Full Title:	Catheter ablation in patients with atrial fibrillation: Mapping refinements, outcome prediction and effect on quality of life
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Thesis Qualification:	Doctor of Medicine (MD)
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Thesis Summary

Chapter 1 presents a literature review, focused primarily on the pathophysiology and management of atrial fibrillation (AF).

Chapter 2 examines correlations between the dominant frequency of AF - calculated using principal component analysis from a modified surface 12-lead ECG (which included posterior leads), a standard 12-lead ECG and intracardiac recordings from both atria. The inclusion of posterior leads did not improve correlation with left atrial activity because of the dominance of lead V_1 in both ECG configurations.

Chapter 3 explores whether acute and 12-month outcome following catheter ablation for AF can be predicted beforehand from clinical and surface AF waveform parameters. Multivariate risk scores combining these parameters can predict arrhythmia outcome following ablation, and could therefore be used to identify those most likely to benefit from this therapy.

Chapter 4 examines the effect of catheter ablation on AF symptoms and quality of life (QoL). AF symptom and QoL scores improved significantly in patients who maintained sinus rhythm after ablation but did not change in those with recurrent AF. AF-specific QoL scales are more responsive to change and correlate better with ablation outcome.

Chapter 5 examines inter-atrial frequency gradients in patients with persistent AF using multipolar contact mapping. A right-to-left atrial frequency gradient was found in a quarter of the patients studied, implying that their arrhythmia was being maintained by high frequency sources in the right rather than the left atrium.

Chapter 6 examines whether targeting high frequency and highly repetitive complex fractionated atrial electrogram sites, identified using multipolar contact mapping during persistent AF, resulted in arrhythmia termination and maintenance of sinus rhythm long-term. The utility of administering flecainide to distinguish critical from bystander AF sites was also investigated. Flecainide did not help refine ablation targets and 12-month outcome after targeting these sites was not superior to other ablation strategies.

Acknowledgements

I would like to start by thanking John Bourke for his help and support with all of the research projects we have undertaken together since my intercalated BMedSci in 2002 culminating in this MD thesis. He has been an excellent academic supervisor and has nurtured and developed my interest and understanding of cardiac electrophysiology. I would also like to thank Phil Langley for composing the signal processing algorithms to analyse the surface and intracardiac ECG data and for his critique of prepared manuscripts, Kim Pearce for her invaluable statistical advice and for introducing me to logistic regression and Alan Murray for his advice and critical appraisal. Finally, I would like to thank Ewen Shepherd, Stephen Lord and Stephen Murray for their help with data collection and the appraisal of prepared manuscripts.

Project Contributions

Daniel Raine:	Study design; Data collection, analysis and interpretation; Drafting and revision of MD thesis; Performing and analysing transthoracic echocardiograms (Chapters 5 and 6)
Philip Langley:	Study design; Composition of signal processing algorithms for data analysis; Critical appraisal of MD thesis
John P. Bourke:	Study design; Data collection; Critical appraisal of MD thesis
Ewen Shepherd:	Study design; Data collection
Stephen Murray:	Study design; Data collection
Stephen Lord:	Study design; Data collection
Alan Murray:	Study design; Critical appraisal of MD thesis
Kim Pearce:	Statistics advice and tuition

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1. Raine, D. et al. (2015) Principal component analysis of atrial fibrillation: Inclusion of posterior ECG leads does not improve correlation with left atrial activity. *Med Eng* Phys, **37**, 251-255.
2. Raine, D. et al. (2015) Effect of catheter ablation on quality of life in patients with atrial fibrillation and its correlation with arrhythmia outcome. *Open Heart*, **2**, e000302.

Chapter 1. Introduction: Atrial Fibrillation

1.1 Definition

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by rapid, chaotic electrical activity in the atria that results in an irregular and frequently uncontrolled ventricular rate. On the surface ECG, AF is characterised by the replacement of regular distinct P waves by fibrillatory waves of varying amplitude and cycle length associated with an irregular ventricular rate (Figure 1.1). Patients can be asymptomatic or can experience symptoms including chest pain, palpitations, dyspnoea, fatigue and dizziness.

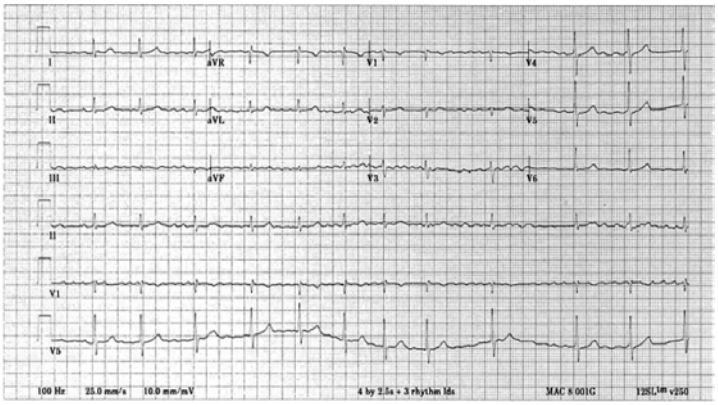


Figure 1.1: 12 lead ECG showing Atrial Fibrillation

1.2 Classification

AF can be classified into five categories based on the clinical presentation and duration of the arrhythmia (Camm et al., 2010):

1. *First diagnosed:* Patients who present with AF for the first time are considered in this category, irrespective of arrhythmia duration and symptoms.
2. *Paroxysmal:* AF episodes that self terminate within 7 days.
3. *Persistent:* AF episodes last longer than 7 days and require termination by either pharmacological or electrical cardioversion.
4. *Long-standing Persistent:* AF has lasted for ≥ 1 year when it has been decided to adopt a rhythm control strategy.
5. *Permanent:* The continuing presence of AF has been accepted and a rate control strategy has been chosen.

1.3 Epidemiology

AF is the most common sustained cardiac arrhythmia encountered in clinical practice and affects 1-2% of the general population. In Scotland, a national epidemiological survey of 362,155 patients between April 2001 and March 2002 found that the overall prevalence of AF was 8.7 per 1000 people (9.4/1000 in men and 7.9/1000 in women) and that the prevalence increased with age from 0.3/1000 <45 years to 30.5/1000 in 65-74 years and more than doubling to 70.7/1000 in patients >85 years. The incidence of AF was 0.9-1/1000 in men and 0.8/1000 in women (Murphy et al., 2007).

1.4 Aetiology

There are many risk factors for the development of AF (Table 1.1):

Cardiac	**Non-Cardiac**
Hypertension	Chronic lung disease
Valvular heart disease (especially mitral pathology)	Pulmonary embolism
Cardiomyopathy	Sepsis
Post cardiac surgery (inflammation)	Thyrotoxicosis
Coronary artery disease	Electrolyte disturbance
Sick sinus syndrome	Diabetes mellitus
Pericardial disease	Obstructive sleep apnoea (Gami et al., 2007)
Congenital heart disease	Chronic kidney disease
Atrial septal defect and myxoma	Obesity (Wanahita et al., 2008) and Metabolic Syndrome (Watanabe et al., 2008)
	Drugs
	Genetic factors
	Endurance athletes (Molina et al., 2008)

Table 1.1: Risk factors for AF

In the Framingham study, the development of AF was associated with increasing age (odds ratio (OR) 2.1 for men and 2.2 for women), diabetes mellitus (OR 1.4 men; 1.6 women), hypertension (OR 1.5 men; 1.4 women) and valvular heart disease (OR 1.8 men; 3.4 women) (Benjamin et al., 1994). Several dietary and lifestyle factors have also been associated with AF including excessive alcohol (Mukamal et al., 2005) and caffeine consumption and emotional and physical stress. AF can also develop in a subset of patients ≤ 60 years of age with no clear aetiology and in the absence of overt cardiopulmonary disease – 'lone AF'. The true prevalence of lone AF is unknown, varying between 1.6% and 30%, depending on the patients' age and inclusion/exclusion criteria used in the study (Brand et al., 1985; Kopecky et al., 1987; Scardi et al., 1999).

1.5 Prognosis

The natural history of AF is marred by serious complications, of which stroke is the most debilitating. AF is associated with a prothrombotic state on account of intra-atrial blood stasis, structural abnormalities in the fibrillating atria and generalised hypercoagulability (Lip, 1995). Coexisting medical conditions such as hypertension and diabetes also increase the risk of stroke. The rate of ischaemic stroke among patients with non-valvular AF is on average 5% per year, which is 2 to 7 times greater than in patients in sinus rhythm (Wolf et al., 1991; AF Investigators, 1994). One in every six strokes occurs in a patient with AF (Hart and Halperin, 1999).

