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Dilated Cardiomyopathy: Normalized Multiparametric Myocardial Strain Predicts Contractile Recovery

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Abstract

Background—Left ventricular (LV) contractile injury in dilated cardiomyopathy (DCM) may occur in a consistently heterogeneous distribution, suggesting that early injury “sentinel” regions may have prognostic significance. Heightened surveillance of these regions with high-resolution contractile metrics may predict recovery in DCM.

Methods—Multiple 3D strain parameters were calculated at each of 15,300 LV grid-points from systolic displacement data obtained from cardiac MRI in 124 test subjects. In 24 DCM patients, z-scores for two strain parameters at each grid-point were calculated by comparison of patient-specific strain values to respective point-specific mean and standard deviation values from a normal human strain database (n=100). Multiparametric strain z-scores were averaged over 6 LV regions at basilar, mid, and apical levels (18 sub-regions). DCM patients were stratified into 3 groups based on a blinded review of clinical contractile recovery (complete[n=7]; incomplete[n=7]; none[n=10]).

Results—Basilar-septal sub-regions were consistently heavily injured. Basilar-septal z-scores were significantly larger (worse) than those for the rest of the LV (2.73 ± 1.27 vs 2.22 ± 0.83 ; $p=0.011$) and lateral wall (2.73 ± 1.27 vs 1.44 ± 0.72 ; $p<0.001$). All patients with sentinel region average multiparametric strain z-scores <2 standard deviations (n=6) experienced complete recovery, while 17/18 DCM patients with z-scores >2 standard deviations experienced incomplete or no contractile recovery.

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Conclusions—Contractile injury in DCM is heterogeneous with basilar-septal regions injured more than lateral regions. The targeting of early-injury sentinel regions for heightened surveillance with high-resolution metrics of micro-regional contractile function may accurately predict recovery on medical therapy. A 2 standard deviation z-score threshold may predict contractile recovery.

Keywords

Cardiomyopathy; heart failure; imaging; MRI; myocardial mechanics

Introduction

Non-ischemic, non-valvular dilated cardiomyopathy (DCM) is associated with predictable left ventricular (LV) geometrical changes, which typically include wall thinning and chamber dilatation. Notably, these LV geometric changes occur in an axisymmetric, circumferentially uniform distribution.[1, 2] It is therefore intuitive that the contractile injury behind these architectural changes should be manifest in a similarly uniform and homogeneous geometrical distribution. However, investigations using multiple imaging modalities to characterize regional contractile function have suggested heterogeneous contractile injury in patients with DCM.[3–10] Despite small sample sizes, our group and others have demonstrated a reasonably consistent pattern of heterogeneous contractile injury distribution primarily localized to the inter-ventricular septum.[9, 10]

A consistent pattern of heterogeneous LV contractile injury distribution finds clinical significance in the logical inference that contractile injury in DCM may occur in the various regions of the LV at different timeframes during the natural course of the disease. Specifically, the consistent finding of basilar-septal injury, whether scanned early or late in the DCM disease process, suggests that the basilar-septum must be sustaining injury earlier than the other LV regions. As such, the early-injury basilar-septal sub-regions can be labeled “sentinel” sub-regions, and their early involvement in the myopathic process may have considerable prognostic significance. This is especially critical in DCM since significant compensation for sentinel region contractile injury may come from non-injured walls, thereby masking the onset and progression of disease if global metrics alone are used to assess contractile function. Indeed, the heterogeneity of contractile injury may offer at least partial explanation for the regrettable inadequacy of global metrics in predicting outcomes in DCM patients.[11, 12] The targeting of early injury sentinel regions for heightened surveillance in DCM patients may offer a solution to the heart failure clinician’s need for clinically applicable metrics to more accurately predict LV recovery. Invasive surgical therapy in heart failure patients is always high-risk and the accurate identification of patients who can expect full recovery on medical therapy—and those who are headed for progressive failure—is of obvious importance.

