phase curves. The spatiotemporal phase unwrapping algorithm implemented for this study consisted of unwrapping along an integral path by integrating the phase differences between local phases which was assisted by a flood-fill quality guided algorithm.^{17,39,40} Temporal fitting in each encoding direction was achieved with fitting displacement data from consecutive phases with periodic (Fourier series) basis functions and whose coefficients were found using discrete Fourier transform of the DENSE data.^{39,40}

Lagrangian Strain Computation with NNFEM

The NNFEM technique used in this study served as common framework for computing phantom and myocardial strains in both modalities is a novel approach unprecedented in any previous study in cardiac mechanics. In conventional FEA shape functions are constructed once for a whole element by using nodes belonging to that element and then accumulated

into a global matrix.⁴⁷ NNFEM is different from conventional numerical analysis techniques in that while its shape functions are constructed for each quadrature point using a set of nodes that are the nearest to the quadrature point (Fig. 1c), these neighboring nodes are not necessarily all located in the same element. There are many advantages to using NNFEM of which the foremost is not requiring the assembly of a global stiffness matrix as required in conventional FEA. In NNFEM monomials and their coefficients contribute directly to generating shape functions which can also be constructed within simplex meshes. Other advantages include setting arbitrarily high orders of shape functions (depending on node availability) and previous studies have demonstrated that NNFEM has a competitive convergence rate compared to conventional FEA.²⁶ Following is a detailed outline of the polynomial interpolation method^{6,26} for constructing shape functions for each quadrature point with n nearest nodes. The polynomial interpolation method can be seen as the approximation of a displacement function, $f(\mathbf{x})$, which is the displacement vector field within the myocardium. With n nearest nodes, the 2D function value at $\mathbf{x}(x, y)$ can be approximated as,

$$\tilde{f}(x, y) = \sum_{i=1}^n b_i q_i(x_i, y_i), \quad (1)$$

where $\mathbf{q} = \{q_1(x_1, y_1), \dots, q_n(x_n, y_n)\}$ are monomial bases and $\mathbf{b} = \{b_1, \dots, b_n\}$ is a vector of coefficients.

The i th displacement function, f_i , using n nodes around the central node is then represented by,

$$\mathbf{q}^T(x_i, y_i) \cdot \mathbf{b} = f_i \quad i=1, \dots, n. \quad (2)$$

The matrix form for $\bar{\mathbf{f}} = \{f_1, \dots, f_n\}$ can then be assembled as

$$\mathbf{Q}\mathbf{b} = \bar{\mathbf{f}}, \quad (3)$$

where $\mathbf{Q}$ is called a Vandermonde matrix^{4,6,26} which represented with second order polynomials is of the form,

$$\mathbf{Q} = \begin{bmatrix} 1 & x_1 & y_1 & x_1^2 & y_1^2 & x_1 y_1 \\ \dots & \dots & \dots & \dots & \dots & \dots \\ 1 & x_n & y_n & x_n^2 & y_n^2 & x_n y_n \end{bmatrix}. \quad (4)$$

Second order polynomials were chosen (Eq. (4)) since linear interpolation was initially found to be highly ill-conditioned for sparsely populated TMRI displacement fields. The coefficient vector $\mathbf{b}$ is determined by the following inverse function,

$$\mathbf{b} = \mathbf{Q}^{-1} \bar{\mathbf{f}} \quad (5)$$

and the approximation in Eq. (1) becomes,

$$\tilde{f}(x, y) = \phi(\mathbf{x})^T \bar{\mathbf{f}}, \quad (6)$$

where $\phi(\mathbf{x})^T = \mathbf{q}^T \mathbf{Q}^{-1}$ are local polynomial shape functions.