In the Framingham Study, stroke risk was increased 17-fold in patients with rheumatic heart disease and AF compared with age-matched controls (Wolf et al., 1978) and the risk was five times greater than in patients with non-rheumatic AF (Wolf et al., 1991). The risk of stroke also increases with age with an annual risk of stroke attributable to AF of 1.5% in patients aged 50-59 years and 23.5% in patients aged 80-89 years (Wolf et al., 1991).

Multiple cohort studies describe an independent association between AF and mortality. The mechanism by which AF confers this independent mortality risk is not completely understood; nevertheless, AF is associated with an odds ratio for death of 1.5 in men and 1.9 in women, which does not vary with age (Benjamin et al., 1998). Cardiac failure is another well-recognised complication of AF and is associated with increased mortality. In addition, the structural and haemodynamic consequences of cardiac failure can result in the development of AF due to loss of atrial transport function and tachycardia-induced cardiomyopathy (Wang et al., 2003; Nerheim et al., 2004). Patients with AF also have a significantly poorer quality of life and reduced exercise capacity when compared to patients in sinus rhythm (Thrall et al., 2006) and can experience cognitive impairment due to recurrent cardioembolic events in the absence of an overt stroke (Knecht et al., 2008).

1.6 Arrhythmia Mechanisms

1.6.1 Atrial Electrophysiology

The resting membrane potential of atrial cardiomyocytes is set by the inwardly rectifying potassium current I_{K1} to a value close to -80mV. When an impulse is conducted from the sinoatrial node, the cell is depolarised by the opening of voltage-gated sodium channels causing an action potential (Figure 1.2).

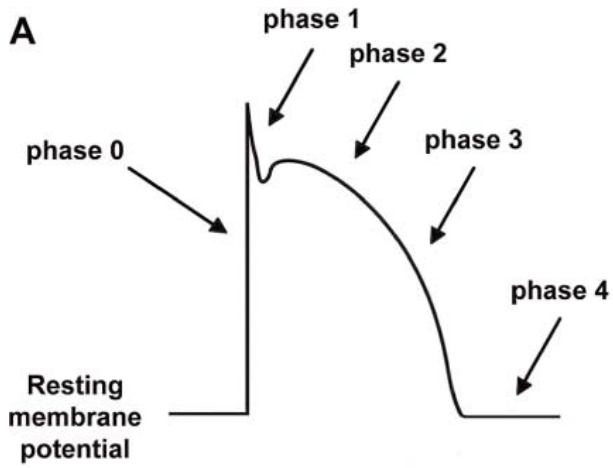


Figure 1.2: Atrial Action Potential
Phase 0: Depolarisation
Phase 1: Early repolarisation
Phase 2: Plateau
Phase 3: Terminal repolarisation
Phase 4: Resting membrane potential

Depolarisation also triggers the entry of calcium through L-type Ca^{2+} channels, which generates the action potential plateau and causes calcium release from intracellular stores in the sarcoplasmic reticulum resulting in myocardial contraction. Repolarisation is governed by a variety of potassium currents, which return the cardiomyocyte to its resting membrane potential thereby restoring cellular excitability.

The electrophysiological mechanisms underlying cardiac arrhythmias are illustrated in Figure 1.3.

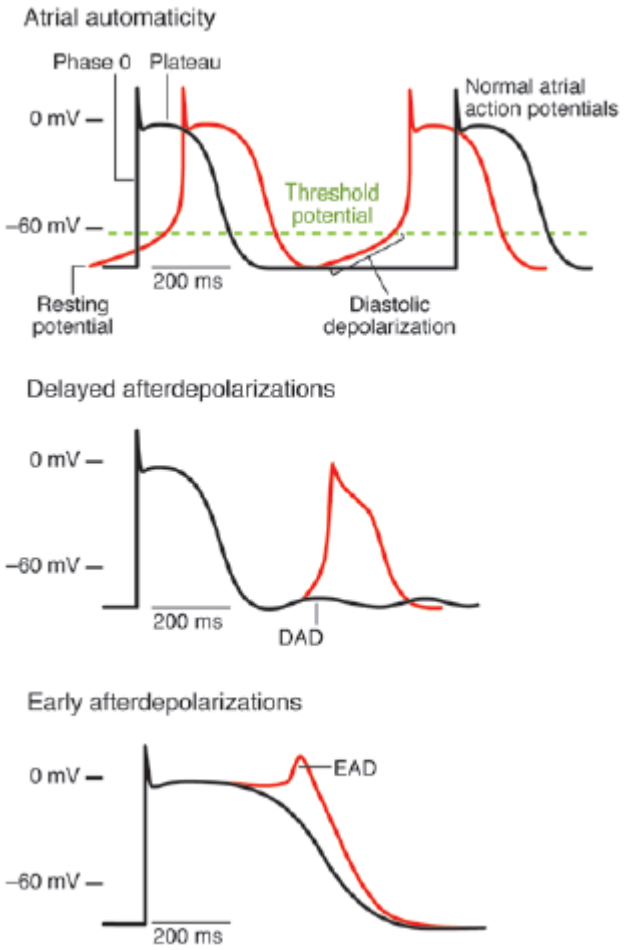


Figure 1.3: Focal Arrhythmia Mechanisms
Adapted with permission from Wakili et al. (2011).

1.6.2 Enhanced Automaticity

Enhanced atrial automaticity is caused by an increase in depolarising Na^+ or Ca^{2+} inward currents or a decrease in repolarising K^+ outward currents, which results in progressive cell depolarisation. When the threshold potential is reached, the cell produces an action potential, which, if it occurs before the next sinus beat, results in ectopic atrial activation. If the slope of diastolic depolarisation is increased, for example by acute myocardial ischaemia, the cell will reach threshold earlier and generate ectopic action potentials at a faster rate than the sinus node.

1.6.3 Early and Delayed Afterdepolarisations

Delayed afterdepolarisations (DADs) are the most important mechanism of focal cardiac arrhythmias. They result from abnormal diastolic leak of Ca^{2+} from the sarcoplasmic reticulum into the cytoplasm. Excess diastolic Ca^{2+} is handled by the cell membrane Na^+/Ca^{2+} exchanger which transports three Na^+ ions into the cell for every Ca^{2+} ion expelled creating a net depolarising current that produces DADs. When DADs become large enough to reach threshold potential, they cause ectopic firing, either as a single beat or as a sustained tachycardia.

Early afterdepolarisations are caused by a depolarising inward Ca^{2+} current which arises in cells with prolonged action potential duration. They, in turn, can cause neighbouring cells with normal repolarisation to reach threshold earlier causing ectopic firing.

1.6.4 Reentry

Reentry arises from variable impulse propagation through different zones of tissue (Figure 1.4). In normal tissue (top panel), an electrical impulse arriving at an area of conduction block (pink triangle) will split and travel down each side of the obstruction (1&2) and the impulses that meet below the obstruction will cancel each other out. Reentry (bottom panel) can occur if pathway 2 has unidirectional block therefore allowing impulses to travel retrogradely but not in an antegrade direction. An impulse travelling down pathway 1 will travel around the obstruction (pathway 3) and then travel retrogradely through the area of unidirectional block in pathway 2. Within this grey area, conduction velocity is reduced due to recent depolarisation. When the impulse exits the grey area, it can reenter pathway 1 if the tissue is excitable and a continuous reentrant circuit is formed.

