Left Atrial Wall Stress Distribution and Its Relationship to Electrophysiologic Remodeling in Persistent Atrial Fibrillation

Ross J. Hunter, MRCP; Yankai Liu, MSc; Yiling Lu, PhD; Wen Wang, PhD; Richard J. Schilling, MD, FRCP

Background—Atrial stretch causes remodeling that predisposes to atrial fibrillation. We tested the hypothesis that peaks in left atrial (LA) wall stress are associated with focal remodeling.

Methods and Results—Nineteen patients underwent LA mapping before catheter ablation for persistent atrial fibrillation. Finite Element Analysis was used to predict LA wall stress distribution based on LA geometry from CT. The relationship was assessed between wall stress and (1) electrogram voltage and (2) complex fractionated atrial electrograms (CFAE), using CFAE mean (the mean interval between deflections). Wall stress varied widely within atria and between subjects (median, 36 kPa; interquartile range, 26–51 kPa). Peaks in wall stress (≥90th percentile) were common at the pulmonary vein (PV) ostia (93%), the appendage ridge (100%), the high posterior wall (84%), and the anterior wall and septal regions (42–84%). Electrogram voltage showed an inverse relationship across quartiles for wall stress (19% difference across quartiles, \( P = 0.016 \)). There was no effect on CFAE mean across quartiles of wall stress. Receiver operating characteristic analysis showed high wall stress was associated with low voltage (ie, <0.5 mV) and electrical scar (ie, <0.05 mV; both \( P < 0.0001 \)) and with absence of CFAE (ie, CFAE mean <120 ms; \( P < 0.0001 \)). However, peaks in wall stress and CFAE were found at 88% of PV ostia.

Conclusions—Peaks in wall stress were associated with areas of low voltage, suggestive of focal remodeling. Although peaks in wall stress were not associated with LA CFAE, the PV ostia may respond differently. (Circ Arrhythm Electrophysiol. 2012;5:351-360.)

Key Words: AF ■ stretch ■ wall stress ■ catheter ablation ■ complex fractionated atrial electrogram ■ CFAE

Increased atrial stretch is a common etiologic factor in patients with atrial fibrillation (AF).\(^1\) Chronic stretch causes atrial dilatation and heterogeneous changes in atrial architecture, including focal myocyte hypertrophy and fibrosis.\(^2\)–\(^5\) Electrophysiologic sequelae of atrial stretch include slowing of conduction, prolongation of the effective refractory period, areas of low voltage and electrical scar, double potentials and fractionated electrograms, and increased inducibility of AF.\(^2\)–\(^10\)

Clinical Perspective on p 360

Although pulmonary vein (PV) isolation is a successful treatment for paroxysmal AF,\(^11\)–\(^12\) additional substrate modification in the form of linear lesions and/or targeting of complex or fractionated atrial electrograms (CFAE) improves outcomes for persistent AF.\(^11\)–\(^12\) Greater understanding of how atrial remodeling supports AF may allow refinement of substrate modification and improve outcomes. Computer modeling has been used to better understand complex processes such as excitation contraction coupling and mechanical function\(^13\)–\(^14\) and may help understand how stretch is distributed in the walls of the left atrium (LA) and how this affects atrial remodeling.

We hypothesized that peaks in LA wall stress are associated with focal electrophysiologic remodeling, which maintains AF. To address this, computer modeling was used to predict wall stress in 3D reconstructions of the LA from patient CT scans and simulated data compared with electrophysiologic data recorded in the same patients at the time of their ablation for persistent AF. The importance of regions with high wall stress in maintaining AF was evaluated by examining how wall stress affects the response to CFAE ablation, as determined by change in AF cycle length (AFCL).

Methods

Study Population
The study population was composed of patients who underwent first-time catheter ablation of persistent AF at a single institution. This study was approved by East London and The City Research Ethics Committee, United Kingdom (reference No. 09/H0703/6). All patients gave written informed consent.

