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Heterogeneity of Systolic Dysfunction in Patients with Severe Aortic Stenosis and Preserved Ejection Fraction

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Abstract

Background and Aim—Left ventricular (LV) systolic strain has been shown to be an early marker of LV dysfunction in patients with severe aortic stenosis (AS) despite preserved ejection fraction (EF). Echocardiography has provided useful data on regional LV strain patterns but is not as sensitive as magnetic resonance imaging (MRI). No prior studies have used MRI-based strain analysis to characterize regional 3D strain in patients with severe AS.

Methods—Twelve patients with severe AS and preserved EF underwent MRI-based multiparametric strain analysis. Circumferential and longitudinal strain values were calculated at individual points throughout the LV and analyzed in 12 discrete regions. Strain values were compared to a database of normal controls.

Results—Compared to control patients, circumferential strain in AS patients was significantly reduced at the base ($p=0.002$), mid ($p=0.042$), and inferior walls ($p<0.001$). Longitudinal strain was significantly reduced at the base ($p<0.001$), mid ($p<0.001$), anterior ($p<0.001$), and septal ($p<0.001$) walls. Among patients with AS, there was heterogeneity in the location and severity of abnormalities in circumferential and longitudinal strain despite the presence of a preserved EF and lack of prior myocardial infarction.

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Conclusions—LV systolic strain is significantly impaired in patients with AS and preserved EF compared to healthy volunteers. Abnormalities in circumferential and longitudinal strain were heterogeneously distributed across the LV of patients with AS, allowing us to identify sentinel regions that may reflect the earliest signs of developing LV dysfunction.

Introduction

Patients with severe aortic stenosis (AS) who present with minimal to no symptoms generally have a preserved left ventricular (LV) ejection fraction (EF) ¹. In the absence of symptoms and with an EF >50%, the American and European guidelines recommend a watchful waiting approach^{2, 3}. However, many of these patients exhibit hypertrophic remodeling of the LV, which may not completely reverse after valve replacement and is associated with poorer clinical outcomes^{4–7}. Accordingly, there has been significant interest in and debate regarding whether earlier surgical intervention should be performed in patients with severe AS even in the absence of symptoms^{8, 9}. In asymptomatic patients, risk stratification with natriuretic peptides and exercise testing is often performed, but often the implications of the findings for clinical management decisions are not clear¹⁰.

Strain has been a useful tool to identify subclinical systolic dysfunction despite a preserved EF in patients with AS^{11–14}. Strain is a measure of the deformation that occurs within an object. Normal strains (such as those measured in this study) are associated with fractional length changes that occur in a given direction within the object. As such, in the heart, they are a measure of contraction or elongation that occur in a particular direction, and thus provide a sensitive, quantitative assessment of contractile function. Reduced longitudinal strain, in particular, has been associated with increased rates of mortality and major adverse cardiac events in this population^{15–17}. Echocardiographic strain techniques may provide insufficiently detailed information to reliably identify and localize heterogeneity in LV systolic dysfunction. Accordingly, we utilized a 3D multiparametric magnetic resonance imaging (MRI) strain-based technique to characterize the longitudinal and circumferential strain pattern of the entire LV in patients with severe AS. This technique has previously been used to identify heterogeneity of LV function in patients with dilated cardiomyopathy and aortic regurgitation^{18, 19}. This approach may allow us to recognize “sentinel” regions of abnormal LV strain that may identify patients with more imminent, overt LV systolic dysfunction in whom earlier surgical intervention may preserve long-term cardiac performance and maintain optimal quality of life.

Materials and Methods

Study population

Twelve patients with severe aortic stenosis (aortic valve area index < 0.6 cm²/m² or peak jet velocity > 4 m/sec) and preserved EF (≥ 50%) were recruited from the cardiology and cardiac surgery clinics at Washington University School of Medicine. Patients with an irregular heart rhythm, pacemaker or defibrillator, severe renal impairment (creatinine clearance <30 mL/min/1.73m²), significant coronary artery disease (greater than a 50% coronary artery lesion at the time of the MRI or prior myocardial infarction), or moderate or greater aortic regurgitation or mitral valve disease were excluded. Referral for aortic valve

replacement (AVR) was not an inclusion criterion for entrance into the study, but all twelve patients studied eventually underwent AVR. Institutional review board approval was obtained (approval date: 03/08/2016) and all patients signed a written informed consent. Separately, a cohort of 103 healthy volunteers with no history of cardiac disease (51% women, average age 35 ± 12 years, EF $61 \pm 8\%$) underwent MRI-based strain analysis and provided normal values for comparison to our AS population

