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Original Articles

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Relationship to Left Atrial Structural Remodeling Detected by Delayed-Enhancement MRI

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Background—Atrial fibrillation (AF) is a progressive condition that begins with hemodynamic and/or structural changes in the left atrium (LA) and evolves through paroxysmal and persistent stages. Because of limitations with current noninvasive imaging techniques, the relationship between LA structure and function is not well understood.

Methods and Results—Sixty-five patients (age, 61.2 ± 14.2 years; 67% men) with paroxysmal (44%) or persistent (56%) AF underwent 3D delayed-enhancement MRI. Segmentation of the LA wall was performed and degree of enhancement (fibrosis) was determined using a semiautomated quantification algorithm. Two-dimensional echocardiography and longitudinal LA strain and strain rate during ventricular systole with velocity vector imaging were obtained. Mean fibrosis was $17.8\pm14.5\%$. Log-transformed fibrosis values correlated inversely with LA midlateral strain ($r=-0.5$, $P=0.003$) and strain rate ($r=-0.4$, $P<0.005$). Patients with persistent AF as compared with paroxysmal AF had more fibrosis ($22\pm17\%$ versus $14\pm9\%$, $P=0.04$) and lower midseptal ($27\pm14\%$ versus $38\pm16\%$, $P=0.01$) and midlateral ($35\pm16\%$ versus $45\pm14\%$ $P=0.03$) strains. Multivariable stepwise regression showed that midlateral strain ($r=-0.5$, $P=0.006$) and strain rate ($r=-0.4$, $P=0.01$) inversely predicted the extent of fibrosis independent of other echocardiographic parameters and the rhythm during imaging.

Conclusions—LA wall fibrosis by delayed-enhancement MRI is inversely related to LA strain and strain rate, and these are related to the AF burden. Echocardiographic assessment of LA structural and functional remodeling is quick and feasible and may be helpful in predicting outcomes in AF. (***Circ Cardiovasc Imaging***. 2010;3:231-239.)

Key Words: atrial fibrillation ■ remodeling ■ atrial strain ■ delayed enhanced MRI

Atrial fibrillation (AF) is thought to be a progressive disease that most often begins with increased hemodynamic load and/or structural remodeling of the atria, including chamber enlargement and interstitial fibrosis. Better understanding of atrial structure and function could lead to improvements in our ability to predict the risk of developing AF and the response to treatments in patients with this arrhythmia. Noninvasive assessment of structure and function of the atria has been limited by a lack of suitable methods for making these measurements.

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Atrial fibrosis is a hallmark of structural remodeling that contributes to the AF substrate. In both patients and animal models of AF or mitral valve disease, left atrial (LA) tissue has been found to contain deposits of fibrillar collagen, expansion of the extracellular matrix, and disorganized myocyte architecture.[1–3] Similar pathological changes have been observed in the atrial tissue of aging populations and in patients with left ventricular (LV) dysfunction. Atrial fibrosis may lead to disruption of normal electric conduction and establishment of reentry circuits and thereby contribute to an increased susceptibility to and maintenance of AF.[4,5] In keeping with this concept, the extent of fibrosis and extracellular matrix expansion determined histologically has been shown to correlate with persistence of AF.[6] Conversely, long-standing AF appears to promote progressive atrial dilation and functional impairment such as reduced atrial compliance and contractility.

Delayed-enhancement MRI (DE-MRI) allows quantification and visualization of the extent of scar tissue in cardiac myocardium.[7] This technique has been used to detect and quantify infarcted ventricular myocardium[8] as well as localized myocardial scarring in a variety of cardiomyopathies. Recently, we reported a method that uses DE-MRI for assessing LA wall enhancement, which is presumed to be fibrosis.[9] Regional myocardial function can be assessed noninvasively by strain and strain rate imaging.[10] Strain by speckle tracking is a relatively simple and reproducible technique that overcomes the limitation of angle dependency that is present with Doppler-based techniques.[11] Strain imaging has been widely used to assess ventricular function in a variety of subclinical or established disease states. However, only a few studies thus far have applied strain imaging to the assessment of atrial mechanics,[12–15] particularly in patients with AF.

We conducted this study with the hypothesis that there should be an inverse relationship between LA structural remodeling assessed by DE-MRI and LA functional remodeling assessed by strain and strain rate imaging in patients with paroxysmal and persistent AF. We also sought to evaluate their relationship with other echocardiographic parameters of structural and functional remodeling that could provide a noninvasive method useful in assessing patients with this arrhythmia.

Methods

We conducted a single-center, retrospective, cross-sectional study at the University of Utah Hospital. This study was approved by the investigational review board at University of Utah and met Health Insurance Portability and Accountability Act requirements. The study population included 65 patients with symptomatic AF referred to the atrial fibrillation clinic from May 2006 and March 2008. Results of the DE-MRI imaging in these patients have been reported previously.[9] All subjects underwent evaluation with both 3D DE-MRI and 2D transthoracic echocardiography before their AF management. Exclusion criteria were uninterpretable MRI and/or echo images and subjects with mechanical valves.