Further investigation to confirm a consistent pattern of heterogeneous LV contractile injury in DCM patients is warranted and yet continues to be problematic because of the natural heterogeneity of strain across the normal human left ventricle.[13] If strain injury is to be accurately compared across regions, this natural contractile heterogeneity must be accounted

for. This mandates direct comparison of DCM patient data to point-specific normal mean $\pm$ standard deviation (SD) strain component values compiled from a normal population. Over many years of investigation, we have built such a database from MRI-based strain data obtained from 100 normal volunteers. Each disease-free subject contributed individual raw values for *all* strain components at each of 15,300 points in a uniform standardized LV mesh. This database allows patient-specific strain measurements to be “normalized” by direct comparison to the normal mean and standard deviation at the corresponding grid-point, thereby enabling the calculation of z-score values. The z-scores provide a numerical quantification of the deviation from the normal population mean value of each patient-specific strain value at each point of the LV grid.

Indeed, patient-specific laboratory blood test values have been interpreted for decades by their direct comparison to “normal ranges” derived by standard deviation from the mean in normal subject populations. In the case of laboratory values, therapeutic intervention is most often triggered by patient-specific test values that fall greater than 2 SD from the mean. We hypothesized that this same 2 SD threshold would also prove valuable in determining clinical significance in regional contractile function, just as it has in the clinical interpretation of laboratory blood test values. By quantifying and normalizing the DCM patient’s regional contractile function in a familiar format, this database normalization of micro-regional LV contractile function may provide a clinically applicable methodology for integrating patient-specific LV micro-regional contractile data into heart failure diagnostic and therapeutic clinical algorithms.

Patients and Methods

Patient Characteristics

The Human Research Protection Office at Washington University (St. Louis, MO) approved this study, and all subjects gave informed written consent. No sex-based or racial/ethnic-based exclusions were present during patient recruitment.

A group of 100 healthy volunteers with no historical, physical, or clinical test evidence for any kind of heart disease underwent cardiac MRI and contributed complete strain parameter information to a *normal human strain database*. An additional 24 patients with documented non-ischemic, non-valvular dilated cardiomyopathy were enrolled in the study and underwent cardiac MRI with radiofrequency tissue tagging. These 24 patients all underwent a full, standardized workup as directed by American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, [18] including coronary angiography. No reversible etiologies were detected. The etiologies in the DCM patient population were idiopathic (21/24), postpartum (1/24), and chemotherapy-induced (2/24). All patients were treated with standardized medical therapy for non-ischemic DCM as per the ACC/AHA guidelines.[18] Demographic and selected clinical data are presented in Table 1.

Cardiac Magnetic Resonance Imaging

All imaging studies were carried out using a 1.5T scanner (Siemens, Erlangen, Germany) as previously described.[10, 19, 20] Briefly, transverse short-axis and radial long-axis tagged

MR images were acquired in multiple planes throughout the entire LV. In each imaging plane, a spatial modulation of magnetization (SPAMM) radio-frequency tissue-tagging preparation was applied, followed by a 2D balanced steady-state free precession cine image acquisition. Typical imaging parameters were: repetition time 32.4ms, echo time 1.52ms, field of view 350x350mm, flip angle 20°, tag spacing 8mm and slice thickness 8mm.

Strain Analysis

Strain measurements were obtained for all study participants using an established and validated method developed in our laboratory.[21, 22] Briefly, endocardial and epicardial wall boundaries were manually identified on each of the tagged images used in the study to create a 3D finite element model of the LV (Figure 1). Tag lines were tracked on each of the images semi-automatically utilizing an active contour approach.[21] Three-dimensional displacements were computed for the systolic interval by tracking the intramyocardial intersection points of the three tag surfaces. Using the anterior and posterior attachment points of the right ventricle with the LV as fiducial landmarks, a standardized 18-element mesh was created for each model. A least squares fitting of the displacement data was used to obtain a continuous description of displacement for the entire model. Using the results of this fitting, circumferential and longitudinal strain values were computed over a standardized grid of 15,300 points encompassing the entire LV. The finite element software package *StressCheck* (ESRD, Inc., St. Louis, MO) was used to obtain the strain measurements for this study.

MRI-based Multi-parametric Strain Z-score Analysis

The strain data from 100 normal volunteers were used to generate a normal mean and standard deviation for each strain metric at each of the 15,300 LV grid-points. This created a normal strain database that allows for strain component-specific, point-by-point comparisons to normal.

A second group of 24 patients with known non-ischemic, non-valvular DCM were compared to the normal database. For each patient, z-scores were calculated for both circumferential and longitudinal strain parameters at each LV grid-point by reference to the normal mean and standard deviation values in the normal strain database. The normalization of the circumferential and longitudinal z-scores allowed averaging to generate a single multiparametric strain z-score at that point. The 15,300 multiparametric strain z-score values were then color contour plotted over patient-specific geometry.