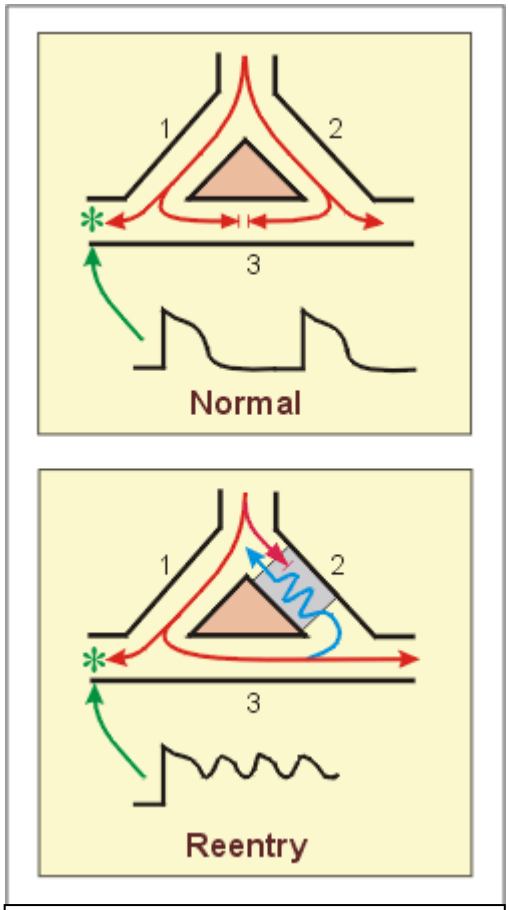


Figure 1.4: Reentry (see text)

Reentry requires appropriate tissue properties including a conduction barrier, unidirectional block within a conduction pathway, critical timing (normally initiated by an ectopic beat) and duration of effective refractory period. Shortening of the action potential duration and therefore refractory period facilitates reentry due to earlier recovery of excitability allowing the reentrant impulse to sustain itself throughout the circuit. Similarly, slowed conduction can facilitate reentry by allowing more time for cells to recover excitability before the reentrant impulse arrives.

1.7 Pathophysiological Mechanisms

The framework for understanding the mechanisms of AF is based largely on ideas developed in the early 20th century (Garrey, 1924). The principal competing theories at the time were that AF is caused by: (1) Rapidly discharging atrial ectopic foci, (2) Single circuit reentry, and (3) Multiple wavelet reentry (Figure 1.5).

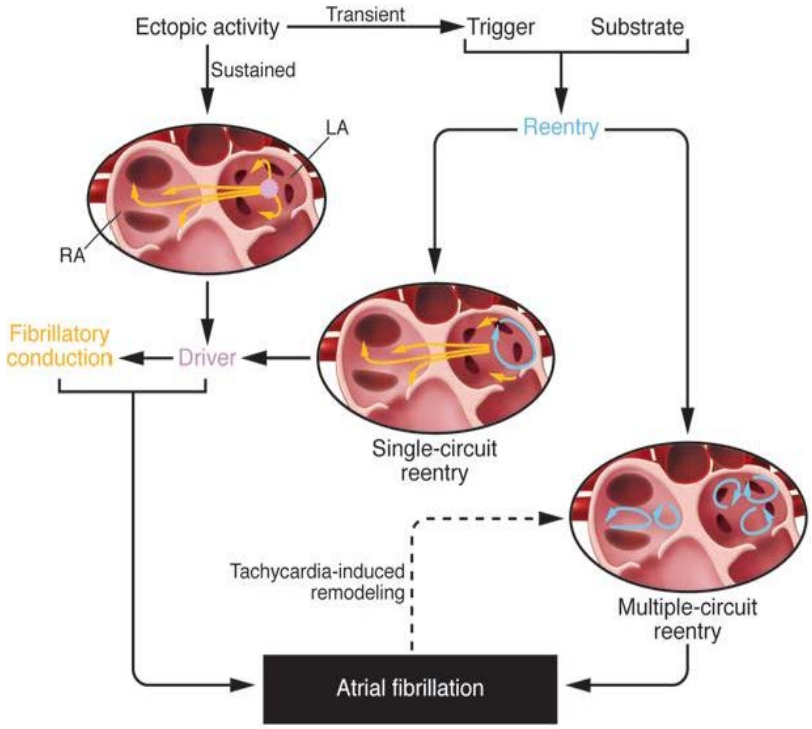


Figure 1.5: Pathophysiological Mechanisms
Reproduced with permission from Wakili et al. (2011).

1.7.1 Focal Ectopic Activity

A focal mechanism of AF was initially supported by experimental models of aconitine and pacing-induced AF in which the arrhythmia was only maintained in isolated areas of atrial myocardium (Scherf et al., 1948 and 1953). This theory received little attention until the landmark observation by Haissaguerre and colleagues in 1994 that AF is often triggered by a focal source and that ablation of that focal trigger can eliminate AF (Haissaguerre et al., 1994; Jais et al., 1997; Haissaguerre et al., 1998). While the pulmonary veins are the most frequent source of these rapidly firing ectopic foci, they have also been found in the posterior wall of the left atrium, coronary sinus, ligament of Marshall, superior vena cava and crista terminalis (Tsai et al., 2000; Lin et al., 2003; Schmitt et al., 2002). The importance of the pulmonary veins in triggering and maintaining AF led to a detailed investigation of their anatomical and electrophysiological properties. There is now general agreement that myocardial muscle fibres extend from the left atrium into the pulmonary veins for between 1 and 3cm (Weiss et al., 2002) and that these fibres contain specialised conduction tissue with pacemaker activity (Jongbloed et al., 2004). Other studies have shown that the pulmonary veins and pulmonary vein-left atrial junction are also preferential sites for local re-entry with signal fractionation, decremental conduction and shorter action potential duration compared to the body of the left atrium (Jais et al., 2002). This heterogeneity of conduction provides the ideal substrate for local reentry, which can maintain AF after initiation by an appropriate trigger.

1.7.2 Single Circuit Reentry and Rotors

Schuessler et al. (1992) demonstrated that increasing concentrations of acetylcholine in an isolated canine right atrium converted multiple reentrant circuits to a single, relatively stable, high frequency reentrant circuit that resulted in fibrillatory conduction. Subsequent advances in the understanding of reentrant arrhythmias have led to the concept of 'rotors', which occur when a wavefront destabilises after colliding with a functional or anatomical obstacle, giving rise to vortices of electrical spiral waves and turbulent electrical activity (Jalife and Pandit, 2005; Cabo et al., 1996) (Figure 1.6). Such rotors are self-sustaining and may be stationary or may drift but subsequently anchor themselves to anatomical structures in the atria.

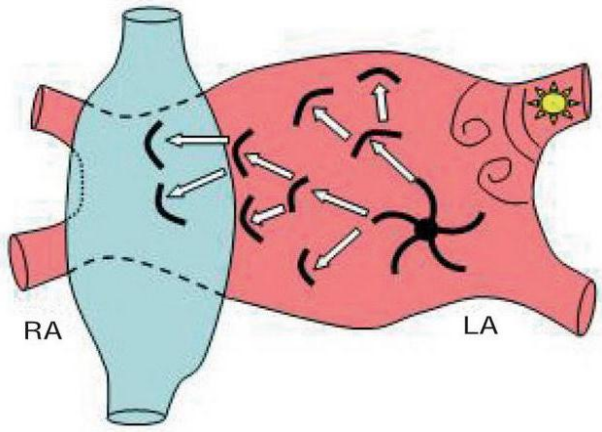


Figure 1.6: Left Atrial Rotor
LA, left atrium; RA, right atrium

Further research has shown that there is a wide spectrum of spatial and temporal organisation of AF in the structurally normal heart (Skanes et al., 1998; Mandapati et al., 2000). At one end of the spectrum, a single drifting rotor can give rise to complex patterns of activation that are reminiscent of AF. At the other end, sustained AF may also depend on the periodic activity of stationary rotors, which activate the atria at very high frequencies (Chen et al., 2000). These findings have been corroborated in humans by observations made during catheter ablation procedures for AF (Haissaguerre et al., 2000b; Lu et al., 2001). In addition, ectopic activity from the pulmonary veins that encounters heterogeneously refractory myocardium at the pulmonary vein-left atrial junction can result in the formation of rotors which generate high frequency impulses that propagate through the rest of the atria as fibrillatory waves (Mandapati et al., 2000; Jalife et al., 1998).

Transmural rotors and the three-dimensional AF substrate

Endo-epicardial dissociation of electrical activity and epicardial breakthrough during AF was first described by Schuessler et al. (1993) in a canine right atrial model. They reported that the differences in epicardial and endocardial activation were related to the heterogeneous architecture of the right atrial wall and that reentry could occur in the three-dimensional plane via transmural muscle fibres (Schuessler et al., 1993). More recently, Eckstein et al. (2011) performed simultaneous high-density endo-epicardial mapping on the left atrial free wall of goats during AF.

