Catheter ablation of fractionated electrograms for atrial fibrillation: does it improve outcomes and can it be refined based on electrogram morphology or knowledge of the remodelling process?

Ross J Hunter

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Abstract

Catheter ablation complex or fractionated atrial electrograms (CFAE) may improve outcomes for persistent AF. However, it is unclear whether CFAE are important in maintaining AF or whether targeting of CFAE can be refined based on electrogram morphology or knowledge of the remodelling process.

A detailed classification of CFAE was described. Assessment of 100 CFAE by visual inspection in real time correlated well with detailed offline measurement.

Targeting of different CFAE morphologies in 20 patients with persistent AF caused cycle length prolongation only with ablation of certain CFAE morphologies. Therefore, targeting CFAE is not simply atrial de-bulking, certain CFAE morphologies are more important for maintaining AF.

A computer model was established to simulate LA wall stress using a 3D reconstruction of the chamber from CT imaging. Electrophysiologic data was acquired in 19 patients in persistent AF and compared to simulated wall stress data. Peaks in wall stress were associated with areas of low voltage suggestive of focal remodelling. CFAE were not associated with peaks in wall stress or areas of remodelling. Wall stress did not determine whether ablation of CFAE caused cycle length prolongation.

Long term outcome of catheter ablation for AF was good with little late recurrence. Outcome for persistent AF was improved by targeting CFAE in addition to pulmonary vein isolation and may reduce late recurrence.

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Declaration

I declare that I am the author of this thesis. The work contained within it is my own and has not previously been accepted for a higher degree.

Publications

The following publications are a direct result of the studies included in this thesis.

Chapter 3

Original research

1. Hunter RJ, Diab I, Thomas G, Duncan E, Abrams D, Dhinoja M, Sporton S, Earley MJ, Schilling RJ. Validation of a classification system to grade fractionation in atrial fibrillation and correlation with automated detection systems. Europace 2009: 11;1587-1596.

Abstracts & presentations at learned societies

1. Hunter RJ, Earley M, Dhinoja M, Abrams D, Sporton S, Schilling RJ. Validation of a classification system to describe fractionated electrograms in human AF. Journal of Interventional Cardiac Electrohpysiology. 2009: 24; 252-253.

Poster presentation at The European Cardiac Arrhythmia Society.

2. Hunter RJ, Earley MJ, Dhinoja M, Abrams D, Sporton S, Schilling RJ. Validation of a classification system to describe fractionated electrograms in human AF and comparison to automated detection. Heart. 2009: 95; A81-

A82.

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Chapter 4: CFAE

Original research

1. Hunter RJ, Diab I, Richmond L, Tayebjee M, Sporton S, Earley MJ, Schilling RJ. Characterisation of fractionated atrial electrograms critical for maintenance of AF: a randomised controlled trial of ablation strategies (the CFAE AF trial). Circ Arrhythm Electrophysiol. 2011: 6; 622-629.

Abstracts & presentations at learned societies

1. Hunter RJ, Diab I, Sporton S, Earley M, Schilling RJ. Characterisation of fractionated electrograms critical for maintenance of AF: a randomised controlled trial of ablation strategies. Heart Rhythm. 2011: 10; S507.

Oral presentation and Finalist for the Young Investigator Award at The Heart Rhythm Society 2011.

2. Hunter RJ, Diab I, Sporton S, Earley M, Schilling RJ. Characterisation of fractionated electrograms critical for maintenance of AF: a randomised controlled trial of ablation strategies. Europace. 2011: 13; 95.

Oral presentation and Finalist for the Young Investigator Award at Heart Rhythm UK 2011.

3. Hunter RJ, Diab I, Sporton S, Earley M, Schilling RJ. Characterisation of fractionated electrograms critical for maintenance of AF: a randomised controlled trial of ablation strategies. Heart. 2011: 30;105-6.

Poster presentation and <u>best abstract in electrophysiology category</u>, British Cardiac Society 2011.

4. Hunter RJ, Diab I, Sporton S, Earley M, Schilling RJ. Characterisation of fractionated electrograms critical for maintenance of AF: a randomised controlled trial of ablation strategies. PACE. 2011: 9; 12.

Poster presentation and <u>best abstract</u>, World Society of Arrhythmias 2011.

5. Hunter RJ, Diab I, Sporton S, Earley M, Schilling RJ. Characterisation of fractionated electrograms critical for maintenance of AF: a randomised controlled trial of ablation strategies. Journal of Interventional Cardiac Electrohpysiology. 2011: 30;105-6.

Oral presentation at The European Cardiac Arrhythmia Society

6. Hunter RJ, Diab I, Sporton S, Earley M, Schilling RJ. Characterisation of fractionated electrograms critical for maintenance of AF: a randomised controlled trial of ablation strategies. Journal of Interventional Cardiac Electrohpysiology. 2010: 30; 102..

Poster presentation at The European Cardiac Arrhythmia Society

<u>Chapter 5: Wall stress</u>

Original research

1. Hunter RJ, Liu YK, Lu Y, Wang W, Schilling RJ. Left atrial wall stress distribution and its relationship to electrophysiologic abnormalities in patients with persistent atrial fibrillation. Circ Arrhythm Electrophysiol. 2012: 5; 351-60.

Abstracts & presentations at learned societies

1. Hunter RJ, Liu Y, Lu Y, Wang W, Schilling RJ. Left atrial wall stress distribution in patients with AF and the relationship with electrophysiologic abnormalities. Journal of Interventinal Cardiac Electrohpysiology. 2011: 30;167.

Oral presentation at The European Cardiac Arrhythmia Society 2011.

2. Hunter RJ, Liu Y, Lu Y, Wang W, Schilling RJ. Left atrial wall stress distribution in patients with AF and the relationship with electrophysiologic abnormalities. Heart Rhythm. 2010: 7; S414

Poster presentation at Heart Rhythm Society 2010.

3. Hunter RJ, Liu Y, Lu Y, Wang W, Schilling RJ. Left atrial wall stress distribution in patients with AF and the relationship with electrophysiologic abnormalities. Journal of Interventional Cardiac Electrohpysiology. 2010: 31;121.

Poster presentation at The European Cardiac Arrhythmia Society 2010.

Chapter 6: Outcomes

Original research

1. Hunter RJ, Berriman TJ, Diab I, Baker V, Richmond L, Thomas G, Kamdar R, Finlay M, Duncan E, Dhinoja M, Abrams D, Earley MJ, Sporton S, Schilling RJ. Long term efficacy of catheter ablation for AF: impact of additional targeting of fractionated electrograms. Heart. 2010: 96; 1372-8.

Review articles

1. Hunter RJ, Schilling RJ. Long term outcome after catheter ablation for AF: safety, efficacy and impact on prognosis. Heart. 2010: 96; 1259-63.

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Poster presentation at The British Cardiac Society 2010

2. Hunter RJ, Berriman TJ, Diab I, Baker V, Abrams D, Dhinoja M, Earley M, Sporton S, Schilling RJ. Long term efficacy of catheter ablation for AF: Impact of additional targeting of fractionated electrograms. Journal of Interventional Cardiac Electrohpysiology. 2010: 30; 96-97.

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3. Hunter R, Berriman TJ, Thomas G, Richmond L, Baker V, Dhinoja M, Abrams D, Earley MJ, Sporton S, Schilling RJ. Long term efficacy of catheter ablation for AF. European Heart J. 2009: 30; 2450.

Poster presentation at the European Society of Cardiology 2009.

4. Hunter, R.J., Berriman, T. Richmond, L., Kamdar, R., Dhinoj, M., Abrams, D., Earley, M., Sporton, S., Schilling, R. J. Results of long term follow up after catheter ablation of atrial fibrillation. Journal of Interventional Cardiac Electrohpysiology. 2009: 24; 222.

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Chapter 1

Introduction

1.1 Atrial Fibrillation in context

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. The prevalence in adults has varied in large population based studies from 1.5-6.2%,[1] although a large cross sectional study of 18 000 subjects suggested the prevalence in adults was nearer 1%.[2] The prevalence of AF increases with age affecting only 0.1% of those under 55 years of age, increasing to 4% of those aged over 65 years and reaching 17% in those aged over 84 years.[2, 3] The prevalence was slightly higher in men than women,[2] and although these were predominantly Western Caucasian cohorts, data suggests a similar prevalence around the world.[4] The lifetime risk of developing AF at the age of 40 was estimated from the Framingham study at 25%.[5] With the demographic change its prevalence is expected to double over the next twenty five years.[6]

Although the precise aetiology of AF is often unclear, population studies such as the Framingham study have shown that factors such as hypertension, diabetes, cardiac failure, or valvular heart disease are all associated with AF.[7] Other factors found to be associated with AF are obesity, sleep apnoea, chronic obstructive pulmonary disease, thyroid dysfunction, renal disease and ischaemic heart disease.[8, 9]

AF causes a number of symptoms, most commonly palpitations, dyspnoea, fatigue, dizziness and pre-syncope which can be disabling in some cases. The presentation can range from discrete paroxysms of rapid palpitations in paroxysmal AF, to the insidious onset of breathlessness and fatigue in persistent AF, or in some cases may be an incidental finding in an

asymptomatic individual. The natural history of AF is thought to involve increasing frequency of AF paroxysms until AF becomes persistent,[10] although this progression may occur less often in those without conditions promoting AF, so called 'lone AF'.[11] To reflect this progression, and also for practical purposes, AF has been categorised in recent guidelines:[12]

- First diagnosed episode of AF
- Paroxysmal AF - self-terminating and usually lasting < 48 hours, (although up to 7 days is allowed within the definition).
- Persistent AF - when an episode of AF lasts > 7 days or requires cardioversion, either with medication or by direct current cardioversion.
- Long-lasting persistent AF – where persistent AF has been present for ≥ 1 year.
- Permanent AF - when the patient and physician accept persistent AF as permanent.

Although previously viewed as a fairly benign condition, the mortality and morbidity associated with AF is actually substantial. The incidence of stroke in AF is increased up to six fold, giving a crude stroke rate in mixed cohorts of approximately 5% per annum.[7, 13] Even after adjusting for other comorbidities, AF is associated with a 2 fold increase in annual mortality.[7] In one large longitudinal study which followed up 15 000 patients for 20 years, AF was associated with an increased risk of cardiovascular events (death or hospitalization) with a relative risk ratio (RR) of 3.0, fatal or nonfatal stroke (RR 3.2) and heart failure (RR 3.4).[14] The direct cost to the NHS associated with AF doubled in the 5 years from 1995, accounting for 1% of the total NHS budget by

2000. [6] With the demographic change and increasing prevalence of AF this figure is expected to continue rising.

1.2 Management of AF

Although the need for risk stratification and early decisions regarding anticoagulation are universally accepted, these concepts are not related to the subject matter of this thesis and hence are not reviewed here. Other aspects of management such as rate control versus rhythm control, which antiarrhythmic drugs (AADs) to use, the place of cardioversion and catheter ablation are all still controversial. The AFFIRM study and others initially showed no benefit in pursuing a rhythm control strategy over rate control in terms of symptoms or mortality.[15-17] Treatment was predominantly pharmacological however, and was not very successful in maintaining sinus rhythm. At any given time point during the AFFIRM study approximately a third of the rate control group were in sinus rhythm compared to two thirds in the rhythm control group, leading some to conclude this was a test of a treatment strategy rather than comparing the effect of sinus rhythm restoration to continued AF.

Subsequent re-analysis of the AFFIRM study has shown that in those achieving sinus rhythm mortality was halved, although this effect was effectively negated if ongoing antiarrhythmic drug (AAD) therapy was used.[18] As a post-hoc finding this association between sinus rhythm and improved mortality must be interpreted with caution. This relationship has been demonstrated subsequently in some studies,[19, 20] but not others.[21] The potential for AADs to increase mortality has been documented in several high profile trials such as CAST and SWORD,[22, 23] but has also been shown in other cohorts of patients taking AADs

for AF such as in the Stroke Prevention in AF (SPAF) study.[24] The toxicity of AADs combined with their limited efficacy in the treatment of AF may be obscuring any symptomatic or prognostic advantage in pursuing sinus rhythm.

More definitive methods of rate control and rhythm control have evolved utilising catheter ablation techniques. A so called 'pace and ablate' approach involves implantation of a permanent pacemaker followed by catheter ablation of the AV node to cause complete heart block. This is a definitive solution to rate control but is an irreversible palliative manoeuvre. AV node ablation may be particularly useful for patients with difficult rate control despite medication and little hope of achieving or maintaining sinus rhythm. An alternative approach is catheter ablation attempting to restore sinus rhythm which is discussed in the relevant sections that follow.

1.3 Aetiology of atrial fibrillation

Historical perspective

There had been several descriptions of maladies involving an irregular pulse going back some centuries, but the first description of AF accompanied by basic electrical recordings was by Lewis in 1909.[25] There were initially two contrasting theories: Engelmann suggested that each muscle fibre became independently rhythmic, whereas Winterberg and Rothberger thought that a single focus discharging at 50 Hz produced a fibrillatory response in the rest of the atrium.[26] However, with the discovery of the reentry phenomena this rapidly gained favour as the most plausible mechanism to explain AF and evidence continues to mount for this today. The theory that AF is supported by focal drivers has

also accumulated evidence over the years, although it appears that there may be overlap between the focal and reentry theories. A variant of the reentry theory is the ‘wandering wavelet hypothesis’ in which wavefronts randomly meandering around the atria sustain AF. Although this theory in its original form now seems implausible as a sole mechanism for maintenance of AF, it may still contribute and there is arguably overlap between this and current concepts of reentry.

Reentry mechanisms in AF

Around the same time as Lewis described AF, Mayer showed that stimulation of rings cut from jelly fish could initiate a visible wave of contraction revolving around the central hole (Figure 1A).[27] Mines replicated this experiment in atrial and ventricular myocardium cut from animals and hypothesized that this phenomena might explain cardiac tachyarrhythmia.[28, 29] Mines defined the basic requirements for initiation and maintenance of reentry: (i) unidirectional conduction block, (ii) a core of inexcitable tissue around which the wavefront can propagate, (iii) excitable tissue ahead of the wavefront. This last point in particular means that there are theoretical limitations on the size of a reentry circuit. The wavefront and associated zone of refractoriness that follows constitute the wavelength, which will extinguish if it meets it’s refractory tail. Therefore, to maintain an ‘excitable gap’, the anatomical circuit must be longer than the wavelength, which is equal to the conduction velocity multiplied by the refractory period of the tissue:

Wavelength = conduction velocity x refractory period

Figure 1.1: Mechanisms of reentry.

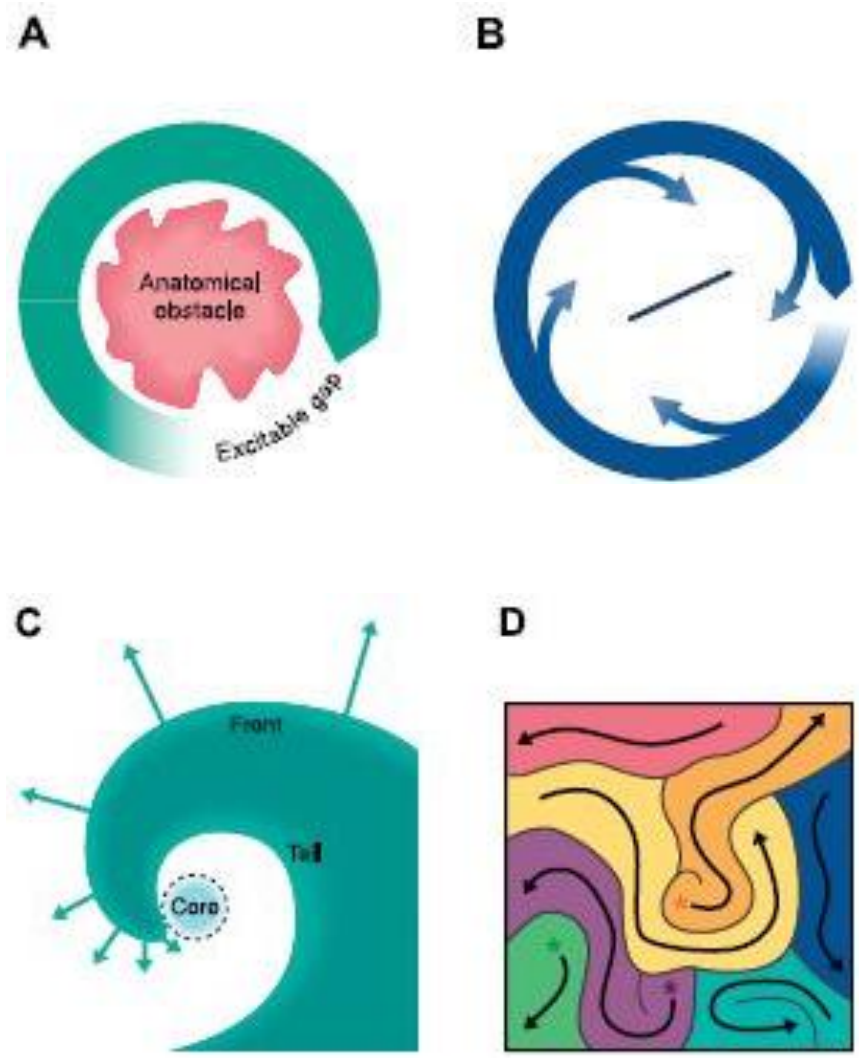


Figure 1.1: A. shows circus movement around an area of anatomical conduction block. B. shows the leading circle reentry hypothesis, with movement around an area of functional block. C. shows a rotor and it's resultant spiral wave. D. shows a chaotic activation pattern due to wandering wavelets. There are lines of block between different wavelets (shown in different colours with arrows to illustrate direction of propagation), with asterisks marking sites at which new wavelets form. (Adapted from Schotten et al, 2011.)[30]

When a reentry circuit occurs in the absence of a central anatomical obstacle, the inexcitable core is due to 'functional block'. This concept was put forward separately by both Lewis and Garrey.[31, 32] However, it was not until the advent of multielectrode cardiac mapping in the 1970s that Allessie was able to confirm this mechanism in rabbit hearts.[33] Allessie went on to show that non-uniform recovery of tissue excitability following extrastimuli might allow unidirectional block and reentry to occur.[34] He put forward the 'leading circle hypothesis', whereby the wavefront moving in the smallest possible circuit allowed by the wavelength is referred to as the leading circle.[35] There is no excitable gap as such ahead of this leading circle, possibly explaining why AF cannot be entrained or pace-terminated. This leading circle activates both the surrounding tissues and the central 'vortex' (Figure 1B). What precisely occurs at this central vortex remains controversial, but Allessie's data suggested that this was in a state of perpetual excitation due to invading centripetal wavelets.

Rotors and spiral waves

The leading circle hypothesis was a significant advance along the original lines of Mines description of reentry, but remained a one dimensional model. The study of wave propagation in other excitable media[36] and subsequent computer modelling of arrhythmia[37] showed that a rotating wavefront in 2 dimensions would assume the form of a spiral wave (Figure 1C). At the centre of the spiral wave is the rotor driving the system. The conduction velocity slows progressively towards the rotor as the curvature of the wavefront increases. This is due to a phenomenon called 'source-sink'. The 'source' of a wavefront is the diffusion gradient generated by excited tissue causing ions to flow towards depolarized downstream cells which act as a 'sink'. When an excited area of

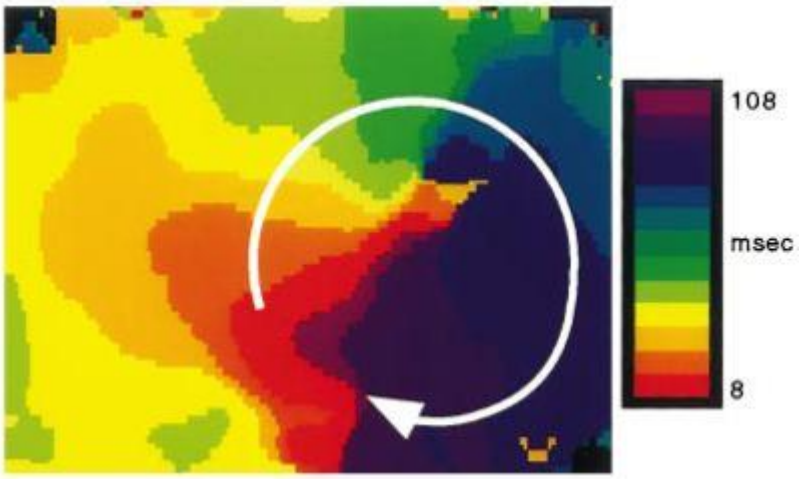
tissue activates a greater volume of tissue through the flow of ions across a convex wavefront, there is a resultant slowing of conduction velocity. This source-sink phenomenon provides an explanation for what may occur at the rotor core, since this places theoretical limits on the curvature of the wavefront at the core meaning that although the core may be excitable it cannot be excited. This core is sometimes called a 'phase singularity', where all phases of the action potential meet: the fully excited tissue at the leading edge of the advancing wavefront, the refractory tissue at the trailing edge of the recovery front and the non-excited tissue at the core.[38] These electrotonic effects reduce conduction velocity and action potential duration, resulting in a very short wavelength which helps to stabilise the rotor.[38, 39] The initiating event for the formation of a rotor is thought to involve the perpendicular collision of a wavefront with the tail of a preceding wave.[38]

With the advent of high resolution mapping techniques rotors and spiral waves have been demonstrated in isolated cardiac tissues.[40, 41] The Jalife/Berenfeld group have published extensively on their optical mapping studies in a Langendorff-perfused ovine model of acetycholine induced AF.[42-46] They were able to demonstrate sustained rotors in AF, most notably on the posterior wall left atrium (LA), but also on the anterior wall of the left atrial appendage (Figure 1.2A). These rotors could be either stationary or meandering, and could be free standing or anchored to structures such as the pulmonary veins.[45] These rotors had an area of only 3.8 ± 2.8 mm^2.[45] Although this experimental evidence appeared convincing, there was concern that rotors had not yet been demonstrated in human AF. However, recent studies using non-contact mapping or basket catheters in the LA have demonstrated rotors in humans

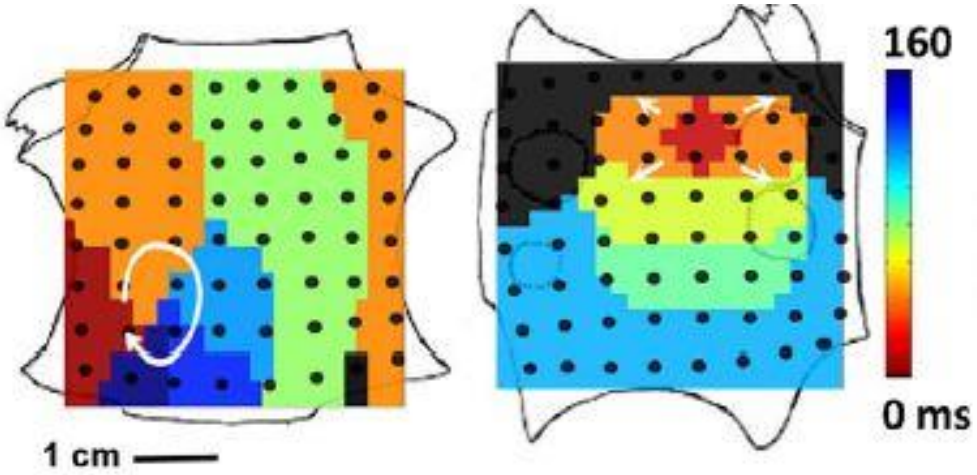
(Figure 1.2B).[47, 48] A recent trial used basket catheters to map and target rotors and other focal drivers in addition to pulmonary vein isolation (PVI), and showed improved outcomes compared to PVI alone.[49] These studies therefore provide strong support for the role of rotors in maintaining AF.

Figure 1.2: Isochronal maps demonstrating rotors in AF.

A



B



Legend to Figure 1.2: A. Optical mapping of a rotor on the posterior wall in a sheep model of AF (adapted from Skanes et al, 1998).[42] B. Mapping of drivers in AF using a basket catheter, figure on the left shows a rotor, figure on the right shows a radial discharge from a focal driver (adapted from Narayan et al, 2012).[49]

A further layer of complexity to this model may be introduced by considering cardiac activation in 3 dimensions. The equivalent of a spiral wave occurring in 3 dimensions is a ‘scroll wave’, which is essentially a continuous stack of spiral waves. The complexities of mapping cardiac tissue in 3 dimensions means that speculation on how this may be relevant to arrhythmias comes mostly from computer modelling.[50] Although the concept of arrhythmias occurring in 3 dimensions may be more relevant to ventricular arrhythmia than atrial arrhythmia due to the thin atrial wall, the wall of the atria are complex with layering of muscle fibres and thicker pectinate muscles endocardialy.

Derakhchan et al showed that during right atrial pacing activation was faster endocardialy than epicardialy and utilised anatomic structures such as the crista terminalis and pectinate muscles endocardialy to create preferential conduction pathways.[51] This disparity was more apparent at rapid pacing rates and during induced tachycardia. Allessie showed that endocardial breakthrough from epicardial sources was common in AF, particularly at the posterior wall where there is complex layering of fibres at the junctions with the pulmonary veins (PVs).[52] Although these tended not to be localised or repetitive, reentry within the LA wall due to edocardial-epicardial dissociation was demonstrated.[52]

The multiple wavelet hypothesis

In 1959 Moe proposed the multiple wavelet hypothesis.[53] He suggested that a single wavefront could be split by islands of refractoriness to produce a number of wavelets which randomly wander the atria, extinguishing as they encounter refractoriness or anatomical block, but also dividing to produce new daughter wavelets. Maintenance of AF was therefore thought to be probabilistic, with AF

only terminating if all wavelets extinguished simultaneously. Moe subsequently produced computer modelling data to support this theory.[54] This incorporated (although modified) the concept of reentry and allowed for block occurring and extinguishing of wavelets intermittently, but made no provision for the possibility of reentry at fixed locations or focal drivers.

Years later Allessie et al produced mapping data that seemed to support Moe's theory. AF was induced in Langendorff perfused canine hearts by rapid atrial pacing in the presence of acetylcholine and atrial activation patterns were mapped by placing a specially designed 'egg' in each atrium with simultaneous recording of 192 endocardial electrograms.[55] This appeared to show multiple random reentry circuits as Moe predicted. Allessie proposed that 4-6 independent wavelets were needed to sustain AF – many fewer than the 15-30 initially suggested by Moe.

Further support for Moe's hypothesis came from mapping studies performed at the time of cardiac surgery in Humans. Konings et al performed high density epicardial mapping of the right atrium after inducing AF in patients undergoing surgical correction of Wolff-Parkinson-White syndrome.[56] Varying degrees of complexity of wavefront propagation were observed (which they graded from type I to III), ranging from single broad wavefronts unimpeded by any conduction delay to complex activation patterns with multiple wavelets and lines of functional block evident. They described both random reentry analogous to Moe's multiple wavelets hypothesis and leading circle reentry, but in keeping with Moe's predictions did not observe fixed reentry circuits or focal drivers.

Cox et al performed a similar mapping study in patients with paroxysmal AF undergoing surgical correction of Wolff-Parkinson-White syndrome, and also in a canine model of AF.[57] In both scenarios areas of non-uniform conduction and block were demonstrated. They again found multiple discrete meandering wavefronts, although also observed macro-reentry. No focal drivers or areas suggestive of rotors were observed.

Moe's hypothesis had been particularly popular because it unites and explains several observations. It predicted that the stability of AF would depend on the surface area of atrial tissue available and the wavelength. The progression from paroxysmal AF to persistent AF is most common in those with structural heart disease and is associated with LA dilatation.[11] Furthermore, refractory periods of atrial myocardium are reduced by episodes of tachyarrhythmia or AF which reduces wavelength and seems to stabilize AF as Moe predicted.[58] Furthermore, the excellent long term results achieved with the Cox-maze procedure (which involves creating lines of scar using a 'cut and sew' technique to compartmentalize the atria, so limiting the contiguous tissue area available for fibrillation) provide support to reentry circuits of some description playing a role in the maintenance of AF.[59]

Areas consistent with random wavelet reentry have been described in other recent mapping studies, but usually in addition to rotors or focal drivers with a radial activation pattern.[42-49] It is therefore difficult to be sure to what extent they contribute to the maintenance of AF and whether they may in fact be bystander. Furthermore, difficulty demonstrating rotors or other focal drivers in certain

studies is not necessarily strong evidence that they are absent. The relevance and importance of wandering wavelets in AF therefore remains uncertain.

Focal mechanisms in AF

In 1949 Scherf et al induced AF in canine hearts by injecting the atrial appendage with acontine (which triggers neurally mediated acetylcholine release) to produce 'auricular fibrillation'.[60] Cooling of the appendage led to termination of AF, although when the appendage rewarmed AF restarted. They proposed that not only were the fibrillating atria driven by the appendage, but that circus movement reentry could not be responsible because this would have been terminated by the cooling. They concluded that this was strong evidence that AF was both initiated and then also maintained by a focal driver.

Perhaps the strongest evidence that AF may depend on focal mechanisms is the observation that AF is often initiated by ectopy arising from the PVs. Haissaguerre et al mapped the sources of ectopy initiating AF in 45 patients with AF and found that the vast majority (94%) arose from the PVs.[61] Chen et al published very similar findings around the same time.[62] These groups both found that elimination of these sources by catheter ablation could eliminate paroxysms of AF. This removal of PV triggers for AF is the rationale behind PV isolation for PAF. However, it is less clear whether such focal mechanisms are as important for sustaining AF.

PVI during persistent AF usually prolongs AF cycle length, suggesting removal of some drivers.[63] However, termination of AF occurs in only a small proportion

of patients at this stage suggesting that drivers elsewhere may also be important. [63, 64]

Schuessler et al showed that in a canine model of acetylcholine induced AF there were initially multiple re-entrant circuits after induction, but that these condensed into a single stable rapid reentry circuit with a cycle length of 39-48 ms, with fibrillatory conduction to the rest of the atria.[65] Several subsequent studies using combinations of optical mapping and high density electroanatomic mapping have suggested stable high frequency drivers in AF due to rotors or focal discharging in the atria. [42-46] More recently studies using non-contact mapping or basket catheters in the LA have demonstrated rotors in human AF.[47, 48] Targeting these LA foci terminated AF in 85% of patients and improved outcome compared to PVI alone.[49] Therefore, although the PVs may be very important to the initiation of AF, other LA drivers may be at least as important for the subsequent maintenance of AF.

The pulmonary veins

The proximal PVs are enshrouded in sleeves of muscular tissue extending from the LA to approximately the first division of the PVs. The orientation of layered muscle fibres surrounding the PVs are far more complex than elsewhere in the atria.[66] The electrophysiologic properties also differ to that of atrial myocardium. Decremental conduction has been demonstrated within the sleeves.[67] The action potential duration and refractory period of the muscular sleeves is shorter than that of the atrial myocardium and actually decreases progressively moving from the atrium towards the more distal PV. [62, 67-69] There is also a slower phase 0 upstroke velocity than in atrial tissue.[68] Cells in the myocardial sleeves also

have an ultrastructure more akin to that of the sinus node than that of atrial cardiomyocytes.[70]

Triggered activity, automaticity and reentry have all been suggested as potential mechanisms by which the PVs might act as triggers.[62, 71-74] High density mapping of AF in dogs showed drivers which appeared to be truly focal, emanating from the proximal PVs towards the atrium and distal PV.[74] Studies of individual PV sleeve cardio-myocytes from canine and rabbit models of AF have shown that cells exhibit more rapid intrinsic depolarisations and were more prone to early and delayed afterdepolarisations than LA tissue.[71, 75]

Clinical studies have shown areas of conduction block within the PVs.[62] Multielectrode mapping of the PVs has suggested this may correlate anatomically with segmentation of the pulmonary sleeves or abrupt changes in myocardial fibre orientation.[76, 77] Optical mapping of canine PVs has demonstrated complete reentry circuits occurring within them measuring only 1-2 cm.[69, 73] Similarly, Kalifa et al used optical mapping in their ovine model of AF to show that rotors could be anchored to the PV-LA junction.[78] Ouyang et al showed that after PVI in patients with AF spontaneous PV tachycardias could be reliably and reproducibly entrained and terminated by pacing within the isolated vein.[79] These data on balance suggest that much of the 'focal' discharging from the PV may in fact be due to reentry of some description.

Other atrial sites of special importance in maintaining AF

Several sites in the atria commonly exhibit focal activity and contribute towards atrial tachycardias. In the right atrium the crista terminalis, tricuspid annulus,

ostium of the coronary sinus, right atrial appendage, the perinodal region and right sided septum are common foci for atrial tachycardias.[80-83] In the LA, foci are commonly found at the ostium of the PVs, mitral annulus, LA appendage and left sided septum.[83-87] Although the most common sites for AF initiation is the PVs, other thoracic venous structures have also been implicated such as the superior vena cava, coronary sinus and ligament of Marshall.[83, 88, 89]

The posterior wall has been shown in several studies to have the highest dominant frequencies and the most rapid cycle lengths in AF.[90-93] Embryologically the primitive PV fuses to the LA forming the smooth posterior wall. The muscular fibres connecting the muscular sleeves of the PVs to the posterior wall form a diffuse complex junction with overlapping fibres in differing orientations.[66] Remodelling and fibrosis in the LA seems to preferentially affect the posterior wall and may further exacerbate conduction heterogeneity and anisotropy.[94-98] Optical mapping studies demonstrating rotors have found them predominantly on the posterior wall. [42-46] Mapping studies in humans have also shown a consistent vertical line of functional block running through the posterior wall.[94, 99] This line of block may protect rotors or wavelets from other circulating wavefronts, whilst still allowing wavelets to escape through it.[99]

1.4 Atrial remodelling

Electrical remodelling in AF

It is recognised that AF is often progressive, with episodes becoming more frequent and lasting longer until AF becomes persistent. The Allessie group

investigated the impact of AF on electrophysiologic properties of the atrial myocardium in goats.[58] After only a few days in AF the cycle length had shortened significantly with a corresponding reduction in refractory periods. AF was easier to induce and episodes lasted longer. These changes clearly promote AF and the authors coined the phrase 'AF begets AF'. Morillo et al observed a similar phenomenon in a canine model of pacing induced AF.[90] After 6 weeks in AF there was a comparable reduction in atrial refractory periods. There also appears to be greater spatial heterogeneity in refractory periods which may further facilitate reentry and AF.[100, 101] Similar findings have been reported in humans with AF.[102, 103]

The mechanism of this shortening of refractory periods appears to be down regulation of the L-type calcium channel, which reduces the calcium current (I_{CaL}) that usually maintains and lengthens the plateau (phase 2) of the cardiac action potential.[104, 105] This electrical remodelling may be a compensatory mechanism to prevent cellular calcium overload during tachycardia.[104, 105] There are also changes to various other membrane potassium currents, such as reduction in the transient outward current (I_{to}) and the G protein–coupled inward rectifying K+ current ($I_{K,Ach}$), although the importance of these changes are less clear.[30, 105, 106] These changes may be protective in the short term, but overall are maladaptive in the long term as they facilitate reentry and hence AF.

In addition to changes in the action potential duration and refractory periods, it has been demonstrated that action potential duration alternans may be a marker for vulnerability to AF. Narayan et al examined the propensity for action potential duration alternans in control patients in sinus rhythm, patients with

paroxysmal AF, and those with persistent AF.[107] They found that action potential duration alternans occurred only at very fast pacing rates in control patients (> 230 bpm) but occurred at rates as low as 100-120 bpm in patients with persistent AF. During rapid pacing action potential duration alternans gave way to complex oscillations in action potential duration immediately before onset of AF. This likely predisposes to dispersion of refractoriness and wave break precipitating AF. It is uncertain why this action potential duration alternans might occur but it is likely a result of abnormalities of calcium handling due to calcium overload, and is probably part of the electrical remodelling in AF.[108-111]

After termination of AF the reduced action potential duration and refractory period reverses within only a few days.[58, 112] However, in a separate study using a similar goat model, AF was induced for 3 consecutive periods of 4 weeks, each separated by 6 days of sinus rhythm to allow refractory periods to normalise.[113] They found that after each episode of AF it became easier to induce AF and induced episodes lasted longer. This suggested that there must be a more gradual and sustained component of remodelling, or possibly a 'second factor' to explain this ongoing and increasing propensity to AF.

Gaspo et al examined the effect of prolonged pacing induced AF on canine atrial electrical properties.[101] Although changes in refractory periods peaked at 7 days, there was a gradual slowing of conduction velocity that continued after this. A similar reduction in atrial conduction velocity has also been demonstrated in humans with AF.[102, 114] This may be due in part to electrical remodelling as a reduction in the inward sodium current (I_{Na}) which causes deoplarisation (phase 0) has been demonstrated.[115] However, alterations in the

intercellular channels between the myocytes has also been implicated in this conduction slowing. Connexin proteins form ion channels at gap junctions between myocytes, and are found predominantly at intercalated disks. In a goat model of chronic AF, the levels of Connexin 40 (the predominant subtype in goats and humans) were reduced and the distribution was no longer concentrated at the intercalated disks.[116] This reduced expression and altered distribution became more marked with time. Kanagaratnam et al showed that in humans, the complexity of circulating wavefronts in AF was inversely proportional to the Connexin 40 content.[117]

The reduction in both refractory period and conduction velocity as a result of AF cause a marked reduction in wavelength which is critical to facilitating reentry. The action potential duration alternans that results from abnormalities of calcium homeostasis causes dispersion of refractoriness and predisposes to wave break which may initiate reentry. However, there is also evidence of structural remodelling resulting from AF, the so called ‘second factor’ by which AF begets AF.

