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

Running title: Hunter et al.; Wall stress and electrophysiology

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Abstract:

**Background** - 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.

**Methods and Results** - 19 patients underwent LA mapping prior to catheter ablation for persistent AF. Finite Element Analysis was used to predict 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, IQR 26 – 51 kP). Peaks in wall stress (≥ 90th percentile) were common at the pulmonary vein (PV) ostia (93%), the appendage ridge (100%), the high posterior wall (84%), 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. ROC analysis showed high wall stress was associated with low voltage (i.e. < 0.5 mV) and electrical scar (i.e. < 0.05 mV; both p < 0.0001), and with absence of CFAE (i.e. CFAE mean < 120ms; 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.

**Key words:** AF, stretch, wall stress, catheter ablation, complex fractionated atrial electrogram, CFAE.

**Abbreviations:** AF, atrial fibrillation; LA, left atrium; PV, pulmonary vein; CFAE, complex fractionated atrial electrogram; AFCL, atrial fibrillation cycle length.
Introduction

Increased atrial stretch is a common aetiologic factor in patients with atrial fibrillation (AF).\textsuperscript{1} Chronic stretch causes atrial dilatation and heterogenous changes in atrial architecture, including focal myocyte hypertrophy and fibrosis.\textsuperscript{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.\textsuperscript{2-10}

Although pulmonary vein (PV) isolation is a successful treatment for paroxysmal AF,\textsuperscript{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.\textsuperscript{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,\textsuperscript{13, 14} and may help understand how stretch is distributed in the walls of the left atrium (LA) and how this impacts on 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’s CT scans, and simulated data compared to 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 impacts on the response to CFAE ablation, as determined by change in AF cycle length (AFCL).
Methods

Study population

The study population was comprised 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, UK (reference number 09/H0703/6). All patients gave written informed consent.

Electrophysiology study

Our peri-procedural management and our method of catheter ablation of persistent AF has been published previously.12 In brief, a decapolar catheter (Viking, Bard EP, MA, USA) was inserted into the coronary sinus and a hexapolar catheter (Supreme, St. Jude Medical, MN, USA) placed in the right atrial appendage. After double trans-septal puncture a 14 pole deflectable PV mapping catheter (Orbiter PV, Bard EP, MA, USA) and a 3.5 mm irrigated ablation catheter (Thermo-Cool Celsius, Biosense Webster, CA, USA) were introduced to the LA. Prior to any ablation a LA geometry was created using a 3D mapping system (Ensite NavX, St Jude, CA, USA).

All patients underwent a gated 128 slice CT scan of the LA within 6 hours of the procedure. All patients were assessed as euvoilaemic before scanning and had a mean central venous pressure between 0 and 15 mmHg 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 12 lead ECG prior to CT scanning. CT scans were segmented on proprietary software (Ensite Verismo, St Jude, CA, USA) to create a 3D reconstruction of the LA, which was then registered with the geometry as described previously.15 CT imaging of the LA provides high quality
reconstructions which 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. 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 electrophysiologic data prior to any ablation in AF. Catheter contact was verified 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, since this has been shown to produce consistent results. 17 The Ensite NavX software recognizes deflections in the waveform based on a number of criteria which can be varied by the user. 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). 18 A minimum of 0.05mV 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.

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 using the PV mapping catheter, then this was 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.\textsuperscript{18} Radiofrequency energy was applied until electrogram amplitude was reduced by $\geq 80\%$ or 60s 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 cavotricuspid isthmus in patients with a history of typical atrial flutter. If at any point AF organised into atrial tachycardia this was mapped and ablated. If sinus rhythm was not restored following these lesions the patient was cardioverted with a DC shock.

Assessment of AFCL

AFCL progressively lengthens during catheter ablation until termination of AF.\textsuperscript{19} AFCL is inversely proportional to the number of drivers maintaining AF, and hence AFCL prolongation is thought to reflect elimination of drivers.\textsuperscript{20} AFCL has been used by others to monitor response to ablation, with an increase $\geq 5$-6 ms considered significant.\textsuperscript{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 prior to any ablation. A change ≥ mean + 2 standard deviations of baseline variability was considered significant.

**Stress Modelling**

The LA reconstruction and electrophysiologic data were exported from the mapping system. Using proprietary software (Finite Element Analysis, ABAQUS Inc, Pawtucket, RI, USA), the LA geometry was used to simulate wall stress distribution. Since 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 towards the first division of the PV). 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 Young’s modulus (a measure of ‘stiffness’) and Poisson’s 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.

