

Early left ventricular regional contractile impairment in chronic mitral regurgitation occurs in a consistent, heterogeneous pattern

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Objectives: The clinical guidelines for asymptomatic patients with chronic mitral regurgitation (MR) use the ejection fraction (EF) to trigger surgical referral. We hypothesized that the EF is not sensitive enough to detect the earliest contractile injury in chronic MR and that the injury associated with chronic MR is not global but heterogeneous, occurring regionally and predictably, before the onset of global left ventricular (LV) dysfunction.

Methods: Fifteen patients with chronic MR and normal LVEF by echocardiography underwent cardiac magnetic resonance imaging with tissue tagging. Point-specific comparisons (at 15,300 LV grid points) of multiple strain parameters to a normal human strain database allowed normalization of patient-specific regional contractile function. Data were mapped over patient-specific 3-dimensional geometry and averaged across 6 LV regions.

Results: Global LV longitudinal and circumferential myocardial strains were normal for all 15 patients with MR compared with normal controls ($P > .05$). Despite preserved global function, the anteroseptum and posteroseptum demonstrated significantly worse contractile function compared with other LV regions ($P = .003$ and $P = .035$, respectively). Hypercontractile regions (lateral walls) appeared to compensate ($P = .002$) for the reduced septal contractile function, masking injury detection by global indexes.

Conclusions: The earliest contractile injury seen in patients with MR is heterogeneous and consistently distributed along the LV septum. Compensatory responses include hypercontractility of other regions. These data suggest that rather than relying on global LV contractile metrics, which cannot detect early injury, patients might be better served by undergoing directed surveillance of “sentinel” LV regions (LV septum) with high-resolution metrics of regional contractile function. (J Thorac Cardiovasc Surg 2014;148:1694-9)

Degenerative mitral valve disease is the most common valvular heart disease in America. Given its increasing incidence with age, it has been estimated that >5 million people will have either moderate or severe mitral regurgitation (MR) by 2030.¹ Several studies have demonstrated that the presence of even moderate MR is associated with increased mortality, and severe MR, even in asymptomatic patients, has been associated with an increase in all-cause mortality, cardiac mortality, and cardiac morbidity.² Moreover, symptomatic patients and patients with even mildly depressed ventricular function (ejection fraction

[EF] < 60%) have fared much worse, with survival as low as 20% at 4 years.³

Mitral valve surgery remains the standard treatment of degenerative mitral valve disease, and advances in surgical technique have allowed experienced centers to achieve high rates of successful valve repair with low observed morbidity and mortality.⁴⁻⁶ The long-term success for patients undergoing mitral valve surgery, however, depends on preservation of LV contractile function. Patients referred for surgery early, before the onset of irreversible contractile injury, have been shown to regain normal life expectancy. Thus, the current American College of Cardiology/American Heart Association guidelines have recommended early referral for mitral valve surgery in patients with minimal symptoms or early signs of ventricular embarrassment if mitral valve repair is likely.⁶⁻⁸

Although clinicians have agreed that surgery for MR should be performed before the onset of significant irreversible myocardial injury, the identification of that specific point for a given individual patient has been problematic. Two fundamental issues have contributed to the difficulty of preserving ventricular function in patients with MR: (1) identifying a metric with the ability to identify the earliest signs of ventricular injury and (2) a lack of knowledge of the manner or pattern by which earliest LV contractile injury presents.

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Abbreviations and Acronyms

- BNP = B-type natriuretic peptide
- EF = ejection fraction
- LV = left ventricular
- MR = mitral regurgitation
- MRI = magnetic resonance imaging

The purpose of the present investigation was to test the hypothesis that multiparametric strain analysis using magnetic resonance imaging (MRI) and tissue tagging could identify early LV dysfunction in minimally or asymptomatic patients and that the volume loading associated with MR creates a contractile injury that is regionally and heterogeneously distributed in a predictable pattern.

METHODS

Patient Characteristics

From August 2010 to July 2013, 15 asymptomatic or minimally symptomatic patients with isolated moderate to severe degenerative MR underwent evaluation of their LV function using transthoracic echocardiography and tagged cardiac MRI. The patient demographics and comorbidities are listed in Table 1. Most patients were New York Heart Association class I, with normal B-type natriuretic peptide (BNP) levels. Of the 15 patients, 3 (20%) were taking afterload reduction medications, 4 (26%) were taking β -blockers, and 2 (13%) were receiving diuretic therapy. No patient had ischemic MR. All patients with any evidence of coronary artery disease were specifically excluded from the study group.