Structural remodelling in AF

The progressive macroscopic LA dilatation that occurs in AF is well established in both animal models and humans.[90, 118] It has been assumed that this LA dilatation is mechanistically important since it appears to be pro-arrhythmic. There is a strong relationship between LA size and the propensity to develop AF. In the Framingham study a 5mm increase in LA size was associated with a 39% increased risk for the development of AF.[119] In patients with AF an enlarged LA also predicts recurrence of AF after direct current cardioversion or

catheter ablation.[120, 121] However, Morillo et al were the first to describe atrial ultrastructural changes in a canine model of pacing induced AF.[90]

Both human and animal studies have suggested a multitude of changes to atrial architecture in AF:[90, 122-124]

- Atrial fibrosis,
- Myocyte hypertrophy,
- central loss of sarcomeres (myolysis),
- changes in quantity and localization of structural cellular proteins,
- fragmentation of sarcoplasmic reticulum,
- perinuclear accumulation of glycogen,
- homogeneous distribution of nuclear chromatin,
- widening of the undifferentiated portions of the intercalated discs
- aggregation of lysosomes
- glycogen accumulation
- Increased mitochondrial size and altered shape
- Cellular dedifferentiation towards a more immature phenotype (comparable to fetal cardiomyocytes)

Although there are clearly several ultrastructural changes that occur as part of structural remodelling, perhaps the most apparent is fibrosis. This occurs due to proliferation of fibroblasts and fibrin deposition in the extracellular matrix. Fibrous tissue can accumulate within myocyte bundles between cells (endomysial fibrous tissue) or between bundles (perimysial fibrous tissue). These can develop into large collagenous septa between muscle fibres. In some contexts with more marked atrial dilatation such as occurs in heart failure,

larger areas of fibrosis are occur which are more similar to ‘replacement fibrosis’ secondary to tissue damage and cell death.[125]

These changes lead to slowing of conduction velocity. The fibrosis and formation of collagenous septa between muscle bundles can cause uncoupling of parallel muscle fibres, causing impulse propagation in the direction perpendicular to muscle fibres to flow in a zigzag fashion, further slowing conduction and causing anisotropy.[126, 127] Fibroblasts are no longer thought to act solely as passive insulators and by electrically coupling with myocytes may affect electrophysiology on a cellular level and an organ level.[96, 128] Computer modelling data suggests that fibroblasts may act as a current sink, causing failure of the myocyte to depolarise and conduction block.[128] Fibroblast-myocyte coupling may also cause elevation of myocyte resting potential, causing slowing of sodium channel recovery which extends post-repolarisation refractoriness. This prolongation of refractoriness is a common consequence of fibrosis, and although it might not be expected to be pro-arrhythmic, it’s heterogenous nature can facilitate reentry. Atrial fibrosis in itself is proarrhythmic and may be sufficient to increase AF vulnerability, as occurs in mice with over expression of TGF-ß1 causing selective atrial fibrosis.[129] The totality of changes that occur as part of structural remodelling promote reentry and further facilitate what Allessie described as the ‘domestication of AF’.[123]

Mechanically induced remodelling of the atria

Conditions causing increased atrial stretch were found to underlie AF in the majority of patients in the Framingham study,[13] and is a consistent aetiological factor in the development of AF.[13, 130-136] Conditions such as valvular heart

disease, heart failure and hypertension all cause chronic atrial stretch leading to LA dilatation, with heterogenous changes in atrial architecture very comparable to those occurring in AF, such as myocyte hypertrophy and fibrosis.[125, 134, 137-140]

Electrophysiologic effects of chronic atrial stretch have been demonstrated in a variety of animal models and clinical scenarios. There is some heterogeneity in the results of these studies, and they are reviewed in Table 1.1. On balance these studies suggest reduced voltage throughout and discrete areas of electrical scar, reduced conduction velocity with conduction heterogeneity, anisotropy and areas of block, complex fractionated atrial electrograms (CFAE) and double potentials, and greater inducibility of AF.[94, 125, 131-136, 139, 140] Interestingly, atrial stretch does not seem to shorten refractory periods as occurs in AF, but in most of these studies the effective refractory period was actually increased. This may owe to the effects of fibroblast myocyte coupling.[128] Although there appears to be a great deal of common ground in these remodelling processes, the shortening of action potential duration and refractory periods appears to be unique to tachyarrhythmias such as AF and may be a compensatory mechanism to prevent calcium overload due to tachycardia.[104, 105] It is noteworthy that the remodelling in AF and particularly in response to chronic mechanical stretch appears to be heterogenous with focal areas of scarring, the reasons for which remain unclear.

Table 1.1: Mechanically induced atrial remodelling.

Author	Model or scenario	Remodelling compared to control group
Li[125]	Canine model of heart failure due to rapid ventricular pacing compared to rapid atrial pacing (with complete heart block and ventricular pacing) and controls.	Heart failure compared to control: • No change in CV overall but discrete areas of slowing • No change in ERP • Extensive fibrosis compared with controls and the rapid atrial pacing group. • Increased duration of induced AF with heart failure and rapid atrial pacing compared to control. Rapid atrial pacing compared to heart failure and controls: • Reduced conduction velocity • Reduced effective refractory period
Kistler[140]	Ovine model of hypertension compared to controls	• Reduced CV • No change in ERP • Reduced wavelength overall • Myocyte hypertrophy, myolysis, fibrosis, focal scarring
Verheule[139]	Canine model of mitral regurgitation compared to control	• No change in CV, • Increased ERP • Sustained AF inducible • Areas of fibrosis and chronic inflammation.
John[133]	Patients with mitral stenosis compared to controls	• Reduced CV and zones of slow CV • Lower atrial voltage and focal electrical scar • Increased ERP • Greater inducibility of AF
Sanders[134]	Heart failure versus control patient	• Decreased CV with regional CV slowing • Areas of low voltage and electrical scar • Increased ERP • A greater number of CFAE and double potentials • AF more sustained once induced.
Roberts-Thomson[136]	Atrial septal defect versus control patient	• Regional slowing of CV • Reduced atrial voltage and areas of electrical scar • Unchanged or prolonged ERP • Greater number of CFAE and double potentials • AF more easily inducible.
Roberts-Thomson[94]	Mitral regurgitation with AF, Mitral regurgitation without AF, and control patients.	Mitral regurgitation groups compared to control: • Zones of slow CV and block • Conduction heterogeneity and anisotropy • Focal scarring ERP increased in mitral regurgitation group without AF compared to both controls and the group with mitral regurgitation and AF, which had the shortest ERP of all.
Sparks[131]	Patients with loss of AV synchrony due to complete heart block versus controls	• Decreased CV • Increased ERP but not uniformly • Lengthening of cSNRT • Restoring AV synchrony normalised, ERP, CV, cSNRTs,

Legend to Table 1.1: Impact of various animal models and clinical conditions on atrial remodelling. ERP, effective refractory period; CV, conduction velocity; cSNRT, corrected sinus node recovery time.

Mechanisms of atrial remodelling

Fibrosis is linked to the release of matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinase (TIMPs) which are secreted from fibroblasts, smooth muscle cells, endothelial cells, and myocytes. Several studies have shown changes to these cellular signalling pathways and others involved in the regulation of interstitial matrix composition and cell-to-cell / cell-to-matrix connections. AF has been associated with down regulation of TIMP-2, up-regulation of MMP-2, MMP-9 and MMP-15, A disintegrin and metalloproteinase-10 (ADAM-10) and ADAM-15, and upregulation of mitogen activated protein kinases (MAPKs).[141-144] These pathways may be activated by neurohumoural factors, but may also be activated directly by mechanical stretch. Mechanical stretch of atrial myocytes has been shown to cause upregulation of MMP-2 and MMP-9, and hence mechanical stretch may be able to directly stimulate release of these cytokines to cause fibrosis.[144, 145]

The renin-angiotensin-aldosterone system (RAAS) may also impact on atrial remodelling in AF.[146, 147] Angiotensin II receptors in cardiac tissue activate MAPKs and stimulate TGF- ß1 production which stimulates fibroblasts and promotes interstitial fibrosis.[148-151] In addition to the systemic effects of angiotensin II, mechanical stress can directly activate type 1 angiotensin II receptors by inducing a conformational change in the protein.[152, 153]

Increased oxidative stress may also contribute to atrial remodelling and is thought to be due to increased NADPH oxidase and xanthine oxidase activity and dysfunctional NO synthase leading to increased production of

superoxide.[154, 155] In addition to systemic factors impacting on oxidative stress, local stretch may also increase superoxide anion production.[156] Therefore mechanical stretch may bring about remodelling through local oxidative stress.

Inflammation may also be important in the atrial remodelling process. Serum levels of inflammatory markers are increased in patients with AF,[157] and human atrial biopsies from patients with AF have shown inflammatory infiltrates and accumulation of myeloperoxidase (MPO), a heme enzyme produced by neutrophils.[124, 158]

There are therefore several mechanisms by which AF and mechanical stretch might cause remodelling. Further work is needed to define the role of these processes relative to each other and explore the potential of 'upstream therapies' that might interrupt the atrial remodelling process.

1.5 Catheter ablation of AF

Since the description of PVI as a successful treatment for AF almost 15 years ago,[61] there has been an exponential increase in the number of catheter ablation procedures performed worldwide.[159] Catheter ablation of AF has evolved since its inception with increasing success rates and decreasing complication rates along the way.[159, 160] Several recent randomised controlled trials have demonstrated the superiority of catheter ablation over medical treatment for AF in terms of maintenance of sinus rhythm and improved symptoms.[161-166] Catheter ablation is now a recognised treatment for patients

with symptoms refractory to drug treatment, or for those intolerant of drug treatment.[12] However, there remains scope for refinement in the procedure and room for improvement in success rates, particularly for persistent AF. There is also still a paucity of long term follow up data to examine outcomes years down the line, leaving questions about the real efficacy of catheter ablation in this context.

Safety of catheter ablation for AF

The World Wide survey on catheter ablation of AF by Cappato et al saw the first large scale reporting of outcome data (albeit voluntary and self reported).[159] A wide variety of techniques were practiced initially, with variable safety and efficacy.[159] Major complications were reported in 6% of patients.[159] Published case series from leading single centres typically report lower rates of major complications in the region of 2-3%.[167-174] These consist mostly of stroke/TIA or tamponade. PV stenosis was initially reported after around 1% of cases but has become much rarer now most groups target ablation at a distance from the ostia to encircle the PVs in pairs (wide area circumferential ablation).[159] Although a serious and often fatal complication, atrio-oesophageal fistula is very rare.[159]

Death following catheter ablation of AF is rare. As few centres have sufficiently large registries and as reporting of results is voluntary, the true mortality is difficult to determine. Expanding on his work with the world wide survey, Cappato has produced an analysis of procedural mortality.[175] Of 45 115 procedures, there were 13 intra-operative deaths (0.02%), the 30 day mortality

was 25 (0.06%), and including all late deaths potentially related to the procedure this rose to 32 (0.07%). This was reported in the study as a mortality of 0.098% per patient, as some patients underwent more than one procedure. Stroke, tamponade and atrio-oesophageal fistula accounted for more than half of these deaths. Other large registries have reported similar mortalities of approximately 0.07-0.2%.[159, 160, 170, 174] Table 1.2 shows the most important complications of catheter ablation for AF as reported in the World Wide surveys and 2 large registries examining this issue. Notably, many patients in these registries also underwent more than one procedure, meaning that the complication rate on a per patient basis may actually be higher than that reported on a per procedure basis.

Efficacy of catheter ablation

Catheter ablation of AF is a relatively new procedure and the long term outcome is therefore only recently being examined. The first world wide survey conducted by Cappato reported registry data from 100 centres between 1995 and 2002 for a mixed cohort of 8745 patients with paroxysmal and persistent AF.[159] Freedom from AF or other atrial tachyarrhythmias (AT) was reported in 52% off AADs, rising to 76% after re-introduction of previously ineffective AAD therapy at almost 1 year. However, techniques have evolved significantly in a short space of time.

Table 1.2: Procedural complications from catheter ablation of AF.

	World Wide Survey I[159]	World Wide Survey II[160]	Bhargava[174]	Dagres[170]
No. procedures	11 762	20 825	1691	1000
TIA or stroke	0.6%	0.7%	0.3%	0.4%
Tamponade	0.9%	1.0%	0.3%	1.3%
Symptomatic PV stenosis	0.4%	0.23%	1.1%	0.1%
Atrio-oesophageal fistula	0%	0.03%	0%	0.2%
Peri-procedural death	0.05%	0.12%	0.06%	0.2%
Total major complications	4.5%	3.6%	2.7%	3.9%

Legend to Table 1.2: Procedural complications of catheter ablation for AF expressed as a percentage per procedure. Major complications are those that are deemed serious, those that have lasting sequelae, or that delay discharge.

Early catheter based techniques tried to replicate the surgical maze procedure with very limited success.[176] Targeting of initiating PV foci was not reported until 1998,[61] and only in 2000 was it realised that all PVs must be targeted to avoid later emergence of ectopy not apparent at the index procedure.[177] High rates of PV stenosis with ostial isolation prompted lesion placement in the LA 1-2cm

outside the vein ostia, forming continuous rings of scar around them (usually with the use of 3D mapping systems).[178] It remains controversial as to whether isolation of the PVs at their ostia or at a distance in pairs is more effective, and data from randomised controlled trials are conflicting.[179, 180] Many groups have used the technically challenging procedural end-point of PV electrical isolation, although firm evidence of incremental benefit from randomised trials has been lacking until recently.[181]

The worldwide survey reflected this progression in techniques, with the most common technique being right atrial maze from 1995-1997, targeting of PV foci from 1998-1999, and PVI from 2000 onwards. The second 'updated' worldwide survey reported registry data from 85 centres for 16 309 patients undergoing catheter ablation of AF from 2003-2008.[160] Freedom from AF had risen to 70% without the need for AADs (80% including those still taking AADs) at 18 months. The proportion of patients with persistent AF and long-lasting persistent AF (i.e. continuous for > 1 year) had also risen markedly. Techniques almost always incorporated PVI for this cohort.

Studies now typically report long term freedom from AF or atrial tachycardias (AT) in 70-90% of patients without the need for AADs, with a small number of studies reporting data up to 7 years.[167-174, 182-184] Table 1.3 summarizes studies reporting greater than 2 years of follow-up for greater than 100 patients. It is an important caveat that many patients require more than one procedure to maintain freedom from AF, particularly for persistent AF, with studies typically reporting a mean of 1.2-2.0 procedures per patient over the long term.[167-174, 182-184]

Since the number of long term follow-up studies remain small, it is still uncertain whether sinus rhythm will be maintained long-term post ablation, or whether catheter ablation is a palliative procedure delaying the inevitable. The small amount of long term data available suggests that most recurrences of AF/AT occur within a year of the procedure. The AF free survival curve appears to flatten between 2-3 years, with approximately 3% per year recurring after this.[167, 169, 172, 174, 182]

However, long term follow-up data often reports success following the last procedure, meaning patients with late recurrence who undergo successful repeat procedures are counted as successes. This may distort perception of success and patterns of recurrence. Some studies with particularly aggressive follow-up have reported rates of late recurrence (occurring ≥ 1 year post ablation) as high as 7-10% per annum.[185, 186] It may therefore be that the harder one looks for asymptomatic paroxysmal arrhythmia, the more one will find. The importance of asymptomatic arrhythmia is uncertain: currently catheter ablation is recommended solely for the alleviation of symptoms, but were it proven as a treatment to reduce rates of stroke or obviate the need for anticoagulation then this may become more important.

Table 1.3: Studies reporting long-term efficacy of catheter ablation for AF.

Authors	Year	Patients	Follow-up (yrs)	PAF (%)	AF free off drugs (%)
Tilz[187]	2012	202	4.7	0	33
Bhargava[174]	2009	1404	4.7	52	88
Wokhlu[185]	2010	774	3.0	55	66
Pappone[169]	2003	589	2.5	69	79
Lee[172]	2004	207	2.5	100	72*
Nademanee[167]	2008	635	2.3	28	81
Miyazaki[188]	2011	574	2.3	79	84
Zado[173]	2008	781	2.2	64	64
Oral[183]	2006	755	2.1	65	71
Cheema[168]	2006	200	2.1	46	41

Legend to Table 1.3: This table summarizes studies reporting follow-up for greater than 2 years following catheter ablation of AF for more than 200 patients. The percentage success rate quoted is after repeated procedures. Note, other publications by the Natale group (first author Bhargava) met this criteria but presumably included the same patients. Therefore the Bhargava paper was included as it was the largest. Note also that published studies resulting from this thesis are excluded (see publications section). * indicates studies where it was not specified how many patients were still taking antiarrhythmic drugs, otherwise the success rate excludes those taking AADs.

Reporting of Success

Success can be difficult to gauge for the reader, as it is reported differently in different studies. Guidelines now suggest trials use frequent monitoring to look for asymptomatic AF, and that use of AADs or the capture of greater than 30 seconds of any atrial tachyarrhythmia (regardless of symptoms) are regarded as failure.[189] This level of monitoring can be difficult to achieve outside clinical trials, and such harsh definitions of success may be seen as artificial and arbitrary. A patient with a short run of asymptomatic AF may well regard their procedure as a success and decline a repeat procedure. In the world of coronary intervention looking for asymptomatic ischaemia, with this or the use of anti-anginal medication counting as failure might be seen as excessive.

Hence, real world registry data typically involves less monitoring of asymptomatic patients, recognizing that further monitoring of asymptomatic patients may reveal an increment in recurrent AF. Nademanee's group report monitoring patients only if they have recurrent symptoms,[167] and although Pappone's group have reported monitoring patients, they defined failure as symptomatic recurrence lasting longer than 10 minutes on ambulatory monitoring and confirmed on an ECG.[169] The reader is then left with the difficult task of comparing results between studies reporting different techniques. Therefore, although these harsh definitions of success form an essential bench mark for comparing trials using different techniques or technologies, they may under represent the benefit some patients derive.

Predictors of success

Not all patients stand equal chances of success following catheter ablation of AF. Factors identified on multivariate analysis as predictors of recurrent arrhythmia (although none uniformly in all studies) include persistent AF, time spent in persistent AF, structural heart disease, left ventricular impairment, hypertension, female gender, and increasing left atrial diameter.[171, 174, 182, 185] Interestingly, there appears not to be an effect of age or ischaemic heart disease, and the impact of structural heart disease and left ventricular impairment appears small. Perhaps the most consistently identified factors predisposing to recurrent arrhythmia are persistent AF and left atrial dilatation. These suggest more advanced structural and electrical remodelling. Given the differing results between studies and the short follow-up in many, further clarification on predictors of long term success/failure is highly desirable to aid patient selection and clinical decision making. Further understanding of the remodelling process and how best to modify the atrial substrate may also clarify how best to treat these patients at risk of recurrent arrhythmia.

Catheter ablation of persistent AF

PVI alone is successful for 70-90% of patients with paroxysmal AF (PAF).[179, 190] This now forms the cornerstone of catheter ablation for AF and is recommended in current guidelines.[189] However, PVI alone maintains sinus rhythm in only 10-30% of patients with persistent AF.[179, 190, 191] Efforts to improve outcomes, particularly for persistent AF, has led to investigation of alternative and adjunctive targets for ablation such as ganglionic plexi,[192] CFAE,[167, 191] linear lesions,[171] isolation of the posterior wall between the PVs,[191, 193] or extensive modification of the posterior and inferior wall.[174] Catheter ablation of persistent

AF now usually involves a hybrid strategy incorporating PVI with further targeting of CFAE and/or linear ablation.[171]

However, there is currently no real consensus as to what constitutes a CFAE, or on how CFAE should be targeted. It remains uncertain what different CFAE morphologies represent, and hence it is unclear exactly what is being targeted. Furthermore, there is precious little long term follow up data for patients who have undergone CFAE ablation, and there remains concern as to whether the resultant atrial scarring may be proarrhythmic over the long term.

1.6 Complex fractionated atrial electrograms in atrial fibrillation

Several mapping studies have described CFAE and alluded to their potential importance in arrhythmia. Nademanee was the first to describe targeting of CFAE as a stand alone approach for catheter ablation of AF in 2004.[194] He targeted CFAE in 121 patients and reported freedom from arrhythmia in 110 (91%) at 1 year. This technique opened the door to a completely novel method of catheter ablation for AF. There has been a great deal of research in subsequent years attempting to answer several key questions:

- What do CFAE represent and why they are important in AF?
- Can CFAE ablation be refined to target only areas important in maintaining AF?
- What is the impact of CFAE ablation in patients with paroxysmal or persistent AF?

- Should CFAE ablation be performed alone, or in combination with PVI or linear lesions?

This section reviews the literature in this area and the current understanding with regard to these key questions.

What are CFAE?

CFAE were first described in the context of ventricular myocardium. In a canine model of ventricular scarring following myocardial infarction, Gardner et al showed that infracted areas were associated with complex or fractionated electrograms, and that this was associated with zones of slow and anisotropic conduction.[195-197] Histological analysis showed that muscle fibres were poorly connected due to fibrosis and formation of collagenous septa, suggesting that electrogram fractionation was due to asynchronous activation of muscle fibres.[127, 197] The uncoupling of parallel muscle fibres means that impulse propagation in the direction perpendicular to muscle fibres can occur in a zigzag fashion, further increasing electrogram complexity.[126, 127] The multiple deflections making up complex or fractionated electrogram may therefore be due to slow conduction along muscle bundles, with partial longitudinal dissociation between parallel fibres leading to asynchronous activation and anisotropy. The asynchronous activation of fibres leads to reduced summation of electrograms, which together with reduced myofibrillar content of tissues reduces electrogram amplitude in these areas.

It is a reasonable supposition that such areas of fibrosis may explain CFAE in AF, but several recent studies have cast doubt on this by suggesting that CFAE

are not dependent on areas of low voltage, and in fact are associated with regions of higher voltage.[198-203] Furthermore, areas supporting CFAE in AF do not necessarily have abnormal or fractionated electrograms in sinus rhythm.[199] This therefore suggests that some CFAE at least must be due to functional abnormalities rather than structural pathology.

Berenfeld et al, examined right atrial conduction in isolated sheep hearts at increasing pacing rates.[204] This showed normal conduction at low pacing rates, but with progressive delay in impulses reaching distal branching sites of the crista terminalis and pectinate muscles at pacing rates between 2-6 Hz. At pacing rates above 6.5 Hz they saw non-uniform intermittent functional block. They described this as the 'breakdown frequency', above which the direction of impulse propagation became completely variable from beat to beat: a state they described as fibrillatory conduction. Increasing electrogram fractionation was also observed at higher pacing rates, with widespread CFAE during fibrillation. This suggests that during rapid stimulation of normal tissue, non-uniform conduction delay interrupts 1:1 conduction around the atria, precipitating fibrillatory conduction.

Computer modelling data suggests that electrogram fractionation may occur as wavefronts enter or exit zones of slow conduction, whether anatomical or functional, and that tissue anisotropy means that the distribution and morphology of CFAE may vary according to the seemingly random direction of impulse propagation in AF.[205, 206] In keeping with this basic explanation of CFAE, mapping studies in AF have suggested that CFAE may be markers of more complex emergent phenomena.

CFAE and rotors

Kalifa et al, examined the impact of rotors on the posterior wall of the LA on electrogram morphology, and in particular the spatial relationship between rotors and CFAE.[207] Using methodology similar to their previous work investigating rotors,[42, 45] rapid pacing of isolated sheep hearts in the presence of acetylcholine was used to induce AF, with simultaneous optical mapping of wavefront propagation and recording of electrograms from the posterior wall. This showed rapid high frequency areas suggestive of rotors with organised electrograms at these sites, with the most fractionated areas occurring approximately 3 mm away forming a band between rotors and nearby low frequency areas. CFAE may therefore occur at the borders of rapid drivers such as rotors, where impulse propagation to surrounding tissues fails to conduct in 1:1 fashion. The same group later used similar techniques to show that meandering of the rotor could reduce the regularity of electrogram deflections, and increase electrogram fractionation.[208]

Despite evidence that rotors may exist from computer models and mapping in animal models, there has been difficulty demonstrating them in human AF. Sequential mapping may not capture a small meandering rotor. Similarly, non-contact mapping of low amplitude signals in AF is problematic and makes this sort of phenomena difficult to detect. Nevertheless, there are recent reports describing rotors in human AF using non-contact mapping,[47] or contact mapping with basket catheters.[48] Furthermore, a recent single centre trial suggested that mapping and targeting of rotors using these techniques may improve outcome when performed as an adjunct to PVI.[49]

Ganglionated plexi and CFAE

A possible mechanism underlying drivers in AF, whether they be rapidly discharging foci or rotors, is autonomic innervation through ganglionated plexi.[209] Although sympathetic innervation of the heart is more widely spread, parasympathetic innervation occurs through epicardial ganglionated plexi which are located in fat pads mostly around the pulmonary veins. Parasympathetic discharge can cause PV discharge to initiate AF.[210] Furthermore stimulation through ganglionated plexi causes a reduction in the effective refractory period which promotes reentry and hence facilitates ongoing fibrillation.[209] Hence, targeting of ganglionated plexi may reduce recurrence of AF when performed in addition to PVI.[211]

Application of acetylcholine to canine atria induces rapid firing and CFAE in a dose dependent fashion.[212] In this model peaks in dominant frequency and CFAE occurred at sites of ganglionated plexi, with a gradient of reducing dominant frequency and decreasing prevalence of CFAE moving further away from the ganglionated plexi.[213] Subsequent ablation of ganglionated plexi slowed rapid electrograms, abolished gradients in dominant frequency, regularised CFAE, and often terminated AF.[212, 213] Therefore, ganglionated plexi innervation may explain the importance of the PVs in AF, and may be a mechanism underlying rapid drivers which sustain AF and the CFAE associated with them.

Mapping studies in AF

Konings *et al* induced AF in patients with Wolff-Parkinson-White undergoing cardiac surgery and performed high density mapping of the right atrial free

wall.[214] It was found that CFAE occurred at areas of slow conduction and pivot points where wave fronts turn and split to allow reentry to occur. This was arguably the first mapping study to attach mechanistic significance to CFAE in AF, and raised the possibility that they could be targeted by catheter ablation.

Other investigators have examined CFAE using non-contact mapping and have found that CFAE can occur due to various passive phenomena such as wave front collision, wave break against electrically inert structures or wave fusion (all of which reduce the number of circulating wavefronts).[47, 215] However, these studies have also shown that CFAE can occur at active sites which sustain AF, such as rotors, rapidly discharging foci, areas of functional block which allow pivot points, and areas of wave division. [47, 215] However, there are conflicting data as to whether CFAE occur at predominantly active[47] or passive[215] sites.

Rostock et al performed high density mapping of CFAE sites in AF using multipolar catheters.[216] As with many studies they found that CFAE were transient. Local AF cycle length shortened progressively until electrograms appeared fractionated, then cycle length increased again until electrograms were no longer fractionated. This could suggest 2 things: it could suggest increasing fractionation as a passive response to increasingly rapid stimulation, or possibly that local effective refractory period reduces until reentry can be supported, at which point rotors or microreentry circuits initiate. Analysis of activation patterns suggests that the majority of CFAE occurred due to passive activation (86%). However, of the remaining 14% approximately half were due to bursts of activity from rapidly discharging foci, and half showed a ‘gradient of activation’ suggesting local reentry, possibly a rotor. This study therefore

suggests that a minority of CFAE sites do perform active roles in supporting AF. Clearly the sensitivity and specificity of CFAE as markers for these phenomena will depend on exactly how they are defined, but in this study at least, CFAE were not specific markers for active phenomena.

Narayan et al, used a duodecapolar pentarray catheter (Biosense-Webster, Diamond Bar, CA, USA) to map CFAE whilst simultaneously recording monophasic action potentials (MAPs) in the same area to define local depolarisation and repolarisation.[217] They found that only 8% of CFAE had continuous activity on bipolar electrograms with discrete rapid MAPs. These areas had higher dominant frequencies and a high organisation index, suggesting they may be drivers. Using the multipolar catheter it was possible to map activation in some cases which demonstrated localised reentry or possibly rotors. This would be consistent with the continuous electrical activity observed at sites of rotors in experimental models.[207, 208] Mapping studies in humans with AF have suggested similar localised reentry circuits at the sites of continuous electrical activity.[216] This might suggest that CFAE with continuous electrical activity are more mechanistically important than other CFAE. However, the fact that this pattern was observed in only 8% of CFAE mapped in this study is consistent with findings of other studies.[216]

Narayan et al also observed local shortening of AFCL before the appearance of CFAE at a further 8% of sites. This was also associated with rapid regular MAPs. This phenomenon was also described by Rostock et al.[216] It remains unclear whether the CFAE that occur after a decrease in AFCL represent a breakdown into fibrillatory conduction, or are perhaps due to more

mechanistically important pnenomena such as bursts of rapid firing, perhaps due to intermittent ganglionated plexi innervation.

However, as with the Rostock study, the majority of CFAE did not appear to be mechanistically important: 67% of CFAE were associated with discrete MAPs with superimposed signals suggestive of far-field electrograms, and for 17% discrete MAPs could not be recorded at all perhaps suggesting fibrillatory conduction. This raises the possibility that targeting CFAE for AF may in fact be targeting bystander phenomena the majority of the time. Given that the bipolar electrogram showed continuous electrical activity at these sites, this suggests that it may be possible to refine targeting of CFAE based on electrogram morphology.

Using a multi-electrode array to perform high density mapping of the posterior left atrium in surgical patients with AF, Lee et al demonstrated that CFAE were prevalent on the posterior wall, and that electrograms with continuous electrical activity usually occurred < 5mm from peaks in dominant frequency. This echos the work of Kalifa et al, demonstrating the proximity of CFAE to high frequency drivers in the posterior left atrium of sheep.[207] Furthermore, this again draws attention to CFAE with continuous electrical activity as a potential marker of drivers in AF.

Atienz et al mapped the posterior LA in 24 patients after inducing AF by rapidly pacing the PVs.[218] They again found that AF cycle length often shortened prior to the onset of CFAE, then slowed after resolution of CFAE. They used computer modelling to simulate the movement of wave fronts and proposed a

novel mechanism for this phenomena: that rotors meandering in the direction of these points might increase the frequency of wave fronts through the Doppler effect. This is supported by other modelling data from the same group showing meandering of rotors.[208]

Clinical impact of CFAE ablation for AF

In Nademanee's original description of CFAE ablation,[194] 121 patients with AF were included (64 with persistent AF). Although the PVs were not routinely isolated, 58 patients (91%) with persistent AF were ablated to sinus rhythm. It is widely quoted that 110 (91%) patients were free from arrhythmia at 1 year. However, 29 required repeat procedures (giving a mean of 1.2 procedures per patient), and 7 of those who were arrhythmia free after the first procedure were still taking antiarrhythmic drugs. This therefore gives a single procedure freedom from atrial arrhythmia off antiarrhythmic drugs of 74/121 (61%), which is possibly more in keeping with other studies. Examining specifically those with persistent AF, 40 of 64 patients (63%) were free of arrhythmia and off antiarrhythmic drugs after a single procedure at 1 year. This rises to 49 (77%) after 2 procedures and 56 (88%) counting those still taking antiarrhythmic drugs. This technique opened a promising new paradigm in catheter ablation of AF. However, although subsequent reports from Nademanee's group appeared to confirm the success of this technique,[167] others have been unable to replicate these results with CFAE ablation alone.[64, 219] Table 1.4 summarizes the randomised and other controlled studies investigating the efficacy of CFAE ablation.

Table 1.4: Randomised trials or controlled studies investigating the efficacy of CFAE ablation for AF.

	Study Design	Follow-up	Cohort	Result
Verma 2007[220]	Matched comparison	1 yr	Paroxysmal (120) & persistent AF (80)	PVI 80% PVI & CFAE 85% (p = 0.054) In persistent only: PVI 72% PVI & CFAE 82%, (p < 0.047)
Verma 2008[221]	Matched comparison	1.1 ± 0.3 yr	Paroxysmal (42) and persistent (28) AF	PVI 71% PVI & CFAE 83% (p = 0.045) [CFAE ablation prolonged AFCL]
Verma 2010[222]	RCT	1 yr	High burden PAF (65) & persistent AF (35)	PVI 29% CFAE 48% PVI + CFAE 74% (p = 0.004)
Di Biase 2009[223]	RCT	1 yr	PAF only (103)	PVI 89% CFAE 23% PVI & CFAE 91% (CFAE alone versus other groups p < 0.001; PVI versus both NS)
Deisenhofer 2009[224]	RCT	1.6 ± 0.7 years	PAF only (98)	PVI 74% PVI & CFAE 83% (p = 0.08)*
Lin 2009[225]	Controlled trial	1.6 ± 0.9 years	Persistent AF (60)	PVI & linear lesions 40% PVI & linear lesions & CFAE 70% (p = 0.013) [AF termination predicted freedom from AF]
Oral 2009[64]	RCT	0.8 ± 0.2 years	Long-lasting persistent AF only (119 included, 100 in AF after PVI randomised)	PVI 36% PVI & CFAE 34% (p = NS) [79% of those who terminated to SR during PVI remained in SR]
Elayi2008[191]	RCT	1.3 years	Long-lasting persistent AF only (144)	PVI (not confirming isolation) 11%, PVI (confirming isolation) and posterior wall isolated 40%, PVI (confirming isolation) and posterior wall isolated & CFAE 61% (p < 0.01)

Legend to Table 1.4: Randomised or otherwise controlled studies investigating the efficacy of CFAE ablation for AF.

CFAE ablation as a standalone strategy

Oral et al, performed CFAE ablation alone in 100 patients with persistent AF.[219] Only 33% remained in sinus rhythm after a single procedure at 14 ± 7 months. 44 patients underwent a repeat procedure and all had evidence of pulmonary vein tachycardia. After a mean of 1.4 procedures, 57% were in sinus rhythm off antiarrhythmic drugs at 13 ± 7 months. These results suggested a fairly poor efficacy of CFAE ablation alone for AF, but it was not until recently that 2 studies compared these strategies formally through randomised controlled trials.[222, 223]

Verma et al,[222] randomised 100 patients with high-burden paroxysmal AF (>4 episodes of AF each lasting >6 hours, in the last 6 months) or persistent AF to 1 of 3 strategies: CFAE ablation, PVI, or both. At 1 year the single procedure success rate was 74% for the PVI and CFAE group compared to 48% in the PVI group and 29% in the CFAE group (p = 0.004). There were significantly more repeat procedures in the CFAE arm (47%) versus PVI (31%) or PVI and CFAE (15%) (p = 0.01). After two procedures, the PVI and CFAE group still had the highest success (88%) compared with PVI (68%) or CFAE (38%) (p = 0.001).

Di Biase et al, [223] performed a similar trial in which 103 patients with PAF were randomised to CFAE ablation alone, PVI, or both. After a single procedure 89% remained free from arrhythmia and off antiarrhythmic drugs at 1 year after PVI,

compared to 23% in the CFAE group, and 91% in the group receiving both (CFAE alone versus other groups $p < 0.001$; PVI versus both not significant).

With the exception of Nademanee's data, these studies suggest that CFAE ablation as a standalone strategy has little clinical efficacy. The data by Oral et al regarding the high prevalence of PV tachycardias at repeat procedures suggest that the PVs remain an important target. [219] Indeed, recurrence of AF after PVI is usually associated with PV reconnection.[226] The study by Verma et al, [222] suggests that CFAE ablation when performed in addition to PVI may be beneficial for patients with persistent AF or PAF with a high AF burden. However, the Di Biase data suggests that CFAE ablation adds little to PVI in an unselected group of patients with PAF. [223] Other studies over a similar time frame have focused on the role of CFAE ablation as an adjunct to PVI.

CFAE ablation as an adjunct to PVI

Oral et al performed pulmonary vein isolation in 119 patients with long lasting persistent AF and randomised the 100 that did not revert to sinus rhythm after PVI to either DC cardioversion or CFAE ablation for up to 2 hours.[64] They were able to terminate AF during CFAE ablation in 9 of 50 patients (18%). After a single procedure sinus rhythm was maintained in 36% of those who were cardioverted after PVI and 34% of those who received additional CFAE ablation at 10 ± 3 months. Interestingly, sinus rhythm was maintained in 79% of those who terminated during PVI (and hence were not randomised), suggesting that termination of AF is associated with subsequent freedom from arrhythmia. After 1.3 procedures, sinus rhythm was maintained in 79% of those who terminated during PVI, 68% in those who were cardioverted after PVI, and 60% of those

who had additional CFAE ablation at 9 ± 4 months. However, at repeat procedures the PVs were reisolated and additional CFAE ablation was performed at the discretion of the operator, regardless of the patient's initial treatment allocation. Therefore the impact of CFAE ablation after repeat procedures is difficult to determine in this study. Notably, at the repeat procedure all patients had PV reconnection in ≥ 1 PV, again suggesting that the PVs are important.

Elayi et al,[191] randomised 144 patients with long standing persistent AF to 1 of 3 groups: anatomical PVI (without confirming electrical isolation), PV antrum isolation (meaning confirmed PVI and isolation of the posterior wall between the PVs), or PV antrum isolation and CFAE ablation. Freedom from arrhythmia was achieved in 11% of patients in the anatomical PVI group, 40% of the PV antrum isolation group, and 61% of the PV antrum isolation and CFAE ablation group.

The studies by Oral and Elayi appear contradictory.[64, 191] Both enrolled patients with long lasting persistent AF (mostly of 5-7 years duration) and applied seemingly similar treatments. In the study by Elayi et al, [191] CFAE were targeted before PVI in the LA, RA and coronary sinus until elimination of all CFAE. However, in the study by Oral,[64] CFAE were targeted for up to 2 hours after PVI. Although it is difficult to be certain, this gives the impression that CFAE may have been targeted rather more extensively and thoroughly in the Elayi study, which may explain the results. Another difficulty interpreting CFAE ablation studies is that although both papers describe CFAE in a similar way, it is difficult to be certain that both groups were targeting the same electrogram morphologies.