Von Mises stress distribution was predicted for a trans-mural pressure difference of 20 mmHg. To describe regional distribution of peaks in wall stress, an area with von Mises stress ≥ the 90th centile was considered to be a peak in wall stress. The distribution of peaks in wall stress
was assessed using a previously published 22 segment model of the LA (as shown in Figure 1). 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 to 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, 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 trans-mural pressure gradient is complex owing to extra-cardiac structures, changing intra-atrial pressure during the cardiac cycle and changing intra-thoracic 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 mmHg and 20 mmHg trans-mural 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 mmHg simulation, and the mean change in the percentile ranking for each element was assessed when the trans-mural pressure was increased to 20 mmHg.

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. 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**

Since this study was completely novel there was 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 ± standard deviation, 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 which 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 (i.e. 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 to (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’s 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:

a. Fractionated electrograms (a CFAE mean <120ms), 18
b. Low voltage areas suggestive of abnormal conduction (<0.5mV), 7, 10
c. Very low voltage areas suggestive of scar (<0.05mV), 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 to 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 using a paired t-test.

The impact of wall stress on the proportion of CFAE lesions causing AFCL prolongation was assessed in 2 ways. Firstly, wall stress at sites where CFAE ablation prolonged AFCL was compared to wall stress at sites where ablation did not prolong AFCL using the Mann-Whitney U test. Secondly, 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 Table 1. All
patients had persistent AF, and 84% had long lasting persistent AF (i.e. ≥ 1 year). There was a high incidence of structural heart disease and LA were dilated (Table 1). 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 haematoma, 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 inter quartile 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%, and 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’s r = 0.184, p = 0.451). The distribution of peaks 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 8 214 data points were acquired. After removing points >5 mm from the LA shell, there were 6 770 points remaining for analysis, 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 towards 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 remodelling 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 
likely 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 left atrial voltage for each patient the (Pearson’s 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 (Pearson’s 
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 = 0.587).

**ROC analysis**

There was an association between high wall stress and electrical scar: A wall stress value ≥ 39.6 
kPa had a sensitivity of 56.1% and specificity 57.0% for predicting electrical scar (area under 
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 ≥ 35.5 kPa there was a sensitivity and specificity both of 54.0% for predicting low voltage (area under curve 0.550, p < 0.0001; Figure 6B). High wall stress was associated with absence of CFAE (area under 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 co-exist in certain areas but not others, and hence their ‘agreement’ (both phenomena being present or absent) was variable. Since both phenomena were almost always present to some extent in the PVs, the agreement there was high (95-100% in the left PVs, and 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 left atrial 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 to 40.8 (27.9 – 67.0) kPa at sites where AFCL did not change (p = 0.408). Receiver operating characteristic 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 curve 0.530, p = 0.355).
Impact of variations in the model

The simulation was comprised of 57 276 ± 12 646 elements. An increase in the trans-mural pressure gradient from 10 to 20 mmHg caused a mean increase in wall stress of 83.6 ± 7.9% for each element. When elements were ranked based on their wall stress value, an increase in trans-mural pressure from 10 to 20 mmHg 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 3mm at the left atrial appendage and the inter-atrial septum were largely confined to these areas. The median wall stress was reduced from 21.8 ± 4.8 kPa to 16.5 ± 4.3 kPa in the left atrial appendage (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 left atrial appendage at either wall thickness.

When wall thickness at the left atrial appendage and the septum were increased to 3mm, the relationship with electrophysiologic parameters was preserved. The decreasing electrogram amplitude across quartiles of wall stress remained evident (p = 0.009). The trend towards higher CFAE mean at higher wall stress was strengthened but remained non-significant (p = 0.058). ROC analysis showed that high wall stress was still associated with electrical scar (area under curve 0.579, 95% confidence intervals 0.548-0.610, p < 0.0001) and absence of CFAE (area under 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. Following PV isolation, regional LA wall stress did not predict response to CFAE ablation.

Cardiac modeling and wall stress

Increasingly complex ‘multi-scale 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 numerical model predicted wall stress based purely on LA anatomy by assuming the LA to be a linear elastic shell. Since 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).

As this model was entirely novel it has necessarily taken a simplified view of LA biomechanics as the first step towards understanding LA wall stress distribution. Although the accuracy of the geometry is the most important factor in determining wall stress, two other important factors
that are difficult to fully account for are: (i) regional differences in wall thickness (since this is beyond the resolution of current imaging technologies), and (ii) the complexities of regional and temporal variations in the trans-mural pressure gradient, which is influenced by extra-cardiac structures and changes over time with intra-cardiac pressure during the cardiac cycle and intra-thoracic pressure with respiration.