Computation of Lagrangian strain and the deformation gradient tensor, $\mathbf{F}$, depends on the derivative function of $f(x, y)$ given by,

$$\frac{\partial \tilde{f}(x, y)}{\partial \alpha} = \frac{\partial q^T(x, y)}{\partial \alpha} \cdot \mathbf{b}, \quad (\alpha = x, y). \quad (7)$$

To implement the above algorithm each pixel of interest within the myocardium was considered a quadrature point at the initial displacement time. N nearest available neighboring pixels and their position vectors were then recruited for the shape function and to construct the matrix $\mathbf{Q}$. The deformed vector $\mathbf{f}$ was constructed at later phases using the corresponding deformed quadrature point and its n nearest neighbors. $\mathbf{Q}$ and $\mathbf{f}$ were then used for computing $\mathbf{b}$ (in x and y coordinate directions) in Eq. (5), therefore resolving all unknowns before computing derivatives. The Lagrange deformation gradient tensor, $\mathbf{F}$, was computed using the four derivatives of $f(\mathbf{x})$ in 2D in Eq. (7). The 2D finite strain tensor, $\mathbf{E}$, was assembled from the deformation gradient tensor using the classical definition of Lagrange strain given by,

$$\mathbf{E} = \frac{1}{2}(\mathbf{F}^T \mathbf{F} - \mathbf{I}), \quad (8)$$

where $\mathbf{I}$ is the identity matrix. An accurate approximation of $f(\tilde{\mathbf{x}})$ is highly dependent on assembling the matrix of monomial bases in the Vandermonde matrix given in Eq. (4).^{6,26} Measures taken to avoid an ill-conditioned Vandermonde matrix included (a) applying a non-singularity criterion based on rejecting a nearest node row contribution to the Vandermonde matrix if it is not linearly independent, which can be tested by locating the zero entries in the diagonal after QR factorization²⁴ and (b) using singular value decomposition (SVD) to circumvent problems with an underdetermined system. To narrow down the differences in spatial resolution between DENSE and TMRI, the TMRI tags were interpolated to obtain twice the number of original tags which reduced original tag spacing from 8.0 mm to 4.0 mm. The accuracy of the relatively new NNFEM method was tested using two different approaches. The first approach was to ensure that results of ϵ_{θ} strains obtained in the phantom device were similar to a three parameter analytical solution in a viscoelastic medium derived from the Navier–Stokes equation of motion in the same phantom in a previous study.⁸ Methods of obtaining analytical ϵ_{θ} strains using a nonlinear FEA simulation approach is outlined in details in that study.⁸ The second approach included simulating the phantom shear strains using yet another more established FEA analysis technique introduced earlier as MEA.^{7,33,41} A similar tag interpolation scheme that reduced tag spacing in the validation study was also used in human experiments reducing tag spacing between 4.0 and 2.0 mm.

Lagrangian Strain Computation with Measurement Analysis

MEA is an established finite element technique which was used for comparing NNFEM strain results obtained in the phantom study. MEA consists of approximating displacement components over a domain, given a set of measured displacements points, where the main objective is to seek polynomial approximations for the displacement field in the least squares sense.^{7,33,41} The mapping is based on higher order polynomial interpolation of spatial variables commonly known as the p -version in FEA which is an approximation technique known to facilitate smooth variations in displacements and strains.^{7,33,41} MEA was used to generate a 2D finite element mesh of the phantom consisting of six tetrahedral

elements as shown in Appendix A. Absolute continuity of displacements and strains were obtained across element boundaries by assembling the fitted displacements from each element into a single stiffness matrix prior to solving a set of linear equations. A continuous distribution of strain was then obtained by computing the derivatives of the spatial variables and using the definition of Lagrange strain.