Deisenhoffer et al, [224] randomised 98 patients with PAF to CFAE ablation or not after PVI. Attempts were made to induce AF in both groups after PVI, with CFAE ablation preformed only in those patients in whom AF could be induced. There was no difference in the proportion of patients maintaining sinus rhythm in the 2 groups (74% versus 83%; p = 0.08). However, looking only at those with inducible AF, sinus rhythm was maintained in a greater proportion of those who received CFAE ablation (89%) compared to those who had no additional ablation (73%; p = 0.003). Although this study appeared not to support CFAE ablation after PVI when a standard 'intention to treat' analysis was applied, it therefore suggested that CFAE ablation may be beneficial in patients whom AF can be induced after PVI. This could be seen as complementing the data from the Di Biase and Verma studies, suggesting that CFAE ablation after PVI is not beneficial in all PAF patients, but may benefit those patients with a high AF burden.

Patients selection & procedural end-points for CFAE ablation

Therefore, the majority of studies suggest that CFAE ablation may improve outcomes when performed in addition to PVI for patients with persistent AF. It is less clear whether this is the case for patients with PAF, although it appears that patients with a high burden of PAF or inducibility of AF after PVI may benefit from CFAE ablation as an adjunct to PVI. It is uncertain why these patients may benefit from CFAE ablation, but it is conceivable that PAF patients with a high AF burden or AF inducible after PVI may have more remodelled atria and may therefore benefit from some form of substrate modification. This is supported by the observation that although extensive LA scarring is

associated with recurrent arrhythmia after ablation, CFAE ablation appears to negate the impact of this remodelling process to some extent.[191]

Non-inducibility after PVI has been suggested as an end point for PAF ablation by others, perhaps helping to select those that require further ablation in whatever form.[63, 227] Haissaguerre et al randomised 70 patients with long episodes of PAF to PVI alone, or PVI plus a mitral isthmus line.[63] At 7 months they found that sinus rhythm was maintained in a similar proportion of those with additional mitral isthmus ablation (83%) compared to PVI alone (74%; difference not significant). However, they also found that non-inducibility of atrial arrhythmia at the end of the procedure predicted subsequent maintenance of sinus rhythm, with recurrent arrhythmia in 13% of those with no inducible arrhythmia compared to 38% of those who remained inducible ($p = 0.03$). Similarly, Oral et al performed PVI and then a posterior line between the PVs and a mitral isthmus line in 100 patients. 60 patients had inducible AF and were randomised to either no further ablation, or further ablation of CFAE and/or linear ablation.[227] At 6 months 86% of those who had additional CFAE ablation ± linear ablation were free from AF, compared to 67% of those randomised to no further ablation ($p < 0.05$). However, when one considers both recurrent AF and AT there was no difference between groups (65% versus 60%; p = NS). Therefore, if ongoing AF or inducibility of AF after PVI identifies patients that may benefit from CFAE ablation, non-inducibility of AF may be a reasonable end point for PAF. However, evidence for such an aggressive approach is limited to these studies and hence this is not widely practised.

There is similar debate regarding end points for CFAE ablation in persistent AF. Data from the Oral study above suggested that outcome was better in their cohort of patients with persistent AF in those whom AF terminated after PVI compared to those who remained in AF requiring either further ablation or DC cardioversion.[64] The Bordeaux group also published outcome data for 153 patients with persistent AF who underwent catheter ablation of AF using a standardised stepwise approach (PVI, followed by CFAE ablation, followed by linear lesions) with termination of AF as the procedural end point (achieved in 85%).[171] They found that termination of AF during ablation was associated with less recurrent AF after a single procedure, although there was no difference in the rate of patients with recurrent atrial arrhythmia suggesting that patients simply had recurrent AT rather than AF. At 30 ± 11 months after an average of 1.5 procedures, 95% of patients in whom AF terminated remained in sinus rhythm compared to only 52% in whom AF could not be terminated by ablation. Therefore, although termination of AF during ablation meant that patients were more likely to re-present with AT than AF (with a similar overall arrhythmia recurrence rate), ultimately these recurrent arrhythmias were more successfully eliminated and patients were more likely to remain in sinus rhythm in the long term. Factors predicting failure to terminate AF during ablation were longer time in AF, greater LA diameter and shorter LA cycle length, perhaps suggesting greater structural and electrophysiologic remodelling.

In contrast to these results, Elayi et al examined the impact of AF termination during ablation on outcome in 306 patients with persistent AF following a similar stepwise approach (PVI followed by CFAE ablation, but no linear lesions routinely).[184] Termination of AF was achieved during ablation in a smaller

proportion (58%). In patients whom AF terminated during ablation a greater proportion of recurrences were due to AT rather than AF, but with a similar recurrence rate overall (68 % versus 70% at 25 ±7 months; difference not significant) as with the Bordeaux data. However, after a second procedure there was still no difference in the success rate (82% versus 83%; difference not significant). Furthermore, successful ablation of macro-reentrant AT did not predict freedom from AT subsequently, although successful ablation of focal AT did predict freedom from further AT.

The reason for this discrepancy remains unclear. Although all agree that termination of AF predicts mode of arrhythmia recurrence (i.e. AT rather than AF), it does not seem to predict the overall rate of recurrent arrhythmia after a single procedure and may or may not affect final outcome. The Bordeaux group argue that the extensive ablation terminating AF is important mechanistically as it eliminates the ability of the atria to fibrillate, leaving only AT which are potentially easier to deal with. Elayi and co-authors argue that striving for AF termination appears unnecessary and that the extensive ablation taken to achieve this may scar and resultant zones of slow conduction which may ultimately be pro-arrhythmic. Opinion therefore remains divided as to whether termination of AF is necessarily an important clinical end-point. The end points for CFAE ablation also remain unclear, with some groups striving for either termination of AF or abolition of all CFAE, whilst others target CFAE more selectively or for only a limited period of time. Clarification of which CFAE are important in maintaining AF may help determine the optimal end point for CFAE ablation.

1.7 Conclusion and formulation of the current studies

AF is a common problem and is associated with substantial morbidity and mortality. Catheter ablation appears to be an effective treatment for AF, but there remains a paucity of extended follow-up data and hence long term outcome remains uncertain. Although high success rates are reported for catheter ablation of paroxysmal AF, results for persistent AF are not as good. This is likely a reflection of the atrial remodelling process that occurs in AF and due to conditions which cause AF in the first place by causing mechanical stretch of the atria.

The role of adjunctive targets beyond PVI remains unclear. It seems that for persistent AF in particular, the atrial remodelling process may mandate further atrial ablation in some form to achieve acceptable outcomes. [191, 228] There is currently some enthusiasm for CFAE ablation as a way of targeting the abnormal atrial substrate in AF. However, it remains unclear how the atrial remodelling process relates to CFAE, and whether CFAE in areas of remodelling might perhaps be more important in maintaining AF. Furthermore, it is unclear whether CFAE really represent drivers of AF, are markers for unhealthy tissue with slow conduction, or are simply passive phenomena of no mechanistic importance in AF (such as wavefront collision). There is disagreement as to what constitutes CFAE and great variation in how CFAE are targeted.[171, 194, 222] In fact, there is currently precious little evidence for targeting any particular location or electrogram morphology during CFAE ablation. This has led some sceptics to conclude that the termination of AF that sometimes occurs during CFAE ablation may simply be due to de-bulking of atrial tissue.

Moreover, although there is some trial data suggesting that CFAE ablation may be beneficial over the short term, there is uncertainty as to whether the creation of wide spread atrial scar using this approach may be pro-arrhythmic over the long term. The studies in this thesis aimed to clarify some of these key issues in CFAE ablation.

Perhaps the most fundamental question in CFAE ablation is whether CFAE are important in maintaining AF, and if they are, what electrogram morphology constitutes an important CFAE and hence ought to be targeted? The hypothesis was therefore formulated that certain CFAE morphologies are of greater importance in the maintenance of AF. If this hypothesis were proved, then it would also prove that CFAE ablation is not simply atrial de-bulking, and provide useful evidence as to what CFAE morphologies ought to be targeted in the clinical setting.

In order to test this hypothesis CFAE first had to be defined more precisely than has been done previously and classified based on morphology. This classification had to be simple enough to be accurately applied by eye in real time, but detailed enough to reproducibly cover all electrogram morphologies. In Chapter 3 of this thesis a classification of CFAE was formulated and its application validated.

This enabled the response to ablation of different CFAE morphologies to be assessed. In Chapter 4, patients undergoing catheter ablation of persistent AF had CFAE classified using this novel classification system and then targeted for ablation according to a strict protocol as part of a randomised trial. The acute

response to ablation of these CFAE morphologies was assessed by monitoring AF cycle length.

To explore the relationship between CFAE and the electrophysiologic remodelling that occurs in AF, a computer model was developed in collaboration with a team of biomedical engineers to simulate wall stress based on left atrial contour and geometry (Chapter 5). Using this model it was possible to test the hypothesis that peaks in LA wall stress are associated with focal electrophysiologic remodelling which maintains AF. The first part of Chapter 5 was therefore to establish a computer model for simulation of wall stress. Secondly, electrophysiologic data were collected during persistent AF and compared to simulated wall stress data from a patient specific LA geometry derived from pre-procedure CT imaging. This allowed assessment of any relationship between LA wall stress, atrial remodelling (as evidence by areas of low voltage or electrical scar), and CFAE. Thirdly, since patients were in persistent AF, it was possible to test the relative importance of peaks in wall stress by examining the response to ablation in these locations. This was assessed by monitoring AF cycle length during CFAE ablation, to see if peaks in wall stress or areas or focal remodelling predicted the response to ablation. It was therefore possible to assess whether the wall stress simulation might be of use in guiding CFAE ablation, potentially offering further refinement of this process beyond the morphological approach being investigated in Chapter 4.

To address these hypotheses it was necessary to study the immediate response to ablation of CFAE in AF. However, important questions remain as to the clinical efficacy of catheter ablation for AF in general, and for CFAE ablation

in particular. There is a paucity of long term follow-up data following catheter ablation of AF with reported success rates varying widely between groups. Some groups report a large difference in results for paroxysmal and persistent AF underscoring a need for further ablation targets beyond PVI, whereas others do not.[174, 182] For CFAE ablation, randomised trials have typically reported results at approximately 1 year. [64, 191, 220-225] This may not reflect truly long term outcome and there is concern that the widespread scar caused by CFAE ablation might be pro-arrhythmic over the long term. To address these issues, it was hypothesised firstly that once sinus rhythm is successfully restored, late recurrence occurring more than a year later is uncommon. Secondly, it was hypothesised that long term freedom from AF is achieved in a significantly lower proportion of patients following catheter ablation of persistent AF than for patients with paroxysmal AF. Thirdly, it was hypothesised that targeting of CFAE in addition to PVI increases the long term freedom from atrial arrhythmia in patients with persistent AF.

To test these hypotheses, a prospective registry of patients undergoing catheter ablation of AF at St Bartholomew's Hospital was analysed and all patients followed up to review their rhythm status (Chapter 6 of this thesis). This enabled analysis of long term outcome and whether results were really significantly worse for persistent AF. Patients at St Bartholomew's have undergone a consistent procedure for persistent AF for several years, including PVI and linear lesions at the roof and mitral isthmus from 2002-2007. The impact of targeting CFAE from 2005 onwards was evaluated in this cohort with an otherwise consistent lesion set, allowing an assessment of how this impacted on long term maintenance of sinus rhythm.

Through the studies comprising this thesis it was therefore hoped that several key issues in CFAE ablation could be clarified. In particular, are CFAE important in maintaining AF? If so, which electrogram morphologies are important to target? How does stretch in the walls of the atria impact on focal remodelling, and is this relevant to CFAE? If CFAE are related to focal remodelling, can predicting sites of remodelling be used to target the most important CFAE? Lastly, what is the impact of CFAE ablation as it has conventionally been performed on long term outcome?

Chapter 2

Materials & Methods

Although the main results chapters all involve catheter ablation of AF, the precise methodology varies for each chapter. Therefore a broad description of the patient selection, personnel, equipment, techniques employed, peri-procedural management and follow-up for catheter ablation of AF at St Bartholomew's Hospital is provided below, followed by a precise methodology specific to each of the results chapters with detail as where practice differed from routine care.

2.1 Study institution and personnel

All recruitment, procedures, data collection and follow-up were conducted at St Bartholomew's Hospital, which is part of Barts Health NHS Trust. This thesis is comprised of several different studies which required different levels of approval:

- Chapter 3 involved retrospective analysis of electrograms initially, then viewing of electrograms during live cases. This did not require an ethics application.
- Chapter 4 involved detailed mapping studies followed by randomisation to different ablation protocols so as to study the response to ablation of different CFAE morphologies in AF. The study protocol was reviewed by the Trust Cardiac Peer Review Committee and was then approved by East London and The City Research Ethics Committee, UK (reference number 09/H0703/6). The study was financially indemnified by the Trust Research and Development department.

- Chapter 5 involved computer modelling based on patient imaging and correlation with mapping data. These studies were included as part of the same ethics application as the studies in Chapter 4.
- Chapter 6 involved collecting data from an existing prospective registry of all patients undergoing catheter ablation of AF at St Bartholomew's Hospital. Follow-up data were acquired by seeing patients in clinic or calling patients by telephone. These data were acquired as audit and service development and did not require an ethics application.

All studies were conceived and designed by the author and the supervisor Professor Richard Schilling who was the principal investigator for the ethics application and subsequent studies constituting chapters 4 and 5. Co-investigators were Dr Simon Sporton and Dr Mark Earley. Chapter 5 involved developing a computer model to simulate left atrial wall stress based on contour and geometry from CT. This model was produced in collaboration with a team of biomedical engineers from the School of Engineering and Materials Science, Queen Mary's University of London. This team included Professor Wen Wang, Dr Yiling Lu, and Dr Yankai Liu. For a detailed list of contributors and their roles see the Acknowledgements section.

2.1 Patients

All patients were recruited for catheter ablation of AF at the Cardiology Department of St Bartholomew's Hospital, a tertiary referral centre serving predominantly the North East Thames and Essex Regions but also taking quaternary referrals from around the country. Patients with AF were offered

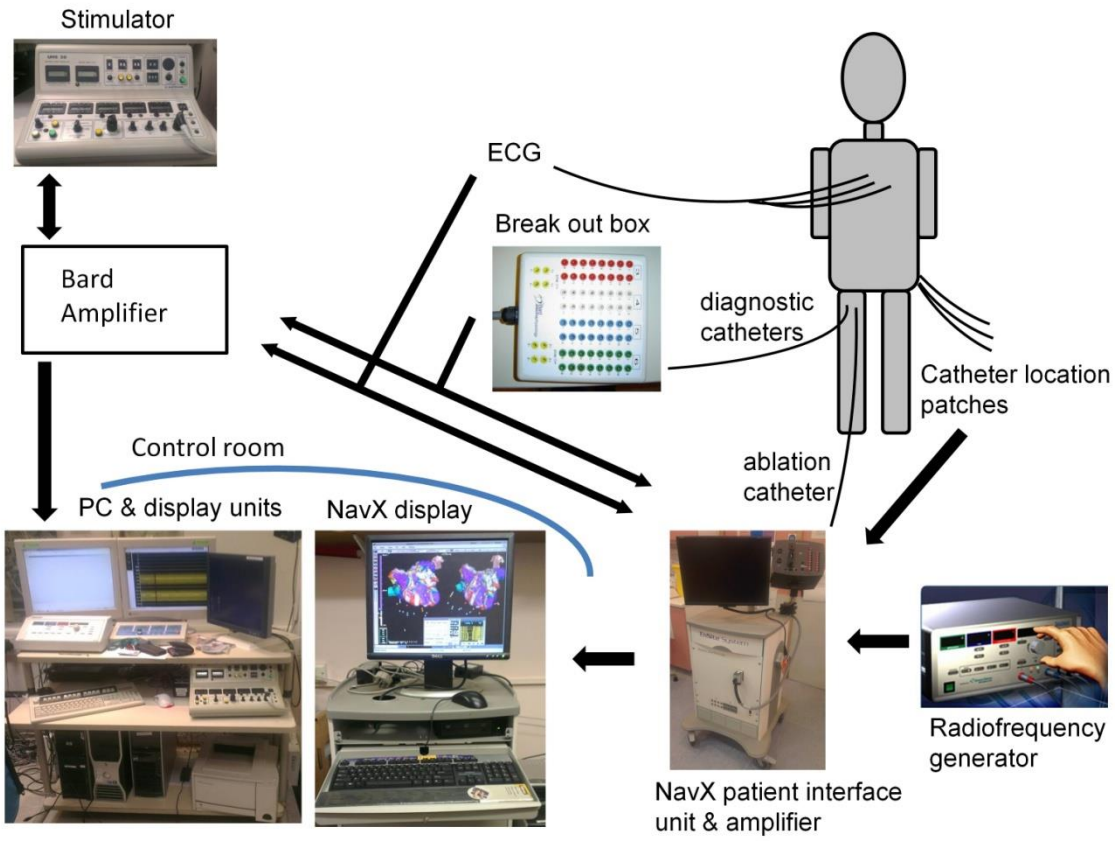
catheter ablation if they had symptomatic AF refractory to at least 1 antiarrhythmic drug, or intolerance to antiarrhythmic drugs. Patients already selected for catheter ablation of persistent AF were approached and recruited for the studies constituting chapters 4 and 5 with the following pre-specified exclusion criteria:

1. Contraindication to catheter ablation, anticoagulation or TOE
2. Contraindication to or intolerance of cardiac CT angiography
3. Intracardiac thrombus which cannot be eliminated by anticoagulation
4. Valve disease requiring surgical intervention
5. Age <18 years or pregnancy
6. Any known acute reversible cause of AF e.g. uncontrolled hypertension
7. Recent acute coronary syndrome, myocardial infarction, percutaneous coronary intervention or cardiac surgery (within one month).

2.3 Catheter laboratory setup

The setup of equipment in the electrophysiology catheter laboratory is complex, particularly for cases such as catheter ablation of AF which involve the use of 3D mapping systems. The setup of equipment is summarized in Figure 2.1.

Figure 2.1: Catheter laboratory setup.



Legend to Figure 2.1: Diagrammatic representation of the equipment setup in the catheter laboratory. There is continuous ECG monitoring and pulse oximetry, with blood pressure routinely cycled every 3 minutes. Electrophysiologic data from the diagnostic catheters passes to the break out box. These signals and the ECG are then split between the Bard amplifier (Labsystem pro, Bard Electrophysiology, MA, USA) and the Ensite NavX patient interface unit (St Jude Medical, CA, USA) which contains its own amplifier. These signals are then amplified, filtered and digitized by the Bard and NavX amplifiers before being displayed on their respective computer systems. Skin patches are also attached to the Ensite NavX patient interface unit. The electrograms are displayed on a live screen and a review screen for measurement and analysis, with a separate station for the Ensite system and screens for fluoroscopy images. Although the Ensite NavX system was used for

all the experimental protocols in chapters 4 and 5, the CARTO XP mapping system (Biosense Webster, Diamond Bar, CA, USA) is also used in our laboratory and hence was used for many patient cases reported in chapter 6.

2.4 Mapping systems

As the number of ablation procedure performed worldwide is increasing exponentially the case mix in many centres is becoming increasingly slanted towards more complex dysrhythmias such as catheter ablation of AF, post ablation atrial tachycardias and ventricular tachycardia. For 'simple' arrhythmias such as typical right atrial flutter or supraventricular tachycardia, mapping using fluoroscopy and the timing of activation relative to a stable reference catheter is usually sufficient to localize the site of earliest activation or the anatomy of the reentry circuit. The ablation required is also often fairly limited. However, this approach requires a sustained, haemodynamically stable and consistent beat to beat mechanism. Complex arrhythmia such as AF cannot be mapped in this way. Furthermore the anatomy of the left atrium is complex and variable between subjects. Lengthy catheter ablation procedures also mean that fluoroscopy use can be excessive. For these reasons, reliance on 3-dimensional (3D) mapping systems and other technologies is increasing.

The two most popular 3D mapping systems in use today are Ensite NavX (St Jude Medical, CA, USA) and CARTO (Biosense Webster, Diamond Bar, CA, USA). When these studies were conducted Carto XP was in use, and although Carto 3 has since been released it was not in use at the time of these studies. Likewise, various versions of Ensite NavX have been used at St Bartholomew's over the years, but only version 8 was used for the study cases in chapters 4

and 5 (as the mapping data and geometry had to be exported in a consistent format for the purposes of computer modelling and subsequent analysis), and the recently released Ensite Velocity was not yet in use. Therefore, discussion here focuses on Carto XP and Ensite NavX.

There are features common to both CARTO and Ensite NavX, such as the ability to build a geometry, to display catheter location, to store corresponding spatial and electrophysiologic data (electroanatomic mapping) and to display this in different ways (as isochrone maps, propagation maps, voltage maps and more). However, there are important differences between the systems.

The Ensite NavX System

Endocardial Solutions Inc. (ESI) was founded in 1992, and was acquired by St Jude Medical (CA, USA) in 2005. The original system allowed non-contact mapping, but this has been largely superseded by Ensite NavX which allows electroanatomic mapping using contact electrograms. The system passes a low amplitude 'locator signal' (5.68 kHz for Ensite NavX, changed to 8.14 kHz in the new Velocity system) which alternates between 3 different pairs of skin patches placed on the body's surface in orthogonal planes. The voltage measured from each catheter electrode can be used to locate the catheter in 3 planes (x, y, and z). Up to 64 electrodes can be located on up to 4 conventional catheters.

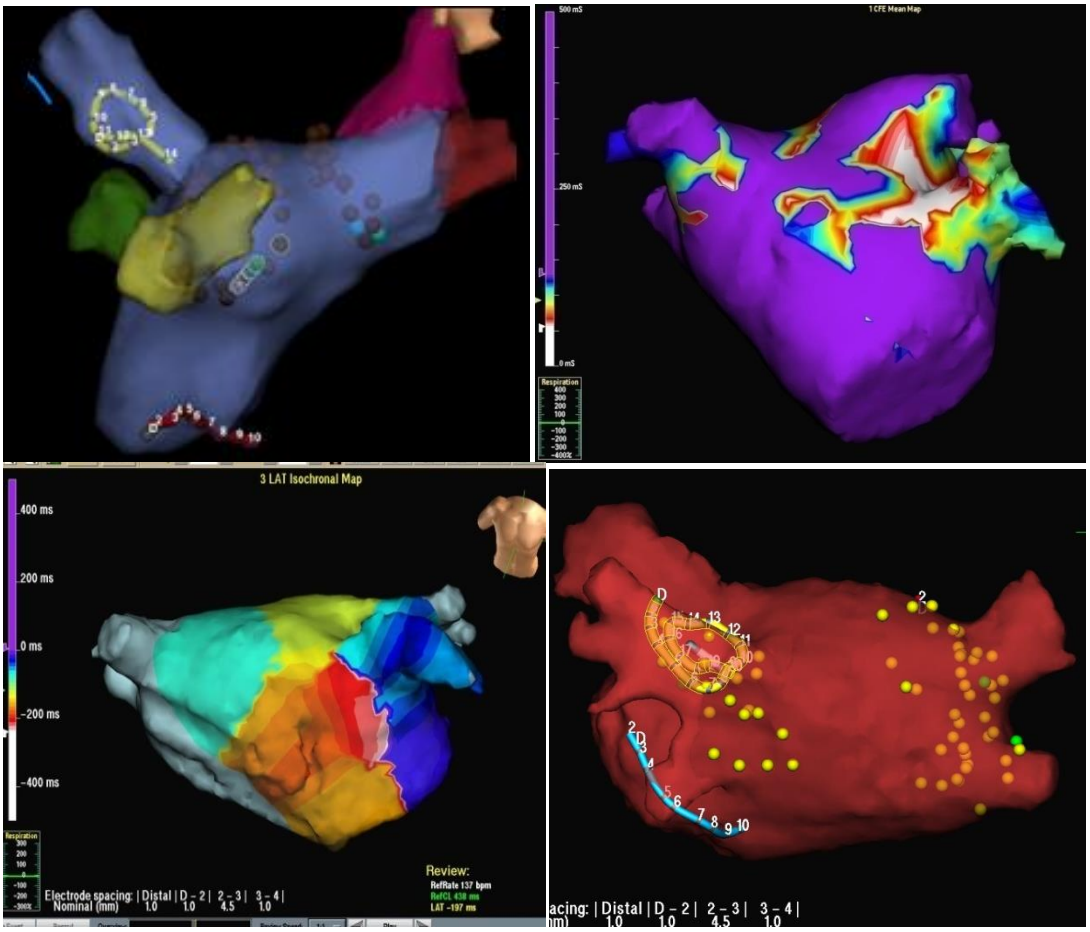
The chamber geometry is stationary relative to a reference electrode, usually a proximal electrode on the coronary sinus catheter in AF cases. Since cardiac structures move with respiration,[229, 230] an intra-cardiac reference point means less movement of the geometry relative to the chamber than if a static extra-

cardiac reference is used (as with CARTO).[230] The drawback of using an intracardiac catheter is that if it displaces, the geometry shifts relative to the chamber and can be difficult to replace exactly using fluoroscopy.

Geometry collection involves selecting a catheter (ideally multipolar such as the pulmonary vein mapping catheter) and moving it around the chamber of interest to collect points from the position of the electrodes in 3D space to create a detailed volume composed of many thousands of points. To improve definition of anatomy separate geometries can be collected for different anatomical features. Alternatively, complex anatomy like the LA can be acquired as a single geometry and points then reassigned to create separate geometries for the left atrial appendage and PVs. This is particularly advantageous in AF cases, since the geometry created very much resembles the LA, particularly at the crucial veno-atrial junction (Figure 2.2).

Another feature of the Ensite system is that it allows simultaneous data collection from all electrodes of any/all catheters if desired. It is therefore relatively quick to create a high density map.

Figure 2.2: Mapping with the Ensite system.



Legend to Figure 2.2: Top left shows wide area circumferential ablation being performed for AF. Note how the geometry resembles LA anatomy, particularly at the veno-atrial junction. Top right shows a CFAE map after PVI, with CFAE concentrated at the appendage ridge and at the orifice of the appendage. Bottom left shows an isochronal map from a patient whose rhythm regularised during CFAE ablation. The colours show rotation around a point at the anterior edge of the left atrial appendage, suggesting a localised macro-reentry circuit or rotor. Bottom right shows a reconstruction of the LA from CT fused with the NavX geometry. A circular mapping catheter is placed in the pulmonary vein and yellow lesions are placed where ablation has been performed in order to isolate the pulmonary veins.

The CARTO system

The CARTO system was invented by Shlomo Ben-Haim who founded Biosense in the early 1990s. This was acquired by Johnson & Johnson in 1997 who merged it with Cordis Webster (which produced predominantly catheters) in 1998. The customised ablation catheter (Navistar, Biosense Webster, Diamond Bar, CA, USA) is located by a magnetic sensor near the tip which senses 3 different weak magnetic fields (5×10^{-6} to 5×10^{-5} Tesla) emitted from 3 coils in a locator pad beneath the catheter lab table. Since the strength of the magnetic fields are inversely proportional to the distance between the sensor and each of the 3 coils, the system can triangulate the position of the catheter tip in 3D space. Catheter orientation (calculated from Euler angles which determine rotation in 3 planes called roll, pitch and yaw) is also displayed, not just in terms of which way the catheter is pointing, but also which aspect the catheter deflects toward (shown as red at the tip).

At the start of a case a reference patch is placed on the patient's back overlying the heart and with the patient lying down the device carrying the magnets is aligned within a defined circumference of the reference patch. The position of the reference patch relative to the magnets is recorded to allow repositioning if needed. Although use of an extra-cardiac reference point may slightly diminish the accuracy of chamber localisation, the stability achieved is actually a real strength of the CARTO system.

Using the ablation catheter, corresponding electrical and spatial endocardial points are taken which the system joins to generate a surface representation of the chamber. The geometry created using surface points is inevitably far fewer

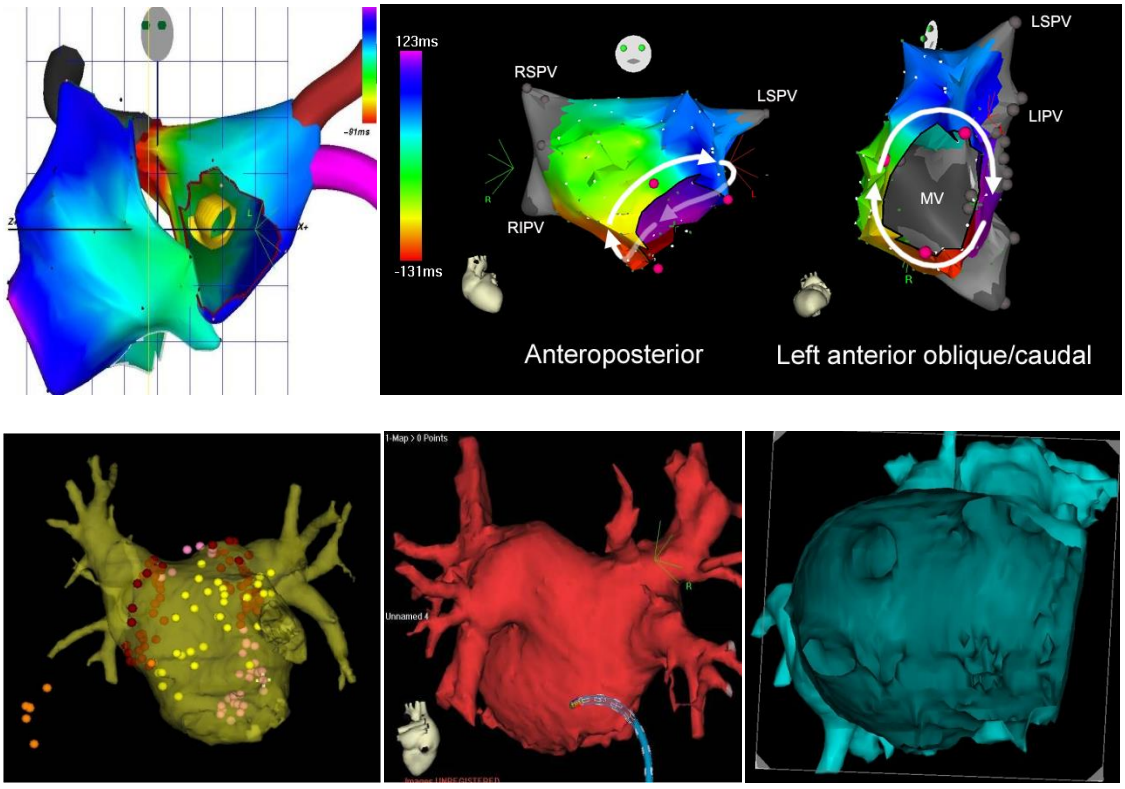
than the thousands of anatomical location only points used by Ensite to create a geometry. Consequently, the geometry on CARTO XP can often appear rather orthogonal, particularly at the critical veno-atrial junction where accurate location and placement of lesions is so critical for catheter ablation of AF (Figure 2.3).

Image integration with CARTO and NavX

Image integration has been widely used for catheter ablation of AF, since variability in anatomy of the pulmonary veins, the dimensions of their ostia and the width of the appendage ridge may impact on the techniques used for PVI. CARTO and Ensite both have the facility to import 3D reconstructions of the LA (or any chamber) from CT or MRI. The chamber of interest is segmented, imported into the case and registered with the geometry. The registration process differs somewhat between the mapping systems.

CARTOMERGE (Biosense Webster, Diamond Bar, CA, USA) has 2 steps.[231] 'Landmark registration' involves moving the catheter to 3 or more sites around the chamber and placing user-defined landmarks on the 3D reconstruction. 'Surface registration' involves creating a point by point geometry of the chamber, which CARTO will then auto-register with the 3D reconstruction (although this can be manually corrected). The reconstruction is then simply displayed in the same uncorrected space as the geometry (Figure 2.3).

Figure 2.3: Ablation guided by CARTO.



Legend to Figure 2.3: Top left image shows an activation map on CARTO XP, with a tachycardia originating from the right upper pulmonary vein. Top right shows an activation map in antero-posterior and left anterior oblique views, demonstrating a flutter circuit running clockwise around the mitral valve annulus. The bottom left image shows a LA geometry with image integration and a lesion set for persistent AF: red lesions are isolating the PVs, pink lesions are linear lesions, and yellow lesions are targeting of CFAE. Bottom middle panel shows image integration being used to guide PVI for AF in a case with variant anatomy (a left common trunk and a right sided roof vein). Bottom right shows a clipping plane looking into the left PVs and appendage to help guide ablation on these complex structures.

Ensite Verismo (St Jude Medical CA, USA) requires the user to define corresponding pairs of fiducial points on the geometry and the reconstruction. Verismo then ‘stretches’ the geometry to fit the reconstruction, assuming the reconstruction to be correct (Figure 2.2). Regardless of these differences, the registration of imaging appears similarly accurate for both mapping systems and are accurate to within 2-3mm.[231, 232]

Data regarding the clinical benefit of image integration in the context of catheter ablation for AF is conflicting. [233-237] It has been suggested that part of the benefit may be derived from simply knowing the anatomy, rather than image integration *per se*.[235] It is also noteworthy that all the trials to date have used CARTOMERGE and there have been no trials examining the role of Ensite Verismo.

2.5 Catheter ablation of AF at St Bartholomew's

Peri-procedural management of patients

Patients stopped warfarin 5 days pre-procedure and self administered enoxaparin (1.5 mg/Kg subcutaneously od) until the day before the procedure. Patients were routinely admitted the day before the procedure for routine blood tests, a transoesophageal echocardiogram (TOE) to rule out intra-cardiac thrombus and left atrial imaging for integration into the 3D mapping system (either CT angiography or cardiac MRI). Patients were taken to the catheter laboratory in the fasted state, and procedures were performed under local anaesthetic (lidocaine) and moderate sedation (midazolam and diamorphine).

Heparin was administered, starting with 5000 units after venous access was obtained, a further 5000 units after transseptal puncture, and further boluses to maintain activated clotting time 300-400 seconds. Post procedure femoral sheaths were removed once activated clotting time had fallen below 150 seconds. Warfarin loading began the day after the procedure with Enoxaparin administered until INR was therapeutic.

Catheter ablation of AF

Typically venous access was via the right femoral vein with 3 sheaths. A multipolar catheter was passed to the coronary sinus (a decapolar catheter for persistent AF or a quadripolar catheter for paroxysmal AF). After double trans-septal puncture a pulmonary vein mapping catheter and an ablation catheter were introduced to the LA. Ablation catheters were irrigated with 2 ml/minute heparinised saline, increased to ≤30 ml/minute where temperature increase

limited energy delivery. Power was generally limited to 25 W and 50˚C near the PV ostia, 30 W and 50 ˚C in the body of the, 40 W and 45˚C at the cavo-tricuspid isthmus.

Catheter ablation of AF at St Bartholomew's has remained fairly consistent over recent years. All procedures were guided by 3D mapping systems (either CARTO or Ensite NavX). Since 2004 CT or MRI imaging was used routinely for image integration.[232, 235] PVI was by wide area circumferential ablation (WACA) with lesions placed 1-2 cm outside the PV ostia to isolate them as ipsilateral pairs, with confirmation of electrical isolation since 2002. All patients with persistent AF had linear lesions added at the mitral isthmus (between mitral valve and left sided WACA ring), the roof between WACA rings, and the cavotricuspid isthmus in patients with a history of typical atrial flutter. Block was verified by examining activation sequence either side of linear lesions after restoration of sinus rhythm. From 2005, after WACA and linear lesions if the patient remained in AF, CFAE were systematically targeted throughout the left then right atria. CFAE were identified visually with operators using a common consensus definition: electrograms with (i) prolonged complexes with continuous deflections from baseline (ii) a rapid cycle length (< 120ms) or (iii) complexes with multiple deflections (without distinguishing between high and low amplitude signals). If at any point AF organised into AT this was mapped and ablated. If sinus rhythm was not restored following these lesions the patient was cardioverted with a DC shock. The exact mapping and ablation protocols for chapters 4 and 5 are described below as they differ slightly from this standardised lesion set.

Follow-up

Patients were discharged the day after the procedure, having stopped all AADs. As early recurrences often settle spontaneously,[172, 238] patients were managed medically for the first 3 months post ablation if symptoms recurred. Patients were followed up at 3 months, and again at 6 months if symptomatic initially, with a period of ambulatory monitoring of 2-7 days. Those with persistent AF/AT or symptomatic PAF at 3 months were offered a repeat procedure. Anticoagulation was continued for a minimum of 3 months and ongoing anticoagulation advised if the CHADS2 score was ≥2 (regardless of rhythm) as per current guidelines.[189, 239]

2.6 Methods for Chapter 3

This chapter involved three key steps which are detailed below:

1) A classification of electrograms had to be described to grade the degree of electrogram fractionation in AF. This was based on retrospective review of CFAE targeted in historical cases.
2) Secondly, the utility of the classification had to be tested to ensure that it could be reproducibly applied in real time live during cases.
3) Thirdly, if the two steps above were successful, this novel grading system could be used to assess automated CFAE detection algorithms available on 3D mapping systems, both in terms of their accuracy in detecting CFAE and their ability to assess the degree of electrogram fractionation.

Study Population

All patients studied underwent first time catheter ablation for persistent AF. All had symptomatic AF despite at least one antiarrhythmic drug.

Analysis of electrograms

Electrograms were recorded after LA catheterisation but before any ablation was performed, at points evenly distributed around the LA as determined by electroanatomic mapping systems. All electrograms were recorded with a 3.5 mm irrigated tip ablation catheter (Navistar Thermo-Cool or Thermo-Cool Celsius, Biosense Webster) with 2-5-2 mm electrode configuration. Unclipped bipolar electrograms were examined on the computer-based digital amplifier/recording system (Labsystem pro, Bard Electrophysiology, MA). Recordings were filtered at 30 to 250 Hz and displayed at 100 mm/Second. Electrograms were examined on digital display (rather than paper printouts) for development and testing of the classification system. After collection of data ablation was performed as described above in section 2.5.

