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A Preliminary Investigation of Multiparametric Strain Z-Score (MPZS) Computation using Displacement Encoding with Stimulated Echoes (DENSE) and Radial Point Interpolation Method (RPIM)

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Abstract

Purpose—To describe and assess an automated, normalization method for identifying sentinel (septal) regions of myocardial dysfunction in non-ischemic, non-valvular dilated cardiomyopathy (DCM) using an unprecedented combination of the Navigator-gated 3D Spiral Displacement Encoding with Stimulated Echoes (DENSE) MRI, Radial Point Interpolation (RPIM) and Multiparametric Strain Z-Score (MPZS).

Materials and Methods—Navigator-gated 3D Spiral DENSE, in a 1.5 Tesla MRI machine, was used for acquiring the displacement encoded complex images, MR Analytical Software System (MASS) for automated boundary detection and automated meshfree RPIM for left-ventricular (LV) myocardial strain computation to analyze MPZS in 36 subjects (with N=17 DCM patients). Pearson's r correlation established relations between global/sentinel MPZS and EF. The time taken for combined RPIM-MPZS computations was recorded.

Results—Maximum MPZS differences were seen between antero-septal and posterolateral regions in the base (2.0 ± 0.3 versus 0.9 ± 0.5) and the mid-wall (2.1 ± 0.4 versus 1.0 ± 0.4). These regional differences were found to be consistent with historically documented septal injury in non-ischemic DCM. Correlations were 0.6 between global MPZS and EF, and 0.7 between sentinel MPZS and EF. The time taken for combined RPIM-MPZS computations per subject was 18.9 ± 5.9 seconds.

Conclusions—Heterogeneous contractility found in the sentinel regions with the current automated MPZS computation scheme and the correlation found between MPZS and EF may lead to the creation of a new clinical metric in LV DCM surveillance.

Keywords

cardiac mechanics; contractile dysfunction; dilated cardiomyopathy; DENSE; MPZS; RPIM

Current task-force statistics from the American College of Cardiology and American Heart Association (ACC/AHA) and others show that the prevalence of dilated cardiomyopathy (DCM) in the United States is approximately 36 people per 100,000, causing numerous

hospitalizations for heart failure and deaths each year [1–3]. DCM is one of the most common causes of heart failure (HF) [1, 4]. Patients diagnosed with DCM in clinical HF have dilated, impaired left-ventricles (LV), ejection fractions (EF) less than 40%, all of which is generally accompanied by septal region (implying the septum) myocardial dysfunction [5, 6]. Hence, we endeavored to develop an appropriate metric, the automated Multiparametric Strain Z-Score (MPZS), for tracking the ventricular remodeling that may be related to adverse outcomes such as surgical intervention, end-organ failure or even sudden death in DCM [1, 5, 6].

The primary objective of this study was to formulate an automated metric for identifying sentinel (septal) regions of myocardial dysfunction that could be used for indexing the severity of disease in non-ischemic dilated cardiomyopathy. There are three important steps undertaken in assignment of this metric and brief descriptions of these steps are given in the following. The first step involves image acquisition where Displacement Encoding with Stimulated Echoes (DENSE) is a higher resolution MR imaging sequence which measures tissue displacement from a fixed encoding point at end-diastole [7–9]. Tissue displacements at the fixed spatial locations were obtained using fast automated unwrapping of the phases, where phase shifts occur between initial position encoding and readout [8–10]. The greatest advantage of DENSE is the automated phase unwrapping in complex images that enables rapid 3D displacement analysis [8, 9, 11–13]. The second step involved automated image-based boundary detection using the MR Analytical Software System (MASS) (Leiden University, Leiden, NL) and 3D reconstruction using an in-house C++ algorithm [14–18]. The third and last step was the development of an automated, high resolution LV myocardial function-based metric, the MRI-based Multiparametric Strain Z-Score (MPZS) [14, 19–21]. While a number of well-validated scoring methods for assessing clinical HF risks exist [22–28], a validated model of risk assessment based on an individual patient's LV biomechanics is yet to become mainstream in clinical HF diagnosis [5, 14, 20, 21]. Hence, we proposed to develop the MPZS metric based on normalization of several individual strain components computed with the meshfree Radial Point Interpolation Method (RPIM) and combined into a single multiparametric composite index. As RPIM is relatively new in numerical analysis techniques, we endeavored to quickly compare the strains generated to a more traditional finite element analysis (FEA) method known as Measurement Analysis (MEA). MEA, which has been previously used for MPZS analysis, is based on higher order polynomial interpolation of spatial variables, also commonly known as the p-version in FEA [5, 14, 16, 20, 29–31].