Imaging Phantom and Human Subjects

The phantom apparatus used for validation was reused from a previous study in HARP analysis where a detailed outline of equipment assembly and experimental procedure can be found.⁸ Displacement fields were measured in a cylinder of approximately 56 mm in radius and 202 mm in length filled with gelatin. The cylinder was then mounted in a custom rotating device with it clamped in the freely rotating inner compartment of the assembly. Releasing a latch to an off-axis counterweight provided torque to initiate rotation, following which repeated angular acceleration of approximately 250 rad/s^2 was provided from impact with a compliant stop. It is this angular acceleration that provided maximum $\varepsilon_{r\theta}$ strains at the outer boundary of the cylinder's gel. MR imaging was synchronized with rotation of the cylinder where a fiber optic sensor detected release of the latch and triggered the MRI pulse sequence. The MR compatible material used for the phantom experiment was Gelatin (Knox, Camden, NJ), which was preset in a capped acrylic cylinder at 10°C for slightly less than a day prior to experimentation. Human subject cine DENSE and TMRI scans were also performed in the same scanner where 12 normal subjects were recruited for DENSE–TMRI comparison and ten for DENSE repeatability studies. Average age of all twenty-two normal subjects was 45.9 ± 13.8 years and average mass was 73.4 ± 13.4 kg. Six female and six male subjects were recruited for the comparison study and six females and four males recruited for the repeatability study. All subjects signed informed consents in accordance with the university's Institutional Review Board (IRB) guidelines. Healthy volunteers participating in the repeatability studies were removed from the scanner after the first scan and repositioned in approximately the same position during the second scan.

Imaging Protocols

Sequences of DENSE and TMRI images of the rotating cylinder were both obtained in a 1.5 T Siemens Avanto (Siemens Medical Systems, Erlangen, Germany) scanner. For the DENSE phantom study, cine data was acquired with displacement encoding applied in two orthogonal in-plane directions and 2D displacements encoded in the phase images.^{39,40} The DENSE sequence, called a_CV_epi_DENSE_611, was a cine echo planar imaging (EPI) one employing phase cycling to suppress an artifact-generating echo.^{2,21} Acquisition matrix size was 64×64 with 3.13 mm (square) pixel spacing, FOV of $200 \times 200 \text{ mm}^2$ and 20° of flip angle. 135 phases at 6 ms of TR, 3.7 ms of TE and ETL of one were acquired in x and y encoding directions. The optimal displacement encoding frequency (k_e) was chosen as 0.1 cycles/mm which was a value recommended in previous literature.^{39,40} TMRI images were acquired using a spatial modulation of magnetization (SPAMM) TrueFISP sequence with added myocardial tagging preparation pulses.⁴⁸ Acquisitions were made with a pair of radio-frequency (RF) pulses applied in combination with magnetic gradients resulting in tagged images at a matrix size of 128×128 pixels, 1.56 mm of pixel spacing, FOV of $200 \times 200 \text{ mm}^2$ and 14° of flip angle. 132 phases were acquired with tag line spacing of 8 mm between intensity peaks, TR of 6 ms, TE of 1.4 ms and ETL of one. The RF coil for receiving signals in both modalities was a four-channel flex coil strapped to the phantom's cradle.

Human subject cine DENSE images were acquired in multi-level short-axis imaging planes, at approximately 10–12 short-axis images per subject depending on individual LV size and using the same EPI sequence as the phantom studies. Typical imaging parameters included FOV of $359 \times 269 \text{ mm}^2$, effective TE of 8.0 ms, TR of 32.5 ms, ETL of nine, matrix size of

112 × 84 pixels, 3.2 mm pixel spacing, 8 mm slice thickness and 12–22 cardiac phases. Scans were acquired in breath holds of 20–30 heartbeats per encoding direction. TMRI images were acquired with the same cine TrueFISP sequence used in the phantom study.^{13,33,48} To acquire each image SPAMM RF tissue-tagging was applied and followed by a 2D balanced steady-state free precession cine image acquisition.¹³ Typical parameters included FOV of 359 × 359 mm², effective TE of 1.5 ms, TR of 32 ms, ETL of one, acquisition matrix size of 256 × 256 pixels, 1.37 mm pixel spacing, 8 mm slice thickness and 16–22 cardiac phases. ECG-gated short-axis TMRI images were acquired in multiple parallel planes between the mitral valve and LV apex. A four-channel body phased array RF coil was used for receiving signals in both modalities.^{39,40}