(1) Development of classification

Electrograms were reviewed from the 118 patients with persistent AF who underwent catheter ablation in our institution over the last 10 months. Using these data we concluded that the following were relevant and distinguishable features of fractionated electrograms:

1. The presence of rapid deflections from baseline. Deflections were distinguished from low amplitude noise and far-field activity by defining them as (a) amplitude ≥ 0.05 mV, (b) amplitude also ≥ 20% of the largest peak to

peak deflection of an atrial electrogram within 500 ms, (c) ‘sharp’. The criterion used for sharp was a slope of ≥45˚ from the isoelectric line for the upstroke and the downstroke. With complex electrograms where the deflections did not reach baseline, an extrapolation of the deflection was extended to cross the isoelectric line as in Figure 2.4. For the purposes of analysis far field ventricular electrograms were easily identified and discarded (See Figure 2.5, example electrogram for grade 5).

2. The proportion of a sample occupied by rapid deflections. We distinguished between discrete complex electrograms (i.e. with multiple deflections per complex), and those with more continuous fractionation. Atrial effective refractory periods as low as 70 ms have been recorded in animal models during autonomic stimulation.[212, 240] This was therefore regarded as an absolute minimum possible and deflections < 70 ms apart were regarded as part of the same complex, since it was not thought possible for this to represent successive wavefronts passing through the same tissue (although it is recognised that other groups have used variable times, typically ranging from 50-70 ms).[194, 241] Complexes lasting ≥ 70 ms were regarded as fractionated and were further subdivided based on the proportion of the electrogram occupied by fractionation and the consistency of fractionated activity. Targeting electrograms fractionated for ≥70% of the recording is associated with an increase in cycle length, and uninterrupted segments lasting ≥1 Second have been proposed as targets based on their increased prevalence in persistent AF.[241-243]

3. The amplitude of the signal was categorised to reflect whether there may be electrically inert scar tissue, a small mass of fibrillating tissue, or an epicardial source of activation.[244] Peak to peak atrial complexes <0.5 mV have been regarded as low amplitude signals previously.[221, 245]

Using these strict criteria our grading system was devised. Each grade of electrogram is defined in Table 2.1 and examples of each are shown in Figure 2.4. A suffix was added to the numerical grade to reflect signal amplitude, with 'a' denoting a peak to peak deflection of ≥0.5 mV in greater than half of all 500 ms intervals during the recording, and 'b' denoting signals not meeting this criterion.

Modification of the classification system during development

Initially grade 5 was divided into normal electrograms which were rapid (cycle length ≤ 120 ms) or slow (cycle length > 120 ms), as a cycle length of 70-120ms has generally been included as criteria for identifying CFAE in clinical trials.[194, 245] However, on testing application of the classification system (see below) this distinction was found to be redundant. When the cycle length was < 120ms, the deflections would often fall within 70ms of the last and hence were classified as continuous fractionation. This would then be classified as grade 1, 2 or 3 depending on the proportion of the sample occupied by this continuous fractionation. Hence this has been removed from the classification system.

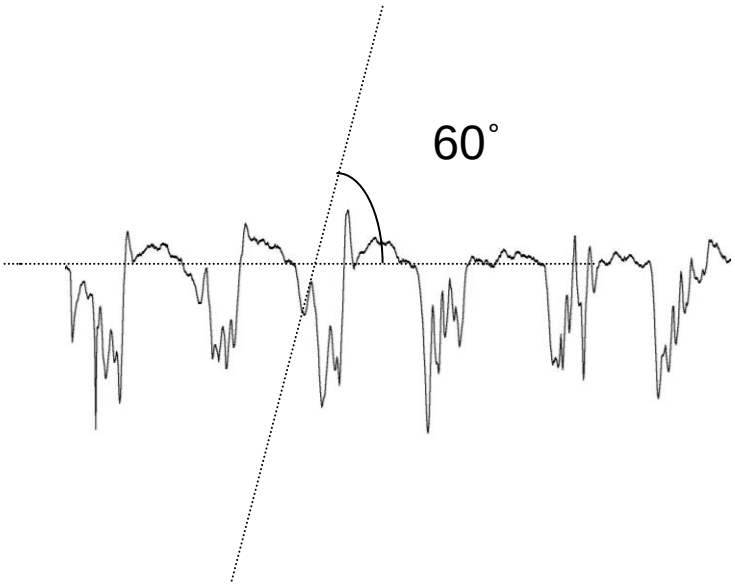
Table 2.1 – Classification system for electrograms

Grade	Electrogram criteria
1	**Uninterrupted fractionated activity** Fractionated activity (defined as continuous deflections without pause at the isoelectric line for ≥ 70ms) occupying ≥70% of sample, ***and*** at least 1 uninterrupted episode of fractionated activity lasting ≥1s.
2	**Interrupted fractionated activity** Fractionated activity occupying ≥70% of sample.
3	**Intermittent fractionated activity** Fractionated activity occupying 30-70% of sample.
4	**Complex electrograms** Discrete electrograms (<70ms) and complex (≥5 direction changes), with any fractionated activity occupying <30% of sample (otherwise grade 3).
5	**Normal electrogram** Discrete electrograms (<70ms) and simple (≤ 4 direction changes).
6	**Scar** No discernible deflections.

Legend to Table 2.1: In assessment of electrograms, for a deflection to be counted it must be a sharp signal discernible from noise, with amplitude both > 0.05 mV and >20% of the largest deflection within 500ms. Deflections occurring within 70ms of the last deflection were regarded as part of the same complex, with complexes lasting ≥70ms regarded as continuous fractionation. In addition

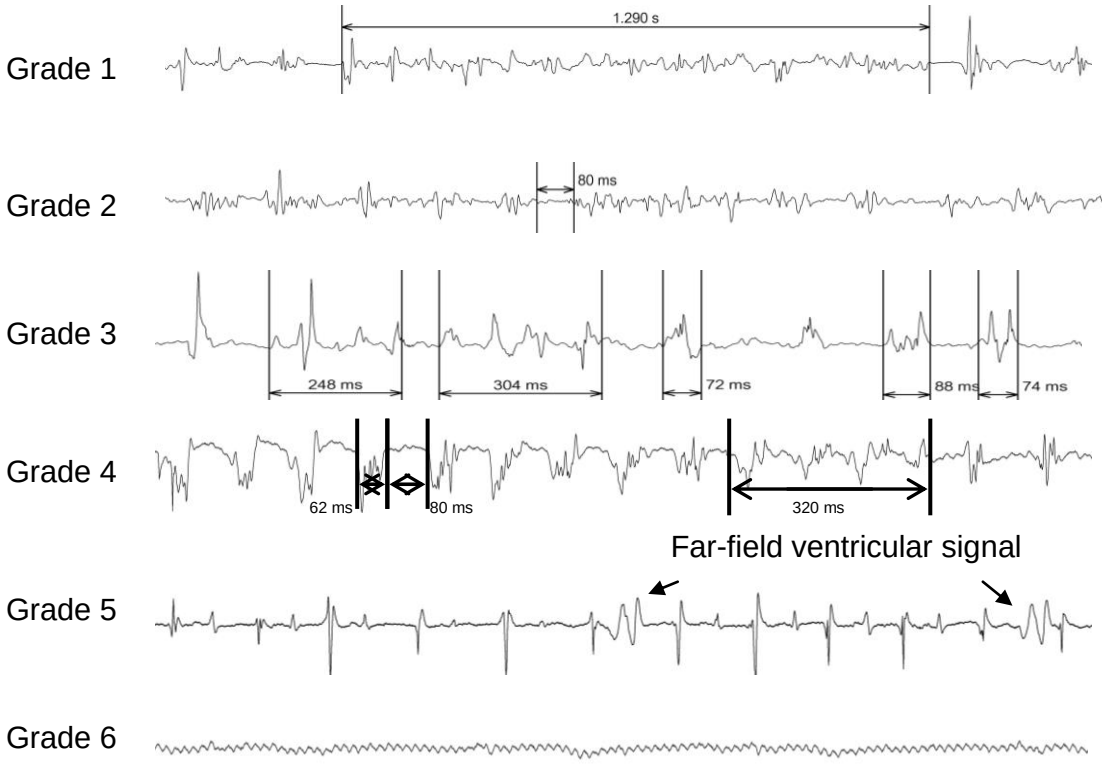
to the numerical grade, a suffix is added to describe amplitude. The suffix ‘a’ denotes a high amplitude signal (at least 1 peak to peak deflection of ≥0.5 mV in the majority of 500ms segments of the recording) and ‘b’ denotes low amplitude signals not meeting this criterion.

Figure 2.4: Analysis of complex electrograms.



Legend to Figure 2.4: To distinguish local electrical signals from far-field electrograms and wandering baseline, an objective criterion to describe ‘sharp’ deflections was developed. The angle between both the up-stroke and the down-stroke of the deflection must be ≥ 45˚ to the isoelectric line. For complex electrograms where the deflections may not reach baseline, an extrapolation of that line was continued to cross the isoelectric line allowing the angle to be measured. In this case the angle is calculated as 60˚.

Figure 2.5: Examples of electrograms from the revised grading system.



Legend to Figure 2.5: Grade 1 shows uninterrupted fractionated activity without pause at the isoelectric line for ≥ 70ms lasting 1 Second. Grade 2 shows fractionated activity which is interrupted by pauses at the isolelectric line of ≥ 70ms but still occupying > 70% of the recording. Grade 3 shows intermittent fractionated activity which occupies between 30 and 70% of the recording. Grade 4 shows complex electrograms (≥ 5 deflections) which are discrete lasting for < 70ms. Towards the end of this sample, some complexes merge to last 320 ms (i.e. longer than 70 ms) and hence this part of the recording is considered fractionated. However, this is still grade 4 as < 30% of the sample is fractionated. Grade 5 shows discrete electrograms (i.e. < 70ms in duration and ≤ 4 direction changes). There are two examples of far-field ventricular electrograms which can be easily distinguished from near field electrograms. Grade 6 shows scar with no discernible deflections.

(2) Application of the classification system

We sought to examine whether the electrogram classification system could be accurately applied during cases by rapid online visual inspection. Electrograms recorded for 10 Seconds were viewed on the computer-based recording system and graded by an experienced electrophysiologist. It has been demonstrated previously that recordings of 5 seconds or greater are adequate for determining the duration and characteristics of CFAEs.[246] Variable times have been used in the literature ranging commonly from 2-10 seconds.[201, 246-248] We used the maximum analysis time (10 Seconds) to ensure accurate results. 100 electrograms over 10 patients (10 per case) were chosen at random from those graded during the case and subjected to detailed manual analysis offline by a second investigator blinded to the previous results. These results were then compared.

As CFAE can be consistent, fleeting or cyclical,[201, 249, 250] the proportion of a sample that is fractionated can vary which may affect the grade determined. Over the short term however, automated assessment of samples longer than 5 seconds has yielded consistent results compared to longer samples.[246] To determine the consistency of fractionation and grade when shorter samples were analysed, the percentage of the sample that was fractionated and the grade determined by manual measurement were calculated for the first 3 Seconds, then recalculated adding successive seconds up to 10 Seconds. The absolute percentage difference in fractionation compared to 10 Seconds was then calculated. Agreement in grade was also compared to 10 Seconds.

(3) Validation of commercial automated detection systems

As electrogram appearance may be altered by differences in amplification and filtering of signals between systems, validation of automated CFAE detection systems was done by viewing electrograms on the 3D mapping systems. The same sample analysed by the mapping system was graded by visual inspection. Electrograms were graded offline by visual inspection on the mapping system and compared to the automated result for the same sample. As this process is slightly different to the process of grading live during cases, the validation process was repeated. In total 1000 electrograms were analysed on the 3D mapping systems (500 on each one assessed). Of these, 100 electrograms (50 from each system) were chosen at random and subjected to detailed manual analysis offline by a second investigator blinded to the previous results. These results were then compared.

The grade determined by visual inspection was compared to the score from automated algorithms. To assess automated CFAE detection, grades 1-4 were considered fractionated. To assess differentiation between highly fractionated signals and less fractionated electrograms, grade 1-2 were considered highly fractionated. Correlation between grade and automated scores were also examined to characterise automated assessment of degree of electrogram fractionation.

Automated detection by Carto

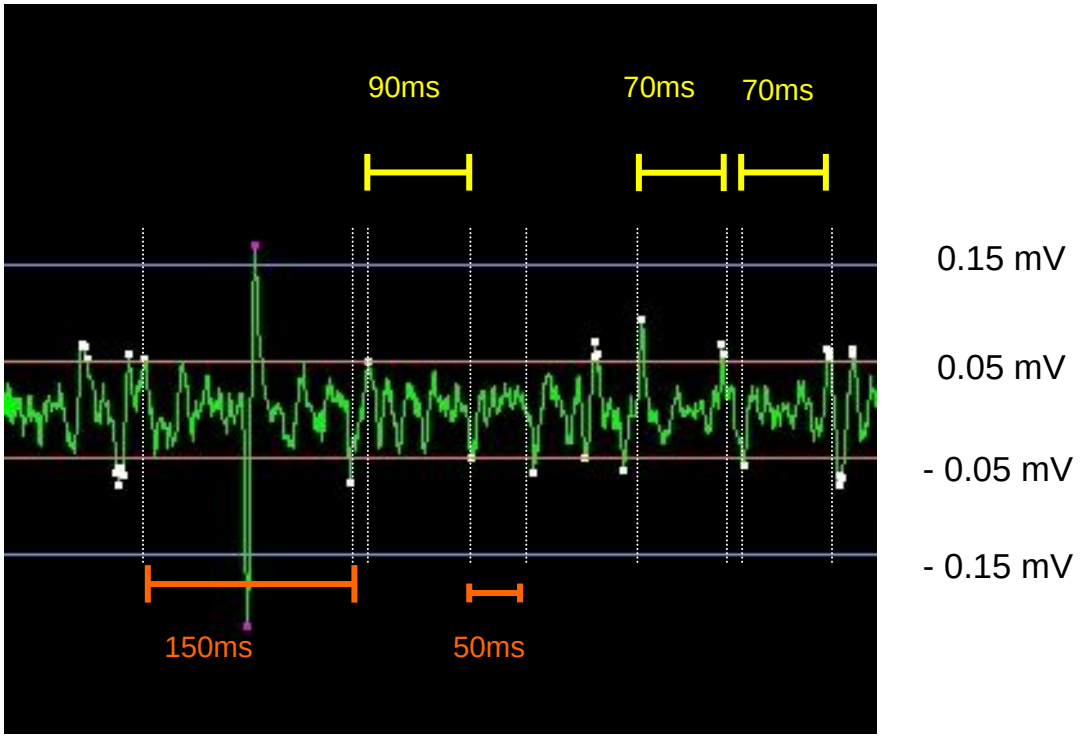
There are three algorithms for CFAE detection available on Carto XP (Biosense Webster Inc., Diamond Bar, CA) which work by assessing intervals between deflections. A deflection must meet certain criteria to be counted by the

software. Each deflection must have a minimum and a maximum width to exclude noise and wandering baselines (15 and 30 ms respectively are default settings). Deflections must also fall within a window of amplitude that can be varied (factory settings suggest low voltage deflections between 0.05 and 0.15 mV be selected). The software tags the deflections meeting these criteria on-screen, and the algorithms then calculate a score as follows:

1. The interval confidence level (ICL) counts the number of intervals between tagged deflections falling within a range (70-120 ms is suggested) as shown in Figure 2.6. The ICL was calculated using the factory settings (ICL-FS) as above, and using previously published optimised settings (ICL-OS) where the upper limit of amplitude for sensing deflections was increased to 1mV.[251]
2. The average complex interval (ACI) calculates the mean interval between tagged deflections which fall within the specified range (70-500 ms was used). Factory settings were used as above.
3. The shortest complex interval (SCI) calculates the shortest interval between tagged deflections which fall within the specified range (70-500 ms). Factory settings were used as above.

2.5 Second bipolar electrograms were reviewed on Carto (this parameter cannot be altered on the software).

Figure 2.6: Automated detection of CFAE using Carto.



Legend to Figure 2.6: This electrogram is shown as it appears on Carto. The software will recognise deflections only if they meet certain criteria. To be counted deflections must be between 15-30 ms in duration, and within a window of amplitude marked by the blue and red lines (in this example between 0.05 and 0.15 mV). Deflections meeting these criteria are marked with white dots, all other deflections are marked with purple dots and ignored. The interval confidence level (ICL) algorithm counts the number of intervals between deflections which fall within a pre-specified range (the factory settings suggest a range of 70-120 ms). The intervals marked with the yellow lines above will be counted and those marked with the orange line below which fall outside of the 70-120 ms range are ignored.

Automated detection by Ensite NavX

The Ensite software uses a similar set of criteria to recognise deflections. We adopted parameters used previously.[221] The minimum amplitude was set at 0.1mV (there is no upper limit for amplitude specified on this software), with a minimum deflection width of 20ms and refractory 'blanking' period of 30ms. The software then tags deflections meeting these criteria on-screen and calculates the mean interval between deflections or 'CFAE mean'. 5 Second electrograms were viewed for Ensite NavX (St. Jude Medical, Minneapolis, MN) as this has been shown to give consistent results.[246]

Statistics

Continuous variables are reported as mean ± standard deviation, or median (range) if not normally distributed. Correlation between observers was tested with Cohen's Kappa coefficient (κ). Correlation between grade and automated scores were examined using Spearman rank correlation coefficient. For each algorithm sensitivity and specificity were calculated using previously defined cut off values. Receiver operating characteristic (ROC) analysis was performed using SPSS 16.0 software (SPSS, Chicago, IL). This was used to determine optimal cut-off for detection of CFAE and selection of highly fractionated signals. Area under ROC curves is presented with 95% confidence intervals. There are currently no standardised statistical tests to compare the area under ROC curves when they are derived from different cases.

2.7 Methods for Chapter 4

Methods

Study population and randomisation procedure

The study population was comprised of 20 patients who underwent catheter ablation of persistent AF at a single institution. Randomisation involved a random number generator, with sealed envelopes opened on the day of the procedure. Although patients and physicians performing clinical follow up were blinded, the nature of the study did not allow blinding of the operator. All patients gave written informed consent. The study was approved by East London and The City Research Ethics Committee, and was prospectively registered on NIH clinicaltrials.gov (NCT00894400).

Study protocol

The peri-procedural management of patients and equipment is as discussed in Section 2.5. AADs were not stopped pre-procedure. Under local anaesthetic (lidocaine) and conscious sedation (midazolam and diamorphine) 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. All electrograms targeted for CFAE ablation were recorded using the 3.5 mm ablation catheter with a 2-5-2 mm electrode configuration. Unclipped bipolar electrograms were examined on a computer-

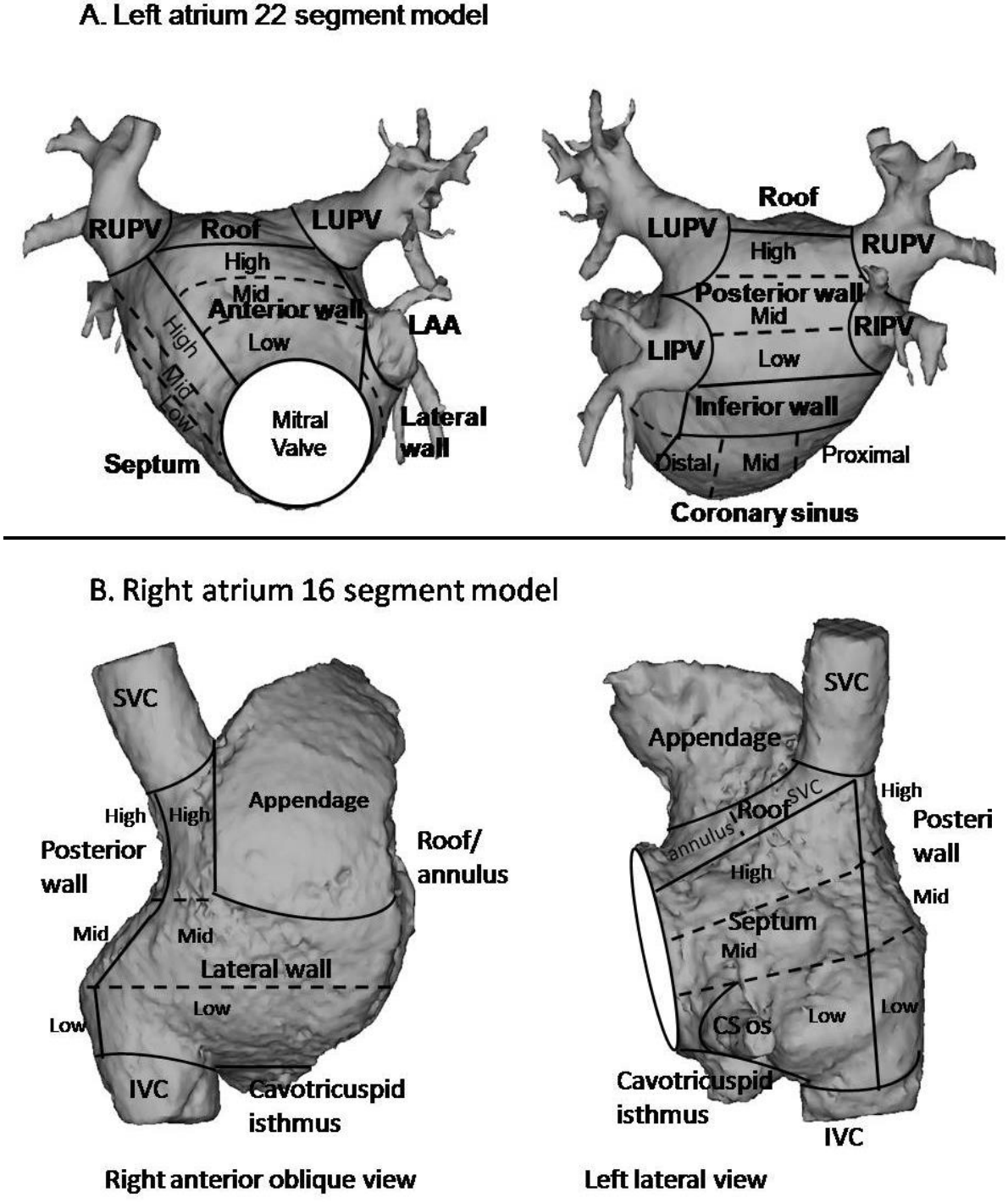
based digital amplifier/recording system (Labsystem pro, Bard EP, MA, USA). Recordings were filtered at 30 to 250 Hz and displayed at 100 mm/Second.

Mapping

Right and left atrial geometries were created using a 3D mapping system (Ensite NavX, St Jude, CA, USA). The PV mapping catheter (0.75 - 5 - 0.75 configuration) was used to record 10 second electrograms at evenly spaced points which were graded according to our validated classification (described in Section 2.6). Electrograms were assigned a number on a scale from 1-6, with 1 being most fractionated and 5 being a normal electrogram (scar being nominally designated grade 6), and a letter ‘a’ or ‘b’ for high or low amplitude respectively (the definition of each grade and the suffix for amplitude are shown in Table 2.1, with examples of each shown in Figure 2.5).

Electrograms were located using 22 and 16 segment models of the left and right atria (Figure 2.7). For each map, at least 1 set of electrograms was recorded using the PV mapping catheter for each segment, and the most fractionated grade recorded.

Figure 2.7: Anatomical division of the left and right atrium.



Legend to Figure 2.7: (A) Anterior and posterior views of the LA, showing the 22 segment model. (B) Right anterior oblique and left lateral views of the right atrium showing the 16 segment model.

After PVI a further LA CFAE map was acquired and used to guide subsequent CFAE ablation. The pre- PVI map of the right atrium was used to guide ablation, since no ablation had yet been performed there. During CFAE ablation, electrogram grade was re-checked in each segment prior to ablation there. The effect of PVI on LA CFAE distribution was determined by comparing pre and post PVI maps. The stability during CFAE ablation was assessed by comparing the maps used to guide ablation with the grade found in each segment during CFAE ablation.

Ablation

PVI was performed by WACA, with electrical isolation confirmed using the PV mapping catheter as described in Section 2.5.

Targeting of CFAE

Patients were randomised to targeting of CFAE starting with the most fractionated grade first (i.e. grades 1 to 5) in group 1, or starting with the least fractionated first (i.e. grades 5 to 1) in group 2. [199, 252]Since grade 5 electrograms were considered normal and served as control lesions, only 5 were ablated per patient. These were placed in locations that could later be incorporated into linear lesions. Once all LA CFAE were abolished and 5 grade 5 electrograms targeted, the process was repeated in the right atrium. Targeting of CFAE continued until atrial tachycardia or sinus rhythm ensued, or all atrial CFAE were abolished. Radiofrequency energy was delivered until electrogram amplitude was reduced by ≥ 80% or 60s of energy delivered.

If AF persisted after abolition of CFAE, linear lesions were added at the mitral isthmus and the roof. A cavotricuspid isthmus line was added only in patients with a history of typical right 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. PVI was then re-confirmed, and if necessary veins were re-isolated.

AFCL is thought to reflect the number of drivers supporting AF.[253] It lengthens progressively during ablation until termination of AF, with prolongation reflecting clinical outcome.[63] AFCL has been used by others to quantify response to ablation, and an increase of ≥ 5-6 ms has been regarded as significant.[241, 254, 255] 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 amplitude and AFCL is unambiguous) before and after each CFAE lesion.

We analysed baseline AFCL variability and considered a change ≥ mean + 2 standard deviations as significant. The cycle length of fractionated electrograms (grades 1-3) was ambiguous and was therefore not quantified. The cycle length of complex electrograms (grade 4) was measured manually over the 10 second sample, with segments of continuous fractionation discarded (< 30% of sample as per definition of grade 4).

The randomised strategy was employed:

(i) To control for any cumulative effect of ablation on AFCL.

(ii) To examine whether elimination of highly fractionated electrograms first reduces the number of less fractionated electrograms remaining.

(iii) To assess whether the order in which CFAE were targeted affects the amount of ablation required to abolish CFAE/terminate AF.

Inter-operator variability

All CFAE targeted were classified in real time by visual inspection. Electrograms were later graded off-line with the benefit of on-screen callipers by a second operator blinded to the earlier grade, and the two grades compared. AFCL was also re-measured by a second operator before 5 lesions chosen at random in each patient to allow assessment of inter-operator variability.

Statistics

Continuous variables are reported as mean ± standard deviation, or median (range) if not normally distributed. Continuous data were compared by Student's t-test if normally distributed or Wilcoxon two-sample test if not normally distributed. Categorical data were compared by chi-squared test.

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 the primary end-point had been met.

To assess the primary end-point, which was a comparison of the response to ablation of each CFAE grade, the mean percentage of lesions causing AFCL prolongation for each grade were compared using repeated measures analysis

of variance. To assess the impact of the order of ablation, group was included as an independent variable (repeated measures MANOVA).

The number of CFAE per patient did not permit inclusion of further dependent variables in addition to CFAE grade in the repeated measures MANOVA design. Therefore, response to ablation was assessed across all lesions using binary logistic regression, including grade, order of ablation, amplitude (categorised as high or low) and location (in the left or right atrium) as covariates. However, it is recognised that this approach did not account for the variable response to ablation between patients.

The effect of the order of ablation on the mean number of lesions per patient for each grade was compared using repeated measures MANOVA. Although comparison of the number of lesions between grades from MANOVA was not thought meaningful, comparison within each grade between groups was using Student's t test.

Agreement between observers for determination of CFAE grade was tested with Cohen's Kappa coefficient (κ).

2.8 Methods for Chapter 5

The methods for this chapter can be broken down into three overlapping stages:

1) A computer model was established to simulate left atrial wall stress in 3D reconstructions of the LA from CT scans. This stage consisted of (i) a pilot phase, (ii) a working model phase, and (iii) exploring variation in the model, to see how challenging certain assumptions within the model affect the simulation.
2) Electrophysiologic data were collected at the time of catheter ablation for persistent AF and compared to simulated wall stress data using a patient specific LA geometry derived from a pre-procedure CT scan. This allowed correlation between wall stress and electrophysiologic parameters, in particular areas of low voltage and CFAE.
3) 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 AFCL.

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

The peri-procedural management and equipment used has been discussed in the Section 2.5. 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 euvolaemic 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.[232] 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.[232, 256]

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.[246] The Ensite NavX software recognizes deflections in the waveform based on a number of criteria which can be varied by the user (as described in Chapter 3). 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). 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.
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 WACA, 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. Radiofrequency energy was applied until electrogram amplitude was reduced by ≥ 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

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 of ≥ mean + 2 standard deviations of baseline variability was considered significant.

Stress Modelling (1): the pilot phase.

Four CT scans were segmented using CARTOMERGE (Biosense Webster, Diamond Bar, CA, USA) to create 3D reconstructions of the LA as described previously.[231] These reconstructions were exported from the mapping system and used to simulate wall stress distribution on proprietary software (Finite Element Analysis, ABAQUS Inc, Pawtucket, RI, USA). The LA and proximal PVs were essentially modelled as a homogenous linear elastic shell. The model was then improved by adding layers of complexity based on the assumptions below:

1. Since the resolution of CT is approximately 1mm, 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 1mm and tapers towards the first division of the PV).[66] Therefore the LA was assumed to have uniform thickness of 2mm.
2. The wall thickness of the PVs were assumed to taper from 2 mm to 1 mm over a distance of 1 cm from the PV ostia. The surface beyond the first division of the PVs was not included in the analysis.
3. The LA was considered suspended by the 4 PVs which were fixed in the model.
4. The PVs were assumed to be open, and the mitral valve assumed to be shut. The mitral valve annulus was not included in the analysis.

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.[257] Von Mises stress distribution was predicted for a trans-mural pressure difference of 20 mmHg.

It had initially been planned to use this methodology for the whole study: using CARTOMERGE to segment CT scans and produce the LA reconstruction, and CARTO (Biosense Webster, Diamond Bar, CA, USA) for the clinical case to collect electroanatomic mapping and ablation data. However, this presented two problems:

1. Using CARTOMERGE, any electroanatomic data exists in the same 3D space as the geometry, but is not truly merged with it. The data extracted from CARTO therefore still requires some degree of registration between the electroanatomic data points and the nearest point on the 3D reconstruction of the LA to allow any comparison with wall stress values (which are simulated on the surface of the LA reconstruction). This registration process presented enormous difficulties from an engineering perspective and meant that comparison between wall stress data and electrophysiologic data might be limited to a visual comparison using a compartmentalised 3D model of the LA (it was initially planned to use the model in Figure 2.7).
2. Electroanatomic data points can only be acquired at the tip of the ablation catheter one point at a time. This was thought to be a limitation for the acquisition of high density electroanatomic data.

Therefore, although a working computer model was developed during this pilot phase, it was decided to change the methodology and use the Ensite NavX mapping system (St Jude Medical, CA, USA) for the clinical correlation and ablation studies. Using the Ensite Verismo software (St Jude Medical CA, USA)

for segmenting CTs, creating the 3D reconstruction of the LA and registering this with the geometry in the clinical case is comparable to using CARTOMERGE (as detailed above in Section 2.4). However, a subtle difference with Ensite Verismo is that the geometry is 'stretched' to fit the nearest parts of the 3D reconstruction of the LA, so that the exported electrophysiologic data points are projected onto the same 3D LA geometry that was used to simulate wall stress. This avoided a technically challenging procedure from an engineering standpoint with the added advantage that this registration process had already been shown to be accurate to within approximately 2 mm.[232] Furthermore, the Ensite NavX system allowed acquisition of multiple electrophysiologic data points simultaneously, allowing a high density map to be created much more quickly.

Stress Modelling (2): the working model phase.

The LA reconstruction and electrophysiologic data were exported from the Ensite NavX mapping system and wall stress simulated as described in the pilot phase. The distribution of peaks in wall stress was assessed using the 22 segment model of the LA shown in Figure 2.7. 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.

Stress modelling (3): Exploring variations of the model

Although the accuracy of the geometry is the most important factor when simulating wall stress,[258] the wall thickness and the transmural pressure

gradient are also very important. Hence, to ascertain whether the assumptions of the model were too simplistic to allow a meaningful wall stress simulation, 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.[259] 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 (see definition below). 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:

1. Fractionated electrograms (a CFAE mean <120ms),[222]
2. Low voltage areas suggestive of abnormal conduction (<0.5mV),[132, 136]
3. Electrical scar, i.e. very low voltage areas suggestive of scar, defined by others as absence of discernable deflections > 0.05 mV.[132, 134, 136]

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 2.7.

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 CFAE ablation caused AFCL prolongation.

2.9 Methods for Chapter 6

All consecutive patients undergoing catheter ablation of AF between 1/4/02 and 1/6/07 were included for analysis. All procedural data and baseline patient information were obtained from a prospective registry. Patients were defined as PAF or persistent AF according to ACC/ESC guidelines.[260] Patients with long standing persistent AF have been included with persistent AF.

Catheter ablation and follow-up

The technique used for catheter ablation of AF has been described in Section 2.5. In brief, PVI was by WACA with confirmation of electrical isolation. All patients with persistent AF had linear lesions added at the mitral isthmus, the roof between WACA rings, and the cavotricuspid isthmus in patients with a history of typical atrial flutter.

From 2005, after WACA and linear lesions if the patient remained in AF, CFAE were systematically targeted throughout the left then right atria. CFAE were identified visually with operators using a common consensus definition: electrograms with (i) prolonged complexes with continuous deflections from baseline (ii) a rapid cycle length (< 120ms) or (iii) complexes with multiple

deflections (without distinguishing between high and low amplitude signals). This is comparable to definitions used by other groups,[171, 194, 222] and is arguably representative of conventional approaches of CFAE ablation. Notably, the work done to classify CFAE occurred after this cohort. If at any point AF organised into AT this was mapped and ablated. If sinus rhythm was not restored following these lesions the patient was cardioverted with a DC shock.

Patients were discharged the day after the procedure, having stopped all antiarrhythmic medication. As early recurrences often settle spontaneously, a 3 month blanking period was observed during which recurrences were managed medically.[172, 238] Those with Persistent AF/AT or symptomatic PAF at 3 months were offered a repeat procedure. Anticoagulation was continued for a minimum of 3 months and ongoing anticoagulation advised if the CHADS2 score was ≥2 (regardless of rhythm) as per current guidelines.[189, 239]

Patients were followed up at 3 months, and again at 6 months if symptomatic initially, with a period of ambulatory monitoring of 2-7 days (83% were either monitored once since their last procedure or had AF/AT documented on ECG). There was open access to arrhythmia nurse specialists subsequently and further monitoring prompted by symptoms (29% underwent monitoring >8 months after their last procedure). Late follow-up with an ECG was obtained from the referring physician for 96% of patients at a median of 18 months. Attempts were made to contact all patients for review between 1/9/09 and 16/10/09 to determine any adverse events, recurrences of AF/AT, current medications and symptoms. Symptoms were assessed using the recent Canadian Cardiovascular Society Severity of AF (CCS-SAF) scale.[261] As this

was not available pre-procedure no objective comparison with the pre-procedure state is possible, so patients were asked for a subjective assessment of whether their symptoms were improved.

Measures of success

Success was defined as freedom from symptoms and/or documented AF/AT lasting >30s following the 3 month blanking period as per guidelines.[189]

Success rates are reported after:

(i) The first procedure,

(ii) The first cluster of procedures (defined below),

(iii) The last procedure,

(iv) The last 6 months (to account for those whose symptoms settled with adjustment of medications subsequent to the blanking period).

The end of the first cluster was defined as the point in time, whether after 1 catheter ablation or several, when ablation was first considered a success as defined above (or the patient declined a repeat procedure). Late recurrence of AF/AT was analysed starting from the last procedure in the cluster, since analysis following the final procedure does not take into account late recurrence occurring prior to successful repeat procedures.

Statistics

Continuous variables are reported as mean ± standard deviation, or median (range) if not normally distributed. Continuous data were compared by Student's t test. Kaplan-Meier curves were used to analyse AF free survival and curves were compared using the log rank test. Multivariate analysis of predictors of

recurrence was by Cox regression. Patient factors were analysed for their effect on final procedure success, whereas procedural factors were analysed for their effect on single procedure success.

Chapter 3

Validation of a classification system to grade fractionation in AF and correlation with automated detection systems.

Abstract

Introduction: We tested application of a grading system describing complex fractionated atrial electrograms (CFAE) in AF and used it to validate automated CFAE detection (AUTO).

Methods: 10s bipolar electrograms were classified by visual inspection (VI) during ablation of persistent AF and the result compared to offline manual measurement (MM) by a second blinded operator: Grade 1 uninterrupted fractionated activity (defined as segments ≥70ms) for ≥70% of recording and uninterrupted ≥1s;Grade 2 interrupted fractionated activity ≥70% of recording; Grade 3 intermittent fractionated activity 30-70%; Grade 4 discrete (<70ms) complex electrogram (≥5 direction changes); Grade 5 discrete simple electrograms (≤4 direction changes); Grade 6 scar.

Results: Grade by VI and MM for 100 electrograms agreed in 89%. 500 electrograms were graded on Carto and NavX by VI to validate AUTO in 1) detection of CFAE (grades 1-4 considered CFAE), and 2) assessing degree of fractionation by correlating grade and score by AUTO (data shown as sensitivity, specificity, r): NavX ‘CFAE mean’ 92%, 91%, 0.56; Carto ‘interval confidence level’ using factory settings 89%, 62%, -0.72, and other published settings 80%, 74%, -0.65; Carto ‘shortest confidence interval’ 74%, 70%, 0.43; Carto ‘average confidence interval’ 86%, 66%, 0.53.

Conclusion: Grading CFAE by VI is accurate and correlates with AUTO.