Clinical Follow-up

The medical records of each of the 24 DCM patients enrolled in the study were thoroughly reviewed by a clinician blinded to the multiparametric strain data. Follow up data was available in 100% of the study participants with a mean follow up of 4.4 years. Patients were stratified into three separate groups based on recovery: complete recovery (n=7), incomplete recovery (n=7), and progressive failure (n=10). Complete recovery was defined as return to New York Heart Association (NYHA) functional class I with a normal left ventricular ejection fraction. Incomplete recovery was defined as a return to NYHA functional class I/II with an ejection fraction between 30 and 40%. The progressive failure group, on the other

hand, remained in NYHA functional class III/IV and persisted with left ventricular ejection fraction's <30%, with most being <20%. Characteristics of each group are in Table 1.

Statistical Analysis

Continuous data are presented as a mean $\pm$ standard deviation, while categorical data are presented as a percentage. Comparisons of regional z-scores were done using a repeated measures analysis of variance (ANOVA). Sphericity was tested using Mauchly's test and the Bonferroni correction was utilized for pairwise comparisons. Basilar-septal z-scores between the three groups of patients were compared using a one-way ANOVA. Homogeneity of variance was tested using the Levene statistic, while post hoc comparisons were done using Gabriel's procedure.

Categorical variable outcomes were compared using the χ^2 or the Fisher exact test. Continuous outcomes were compared using the *t*-test for means of normally distributed continuous variables and the Mann-Whitney U nonparametric test for skewed distributions. Statistical tests were done using the statistical software package IBM SPSS 22 (IBM SPSS, Inc., Chicago, IL) or SYSTAT 13 software (Systat Software, Inc., Chicago, IL).

Results

Multiparametric strain information was successfully obtained in all 24 DCM patients with post-processing display of "normalized" micro-regional contractile function on patient-specific LV geometry. A composite display of normalized micro-regional contractile function by z-score color contour mapping for all 24 DCM patients is represented in Figure 2. This 3D model is fully rotatable, and semi-transparent, but for ease of display, four views of the composite 24-patient model is shown in this illustration. Further, in order to display the functionality and applicability of this methodology in a paradigm with which most clinicians are familiar, we scaled the color contouring based upon thresholds similar to those utilized in the clinical integration of patient blood laboratory test values. Specifically, <1 standard deviation from the normal mean was colored blue; 1 – 2 SD, yellow; and > 2 SD, red.

For each of the patients in the study, point wise measurements of the multiparametric z-scores were averaged to produce mean z-scores over the six ventricular regions (posteroseptal, anterosseptal, anterior, anterolateral, posterolateral and posterior). Mean multiparametric z-scores ranged from a high of 2.71 in the posteroseptal region to a low of 1.25 in the anterolateral region (Figure 3). Regional z-scores were compared using repeated measures ANOVA. Overall, multiparametric z-scores were found to vary significantly by region ($p < 0.001$), so pairwise comparisons were obtained using the Bonferroni correction for multiple comparisons. Z-scores in the posteroseptal wall were significantly larger than those in the anterior, anterolateral, posterolateral and posterior regions ($p < 0.025$ for all). Similarly, z-scores in the anterosseptal wall were significantly greater than those in anterior, anterolateral and posterolateral walls ($p = 0.007$ for all). Additional significant differences were seen between the anterolateral wall and the anterior, posterolateral and posterior walls ($p = 0.01$ for all) and between the posterolateral wall and posterior wall ($p < 0.001$). Lastly, z-

scores in the posterior wall were found to be significantly greater than in the anterior wall ($p=0.007$).

The results of this regional analysis suggest not just heterogeneity of contractile injury, but a consistent pattern of heterogeneity in this group of DCM patients. Multiparametric strain z-scores were consistently larger in the septal regions, especially at the base of the ventricle, while the lateral wall exhibited function that was closest to normal. To further clarify these differences, a comparison of z-scores between the basilar-septum, lateral wall and all other ventricular regions was conducted. The repeated measures ANOVA revealed an overall significant difference in z-scores between the three regions ($p<0.001$). Basilar-septal z-scores were significantly higher than the rest of the ventricle (2.73 ± 1.27 vs 2.22 ± 0.83 ; $p=0.011$) and lateral wall (2.73 ± 1.27 vs 1.44 ± 0.72 ; $p<0.001$) (Figure 4).