Statistical Analysis

Bland–Altman statistical analyses were used for establishing agreement between the modalities and also in repeatability studies.¹⁰ Upper and lower limits of agreement (LA) were found to determine the 95% confidence ranges for the differences between the modalities and repeatability studies. For regional Bland–Altman analysis, measurements were taken from six regions in the basal and mid-ventricular slices and four from the apical slice making it a total of 16 regions per subject. Averages from each of the three slices per subject were used for whole slice analysis. Correlations between strain differences and averages were computed to find the likelihood of differences increasing with increased magnitudes of strains. Paired student *t*-tests were used to investigate the likelihood of similar mean strains between the modalities and also within repeatability studies.

RESULTS

Figure 2a shows the deformed (interpolated) tags and the unwrapped phase map in the phase-encoding direction in DENSE at maximum $\varepsilon_{r\theta}$ in the phantom validation experiments. Figure 2b shows the TMRI displacements using original and interpolated tags and the DENSE displacement maps. Figure 2c shows the contours of maximum $\varepsilon_{r\theta}$ strains in the phantom study in both DENSE and TMRI. Maximum shear strains computed with NNFEM in the phantom was ~11% for both DENSE and TMRI. Higher outer bands of shear in both DENSE and TMRI can be seen as a result of the outer torque applied to rotate the cylinder. Average heart rate (HR) monitored for the duration of the comparison studies was 68.0 ± 8.1 bpm and average blood pressure (BP) was $128.4 \pm 18.7/79.7 \pm 13.1$ mmHg. Average HR monitored for the duration of the repeatability studies was 68.7 ± 7.2 bpm and average BP was $124.3 \pm 11.2/76.5 \pm 7.3$ mmHg. Figures 3a and 3b show Bland–Altman agreements between DENSE and TMRI studies in regional and whole slice circumferential and radial strains. Figures 4a and 4b show Bland–Altman agreements in repeatability studies in regional and whole slice circumferential and radial strains. The differences and means of strains from both comparison and repeatability studies were uncorrelated with $p > 0.05$. Figure 5 show displacements and contour maps of the circumferential and radial strains computed with NNFEM from both DENSE and TMRI in the mid-ventricular slice with each slice divided into six regions. Figure 6 shows DENSE displacements and strain contours in the basal slice (divided into six regions) and apical slice (divided into four regions). Table 1 shows the regional strain averages from the DENSE–TMRI comparison and DENSE repeatability studies where it is seen that the variability (given by the standard deviation) in radial strains is higher than those in circumferential strains. The differences obtained between modalities using Bland–Altman analysis in regional strain were -0.01 ± 0.09 in circumferential and 0.01 ± 0.29 in radial strains. The confidence ranges were further narrowed in whole slice agreements which were -0.01 ± 0.06 in circumferential and 0.01 ± 0.16 in radial strains. The differences in regional strains in the repeatability studies were -0.01 ± 0.07 in circumferential and 0.02 ± 0.27 in radial strains. Once again the confidence

ranges were narrower in whole slice agreements which were -0.01 ± 0.05 in circumferential and 0.02 ± 0.12 in radial strains. Paired student *t*-tests conducted between DENSE and TMRI showed significant differences in means in circumferential strain ($p < 0.005$) but not in radial strain ($p = 0.2$). Similar results were obtained from paired student *t*-tests in DENSE repeatability studies showing significantly different means in circumferential strain ($p < 0.005$) but not in radial strain ($p = 0.1$). Appendix A shows the contours of shear strain computed with MEA on TMRI data in the phantom. Table A1 (Appendix A) shows the $\varepsilon_{r\theta}$ strains computed with NNFEM and MEA.