Introduction

Although PVI remains the cornerstone of catheter ablation for paroxysmal AF, persistent AF requires more extensive ablation to achieve acceptable clinical results.[171, 191] Targeting CFAE in addition to PVI has improved results in some studies but not others. [64, 191, 220-225] Difficulty reproducing results with CFAE guided ablation may be due to the lack of a clear objective description of CFAE in the literature and resultant differences in what is being targeted in different studies. [171, 194, 222] Furthermore, there remains uncertainty as to whether CFAE are of real mechanistic importance in maintaining AF, or whether they are bystander phenomena. It remains possible that the termination of AF that sometimes occurs during CFAE ablation may simply be due to the de-bulking of atrial tissue.

In order to test the hypothesis that certain CFAE morphologies are of greater importance in the maintenance of AF in Chapter 4, it was first necessary to (1) develop a classification system to grade degree of electrogram fractionation in AF, and (2) test the hypothesis that CFAE can be accurately characterised by rapid visual inspection using this grading system, by comparing classification of CFAE by visual inspection to detailed manual measurement offline. Although these were essential steps in this thesis, they were also important endeavours in their own right. If a validated system could be provided that allows operators to categorize CFAE live during cases, this would allow clinical trials to indicate more clearly what has been targeted and therefore allow the electrophysiology community to elucidate which CFAE are important in the catheter ablation of AF.

Attempts have been made to bring objectivity to CFAE ablation by applying automated algorithms on 3D mapping systems to analyse electrograms.[93, 221, 247, 249-251, 262, 263] Previous attempts to validate these algorithms have been limited by the lack of objective definition for CFAE and no means by which to grade the degree of fractionation.[221, 250, 251, 264] Substrate modification guided by these algorithms has proved successful, although these studies have not compared this approach to alternative means for identifying and targeting CFAE.[191, 221, 265] Pending successful development of a grading system for CFAE and validation of its application, a third aim for this chapter of the thesis was to validate commercial automated CFAE detection systems. The hypothesis for this sub-study was that automated CFAE detection is accurate and reflects degree of fractionation as assessed by visual inspection using the grading system.

Results

Patient characteristics

Electrograms were studied from a total of 20 patients. 15 were male with age 60 ± 8 years. 8 had hypertension, 2 had ischaemic heart disease, and 8 had left ventricular systolic dysfunction. Mean LA diameter was 4.6 ± 1.1 cm. Duration of continuous AF at the time of ablation was 26 (8-72) months.

Application of the classification system

100 electrograms recorded from 10 patients were examined. At detailed analysis the break-down of grades was as follows: 17% were grade 1; 15% grade 2; 42% grade 3; 17% grade 4; 9% grade 5 (no grade 6 electrograms were included for analysis). The numerical grade determined by rapid visual inspection agreed with that at manual measurement in 89%. The grade was in agreement within ± 1 grade in 99%. There was agreement in assessment of amplitude (i.e. ‘a’ or ‘b’) in 99%. There was agreement for both number and letter in 88% ($\kappa = 0.87$).

To test the consistency of fractionation and grade in shorter samples 100 electrograms were analysed. The percentage of the sample that was fractionated was remarkably consistent, with less than 5% difference between 3 and 10s (Table 3.1). The grade determined was also consistent with agreement between 10s and 3s in 85% (Table 3.1).

Table 3.1: Consistency of fractionated activity and grade.

Seconds Analysed	Absolute difference in % of sample fractionated from 10 Seconds	Grade agreement with 10 Seconds (%)
3	4.9	85
4	4.2	87
5	3.5	90
6	3.0	90
7	2.5	95
8	1.7	98
9	1.0	97

Legend to Table 3.1: The percentage continuous fractionation and grade was determined by detailed manual measurement at 1 second increments from 3 up to 10 Seconds. Numbers show absolute difference in the percentage of the sample fractionated and the percentage agreement in grade by manual measurement for each time interval compared to 10 Seconds.

Validation of commercial automated detection systems

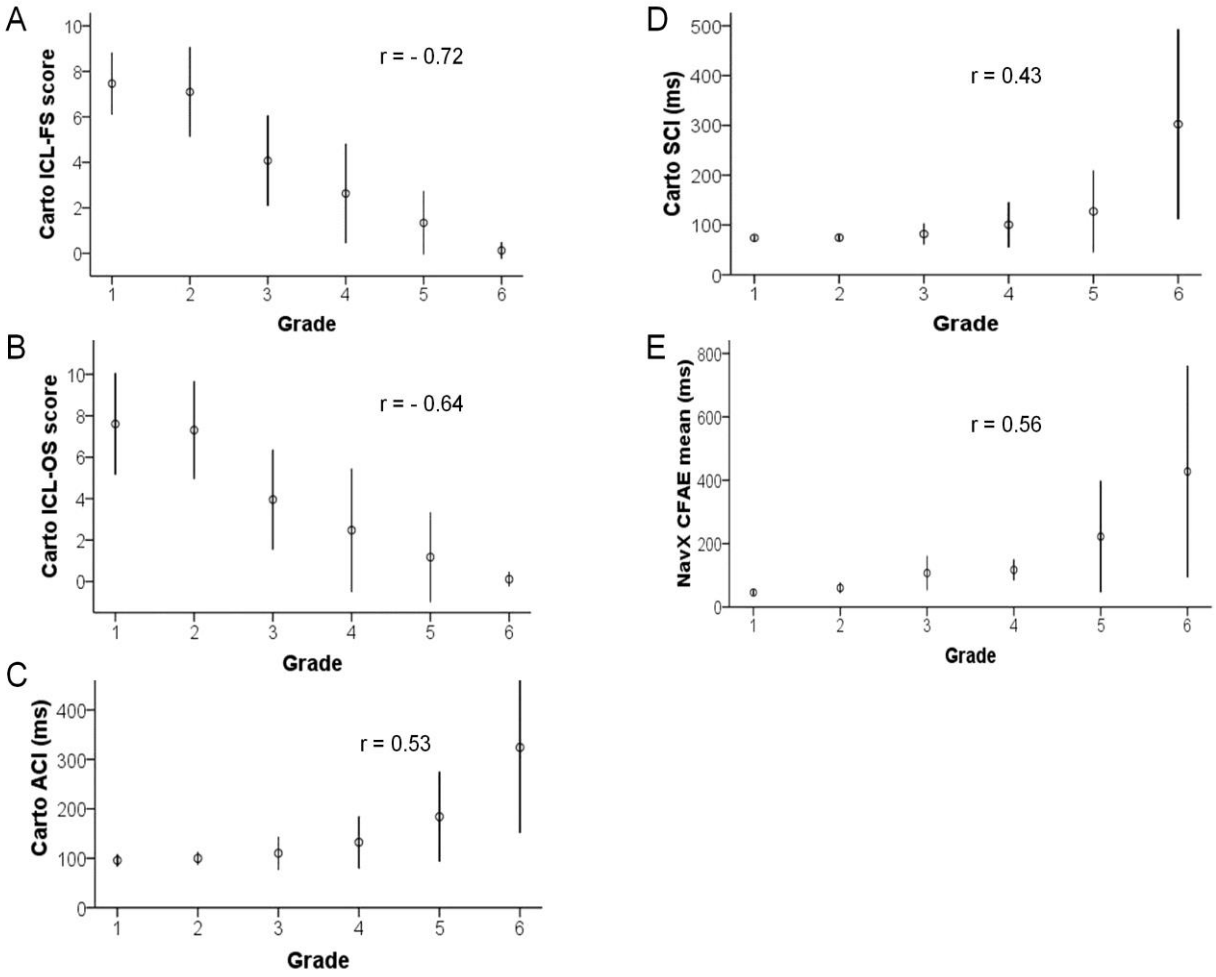
500 electrograms over 5 cases were reviewed for each of Carto and Ensite NavX. To validate visual assessment of electrograms on the 3D mapping system, 100 electrograms were subjected to detailed manual analysis. The numerical grade determined by rapid visual inspection agreed with that at manual measurement in 93%. The grade was in agreement within ± 1 grade in 100%. There was agreement in assessment of amplitude (i.e. ‘a’ or ‘b’) in 99%. There was agreement for both number and letter in 93% ($\kappa = 0.92$).

The automated score is shown plotted against grade for each algorithm in Figure 3.1. All algorithms show moderate correlation between score and grade, with ICL-FS showing the best correlation.

Receiver operating characteristic analysis (shown in Figures 3.2 and 3.3) was used to determine optimal cut-off for each algorithm. Cut-offs for CFAE detection are shown in Table 3.3. Cut-offs for selecting highly fractionated signals were: ICL-FS ≥5, ICL-OS ≥6, ACI ≤99 ms, SCI ≤76ms, NavX CFAE Mean ≤80ms.

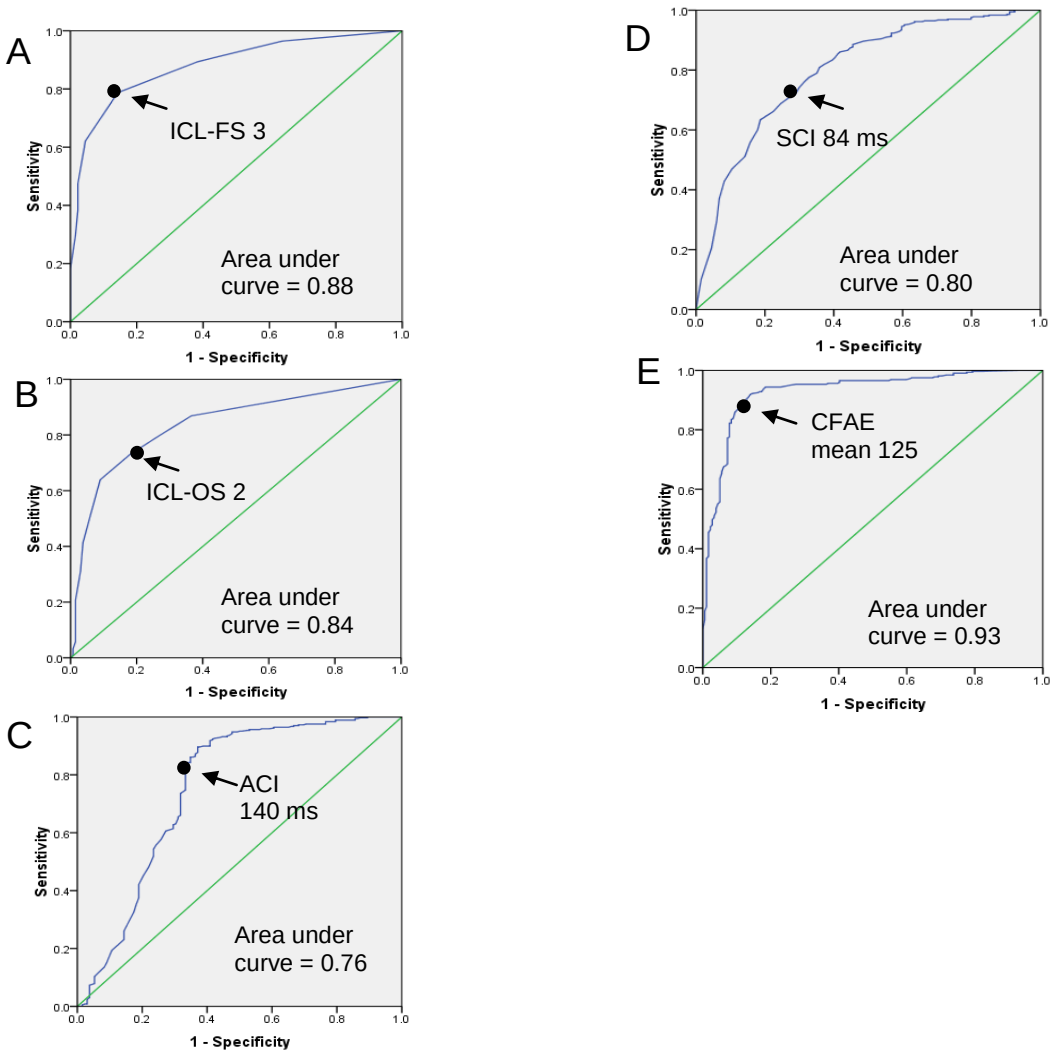
Sensitivity and specificity of each algorithm for detecting CFAE using both the optimal cut-offs determined here and using cut-offs from other studies is shown in Table 3.2. Positive and negative predictive values are also shown for detection of CFAE and selection of highly fractionated signals in Table 3.3.

Figure 3.1: Correlation between grade and score by automated detection systems.



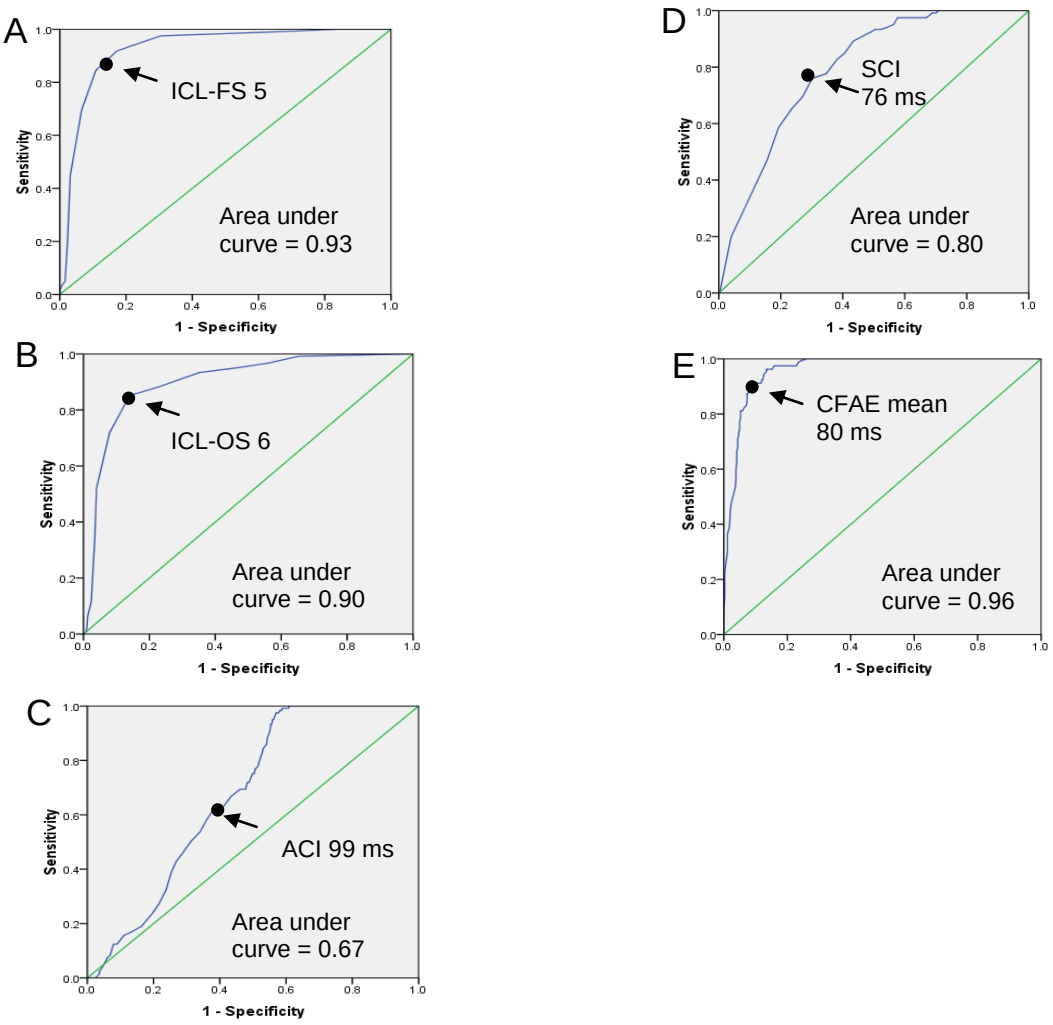
Legend to Figure 3.1: Grade by visual inspection is shown plotted against automated score for each algorithm: **(A)** Interval Confidence Level on factory settings (ICL-FS), **(B)** Interval Confidence Level on previously published optimised settings (ICL-OS), **(C)** Average Complex Interval (ACI), **(D)** Shortest Complex Interval (SCI), **(E)** CFAE mean. Data is presented as mean values for categorical data (i.e. ICL score) or a scatter-plot for continuous data (all other scores). The Spearman Rank correlation coefficient is shown at the top right of each figure.

Figure 3.2: Receiver operating characteristic curves for detection of CFAE (defined as grades 1-4) by each algorithm.



Legend to Figure 3.2: The point marked with the arrow shows the optimal value for detection of CFAE. The area under the curve (AUC) is shown at the bottom right of each figure with 95% confidence intervals in brackets. ROC curves are shown for **(A)** Interval Confidence Level using factory settings (ICL-FS), **(B)** Interval Confidence Level using previously published optimised settings (ICL-OS), **(C)** Average Complex Interval (ACI), **(D)** Shortest Confidence Interval (SCI), **(E)** NavX CFAE mean.

Figure 3.3: Receiver operating characteristic curves for detection of highly fractionated electrograms (defined as grades 1-2) by each algorithm.



Legend to Figure 3.3: The point marked with the arrow shows the optimal value for detection of CFAE. The area under the curve (AUC) is shown at the bottom right of each figure with 95% confidence intervals in brackets. ROC curves are shown for **(A)** Interval Confidence Level using factory settings (ICL-FS), **(B)** Interval Confidence Level using previously published optimised settings (ICL-OS), **(C)** Average Complex Interval (ACI), **(D)** Shortest Confidence Interval (SCI), **(E)** NavX CFAE mean.

Table 3.2: Accuracy of automated CFAE detection using published cut off values and using optimal values from ROC analysis.

	Detection using ROC determined cut off			Detection using previously published cut off		
	Cut off for CFAE	**Sensitivity** (%)	**Specificity** (%)	**Cut off for CFAE**	**Sensitivity** (%)	**Specificity** (%)
NavX	≤125ms	92	91	<120ms	86	91
ICL-FS	≥3	79	86	≥5	38	98
ICL-OS	≥2	80	74	≥5	41	96
ACI	≤140ms	86	66	100≤ms	54	77
SCI	≤84 ms	74	70	≤120ms	96	36

Legend to Table 3.2: Detection of CFAE, using values determined by receiver operating characteristic (ROC) analysis or using previously published values for NavX CFAE mean[251], ICL[250], ACI[93], and SCI.[93]

Table 3.3: Accuracy of Automated CFAE detection.

	Proportion of CFAE (%)	**Sensitivity** (%)	**Specificity** (%)	**PPV** (%)	**NPV** (%)	**Accuracy** (%)
Detection of FE (grade >6)						
NavX	64	92	91	95	87	92
ICL-FS	73	79	86	94	59	81
ICL-OS	73	80	74	89	57	78
ACI	73	86	66	88	62	81
SCI	73	74	70	87	50	73
Detection of highly fractionated electrograms (grade 1-2)						
NavX	32	91	91	82	96	91
ICL-FS	24	92	83	63	97	85
ICL-OS	24	85	86	67	95	86
ACI	24	63	62	35	84	62
SCI	24	76	70	45	90	71

Legend to Table 3.3: The accuracy of algorithms used by Carto and NavX to detect CFAE is assessed using operator selected CFAE (utilizing the grading system described) as the gold standard.

Discussion

Main findings

This study provides the first clear definition for CFAE and a classification system to grade fractionation. This can be accurately applied visually in real time. We have validated automated CFAE detection software and demonstrated that they are capable of accurately distinguishing CFAE from non-fractionated electrograms. Optimum values for detection of CFAE and selection of highly fractionated signals using these algorithms were also determined for the first time.

Classification of electrograms

Imprecise definition of CFAE may account for the difficulty in reproducing results with CFAE guided ablation of AF. Several features in electrograms have been described in the literature as fractionated, most notably continuous deflections from baseline, discrete complexes with multiple deflections and complexes with short cycle length, although the precise definition of these varies between studies. Proposed mechanisms underlying CFAE include pivot points, focal drivers (including rotors and rapidly discharging foci) and ganglionated plexi.[90, 207, 208, 214, 216] Evidence from optical mapping has suggested that rapid deflections producing continuous fractionation may represent areas within a few millimetres of focal drivers where wave fronts collide and fail to propagate in a 1:1 fashion.[207, 208] These phenomena may co-exist but it is uncertain which electrogram appearance represents which pathophysiology, and which ought to be targeted for ablation. The classification system described is therefore based partly on pathophysiology and partly on clinical studies regarding efficacy.

During AF, targeting electrograms with a high proportion of fractionated activity (≥70% of recording), or areas with concentric activation have all been shown to produce a significant step up in AFCL.[241, 255] Sites with uninterrupted fractionated activity lasting longer than 1 second have been shown to be more prevalent and more diffuse in patients with persistent AF than paroxysmal AF and hence this has been proposed as a target for ablation.[216] We used these data in development of our CFAE classification, with these features used as criteria to describe highly fractionated electrograms (i.e. grades 1-2). Other features incorporated into the grading system were criteria used by Nademanee and others in clinical trials, such as less consistent fractionation and complex electrograms.[191, 194] Evidence for targeting these electrograms is more limited, as they have only been targeted in combination with others to produce clinical outcomes. These features were incorporated into the less fractionated signals (grades 3-4).

Application of classification and time intervals for analysis

Application of the grading system was simple and accurate. Detailed manual analysis of electrograms showed that the percentage of a recording with continuous fractionation is relatively constant over time, with only 5% absolute difference between 3 and 10s. Accurate application of the classification system required 5 Seconds to give an accuracy of 90%.

These data therefore validate the classification system in terms of its accurate application. It was essential to establish whether different CFAE morphologies could be accurately distinguished before attempting to study the impact of

ablating those different CFAE morphologies. These data therefore demonstrate the feasibility of this approach, with operators grading fractionated electrograms by eye and allowing CFAE morphologies to be targeted in a specific order live during a clinical case. Having performed this necessary validation step it was thought reasonable to proceed with the study comprising Chapter 4 of this thesis.

Automated analysis of fractionated electrograms

These results show that all of the algorithms tested are good at detecting CFAE and selecting highly fractionated signals. The Ensite NavX CFAE mean algorithm gave the best results in terms of CFAE detection. Of the Carto algorithms, the ICL algorithm using factory settings was marginally better than the others tested. There was moderate correlation between the grade determined and the score for each algorithm. The Carto ICL-FS algorithm showed the best correlation with grade (Figure 3.1). None of the algorithms distinguished well between grades 1 and 2, or grades 3 and 4. The CFAE mean algorithm was therefore the most accurate in terms of CFAE detection, whereas the ICL-FS score correlated best with the degree of electrogram fractionation.

The few studies examining accuracy of automated CFAE detection have compared an operator's visual assessment to the automated scores using an arbitrary cut off.[221, 247, 250, 251] This is the first study to validate automated assessment of degree of fractionation or to determine optimal cut-off for CFAE detection. The studies examining the NavX CFAE mean algorithm found similar sensitivity and specificity to that presented here.[221, 247]

A study examining the Carto ICL algorithm found a sensitivity and specificity of 58 and 64% respectively using factory settings, but improved this to 90 and 91% respectively using their optimised settings (the settings used for the ICL-OS group).[251] A study comparing ICL and ACI found poor results for the ICL algorithm but a sensitivity and specificity both of 92% for ACI in detecting CFAE.[250] Although no studies have assessed diagnostic accuracy of the SCI algorithm, retrospective application has shown that a low SCI predicted a significant increase in cycle length on ablation.[93] Studies using automated detection systems to guide CFAE ablation have been 'proof of concept' as they have not compared this approach to alternative means of identifying CFAE.[221, 265, 266]

Limitations

Although this classification system is based on previous evidence regarding what constitutes CFAE and which are important to target, it is recognised that this evidence remains week. However, the classification of CFAE on morphological grounds is a necessary first step before one can study the effect of ablating these different morphologies (which is explored further in the chapters that follow).

The classification of electrograms by visual inspection to validate automated CFAE detection systems (rather than detailed manual assessment of all electrograms) is also a limitation. However, the initial step validating application of the grading system has demonstrated for the first time that this approach is accurate and hence reasonable to use as a surrogate for manual analysis. Previous studies examining automated CFAE detection have also used the

visual inspection method, as the volume of samples needed for meaningful validation precludes manual analysis.[221, 247, 250, 251]

Conclusion

For the first time a precise definition of different CFAE sub-types has been given. The classification system proposed can be quickly and accurately applied by eye to distinguish between different patterns of CFAE. Adopting this standardised description of CFAE will enable clinical trials of CFAE ablation to use reproducible methodology and thus allow meaningful comparison of results. Having validated the application of this classification system, further work studying the impact of targeting different CFAE morphologies now appears feasible. Use of this grading system has also allowed validation of the current Carto and NavX algorithms.

Chapter 4

Characterization of fractionated atrial electrograms critical for maintenance of AF: a randomized controlled trial of ablation strategies (the CFAE AF trial).

Abstract

Introduction: Whether ablation of complex fractionated atrial electrograms (CFAE) modifies AF by eliminating drivers or atrial de-bulking remains unknown. This randomised study aimed to determine the effect of ablating different CFAE morphologies compared to normal electrograms (i.e. de-bulking normal tissue) on the cycle length of persistent AF (AFCL).

Methods: After pulmonary vein isolation left and right atrial CFAE were targeted, until termination of AF or abolition of CFAE prior to DC cardioversion. 10s electrograms were classified according to a validated scale, with Grade 1 being most fractionated and grade 5 normal. Patients were randomised to have CFAE grades eliminated sequentially, from grade 1 to 5 (group 1) or grade 5 to 1 (group 2). An increase in AFCL (mean of left and right atrial appendage) ≥5 ms following a lesion was regarded as significant.

Results: 968 CFAE were targeted in 20 patients. AFCL increased after targeting 51 ± 35% of grade 1 CFAE, 30 ± 15% grade 2, 12 ± 5% grade 3, 33 ± 12% grade 4, and 8 ± 15% grade 5 CFAE ($p < 0.01$ for grades 1, 2, and 4 versus 5, 3 versus 5 not significant). The proportion of lesions causing AFCL prolongation was unaffected by the order in which CFAE were targeted.

Conclusion: Targeting CFAE is not simply atrial de-bulking. Ablating certain grades of CFAE increases AFCL, suggesting they are more important in maintaining AF.

Clinical Trial Registration Information: www.clinicaltrials.gov NCT00894400.

Introduction

Although Nademanee demonstrated that CFAE ablation could eliminate AF,[194] there has been difficulty reproducing this success using CFAE ablation alone.[222, 265, 267] Incremental benefit of CFAE ablation in addition to PVI has been demonstrated,[191, 221, 222, 225] although not consistently.[64, 224]

The variable definition of CFAE may partly explain these disparate results.[194, 267-269] It is uncertain what the various CFAE morphologies represent, and few studies have examined the importance of different electrogram characteristics of CFAE.[241, 254] It therefore remains unclear whether CFAE are sites critical to the maintenance of AF or whether the slowing or termination of persistent AF is the inadvertent result of de-bulking electrically active atrial tissue.

It was hypothesised that certain CFAE morphologies are more likely to represent drivers of AF. To prove this, the impact of targeting different CFAE morphologies on the cycle length of persistent AF was assessed, with ablation performed according to a strict protocol as part of a randomised controlled trial.

Results

Patients and procedures

The characteristics of the 20 patients randomised are shown in Table 4.1. All patients had persistent AF, and 90% of these were long lasting persistent AF (i.e. ≥ 1 year). Although the patients were older in group 2, the other baseline characteristics were well matched between groups. Procedural characteristics are shown in Table 4.2. There was no difference between groups in procedure time or fluoroscopy time (Table 4.2). The only procedural complication was 1 groin haematoma, which did not require any intervention.

Inter-operator variability

The CFAE grade determined by rapid visual inspection for the 968 electrograms targeted agreed with that at off-line manual measurement in 92.7%. The grade was in agreement within ± 1 grade in 99.0%. There was agreement in assessment of amplitude (i.e. ‘a’ or ‘b’) in 99.1%. There was agreement for both number and letter in 91.9% ($\kappa = 0.91$). Inter-operator variability for measurement of AFCL was 0.3 ± 0.2 ms.

Table 4.1: Patient Characteristics.

	Group 1 (grade order 1 to 5)	Group 2 (grade order 5 to 1)	p value
Number	10	10	-
Male	90%	80%	1.000
Age	60 ± 7	66 ± 6	0.042
Months of continuous AF	25 ± 19	20 ± 9	0.424
NYHA class	2.1 ± 0.6	2.3 ± 0.5	0.407
Hypertension	50%	50%	1.000
Ischaemic heart disease	20%	40%	0.629
Left atrial diameter	4.5 ± 0.8	4.6 ± 0.8	0.935
Ejection fraction	51 ± 13	46 ± 15	0.379

Legend to table 4.1: Data is presented as percentage of patients, or mean ± standard deviation.

Table 4.2: Procedural characteristics and success.

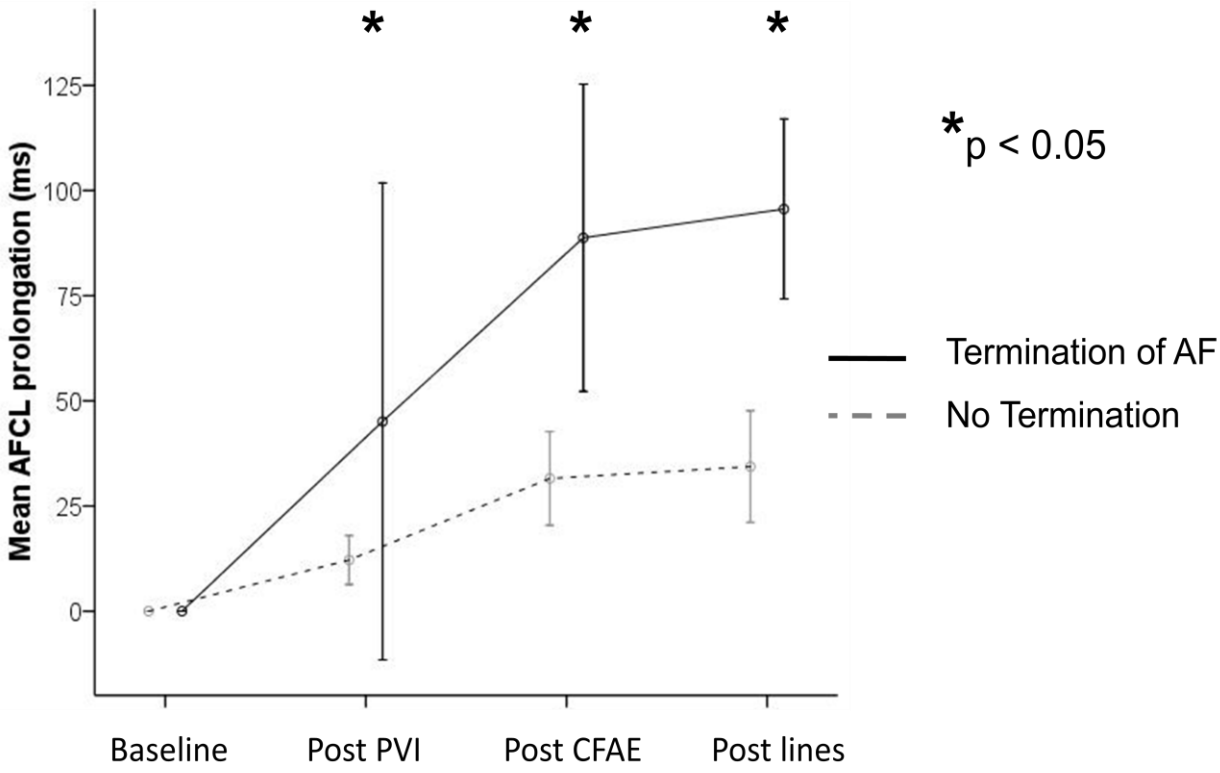
	Group 1 (grade order 1 to 5)	Group 2 (grade order 5 to 1)	p value
Procedure time (mins)	300	305 (300-450)	0.327
Time targeting CFAE (mins)	90 (0-143)	96 (0-148)	0.500
Fluoroscopy time (mins)	63 (35-114)	57.5 (28-78)	0.456
CFAE lesions per patient	43 ± 16	68 ± 18	0.007
Termination of AF by ablation	30%	30%	1.000
Single procedure success	40%	20%	0.629
Recurrence due to AT/AF	4/2	3/5	0.592

Legend to Table 4.2: Data is presented as percentage of patients, mean ± standard deviation, or median (range).

Definition of AFCL prolongation

Baseline AFCL variability prior to any ablation over 10 successive cycles from each patient showed variation of 1.49 ± 1.74 ms. As mean + 2 standard deviations was 4.97 ms, ≥ 5.0 ms was subsequently regarded as significant AFCL prolongation. The impact of ablation on AFCL is shown in Figure 4.1, illustrating it's potential value in monitoring response to ablation.

Figure 4.1: Impact of ablation on AF cycle length.



Legend to Figure 4.1: The mean (± standard deviation) change in AFCL from baseline is shown at each stage of the procedure. The progressive prolongation of AFCL was more marked in patients whom AF was terminated during ablation.

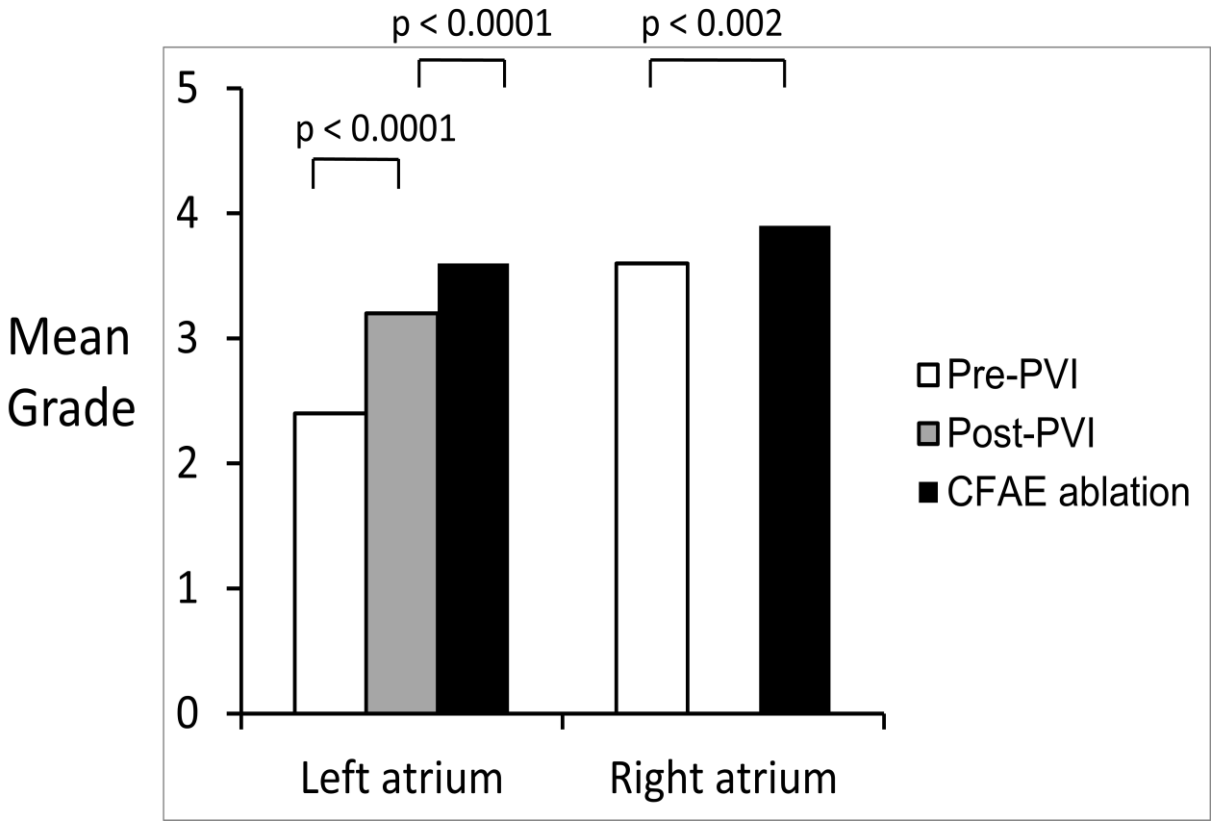
Distribution of CFAE

Mean CFAE grade pre-PVI was lower in the LA than the right atrium (2.4 ± 1.1 versus 3.7 ± 1.2, $p < 0.001$) reflecting decreased organisation in the LA. The most common sites for highly fractionated electrograms (grade 1-2 CFAE) in the LA were the PVs (55-75%), the LA appendage ridge (75%), the high and low left septum (80% and 70%), and the high and mid anterior wall (75% and 65%). The most common sites for highly fractionated electrograms in the RA were the mid and low right septum (both 38%), the roof/SVC (38%), and the high, mid and low lateral wall (31-38%).

Impact of Ablation on CFAE grade

All 40 PV pairs were successfully isolated by WACA, and 36 of 40 PV pairs contained at least 1 highly fractionated electrogram (grade 1-2 CFAE). AFCL prolongation occurred after isolation of 23 PV pairs. As 2 patients reverted to sinus rhythm during PVI and 1 during LA CFAE ablation, 18 patients had full maps of the LA pre-PVI, post-PVI, and during CFAE ablation, and 17 patients had maps of the right atrium pre-PVI and during CFAE ablation. Because all 4 PVs were electrically silent post-PVI, in effect 18 LA and 16 right atrial segments were available for comparison with baseline maps (324 LA segments and 272 right atrial segments in total for each stage). PVI caused an increase in the mean grade of LA segments (representing increased organisation of electrograms) from 2.4 ± 1.1 to 3.2 ± 1.4 ($p < 0.0001$). During LA CFAE ablation there was a further increase in mean grade from 3.2 ± 1.4 to 3.6 ± 1.5 ($p < 0.0001$). Similarly, during right atrial CFAE ablation there was an increase in grade from 3.6 ± 1.3 to 3.9 ± 1.4 ($p = 0.002$). The impact of ablation on mean CFAE grade in the left and right atria are summarised in Figure 4.2.