DE-MRI

As previously described,[9] DE-MRI studies were performed on a 1.5-T MR system (Avanto Siemens Healthcare, Erlangen, Germany). High-resolution DE images of the LA were acquired approximately 15 minutes after contrast agent injection (0.1 mmol/kg, Multihance, Bracco Diagnostic Inc, Princeton, NJ), using a 3D respiration-navigated, inversion-recovery prepared gradient echo pulse sequence (TR/TE=2.38/5.4 ms, flip angle of 20°, bandwidth=220 Hz/pixel, FOV=360×360×100 mm, matrix size=288×288×40, voxel size=1.25×1.25×2.5 mm). The inversion pulse was applied at every heart beat, and fat saturation was applied immediately before data acquisition (23 views per heart beat) during LA diastole. To preserve magnetization preparation in image volume, the navigator was acquired immediately after data acquisition block. Typical scan time for DE-MRI sequence was 5 to 10 minutes, depending on patient heart rate and respiration pattern. To quantify the extent of abnormal enhancement in the LA wall, LA epicardial and endocardial borders were manually segmented and the adjacent structures were removed. A histogram of pixel intensity was computed for each segment. Higher pixel intensity values were assumed to represent fibrosis. The mean of the histogram was calculated and a threshold was applied at 3 standard deviations from that mean. Values beyond the threshold were correlated with hyperenhanced areas. These pixel locations were overlaid on the original MRI image to verify the accuracy of the

automated algorithm. The fibrosis was reported as percentage of the total LA wall volume.

Transthoracic Echocardiography

Echocardiography was performed using standard views and harmonic imaging (Sequoia, Siemens, Mountain View, Calif). For patients in AF, images were acquired over 2 seconds or for 2 heart beats. In the parasternal long-axis views, LA maximum antero-posterior (A-P) diameter was measured. In the apical 4-chamber view, LV end-diastolic and end-systolic volumes were measured and LV ejection fraction was calculated by the Simpson method. In the same view, LA maximum volume at the end of LV systole, just before the opening of the mitral valve and LA minimum volume at the end of LV diastole, just after the closure of the mitral valve, were measured and LA "emptying" fraction was calculated as (maximum volume−minimum volume)/maximum volume. Emptying fraction rather than ejection fraction is reported because LA contraction is absent in AF. The LA maximum volume was also measured by biplane area-length method (0.85×area 1×area 2 divided by the length) indexed by body surface area.[16] LA superior-inferior diameter was measured from the mitral annular plane to the posterior wall of the LA in the apical 4-chamber view. Pulsed-wave Doppler at the tips of mitral valve leaflets allowed us to measure early (E) and late (A) diastolic filling velocities ("A" velocity only in those with sinus rhythm), E/A ratio, and E deceleration time. The LV early diastolic tissue velocity (E′) was measured by tissue Doppler imaging of the medial mitral annulus. E/E′ was calculated, and a value >15 was considered to represent elevated LV filling pressure.[17] In AF, the diastolic filling pattern is variable. Hence, we averaged the E and E′ in 3 cardiac cycles to get the E/E′. Mitral regurgitation was semiquantitatively assessed by color Doppler across mitral valve and graded as none/trace (0), mild (1), moderate (2), moderately severe (3), and severe (4), respectively.[18]

Velocity Vector Imaging

Offline analyses of the gray scale images obtained by 2D echocardiography were done by using Velocity Vector Imaging (VVI) software (Siemens Medical Solutions, Mountain View, Calif). The endocardium of the LA wall was manually traced starting from the medial to the lateral mitral annulus and was tracked by the VVI software along the border throughout 1 or more cardiac cycles. Accuracy of border tracking was manually verified and adjusted if needed. Speckle tracking has been reported to be a feasible and reproducible method to assess LA longitudinal deformation properties, and reference values in healthy individuals have been reported by Cameli et al.[15]

In the apical 4-chamber view, the regional analysis consisted of placing the sample in the midseptal and midlateral LA walls in the same cardiac cycle. In the mid septal wall, the sample was placed 1 to 2 cm proximal to the medial mitral annulus, and the fossa of ovalis was avoided for optimal tracking of the endocardium. In the lateral wall, the sample was placed 1 to 2 cm proximal to the lateral mitral annulus, and the point of entry of the pulmonary veins was avoided (Video 1). Thus, strain versus time and strain rate versus time curves were generated from these regions of interest (Figure 1). The investigator evaluating the echocardiographic strain and strain rate was blinded to the DE-MRI fibrosis data.

In addition to the study patients, we selected 25 echocardiograms for strain and strain rate measurement, performed in patients ages ≥18 to <50 years, with no diagnosis of AF, done for evaluation of palpitations, chest pain, dizziness, or preoperative evaluation that were reported as normal. We analyzed these to derive control values for strain and strain rate.