Clinical and echocardiographic data

Clinical variables were obtained through patient interview and chart abstraction. Symptoms of AS included dyspnea, chest pain consistent with angina, syncope, or pre-syncope. Echocardiograms were obtained at a similar time as the cardiac MRI and measurements made according to recommendations from the American Society of Echocardiography^{20, 21}.

Magnetic Resonance Imaging and Strain Analysis

MRI imaging was performed using a 1.5 Tesla scanner (Sonata, Siemens Medical Systems, Malvern, PA). ECG-gated images were obtained in short-axis and long-axis views for a full cardiac cycle beginning at end-diastole. Short axis slices were obtained every 8mm from the level of the mitral valve to the apex of the LV. Four long-axis image sets were obtained in radially oriented planes. Tissue tagging was then performed on each image using a SPAMM (Spatial Modulation of Magnetization) radiofrequency tissue tagging preparation, followed by 2-D balanced steady-state free precession cine image acquisition. Tagged and non-tagged images were both acquired during the same breath hold to ensure similar anatomic positioning between images. Typical imaging parameters were tag spacing 8mm, slice thickness 8mm, repetition time (TR) 32.4ms, echo time (TE) 1.52ms, field of view 350×350 mm, image matrix 192×256 , flip angle 20° and bandwidth 558 Hz/px.

Strain Analysis

The strain analysis process has been described in detail previously^{22–24}. Briefly, the epicardial and endocardial wall boundaries of the LV were defined in both short axis and long axis non-tagged images. Tag lines were delineated using a semi-automated algorithm utilizing an active contour approach. The anterior and inferior boundaries of the septum were then manually identified using intersection points within the RV free wall on the most basal short-axis image. These points were used in conjunction with a geometric model of the LV to create a finite element model of the LV. An eighteen element mesh for the model was constructed consisting of six elements representing the anterior, inferior, anteroseptal, inferoseptal, anterolateral and inferolateral regions at the base, mid and apical levels. For the purposes of our analysis, the anteroseptal and inferoseptal regions were combined into a single septal region and the anterolateral and inferolateral regions were combined into a single lateral region, yielding a total of 12 discrete regions.

Strain was measured based on the deformation of the tagged surfaces throughout systole. Three-dimensional displacements were calculated from the movement of intramural tag surface intersection points during systole. StressCheck (ESRD, Inc., St. Louis, Missouri) was then used to fit the displacement data and provide a continuous description of

displacement throughout the LV. Strain values in circumferential and longitudinal directions were calculated from this fitting.

Multiparametric Systolic Strain Z-scores

Regional strain differences among the AS patients were assessed by comparison to our normal strain database. Our control population of 103 healthy volunteers was used to compute normal average strain values and standard deviations at each point of a standardized grid of 15,300 points. For each patient in the AS group, Z-scores were calculated by performing point-by-point comparisons of circumferential and longitudinal strains to the corresponding values in our normal population. The Z-score represents the number of standard deviations a strain value differs from the normal strain average at a particular point. This score provides a quantitative assessment of normalized systolic function, with a higher Z-score indicating more abnormal function. Z-scores were then averaged across each of the 12 discrete regions highlighted above to quantify regional differences among the AS patients in systolic function. Circumferential and longitudinal strain Z-scores were also combined into a composite multiparametric strain value, and 3D color contour maps of the LV were generated based on composite Z-scores.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ SD. Circumferential and longitudinal strains were compared between patients with AS and controls using a Student's t-test. Comparison of regional Z-scores with the AS population was conducted through a repeated measures analysis using a mixed model methodology. A significant overall test was followed by examining all pairwise comparisons, and a Tukey adjustment for multiple comparison testing was applied. The linear association between overall strain and select variables within AS patients was assessed by the Spearman correlation. All analysis was conducted in SAS v9.4 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

The 12 patients with AS included in this study had a mean age of 64 years with mean aortic valve area index of 0.40 cm²/m², 25% had diabetes mellitus, and 17% were female (Table 1). A majority had some symptoms related to AS, but only one (8%) had more advanced heart failure symptoms (NYHA III or IV). All patients had an EF 50% with similar measurements by echocardiography and MRI.