They demonstrated that the degree of dyssynchrony between epicardial and endocardial activation increased from 17% after AF onset to 39% after 3 weeks, and 68% after 6 months of continuous AF. They postulated that this was due to progressive uncoupling between the epicardial and endocardial layers, which correlated with increasing stability and complexity of the AF substrate. In a sheep model of persistent AF, Yamazaki et al. (2012) demonstrated that atrial scroll waves, defined as transmural rotors around a filament spanning the epicardial and endocardial surface, were the primary pattern of electrical activation. Interestingly, the majority of atrial scroll waves were identified in thinner parts of the atrial wall or at the junction between thin and thick sections, which suggests that variability in atrial wall thickness is an important factor for AF persistence.

1.7.3 Multiple Wavelet Reentry

Over the past 50 years, multiple wavelet reentry has been the dominant conceptual model of AF (Figure 1.7). It was proposed by Moe and Abildskov (1959) who reported that fractionation of wavefronts propagating through the atria resulted in self-perpetuating 'daughter wavelets'. The number of wavelets present at any one time depended on the refractory period, conduction velocity and mass in different parts of the atria; whereby, a large atrial mass with short, heterogeneous refractory periods and delayed conduction increased the number of wavelets, favouring maintenance of AF. Experimental support for this hypothesis came from Allessie (1985) who estimated that four to six wavelets were needed to maintain AF in dogs. This theory was strengthened by the clinical observation that persistent AF could be cured in some patients by the creation of multiple surgical lesions ("Maze procedure") to compartmentalise the atria into small areas that were unable to sustain the required number of wavelets (Cox et al., 1991).

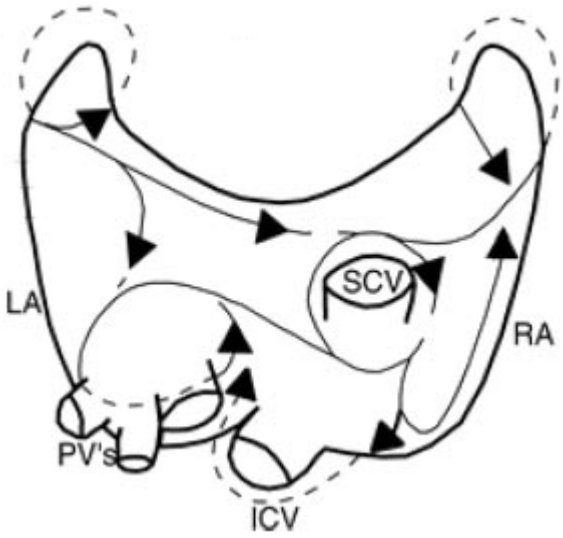


Figure 1.7: Multiple Wavelet Reentry (reproduced with permission from Konings et al. (1994)). ICV, inferior vena cava; LA, left atrium; PVs, pulmonary veins; RA, right atrium; SCV, superior vena cava

1.8 Autonomic nervous system

The importance of the autonomic nervous system in initiating and maintaining atrial tachyarrhythmias was first described by Coumel in 1996. Sympathetic stimulation increases ectopic activity via abnormal automaticity and afterdepolarisations; whereas, vagal stimulation shortens the atrial refractory period and increases its heterogeneity, which facilitates AF induction and maintenance via re-entrant mechanisms. However, an imbalance between sympathetic and vagal stimulation rather than enhanced activity per se appears to be the critical factor particularly in paroxysmal (Tomita et al., 2003) but also persistent AF (Arora, 2012). AF onset is often preceded by increased sympathetic tone followed by predominantly parasympathetic activity (Amar et al., 2003). The high density of adrenergic and cholinergic fibres in the posterior left atrium and pulmonary vein ostia likely contribute to the high frequency drivers and rotors primarily located at these sites (Yamazaki et al., 2009; Ng et al., 2011) (Figure 1.8). Finally, Gould et al. (2006) demonstrated heightened atrial sympathetic innervation in patients with persistent AF and proposed that autonomic remodelling may play a role in the development of the AF substrate.

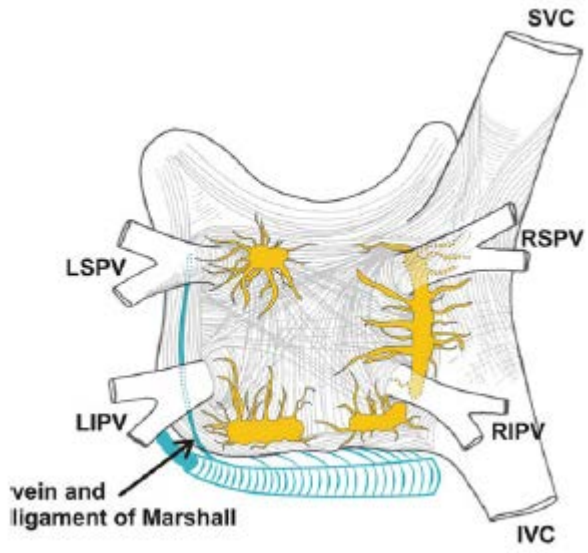


Figure 1.8: Major Left Atrial Ganglionic Plexi
IVC, inferior vena cava; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava.

1.9 AF-induced Remodelling

The concept of tachycardia-induced remodelling was proposed by two independent experimental studies. In a canine model of prolonged rapid atrial pacing, Morillo et al. (1995) found that the atrial refractory period was reduced by 15% and that after 6 weeks, they could induce AF episodes > 15 minutes duration in 82% of the dogs. In a goat model, Wijffels et al. (1995) maintained AF using epicardial burst pacing as soon as sinus rhythm returned. This resulted in more pronounced shortening of atrial refractory periods (45% reduction) and a loss of their normal physiological rate adaptation.

During the control period, only short paroxysms of AF were induced by burst pacing. After 2 days of AF, the paroxysms lasted longer than four hours and after 2-3 weeks, 90% of the goats were in persistent AF (Figure 1.9). This observation of tachycardia-induced remodelling led to the concept that 'AF begets AF' (Wijffels et al., 1995). AF-induced remodelling can be subdivided into three categories: (1) Electrical (2) Contractile and (3) Structural, with each contributing synergistically to the development of the AF substrate.

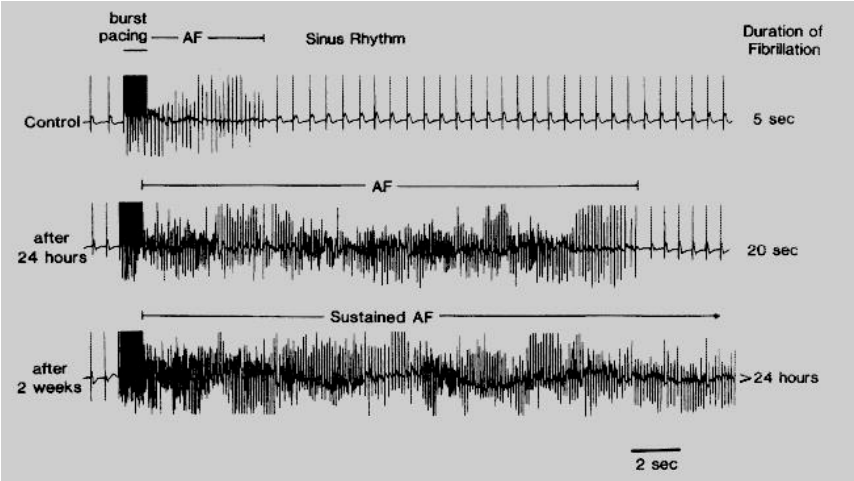


Figure 1.9: AF-induced Remodelling. Prolongation of AF episodes after electrically maintaining AF for 24 hours and 2 weeks in a goat model (reproduced with permission from Wijffels et al. (1995)).

1.9.1 Electrical Remodelling

The increased susceptibility to AF is explained by shortening of the wavelength of the atrial reentrant circuit (Rensma et al., 1988). When the wavelength is short, small areas of intra-atrial conduction block may serve as the origin of a re-entrant circuit, thus increasing the propensity for AF. In addition, wavelength shortening allows more reentrant wavelets to coexist in the atria thus stabilising the arrhythmia. The most important impact of AF on the ion channels in atrial cardiomyocytes is a marked reduction in the L-type Ca^{2+} current, which explains the shortening of the atrial action potential and the loss of its normal physiological rate adaptation (Yue et al., 1997; Bosch et al., 1999). In addition, intracellular Ca^{2+} overload can cause delayed afterdepolarisations, which in turn can trigger ectopic activity and AF initiation.