Statistical Analysis

Continuous variables are presented as mean±SD and dichotomous data are presented as numbers and percentages. The raw fibrosis data by DE-MRI showed clustering on the low fibrosis side of the data spectrum; therefore, a log transformation was applied and it resulted in a normalized distribution. Univariate linear regression analysis
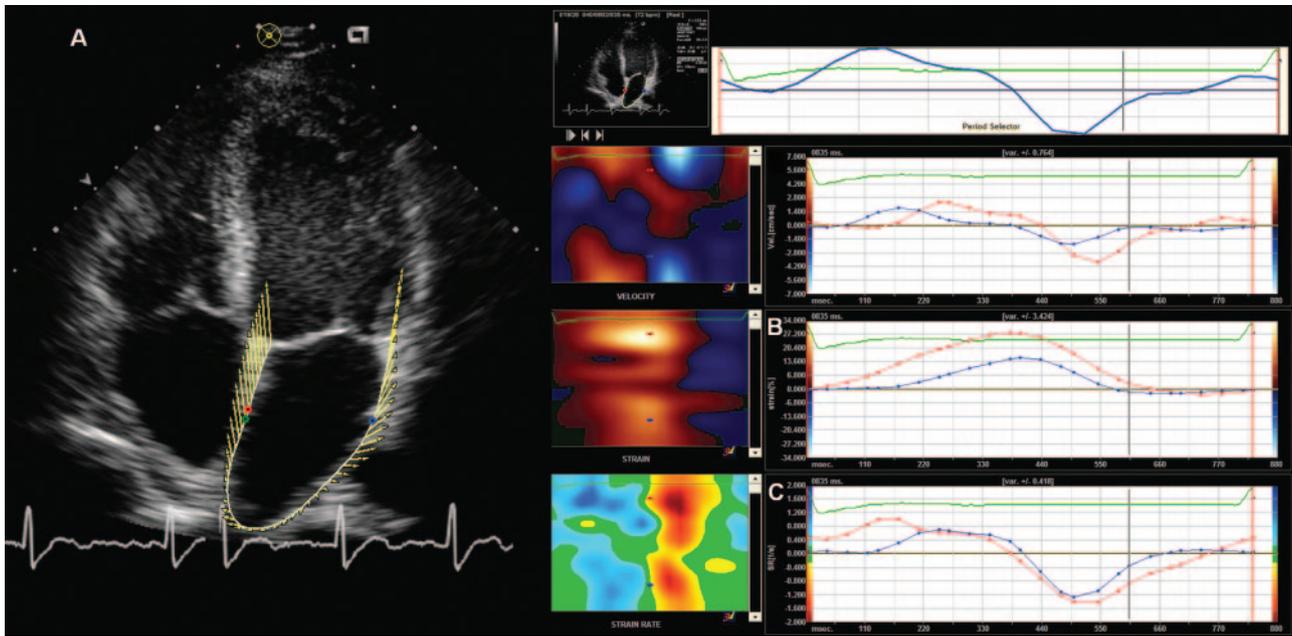
Figure 1. Example of assessment of LA strain and strain rate using VVI. A, Tracing of the LA endocardial border in apical 4-chamber view showing velocity vectors. B, Strain and C, strain rate verses time curves in midseptal (red) and midlateral (blue) LA wall samples. Note the long superior-inferior diameter in this subject.

was used to examine relationships of log(fibrosis) and LA strain and strain rate parameters, as well as several echocardiographic parameters of structural and functional remodeling. Stepwise multivariable analysis with log(fibrosis) by DE-MRI as dependent variable and echocardiographic parameters, including the rhythm (sinus versus AF) at the time of imaging, as independent variables was done to assess the echocardiographic predictor of increased LA fibrosis. A probability value of ≤0.05 was considered statistically significant. Intraobserver variability and interobserver variability were examined using Pearson bivariate correlation.

Results

Of the 65 eligible patients, 55 patients met inclusion criteria (age, 61±14 years; 67% men). Of the 55 patients, only 16 (29%) were in AF at the time of echo and MRI, and even these were relatively well rate-controlled, with an average heart rate of 86±12 beats per minute. Of these, 11 of 16 patients with AF had echocardiographic acquisition over 2-second duration or for 2 heart beats. Table 1 shows the baseline 2D echocardiographic and VVI findings. The average amount of fibrosis in the LA wall by DE-MRI was 17.8±14.5%. There were 18 women who were older than the men (68±13 versus 58±14, $P=0.01$) and showed a trend toward more fibrosis, but it was not statistically significant (21±14.7% in women versus 15.9±14.3% in men, $P=NS$). There were 25% of patients taking antiarrhythmic drugs and 30% taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Mitral regurgitation was absent in 61% of patients, mild in 25%, and moderate in 14%. Of the 55 patients, 44% had paroxysmal AF, 56% had persistent AF, 33% had hypertension, 9% had coronary artery disease, and 3% had diabetes mellitus.

Intraobserver and interobserver correlations were: midseptal strain ($r=0.9$, $P<0.005$ and $r=0.8$, $P=0.001$), midlateral strain ($r=0.8$, $P=0.002$ and $r=0.9$, $P=0.001$), midseptal strain rate ($r=0.8$, $P<0.05$ and $r=0.7$, $P=0.01$), and midlat-

eral strain rate ($r=0.8$, $P<0.05$ and $r=0.8$, $P=0.02$), respectively. Similar agreements were obtained in the 25 control echocardiograms.

Comparison Between Paroxysmal and Persistent AF

Patients with persistent AF as compared with paroxysmal AF had more LA wall fibrosis (22±18% versus 14±9%,

Table 1.   Baseline Characteristics of Patients With Paroxysmal and Persistent Atrial Fibrillation