Normal Strain Database

Sixty healthy volunteers (Table 1) with no known cardiac disease or hypertension underwent similar myocardial strain analysis and contributed complete LV systolic strain information to a normal human strain database. The Human Research Protection Office at Washington University (St Louis, Mo) approved the present study, and all subjects gave written informed consent. No sex-based or racial/ethnic-based exclusions were used during patient recruitment.

Cardiac MRI

Electrocardiogram-gated short- and long-axis tagged MRI scans were acquired from end-diastole through systole using a 1.5T scanner (Avanto; Siemens Medical Systems, Malvern, Pa). In each imaging plane, a spatial modulation of magnetization radiofrequency tissue-tagging preparation⁹ was applied, followed by a 2-dimensional balanced steady-state free precession cine image acquisition. Short-axis images covered the entire heart, and long-axis images were acquired in 4 radially oriented planes. The typical imaging parameters were as follows: tag spacing, 8 mm; slice thickness, 8 mm; repetition time, 32.4 ms; echo time, 1.52 ms; field of view, 350 $\times$ 350 mm; and image matrix, 192 $\times$ 256. In the same breath hold, anatomic and tagged images were acquired at the corresponding slice positions.

Strain Analysis

Strain measurements were obtained using a previously described and validated method.^{10,11} In brief, endocardial and epicardial wall boundaries were manually segmented on the anatomic MRI scans. These wall boundaries were transferred to the tagged images to process the tagged data. The tag lines were tracked on the images in a semiautomated fashion using an active contour approach. Displacements were calculated

TABLE 1. Characteristics of patients with mitral regurgitation and healthy volunteers

Characteristic	Patients with MR	Healthy volunteers
Age (y)	49.3 $\pm$ 11.3	33.1 $\pm$ 10.8
Female sex	20 (3/15)	53 (32/60)
Diabetes	0	0
HTN	13 (2/15)	0
COPD	0	0
CRI	0	0
Atrial fibrillation	0	0
NYHA I	67 (10/15)	100 (60/60)
NYHA II	33 (5/15)	0
BNP	34.0 $\pm$ 28.5*	NA
Echocardiographic ejection fraction (%)	61.5 $\pm$ 5.8	NA
Echocardiographic end-systolic dimension (cm)	3.4 $\pm$ 0.4	NA
Echocardiographic left atrial size (cm)	4.4 $\pm$ 0.5	NA
Pulmonary artery pressure (mm Hg)	26.1 $\pm$ 4.9	NA
MR		
Moderate	13 (2/15)	NA
Severe	87 (13/15)	

MR, Mitral regurgitation; HTN, hypertension; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; BNP, B-type natriuretic peptide; NA, not available; NYHA, New York Heart Association. *Number of patients, 9.

from end-diastole to end-systole at each intersection point within the myocardium (Figure 1). For registration, the user identified the posterior and anterior intersection points of the right ventricular free wall with the septum on the most basal short-axis image. Using these 2 points, and information from the LV geometry, the individual heart was registered to a standard 18-region finite element mesh (Figure 2). Within each element of the finite element mesh, displacements were fit in the least-squares sense to basis functions. The continuity of the displacement components was enforced at the element boundaries. The fitting of the basis functions to approximate the displacement data and calculation of the longitudinal and circumferential myocardial strain was performed using StressCheck (ESRD, Inc, St Louis, Mo).

MRI-Based Multiparametric Strain Z-Score Analysis

A composite strain index was created using the circumferential and longitudinal strains, equally weighted, reflecting contractile function within the circumferential and longitudinal directions. Owing to the heterogeneous pattern of normal LV strain, the raw values were normalized to supply clinically relevant information. The method to relate individual patient-specific regional contractile function to a normal strain database (multiparametric strain analysis) has been previously described.¹²⁻¹⁶ In brief, z-scores generated from the raw strain values represent the number of standard deviations each raw value is from the mean of the group. The mean and standard deviations for both circumferential and longitudinal strain were calculated at each point of an encompassing grid of 15,300 LV points from the 60 normal volunteers. For comparison with this normal strain database, patient-specific z-scores for both strain measures were calculated and averaged to obtain a multiparametric strain z-score representing the LV point-specific contractile function relative to normal. For each patient with MR, the z-scores were averaged over the 6 regions of the LV model (posteroseptal, anteroseptal, anterior, anterolateral, posterolateral, and posterior).

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