Materials and Methods

Human Subject Recruitments

A total of 36 subjects (normals = 19, DCM patients = 17) were imaged in a 1.5 Tesla Avanto (Siemens, Erlangen, Germany) MRI scanner using the 3D Navigator-gated Spiral DENSE sequence [10]. All subjects signed informed consents in accordance with the university's Institutional Review Board (IRB) guidelines. MRI data from the normal volunteer data formed the healthy subjects' database for normalizing patient strains and computing MPZS

[7, 14, 20]. The normal subjects filled out a questionnaire approved by the IRB that established absence of any form of cardiac disease.

DENSE Acquisition and Protocols

Navigator-gated 3D DENSE data was acquired with displacement encoding applied in two orthogonal in-plane directions and one through plane direction. A flexible, anterior 6-channel body matrix RF coil (Siemens Healthcare, Erlanger, Germany) was used for receiving signals [7–9]. Typical imaging parameters included FOV of $380 \times 380 \text{ mm}^2$, TE of 1.04 ms, TR of 15 ms, matrix size of 128×128 pixels, $2.97 \times 2.97 \times 5 \text{ mm}^3$ voxel spacing, 6 mm slice thickness, 21 cardiac phases, encoding frequency of 0.6 cycles/cm, simple 4-points encoding [32], 3-points phase cycling for artifact suppression [10, 12]. The acquisition time was about 10 minutes, depending on the heart rate and navigator acceptance rate of individual subject.

Continuous monitoring of heart rates (HR) and blood pressures (BP) were conducted during the scans for both patients and healthy subjects. Additionally patients underwent Doppler echocardiography tests for heart failure analysis and were assigned an NYHA class by their physicians. The time taken for scanning each subject was recorded.

Segmentation

Offline automated segmentation of the myocardium was facilitated using MASS [17, 18] and automated phase unwrapping in DENSE and reconstruction of 3D volume splines and surfaces for 3D geometry accomplished with a C++ in-house application [7, 14, 19, 31]. The automated MASS detection of endocardial and epicardial boundaries is based on an Active Appearance Motion Model (AAMM). Manual contours were first defined at end-diastole and end-systole in multiple slices from base to apex and the AAMMs created using a leave-one-out procedure [17, 18]. What follows is iteratively deforming the AAMM within statistical limits until an optimal match is found between the deformed AAMM and the underlying image (leave-out) data. The only manual intervention required for 3D reconstruction was identifying the anterior and posterior septal points at the RV boundary. This was followed by segmenting the LV plane into six regions and creating the 3D epicardial and endocardial wire frame meshes [14–16, 20]. The LV volume was then segmented into 16 AHA recommended segments for strain analysis with equally spaced intramural grid points as shown in Fig. 1 [33]. Ejection volume (EV), end-diastole volume (EDV), end-systole volume (ESV), EF and mass for all subjects (N=36) were computed using MASS [14–16, 20]. Computation of patient EF was also facilitated by clinical echocardiography tests and the results from MASS verified to lie within 10% variation of the echocardiography tests [34]. The approximate time (in minutes) for segmentation was recorded.

Meshfree Strain Analysis

Strain parameters in 3D (radial, circumferential and longitudinal) were computed using RPIM at each voxel in patient-specific DENSE magnitude image-based reconstructed 3D grid geometries. RPIM is a meshfree numerical analysis technique that facilitates fast multidimensional computation of Lagrangian strains [7, 31, 35–37]. DENSE-based RPIM

computation was primarily designed as a model-based approach involving 4D analysis of motion with deformations and strains readily computed at a given point in the three spatial dimensions and the dimension of time [9, 12, 38]. Similar model-based and pointwise cardiac strain computation techniques have been used in previous DENSE studies [9, 10, 12]. Furthermore, the RPIM strains were computed at 16 circumferentially arranged cardiac segments in accordance with AHA segmentation guidelines [33]. The greatest advantage of RPIM lies in eluding intensive computational techniques like remeshing which can be the most time-consuming component of conventional finite element analysis (FEA). Thus, the combination of fully automated 3D tissue displacement and strain computation using meshfree RPIM was undertaken to deliver high-resolution MPZS analysis with minimum operator time and interaction. A brief description of RPIM is given next.