	Total (n=55)	Paroxysmal AF (n=24)	Persistent AF (n=31)	P Value
Age, y	61.2±14.2	60.1±16.8	62.1±12.1	0.6
Sex, male=0, female=1	67%	63%	71%	0.5
Hypertension, no=0, yes=1	36%	33%	39%	0.3
LA wall fibrosis, %	19±15	14±9	22±18	0.04
LA antero-posterior diameter, cm	4.1±0.7	3.7±0.6	4.4±0.7	0.0007
LA superior-inferior diameter, cm	6.0±1	5.6±0.8	6.3±0.9	0.005
LA biplane volume index, mL/m²	35±11	31±11	37±10	0.04
LA midseptal strain, %	33±16	38±15	27±15	0.01
LA midseptal strain rate, cm/s	1.6±0.8	1.7±0.9	1.5±0.9	0.46
LA midlateral strain, %	38.3±16.1	45±14	35±18	0.03
LA midlateral strain rate, cm/s	1.8±0.8	2.0±0.9	1.7±0.8	0.21
LA emptying fraction, %	48±16	53±13	45±18	0.07
LV ejection fraction, %	55±9	55±11	54±10	0.55
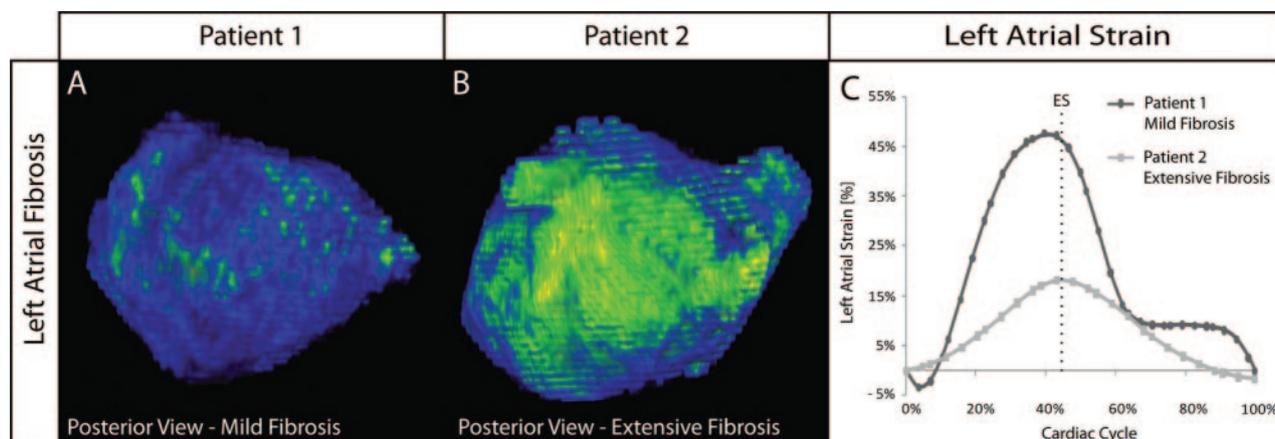
Figure 2. Comparison of LA midlateral strain by VVI and extent of LA posterior wall fibrosis by delayed enhancement MRI in 2 patients.

$P=0.04$) and lower midseptal ($38\pm15\%$ versus $27\pm15\%$, $P=0.01$) and midlateral ($45\pm14\%$ versus $35\pm18\%$, $P=0.03$) strain. There was no significant difference in the strain rates between those with persistent AF and those with paroxysmal AF. The average strain and strain rate in the control subjects with normal echocardiograms were: midseptal strain ($67\pm20\%$), midlateral strain ($68\pm24\%$), midseptal strain rate (2.3 ± 0.5 cm/s), and midlateral strain rate (2.7 ± 0.9 cm/s). These were significantly higher as compared with the values in paroxysmal and persistent AF ($P<0.05$, control versus paroxysmal AF and persistent AF).

Significantly larger biplane LA volume index (37 ± 10 mL/m^2 versus 31 ± 11 mL/m^2, $P<0.05$), LA A-P diameter (4.4 ± 0.7 cm versus 3.7 ± 0.6 cm, $P<0.05$), and superior-inferior diameter (6.3 ± 1 cm versus 5.6 ± 0.9 cm, $P<0.05$) were present in persistent AF as compared with paroxysmal AF (Table 1).

Relationship Between LA Strain and Strain Rate With LA Structural Remodeling by DE-MRI
Representative examples of DE-MRI images and strain curves for 2 patients are shown in Figure 2. Patient 1 (A) has mild fibrosis and patient 2 (B) has extensive fibrosis. Patient 1 shows higher strain than patient 2. For the entire group, there were significant negative correlations between LA wall log(fibrosis) and midlateral strain/strain rate and midseptal strain rate, but the correlation with midseptal strain was weak (Table 2 and Figure 3).

Table 2. Correlation Analysis Between Midseptal and Midlateral Strains and Factors Associated With Atrial Fibrillation

Parameter	Midseptal Strain		Midlateral Strain	
	r Value	P Value	r Value	P Value
Age, y	−0.3	0.08	−0.0	0.70
Sex, male=0, female=1	−0.0	0.63	−0.1	0.44
Type of AF, paroxysmal=0, persistent=1	−0.4	0.02	−0.3	0.09
Hypertension, no=0, yes=1	−0.3	0.09	−0.3	0.09
LV ejection fraction, %	0.3	0.02	0.2	0.11
Midlateral strain	0.7	<0.005		

Midlateral strain correlated significantly with LA wall log(fibrosis) in persistent AF but not in paroxysmal AF (Figure 3). Further subgroup analyses in patients with and without hypertension and those with LV ejection fraction above and below 50% showed no significant difference in the extent of fibrosis and strain and strain rate.

Multivariable stepwise regression analysis was performed to analyze echocardiographic predictors of LA fibrosis by DE-MRI. Log(fibrosis) was entered as dependent variable and echocardiographic LA variables as independent variables. Four separate regression models were analyzed by entering midseptal strain, midlateral strain, midseptal strain rate, and midlateral strain rate with other independent variables such as LA superior-inferior and anterior-posterior diameters, LA maximum biplane volume index, LA emptying fraction, transmitral E/E′, and the rhythm during imaging (sinus or AF). Lower midlateral strain and strain rate and midseptal strain rate were independent predictors of a larger extent of fibrosis (Table 3).

Relationship Between LA Strain and LA Dimensions, LA Volume, and LA Emptying Fraction
Midseptal strain was inversely associated with LA superior-inferior diameter but was not associated with A-P diameter ($r=-0.4$, $P<0.05$ versus $r=-0.2$, $P=0.1$). Both midseptal and midlateral strains correlated inversely with LA volume indexed to body surface area ($r=-0.4$, $P<0.05$) and correlated with higher LA emptying fraction ($r=0.3$, $P=0.08$ and $r=0.5$, $P=0.001$). There was no correlation between midseptal or midlateral LA strain and LV filling pressure estimated from E/E′, entered as a continuous variable ($P=$NS) (Table 2 and Figure 4).