Strain in patients with AS versus controls

Tissue tagging was performed as described and shown in Figure 1 and strain was calculated in the circumferential and longitudinal dimensions. Compared to healthy volunteers, patients with AS had reduced circumferential strain in the base and mid-levels of the heart as well as the inferior region, but not in the apex or in the septal, anterior and lateral regions (Table 2). Similarly, for longitudinal strain significant difference between AS patients and healthy controls were seen at the base and mid-ventricle, and in the septal and anterior walls (Table 3).

Regional strain patterns in patients with AS

Z-scores varied significantly by ventricular level. Circumferential, longitudinal and multiparametric Z-scores were larger at the base of the heart compared to the apex. Additionally, longitudinal and multiparametric strain Z-scores were larger at the mid-ventricle compared to the apex (Table 4). In comparing Z-score between ventricular regions, a significant main effect was seen for circumferential strain ($p=0.018$) and longitudinal strain ($p=0.05$), but not for multiparametric strain ($p=0.19$) (Table 5). Pairwise comparisons demonstrated larger circumferential strain Z-scores in the inferior wall compared to the anterior wall. Across the LV as a whole, abnormalities of longitudinal strain were generally more pronounced than for circumferential strain.

Contour plots with Z-scores for circumferential and longitudinal strain across the entire LV are shown for representative patients in Figures 2 and 3. The availability of pointwise data over the standardized grid of LV points allows for a unique visual presentation of the group's mean regional Z-score data. By averaging the Z-scores at each grid point from all patients, a color contour plot can be generated that represents regional normalized contractile injury of an average patient with AS (Figure 4). These plots visually demonstrate the more pronounced impairment of longitudinal strain in the base of the heart, particularly in the anterior and septal regions. In contrast, circumferential strain is most abnormal in the inferior region of the heart.

Correlation of global strain with other variables

The relationship between global circumferential and longitudinal strain with mean valve gradient and LV mass index was assessed by the Spearman correlation. Correlation coefficients were generally small, ranging from -0.05 to 0.43 , and none of the relationships were found to be significant. Complete results of this analysis are presented in Table 6.

Discussion

These findings show that patients with severe AS have LV systolic dysfunction despite a preserved EF. Moreover, we showed that the contractile impairment is distributed heterogeneously across the ventricle. The largest decrease in contractile function was seen at the LV base, as both circumferential and longitudinal strain differed significantly in comparison to the apex, which was relatively spared. When broken down by wall segment, longitudinal strain was most impaired in the anterior and septal walls, while circumferential strain was most impaired in the inferior wall. Perhaps, these sensitive MRI-based strain methods may facilitate earlier detection of abnormalities in sentinel regions and identify patients with severe AS who may benefit from earlier valve replacement before more extensive LV dysfunction occurs. Although the small number of subjects limits our ability to detect a significant correlation, the lack of association between circumferential or longitudinal strain and (1) the severity of AS (transvalvular mean gradient) or (2) the extent of hypertrophic remodeling (LV mass index) indicates that strain may provide complementary information in assessing patients with severe AS.

Comparison to prior studies

Our study corroborates findings from prior imaging studies using speckle-tracking echocardiography to assess strain in patients with severe AS. Studies looking only at longitudinal strain in this population have found significant differences in longitudinal strain globally across the LV. These differences have been correlated with increased all-cause mortality and major adverse cardiac events, as well as decreased exercise tolerance^{17, 25}. One study also looked specifically at basal longitudinal strain (BLS) and found that patients with significant differences in BLS were more likely to be symptomatic²⁶. Our study builds on these prior studies by utilizing the increased 3D spatial resolution of cardiac MRI to generate detailed regional strain maps across the entire LV. We also incorporated measurements of circumferential strain, which were not assessed in prior echocardiographic studies, and we showed that both circumferential strain and combined multiparametric strain were impaired in these patients.