The core of the RPIM methodology involves a continuous displacement field function, $u(\mathbf{x})$, passing through a group of scattered nodes, $\mathbf{x}$, within a domain [7, 35, 36],

$$u(\mathbf{x}) = \sum_{i=1}^n B_i(\mathbf{x})a_i + \sum_{k=1}^m p_k(\mathbf{x})b_k = \mathbf{B}^T(\mathbf{x})\mathbf{a} + \mathbf{p}^T(\mathbf{x})\mathbf{b} \quad (1)$$

where $\mathbf{p}(\mathbf{x})$ is the matrix of monomial bases and $\mathbf{b}$ is vector of coefficients to which radial basis functions (RBF), $\mathbf{B}(\mathbf{x})$, with $\mathbf{a}$ as the coefficient vector, are added. It is the existence of $\mathbf{B}^{-1}$ for arbitrary scattered nodes that is considered a major advantage of RBFs [7]. The RBFs added were of the Multiquadrics (MQ) type [35–37]. Following developments of the deformation gradient tensor, $\mathbf{F}$, and Lagrangian strain tensor, $\mathbf{E}$, with RPIM are outlined extensively in previous literature [7, 31, 35–37].

Multiparametric Strain Z-Score Analysis

The computation scheme for MPZS is based on the normalization of individual strain components (circumferential, radial and longitudinal) combined into a single composite index. Each LV was segmented into 16 sub-regions with three levels and six annular divisions (anteroseptal, anterior, anterolateral, posterolateral, posterior and posteroseptal) per level (Fig. 1). The apex had four sub-regions (septal, anterior, lateral, and posterior) as outlined by the AHA guidelines on segmentation and shown in Fig. 1 [33]. The strain components were averaged and standard deviations computed for each of the 16 sub-regions for both healthy subjects and patients. The formula for computing sub-regional MPZS is given by,

$$\text{MPZS} = \frac{1}{3} \left[\frac{(\varepsilon_c - \mu_{n,c})}{\sigma_{n,c}} + \frac{(\varepsilon_l - \mu_{n,l})}{\sigma_{n,l}} - \frac{(\varepsilon_r - \mu_{n,r})}{\sigma_{n,r}} \right] \quad (2)$$

where ε_r , ε_c and ε_l represents the patient-specific average strains, $\mu_{n,r}$, $\mu_{n,c}$ and $\mu_{n,l}$ are the average strains and $\sigma_{n,r}$, $\sigma_{n,c}$ and $\sigma_{n,l}$ are standard deviations in healthy subjects at a given myocardial point in the radial, circumferential and longitudinal directions, respectively. It is noted that the ε_r , ε_c and ε_l strains have much lower magnitudes in dysfunction in

comparison to those found in healthier populations [5, 6, 20, 39]. The terms $\epsilon_c - \mu_{n,c}$ and $\epsilon_l - \mu_{n,l}$ yield positive values and the negative of $\epsilon_r - \mu_{n,r}$ yields a positive value. Ultimately, a computed z-score greater than zero implies a dysfunctional sub-region where it would be less than or equal to zero in a normally performing region [5, 14, 19–21]. MPZS therefore compares contractility to an established normal in the same myocardial sub-region in a database of healthy subjects.

It is noted that two of the shear strain-based components, circumferential-longitudinal and longitudinal-radial, were not included in the MPZS composition due to issues of confounding and/or collinearity which can arise in a formula with multiple parameters [40, 41]. Multi-collinearity between the six independent strain components which were the three normal: circumferential, radial and longitudinal and the three shear: circumferential-longitudinal, longitudinal-radial and circumferential-radial strains were examined using Matlab (MathWorks, Natick, MA). The choice of adding the shear strain-based z-score components in the composite MPZS (Eqn. 2) was determined by the significance of correlation with the three normal strain z-scores. Additionally the circumferential-radial shear was unused due to abnormally high variations in inter-subject values. Previous studies have reported this variability where the likely cause is the inclusion of patients with high torsions between the endocardium and epicardium [38, 39, 42, 43].