Discussion
In this study, we describe an inverse relationship between the extent of LA structural remodeling detected by DE-MRI and echocardiographically derived LA strain and strain rate. This relationship was more prominent in patients with persistent AF compared with paroxysmal AF. Moreover, LA strain was inversely related to LA volume but not apparently related to
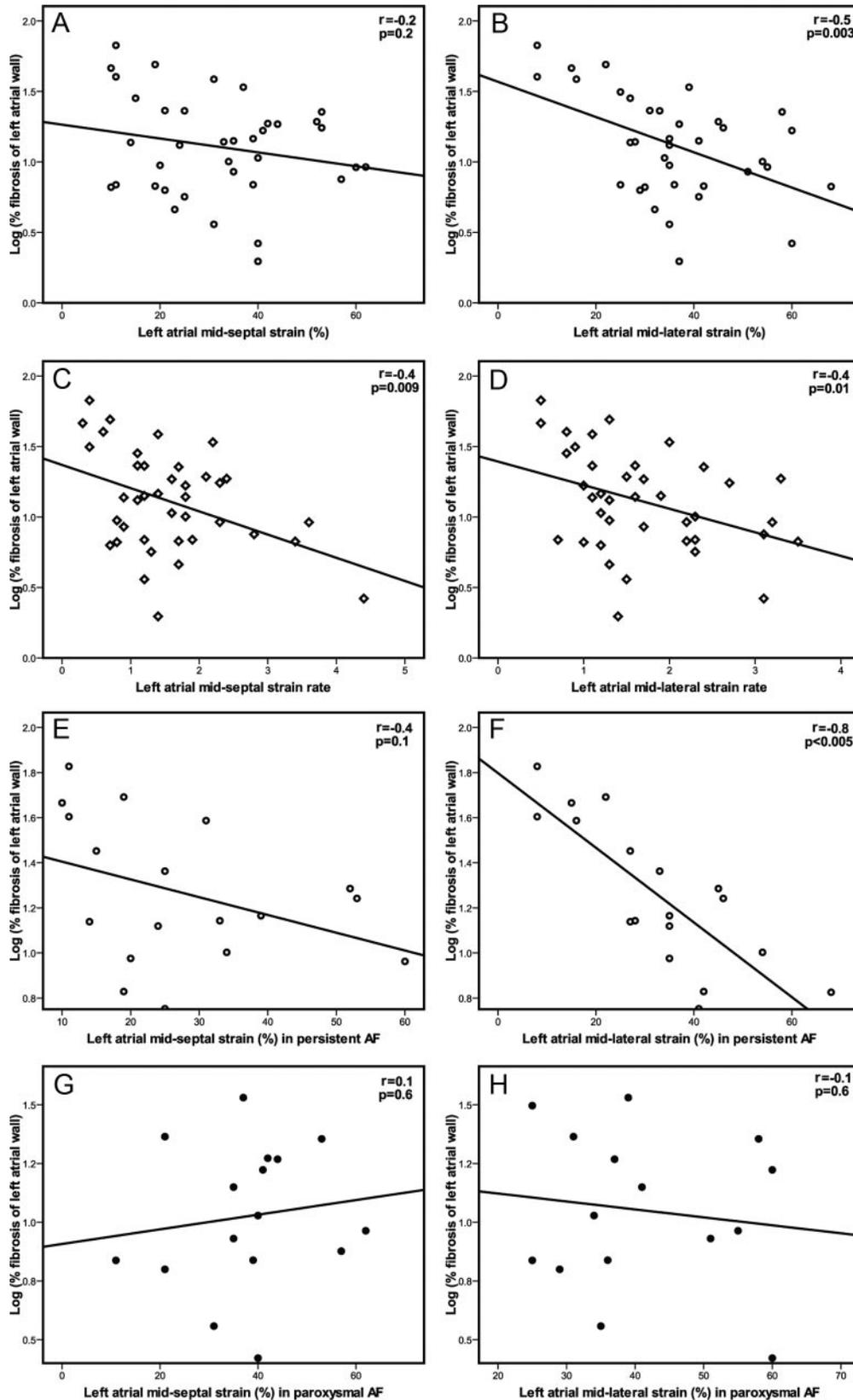
Figure 3. Relationship between LA (A) midseptal and (B) midlateral strain and (C and D) strain rate by VVI and LA wall log(fibrosis) by DE-MRI in all patients (n=55). Subgroup analysis of the relationship between strain and log(fibrosis) in patients with persistent AF (E and F) and paroxysmal AF (G and H).

Table 3. Echocardiographic Predictors of LA Fibrosis by DE-MRI

Predictors of LA Fibrosis	r Value	P Value
1. Midseptal LA strain	−0.1	0.5
LA biplane volume index	0.4	0.02
2. Midlateral LA strain	−0.5	0.006
3. Midseptal LA strain rate	−0.5	0.003
4. Midlateral LA strain rate	−0.4	0.01

Multivariable stepwise regression analysis with log(fibrosis) as dependent variable and echocardiographic LA variables as independent variables. Four separate regression models were analyzed, by entering midseptal strain, midlateral strain, mid-septal strain rate, and midlateral strain rate with other independent variables such as LA superior-inferior and anterior-posterior diameters, LA maximum biplane volume index, LA emptying fraction, transmitral E/E′, and the rhythm during imaging (sinus or atrial fibrillation).

patient age, history of hypertension, LV filling pressure, or mitral regurgitation severity.

Patients with AF have extensive abnormalities in atrial ultrastructure. Initial studies in animal models showed remodeling in atrial ultrastructure and dedifferentiation of atrial myocytes to a more fetal stage after sustained atrial pacing.[19,20] Similar changes were reported in human atrial tissue in patients with AF who were undergoing valve surgery[1,3] and in patients with lone AF.[2] These studies showed that in addition to an increase in cell size, myolysis, and perinuclear accumulation of glycogen, tissue from patients with chronic AF also showed increased interstitial fibrosis. Oakes et al[9] recently reported a novel DE-MRI technique that is able to detect the extent of LA structural remodeling in patients with AF.