Electrophysiology Study
Our periprocedural management and our method of catheter ablation of persistent AF have been published previously.\(^12\) In brief, a decapolar catheter (Viking, Bard EP, Lowell, MA) was inserted into...
the coronary sinus and a hexapolar catheter (Supreme, St Jude Medical, St. Paul, MN) placed in the right atrial appendage. After double transseptal puncture, a 14-pole deflectable PV mapping catheter (Orbiter PV, Bard EP, Lowell, MA) and a 3.5-mm irrigated ablation catheter (Thermo-Cool Celsius, Biosense Webster, Diamond Bar, CA) were introduced to the LA. Before any ablation, LA geometry was created with the use of a 3D mapping system (Ensite NavX, St Jude, St. Paul, CA).

All patients underwent a gated 128-slice CT scan of the LA within 6 hours of the procedure. All patients were assessed as euvolemic before scanning and had a mean central venous pressure between 0–15 mm Hg at the start of the procedure subsequently. All patients were in rate-controlled persistent AF, with a resting ventricular rate below 100 beats per minute on a 12-lead ECG before CT scanning. CT scans were segmented on proprietary software (Ensite Verismo, St Jude, St. Paul, CA) to create a 3D reconstruction of the LA, which was then registered with the geometry as described previously.\(^\text{13}\) CT imaging of the LA provides high-quality reconstructions that can be registered to the LA geometry with an error of only 1–3 mm, regardless of whether CT scans and/or geometries are acquired in AF or sinus rhythm.\(^\text{15,16}\)

**Signal Processing and Waveform Analysis**

The PV mapping catheter was moved around the LA to acquire electrograms at evenly spaced points, creating a map of electrophysiological data before any ablation in AF. Catheter contact was verified by using a combination of the 3D mapping system, the catheter shape on fluoroscopy, and electrogram inspection. However, no catheter contact monitoring technology was used, and it is recognized that variation in contact force may change electrogram properties to some extent. Five-second electrograms were recorded for analysis because this has been shown to produce consistent results.\(^\text{17}\) The Ensite NavX software recognizes deflections in the waveform, based on a number of criteria that can be varied by the user.\(^\text{18}\) Each deflection must have a minimum width to exclude noise and a blanking period to prevent double counting (20 ms and 30 ms, respectively, have been shown to correlate with visual assessment of electrograms).\(^\text{18}\) A minimum of 0.05 mV was used. The software tags deflections meeting these criteria on-screen and uses algorithms to generate a score for (1) electrogram voltage amplitude: the mean of the largest “peak-to-peak” deflection in each electrogram complex; and (2) CFAE mean: the mean interval between deflections, or mean cycle length. This is a continuous variable with shorter mean cycle length taken to mean greater electrogram fractionation. However, for assessment of CFAE distribution <120 ms was considered a CFAE. Therefore, for each electrophysiologic data point where a waveform was obtained, the mapping system ascribed a coordinate (in the same 3D space as the LA reconstruction) and calculated a value for each of these 2 parameters.

**Ablation**

The PVs were isolated by wide area circumferential ablation, with lesions placed 1–2 cm outside the PV ostia to isolate them in ipsilateral pairs. Electrical isolation was confirmed by using the PV mapping catheter; this was then placed in the LA appendage for monitoring of LA AFCL. Next, CFAE were systematically targeted throughout the left then right atria until sinus rhythm was restored or all CFAE were abolished. The NavX CFAE maps were used to guide and focus ablation in key areas, although CFAE were ultimately identified and targeted, based on electrograms recorded by the ablation catheter as described previously.\(^\text{18}\) Radiofrequency energy was applied until electrogram amplitude was reduced by ≥80% or 60 seconds of energy delivered. If patients remained in AF after abolition of all CFAE, linear lesions were added at the mitral isthmus (between mitral valve and left inferior PV), the roof between left and right PVs, and the cavitricuspid isthmus in patients with a history of typical atrial flutter. If at any point AF organized into atrial tachycardia, this was mapped and ablated. If sinus rhythm was not restored after these lesions, the patient was cardioverted with a DC shock.