The time taken for the combined computation of RPIM strains and final MPZS for each patient was recorded to show that strains and z-scores' computation using our current methodology is much quicker than using traditional methods. The sentinel region of myocardial dysfunction was determined by the highest MPZS value among the 16 regions.

Rendering 3D MPZS Contour Maps

Along with automated RPIM and MPZS computations, rapid and automated rendering of MPZS surface maps with 3D visual formatting via Matlab were conducted [7, 8, 31]. Briefly, strains at the grid points shown in Fig. 1 were generated by interpolating the original voxel-based strain data, in DCM patients and normal subjects, and their composite MPZS computed (Eqn. 2). Local 3D epicardium and endocardium patches were then rendered using the four nearest grid point MPZS values to display myocardial surfaces segments. Such MPZS surface contour maps can be generated for both healthy and patient populations.

Statistical Analysis

Pearson's r correlation was computed between patient global/sentinel MPZS and EF in an effort to show that MPZS is a metric of significance in DCM. Appendix A shows the means and standard deviations of normal strains computed with RPIM, compared to those computed with the more traditional MEA. It is noted that MPZS computed with MEA has traditionally included the circumferential and longitudinal strains, exclusive of radial strains [16, 29].

Results

Patient Details

Details of HR, BP and other demographic are given in Table 1. Specific details on DCM patients such as physician assigned NYHA classes are given in Table 1. Table 1 also shows the global/sentinel z-scores assigned to the N=17 DCM patients using the DENSE-RPIM-MPZS framework. The time taken for each scan was 15 ± 9 minutes.

Statistical Results

The correlation between all three normal global MPZS components were found not to be significant ($p=0.1$). However, significant correlation were found between circumferential and circumferential-longitudinal shear ($r=0.7$, $p=0.007$) and the longitudinal and longitudinal-radial shear ($r=0.6$, $p=0.009$) z-score components. Time taken for 3D automated myocardial segmentation was typically 15 minutes per patient. Time taken for phase unwrapping (displacement analysis) was 3.65 ± 1.95 minutes and depended on the short-axis stack size, where processing configuration included a 3.4 GHz Intel Core processor, 16 GB of RAM and a 64-bit operating system. Average MPZS were calculated for each of the 16 LV regions where the septal sub-regions were found to be the most consistently and heavily injured of all (Fig. 2). Some of the highest contrast in average MPZS was found between the basal antero-septal and posterolateral sub-regions (2.0 ± 0.3 versus 0.9 ± 0.5 , $p=0.001$), and between the mid-wall antero-septal and posterolateral sub-regions (2.1 ± 0.4 versus 1.0 ± 0.4 , $p=0.001$) as shown in Fig. 2. The time taken for combined computations of RPIM strains and MPZS was 18.9 ± 5.9 seconds per patient. In comparison, tissue tagging and strain analysis in tagged-MRI can take approximately 6–8 hours of processing time as reported in earlier studies [14, 20, 21]. Fig. 3 shows the relationship between global/sentinel MPZS and EF. A Pearson's r correlation equal to 0.6 was obtained between global MPZS and EF and 0.7 was obtained between sentinel MPZS and EF. Appendix A shows the comparison of strains between the RPIM and MEA techniques.

Three-Dimensional Contouring

Fig. 4A–C shows contour maps of left-ventricular circumferential, longitudinal and radial strain-based MPZS on the epicardium and endocardium surfaces prior to summing for the final MPZS. Each strain-based z-score map individually reflects sentinel regions of dysfunction in a total of 16 regions. Fig. 4D shows the composite MPZS contours generated from summing the individual z-scores in the same patient. It is noted here that Fig. 4 shows the sum of normalized strains in one single patient. While Fig. 4 is indicative of how the normalized strains are summed to compute MPZS, the contributions of the three normalized strains may vary from case to case. The red and yellow zones in Fig. 4D indicate contractile dysfunction ($MPZS > 0$) and the zones in blue indicate normally functioning myocardium ($MPZS \leq 0$). Similarly, Fig. 4E–G shows contour maps of the three normal strain-based MPZS and Fig. 4H shows the combined MPZS in a healthy subject. Shown in Fig. 5 are MPZS computed with the three normalized strains in nine patients with a consistent pattern of sentinel dysfunction. The last contour (bottom-right) in Fig. 5 is an interesting case where the patient was diagnosed with hypertrophy, as well. Indeed, the spread of heterogeneous