An important aspect of electrical remodelling is its reversibility. Even after several years of continuous AF, atrial refractory periods can return to baseline with normal physiological rate adaptation within a few days of restoring sinus rhythm (Wijffels et al., 1995; Yu et al., 1999). This has important clinical implications as recurrences of AF that occur after one week of sinus rhythm cannot be attributed to electrical remodelling.

Connexins

Connexins are transmembrane ion channel proteins that are present in the gap junctions of cardiomyocytes and are responsible for transferring ions or molecules freely between cells, thereby coupling them electrically. Cx40 and Cx43 are the two main connexins expressed in human atria (Saffitz et al., 1999). Given the pivotal role that connexins play in cell-to-cell coupling, changes in their expression and distribution would be expected to have profound effects on cardiac conduction (Wakili et al., 2011). However, the results from a wide range of clinical and experimental studies show significant variations, with opposing results observed within the same model (Haugan et al., 2006; Ryu et al., 2007). Pharmacological drugs that enhance gap junction conductance have been shown to be of benefit in some AF models (mitral valve disease and ischaemia) but not others (heart failure) (Guerra et al., 2006; Shiroshita-Takeshita et al., 2007). Therefore, the role of connexin abnormalities and the therapeutic value of augmenting gap junction conductance in AF remain unclear.

1.9.2 Contractile Remodelling

Logan et al. (1965) documented that the A-wave in the atrial pressure curve was lost after electrical cardioversion of AF to sinus rhythm. Subsequent echocardiographic research revealed that this atrial contractile dysfunction correlated with the duration of AF and could take months to fully recover (Manning et al., 1994 and 1995). This delayed recovery of atrial contractility may play a role in the occurrence of thromboembolic events in the initial period following cardioversion (Black et al., 1994). Experimental and clinical studies have shown that verapamil (a calcium channel antagonist) was able to substantially reduce the degree of atrial contractile dysfunction after short periods of AF, indicating that "atrial stunning" in this population is mediated by Ca^{2+} overload (Leistad et al., 1996; Daoud et al., 1999). Longer episodes of atrial fibrillation are associated with a 70% downregulation of the L-type Ca^{2+} current in a canine model (Yue et al., 1997). This Ca^{2+} current is a major factor in determining both the calcium content and its release from the sarcoplasmic reticulum, which explains its role in AF-induced contractile dysfunction and remodelling.

1.9.3 Structural Remodelling

The development of a fixed structural reentry substrate is a critical component in the progression of AF from paroxysmal to persistent and finally permanent forms (Figure 1.10). Atrial structural changes observed in animal models and in atrial biopsies from patients with AF include atrial dilatation and hypertrophy, dedifferentiation, fibrosis, apoptosis and myolysis (Ausma et al., 1997; Everett et al., 2000; Bauer et al., 2004; Anne et al., 2007).

Figure 1.10: AF Progression. Focal ectopic drivers are principally associated with paroxysmal AF, functional reentry substrates with persistent AF and fixed structural reentry substrates with permanent AF. Reproduced with permission from Wakili et al. (2011).

Atrial dilatation and hypertrophy

Atrial dilatation has been frequently observed in animal models of AF (Everett et al., 2000; Bauer et al., 2004). Schoonderwoerd et al. (2004) observed no atrial dilatation after rapid atrial pacing with a controlled ventricular rate for 4 weeks in a goat model, in contrast to the goats that were rapidly paced in both the atria and ventricles. This suggests that a concurrent high ventricular rate resulting in haemodynamic decompensation is an important determinant of atrial dilatation. Atrial cardiomyocyte hypertrophy has also been seen in pacing-induced animal models of AF (Ausma et al., 1997; Anne et al., 2007). Atrial dilatation and cardiomyocyte hypertrophy are commonly observed in patients with AF and are related to the severity of underlying cardiovascular disease and AF burden (Anne et al., 2005; Sanfilippo et al., 1990; Frustaci et al., 1997).

Dedifferentiation

Another adaptive mechanism contributing to structural remodelling involves a change in the gene expression profile to a more foetal phenotype – 'dedifferentiation'. Genes expressed during development are re-expressed, including skeletal α-actin, β-myosin heavy chain and atrial natriuretic peptide, and adult isoforms are downregulated (Ausma and Borgers, 2002).

Structural manifestations of dedifferentiation include myolysis, glycogen accumulation, mitochondrial changes, chromatic dispersion and loss of sarcoplasmic reticulum, which have been demonstrated in animal models (Ausma et al., 1997; Bauer et al., 2004; Schoonderwoerd et al., 2004) and in atrial biopsies from patients with AF (Rucker-Martin et al., 2002). It is thought that re-expression of a more foetal phenotype is an adaptive mechanism to meet the high energy demands associated with AF by allowing cardiomyocytes to use energy more efficiently (Barth et al., 2005).

Fibrosis

Fibrosis is the hallmark of structural remodelling (Li et al., 1999). It is caused by an accumulation of collagen deposits, occurring most commonly as a reparative process to replace degenerating myocardial parenchyma in conjunction with reactive fibrosis, which causes interstitial expansion (Assayag et al., 1997; Silver et al., 1990). Atrial fibrosis involves multifactorial processes that result from complex interactions between neurohormonal and cellular mediators. In addition, there are extensive interactions between cardiomyocytes and fibroblasts (Burstein and Nattel, 2008). Fibroblasts produce fibrotic extracellular matrix proteins and cardioactive mediators that affect the cardiomyocyte phenotype, whereas cardiomyocyte-derived products, such as angiotensin II, transforming growth factor β_1, platelet-derived growth factor and connective tissue growth factor modulate fibroblast properties and synthesis of the extracellular matrix. Reparative fibrosis replaces dead cardiomyocytes and therefore interferes with electrical continuity and slows conduction, whereas fibroblasts couple electrically to cardiomyocytes and promote ectopic activity and reentry (Burstein and Nattel, 2008; Yue et al., 2011).

Apoptosis and Myolysis

Apoptosis is defined as programmed cell death, whereas necrosis involves cell death that is caused by external factors (Hengartner, 2000). Atrial biopsies from patients with AF have shown both apoptosis and necrosis (Frustaci et al., 1997; Aime-Sempe et al., 1999). As previously described with atrial dilatation (Schoonderwoerd et al., 2004), there was no evidence of atrial cell death in a goat model with rapid atrial pacing and a controlled ventricular rate. However, atrial cell death was observed in two animal models that received combined rapid atrial and ventricular pacing (Schoonderwoerd et al., 2004; Li et al., 1999), which highlights the importance of a high ventricular rate and subsequent haemodynamic deterioration in structural remodelling.

Myolysis is defined as loss of cellular myofibril structure and is more consistently seen in models of persistent AF and cardiac failure than in patients with paroxysmal AF and structurally normal hearts (Frustaci et al., 1997).

1.9.4 Atrial Stretch

Studies using animal models of atrial volume (Nazir and Lab, 1996) and pressure (Bode et al., 2000) overload have shown an association between atrial stretch and an increased vulnerability to atrial arrhythmias. Interestingly, no spontaneous AF occurred in these animals suggesting the presence of an AF substrate without initiating triggers. In humans, hypertension, mitral valve disease and other models of left atrial overload are associated with atrial stretch and dilatation and an increased vulnerability to AF (Lau et al., 2010; Verheule et al., 2003). Atrial stretch facilitates the development of AF by causing both structural and electrical remodelling (Saygili et al., 2007; De Jong et al., 2011).

1.9.5 Inflammation and Oxidative Stress

Inflammation has been linked to AF with inflammatory infiltrates seen in atrial biopsies from patients with lone AF (Frustaci et al., 1997). Furthermore, serum levels of inflammatory markers are increased in both lone AF, as well as in AF associated with other comorbidities (Li et al., 2010). Myeloperoxidase (MPO), a neutrophil component that is part of the inflammatory response, has been found in the atria of patients with AF. An MPO infusion in MPO-deficient mice induced fibrosis and increased AF vulnerability, suggesting that MPO is a major protagonist in the development of atrial fibrosis (Rudolph et al., 2010). Oxidative stress in the form of oxygen and nitrogen free radicals also plays a role in the development of AF by promoting structural remodelling in the form of atrial fibrosis and cardiomyocyte hypertrophy (Mihm et al., 2001; Reil et al., 2010).