**Assessment of AFCL**

AFCL progressively lengthens during catheter ablation until termination of AF.\(^\text{19}\) AFCL is inversely proportional to the number of drivers maintaining AF, and hence AFCL prolongation is thought to reflect elimination of drivers.\(^\text{20}\) AFCL has been used by others to monitor response to ablation, with an increase ≥5–6 ms considered significant.\(^\text{21–23}\) Mean AFCL was determined manually over 30 cycles from bipolar electrograms recorded at the apex of the left and right atrial appendages, where electrograms are high-voltage and hence AFCL is unambiguous, before and after ablation of each CFAE lesion. Baseline AFCL variability was measured over 10 successive segments of 30 cycles in all patients before any ablation. A change greater than or equal to mean +2 SD of baseline variability was considered significant.

**Stress Modeling**

The LA reconstruction and electrophysiologic data were exported from the mapping system. Using proprietary software (Finite Element Analysis, ABAQUS Inc, Pawtucket, RI), the LA geometry was used to simulate wall stress distribution. Because the resolution of CT is approximately 1 mm, this is insufficient to accurately determine regional differences in thickness of the LA wall (which varies from 1–5 mm) or the muscular sleeves at the PVs (which is approximately 1 mm and tapers toward the first division of the PV).\(^\text{24}\) Therefore, the LA was assumed to have uniform thickness of 2 mm, tapering over a distance of 1 cm from the PV ostia to a thickness of 1 mm in the PVs. The LA was considered suspended by the 4 PVs, which were fixed in the model. The PVs were assumed to be open and the mitral valve assumed to be shut. The surface beyond the first division of the PVs and the mitral valve annulus were not included in the analysis.

The LA and proximal PVs were essentially modeled as a homogenous linear elastic shell. Values for LA physical properties including the Young modulus (a measure of “stiffness”) and Poisson ratio (a measure of the degree to which stress causes deformation parallel to and perpendicular to the force applied to a surface) were adopted from the literature.\(^\text{25}\)

Von Mises stress distribution was predicted for a transmural pressure difference of 20 mm Hg. To describe regional distribution of peaks in wall stress, an area with von Mises stress ≥90\(^\text{th}\) percentile was considered to be a peak in wall stress. The distribution of peaks in wall stress was assessed with the use of the previously published 22-segment model of the LA (as shown in Figure 1).\(^\text{23}\) To assess the relationship between LA electrophysiology and wall stress, the values derived for each electrophysiologic data point (electrogram voltage amplitude and CFAE mean) were compared with simulated wall stress at the nearest point on the LA reconstruction.

**Exploring Variations of the Model**

Although the accuracy of the geometry is the most important factor when simulating wall stress,\(^\text{26}\) the wall thickness and the transmural pressure gradient are also very important. Hence, the impact of varying these parameters on wall stress distribution was explored.

The transmural pressure gradient is complex, owing to extracardiac structures, changing intra-atrial pressure during the cardiac cycle, and changing intrathoracic pressure during respiration. Although it is not possible to fully account for this regional and temporal variation, we addressed the impact of a uniform change in the transmural pressure gradient. Simulated wall stress values were compared when 10 mm Hg and 20 mm Hg transmural pressure gradients were used. The increase in wall stress resulting from this increase in pressure was evaluated by examining the mean percentage increase in stress for each element in the model. To examine whether the pattern of wall stress distribution was altered, the elements in the model were ranked from highest to lowest wall stress values in the 10 mm Hg simulation, and the mean change in the percentile ranking for each element was assessed when the transmural pressure was increased to 20 mm Hg.
Although current imaging modalities do not permit regional assessment of wall thickness, it is recognized that certain areas of the LA are usually thicker, in particular the septum and the left atrial appendage.\footnote{CirCEP 2017} Therefore, the simulation was repeated with a 3-mm wall thickness at these sites. The impact on wall stress at these sites and any resultant effect on the correlation with electrophysiologic parameters were evaluated.

**Statistics**

Because this study was completely novel, there were no pilot data available for sample size estimation. After 20 patients, interim analysis was conducted to clarify sample size but showed that key comparisons had reached statistical significance.