dysfunction can be seen throughout the myocardium along with a thickening of the wall and a smaller endocardium.

Discussion

The foremost objective of this study was to conduct MPZS computations for identifying sentinel regions of dysfunction in DCM, by constructing patient-specific 3D DENSE-based grids, computing point-wise Lagrangian strains and combining multi-strain parameters into z-scores. Where MPZS might ultimately distinguish abnormal myocardial contractile patterns in comparison to normal ones in healthy subjects [5, 14, 19–21]. The primary finding of this study is the differences in regional MPZS values (between septal and lateral sub-regions) in HF patients established with the DENSE-RPIM-MPZS framework as shown in our artwork. A similar pattern was shown with a previous tagged-MRI study which showed similarly high septal MPZS compared to the lateral myocardial wall [5]. However, it is noted that MPZS strain parameters used in the previous study were different from the current, thus making trends in regional MPZS comparable between the studies rather than magnitude [14, 20, 35–37]. The Pearson's correlation values between global/sentinel MPZS and EF show that strong relationships exists between the two metrics. However, the table does show a patient with normal ejection fraction. In this context, the role of diastolic dysfunction is likely to have played a role in producing symptomatic heart failure. Also, as mentioned in the results, this patient was diagnosed with hypertrophy and a general lack of contractile abilities in the entire myocardium. In relation to this diastolic dysfunction/hypertrophy that was seen, the AHA/ACCF task force does report that in patients with clinical HF, the estimated prevalence of preserved EF is approximately 50% (range of 40–71%) [1]. Current literature also suggests that a high magnitude of hypertrophy or abnormal increases in myocardial stiffness due to collagen restructuring could be the cause of cardiomyopathy [44, 45]. Future efforts will closely examine the cause of cardiomyopathy as well as the relationship between the metrics. The difference in MPZS distribution between a DCM patient and normal subject is illustrated which reinforces our goal to visually identify heterogeneous injury in DCM in the clinical setting. It can be seen from inter-patient similarities that the predominant sentinel region of injury (region of heterogeneity) is the basal-to-mid-ventricular septum.

This study in particular shows that high resolution, detailed 3D strain maps can be generated with DENSE motion tracking and meshfree RPIM numerical analysis and modeling [5, 7, 9, 10, 15]. As evidenced in literature, MRI DENSE can accurately characterize regional LV functionality and have numerous advantages over modalities such as echocardiography [6, 7, 10, 14, 46, 47]. We also mentioned in Materials and Methods that the DENSE-RPIM (displacement-strain) analysis is essentially a model-based technique involving 4D spatio-temporal motion tracking and subsequent strain analysis with RPIM; a technique applicable for large deformation analysis in an arbitrary nonlinear material [35–37]. Traditional FEA requires mapping of field variables between elements and meshes and computationally expensive node generations for shape functions in a pre-defined element. In contrast, meshfree RPIM requires node generation for directly solving the local discretized system of equations. One of the disadvantages in traditional FEA is the higher continuity requirement on the shape functions, which can limit their usage. In comparison, meshfree methods can

easily be constructed to have any desired order of continuity. Additionally, there is no requirement for *a-priori* information on the relationship between nodes which enables more accurate intra and inter-subject comparisons [14, 20, 35–37]. Hence, improving the speed and efficiency of 3D strain parameter computations for combining them into point-wise, regional and global composite indices. Finally, in regards to adapting a meshfree method, it was shown that RPIM strains computed for MPZS are indeed comparable to traditional FEA (MEA) techniques for strain analysis.