DISCUSSION

Computation of $\varepsilon_{r\theta}$ strains propagated by angular acceleration of the outer boundary of a gelatinous (cylinder) sample was used for validation because the solution has been described previously and shear strain analysis for validating MRI techniques have been used previously.^{8,43} Figure 2 shows the close agreement between DENSE and TMRI $\varepsilon_{r\theta}$ strains computed with NNFEM in the phantom study. Additionally, the estimated $\varepsilon_{r\theta}$ strains were found similar to simulations of an analytical solution in the same phantom in a preceding study.⁸ A third study that performed similar validation with a deformable gel in a cylindrical annulus had an inner cylinder rotating in a cyclical sinusoidal manner with the help of a stepper motor.⁴³ Similar to this and the preceding study,⁸ both DENSE and TMRI image acquisitions in the third study enabled experimental estimations of strains and the annular geometry and displacement boundary conditions facilitated obtaining an analytical solution. However the actual rotation of the inner cylinder in the third study was determined from TMRI data due to issues of compliance.⁴³ In contrast, angular accelerations of the gel cylinder in this study were recorded directly from linear acceleration measurements. Another advantage of this phantom study was the similar $\varepsilon_{r\theta}$ strains obtained with a third image processing modality, HARP, in the preceding study.⁸ In general, the effectiveness of a phantom device is dependent on the techniques of data measurement and numerical simulations used to match an existing analytical solution and the phantom experiments show that it was successfully accomplished in this study.

Past studies have compared newer techniques claiming to provide higher image resolution, faster acquisition, and faster analysis in reference to TMRI as the accepted standard. Development of fast automated 2D myocardial motion analysis with PC, HARP imaging for rapid quantification of strain, accuracy of SENC in detecting wall motion during high-dose dobutamine stress-testing, combining tagging, and tissue phase mapping (TPM) to accelerate myocardial motion measurements and others have all been evaluated with reference to TMRI.^{9,16,23,29} Two past studies have also compared DENSE with TMRI, of which the first provided agreement between the modalities in circumferential but not in radial strains.²¹ The second study presented agreements for both of the above strains but analyses in that study were accomplished with a single strain value averaged over whole slices and details of regional strain agreements (with segmentation according to AHA guidelines or otherwise) were not presented there.⁴³ This study presents details of regional radial and circumferential strain agreements between DENSE and TMRI, as well as repeatability measurements in DENSE, from the standpoint of regional segmentation rules as outlined by the AHA.¹¹

With *in vivo* DENSE–TMRI comparison and repeatability studies, peak end-systolic regional strains were measured in apical, mid-ventricular, and basal slices. The Bland–Altman plot in Fig. 3a shows there is good agreement between measurements of regional circumferential strain from the two modalities. Figure 4a shows similar good agreement between circumferential strains from the repeatability studies. These differences are further narrowed when circumferential strain is averaged over whole slices. The upper and lower

LA values from both regional and whole slice analysis are comparable to ranges from similar Bland–Altman analysis in previous studies.^{21,43} Bland–Altman analysis on whole slices (in addition to regional analysis) might seem extraneous but differences in agreements between modalities in regional comparison vs. whole slice require close investigation. Additionally, in regional distribution of circumferential strains computed with DENSE (Table 1) with highest values in the lateral region, followed by posterior, anterior, and septal regions is a distinguishable pattern established in previous studies.^{13,37,42} These regional strains were also similar to those in an existing database of TMRI strains in normal subjects ($n = 90$).¹³ Results of t -tests showed that means of circumferential strains from the comparison and repeatability studies were significantly different but not in radial strains. The similarities in the means of radial strain are likely due to their higher variability which can be seen from the standard deviations in Table 1 and also in the Bland–Altman plots (Figs. 3b and 4b) with broader confidence ranges or LA. This higher variability in radial strains was also observed in previous studies.^{21,39,42,43} One explanation for the variations in radial strains exceeding expectations is the large transmural strain gradients and largely varying systolic radial wall thickening.^{1,18,30} Transmural wall thickening could be influenced by end-diastolic volume which then causes changes to the local wall geometry and therefore radial strain between heartbeats. Another study argued that the differences in radial strain between the modalities could be propagated by matters of accuracy where the higher spatial resolution of DENSE (3.2 mm pixel spacing) is more accurate than TMRI (8 mm tag spacing).⁴³ A second cause of limited resolution in TMRI is Fourier space spectral peak interferences and methods to remove it were not undertaken during this study.¹ However, a lack of resolution in TMRI cannot justify the high variability in radial strains observed in the repeatability studies. Hence, it can be strongly argued that the higher variability in radial strain is due to naturally occurring wall motion variations as mentioned earlier. Another important finding was that differences and means from the comparison (Fig. 3) and repeatability studies (Fig. 4) were uncorrelated ($p > 0.05$) indicating the unlikelihood of differences in strains increasing with increasing magnitudes.