Continuous variables are reported as mean±SD or median (range) if not normally distributed. Correlation is inevitably affected by confounding factors including variation in catheter contact force and the small proportion of points that have poor contact. The electrophysiologic data points for each patient were therefore divided into quartiles, based on wall stress at their location, with the median value taken as representative of each quartile to reduce the impact of outlying data. The changes in electrophysiologic parameters (voltage amplitude and CFAE mean) were therefore assessed across quartiles of wall stress for each patient (with a single median value per patient for each quartile of wall stress), using repeated-measures analysis of variance (MANOVA). To assess any interaction between the effect of LA volume and wall stress on electrophysiologic parameters, LA volume was included as a covariate in the MANOVA design. To examine the relationship between electrogram voltage amplitude and CFAE (ie, independent of wall stress), the effect on CFAE mean across quartiles of electrogram voltage for each patient was assessed in the same fashion.

To evaluate the relationship between LA voltage and CFAE, the percentage of the LA occupied by CFAE in each patient was compared with (1) the median value for LA voltage and (2) the percentage of the LA meeting the criterion for electrical scar. Correlation was assessed using Pearson correlation coefficient, using a single value for each of these variables per patient.

Receiver operating characteristic (ROC) analysis was used to assess whether high wall stress was associated with certain defined electrophysiologic abnormalities and to determine whether a discrete threshold of wall stress precipitated such abnormalities: (1) fractionated electrograms (a CFAE mean $<120$ ms)$^{19}$; (2) low-voltage areas suggestive of abnormal conduction ($<0.5$ mV)$^{7,10}$; and (3) very low-voltage areas suggestive of scar ($<0.05$ mV)$^{7,10}$.

To compare the distribution of peaks in wall stress and the above electrophysiologic abnormalities, their presence or absence (and their concordance) was assessed in each region of the 22-segment model shown in Figure 1.

To assess the impact on simulated wall stress of increasing wall thickness from 2–3 mm at the septum and left atrial appendage, the median wall stress and the percentage of the surface meeting the criterion for a peak in wall stress at each wall thickness was compared by use of a paired $t$ test.

The impact of wall stress on the proportion of CFAE lesions causing AFCL prolongation was assessed in 2 ways. First, wall stress at sites where CFAE ablation prolonged AFCL was compared with wall stress at sites where ablation did not prolong AFCL, using the Mann-Whitney $U$ test. Second, ROC analysis was used to determine whether wall stress predicted sites where CFE ablation caused AFCL prolongation.

**Results**

**Patients**

Although 20 patients were recruited, 1 had poor-quality CT images and was excluded from the analysis. The characteristics of the remaining 19 patients recruited are shown in the Table. All patients had persistent AF, and 84% had long-lasting persistent AF (ie, ≥1 year). There was a high incidence of structural heart disease, and LA were dilated (Table). No patients had significant valvular heart disease. Procedure duration was 300 (210–480) minutes, with fluoroscopy time of 57 (28–76) minutes. The only procedural complication was 1 groin hematoma, which did not require any intervention.

**Stress Distribution**

Figure 2 shows examples of wall stress distribution. Wall stress varied widely from region to region, with a median value of 36.4 kPa and an interquartile range of 26.2–51.6 kPa. Figure 3 shows the proportion of patients who had peaks in wall stress over the different regions shown in Figure 1. Peaks in wall stress were particularly common around the ostia of the PVs (left PVs, both 100%; right PVs, 84% and 89%), the LA appendage ridge (100%), the high posterior wall and roof (84% and 47%, respectively), the anterior wall regions (68–84%), and the septal regions (42–74%). There was no significant correlation between LA volume and median wall stress (Pearson $r=0.184$, $P=0.451$). The distribution of peaks

**Table. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, %</td>
<td>84</td>
</tr>
<tr>
<td>Age, y</td>
<td>64±7</td>
</tr>
<tr>
<td>Months of continuous AF</td>
<td>23±16</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>53</td>
</tr>
<tr>
<td>Ischemic heart disease, %</td>
<td>32</td>
</tr>
<tr>
<td>Left atrial volume, mL</td>
<td>159.0±46.8</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>48±14</td>
</tr>
</tbody>
</table>

Data are presented as percentage of patients or mean±SD.
in wall stress in the areas shown in Figure 1 did not differ when comparing the 9 most dilated LA to the 9 smallest.