Basilar-septal z-scores were compared between the three groups (complete recovery, incomplete recovery, and progressive failure) using a one-way ANOVA. The overall ANOVA indicated a significant difference in z-scores between the groups ($p=0.001$), so pairwise comparisons were done between the groups. Basilar-septal z-score values in the progression group were significantly larger than those with complete recovery (3.50 ± 1.05 vs 1.47 ± 0.92 , $p=0.001$). There was also a significant difference between the incomplete recovery and complete recovery group (2.89 ± 0.87 vs 1.47 ± 0.92 , $p=0.035$) (Figure 5). No significant difference was found between the incomplete and progression group (2.89 ± 0.87 vs 3.50 ± 1.05 , $p=0.489$).

Scatter plots were constructed showing each individual patient's average basilar-septal z-scores and lateral z-scores. In the basilar-septal sentinel region, all patients with an average multiparametric strain z-scores below 2 SD completely recovered while 17/18 patients with average z-scores greater than 2 SD obtained at most partial recovery and predominantly progressive failure (Figure 6). In the less injured lateral region, most individuals with average multiparametric strain z-score values that exceeded 2 SD had progressive failure (Figure 7). This suggests that not only is a lack of sentinel region injury a marker of good prognosis, but also a severe contractile injury in the usually spared lateral wall is a marker of bad prognosis.

Sentinel region z-scores were also used to construct a receiver operator characteristic (ROC) curve. For this analysis the partial recovery and progression group were combined into a single group termed incomplete recovery. The area under the curve was found to be 0.933 ($p<0.001$, standard error=0.067, 95% confidence interval = 0.802 – 1.000). Using a sentinel z-score of 2.00 as a cutoff value resulted in a sensitivity of 85.7% and a specificity of 100%. Overall, this approach accurately classified 95.8% (23/24) of the patients in this study.

Comment

The findings of this investigation confirm that contractile injury in DCM is not only heterogeneous in distribution, but occurs in a consistent pattern in which basilar-septal injury predominates. The relative sparing of the lateral wall that was also found in our preliminary study group is also confirmed.[10] This heterogeneous pattern of injury in DCM

patients is also consistent with previous reports from other groups using both MRI tissue-tagging [9] and two-dimensional echocardiography. [3]

In regard to contractile injury distribution, not only are these two findings the most profound, but so also does their correlation to clinical contractile recovery make them the most clinically relevant. Further, this investigation suggests that the paradigm of defining clinically significant pathology at the 2 SD threshold, which has been so valuable in the clinical implementation of blood laboratory testing, may also be applicable to the clinical use of strain metrics in the characterization of micro-regional LV contractile injury.

This 2 SD threshold differentiated clinical outcomes when our high-resolution metrics were focused upon the two regional extremes identified by our heterogeneity analysis. Specifically, our focused surveillance of the early injury basilar-septal sentinel region demonstrated a striking correlation between average multiparametric strain z-scores exceeding 2 SD and subsequent clinical contractile recovery. In fact, only one patient whose sentinel region average z-score exceeded 2 SD later achieved complete contractile recovery on medical therapy. All others (n=17) experienced only partial or no contractile recovery at all. In direct contrast, *all* patients (n=6) whose sentinel region average multiparametric strain values were *less than* 2 SD experienced *full* contractile and NYHA functional recovery. This suggests that if the basilar-septal region is spared (as indicated by a z-score of <2) in a DCM patient, then that patient is likely to have full contractile and NYHA functional recovery on medical therapy alone. The fact that the ROC curve statistical analysis cut-off correlated so closely with a 2 SD threshold seems to confirm our hypothesis regarding the application of z-scores in the clinical implementation of this high-resolution LV strain analysis.

Further, the nearly uniform poor response to medical therapy demonstrated in the subgroup of patients whose lateral wall multiparametric strain average z-score values exceeded 2 SD might be of special interest to heart failure clinicians. In the overall study group of 24 DCM patients, the lateral wall was most often spared from severe contractile injury. If, on the other hand, the lateral wall was found to have severe contractile injury (as indicated by an average z-score >2), that patient is not likely to have contractile or NYHA recovery on medical therapy alone. This suggests that *medical* management in these patients will be futile in regard to ultimate long-term contractile and functional recovery. The identification of these patients early in the course of their disease process would allow closer scrutiny, and would likely lower the heart failure clinician's threshold for early surgical intervention. Clearly further investigation to confirm these findings is warranted before widespread clinical application.