There is no precedence to using NNFEM as a common framework for computing $\varepsilon_{r\theta}$ strains in a phantom or strains in the myocardium in either modality. Finding similar $\varepsilon_{r\theta}$ strains in the phantom device with NNFEM and MEA (Table A1 in Appendix A) was an important step taken to establish NNFEM as an accurate technique. However, the six element MEA mesh could benefit from further refinement and therefore better convergence as expected in conventional FEA techniques. Further processing with MEA was considered less important since $\varepsilon_{r\theta}$ strains predicted with NNFEM were already similar to an analytical solution.⁸ This study is novel in showing that NNFEM provides accurate and real time analysis of cardiac strain using polynomial shape functions and their derivatives where shape functions can be quickly constructed using nodes in a compact support domain. The greatest advantage of NNFEM is in avoiding mesh generation required in conventional FEA. Interpolation at a NNFEM node is performed over the influence domain of the point while FEA meshes consisting of simplexes (Appendix A) are easily generated but low order and slow to converge. Similarities observed in circumferential and radial strains computed with NNFEM with those in previous studies also show the method's accuracy.^{21,35,39,42,43}

There were several limitations with this study where the first was not using HARP analysis, which is considered an emerging independent technique for estimating TMRI strain, to validate the cine DENSE measurements.^{35–37} However, this study shows strain results that are similar to radial and circumferential strains obtained from literature in HARP,^{35,37} other modalities such as PC²⁷ and even non-MRI techniques such as echo-Doppler.¹⁵ A second limitation was to present only end-systolic comparison of cardiac deformation for the modalities where trajectories (between end-diastole and end-systole) of DENSE strains, before and after temporal fitting, need further investigation in reference to TMRI. A

previous study that compared fitted (and unfitted) rotating phantom trajectories to an analytical solution found a tracking error less than 0.2 pixels.³⁹ Similar tracking errors must be found for the myocardium by comparing DENSE trajectories to ones from a more standard technique like TMRI. Furthermore, comparison with TMRI trajectories will strongly establish the benefits of fitting with Fourier basis functions in DENSE. A third limitation was obtaining 2D strain from short-axis slices when regional heart function occurs naturally in 3D.^{28,38,45} Ideally, any imaging technique used and subsequent strain computations should correct for tissue through-plane motion and 2D analysis inherently bypasses denser strain computation that is possible only within a 3D continuum.

The first objective accomplished with this study showed that $\varepsilon_{r\theta}$ strain computed with DENSE images in a phantom study were similar to TMRI (standard) strains. It was also similar to HARP strains and an analytical solution for the same device in a previous study.⁸ Established next were agreements in regional myocardial strain between DENSE and TMRI, computed in 16 AHA recommended segments which was a novel approach unprecedented in previous studies. A second novel aspect was using NNFEM as the numerical analysis technique and common framework for computing strains in both DENSE and TMRI. The advantages of NNFEM have been outlined and demonstrated by comparisons to MEA, a more conventional FEA method. A third novel aspect of this study established reliability in DENSE using repeatability studies, which is once again unprecedented in previous studies. This study shows that DENSE is a technique that produces reliable high resolution estimates of both circumferential and radial strains in normal human subjects and shear strain in a phantom study. Furthermore, validating DENSE as an accurate regional strain measuring technique in normal human subjects is an important precursor to using DENSE in the future for identifying regional abnormalities in pathological conditions like ischemia, cardiomyopathy and other cardiac conditions like aortic insufficiency.^{22,34} The future of DENSE lies in 4D (3D plus time) unwrapping of phase data to provide a comprehensive view of cardiac motion and strain. Hence, the next step is a proposed 4D phase unwrapping algorithm containing noise-immune techniques and a robust approach to avoiding singularity problems.