Electrophysiologic Data Points
A total of 8214 data points were acquired. After removing points >5 mm from the LA shell, there were 6770 points remaining for analysis, or 356±80 per patient.

Relationship Between Wall Stress and Electrophysiologic Parameters
Electrogram amplitude showed a linear inverse relationship across quartiles for wall stress, meaning lower electrogram amplitude at sites of higher wall stress, with a 19% difference between the highest and lowest quartiles for wall stress (P=0.016, Figure 4A). There was a trend toward higher
CFAE mean (meaning less fractionated electrograms) at higher wall stress, but values for CFAE mean were highly variable between subjects, and this effect was not significant ($P=0.256$, Figure 4B).

**Relationship Between Remodeling and CFAE**

There was a significant decrease in CFAE mean across quartiles of voltage amplitude (Figure 5; $P<0.0001$). The lowest quartile for electrogram voltage had a markedly higher CFAE mean value (meaning less fractionated electrograms). The lowest quartile for electrogram voltage probably contained the most points with poor contact, and the absence of detected deflections at these points may therefore have artificially increased the CFAE mean score. However, even if the lowest quartile of electrogram voltage is discarded, the decrease across the remaining 3 quartiles was still significant ($P<0.0001$). Notably, the percentage of the LA that was occupied by CFAE correlated with median LA voltage for each patient ($r=0.71$, $P<0.001$) and was inversely proportional to the percentage of the LA meeting the criterion for electrical scar ($r=-0.54$, $P=0.017$).

LA volume correlated with the percentage of the LA, meeting the criterion for electrical scar ($r=0.46$, $P=0.046$), but did not correlate with the percentage of the LA occupied by CFE ($r=0.07$, $P=0.790$). There was no significant interaction between the effects of LA volume and increasing wall stress on LA voltage ($P=0.079$).

**ROC Analysis**

There was an association between high wall stress and electrical scar: A wall stress value of 39.6 kPa had a sensitivity of 56.1% and specificity 57.0% for predicting electrical scar (area under the curve, 0.574; $P=0.0001$; Figure 6A). There was a modest association between high wall stress and low voltage; with a wall stress value of 35.5 kPa, there was a sensitivity and specificity both of 54.0% for predicting low voltage (area under the curve, 0.550; $P<0.0001$; Figure 6B). High wall stress was associated with absence of CFAE (area under the curve, 0.453; $P<0.0001$; Figure 6C).

**Assessment of Relationships by Region**

Low-voltage electrograms and electrical scar were present in all areas, precluding meaningful analysis of any relationship by region. CFAE occurred in more discreet areas, and the distribution is shown in Figure 3. CFAE and peaks in wall stress coexist in certain areas but not others, and hence their “agreement” (both phenomena being present or absent) was variable. Because both phenomena were almost always present to some extent in the PVs, the agreement there was high (95–100% in the left PVs; 79% in both right PVs). Overall agreement occurred in 61%.

**Wall Stress and Response to Ablation**

Baseline AFCL variability was 1.50±1.75. Therefore, AFCL prolongation ≥5.0 ms was considered significant. In total, 933 CFAE were targeted (49±26 lesions per patient). Of
these, 614 were in the LA. The 425 LA lesions within 5 mm of the LA shell were included for analysis. Of the 425 lesions, 108 caused significant AFCL prolongation.

Wall stress values at sites where CFAE ablation caused AFCL prolongation was 40.1 (27.7–58.4) kPa compared with 40.8 (27.9–67.0) kPa at sites where AFCL did not change ($P=0.408$). ROC analysis showed that wall stress could not be used to distinguish between areas that would and would not cause AFCL prolongation during CFAE ablation (area under the curve, 0.530; $P=0.355$).