Figure 4.2: Impact of ablation on mean grade in the left and right atria.



Legend to Figure 4.2: Mean CFAE grade in the left and right atrium at different stages of the procedure.

Impact of targeting different CFAE grades on AF cycle length

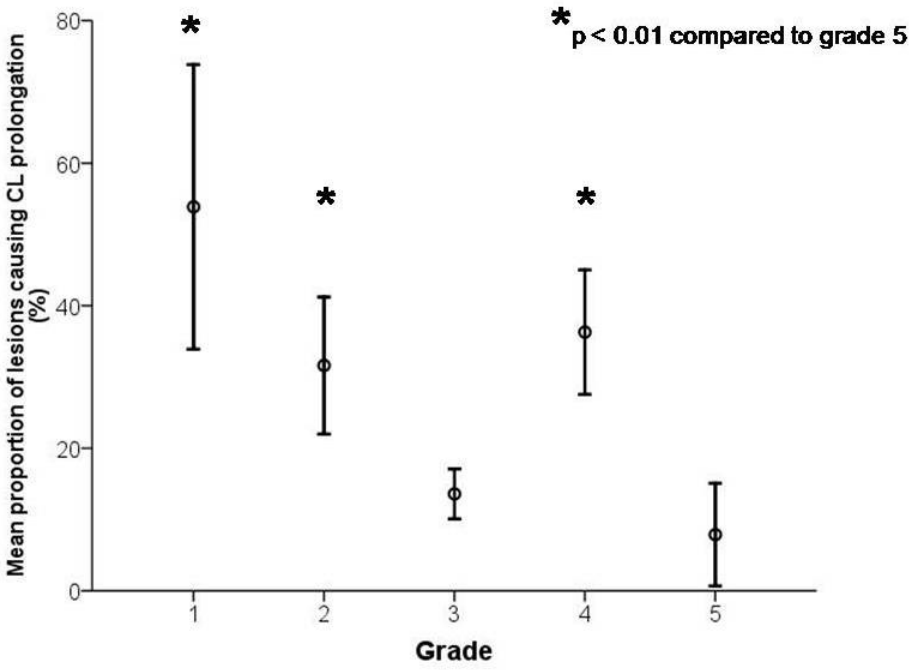
There was a significant overall effect of CFAE grade on the mean proportion of lesions causing AFCL prolongation ($p < 0.001$; Figure 4.3A). The mean proportion of lesions which caused a significant increase in AFCL was significantly greater for grade 1, 2 and 4 CFAE compared to grade 5 ($p < 0.01$ for each). There was no difference between grade 3 and 5 in the proportion of lesions affecting AFCL, with prolongation occurring no more often than during baseline variability testing (i.e. during no ablation). There was no effect of the order of ablation on the proportion of lesions causing AFCL prolongation ($p = 0.371$), and no interaction between grade and the order of ablation ($p = 0.449$; Figure 4.3B).

Analysis of the proportion of lesions causing AFCL prolongation pooled across all CFAE showed a similar pattern of response to ablation across grades (Figures 4.5A & 4.5B). Binary logistic regression confirmed the effect of grade on the proportion of lesions causing AFCL prolongation ($p < 0.001$), but showed no effect of group ($p = 0.320$), amplitude ($p = 0.717$; Figure 4.4A), or location in the left or right atrium ($p = 0.987$; Figure 4.4B).

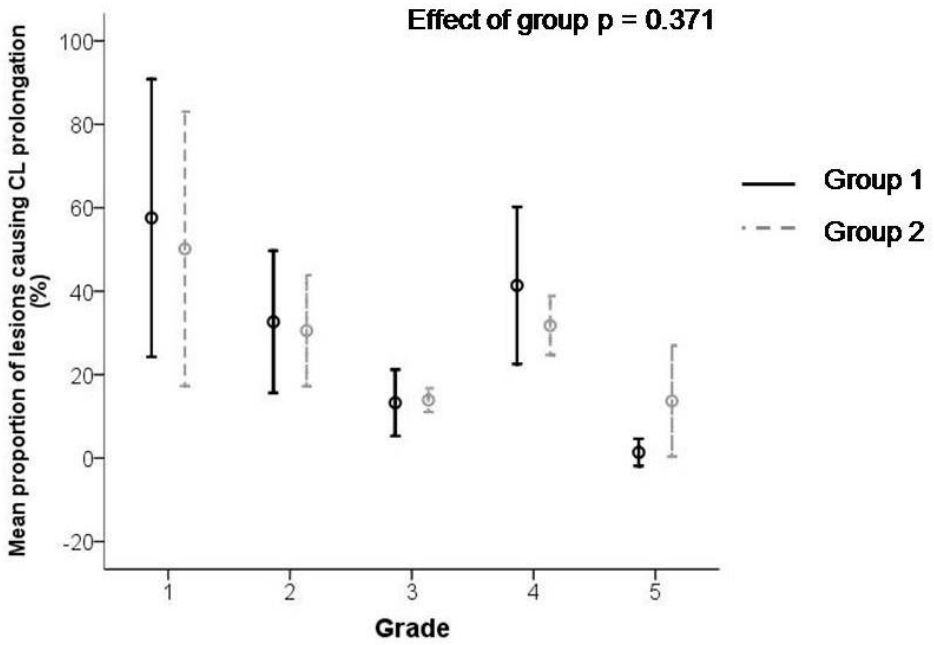
The CL of grade 4 CFAE was > the appendage CL of the atria in which it was located in 77% of cases , and this did not affect the proportion of lesions causing AFCL prolongation (31% when CL was shorter and 34% when CL was longer than that in the appendage CL, $p = 0.683$)

Figure 4.3: Mean proportion CFAE lesions causing AFCL prolongation.

A. Overall impact of CFAE grade.



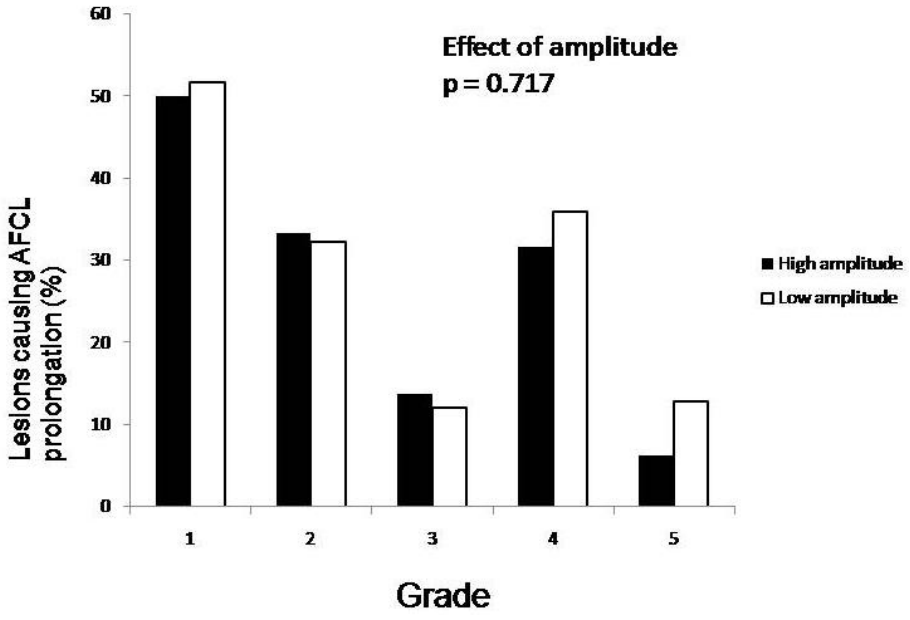
B. Impact of order of CFAE ablation .



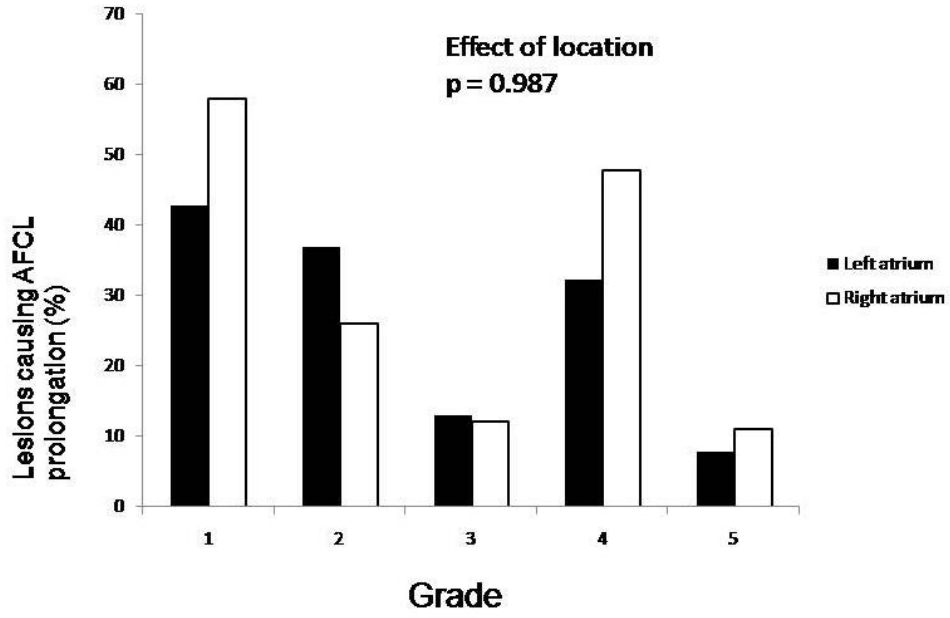
Legend to Figure 4.3: The mean percentage of lesions causing AFCL prolongation (A) by grade for all patients, and (B) divided for groups 1 and 2. Bars show 95% confidence intervals.

Figure 4.4: Proportion of CFAE lesions causing AFCL prolongation.

A. Impact of CFAE amplitude.



B. Impact of CFAE location.



Legend to Figure 4.4: The percentage of all lesions causing AFCL prolongation by grade, divided according to (A) amplitude (either high 'a' or low 'b'), and (B) location in the left or right atrium.

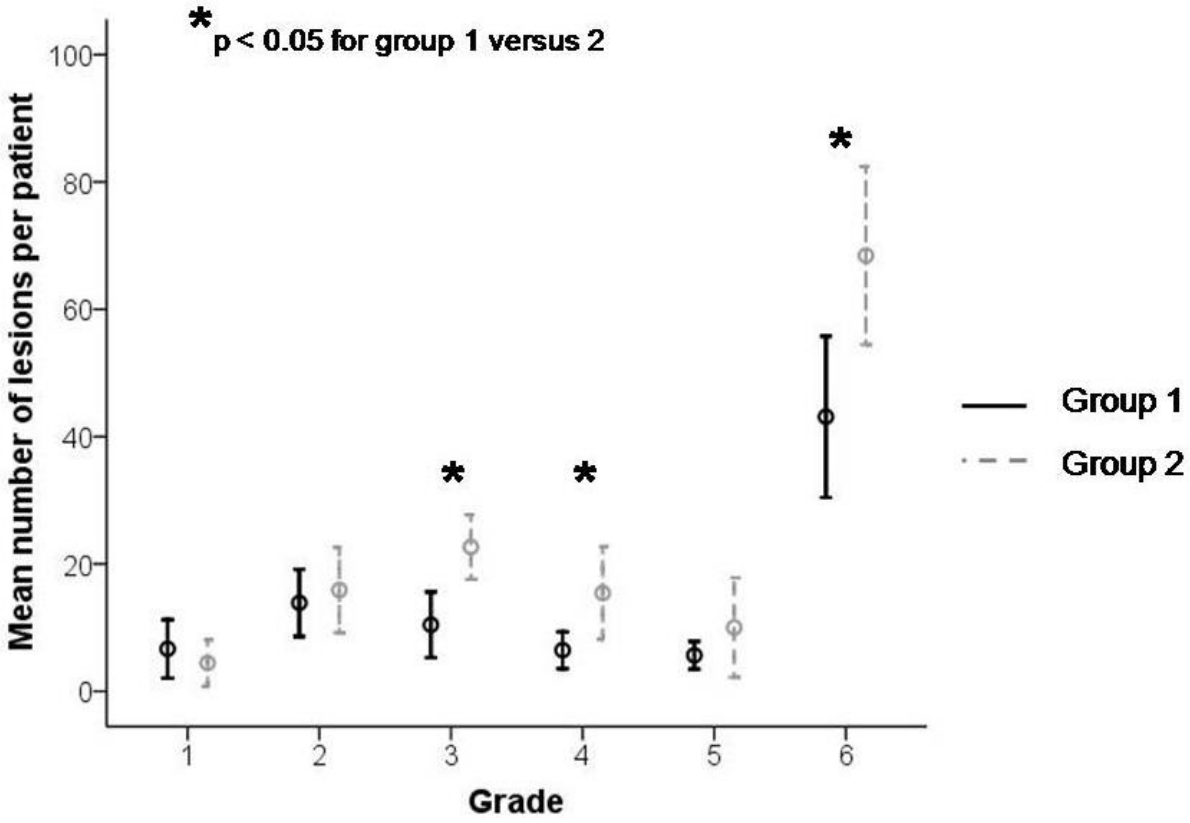
Location of CFAE targeted

No CFAE were targeted inside the PVs (since they were electrically silent post WACA), or the vena cavae. Otherwise, pooling CFAE lesions from all patients, the proportion of lesions per region (divided as shown in Figure 4.1) was normally distributed with 3.0 ± 2.2% of lesions per region. The most targeted regions in the LA were the border of the LA appendage (7.3% of all lesions), the mid anterior wall (7.2%), the roof (7.1%), the lateral wall bordering the left atrial appendage (6.9%), the ridge between the left atrial appendage and the left PVs (6.0%), and the mid septum (5.9%). The most targeted regions in the right atrium were the high and mid lateral wall (5.7 and 3.3% of all lesions respectively), the high septum (5.1%), the roof bordering the SVC (3.6%), and the right atrial appendage (2.6%). The proportion of lesions that prolonged AFCL was also normally distributed between regions (30 ± 11% of lesions). The number of lesions per region was insufficient to allow meaningful comparison of these small regional differences.

Impact of order of ablation on the number of CFAE encountered

There was a significant overall effect of the order of ablation on the mean number of CFAE targeted per patient for each grade ($p < 0.01$; Figure 4.5). Fewer grade 3 and 4 CFAE were encountered per patient in group 1 than group 2 (both $p < 0.05$; Figure 4.5) suggesting that elimination of the most fractionated electrograms (grade 1 and 2) changed the degree of fractionation of electrograms at other sites. This translated to a lower total number of lesions per patient in group 1 ($p < 0.01$; Figure 4.5). There was no difference between groups in the number of grade 1 or 2 CFAE ablated, or the number of grade 5 lesions created.

Figure 4.5: Impact of order of ablation on the number of CFAE subtypes.



Legend to Figure 4.5: The mean number of CFAE targeted per patient in groups 1 and 2. Bars show 95% confidence intervals.

Impact of order of CFAE ablation on outcome

Three patients were ablated to sinus rhythm in each group (two via an atrial tachycardia in each group). In group 1, this occurred once during PVI, once during CFAE ablation, and once during linear lesions. In group 2, this occurred once during PVI, and twice during CFAE ablation. The number free from AF after a single procedure at 12 months off anti-arrhythmic drugs, and the proportion of recurrence due to AF/AT did not differ between groups (Table 4.2).

Discussion

This study is the first to prospectively compare the effect of targeting different CFAE morphologies in persistent AF. The grading of CFAE using our classification system was easily applied, accurate, and reproducible, and enabled distinction between CFAE subtypes which produce a differential effect on AFCL when ablated. Importantly, targeting normal electrograms had no significant effect. PVI had an organising effect on electrograms in all locations. Ablation of highly fractionated electrograms first resulted in a reduction in the number of grade 3 and 4 CFAE encountered subsequently, and consequently a reduction in the total number of lesions delivered.

Mapping studies have shown that targeting areas with concentric activation or slow conduction prolong AFCL, although these mechanisms may be difficult to infer from an ablation catheter electrogram.[241, 255] Takahashi *et al.* analysed electrogram characteristics associated with AFCL prolongation during CFAE ablation.[241] Although dominant frequency and electrogram amplitude had no effect, fractionated activity for ≥ 70% of the recording was associated with AFCL prolongation. Our study has confirmed this firstly by prospectively targeting CFAE with this characteristic, and secondly by varying the order of CFAE ablation to ensure this effect was not a result of targeting this characteristic first or last.

Lin *et al* demonstrated improved outcomes after PVI with selective targeting of CFAE which were ‘consistent’, defined using an automated algorithm over a 1 minute recording.[225] Sites with uninterrupted fractionated activity ≥ 1 second

have been proposed as targets for ablation based on the observation that they are more prevalent and more diffuse in patients with persistent AF than paroxysmal AF.[216] The current study has demonstrated the incremental importance of these sites over those with interrupted fractionation.

Fractionated activity may represent areas within a few millimetres of focal drivers, whether they are rotors or rapidly discharging foci.[207, 208] Ibutilide has been shown to limit re-entry in an animal model of AF using high density mapping, but did not affect focal sources.[270] Similarly, procainamide has been shown to organise electrograms with either multiple deflections or limited fractionation in an animal model of AF, but had little effect on more fractionated signals.[271] These authors concluded that continuous fractionated activity (perhaps analogous to grades 1 and 2 in the present study) may represent focal mechanisms, whereas less fractionated signals (more like grades 3 and 4) are more likely to represent re-entry.[270, 271]

The results of the present study would be compatible with grade 1 and 2 CFAE representing such focal drivers. The increased efficacy when ablating areas with uninterrupted fractionated activity (grade 1 CFAE) may suggest greater proximity to these foci, or perhaps that the drivers are more stable spatially and temporally. We did not incorporate a grade for rapid regular electrograms because in Chapter 3 these were found to be invariably interspersed with fractionated activity, and hence met the criteria for other grades of CFAE. Therefore, more consistent CFAE (grade 1) may have had different organisational characteristics which were not discernable by eye.

An interesting finding was that an apparently less fractionated electrogram (grade 4) had a greater effect than a more fractionated electrogram (grade 3). We postulate that grade 3 electrograms are produced by passive wave front phenomena or superimposition of far-field and local electrograms, which are not critical for maintenance of AF. Grade 4 electrograms were not rapid, and in particular were not usually faster than the AFCL of the atria in which they were located. Therefore, whilst grade 4 CFAE are unlikely to be rapid drivers, they may represent other phenomena which facilitate AF, such as zones of slow conduction, pivot points, or wave-break.[47, 214]

The optimal amplitude of CFAE to target is controversial. Whilst some authors consider only low amplitude signals (< 0.5 mV) to be CFAE,[194] others disregard amplitude.[268] Our data suggest that electrogram amplitude does not predict response to ablation.

Ablation of right atrial CFAE is also controversial. Although a small randomised controlled trial showed that right atrial CFAE ablation in addition to PVI and LA CFAE did not improve outcome,[272] another study demonstrated that in those with continuing AF despite PVI and LA CFAE ablation, right atrial CFAE ablation prolonged AFCL and terminated AF in 55%.[273] This study suggests that targeting CFAE in the right atrium was equally efficacious as in the left.

The lesions which caused AFCL prolongation were evenly distributed throughout the atria. A previous study which targeted CFAE in a randomised order of locations found no effect of ablation location on AFCL.[241] However, it

remains possible that CFAE are surrogate markers for ganglionated plexi, since their anatomy is variable.

The impact of PVI and CFAE ablation on electrogram organisation

The reduction in LA CFAE burden after PVI has been demonstrated by others.[202, 274] This may simply reflect the removal of PV drivers, although this would not fully account for (a) the impact at sites distant to the PV ostia, and (b) the impact on areas with continuous fractionation suggestive of focal drivers.

Injection of epicardial fat pads with acetylcholine has been shown to cause continuous fractionation or rapid regular 'rotor-like' electrograms, both locally and at distant atrial sites due to a wider activation of the cardiac neural network.[212] Targeting of ganglionated plexi eliminated these areas of continuous fractionation, both locally and at distant sites.[212, 270] Hence, PVI may impact on atrial CFAE by reducing ganglionated plexi innervation.

Significantly fewer CFAE were targeted in group 1, powered by the reduction in grade 3 and 4 CFAE. To some extent these grades may be epi-phenomena, with a greater functional component supported by the highly fractionated grade 1 and 2 CFAE. The number of grade 1 and 2 CFAE were unaffected by prior ablation of grades 3 and 4, consistent with their proposed focal mechanisms.

Limitations

This mechanistic study was not designed to assess the impact of CFAE ablation on outcomes, nor was it intended or powered to demonstrate superiority of either targeting strategy in terms of clinical end-points. Nevertheless, by

studying the response to ablation of different CFAE morphologies we have clarified many key issues in CFAE ablation. Although this information could not have been gleaned from conventional randomised controlled trials looking at clinical outcomes, we recognise that such studies remain essential for determining the optimal approach to CFAE ablation.

Although ablation to sinus rhythm is a hard end-point, this was achieved in a minority, and it is recognised that the alternative of elimination of all CFAE is more subjective. However, this cohort consisted mostly of patients with dilated atria and long-lasting persistent AF, and hence although the proportion ablated to sinus rhythm and the proportion free from AF at 1 year were disappointing, this was in keeping with reports for comparable cohorts.[64, 182, 275]

Conclusion

The differential effect of targeting different CFAE morphologies provides strong support for the hypothesis that certain CFAE represent focal drivers of AF. Therefore targeting of CFAE is not simply de-bulking the atria. These results support ablating certain CFAE morphologies whether in the left or right atria, and regardless of their amplitude. A selective strategy targeting only certain CFAE (grades 1, 2 and 4) and starting with the most fractionated (grades 1 and 2) should minimize LA destruction and time spent targeting CFAE.

Chapter 5

Left atrial wall stress distribution and its relationship to electrophysiologic remodelling in persistent atrial fibrillation.

Abstract

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

Methods: 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).

Results: 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 remodelling. Although peaks in wall stress were not associated with LA CFAE, the PV ostia may respond differently.

Introduction

Increased atrial stretch is a common aetiological factor in patients with AF.[13] Chronic stretch causes atrial dilatation and heterogenous changes in atrial architecture, including focal myocyte hypertrophy and fibrosis.[134, 137, 139, 140] 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.[94, 132-137, 139, 140]

Although PVI is a successful treatment for paroxysmal AF,[191] additional substrate modification in some form or another appears to be necessary to achieve acceptable results for persistent AF. [191, 228] Greater understanding of the relationship between atrial stretch and remodelling may allow refinement of substrate modification. Computer modelling has been used to better understand complex processes such as excitation contraction coupling and mechanical function,[276, 277] and may help understand how stretch is distributed in the walls of the LA and how this impacts on atrial remodelling. The relationship between this remodelling process and CFAE is of particular interest, since CFAE localising to foci of remodelling could feasibly be more mechanistically important in maintaining AF than those found in healthy tissue.

We hypothesized that peaks in LA wall stress are associated with focal electrophysiologic remodelling which maintains AF. There were three stages required to address this, each dependent on the success of the preceding stage:

1) A computer model was established to simulate LA wall stress in 3D reconstructions of the LA from CT scans.
2) Electrophysiologic data were collected at the time of catheter ablation for persistent AF and compared to simulated wall stress data using a patient specific LA geometry derived from a pre-procedure CT scan. This allowed correlation between wall stress and electrophysiologic parameters, in particular areas of low voltage and CFAE.
3) 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 AFCL.

Results

Patients

Although 20 patients were recruited, one patient had poor quality CT imaging and was excluded from the analysis Patient demographics for the 19 patients forming the study group are shown in Table 5.1. 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. No patients had significant valvular heart disease.

Stress Distribution

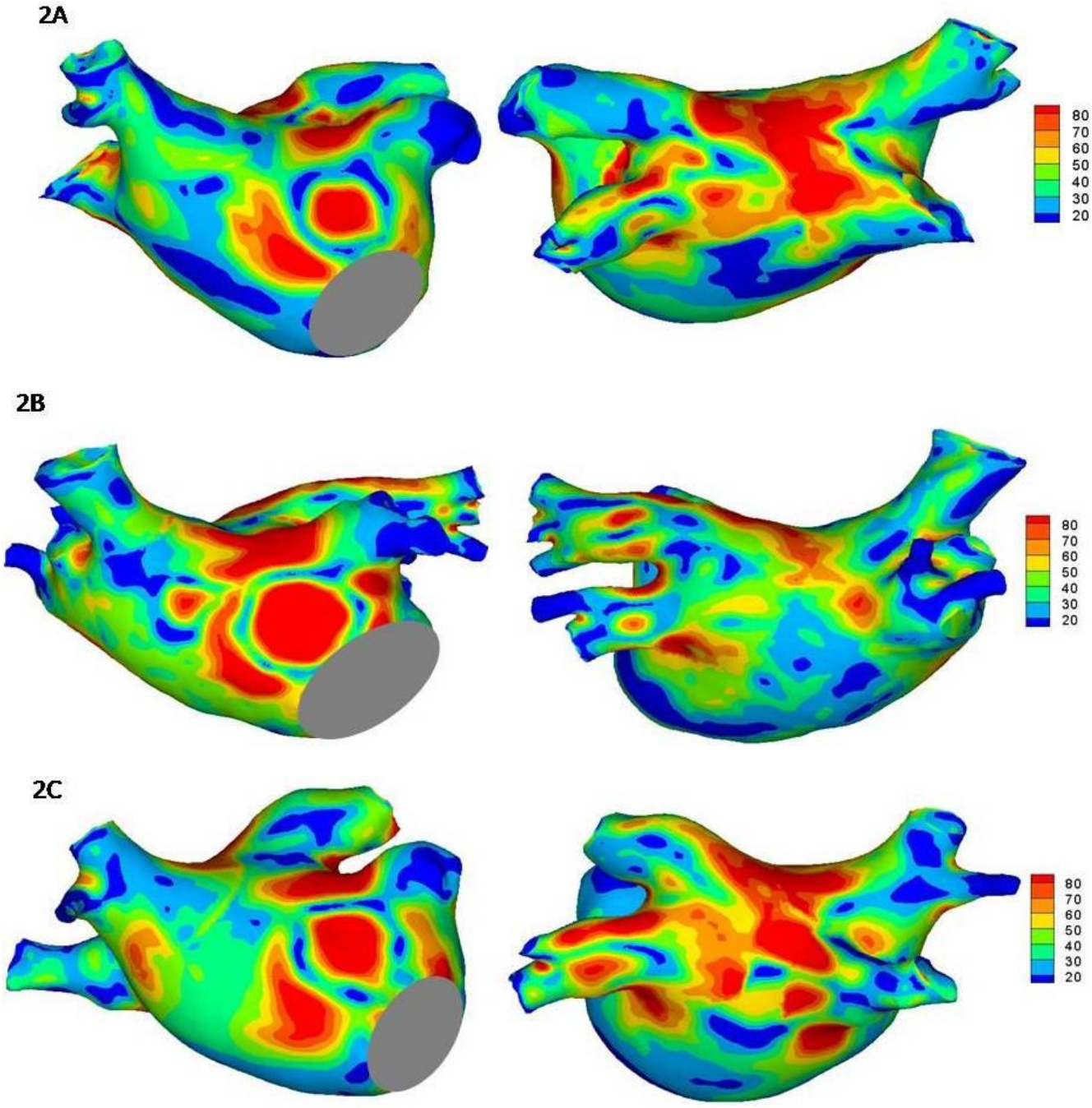
Figure 5.1 shows examples of wall stress distribution. Wall stress varied widely from region to region, with a median value of 36.4 kPa and an inter quartile range of 26.2 – 51.6 kPa. Figure 5.2 shows the proportion of patients who had peaks in wall stress over the different regions shown in Figure 5.1. 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 5.1 did not differ when comparing the 9 most dilated LA to the 9 smallest.

Table 5.1: Patient Characteristics.

Male	84%
Age	64 ± 7 yrs
Months of continuous AF	23 ± 16
Hypertension	53%
Ischaemic heart disease	32%
Left atrial volume	159.0 ± 46.8 ml
Ejection fraction	48 ± 14 %

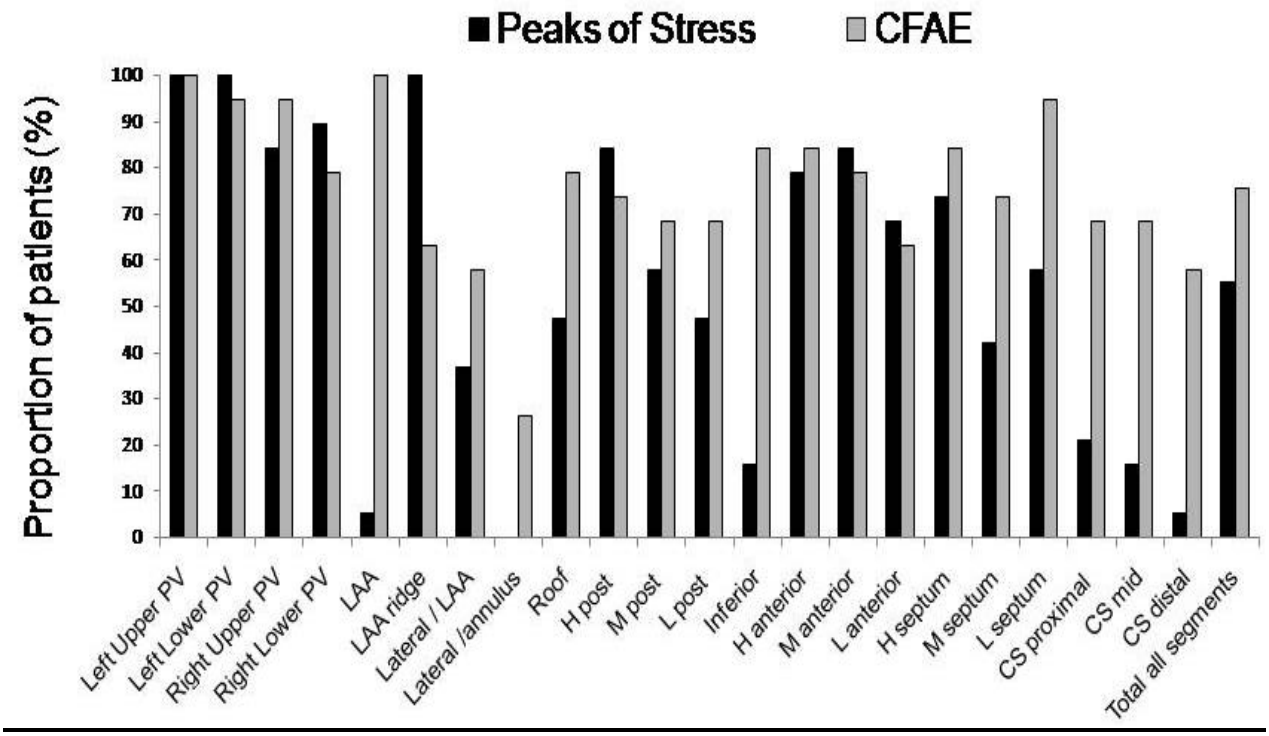
Legend to table 5.1: Data is presented as percentage of patients, or mean ± standard deviation.

Figure 5.1: Left atrial wall stress distribution.



Legend to Figure 5.1: Colour coded maps of the left atrium showing wall stress distribution in 3 patients (A-C). The scale is kPa.

Figure 5.2: Distribution of peaks in wall stress and CFAE.



Legend to Figure 5.2: 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 appendage; CS, coronary sinus; H, high; M, middle; L, low.

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.

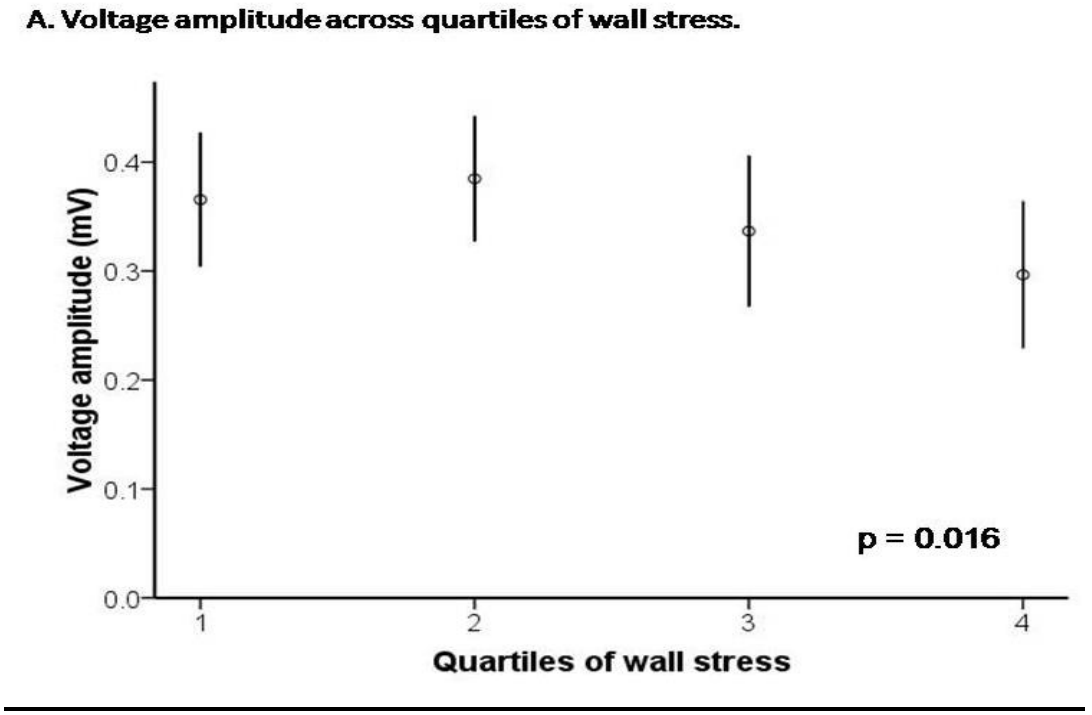
Relationship between wall stress and electrophysiologic parameters

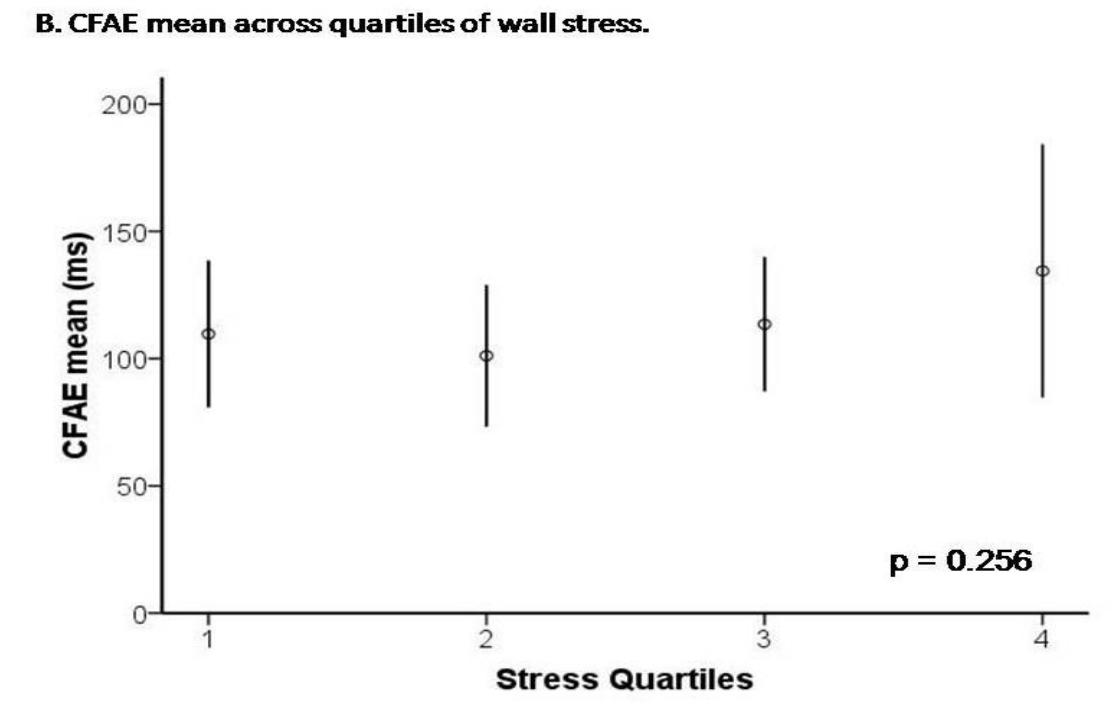
Electrogram amplitude showed a linear inverse relationship across quartiles for wall stress meaning lower electrogram amplitude at sites of higher wall stress, with a 19% difference between the highest and lowest quartiles for wall stress ($p = 0.016$, Figure 5.3A). There was a trend towards higher CFAE 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 5.3B).

Relationship between remodelling and CFAE

There was a significant decrease in CFAE mean across quartiles of voltage amplitude (Figure 5.4; $p < 0.0001$). 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 ($r = -0.54$, $p = 0.017$).

Figure 5.3: Relationship between electrophysiology and wall stress.





Legend to Figure 5.3: 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.

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 CFAE (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 ($p = 0.587$).