The ultrastructural changes caused by AF may lead to further electric and contractile remodeling. For the first time, Mary-Rabine et al[21] attempted to show the relationship between atrial ultrastructural changes by using optical and electron microscopy and cellular electrophysiological derangements to clinical hemodynamic manifestations. Their study showed that the contractile force of the atria is reduced due to myolysis and due to an imbalance in collagen synthesis and degradation. Longer duration of AF is associated with worsening atrial contractility and also takes longer for recovery of atrial mechanical function after cardioversion.[22] Patients with paroxysmal AF often progress to persistent or permanent AF. In our study, those with persistent AF had significantly more delayed enhancement as a marker for fibrosis and reduced strain and strain rate as compared with those with paroxysmal AF. These findings support the notion that there is a progressive remodeling process that occurs once AF is initiated. The inverse relationship between LA enhancement and strain was evident in persistent AF but not in paroxysmal AF. The patients with paroxysmal AF had less fibrosis. The weak association between fibrosis and strain in paroxysmal AF is intriguing, and other mechanisms such as cellular dysfunction that may precede development of fibrosis are likely to be important. In longer-standing AF, fibrosis appears to be the dominant factor causing mechanical dysfunction. Neither the extent of fibrosis nor the degree of reduction in strain was influenced by age, sex, severity of

mitral regurgitation, or history of hypertension, suggesting that the changes may be primarily due to AF.

Assessment of atrial function with conventional approaches is very challenging. Transmitral flow velocity with pulsed Doppler imaging shows the flow velocity due to atrial contraction. This can be used to measure atrial force, an indirect measure of atrial function. Unfortunately, the A wave is absent in AF, recovers gradually after successful electric cardioversion,[22] and is highly dependent on loading conditions (ie, LA and LV pressures) and diastolic function. Thus, the A wave is a limited tool for assessing atrial mechanical function. Another way of assessing atrial function is to measure the LA emptying fraction. In sinus rhythm, atrial emptying comprises both passive and active phases. In AF, there is only a passive phase, hence the term "emptying fraction" rather than "ejection fraction." Myocardial mechanics by strain imaging, which is widely used to assess ventricular function, has been used to assess atrial function in a few studies. Di Salvo et al[12] measured regional atrial strain by color Doppler imaging and reported LA lateral wall strain of 79% and septal strain of 98% in healthy control subjects. Cameli et al[15] measured LA longitudinal strain by speckle tracking and reported a global LA strain of 42%. Our values of regional strain in healthy control subjects by VVI in midseptal and midlateral walls were lower than that by color Doppler and higher than that by speckle tracing. VVI tracks the motion of mitral annular plane in addition to speckle tracking to generate strain curves. Differences in the 3 techniques probably resulted in different values for strain and strain rate in normal subjects. Studies in a larger population comparing the different approaches are needed to provide standard or reference values. Our study demonstrates that LA fibrosis by DE-MRI has significant correlation with midlateral strain and strain rate as compared with midseptal strain, independent of other LA measurements. The midseptal area is thin because of the presence of fossa of ovalis or septal aneurysms, and its movement can be influenced by the filling pressure in the right atrium. The lateral wall strain can be reliably imaged and is not constrained by other cardiac chambers and may be used as the best surrogate of LA wall fibrosis by DE-MRI.