**Impact of Variations in the Model**

The simulation was composed of 57 276 ± 12 646 elements. An increase in the transmural pressure gradient from 10–20 mm Hg caused a mean increase in wall stress of 83.6 ± 7.9% for each element. When elements were ranked on

![Figure 6. Relationship between high wall stress and electrophysiologic abnormalities. Receiver operating characteristic curves demonstrate the relationship between high wall stress and electrophysiologic abnormalities: A, Electrical scar (defined as voltage amplitude <0.05 mV); B, low voltage (defined as <0.5 mV); and C, complex fractionated atrial electrogram (CFAE) (defined as CFAE mean <120 ms). Area under the curve and confidence intervals (CI) are shown.](image-url)
the basis of their wall stress value, an increase in transmural pressure from 10–20 mm Hg caused a change in the mean percentile ranking of 2.9±1.0%.

The changes in wall stress distribution produced by an increase in wall thickness to 3 mm at the LA appendix and the interatrial septum were largely confined to these areas. The median wall stress was reduced from 21.8±4.8 to 16.5±4.3 kPa in the LA appendix (P<0.0001) and 39.5±11.1 to 30.5±9.9 kPa in the septum (P<0.0001). The proportion of the septum occupied by peaks in wall stress was reduced from 9.3±11.3% to 2.7±4.2% (P=0.002). There were no peaks in wall stress in the LA appendix at either wall thickness.

When wall thickness at the LA appendix and the septum were increased to 3 mm, the relationship with electrophysiologic parameters was preserved. The decreasing electrogram amplitude across quartiles of wall stress remained evident (P=0.009). The trend toward higher CFAE mean at higher wall stress was strengthened but remained nonsignificant (P=0.058). The ROC analysis showed that high wall stress was still associated with electrical scar (area under the curve, 0.579; 95% confidence intervals, 0.548–0.610; P<0.0001) and absence of CFAE (area under the curve, 0.469; 95% confidence intervals, 0.453–0.485; P<0.0001).

Discussion

Major Findings
LA wall stress varies widely in different regions of the same LA and also in the same regions between subjects. There was an inverse relationship between regional wall stress and electrogram voltage, and foci of high wall stress were associated with low voltage and electrical scar. Areas with high wall stress were less likely to support CFAE, although the PV ostia may be an exception in that they were consistently high stress and harbored CFAE. After PV isolation, regional LA wall stress did not predict response to CFAE ablation.

Cardiac Modeling and Wall Stress
Increasingly complex “multiscale models” are being used to further understanding of complex interacting processes, such as excitation contraction coupling and mechanical function, and the role of myocardial stretch in arrhythmia in the context of commotio cordis.

This numeric model predicted wall stress based purely on LA anatomy by assuming the LA to be a linear elastic shell. Because the anatomy of the LA is highly variable wall stress varied widely between subjects. Wall stress was raised at “saddle points” where invagination of the LA surface occurred, for example, at the PV ostia and the appendage ridge. More subtle examples include the imprint produced by the aortic root on the anterior wall, the septum, and the roof/high posterior wall (Figure 2).

Because this model was entirely novel, it has necessarily taken a simplified view of LA biomechanics as the first step toward understanding LA wall stress distribution. Although the accuracy of the geometry is the most important factor in determining wall stress, 2 other important factors that are difficult to fully account for are (1) regional differences in wall thickness (because this is beyond the resolution of current imaging technologies), and (2) the complexities of regional and temporal variations in the transmural pressure gradient, which is influenced by extracardiac structures and changes over time with intracardiac pressure during the cardiac cycle and intrathoracic pressure with respiration.

Variations in the model were tested to evaluate the impact of these factors. Although doubling of the transmural pressure gradient from 10–20 mm Hg caused a uniform increase in wall stress, there was only a minimal change in the percentile ranking of wall stress for each element, suggesting that the relative distribution of wall stress was effectively unchanged. Therefore, changes in transmural pressure that are relatively uniform (such as those caused by changing intra-atrial pressure and intrathoracic pressure) would not be expected to significantly alter wall stress distribution. Another variation tested was to increase the wall thickness at sites where the atrial wall was thought to be thicker, in particular the interatrial septum and the LA appendix. Increasing wall thickness from 2 mm to 3 mm at these sites caused a small reduction in wall stress locally, although this did not affect the overall relationship with electrophysiologic parameters.