Variations in the model were tested to evaluate the impact of these factors. Although doubling of the trans-mural pressure gradient from 10 to 20 mmHg 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 trans-mural pressure which are relatively uniform (such as those caused by changing intra-atrial pressure and intra-thoracic 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 inter-atrial septum and the left atrial appendage. 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 aetiological factor in the development of AF. Chronic stretch causes LA dilatation, with heterogenous 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.\textsuperscript{2-10}

**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 remodelling in AF.\textsuperscript{30-32} 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.\textsuperscript{31, 32} Furthermore, low voltage may denote zones of slow conduction.\textsuperscript{33} Foci of high wall stress may induce remodelling by directly activating signaling pathways such as cyclic AMP, angiotensin II, and others.\textsuperscript{34} 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.\textsuperscript{7, 35} It is also noteworthy that voltage is lower when assessed in AF compared to sinus rhythm,\textsuperscript{36, 37} and the extent to which areas of low voltage in AF correspond to those in sinus rhythm is uncertain.\textsuperscript{36-38} Other proposed mechanisms by which voltage may be reduced in AF include propagation of wavefronts through partially repolarized tissue, a variable direction of wavefront propagation, and electrical dissociation of myocardial fibres reducing the summation of local potentials.\textsuperscript{36, 37}

**Wall stress and CFAE**

There was a trend towards 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 voltage but is at odds with conventional wisdom.30

Focal remodeling might be expected to contribute to zones of slow conduction, pivot points, or block,42 and resultant micro- or macro-reentry,43 but is less likely to bear any relationship to rotors or rapidly discharging foci which 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 remodelling are actually less likely to support CFAE. One plausible explanation is that stretch and remodelling might lengthen atrial refractoriness3, 4, 8-10 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,\textsuperscript{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, as LA CFAE ablation was always performed following 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 findings\textsuperscript{47} and biophysical properties when direct testing is feasible.\textsuperscript{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.\textsuperscript{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\textsuperscript{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 remodelling 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 as electrograms were recorded in AF it remains uncertain whether this represents focal remodelling. Regional differences in wall stress may explain the heterogenous 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.

**Acknowledgements:** This work was facilitated by Barts and The London NHS Trust NIHR Biomedical Research Unit.

**Funding Sources:** Dr Hunter is supported by a grant from the British Heart Foundation (PG/08/130).
Conflict of Interest Disclosures: Professor Schilling is a member of the scientific advisory board for Biosense Webster and Endocardial Solutions.

References:


**Table 1:** Patient Characteristics. Data is presented as percentage of patients, or mean ± standard deviation.

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Figure Legends:

**Figure 1.** Anatomic divisions of the left atrium. Antero-posterior (FP) and postero-anterior (PA) views of the left atrium showing how it was divided for analysis of wall stress distribution.

**Figure 2.** Left atrial wall stress distribution. Colour coded maps of the left atrium showing wall stress distribution in 3 patients (A-C). The scale is kPa.

**Figure 3.** Distribution of peaks in wall stress and CFAE. The proportion of patients with peaks in wall stress (>90th percentile) and CFAE (CFAE mean < 120 ms) in each region of the left atrium. Abbreviations: PV – pulmonary vein; LAA – left atrial appendages; CS – coronary sinus; H – high; M – middle; L – low.

**Figure 4.** Relationship between electrophysiology and wall stress. Figures show the effect on electrophysiologic parameters (mean and 95% confidence interval) across quartiles for wall stress (1 being lowest and 4 being highest), (4A) shows electrogram voltage amplitude and (4B) shows CFAE mean. Significance was tested using repeated measures ANOVA.

**Figure 5.** Relationship between CFAE and voltage amplitude. Figure shows the effect on CFAE mean (mean and 95% confidence interval) across quartiles of Voltage amplitude (1 being lowest and 4 being highest). Note a higher score reflects a longer cycle length and hence less fractionated electrograms. Significance was tested using repeated measures ANOVA.

**Figure 6.** Relationship between high wall stress and electrophysiologic abnormalities. Receiver operating characteristic curves demonstrating the relationship between high wall stress and electrophysiologic abnormalities: 5A electrical scar (defined as voltage amplitude < 0.05 mV; 5B low voltage (defined as < 0.5 mV), and 5C CFAE (defined as CFAE mean < 120ms). Area under curve and confidence intervals (CI) are shown.
2A. Patient 15
2B. Patient 17
4A. Voltage amplitude across quartiles of wall stress.

\[ p = 0.016 \]
4B. CFAE mean across quartiles of wall stress.

\[ p = 0.256 \]
6A. Wall stress as a predictor of scar.

Area under curve = 0.574
CI 0.547 – 0.601
p < 0.0001
6B. Wall stress as a predictor of low voltage.

Area under curve = 0.550
CI 0.535 – 0.565
p < 0.0001
6C. Wall stress as a predictor CFAE.
Left Atrial Wall Stress Distribution and Its Relationship to Electrophysiologic Remodeling in Persistent Atrial Fibrillation
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Circ Arrhythm Electrophysiol. published online January 31, 2012;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue,
Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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