1.10 Management

Management of AF is primarily aimed at reducing morbidity and mortality and improving quality of life. More specific goals are ventricular rate control, restoration of sinus rhythm and prophylaxis against thromboembolism (Fuster et al., 2011). For the purpose of this thesis, I will focus on rate vs. rhythm control and specifically catheter ablation as a therapeutic intervention for patients with AF.

1.10.1 Rhythm vs. Rate Control

The fundamental decision of whether to choose rate-control vs. rhythm control as a treatment strategy in patients with AF has been the source of much debate amongst cardiologists (Cohen and Naccarelli, 2008). Theoretically, the restoration and maintenance of sinus rhythm should be favourable compared to a rate-control strategy due to the normalisation of heart rate and restoration of chronotropic competence, atrial contractile function and atrioventricular synchrony. Maintenance of sinus rhythm is associated with reduced atrial remodelling and AF symptoms, improved left ventricular function and exercise tolerance, and improved quality of life. However, prior to the development of AF ablation, the theoretical benefit of rhythm control relied on the availability of safe, tolerable and effective antiarrhythmic drugs. Comparative studies such as Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) (Wyse et al., 2002), Pharmacological Intervention in Atrial Fibrillation [PIAF] (Hohnloser et al., 2000) and Atrial Fibrillation and Congestive Heart Failure (AF-CHF) (Roy et al., 2008) have shown suboptimal rates of restoration and maintenance of sinus rhythm with no survival benefit over rate-control therapy (Steinberg et al., 2004). This is likely because the antiarrhythmic drugs studied had limited efficacy, poor tolerability and the potential for ventricular pro-arrhythmia.

Figure 1.11: Choice of Antiarrhythmic Drug according to Comorbidity. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CHF = congestive heart failure; HT = hypertension; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; Antiarrhythmic drugs are listed in alphabetical order within each treatment box. Reproduced from Camm et al. (2010).

More importantly, there was a significantly higher incidence of non-cardiovascular deaths in the rhythm-control group (12%) versus the rate-control group (8%), which were attributed to pulmonary and cancer-related deaths (Wyse et al., 2002). These results have strongly influenced current treatment guidelines to recommend rhythm-control therapy only in AF patients with disabling symptoms (Fuster et al., 2011). When a rhythm-control strategy is chosen, the choice of antiarrhythmic drug is based on the patients' comorbidities including hypertension, coronary artery disease and heart failure (Figure 1.11). Regardless of whether restoration of sinus rhythm will be attempted, treatment of AF should always include control of the ventricular rate (Camm et al., 2010). Pharmacological agents for rate control (β-blockers, non-dihydropyridine calcium channel antagonists, digoxin) either alone or in combination should be tailored to the individual patient based on underlying comorbidity and side effects such as bradycardia and hypotension. A rate-control strategy may be appropriate for elderly patients with minimal AF symptoms and in patients who are likely to have significant structural remodelling already present on account of underlying disease where a rhythm-control strategy is unlikely to be successful (Cosio et al., 2008).

1.11 Catheter Ablation

The disappointing performance of antiarrhythmic drugs coupled with the consistently high success and low complication rates routinely achievable using catheter ablation for other cardiac arrhythmias led to the development of catheter-based ablation strategies for AF. The initial procedures were designed to reproduce the success of the Cox Maze III surgical procedure using a transvenous catheter-based approach. The Cox Maze III procedure (Cox et al., 1995) was based on the "multiple wavelet reentry" model of AF (Moe and Abildskov, 1959) and the concurrent observation that 4 to 6 wavelets were required to maintain AF in a canine model (Allessie, 1985). It involved creating surgical incisions to divide the atria into small compartments to abort or block all possible anatomical reentrant circuits so that AF could not be initiated or maintained (Figure 1.12). The Cox Maze III procedure eliminated AF in 97% of patients among whom 76% maintained sinus rhythm off antiarrhythmic drugs at 5-year follow up (Prasad et al., 2003). However, the need for cardiopulmonary bypass along with its inherent risks and prolonged recovery time restricted its use to patients requiring additional cardiac surgery.

Unfortunately, attempts to replicate the Cox Maze III procedure using intracardiac catheters have had limited success despite the use of three-dimensional electroanatomical mapping systems and multipolar ablation catheters (Haissaguerre et al., 1996; Pappone et al., 1999).

1.11.1 Pulmonary Vein Ablation

The landmark observation by Haissaguerre and colleagues that AF was often triggered by ectopic foci within the pulmonary veins (Haissaguerre et al., 1994; Jais et al., 1997; Haissaguerre et al., 1998) led to a monumental shift in the direction of AF ablation towards abolishing these focal triggers. Catheter ablation of these ectopic foci was hampered by the difficulty in precisely mapping their location within the three-dimensional pulmonary venous structure and therefore, Haissaguerre and colleagues developed a segmental ablation technique that was designed to electrically isolate the myocardial sleeves of the pulmonary veins at their ostium (Haissaguerre et al., 2000a). The subsequent discovery that delivery of radiofrequency energy within the pulmonary veins could cause pulmonary vein stenosis (Robbins et al., 1998), coupled with the identification of focal triggers in the body of the left atrium led to the development of more extensive ablation strategies incorporating both the pulmonary veins and the atrial tissue surrounding the pulmonary veins – 'pulmonary vein antrum'. Ablation at these sites was either performed segmentally guided by a circular mapping catheter close to the pulmonary vein ostium (Haissaguerre et al., 2000a; Oral et al., 2002) or by wide area circumferential ablation (WACA) which involves the creation of wider continuous circumferential ablation lesions around the right and left pulmonary veins guided by three-dimensional electroanatomical mapping systems (Pappone et al., 1999 and 2000), fluoroscopy or intracardiac echocardiography (Callans et al., 2004).

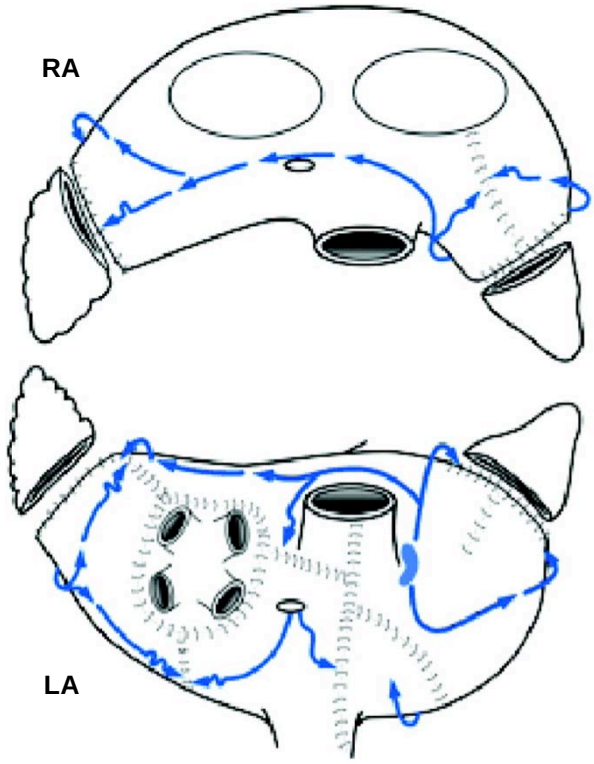


Figure 1.12: Original cut-and-sew Cox Maze procedure III. RA (right atrium): Excision of right atrial appendage, free wall incision, linear incision from superior vena cava to inferior vena cava (IVC) and from IVC to tricuspid valve annulus. LA (left atrium): Excision of left atrial appendage, pulmonary vein encirclement with extension to mitral valve annulus, and atrial septal incision. Reproduced from Weimar et al. (2012).

WACA targets arrhythmogenic foci within the pulmonary veins as well as high-frequency sources and sites of local reentry in the pulmonary vein-left atrial junction and posterior left atrium, which are not included in segmental pulmonary vein ablation (Figure 1.13). It can also result in atrial debulking as 25-30% of left atrial tissue can be electrically isolated from the remaining left atrium. In line with the above, WACA was found to be more effective that segmental pulmonary vein ablation in patients with paroxysmal AF in a randomised study (Oral et al., 2003). The same group showed that WACA is also effective in patients with persistent AF with 74% of patients maintaining sinus rhythm off antiarrhythmic drugs at 1 year follow up (Oral et al., 2006b).