Limitations

We utilized a composite metric average of circumferential and longitudinal strain components to target the sentinel regions in the DCM patients. This combination of strain components with widely varying normal ranges is made possible only by the normalization process. Radial strain, the third component, was not included in this analysis since it has traditionally demonstrated less consistency when applied clinically.[23] We are hopeful that the clinical introduction of MRI DENSE methodologies may change this by the inclusion of a higher density of systolic displacement information. Lastly, since the majority of these

DCM patients undergo AICD placement, they are unable to undergo repeat MRIs for further multiparametric strain z-score analysis follow-up investigation.

In conclusion, when micro-regional contractile metrics that account for the natural heterogeneity of normal human strain are used, the pattern of contractile injury in DCM patients is heterogeneous, consistent, and has basilar-septal predominance with relative lateral wall sparing. Heightened surveillance of the early injury basilar-septal “sentinel region” may assist clinicians in predicting contractile recovery, especially if mildly injured. Since the lateral wall is relatively spared from severe contractile injury, the presence of severe injury may also have prognostic significance. We believe the use of a multiparametric strain analysis that utilizes the two most consistently accurate strain components, circumferential and longitudinal strain, can be a valuable tool in evaluating DCM patients. Further investigation is warranted.

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Figure 1.
Finite element model of left ventricle (LV) with a grid of 15,300 LV points divided into 18 sub-regions.

Figure 2.

The composite display of “normalized” micro-regional contractile function by intuitive z-score color contour mapping (<1 standard deviation = blue; $1-2$ = yellow; >2 = red) over patient-specific 3D LV geometry for all 24 DCM patients. *LV*, left ventricle; *DCM*, dilated cardiomyopathy.

Figure 3.

Average multiparametric z-scores over the six left ventricular regions from all 24 dilated cardiomyopathy patients. Data are represented as mean $\pm$ standard deviation. By analysis of variance, multiparametric z-scores were found to vary significantly by region ($p < 0.001$), confirming regional heterogeneity.

Figure 4.

Average multiparametric z-scores by left ventricular sub-region. Data are represented as mean $\pm$ standard deviation. Basilar-septal “sentinel region” z-scores were significantly higher (worse) when compared to the lateral wall or all other left ventricular regions.

Figure 5.

Average basilar-septal “sentinel region” multiparametric z-scores of all 24 dilated cardiomyopathy patients grouped by recovery. Data are represented as mean $\pm$ standard deviation. The group with complete recovery had significantly lower (better) z-scores when compared to the progressive failure group.

Figure 6. Basilar-septal wall scatter plot of multiparametric z-scores in all 24 dilated cardiomyopathy patients.

Figure 7. Lateral wall scatter plot of multiparametric z-scores in all 24 dilated cardiomyopathy patients.

Table 1**Dilated Cardiomyopathy Patient Demographics**

Demographic	Overall (N=24)	Complete Recovery (N=7)	Partial Recovery (N=7)	Progressive Failure (N=10)	P-Value
Age (years)	49 ± 12.8	42 ± 12.5	60 ± 11.5	45 ± 9.3	0.013
Male	16/24 (67%)	4/7 (57%)	5/7 (71%)	7/10 (70%)	0.816
LVEF (%)	23 ± 8.9%	26 ± 13.9%	23 ± 8.5%	21 ± 3.7%	0.431
NYHA 3/4	17/24 (71%)	5/7 (71%)	3/7 (43%)	9/10 (90%)	0.676
Hypertension	11/24 (46%)	3/7 (43%)	2/7 (29%)	6/10 (60%)	0.433
Atrial Fibrillation	2/24 (8%)	1/7 (14%)	0/7 (0%)	1/10 (10%)	0.607
Chronic Lung Disease (Moderate-Severe)	0/24 (0%)	0/7 (0%)	0/7 (0%)	0/10 (0%)	0.687
Diabetes	7/24 (29%)	2/7 (29%)	1/7 (14%)	4/10 (40%)	0.517
Chronic Renal Insufficiency	2/24 (8%)	1/7 (14%)	0/7 (0%)	1/10 (10%)	0.217

* Mean ± standard deviation for continuous variables