Heterogeneity of LV dysfunction

Although the entire LV faces a single obstruction at the valvular level in patients with AS, our data suggest that the contractile injury resulting from this impairment to flow is distributed in a non-uniform manner across the ventricle. A prior study from this lab looked at multiparametric strain in patients with dilated cardiomyopathy and showed a similar pattern of contractile dysfunction in the LV base and septum¹⁸. Fibrosis appears to be more focally increased in the basal septal region of the heart in patients with AS, which corresponds to areas of abnormal strain in our study²⁷. The asymmetric distribution of fibrosis may underlie the abnormalities in strain. Accordingly, abnormalities in MRI-based strain in these regions may be markers of adverse remodeling that may not reverse after valve replacement.

Clinical implications

There is currently significant debate regarding the optimal timing of valve replacement surgery in patients with asymptomatic severe AS^{8, 9}. While all patients with asymptomatic severe AS may not benefit from a strategy of early valve replacement, there may be subgroups that might benefit. The issue is not simply one of operative and postoperative mortality. For relatively younger patients with several years of anticipated life expectancy after valve replacement, optimal long-term cardiac performance and freedom from heart failure are very important. Relevant to this, increased pre-operative natriuretic peptide levels and more extensive myocardial fibrosis have been associated with worse LV function and worse heart failure symptoms after valve replacement^{10, 27}. In this context, our findings may have potential clinical significance. The ability to detect pre-clinical LV dysfunction—strain abnormalities in these sentinel regions—may help identify patients at risk for a progressive decline in LV function, which may lead to worse postoperative survival, cardiac performance, and symptom status if valve replacement is delayed.

Tagging sequences are widely available on MRI scanners. Acquiring a full set of images typically takes about an hour, while the post processing of tagged data to obtain strain measurements usually takes 4–6 hours for an experienced user. These factors limit the generalizability of the techniques used in this study. However, recent advances in both

imaging and image processing have substantially reduced the time required to generate these strain measurements which could make more widespread application of these methods clinically feasible^{28, 29}.

Limitations

The primary limitation of this study is its relatively small sample size. Another potential limitation of this study is the lack of age-matched healthy controls used for strain comparisons to the AS patients. This allows for the possibility that some of the observed differences in strain between the two groups could be related to age rather than the disease process itself. However, a recent study looking at age-related strain differences, did not detect significant differences in either circumferential or longitudinal strains among groups covering the ages of subjects used in this study³⁰. Lastly, the lack of follow-up data in these patients makes it difficult to gauge the significance of the findings presented in this paper. Clearly, further studies are needed to confirm and clarify these results.

Conclusion

Our study shows that patients with severe AS exhibit both global and regional LV dysfunction even in the setting of a preserved EF. These findings raise interesting clinical questions about the role of multiparametric strain analysis and other non-invasive imaging modalities particularly in the assessment of asymptomatic patients with severe AS. Further studies are needed to characterize the clinical implications of these findings to know whether detection of abnormal strain in these sentinel regions ought to prompt a referral for earlier valve replacement to optimize long-term cardiac performance.

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Figure 1.
Representative short- and long-axis images at end-diastole A) and end-systole B).

Figure 2. Representative circumferential strain Z-score contour plots from four individual patients. All plots are oriented with the anterior wall to the front with the ventricular septum on the left. Blue areas indicate regions with Z-scores less than 1, yellow regions between 1 and 2 and red regions greater than 2.

Figure 3.

Representative longitudinal strain Z-score contour plots from four individual patients. All plots are oriented with the anterior wall to the front with the ventricular septum on the left. Blue areas indicate regions with Z-scores less than 1, yellow regions between 1 and 2 and red regions greater than 2.

Figure 4.

Z-score values from each patient were averaged at each point of the encompassing LV grid to generate composite contour plots that indicate the normalized contractile injury of an average AS patient. Contour plots for circumferential strain A), longitudinal strain B) and multiparametric strain C) are demonstrated. Blue regions indicate areas with Z-scores less than 0.5, yellow regions between 0.5 and 1, and red regions greater than 1.

Table 1

Characteristics of patients with aortic stenosis.