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APPENDIX A

Radial-circumferential shear strain ($\varepsilon_{r\theta}$) calculated using two different FEA techniques which were (left) nearest neighbor finite element method (NNFEM) and (right) Measurement Analysis (MEA). MEA involved division into six unequal tetrahedron elements in the same way a single 2D myocardial slice is segmented.

TABLE A1

Regional radial-circumferential shear strain ($\varepsilon_{r\theta}$) values using NNFEM and MEA.

Method	Strain	Element					
		E1	E2	E3	E4	E5	E6
NNFEM	Max $\varepsilon_{r\theta}$	0.12	0.12	0.12	0.16	0.14	0.12
	Avg. $\varepsilon_{r\theta}$	0.05	0.06	0.06	0.06	0.06	0.04
MEA	Max $\varepsilon_{r\theta}$	0.14	0.11	0.11	0.16	0.15	0.12
	Avg. $\varepsilon_{r\theta}$	0.07	0.06	0.06	0.08	0.06	0.03

The NNFEM domain was divided into the same six elements for regional strain computation as MEA.

FIGURE 1.

(a) Flood-filled quality image that guide finding displacements encoded in the phase images in DENSE. (b) Intersections of interpolated tag lines (deformed shown) used for finding displacement fields in TMRI. (c) NNFEM for constructing shape functions with quadrature point (red) and neighbors (blue) where contributions from numerical quadrature points are put directly into a matrix of monomial bases.

FIGURE 2.

(a) Basis of displacement analysis in the phantom validation experiments which are interpolated tags in TMRI (left) and phase unwrapping (phase-encoding direction shown) in DENSE (right). (b) Displacements at maximum radial-circumferential shear strain ($\varepsilon_{r\theta}$) in TMRI (left) and DENSE (right). (c) Contours of maximum $\varepsilon_{r\theta}$ strains in TMRI (left) and DENSE (right).

FIGURE 3. Bland–Altman agreement from the DENSE–TMRI comparison studies in human subjects for regional and whole slice (a) circumferential and (b) radial strains.

FIGURE 4. Bland–Altman agreement from the DENSE repeatability studies in human subjects for regional and whole slice (a) circumferential and (b) radial strains.

FIGURE 5.

Nearest node finite element method (NNFEM) simulated mid-ventricular systolic circumferential and radial strains estimated with (a) DENSE and (b) TMRI displacements. Displacement vectors are shown in red. A, Ant = anterior, AL = anterolateral, PL = posterolateral, P, Post = posterior, PS = postero-septal, AS = antero-septal.

FIGURE 6.

Nearest node finite element method (NNFEM) simulated (a) basal and (b) apical systolic circumferential and radial strains estimated with DENSE in the same subject as Fig. 5. Displacement vectors are shown in red. Ant = anterior, Post = posterior.

TABLE 1

Regional circumferential and radial strains calculated from (a) DENSE-TMRI comparison study and (b) DENSE repeatability study.