LA Structural and Electrophysiologic Response to Stretch
Increased atrial stretch is a consistent etiologic factor in the development of AF. Chronic stretch causes LA dilatation, with heterogeneous remodeling of atrial architecture including myocyte hypertrophy, fibrosis, and gap junction remodeling. Electrophysiologic effects include conduction heterogeneity and anisotropy, areas of low voltage and electrical scar, prolonged effective refractory period, a greater proportion of double potentials and CFAE, and greater inducibility of AF.

Impact of Wall Stress on Electrophysiology
Our results showed an inverse relationship between LA wall stress and electrogram amplitude. Similarly, the ROC analysis demonstrated an association between areas of high wall stress and low voltage and electrical scar. Such areas have been interpreted as evidence of remodeling in AF. Areas of low voltage and electrical scar in persistent AF correlate with areas of late gadolinium enhancement suggestive of scar on MRI and predict a poor outcome after catheter ablation of AF. Furthermore, low voltage may denote zones of slow conduction. Foci of high wall stress may induce remodeling by directly activating signaling pathways such as cAMP, angiotensin II, and others. However, the observation that an acute decrease in intra-atrial pressure can cause an immediate increase electrogram amplitude and conduction velocity suggests a role for focal activation of stretch activated ion channels. It is also noteworthy that voltage is lower when assessed in AF compared with sinus rhythm, and the extent to which areas of low voltage in AF correspond to those in sinus rhythm is uncertain. Other proposed mechanisms by which voltage may be reduced in AF include propagation of wave fronts through partially repolarized tissue, a variable direction of wave front propagation, and
Wall Stress and CFAE
There was a trend toward increasing CFAE mean across quartiles of wall stress (suggesting more organized and less rapid electrical activity at higher wall stress), although this did not reach significance. The ROC analysis showed that high wall stress was associated with absence of CFAE. This suggests a weak relationship whereby high wall stress reduces the propensity of the atrial tissue to support at least some mechanisms of CFAE.

Our data also showed an inverse correlation between CFAE mean and voltage, suggesting increased fractionation at higher voltage. Furthermore, the percentage of the LA occupied by CFAE was inversely proportional to the percentage occupied by scar, suggesting fewer CFAE in more remodeled atria. This is in keeping with other recent studies showing that CFAE are not associated with areas of low voltage46,39–41 but is at odds with conventional wisdom.50

Focal remodeling might be expected to contribute to zones of slow conduction, pivot points or block,42 and resultant micro- or macro-reentry43 but is less likely to bear any relationship to rotors or rapidly discharging foci that may be more dependent on autonomic drive and proximity to ganglionated plexi.43 Therefore, although atrial remodeling promotes AF,2–10 peaks in wall stress and areas of remodeling are actually less likely to support CFAE. One plausible explanation is that stretch and remodeling might lengthen atrial refractoriness3,48–10 which may limit localized reentry and automaticity.

Peaks in wall stress and CFAE were found to coexist at the PV ostia. Although this may suggest an excitatory response, there are numerous proposed mechanisms for CFAE at the PV ostia and they may simply reflect proximity to PV drivers. Stretch has been shown to increase the frequency of depolarization at the PVs without affecting the body of the LA.44,45 This may owe to activation of stretch-activated ion channels causing membrane depolarization, although it is unclear why the muscular sleeves surrounding the proximal PVs should respond differently to LA myocardium. The PV ostia can dilate in response to chronic atrial stretch,46 potentially altering wall stress distribution and further exacerbating stretch at the ostia and proximal PVs. This therefore provides a rationale for the association between acutely and chronically elevated LA pressure and increased PV ectopy and initiation of AF.

Wall Stress and Response to Ablation
Local wall stress had no impact on whether CFAE ablation caused cycle length prolongation, suggesting that it is unlikely to be useful in guiding LA CFAE ablation. However, because LA CFAE ablation was always performed after wide area circumferential ablation, it remains uncertain whether the peaks in wall stress at the PV ostia were important in maintaining AF.