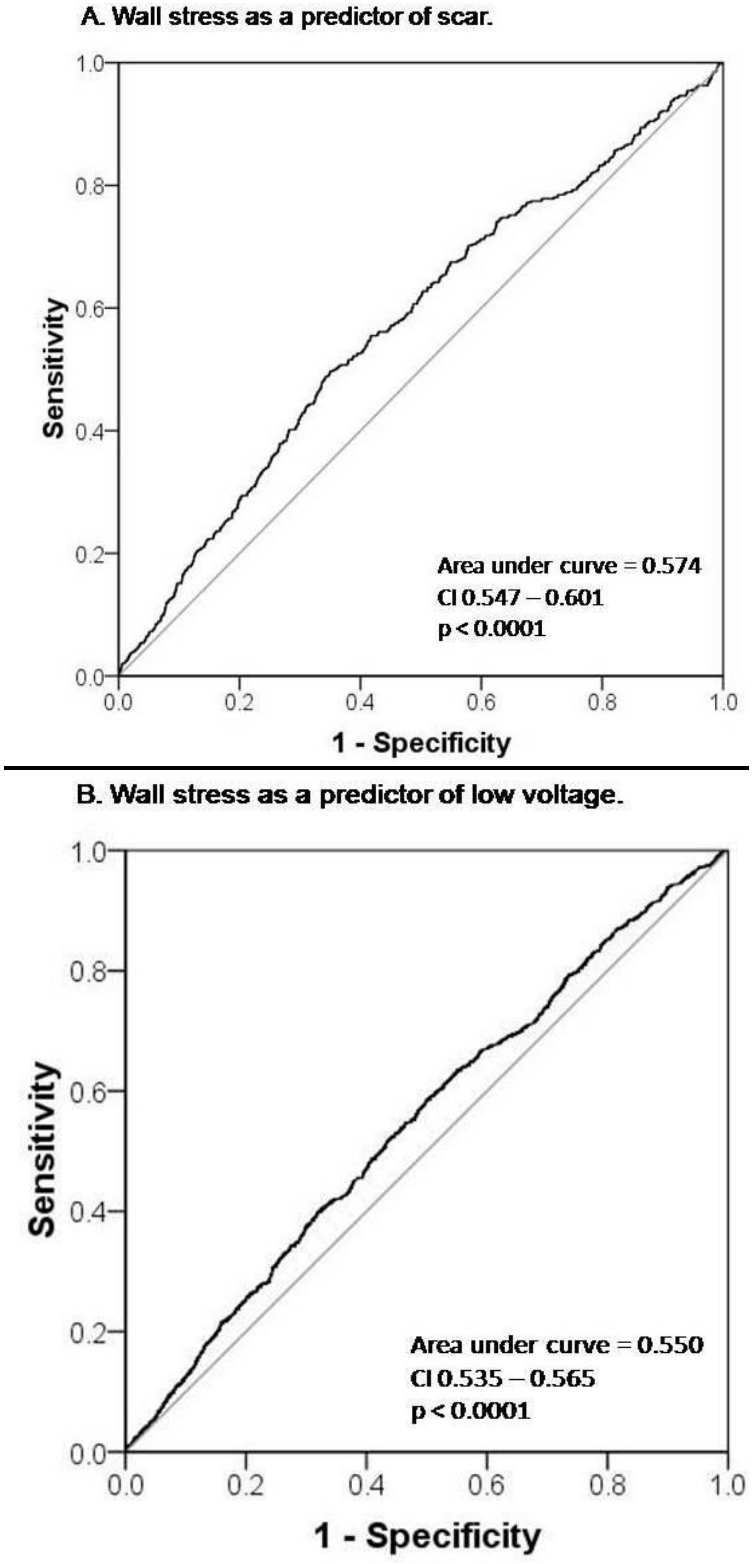
ROC analysis

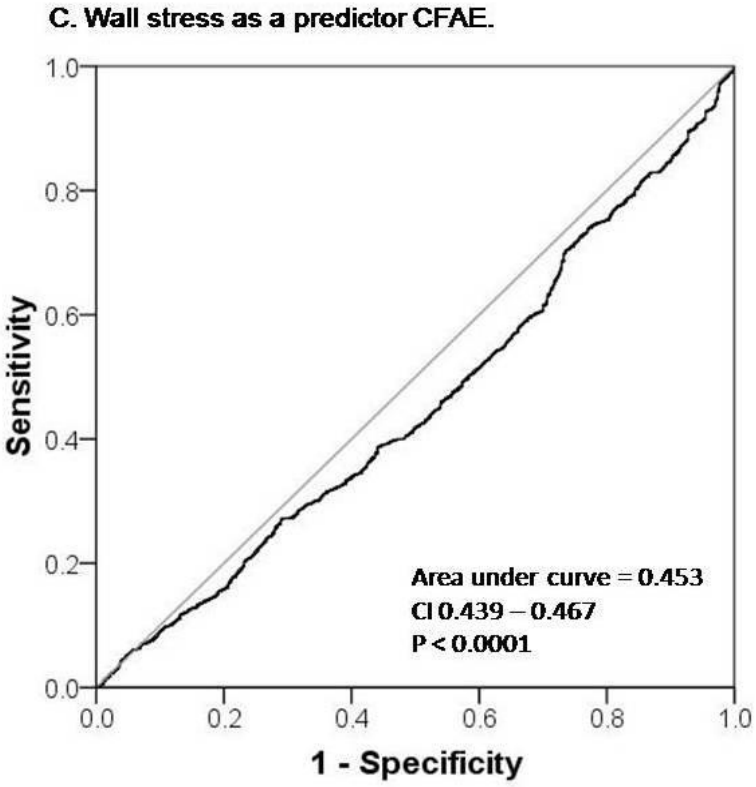
There was an association between high wall stress and electrical scar: A wall stress value ≥ 39.6 kPa had a sensitivity of 56.1% and specificity 57.0% for predicting electrical scar (area under curve 0.574, $p < 0.0001$; Figure 5.4A). There was a modest association between high wall stress and low voltage, 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 5.4B). High wall stress was associated with absence of CFAE (area under curve 0.453, $p < 0.0001$; Figure 5.4C).

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%.

Figure 5.4: Relationship between high wall stress and electrophysiologic abnormalities.





Legend to Figure 5.4: 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.

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 harboured CFAE. Following PV isolation, regional LA wall stress did not predict response to CFAE ablation.

Cardiac modelling and wall stress

Clearly, the first step in this study was to establish a working computer model to simulate 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,[276, 277] and the role of myocardial stretch in arrhythmia in the context of *commotio cordis*.[278] 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 (Figures 5.1 & 5.2).

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,[258] 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.[259] 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.[13, 132-136] Chronic stretch causes LA dilatation, with heterogenous remodelling of atrial architecture including myocyte hypertrophy, fibrosis, and gap junction remodelling.[134, 137, 139, 140, 279] 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.[94, 132-137, 139, 140]

Impact of wall stress on electrophysiology

The second stage of this study was to investigate the relationship between wall stress and 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.[194, 280, 281] 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.[280, 281] Furthermore, low voltage may denote zones of slow conduction.[282]

Foci of high wall stress may induce remodelling by directly activating signalling pathways. Mechanical stretch of atrial tissue has been shown to cause upregulation of MMPs.[144, 145] Likewise, mechanical stress can directly activate type 1 angiotensin II receptors by inducing a conformational change in the protein.[152, 153] Stretch of ventricular cardiomyocytes increases superoxide anion production *in vitro,* suggesting a role for oxidative stress in this process.[156] Furthermore, inflammation plays a key role in atrial remodelling and could feasibly be affected by local stretch.[124, 157, 158] However, the observation that an acute decrease in intra-atrial pressure can cause an immediate increase electrogram amplitude and conduction velocity suggests a possible role for focal activation of stretch activated ion channels. [132, 283]

It is also noteworthy that voltage is lower when assessed in AF compared to sinus rhythm,[198, 203] and the extent to which areas of low voltage in AF correspond to those in sinus rhythm is uncertain. [198, 203, 284] 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.[198, 203]

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 remodelled atria. This is in keeping with other recent studies showing that CFAE are not associated with areas of low voltage[198, 200-203] but is at odds with conventional wisdom.[194]

Focal remodelling might be expected to contribute to zones of slow conduction, pivot points, or block,[56] and resultant micro- or macro-reentry,[271] 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. [271] Therefore, although atrial remodelling promotes AF,[94, 132-137, 139, 140] 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 refractoriness[133-136, 139] 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.[78, 285] 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,[286] 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

It was initially uncertain whether it would be meaningful to study the impact of regional wall stress on the response to CFAE ablation. The results of Chapter 5 suggested that CFAE are important in maintaining AF and that there is an acute response to ablation which is to some extent measurable using AFCL. The preceding stages of this chapter of the thesis had been successful, firstly in establishing the computer model to simulate wall stress distribution, and secondly that despite the model's limitations a relationship had been demonstrated between regional wall stress and electrophysiology. Therefore, given that the response to CFAE ablation was quantifiable and the model was shown to have measurable electrophysiologic correlates, it was thought appropriate to proceed with this third line of investigation. However, 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[287] and biophysical properties when direct testing is feasible.[288] 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.[258] 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[258] 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, [194, 280, 281] it is recognized that such areas may not all represent scar. [198, 203] Further exploration of the relationship between wall stress and areas of low voltage in sinus rhythm is warranted.

Conclusions

The novel computer model described in this study has provided the first data on LA wall stress distribution. Peaks in LA wall stress were associated with areas of low voltage and electrical scar. Regional differences in wall stress may explain the heterogenous remodelling that results from elevated intra-atrial pressure and promotes AF. However, peaks in wall stress were associated with absence of CFAE and did not predict response to CFAE ablation, suggesting that foci of remodelling do not act as drivers of AF. The observation that the PV ostia had consistently high wall stress and harboured 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,[78, 285] suggesting a potential mechanism by which elevated intra-atrial pressure might facilitate initiation of AF.

Chapter 6

Long term efficacy of catheter ablation for AF: impact of additional targeting of fractionated electrograms.

Abstract

Introduction: We investigated the long term efficacy of catheter ablation for AF and the impact of ablating complex or fractionated electrograms (CFAE) in addition to pulmonary vein isolation (PVI) and linear lesions in persistent AF.

Methods: Consecutive cases from 2002-2007 were analysed. All patients underwent wide area circumferential ablation with confirmation of electrical isolation. For persistent AF linear lesions were added, with additional targeting of CFAE from 2005. Data were collected in a prospective database. Attempts were made to contact all patients for follow-up.

Results: 285 patients underwent 530 procedures. Mean age was 57±11 years, 75% male, 20% had structural heart disease and 53% paroxysmal AF. Mean number of procedures was 1.9 per patient (1.7 for PAF and 2.0 for persistent AF). Procedural complications included stroke or TIA in 0.6% and pericardial effusion requiring drainage in 1.7%. During 2.7 (0.2 to 7.4) years of follow-up from the last procedure, there were 7 deaths (unrelated to their ablation or AF) and 3 strokes or TIA (0.3% per year). Freedom from AF/AT was 86% for PAF and 68% for persistent AF. Late recurrence was 3/100 years of follow up after >3 years. Kaplan-Meier analysis showed CFAE ablation improved outcome for persistent AF after the first cluster of procedures (p=0.049), with a trend towards improved final outcome (p=0.130).

Conclusion: Long term freedom from AF is achievable in the majority of patients with PAF and persistent AF with low rates of late recurrence. Additional targeting of CFAE improves outcome for persistent AF. Late adverse events including stroke are few.

Introduction

Catheter ablation is now successful in restoring sinus rhythm for the majority of patients with paroxysmal and persistent AF in the short term, with studies typically reporting freedom from AF or other AT in 70-90% of patients up to a year.[159, 167, 169, 171, 174, 191] However, follow-up is often short and success is usually reported after the last procedure, meaning patients with late recurrence who undergo successful repeat procedures are counted as successes. This may distort perception of success and patterns of recurrence.

Most studies quote a marked difference in success rates for paroxysmal and persistent AF suggesting a need for further ablation beyond PVI, but some studies do not.[174, 182, 289] There have been several randomised trials investigating the impact of CFAE ablation for AF (see Table 1.5 for summary). On balance, these suggest a positive impact when CFAE are ablated as an adjunct to PVI for persistent AF.[290] However, these studies have typically examined outcome at approximately 1 year and there remains concern that the widespread scar created by CFAE ablation might be pro-arrhythmic over the long term.

To address these issues it was hypothesised firstly that once sinus rhythm is successfully restored following catheter ablation of AF, late recurrence occurring more than a year later is uncommon, as is typically reported for final procedure success in the literature.[169, 172, 291, 292] Secondly, it was hypothesised that long term freedom from arrhythmia is achieved in significantly fewer patients with persistent AF than with paroxysmal AF. A third hypothesis was

that catheter ablation of CFAE in addition to PVI and linear lesions improves long term freedom from arrhythmia for patients with persistent AF.

To ascertain this, a prospective registry at St Bartholomew's was analysed and patients followed up to determine long term freedom from AF. Catheter ablation of AF at St Bartholomew's has consistently used wide area circumferential ablation (WACA) with confirmation of electrical isolation of the PVs as a procedural end-point since 2002.[293] For persistent AF additional substrate modification has been performed. This was initially limited to linear lesions but has incorporated targeting of complex or fractionated electrograms (CFAE) since 2005. The introduction of CFAE ablation to an otherwise consistent lesion set therefore allowed a unique opportunity to study the impact of CFAE ablation on long term outcome.

Results

Patients & procedures

Analysis included 285 patients aged 56.5 ± 10.5 years. 14% were over 65 years of age, 75% were male. 151 (53%) had PAF, 134 (47%) had persistent AF and the majority of these (84%) were long lasting persistent AF (i.e. continuous for >1 year). 20% had structural heart disease, 37% had hypertension, and 5% had prior stroke or TIA. Left atrial diameter was 4.3 ± 0.8cm and 17% had left ventricular systolic dysfunction (ejection fraction < 50%).

In total 530 procedures were performed, with a mean per patient of 1.9 ± 1 (1.7 ± 0.9 for PAF, 2.0 ± 1.0 for persistent AF). 122 patients had 1 CA, 105 had 2, 41 had 3, 11 had 4, 5 had 5, and 1 had 6. Patients underwent 1.5 ± 0.7 procedures in their initial cluster, with a further 0.4 ablations for late recurrence. Mean time between procedures in the first cluster was 6.9 months. The mean period between the first cluster of procedures and ablation for late recurrence was 1.4 years. Of those with recurrent arrhythmia 70% were AF, 29% were left atrial flutter, and 1% were typical right atrial flutter.

Median procedure time was 240 (145 - 510) minutes, with fluoroscopy time 53 (17 - 120) minutes. Ablation to sinus rhythm occurred in 12.5% of catheter ablations for persistent AF. Procedural complications (shown in Table 6.1) included stroke or TIA in 0.6% and pericardial effusion requiring drainage in 1.7%, Of these 9 tamponades, 2 occurred during transseptal puncture, 1 occurred after a pop heard whilst isolating the right sided veins, and 6 occurred late despite the absence of an effusion on the echocardiogram routinely performed after cases (5 within 12 hours and one presented to another hospital at 10 days).

Follow up

Of 285 patients 15 could not be traced and were excluded from the analysis, leaving 270 patients. Of these 125 (46%) had persistent AF and 145 (54%) had PAF. Patients were followed-up for a median of 3.3 (2.4-7.5) years from their first procedure, 3.1 (1.3-7.5) years from their initial cluster of procedures, and 2.7 (0.2-7.4) years from their last procedure.

Table 6.1: Procedural complications of catheter ablation for AF.

Procedural Complications	Frequency of 530 procedures	% of procedures	% of patients
Procedural death	0	0	0
TIA or stroke (all resolved)	3	0.6	1.1
Tamponade (all drained without sequelae)	9	1.7	3.0
Symptomatic PV stenosis	3	0.6	1.1
Groin haematoma	77	14.5	27.0
Haematoma delaying discharge or causing readmission	17	3.2	5.9
Femoral pseudo-aneurysm (treated with thrombin injection)	1	0.2	0.4

Legend to Table 6.1: Procedural complications of catheter ablation are given in total for the 530 procedures, as a percentage per procedure, and as a percentage overall per patient (assuming a mean of 1.9 procedures per patient).

Adverse events during follow-up

There were 7 deaths in the cohort, 2 of which were cardiac. One occurred at 27 days post procedure due to myocardial infarction, the other was a sudden cardiac death in a patient with pre-existing heart failure and an ICD in situ more than 2 years post ablation. The non-cardiac deaths were due to 3 malignancies and 2 pneumonias complicating pre-existing pulmonary disease. Other adverse events during follow-up included 1 myocardial infarction, 2 TIAs and a stroke

which resolved without long term neurological deficit. There were no cases of new onset heart failure. 2 patients went on to have AV node ablation and pacemaker implantation.

Freedom from AF

Freedom from AF/AT with and without anti-arrhythmic medication is shown in Table 6.2. AF free survival was significantly better for PAF than PeAF following the first procedure, the initial cluster, and the final procedure ($p < 0.001$ for each; Figure 1). There was no difference in success for repeat procedures whether the recurrent arrhythmia was AF (53%) or left atrial tachycardia (47%).

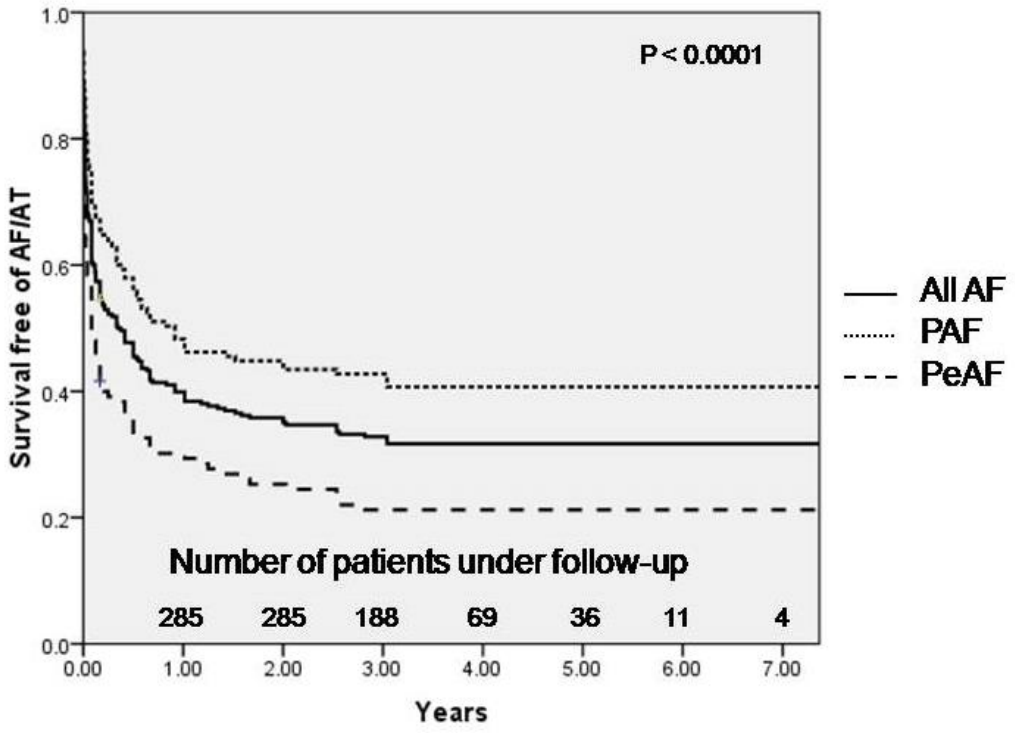
Table 6.2: Freedom from AF post catheter ablation.

	All patients (%)	PAF (%)	Persistent AF **(%)**
After first procedure	32.3	40.6	22.5
(off drugs)	(30.0)	(38.5)	(20.0)
After first cluster	58.9	68.5	47.5
(off drugs)	(52.1)	(62.9)	(39.2)
After last procedure (off	77.9	86.0	68.3
drugs)	(70.3)	(79.0)	(60.0)
Last 6 months	83.3	90.2	75.0
(off drugs	(73.8)	(81.1)	(65.0)

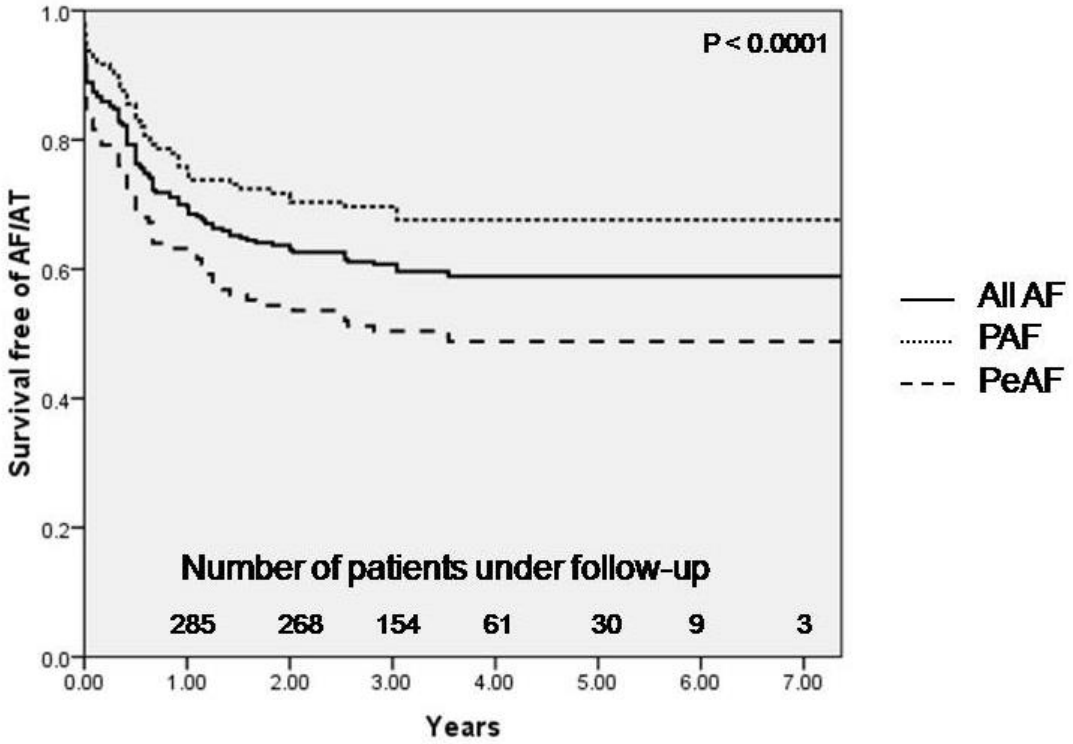
Legend to Table 6.2: Figures are percentage of patients free from any detected atrial tachyarrhythmia lasting >30 seconds. Numbers in brackets are those off any antiarrhythmic medication. The breakdown is shown for patients with PAF and persistent AF.

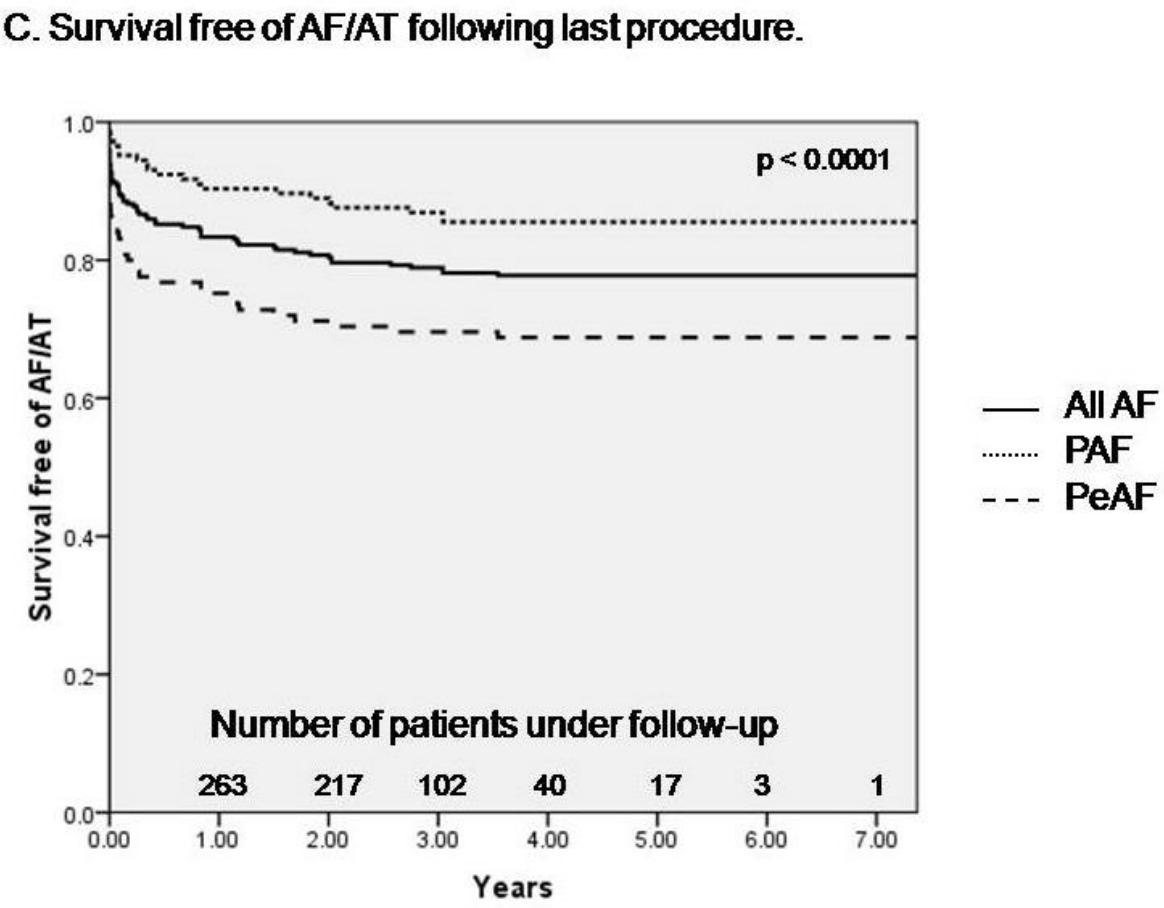
Figure 6.1: Long term outcome after catheter ablation of AF.

A. Survival free of AF/AT following first procedure.



B. Survival free of AF/AT following first cluster of procedures.

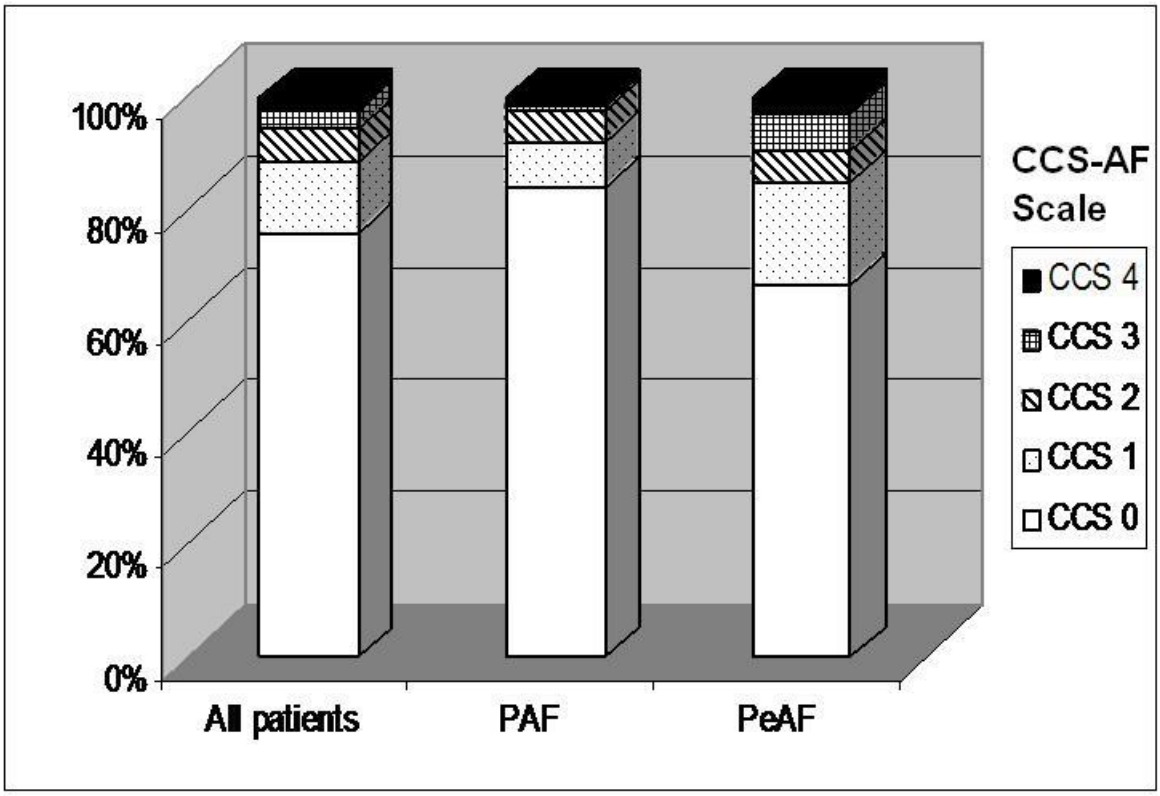




Legend to Figure 6.1: Kaplan-Meier curves showing AF free survival (A) following the first procedure, (B) following the first cluster of procedures, and (C) following the final procedure. Significance was assessed using the Log rank test. Late recurrence of AF/AT was analysed starting from the last procedure in the cluster (B), since recurrence of AF/AT following the final procedure (C) does not taken into account late recurrence occurring prior to successful repeat procedures. PAF denotes paroxysmal AF. PeAF denotes persistent AF.

Symptom severity assessed using the CCS-SAF scale is shown in Figure 6.2. Overall 95.1% of patients reported improved symptoms compared to pre-ablation.

Figure 6.2: Symptomatic benefit following catheter ablation of AF.



Legend to Figure 6.2: This bar chart shows the symptomatology of patients at follow-up. Symptoms were assessed using the Canadian Cardiovascular Society Severity of AF (CCS-AF) scale. On this validated scale patient symptoms and limitation are scored from 0 (asymptomatic) to 4 (disabling symptoms). PAF denotes paroxysmal AF. PeAF denotes persistent AF.

At final follow-up 24.4% of the cohort remained on antiarrhythmic drugs: 1.1% on amiodarone, 3.8% on digoxin, 5.7% on class 1 agents, 5.0% on sotalol, 11.0 % on other ß-blockers, and 9.9% on rate controlling calcium channel blockers.

Late recurrence

Kaplan-Meier analysis showed that most recurrences occur within 1-2 years (Figure 6.1). Actuarial analysis of the rate of recurrence per 100 patient years of follow-up showed recurrence beyond 3 years in only 3%per year (Table 6.3).

Multivariate analysis

Patient factors predicting success after the final procedure are shown in Figure 6.3A. Independent predictors of recurrence were persistent AF ($p < 0.01$), female gender ($p < 0.05$), and structural heart disease ($p < 0.001$), with a non significant trend towards an effect of time spent in AF ($p = 0.148$). No procedural factors analysed impacted significantly on first procedure success (Figure 6.3B). Analysing persistent AF cases alone, there was a trend towards improved first procedure success with the use of image integration ($p = 0.059$; Figure 6.3C). There was no independent effect of a later time of inclusion in the cohort.

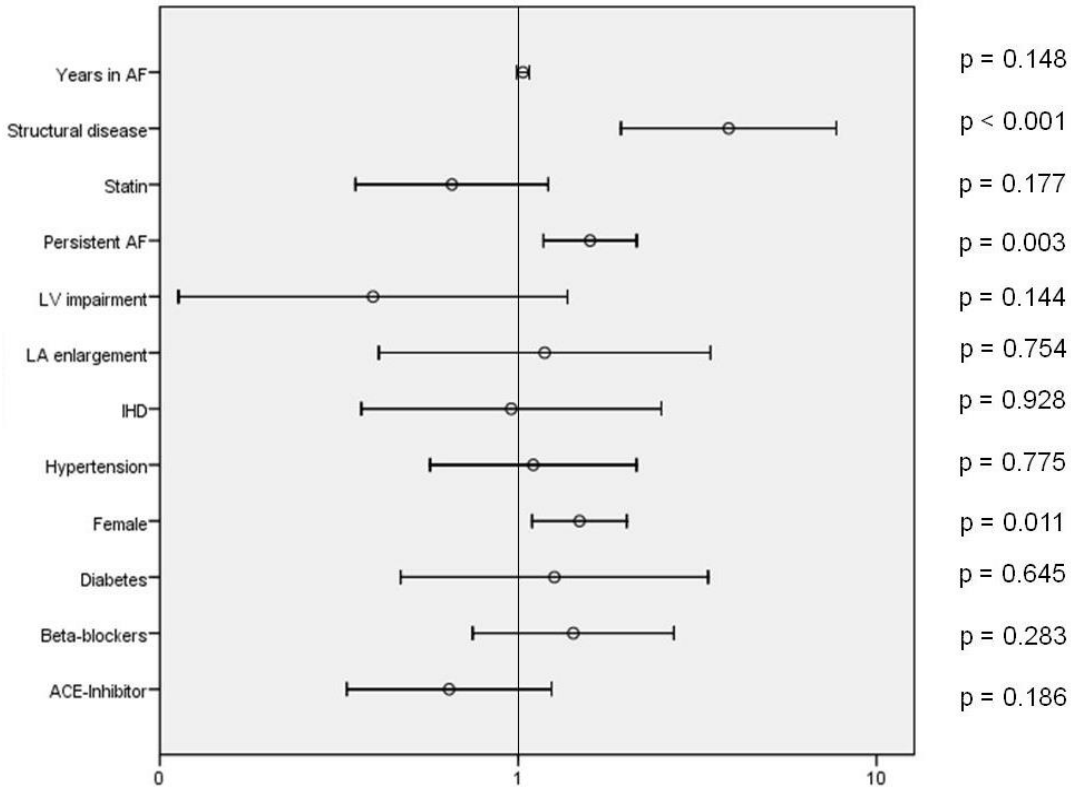
Table 6.3: Actuarial analysis of recurrence of AF/AT following the first cluster of ablation procedures for AF.

	0-1 years	1-2 years	2-3 years	>3 years
All AF	30.0%	6.4%	4.0%	3.0%
(patient years studied)	(270)	(267)	(200)	(164)
PAF	24.1%*	4.2%	2.8%	4.2%
(patient years studied)	(145)	(143)	(109)	(72)
Persistent AF	36.8%	8.9%	5.5%	2.2%
(patient years studied)	(125)	(123)	(91)	(93)
Persistent AF - CFAE targeted	34.2%	7.0%	2.2%	0%
(patient years studied)	(73)	(72)	(46)	(16)
Persistent AF - CFAE not targeted	40.2%	11.6%	8.8%[A]	2.6%
(patient years studied)	(52)	(52)	(45)	(77)

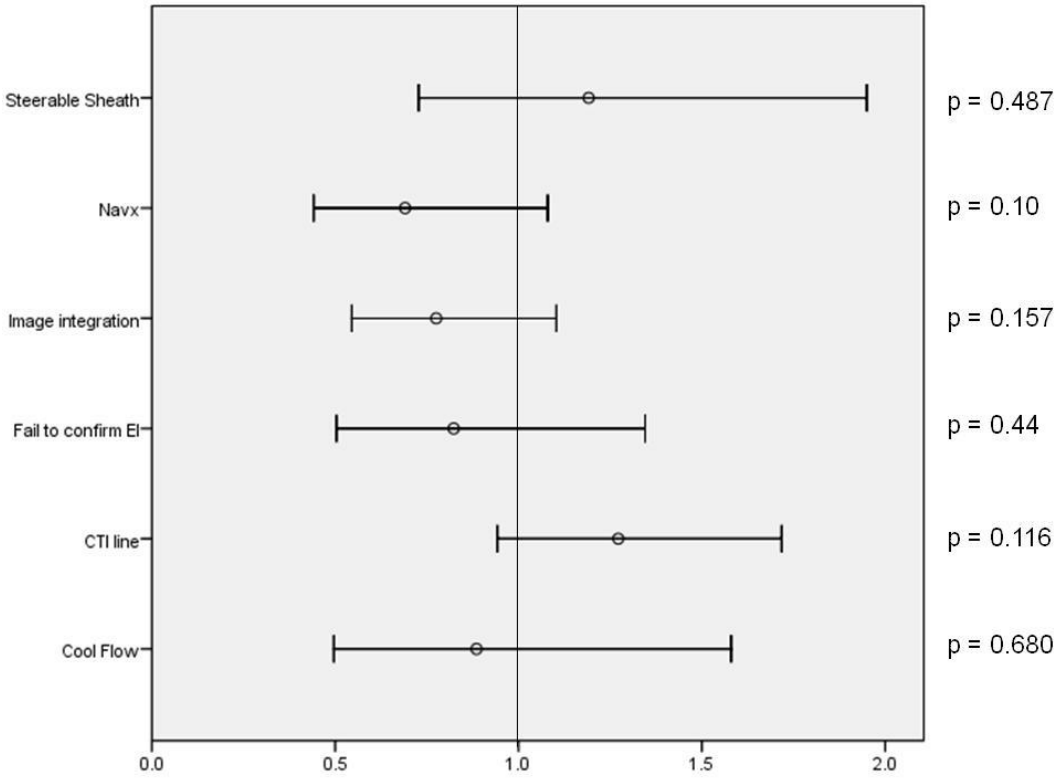
Legend to Table 6.3: Figures show number of recurrences of AF/AT following the first cluster of procedures per 100 years of patient follow-up. This eliminates the effect of diminished numbers followed up on the apparent recurrence rate. The figure in brackets show the number of patient years of follow-up studied. * denotes significant difference for PAF versus persistent AF. [A] denotes trend towards significance with p = 0.086.

Figure 6.3: Multivariate analysis of factors predicting recurrence of AF.