The first limitation of this study was not comparing the DENSE based MPZS to that computed from a more established sequence such as tagged-MRI. In past studies we have used the Bland-Altman methodology for assessing agreement between methods [48]. Although, we have conducted direct validations between DENSE and tagged-MRI strains (not MPZS) in previous studies [7, 31]. A second limitation was processing time for left-ventricular segmentation. Despite automated procedures, some manual intervention is still required for accurate boundary detection and reconstructions of LV geometry [17, 49]. A third limitation was the operator selected end-systole timeframes for generating z-scores and not identifying it by peak strains as done in echocardiography studies [50]. The nine years plus age difference between DCM patients and healthy subjects can be considered a fourth limitation. However, previous echocardiography based analysis show that no significant errors occur when this range of age-related differences exist between patients and healthy volunteers during strain normalization [38, 51, 52].

The current study shows how the fast and automated DENSE-RPIM-MPZS paradigm can be used for uniquely indexing sentinel ventricular injury. Additionally, the MPZS metric was shown to correlate well with an important cardiovascular marker, the EF. We also demonstrated how heterogeneous distribution of LV regional dysfunction can be illustrated with 3D surface rendering of MPZS. With extensive validations, the MPZS metric can become an automated, computationally inexpensive and visual tool that helps the clinician diagnose the severity of DCM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Figure 3.

Figure 4.

Figure 5.

Table 1

Demographic and Clinical Details of DCM Patient and Normal Subjects Summary

ID	GN	Age years	Weight lbs	BPS mmHg	BPD mmHg	HR bpm	EDV ml	ESV ml	EF %	Mass gm	NYHA Class	Max MPZS	Avg. MPZS
1	M	70	180	65	102	67	332.1	235.8	29	205.7	2	2.1	1.1
2	M	70	177	67	106	73	203.5	147.3	28	173.9	2	2.1	1.2
3	F	54	162	62	106	90	254.8	191.9	25	154.0	3	2.4	1.4
4	M	46	202	66	111	64	237.3	156.6	34	196.5	3	2.1	1.1
5	M	59	163	78	115	80	231.5	167.3	28	201.9	2	2.3	1.0
6	M	59	167	75	104	82	301.8	228.4	24	175.7	2	2.7	1.3
7	M	42	210	60	104	52	260.4	213.2	18	215.0	2	2.3	1.3
8	M	61	157	90	130	74	384.9	318.6	17	229.0	2	2.5	1.3
9	M	61	157	82	118	70	392.7	315.2	20	254.7	2	2.2	1.3
10	F	40	115	60	100	80	324.3	261.4	19	185.3	2	2.7	1.4
11	F	67	265	75	125	67	277.1	162.5	41	202.4	2	2.0	1.1
12	M	59	230	70	125	66	288.1	181.7	37	248.2	2	2.0	1.1
13	M	42	256	65	117	80	572.3	524.2	18	299.0	3	2.0	1.1
14	M	49	237	80	125	83	139.0	52.5	57	133.5	2	1.8	0.9
15	F	53	180	84	145	95	124.1	82.7	33	149.5	3	2.1	1.3
16	M	59	256	72	121	63	97.1	36.3	61	187.5	2	1.9	1.0
17	F	37	152	63	110	72	126.7	73.2	20	124.4	3	2.4	1.0
<hr/>													
HF Avg.	1:3	54.6	192.1	71.4	115.5	74.0	267.5	197.0	30.1	196.2	2.3	2.2	1.2
SD		10.4	43.5	9.1	12.0	10.7	118.3	118.4	13.3	45.0	0.5	0.2	0.3
HV Avg.	1:0.7	46.1	164.2	75.0	121.8	70.0	147.0	52.1	64.7	124.9	-	0	0
SD		11.5	21.7	8.1	11.4	6.5	34.3	15.6	5.7	24.8	-	0	0

Abbreviations: HF: heart failure, HV: healthy volunteer, GN: gender, BPS: blood pressure at end-diastole, BPS: blood pressure at end-systole, HR: heart rate, EDV: end-systole volume, EDV: end-diastole volume, EF: ejection fraction, MPZS: Multiparametric strain Z-Score, NYHA: New York Heart Association, Max MPZS: highest region MPZS, Avg. MPZS: averaged (16-region) MPZS.