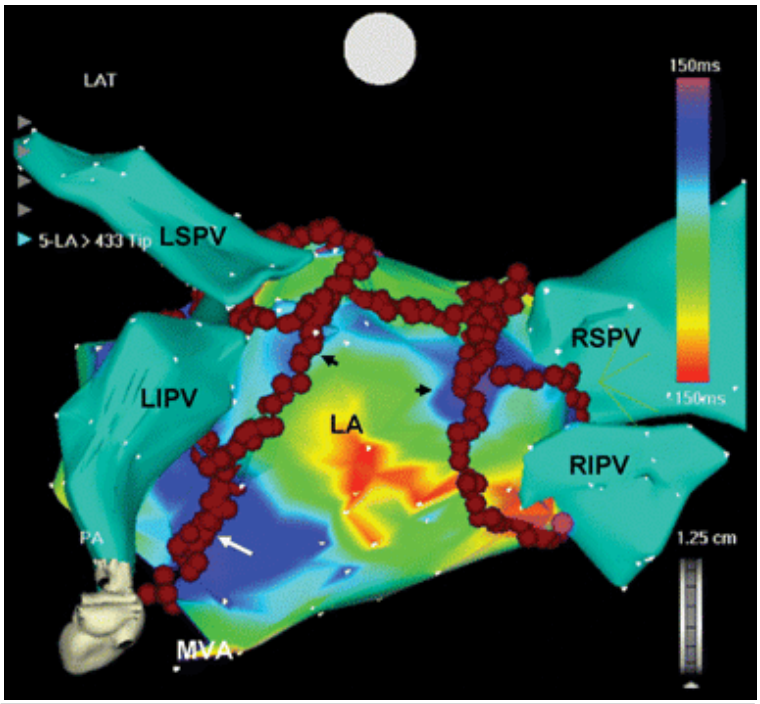


Figure 1.13: Electroanatomical map showing wide area circumferential ablation (WACA). Ablation lines circumscribe and divide the left and right pulmonary veins. A "Roof line" connecting the left and right superior pulmonary veins and "Mitral line" connecting the left inferior pulmonary vein to the mitral valve annulus are also shown. LA – left atrium, LIPV – left inferior pulmonary vein, LSPV – left superior pulmonary vein, MVA – mitral valve annulus, RIPV – right inferior pulmonary vein, RSPV – right superior pulmonary vein. Reproduced from Packer (2004).

1.11.2 Efficacy of Catheter Ablation

Pulmonary vein isolation (PVI) alone is reported to achieve durable sinus rhythm without the need for antiarrhythmic drugs in 59-93% of patients (Oral et al., 2003; Van Belle et al., 2008; Fiala et al., 2008; Dixit et al., 2008; Arentz et al., 2003). In addition, meta-analyses of studies (including mostly patients with paroxysmal AF) comparing antiarrhythmic drugs with catheter ablation, have shown a significantly higher proportion of patients maintain sinus rhythm after catheter ablation (Wilber et al., 2010; Calkins et al., 2009; Noheria et al., 2008; Jais et al., 2008; Wazni et al., 2005; Pappone et al., 2006). These results have led to catheter ablation being recommended in patients with symptomatic paroxysmal AF that is resistant to at least one antiarrhythmic drug (Camm et al., 2010).

It can also be considered as a first-line management strategy in patients with symptomatic paroxysmal AF and no/minimal structural heart disease (Camm et al., 2010). Unfortunately, the acute and longer-term success rates of catheter ablation for patients with persistent AF remain significantly lower than for patients with paroxysmal AF despite the development of additional ablation strategies aimed at positively modifying the AF substrate. These additional ablation strategies include linear left atrial, complex fractionated atrial electrogram (CFAE) and ganglionic plexus ablation (autonomic denervation). In a systematic review and meta-analysis of long-term outcomes (≥ 3 years) of catheter ablation in 6167 patients with AF, Ganesan et al. (2013) reported an overall single procedure success rate of 53.1% (54.1% paroxysmal; 41.8% persistent, p=0.3), which increased to 79.8% (79% paroxysmal; 77.8% persistent, p=0.9) after multiple procedures (mean 1.51 procedures per patient – 1.45 paroxysmal vs. 1.67 persistent AF, p=0.2). The authors noted that there was significant heterogeneity in the procedure outcome data and also did not include any patients with longstanding persistent AF in the meta-analysis due to the small number of patients with long-term follow up. A systematic review of catheter ablation outcomes in patients with longstanding persistent AF concluded that, with the exception of PVI alone (21% success) and CFAE ablation alone (37% success), all substrate ablation techniques including WACA alone or in combination with linear left atrial or CFAE ablation provided comparable clinical outcomes (mean success 47%) (Brooks et al., 2010). In light of the lower success rates observed with persistent and longstanding persistent AF, there is currently much debate amongst electrophysiologists regarding the optimum ablation strategy for these patients.

1.11.3 Linear Left Atrial Ablation

Linear ablation was conceived with the aim of reproducing the success of the Cox Maze III surgical ablation procedure (Cox et al., 1995) by compartmentalising the left atrium, thereby preventing the formation of macroreentrant circuits that can maintain AF. It involves the creation of linear ablation lesions that connect electrically inert structures with the commonest being the “Roof line” (connecting the right upper and left upper pulmonary veins), “Mitral line” (connecting the left lower pulmonary vein to the mitral valve annulus) and “Inferior line” (connecting the right lower pulmonary vein to the roof of the coronary sinus). Ablation strategies using a stepwise combination of PVI, CFAE and linear left atrial ablation achieved higher success rates compared to PVI alone in patients with persistent AF (42-95% freedom from AF without antiarrhythmic drugs) with most centres reporting success rates >70% (Haissaguerre et al., 2005;

Willems et al., 2006; Fassini et al., 2005; O'Neill et al., 2009; Estner et al., 2008a). However, two or more ablation procedures were required in ~50% patients to control persistent AF. In addition, incomplete bidirectional block across linear ablation lesions can be responsible for the occurrence of macroreentrant left atrial flutter post procedure, which can be incessant and frequently associated with significant symptoms (Matsuo et al., 2010; Ouyang et al., 2002; Tzeis et al., 2010).

1.11.4 Complex Fractionated Atrial Electrogram (CFAE) Ablation

This approach was first described by Nademanee et al. (2004) and involves targeting areas of myocardium that demonstrate CFAEs. CFAEs are defined as: (1) atrial electrograms that have two or more deflections from the baseline and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-second recording period (Figure 1.14); (2) atrial electrograms with a cycle length ≤120ms averaged over a 10-second recording period. Konings et al. (1997) reported that CFAEs observed during intraoperative mapping of AF were mostly found in areas of slow conduction and/or at pivot points where reentrant wavelets enter areas of functional block. Therefore, it has been hypothesised that CFAEs represent areas of the atrial substrate that are critical to the perpetuation of AF (Nademanee et al., 2004; Konings et al., 1997; Jais et al., 1996).

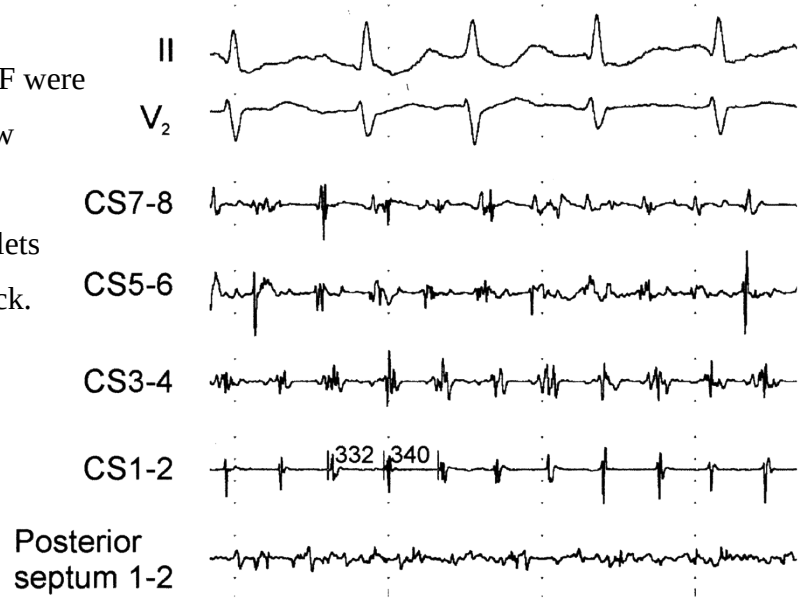


Figure 1.14: CFAEs in the posterior septum. Reproduced from Nademanee et al. (2004).