Strains	Anterior	Antero-lateral	Postero-lateral	Posterior	Postero-septal	Antero-septal
(a)						
TMRI						
Circumferential						
Apical	-0.17 ± 0.04	-0.19 ± 0.02		-0.16 ± 0.03	-0.14 ± 0.04	
Mid-ventricular	-0.13 ± 0.03	-0.16 ± 0.03	-0.18 ± 0.03	-0.18 ± 0.04	-0.14 ± 0.03	-0.14 ± 0.03
Basal	-0.16 ± 0.04	-0.17 ± 0.03	-0.18 ± 0.04	-0.16 ± 0.04	-0.15 ± 0.03	-0.15 ± 0.03
Radial						
Apical	0.13 ± 0.08	0.15 ± 0.06		0.15 ± 0.09	0.15 ± 0.09	
Mid-ventricular	0.14 ± 0.10	0.13 ± 0.10	0.25 ± 0.17	0.15 ± 0.12	0.21 ± 0.14	0.18 ± 0.13
Basal	0.12 ± 0.08	0.21 ± 0.11	0.24 ± 0.12	0.19 ± 0.10	0.17 ± 0.09	0.15 ± 0.07
DENSE						
Circumferential						
Apical	-0.18 ± 0.03	-0.20 ± 0.02		-0.15 ± 0.04	-0.16 ± 0.05	
Mid-ventricular	-0.17 ± 0.04	-0.19 ± 0.04	-0.20 ± 0.03	-0.14 ± 0.04	-0.14 ± 0.04	-0.18 ± 0.04
Basal	-0.15 ± 0.05	-0.18 ± 0.05	-0.19 ± 0.03	-0.14 ± 0.03	-0.15 ± 0.05	-0.16 ± 0.05
Radial						
Apical	0.13 ± 0.08	0.21 ± 0.14		0.13 ± 0.11	0.16 ± 0.10	
Mid-ventricular	0.17 ± 0.08	0.16 ± 0.09	0.24 ± 0.11	0.18 ± 0.10	0.17 ± 0.10	0.20 ± 0.14
Basal	0.09 ± 0.07	0.25 ± 0.16	0.32 ± 0.09	0.17 ± 0.10	0.15 ± 0.12	0.15 ± 0.11
(B)						
Study-1						
Circumferential						
Apical	-0.20 ± 0.04	-0.23 ± 0.04		-0.19 ± 0.03	-0.19 ± 0.03	
Mid-ventricular	-0.19 ± 0.04	-0.20 ± 0.05	-0.20 ± 0.03	-0.16 ± 0.05	-0.18 ± 0.04	-0.18 ± 0.03
Basal	-0.16 ± 0.04	-0.15 ± 0.05	-0.18 ± 0.03	-0.13 ± 0.05	-0.16 ± 0.04	-0.14 ± 0.04
Radial						
Apical	0.13 ± 0.08	0.27 ± 0.15		0.17 ± 0.10	0.23 ± 0.11	
Mid-ventricular	0.14 ± 0.06	0.24 ± 0.10	0.32 ± 0.11	0.22 ± 0.09	0.22 ± 0.09	0.20 ± 0.09
Basal	0.10 ± 0.07	0.22 ± 0.17	0.36 ± 0.17	0.18 ± 0.11	0.20 ± 0.10	0.16 ± 0.09

Strains	Anterior	Antero-lateral	Postero-lateral	Posterior	Postero-septal	Antero-septal
Study-2						
Circumferential						
Apical	-0.21 ± 0.04	-0.23 ± 0.04		-0.20 ± 0.05	-0.21 ± 0.03	
Mid-ventricular	-0.18 ± 0.03	-0.19 ± 0.04	-0.19 ± 0.03	-0.14 ± 0.04	-0.17 ± 0.03	-0.17 ± 0.03
Basal	-0.17 ± 0.05	-0.16 ± 0.05	-0.17 ± 0.03	-0.13 ± 0.04	-0.15 ± 0.03	-0.15 ± 0.04
Radial						
Apical	0.15 ± 0.10	0.25 ± 0.17		0.15 ± 0.11	0.23 ± 0.16	
Mid-ventricular	0.13 ± 0.10	0.21 ± 0.10	0.29 ± 0.09	0.18 ± 0.09	0.22 ± 0.09	0.22 ± 0.12
Basal	0.07 ± 0.07	0.20 ± 0.17	0.30 ± 0.11	0.23 ± 0.06	0.19 ± 0.11	0.15 ± 0.09