Dilated Cardiomyopathy: Normalized Multiparametric Myocardial Strain Predicts Contractile Recovery

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Background. **Left ventricular 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 three-dimensional strain parameters were calculated at each of 15,300 left ventricular grid points from systolic displacement data obtained from cardiac magnetic resonance imaging 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 six left ventricular regions at basilar, mid, and apical levels (18 subregions). Patients with DCM were stratified into three groups on the basis of a blinded review of clinical contractile recovery (complete, n = 7; incomplete, n = 7; none, n = 10).**

Results. **Basilar-septal subregions were consistently heavily injured. Basilar-septal *Z*-scores were significantly larger (worse) than those for the rest of the left ventricle (2.73 ± 1.27 versus 2.22 ± 0.83; $p = 0.011$) and lateral wall (2.73 ± 1.27 versus 1.44 ± 0.72; $p < 0.001$). All patients with sentinel region average multiparametric strain *Z*-scores less than two standard deviations (n = 6) experienced complete recovery, whereas 17 of 18 DCM patients with *Z*-scores greater than two standard deviations experienced incomplete or no contractile recovery.**

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 microregional contractile function may accurately predict recovery on medical therapy. A two standard deviation *Z*-score threshold may predict contractile recovery.**

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Nonischemic, nonvalvular dilated cardiomyopathy (DCM) is associated with predictable left ventricular (LV) geometric 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 geometric 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 interventricular 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 various regions of the LV at different time frames 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 other LV regions. As such, the early-injury basilar-septal subregions can be labeled sentinel subregions, and their early involvement in the myopathic process may have considerable prognostic significance. This is

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especially critical in DCM because significant compensation for sentinel region contractile injury may come from noninjured 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 a 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 ± standard deviation (SD) strain component values compiled from a normal population. Over many years of investigation, we have built such a database from magnetic resonance imaging (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 with the normal mean and SD at the corresponding grid point, thereby enabling the calculation of *Z*-score values. The *Z*-scores provide a numeric quantification of the deviation from the normal population mean value of each patient-specific strain value at each point of the LV grid [14].

Indeed, patient-specific laboratory blood test values have been interpreted for decades by their direct comparison to normal ranges derived by SD 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 two SDs from the mean. We hypothesized that this same two-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 microregional LV contractile function may provide a clinically applicable methodology for integrating patient-specific LV microregional 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- or 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 nonischemic, nonvalvular DCM 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 the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines [15], including coronary angiography. No reversible etiologies were detected. The etiologies in the DCM patient population were idiopathic (21 of /24 patients), postpartum (1 of 24 patients), and chemotherapy-induced (2 of 24 patients). All patients were treated with standardized medical therapy for nonischemic DCM as per the ACC/AHA guidelines [15]. Demographic and selected clinical data are presented in Table 1.

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 (y)[a]	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[a]	0.23 ± 0.089	0.26 ± 0.139	0.23 ± 0.085	0.21 ± 0.037	0.431
NYHA class III or IV	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

[a] Mean ± standard deviation for continuous variables.

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.