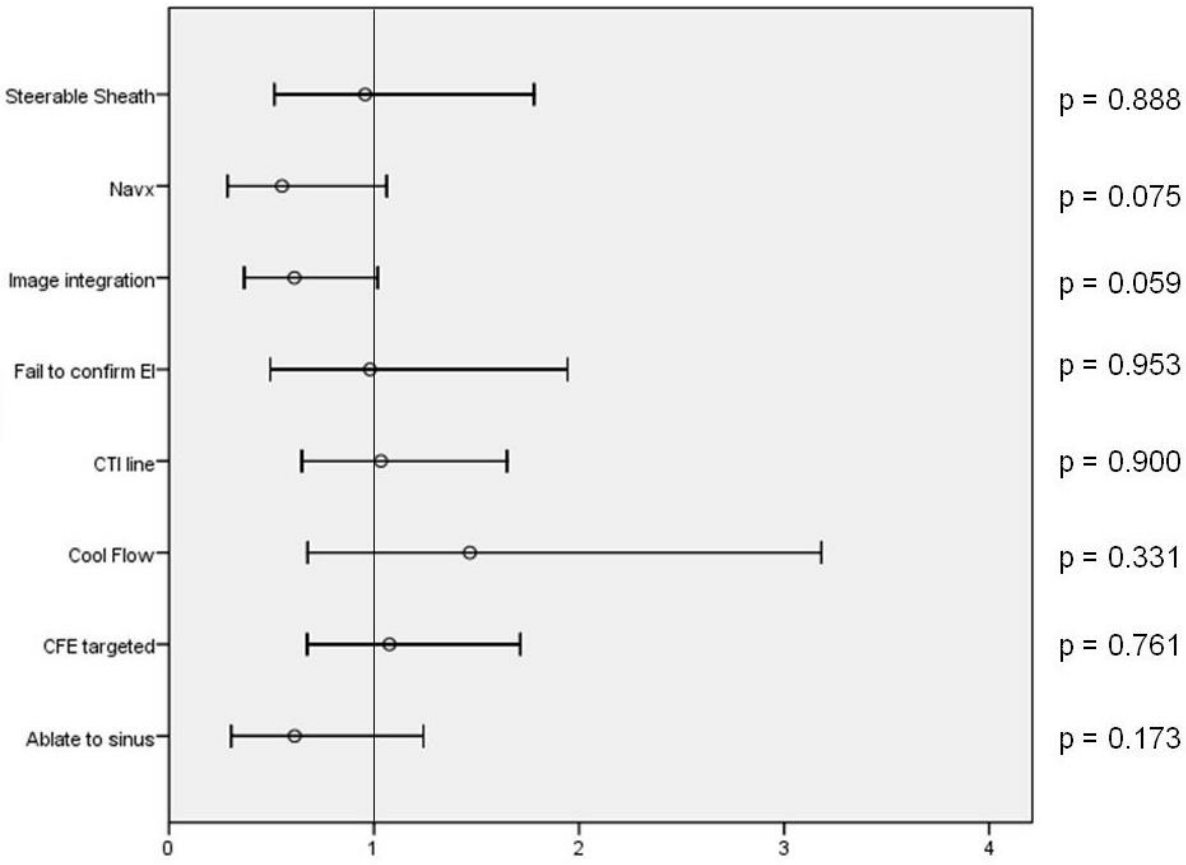
A. Patient factors predicting recurrence of AF after final procedure.



B. Procedural factors predicting failure after first procedure for all AF.



C. Procedural factors predicting failure after first procedure for Persistent AF.



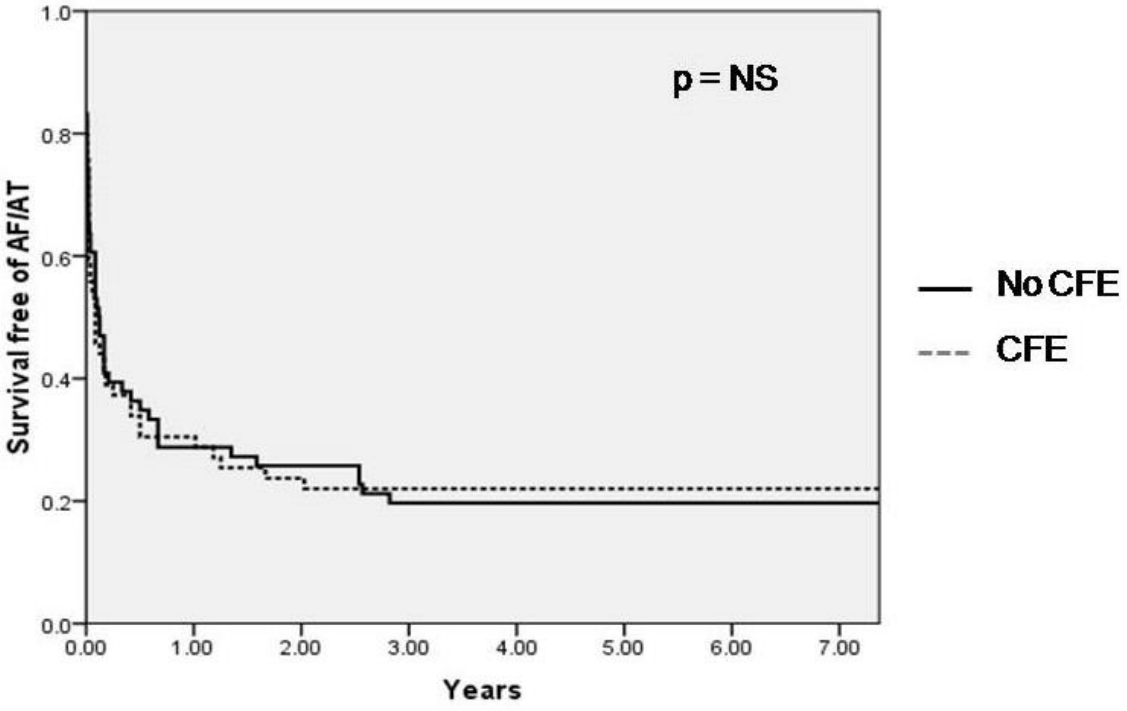
Legend to Figure 6.3: Figures show hazard ratios for recurrence of AF derived from Cox regression analysis, with p values shown to the right. (A) shows patient factors predicting recurrence after the final procedure. (B) shows procedural factors affecting recurrence after a single procedure. (C) shows procedural factors affecting recurrence for patients with persistent AF after a single procedure.

Impact of CFAE ablation on outcome

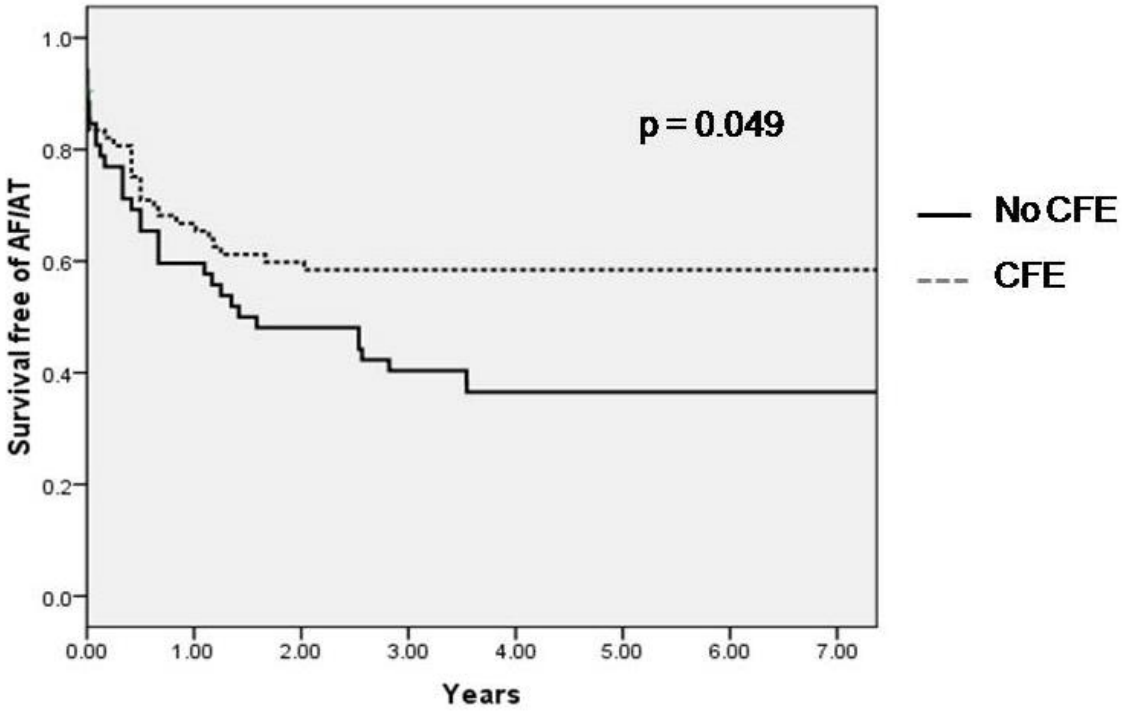
AF free survival was assessed according to whether patients had CFAE targeted during their first procedure (49% of cohort, Figure 6.4A), whether they had CFAE targeted in at least one procedure in their first cluster (59% of cohort, Figure 6.4B), and whether CFAE were targeted at least once in any of their procedures (65% of cohort, Figure 6.4C). Since CFAE were targeted only from 2005 onwards, those who did not have CFAE targeted were followed up longer. To avoid temporal bias the log rank test was calculated for follow-up truncated at 3 years. Although there was no effect of CFAE ablation on single procedure outcome, there was a 21.6% absolute increase in success after the first cluster of procedures ($p = 0.049$). This translated to a non-significant trend towards improved final outcome with CFAE ablation (13.4% absolute difference; $p = 0.130$). There was also a non significant trend towards reduced late recurrence with CFAE ablation ($p = 0.086$ for recurrences between 2 and 3 years; Table 6.3). There was no difference in the procedure time or the number of procedures (in the first cluster or in total). CFAE ablation did not affect the proportion of recurrences after the first procedure due to left atrial tachycardia (22.0% in those who had CFAE targeted versus 17.5% in those who did not; not significant).

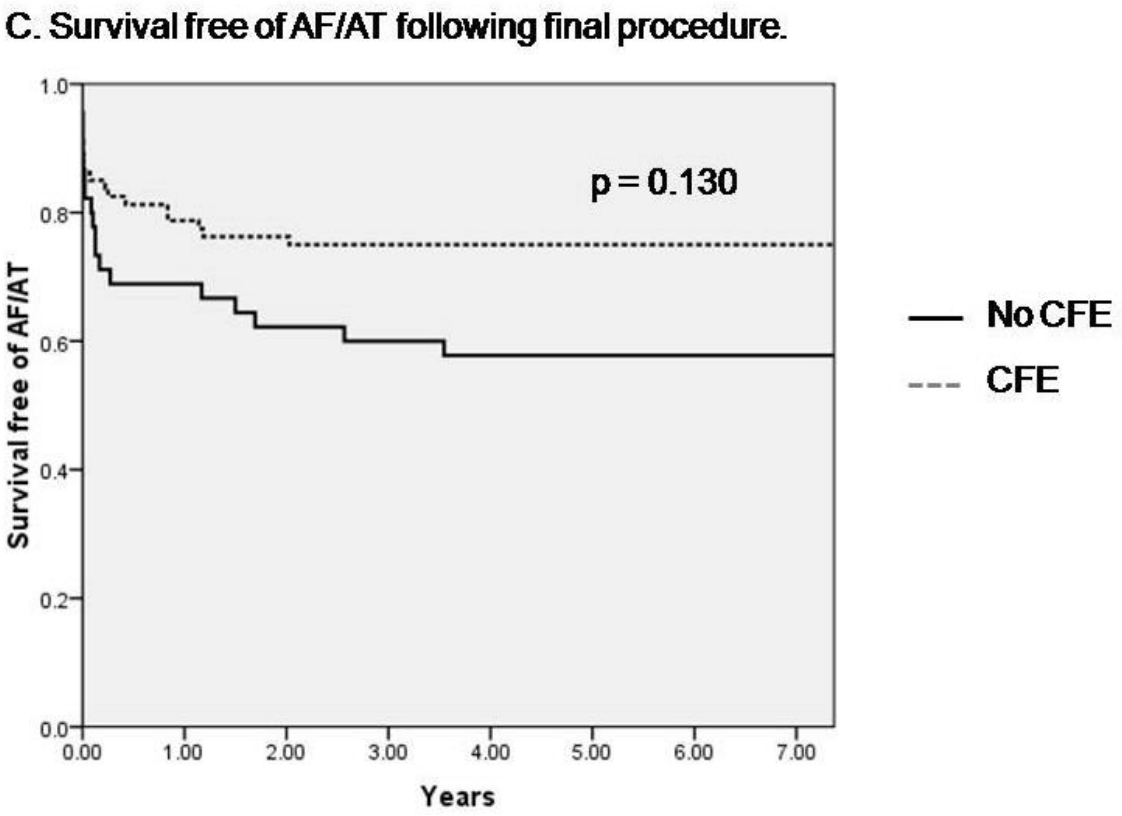
Figure 6.4: Impact of additional CFAE ablation on outcome after persistent AF.

A. Survival free of AF/AT following first procedure



B. Survival free of AF/AT following first cluster of procedures.





Legend to Figure 6.4: Kaplan-Meier curves showing AF free survival (A) following the first procedure, (B) following the first cluster of procedures (i.e. when AF is first eliminated whether after 1 catheter ablation or several), and (C) following the final procedure. The cohort has been divided according to whether patients had CFAE targeted during their first procedure (A), whether they had CFAE targeted in at least one procedure in their first cluster (B), and whether CFAE were targeted at least once in any of their procedures (C). Significance was assessed using the Log rank test. Since CFAE were targeted only from 2005 onwards, those who did not have CFAE targeted were followed up longer. To avoid temporal bias the log rank test was calculated for follow-up truncated at 3 years.

Discussion

Main findings

Long term freedom from AF is achievable in a majority of patients after catheter ablation. Recurrence occurs mostly in the first year, with an annual recurrence rate of approximately 3-5% from 1-3 years, falling to 3% per year thereafter. The success rate was significantly higher for patients with paroxysmal AF than persistent AF (86% off AADs for paroxysmal AF versus 68% for persistent AF). Despite conflicting evidence previously, we have demonstrated incremental benefit in targeting CFAE in persistent AF. This benefit was maintained at long term follow up without any excess of late recurrence of AF or AT in those undergoing CFAE ablation.

Efficacy of catheter ablation for AF

The final procedure success was comparable to other high turnover centres, typically in the region of 70-90%.[167, 169, 174, 191] The low CCS-SAF scores suggest that those with recurrent AF may still have derived symptomatic benefit, indeed 95% of patients reported improved symptoms.

The single procedure efficacy of catheter ablation for persistent AF was disappointing, but in keeping with other reports.[64, 168, 182, 191, 267] A recent study reported excellent long term single procedure success. Their use of intra-cardiac echo to monitor tissue contact may have reduced PV reconnection.[174] However, 5 year outcome reported by the Bordeaux group suggest a low single procedure success rate more in keeping with these data. [182] New technologies such as robotic navigation to improve catheter stability, catheters that allow

monitoring of tissue contact, or advanced mapping techniques that allow targeting of rotors may improve outcomes.

Multivariate analysis of patient factors impacting on outcome identified structural heart disease, persistent AF and female gender as independent predictors of recurrent arrhythmia. The impact of gender has been noted previously and may relate to subtle differences in cardiac anatomy or possibly more non-PV triggers.[174, 294] However, it has also been noted that fewer women are referred for ablation and that they generally seem to be referred later in their disease process, having been in AF longer and failed more antiarrhythmic drugs than male patients referred for ablation.[294] This gender bias in referral patterns may therefore mean that women presenting for ablation have more remodelled atria than male patients. LA size was not an independent predictor of recurrence despite being identified by others previously, perhaps as there is a relationship between this and time spent in AF.[174]

A multivariate analysis of procedural factors impacting on outcome showed no discernable effect of technologies introduced over the course of the study period. In particular the use of steerable sheaths, irrigated catheters, and image integration for mapping systems had no effect.

Patterns of recurrence

Studies report flattening of the AF free survival curve after 1-3 years.[169, 172, 291, 292] However, this effect may be artificial due to diminished numbers at longer follow-up, and re-listing patients with late recurrence preventing them counting as failures. To circumvent these issues we examined recurrence following the

initial cluster of procedures, with late recurrences counted as failures. Most recurrences occurred by 1 year. Kaplan-Meier curves flattened by 3 years, with only 3 recurrences/100 years of follow-up subsequently (i.e. 3% per year).

Impact of CFAE ablation

There has been difficulty reproducing Nademanee's early success using CFAE ablation alone.[265, 267] Incremental benefit of CFAE ablation in addition to PV isolation has been demonstrated over the short term,[191, 221, 225] although not consistently.[64, 224]

The lack of benefit following a single procedure in this study may reflect the fact that most early recurrence is associated with PV reconnection.[226] Once AF was eliminated following the first cluster of procedures, CFAE ablation resulted in a 21.6% absolute increase in the number maintaining sinus rhythm long term. Hence the decreased ability of the modified atrial substrate to initiate and sustain AF may not become apparent until PV triggers/drivers are removed.

Although Kaplan-Meier analysis showed an early benefit of CFAE ablation, there was also a trend towards reduced late recurrence. CFAE ablation did not affect the proportion of recurrence due to AF and AT, suggesting fears over increased propensity to macro-reentry are unfounded. Notably there was only a trend towards improved final outcome with CFAE ablation (13.4% absolute difference). However, many patients with late recurrence had additional CFAE ablation at their repeat procedure, meaning that the majority of patients with recurrent arrhythmias would have crossed over into the CFAE ablation group. This artefact may have obscured any benefit derived by CFAE ablation

Safety of catheter ablation of AF

The 3.1% major complication rate is comparable to that reported by other high turnover centres (typically 2-3%), and consisted mostly of stroke/TIA and tamponade.[167-169, 172, 191, 194, 267] Stroke/TIA was infrequent (0.6%) and all resolved. However, our aggressive anticoagulation policy may have resulted in a slightly higher tamponade rate of 1.7% (0.4-1.3% in other large series), although all were drained without sequelae.[159, 170, 174] Two thirds of tamponades were late, emphasizing the need for vigilance post procedure. The 3 PV stenoses occurred in the first 50 cases, and with more caution to avoid the PV ostia there were none subsequently.

Over 3.3 years the 7 deaths were unrelated to CA or AF. The CHADS2 score for the cohort was 0.8 with an expected stroke rate of 2-3% (1% if anticoagulated).[239] The rate of 0.3% per year confirms the low stroke rate after catheter ablation of AF.[167, 169, 174]

Limitations

Aggressive screening has revealed that a proportion of apparently cured patients have episodes of asymptomatic AF.[295] Although patients underwent ambulatory monitoring, it is recognised that further screening may uncover an increment in asymptomatic recurrent AF. However, the extent to which asymptomatic patients were screened for arrhythmia was comparable to that reported for many other registries and trials.[64, 159, 167-169, 224, 225]

Over the 5 years of this cohort it is possible that factors other than CFAE ablation have improved outcome in later patients. However, (i) the procedure has been consistent throughout other than the addition of CFAE ablation, (ii) multivariate analysis did not show a significant effect of any procedural factors, and (iii) inclusion of time as a covariate showed no benefit of later inclusion in the cohort. Nevertheless we acknowledge that registry data can be flawed and it is possible there may have been some confounding due to this.

Conclusion

Catheter ablation of AF can achieve long term sinus rhythm for a majority of patients. As most recurrences occur within a year, trials reporting efficacy of catheter ablation for AF should perhaps consider this a minimum for reporting results. The success rate following catheter ablation of persistent AF is still significantly lower than for paroxysmal AF. The addition of CFAE ablation to PVI may improve long term outcome for those with persistent AF. Importantly, CFAE ablation does not appear to be pro-arrhythmic over the long term and does not increase rates of late recurrence with AF or AT.

Chapter 7

Conclusions

Conclusions

The first essential part of this thesis was to establish a detailed definition and classification of CFAE which could be applied in real time live during cases. The description provided for each grade of CFAE was broad enough that all electrograms met the criteria for one grade or another and detailed enough that it could be reproducibly applied during clinical cases. This was a crucial part of this thesis, as clearly it was necessary to accurately distinguish between different CFAE morphologies in order to target them separately and study the effect of ablating them.

Although this was the primary purpose of this chapter of the thesis, it has provided further useful information in two respects. Firstly, this classification has provided a framework that other operators and clinical trialists could use to ensure reproducibility in the targeting CFAE, and indeed allow others to interpret their clinical results with a fuller understanding of exactly what they targeted. Secondly, it was possible to use this grading of fractionation to validate automated CFAE detection algorithms on the two commonly used 3D mapping systems, not only in terms of the accuracy of detection, but also in assessing the degree of electrogram fractionation. The CFAE mean algorithm on the Ensite NavX system and the ICL algorithm on Carto both fared well with similar accuracy, but the other algorithms on Carto such as the ACI and SCI were not as accurate. Although other studies have looked at the accuracy of these algorithms with similar conclusions, [221, 247, 250, 251] this study was the first to investigate how well they quantify electrogram fractionation. This is clinically useful, since CFAE burden can be high in some patients covering most of the

atria. Some groups therefore elect to begin by targeting only the most fractionated electrograms on a CFAE map and then remapping before ablating more widely.[221, 296]

During the course of this work, other descriptions of CFAE have been published. Kremen et al,[264] categorized electrograms as either (1) normal, (2) mildly fractionated, (3) moderately fractionated, or (4) severely fractionated. Although they demonstrated a low inter-observer variability, they did not fully define the characteristics of these 4 categories and hence it would be difficult for other centres to adopt the system in a reproducible manner. A physiological classification of CFAE has also been described by Narayan et al, who measured monophasic action potential recordings at CFAE sites and showed that a small proportion of these sites have evidence of rapid depolarisations suggestive of drivers.[217] These sites of rapid depolarisation were associated with more continuous electrical activity, a shorter cycle length and a lower voltage amplitude. Although this work was physiologically interesting and broadly supports the notion of targeting rapid electrograms or those with continuous fractionation, the classification could not be translated directly into the clinical setting due to its reliance on special equipment.

After establishing that CFAE could be accurately classified using this system, it was then possible to study the effect of ablating different CFAE morphologies. There are a limited number of ways to assess the impact of ablation. Arguably the most definitive effect of ablation is the termination of AF. However, this usually occurs no more than once in a procedure and indeed occurred in only 30% of the patients comprising chapter 4 of this thesis. For this reason, others

have used AFCL prolongation as a marker of response to ablation. [241, 254, 255] Although this is a surrogate end-point, it has been shown to correlate with clinical outcome and there is computer modelling which suggests that it may reflect elimination of drivers. [63, 253]

It is also recognised that there is a cumulative effect of ablation on AF cycle length, [63] hence it was thought necessary to vary the order in which the different CFAE morphologies were targeted. The order could have been completely randomised, but instead patients were randomised to targeting of CFAE starting with the most fractionated grade first (i.e. grades 1 to 5), or starting with the least fractionated first (i.e. grades 5 to 1). This made it possible to study the effect of ablating CFAE in two distinct orders.

The data from 'The CFAE AF trial' in chapter 4 of this thesis showed that certain CFAE morphologies were more likely to cause AFCL prolongation than others. In particular, ablating CFAE with fractionation for ≥ 70% of the sample, especially when there were segments of continuous electrical activity lasting ≥ 1 second (i.e. grade 1 & 2 CFAE), were more likely to prolong AFCL than ablation of normal electrograms. Ablation of less fractionated electrograms (≤ 70% of the sample, i.e. grade 3 CFAE) was no more likely to prolong AFCL than ablation of normal electrograms. Interestingly, ablation of more organised electrograms with multiple deflections (grade 4 CFAE) also caused cycle length prolongation compared to normal electrograms. These data strongly suggest that areas where certain CFAE morphologies are recorded are important in maintaining AF.

This was not a mapping study aimed at elucidating the underlying physiology at CFAE sites. The intention was to prove that certain CFAE morphologies are more likely to represent drivers of AF. The differential effect of targeting different CFAE morphologies certainly supports this hypothesis. However, several questions still remain. Since uncertainty remains as to how AF is maintained, these drivers could be a rotors, focal sources with radial activation, zones of slow conduction, or possibly other phenomena. Until these phenomena can be reliably distinguished it will not be possible to compare electrogram properties for each, and it therefore remains uncertain exactly what each CFAE morphology represents. Nevertheless, the classification of CFAE should be clinically useful as it allows an operator to distinguish which CFAE morphologies are important to target. At the time of writing, there have been no other studies prospectively evaluating the effect of targeting different CFAE morphologies.

Another remaining question is whether these data prove that CFAE ablation is not simply de-bulking atrial tissue. Targeting different CFAE morphologies certainly had a differential effect on AFCL, and targeting highly fractionated electrograms first organised the less fractionated electrograms meaning that fewer CFAE were targeted in total. Nevertheless, it could be argued that CFAE simply represent diseased tissue necessary for the maintenance of AF rather than physiologically active drivers. However, these data do not support this. Electrogram amplitude did not predict the response to ablation, meaning that ablation of low amplitude CFAE suggestive of scar tissue were no more likely to cause cycle length prolongation than ablation of high amplitude CFAE. By mapping the same patients in AF and in sinus rhythm, others have shown that areas where CFAE are recorded in AF do not correspond to fractionated or low

amplitude electrograms in sinus rhythm.[199, 252, 297, 298] Furthermore, CFAE do not correspond to areas of scar on magnetic resonance imaging.[252] Taken in conjunction with the data in chapter 4 of this thesis, these data suggest that CFAE are functional phenomena rather than representing a fixed structural lesion. Ablation of certain CFAE morphologies therefore destroys functional phenomena important in maintaining AF rather than de-bulking unhealthy tissue.

In chapter 5, a novel computer model to simulate left atrial wall stress was described. This model, built in collaboration with biomedical engineers, simulated LA wall stress based on contour and geometry using a patient specific geometry from CT. By comparing this simulated wall stress data to electrophysiologic data recorded at the time of catheter ablation of AF, it was possible to firstly explore the relationship between wall stress and LA electrophysiologic remodelling, and secondly to test the importance of peaks in wall stress by assessing the response to ablation there.

It was found that peaks in LA wall stress were associated with areas of low voltage and electrical scar. There was also a trend towards less fractionated electrograms at peaks of wall stress. Furthermore, CFAE were found to be less likely to occur in areas of low voltage than elsewhere. Left atrial CFAE burden was actually inversely proportional to both the median LA voltage and the degree of LA scarring. This is in keeping with the findings of others discussed above, that CFAE do not correspond with areas of low voltage or scar on magnetic resonance imaging. [199, 252, 297, 298]

To evaluate the importance of peaks in wall stress in maintaining AF and to assess whether the computer model might have a role in guiding CFAE ablation, the impact of CFAE ablation on AFCL was assessed as a function of the local wall stress. Although the model remained simplistic, the above correlation with electrophysiologic data provided some internal validation for the wall stress simulation, suggesting that further analysis along these lines was reasonable. Furthermore, the results of Chapter 4 suggested that CFAE ablation is not simply de-bulking the atria and that some CFAE are important in maintaining AF, and hence that there is potential to refine CFAE ablation. It was also demonstrated that the acute effect of CFAE ablation can be quantified to some extent using AFCL.

However, there was found to be no difference between wall stress at sites where CFAE ablation caused cycle length prolongation compared to sites where it did not. Furthermore, receiver operating characteristic analysis showed that wall stress could not be used to distinguish between areas that would and would not cause AF cycle length prolongation during CFAE ablation.

Although these data do not suggest that peaks in wall stress are important in maintaining AF, nor do they entirely refute the hypothesis. It is possible that the model is too basic to elucidate such a relationship, although given that there was a demonstrable relationship between wall stress and electrophysiology, this ought not to have been the case. The distribution of peaks in wall stress was in many cases concentrated at the pulmonary vein ostia. As these were isolated by WACA prior to CFAE ablation, the impact of ablating here was not assessed. Furthermore, others have demonstrated an excitatory response with mechanical

stretch at the pulmonary vein ostia which is not elicited elsewhere in the atria.[78, 285] There may therefore be important differences in the response to stretch at the pulmonary vein ostia where we did not observe the impact of ablation. Lastly, although AFCL may be a reasonable measure of the response to ablation, it is thought to gage whether drivers are being eliminated and is ultimately a surrogate end-point. The real end point of interest is the impact of ablation on long term maintenance of sinus rhythm. Rather than evaluating the impact of wall stress on response to ablation of CFAE, it may be that a more refined model could be used to target areas of advanced remodelling for ablation and that a procedure aiming to homogenise atrial scar might be successful regardless of the short term impact on AFCL.

As this model was entirely novel it necessarily took a simplified view of LA biomechanics as the first step towards understanding wall stress distribution. Although the accuracy of the geometry is the most important factor in determining wall stress,[258] two other important factors that are difficult to fully account for are: (i) regional differences in wall thickness, and (ii) the regional and temporal variations in the trans-mural pressure gradient.

The impact of small changes in regional wall thickness and of changes in the global trans-mural pressure gradient were explored in Chapter 5 and appeared to have a very limited effect on the relative distribution of wall stress. However, the scale of the complexities *in vivo* are far greater. The anatomical complexities are not limited simply to differences in regional wall thickness, but also differences in fibre orientation and layering. Furthermore, changes in the trans-mural pressure gradient are not uniform and are impacted by extra-

cardiac structures and changes over time with intra-cardiac pressure during the cardiac cycle and intra-thoracic pressure with respiration.

The fact that there was a demonstrable relationship between simulated LA wall stress and left atrial electrophysiology provides some internal validation for this model. Nevertheless it is recognised that the model is at an early stage and needs further work to enrich it and make it more realistic. Further work plans to derive generic LA anatomical data from cadaveric specimens, so that data on regional wall thickness, fibre layering and orientation can be included in the model. Furthermore, we plan to record intra-atrial pressures and regional pericardial pressures in patients undergoing catheter ablation for ventricular tachycardia to determine regional atrial transmural pressure gradients for inclusion in the model.

Other than refinements of the model, there are other methodological differences that might be incorporated into further work. The intention of the study comprising Chapter 5 of the thesis was not just to establish the wall stress model and to examine the relationship with left atrial electrophysiology, but to examine the importance of regions with high wall stress in maintaining AF, and ultimately whether wall stress might be useful in guiding CFAE ablation. Clearly this is several steps at once. Further work will focus on better defining the relationship between LA wall stress and electrophysiology in the first instance. In particular, there is now evidence that electrogram voltage amplitude in AF may not correlate very well with that in sinus rhythm. [198, 203] It would therefore be useful to re-examine the relationship between wall stress and electrogram voltage in sinus rhythm. This would also allow assessment of the impact on

conduction velocity and refractory periods. Furthermore, the current study used a pulmonary vein mapping catheter to acquire electroanatomic mapping data points as several can be acquired simultaneously. However, this inevitably means that some of the points assumed to be low voltage or electrical scar were in fact just poor contact between the electrodes and the myocardium. Future studies will therefore use point by point data collection. Since this data was acquired, catheters capable of measuring contact force have also become available. Using a catheter to collect data points one by one with a pre-specified contact force will be the ideal way to collect further data.

Chapter 6 of this thesis examined the long term outcome after catheter ablation of AF, the rates of late recurrence, and the difference in outcomes for paroxysmal and persistent AF. This enabled an assessment of how CFAE ablation impacts on long term outcome in patients with persistent AF, complementing the work in the other chapters of this thesis examining the acute effects of CFAE ablation.

Other studies examining long term outcome after catheter ablation of AF are summarised in Table 1.4. The data presented in Chapter 6 still represents one of the longest follow-up studies to date following catheter ablation of AF. The dataset has been expanded subsequently as part of other studies examining long term outcome,[299-301] and have recently been included in a meta-analysis.[289] These data show that the long term outcome after catheter ablation remains relatively poor after a single procedure, particularly for persistent AF. However the outcome after repeated procedures (a mean of 1.7 procedures for paroxysmal AF or 2.0 for persistent AF) was actually much better, with sinus

rhythm maintained in 86% for paroxysmal AF and 68% for persistent AF off anti arrhythmic drugs at 2.7 years from the last ablation procedure. Late recurrence at greater than 3 years following the last procedure was uncommon at approximately 3% per year. These data remain an important part of the literature on outcome after catheter ablation of AF. Much of the long term follow up data following catheter ablation of AF has been published by the Natale group, who quote much higher success rates with few repeat procedures and only very rare complications.[174, 289] The data from the current study therefore forms part of an important counterbalance to the literature and may arguably better reflects the experience of many other centres.[160]

These registry data pre-date the work in Chapters 3-5 aiming to refine CFAE ablation. Chapter 6 therefore examines the clinical impact of a conventional approach to CFAE ablation. Although there was no impact of targeting CFAE in persistent AF after a single procedure, there was a 22% absolute increase in the success rate following repeat procedures. It is unclear why this effect was evident only after repeated procedures. It is possible that many of the early recurrences were due to pulmonary vein reconnection, and that the impact of CFAE ablation may not be evident until after lasting PVI has been achieved. Table 1.4 summarizes randomised controlled trials investigating the efficacy of CFAE ablation for AF. The majority of these studies support CFAE ablation for persistent AF, and a recent meta-analysis also concluded that this was the case.[290] The data from Chapter 6 of this thesis also suggest a positive impact of CFAE ablation on long term outcome and add to the literature in two respects. Firstly, CFAE ablation was performed as an adjunct to both PVI and linear lesions, whereas the majority of previous studies evaluated CFAE ablation as

an adjunct to PVI alone. Secondly, follow up for previous studies were typically up to 1 year, with concern from some quarters that long term outcome might be poor due to LA scar post CFAE ablation. The current study provides the longest follow up to date following CFAE ablation at 3.3 years. These data are therefore reassuring in that the rates of late recurrence (AF or AT) are certainly no higher after CFAE ablation, and may actually be lower than the control group.

The main limitation of the data comprising Chapter 6 is that it is a single centre retrospective study. Outcome was examined before and after the incorporation of CFAE ablation into an otherwise consistent lesion set. Nevertheless, it is possible that other factors which changed over this time period may have influenced the results. Although a multivariate analysis did not show a significant effect of any of these other changes, and in particular inclusion of time as a covariate did not show any benefit of later inclusion in the cohort, it is difficult to fully account for these factors and there may be a degree of confounding relating to this.

When this thesis was originally conceived, Nademanee's work showing high success rates with CFAE ablation as a standalone strategy for AF had recently been published. The Morady group had also published their experience with CFAE ablation, showing much the opposite. There was therefore immense interest and controversy surrounding CFAE ablation. Over the subsequent years the randomised studies summarised in Tale 1.5 were published. There remains controversy, but meta-analysis suggests that CFAE ablation improves outcomes when performed in addition to PVI for persistent AF.[290] Unfortunately,

there has arguably been little other progress in the field of CFAE ablation, with few publications on how CFAE ablation might be refined.

Although performing CFAE ablation as an adjunct to PVI and linear lesions may improve outcomes, the technique as it stands has significant draw backs. It is not an ideal way of targeting drivers, since many patients remain in AF following elimination of CFAE, and ablation of many CFAE produces no impact whilst causing unnecessary scarring. CFAE are therefore not terribly sensitive or specific markers of drivers in AF. At the time of writing there is ongoing work by others attempting to refine CFAE ablation.

The Selective CFAE targeting for AF (SELECT AF) study is currently randomising 80 patients with AF to PVI followed by either conventional targeting of CFAE to eliminate all CFAE, or targeting of only CFAE with continuous electrical activity.[296] The primary end-point is freedom from AF at 1 year. This will demonstrate whether targeting a limited number of CFAE can achieve the same clinical results without destroying so much atrial tissue leaving scar that is potentially pro-arrhythmic. Similarly, the Modified Ablation Guided by Ibutilide in Chronic AF (MAGIC AF) study is currently enrolling and is randomising 200 patients with persistent AF to PVI followed by either conventional CFAE ablation or CFAE ablation after administration of Ibutilide.[302] The hope is that Ibutilide administration may organise AF, reduce CFAE burden and thereby limit the amount of ablation required to eliminate important drivers, with the primary end-point being freedom from AF at 1 year. Data from these studies will help refine CFAE ablation, maximising efficacy whilst minimising collateral damage to the atria. However, data from this thesis and elsewhere suggest that CFAE ablation

is likely to remain an imprecise way of targeting drivers in AF. Ultimately it may be that these drivers can be mapped directly,[48, 49, 303] perhaps dispensing with the need for ablation of surrogates such as CFAE at all.

In conclusion, these data demonstrate that it is possible to reliably discern different CFAE morphologies by eye. Furthermore, ablation of certain CFAE morphologies are more likely to prolong AFCL, suggesting firstly that CFAE ablation is not simply de-bulking the atria, and secondly that these CFAE are important in maintaining AF. However, targeting CFAE remains an imprecise process and ablation should be limited to those CFAE most likely to have an effect. Correlating electrophysiologic data with simulated wall stress demonstrated a relationship between peaks in wall stress and areas of low voltage areas and electrical scar, suggesting that peaks in wall stress may directly induce foci of remodelling. However, peaks in wall stress did not cause CFAE and there was in fact a weak relationship whereby less fractionated electrogram were found in areas of higher wall stress. These preliminary data do not suggest that these foci of remodelling act as drivers maintaining AF, and furthermore do not suggest a role for wall stress simulation in guiding or refining CFAE ablation. These data confirm that there remains a difference in long term outcomes following catheter ablation of paroxysmal and persistent AF, but that CFAE ablation in addition to PVI and linear lesions improves outcomes for persistent AF. Importantly, the rate of late recurrence due to AF or AT was not higher with CFAE ablation, suggesting that the widespread scar that can be created by CFAE ablation did not seem to be proarrhythmic over the long term. Although these data support conventional targeting of CFAE when it is performed as an adjunct to PVI and linear lesions for persistent AF, selective

targeting of CFAE based on electrogram morphology may help limit unnecessary damage to the atria. Further refinement of CFAE ablation, or ultimately its replacement by a more precise means of targeting mechanisms sustaining AF remains desirable.

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