Limitations
It is difficult to validate wall stress simulation by finite element analysis. However, it has been widely used in biomechanics and has produced results that correlate with both clinical findings47 and biophysical properties when direct testing is feasible.48 It is recognized that this novel model has necessarily taken a simplified view of LA biomechanics. Patient-specific and site-specific data on LA material properties were not available, although variation in these parameters has only a modest effect on predicted wall stress.26 The resolution of current imaging modalities does not allow regional differences in wall thickness to be incorporated into the model, and this is accepted as a limitation. It is also difficult to account for the impact of temporal and regional variation in transmural pressure. However, the accuracy of the geometry is the main determinant of wall stress,26 and, although refinement of the model may alter the simulated wall stress distribution to some extent, the variations in the model that we have tested suggest these changes are likely to be small and are therefore more likely to clarify the relationship with electrophysiology than change it altogether.

Although areas of low voltage and electrical scar in persistent AF are thought to represent atrial remodeling and correlate with areas suggestive of scar on MRI,30–32 it is recognized that such areas may not all represent scar.36,37 Further exploration of the relationship between wall stress and areas of low voltage in sinus rhythm is warranted.

Conclusions
Peaks in LA wall stress were associated with areas of low voltage and electrical scar; although, because electrograms were recorded in AF, it remains uncertain whether this represents focal remodeling. Regional differences in wall stress may explain the heterogeneous remodeling that results from elevated intra-atrial pressure and promotes AF. The observation that the PV ostia had consistently high wall stress and harbored CFAE is compatible with the observations by others that stretch may elicit an excitatory response at the PV ostia without doing so elsewhere in the LA.44,45 suggesting a potential mechanism by which elevated intra-atrial pressure might facilitate initiation of AF. This study adds to the rationale for lowering intra-atrial pressure in those at risk of AF to limit this remodeling process.

Acknowledgments
This work was facilitated by Barts and the London NHS Trust NIHR Biomedical Research Unit.

Sources of Funding
Dr Hunter is supported by a grant from the British Heart Foundation (PG/08/130).

Disclosures
Dr Schilling is a member of the scientific advisory board for Biosense Webster and Endocardial Solutions.

References
2. Verheule S, Wilson E, Banthia S, Everett TH, Shanbhag S, Sih HJ, Olgin J. Direction-dependent conduction abnormalities in a canine model of


clinical perspective

Atrial stretch causes remodeling that predisposes to atrial fibrillation (AF). We tested the hypothesis that peaks in left atrial (LA) wall stress are associated with focal remodeling. A novel computer model was used to simulate LA wall stress distribution, based on anatomy form computerized tomographic imaging. Patients with persistent AF underwent high-density LA mapping, and the electroanatomic data were compared with simulated wall stress distribution. Electrogram voltage correlated inversely with local wall stress, and peaks in wall stress were associated with areas of scar. There was also a weak relationship whereby peaks in LA wall stress were less likely to support complex fractionated electrograms (CFAE). However, both peaks in wall stress and CFAE were observed at the pulmonary vein ostia. Regional differences in wall stress may explain the heterogeneous remodeling that results from elevated intra-atrial pressure and promotes AF. The observation that the pulmonary vein ostia had consistently high wall stress and harbored CFAE is compatible with the observations by others that stretch may elicit an excitatory response at the pulmonary vein ostia without doing so elsewhere in the LA, suggesting a potential mechanism by which elevated intra-atrial pressure might facilitate initiation of AF. This study adds to the rationale for lowering intra-atrial pressure in those at risk of AF to limit this remodeling process.
Left Atrial Wall Stress Distribution and Its Relationship to Electrophysiologic Remodeling in Persistent Atrial Fibrillation
Ross J. Hunter, Yankai Liu, Yiling Lu, Wen Wang and Richard J. Schilling

Circ Arrhythm Electrophysiol. 2012;5:351-360; originally published online January 31, 2012; doi: 10.1161/CIRCEP.111.965541
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/5/2/351

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org//subscriptions/