Strain by Doppler techniques has inherent limitations caused by angle dependency and influence by loading conditions. With the advent of speckle tracking technology, it is now possible to quantify atrial strain and strain rate throughout the cardiac cycle, and it overcomes many of the limitations of Doppler-based methodologies.[11] Nonetheless, the very thin LA wall poses challenges to pure speckle tracking techniques as well. LA contraction, which is seen as negative strain and strain rate, is absent in AF. LA relaxation or peak lengthening strain during ventricular systole, represented by positive strain and strain rate, are important indicators of LA compliance or reservoir function that is impaired in AF caused by fibrosis. Our study showed that reduction in atrial strain did not appear to be caused by elevation of filling pressure as assessed by E/E′. Interestingly, there was also no correlation between LV filling pressure and the amount of fibrosis. The exact pathogenesis of AF is still unclear, and both hemodynamic and nonhemodynamic mechanisms are
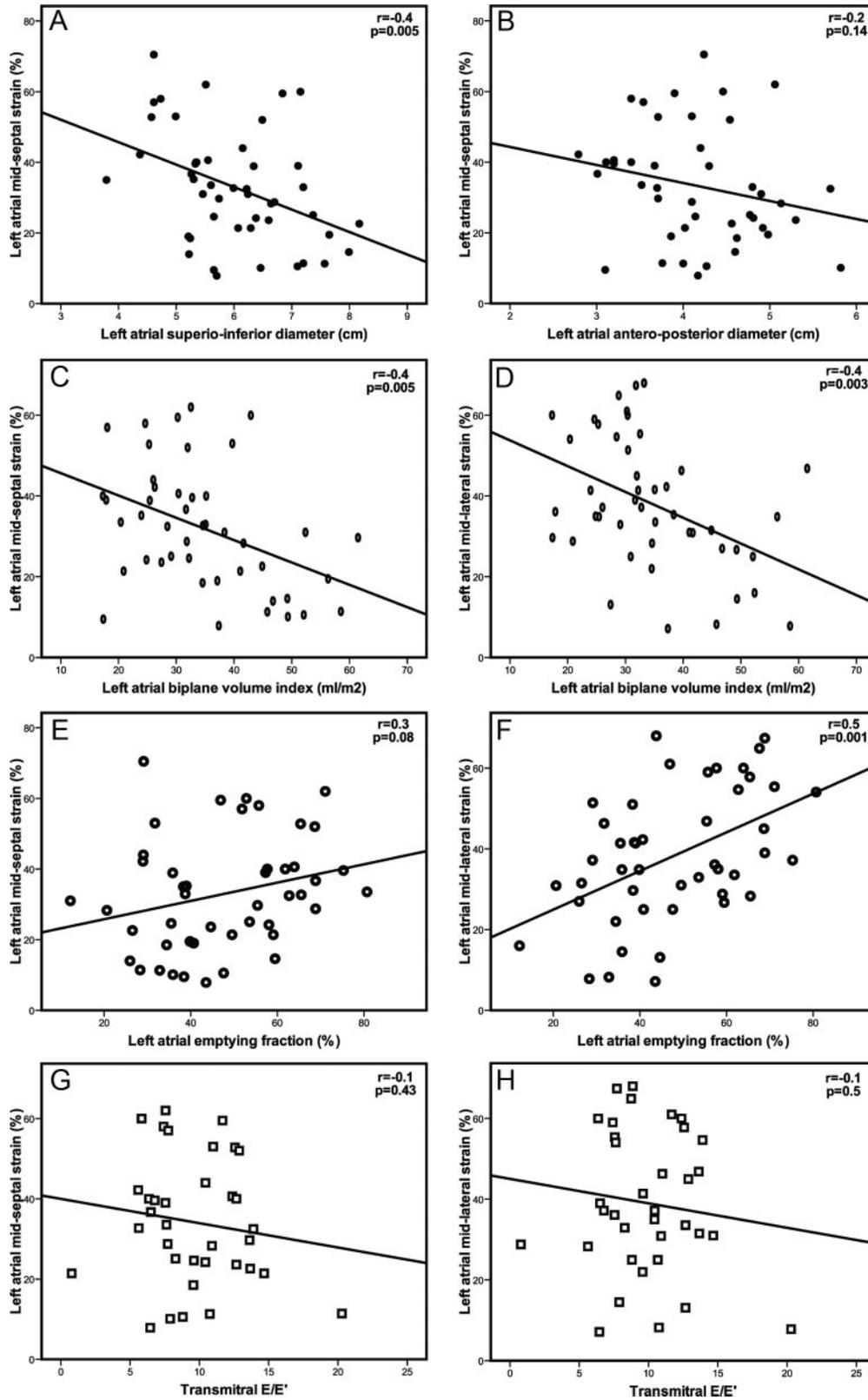
Figure 4. Relationship between LA strain and LA (A) superior-inferior and (B) antero-posterior diameters, (C and D) LA maximum biplane volume index, (E and F) emptying fraction and (G and H) LV filling pressure (E/E′).

contributory. Focal areas of fibrosis may initiate AF by reentry mechanism in the presence of normal LV structure and filling pressure, as seen in patients with lone AF. Persistence of AF, over time, can deteriorate LV function and

vice versa. Moreover, the E/E′ is subject to changes over time and is based on the volume status, blood pressure, and medications. That might explain the lack of correlation between E/E′ and LA strain and fibrosis in our study.

The rhythm, sinus or AF, during strain imaging did not affect the analysis of LA strain or strain rate. The study patients with the diagnosis of AF, who were in sinus rhythm during imaging, demonstrated impaired strain as compared with the control subjects. The contribution of the LA kick during sinus rhythm in AF patients did not appear to improve their filling and strain suggesting an inefficient LA contraction by the diseased LA. Lower LA strain and strain rate by tissue Doppler imaging have been reported in patients with AF as compared with healthy adults, and measures of atrial strain also correlate with the success of catheter ablation and cardioversion.[12–14] In our study, the significant negative relationship between the severity of structural remodeling by DE-MRI and LA compliance by strain and strain rate strongly suggests that LA compliance is impaired in AF, due to fibrosis of the atrial wall. This relationship remains significant even after controlling for the commonly used echocardiographic parameters of structural remodeling such as LA dimensions and volume, as these parameters are also abnormal in patients with diastolic heart failure without AF. The DE-MRI technique may be able to quantify the extent of structural remodeling and in identifying AF substrate in patients with enlarged LA who are in sinus rhythm.

A traditional and widely used method of assessing structural remodeling of the LA by echocardiography is to measure the LA A-P diameter in the parasternal long-axis view. Studies have correlated increasing A-P diameter with chronicity of AF.[23] However, the utility of this approach is limited because the LA may enlarge in an asymmetrical fashion. Hence, we examined the LA superior-inferior diameter also and found it to have a stronger association with lower LA strain than A-P diameter. Interestingly, neither LA A-P nor superior-inferior dimensions on echo correlated with the extent of fibrosis by DE-MRI. We found larger LA volume as an echocardiographic parameter of structural remodeling that was associated with both reduced strain and increased enhancement on MRI and also with larger superior-inferior dimension. This finding supports the use of atrial volume, rather than linear dimensions, as a means for assessing atrial geometry.[16] Unfortunately, measurement of biplane volumes is time-consuming and may have problems with reproducibility due to poor visualization of endocardial surfaces in both views. Superior-inferior diameter, which is related to the larger A-P diameter, larger volume and lower strain, may be useful as a quick measure to identify remodeled LA.