Clinical characteristics	
Age (years)	64 ± 15
Female sex (%)	17
BMI (kg/m ²)	30.3 ± 4.6
Diabetes mellitus (%)	25
GFR (mL/min/1.73m ²)	79 ± 23
Symptoms from aortic stenosis (%)	58
NYHA class III/IV (%)	8
Echocardiographic measurements	
Ejection fraction (%)	67 ± 6
LV end-diastolic dimension (cm)	4.3 ± 0.7
LV end-systolic dimension (cm)	2.5 ± 0.8
Relative wall thickness	0.72 ± 0.20
AVA index (cm ² /m ²)	0.40 ± 0.12
Mean gradient	49 ± 15
Peak gradient	77 ± 22
Cardiac MRI measurements	
Ejection fraction (%)	66 ± 7
LV end-diastolic volume (ml)	121 ± 45
LV end-systolic volume (ml)	40 ± 16
LV mass (g)	230 ± 74
LV mass index (g/m ²)	110 ± 26

Data reported as mean ± standard deviation or %.

AVA=aortic valve area;

BMI=body mass index; GFR=glomerular filtration rate; LV=left ventricular; NYHA=New York Heart Association.

Table 2

Circumferential strain comparison between aortic stenosis patients and healthy volunteers

	AS patients (n=12)	Controls (n=103)	p-value
Base	-0.16 ± 0.03	-0.18 ± 0.03	0.002
Mid	-0.19 ± 0.03	-0.21 ± 0.03	0.042
Apex	-0.19 ± 0.04	-0.20 ± 0.04	0.49
Septum	-0.17 ± 0.04	-0.18 ± 0.03	0.18
Anterior	-0.19 ± 0.03	-0.20 ± 0.04	0.55
Lateral	-0.20 ± 0.04	-0.22 ± 0.03	0.16
Inferior	-0.14 ± 0.05	-0.19 ± 0.03	<0.001

Data reported as mean $\pm$ standard deviation.

Table 3

Longitudinal strain comparisons between aortic stenosis patients and healthy volunteers.

	AS patients (n=12)	Controls (n=103)	p-value
Base	-0.08 ± 0.03	-0.14 ± 0.03	<0.001
Mid	-0.10 ± 0.04	-0.15 ± 0.03	<0.001
Apex	-0.15 ± 0.07	-0.17 ± 0.04	0.34
Septum	-0.10 ± 0.04	-0.15 ± 0.03	<0.001
Anterior	-0.10 ± 0.04	-0.14 ± 0.04	<0.001
Lateral	-0.12 ± 0.05	-0.15 ± 0.03	0.07
Inferior	-0.12 ± 0.07	-0.16 ± 0.03	0.15

Data reported as mean ± standard deviation.

Table 4

Average Z-scores for patients with aortic stenosis grouped by ventricular level.

	Base	Mid	Apex	p-value
Circumferential strain	0.57 ± 0.54	0.35 ± 0.51	0.16 ± 0.71^a	0.004
Longitudinal strain	1.17 ± 0.61	0.97 ± 0.80	$0.37 \pm 0.94^{a,b}$	<.001
Circumferential + Longitudinal Strain Combined	0.87 ± 0.48	0.66 ± 0.58	$0.27 \pm 0.73^{a,b}$	<.001

Data reported as mean $\pm$ standard deviation.

^a p<.05 vs. Base

^b p<.05 vs. Mid

Table 5

Average Z-scores for patients with aortic stenosis grouped by ventricular region.

	Septum	Anterior	Lateral	Inferior	p-value
Circumferential strain	0.32 ± 0.81	0.13 ± 0.56	0.28 ± 0.63	0.84 ± 0.83 ^a	0.018
Longitudinal strain	1.03 ± 0.77	1.06 ± 0.68	0.60 ± 0.81	0.69 ± 1.06	0.05
Circumferential + Longitudinal Strain Combined	0.68 ± 0.65	0.60 ± 0.51	0.44 ± 0.64	0.76 ± 0.80	0.19

Data reported as mean ± standard deviation.

^ap<0.05 vs. Anterior

Table 6

Correlation between global strain, mean transvalvular gradient and LV mass index.

	Mean Transvalvular Gradient	LV Mass Index
Global circumferential strain	$r_s = 0.27$ (p=0.48)	$r_s = -0.05$ (p=0.90)
Global longitudinal strain	$r_s = 0.29$ (p=0.37)	$r_s = 0.43$ (p=0.16)

r_s = Spearman's correlation coefficient.