There are several limitations to our study. First, we have a relatively small sample size. This number of patients is not adequate to address noninvasive predictors of outcome. The severity of structural and functional remodeling leading to AF is not known, and further studies with longitudinal follow-up are needed to identify the precursor and early disease stages and to design therapies to prevent occurrence of this arrhythmia. Second, quantification of LA wall fibrosis by DE-MRI is limited by the inadequate spatial resolution and cannot give information on the transmurality of fibrosis. Third, the LA strain and strain rate were assessed in only the septal and lateral walls of the LA because those walls were consistently imaged without significant dropout. However, the most severe fibrosis has been reported in the posterior wall by our group.[9] Strain imaging is difficult in this location because of the distance from the chest wall and the presence of pulmonary veins. Nonetheless, our data suggest that the amount of fibrosis in the posterior wall is reflective of the overall pathological disturbances in the LA. Three-dimensional echocardiographic acquisition techniques may allow the inclusion of strain data from multiple sites as well as providing more accurate measurements of atrial volume. However, because of marked beat-to-beat variability in AF, single cardiac cycle 3D acquisitions will be required to do accurate 3D reconstructions of the atria. This technique is currently being brought into the clinical arena but is not yet widely available. We also acknowledge single-beat echocardiographic analysis in 5 patients with AF as a limitation.

In conclusion, LA wall fibrosis, implied by delayed enhancement on MRI, is inversely related to LA strain and strain rate. Echocardiographic assessment of structural and functional remodeling of the LA is possible from gray-scale images. These techniques appear to have some discriminatory power in assessing patients with paroxysmal versus persistent AF. Combined, noninvasive imaging with atrial strain and strain rate and quantification of LA wall fibrosis by DE-MRI may be helpful in predicting outcomes and guiding therapeutic strategies in patients with AF. Novel imaging strategies such as those described in this report may allow us to identify patients earlier in their disease process, before the development of severe or irreversible abnormalities. Echocardiographic strain imaging of the atria may be particularly useful in centers where DE-MRI is unavailable or in patients who are not candidates for MRI.

Disclosures
Dr Litwin received honoraria from Siemens for a lecture.

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CLINICAL PERSPECTIVE

The underlying substrate for atrial fibrillation (AF) is fibrosis, a marker of structural remodeling. AF leads to progressive structural and functional changes in the left atrium (LA). Delayed-enhancement (DE) MRI has been shown to detect LA fibrosis. With vector velocity imaging, using speckle tracking technology, quantification of atrial strain throughout the cardiac cycle from gray-scale images is feasible. Strain is an indicator of LA compliance or reservoir function, which is impaired in AF caused by fibrosis. Vector velocity imaging overcomes some of the limitations of Doppler-based strain measurements such as angle dependency and influence by loading conditions. In our study, we demonstrated an inverse relationship between LA fibrosis by DE-MRI and LA midlateral strain and strain rate by vector velocity imaging. This relationship was more prominent in patients with persistent compared with paroxysmal AF. Lateral wall strain can be reliably imaged and may be used as a surrogate of LA wall fibrosis by DE-MRI. Interestingly, LA fibrosis and strain were not related to common etiologies for AF such as patient age, hypertension, left ventricular filling pressure, or mitral regurgitation. Regardless of the underlying etiology or the duration of AF, the degree of atrial fibrosis was the main determinant of severity of arrhythmia in this cohort. Noninvasive imaging of LA fibrosis may be helpful in predicting the risk of developing AF, guiding therapeutic strategies, and predicting the outcomes in patients with AF. It may allow us to identify patients earlier in their disease process, before the development of severe or irreversible abnormalities.

SUPPLEMENTAL MATERIAL

Supplement 1

The details of VVI technique to compute strain:

VVI uses multiple tracking techniques to determine the cardiac motion. One is the longitudinal motion of the velocity vectors in relation to the movement of the reference plane (mitral annular plane) towards the apex. As the ventricle shortens during contraction, points along the trace are adjusted in position throughout the cardiac cycle, using a scaled portion of the reference plane motion during the cardiac cycle to maintain the topological shape of the trace. Second is the inward and outward motion of the endocardium (border tracking) and third is the motion of tissue along the tracing (speckle tracing). By constraining all the above tracking, VVI computes robust estimates of the cardiac motion for one or multiple cardiac cycles. In atrial fibrillation, it averages multiple cardiac cycles.

Supplement 2

Short Commentary

The underlying substrate for atrial fibrillation (AF) is fibrosis, a marker of structural remodeling. AF leads to progressive structural and functional changes in the left atrium (LA). Delayed enhancement (DE) MRI has been shown to detect left atrial fibrosis. With vector velocity imaging (VVI), using speckle tracking technology, quantification of atrial strain throughout the cardiac cycle from the grey scale images is feasible. Strain is an indicator of LA compliance or reservoir function which is impaired in AF due to fibrosis. VVI overcomes some of the limitations of Doppler-based strain measurements like angle dependency and influence by loading conditions. In our study, we demonstrated an inverse relationship between LA fibrosis by DE-MRI and LA mid-lateral strain and strain rate by VVI. This relationship was more prominent in patients with persistent compared to paroxysmal AF. Lateral wall strain can be reliably imaged and may be used as a surrogate of LA wall fibrosis by DEMRI Interestingly, LA fibrosis and strain were not related to common etiologies for AF like patient age, hypertension, left ventricular filling pressure or mitral regurgitation. Regardless of the underlying etiology or the duration of AF, the degree of atrial fibrosis seems to be the main determinant of severity of arrhythmia. Noninvasive imaging of LA fibrosis may be helpful in predicting the risk of developing AF, guiding therapeutic strategies and predicting the outcomes in patients with AF. It may allow us to identify patients earlier in their disease process, prior to the development of severe or irreversible abnormalities.

Legend for Movie file:

Video 1: Velocity Vector Imaging: Left atrial endocardium is manually traced starting from the medial to the lateral mitral annulus which is then tracked by the VVI software along the border throughout one or more cardiac cycles. The details of the Velocity Vector Imaging technique are provided in the online supplement.