The aforementioned study by Nademanee et al. (2004) targeted and eliminated CFAEs in 121 patients with AF (64 persistent). At the end of procedure, all of the patients with paroxysmal AF and 58 (91%) patients with persistent AF were in sinus rhythm. At 1 year follow up, 110 (91%) patients were free from symptomatic AF. However, other groups have not been able to replicate these impressive results, which has cast doubt on the value of CFAE ablation.

Estner et al. (2008b) reported that only 2/23 (9%) patients with persistent AF who underwent CFAE ablation alone were in sinus rhythm without the need for antiarrhythmic drugs after a single procedure, compared with 22/54 (41%) patients who received CFAE ablation and PVI. Oral et al. (2009) reported the effect of CFAE ablation in conjunction with PVI in 119 patients with persistent AF. AF terminated during PVI in only 16% of patients and no difference in outcome was observed among the remaining patients who were randomised to either CFAE ablation or electrical cardioversion. The subjective nature of defining CFAEs by visual inspection alone could explain why other groups have been unable to replicate the success of Nadamanee and colleagues. In light of this, software algorithms to automatically identify CFAE sites have been developed (Calo et al., 2008). The other possible explanation is that CFAEs simply represent areas of wavelet collision, which are not critical to the maintenance of AF.

1.11.5 Autonomic Ganglion Plexus Ablation

The intrinsic cardiac autonomic nervous system contains plexi of autonomic ganglia located in epicardial fat pads and the ligament of Marshall (Armour et al., 1997). Ganglionic plexi (GP) contain afferent neurons from the atrial myocardium and central autonomic nervous system and efferent cholinergic and adrenergic neurons, which innervate the adjacent pulmonary vein and atrial myocardium. For endocardial GP ablation, a vagal response to high frequency stimulation is used to identify GPs, which are targeted with radiofrequency energy. A meta-analysis of 1147 patients who underwent catheter ablation demonstrated that PVI + cardiac autonomic denervation (CAD) significantly reduced the recurrence rate of atrial arrhythmias in both paroxysmal (OR 1.69; 95% CI: 1.09-2.62) and persistent (OR 2.11; 95% CI: 1.14-3.90) AF groups (Zhang et al., 2012). The authors also compared CAD to PVI and found no difference in ablation outcome (OR 0.31; 95% CI: 0.11-0.86).

1.11.6 Focal Impulse and Rotor Modulation (FIRM) Ablation

Narayan et al. (2012) have recently developed a novel computational mapping approach to detect rotors and focal impulses from atrial electrograms recorded during AF using the Constellation™ full-contact 64-pole basket catheter (Boston Scientific) (Figure 1.15). In a cohort of 92 patients (107 consecutive ablation procedures) with AF (72% persistent), they observed localised rotors or focal impulses in 98 (97%) cases with sustained AF, with a mean of 2.1 ± 1.0 sources per patient.

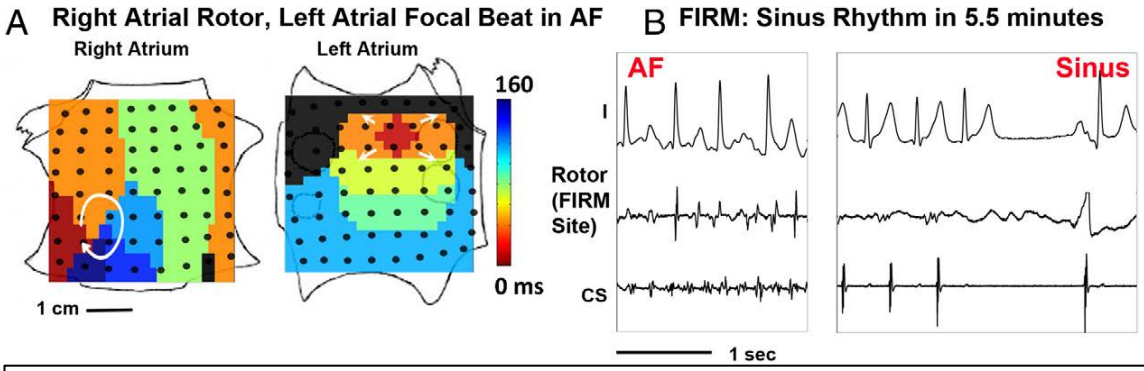


Figure 1.15: Acute termination of AF to sinus rhythm by FIRM Ablation. (A) Right atrial clockwise rotor and simultaneous left atrial focal impulse in a patient with persistent AF. (B) FIRM ablation at the site of the right atrial rotor terminated AF in 5.5 minutes. CS = coronary sinus electrogram. Reproduced from Narayan et al. (2012).

Patients were prospectively allocated to FIRM followed by conventional ablation (PVI using WACA in all patients and additional left atrial roof line in patients with persistent AF) (n=36) or conventional ablation alone (n=71). The acute endpoint (AF termination or ≥10% increase in AF cycle length) was achieved in 86% of FIRM + conventional ablation group vs. 20% conventional ablation group ($p<0.001$). After a single procedure, 82.4% patients in the FIRM group were free from AF vs. 44.9% in the conventional ablation group ($p<0.001$) at a median follow-up of 273 days (Narayan et al., 2012). FIRM ablation is the most exciting development in AF ablation in recent years although it remains to be seen whether these impressive results can be replicated in large multicentre randomised controlled trials comparing FIRM vs. conventional ablation strategies.

1.11.7 Ablation Technologies

Radiofrequency Energy

The theoretical basis of successful AF ablation is the production of transmural myocardial lesions that electrically isolate rapidly firing ectopic foci coupled with modification of the arrhythmogenic atrial substrate that facilitates reentry. Radiofrequency energy achieves myocardial ablation by the conduction of alternating electrical current through myocardial tissue, which exhibits electrical resistance. This tissue resistance results in the dissipation of RF energy as heat resulting in irreversible coagulation necrosis and ultimately the formation of non-conducting myocardial scar (Haines, 2006). High power delivery and good electrode-tissue contact using large-tip or irrigated-tip catheters promote the formation of larger ablation lesions and improve procedural efficacy.

Comparative trials of open-loop irrigated-tip and standard 4mm-tip catheters have demonstrated an improvement in the maintenance of sinus rhythm after ablation with open-loop irrigated-tip catheters in conjunction with a similar complication rate (Thomas et al., 2004; Chang et al., 2009).

Multielectrode circumferential ablation catheters

The principal purpose of multielectrode circumferential ablation catheters is to provide mapping and ablation in a single platform. One example is the PVAC® catheter (Medtronic Ablation Frontiers) which is a circular, decapolar catheter that creates ablation lesions by delivering radiofrequency energy at a relatively low power (Figure 1.16). In a prospective cohort study of 110 patients with symptomatic paroxysmal AF, 57 (52%) patients were arrhythmia free off antiarrhythmic drugs at 1-year follow up (Mulder et al., 2011). This compares favourably to the radiofrequency and cryoballoon-based AF ablation literature (Andrade et al., 2011 and 2012; Ganesan et al., 2013).

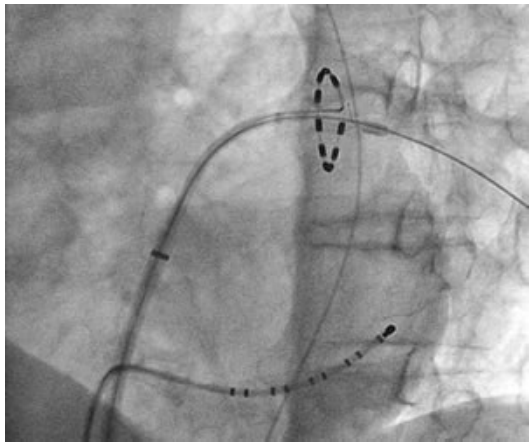


Figure 1.16: PVAC® catheter in the ostium of the left lower pulmonary vein. A decapolar catheter in the coronary sinus is also shown.

Cryoablation

Within the last decade, cryoablation has superseded the original "cut and sew" technique for performing the Cox Maze procedure for the surgical treatment of AF on account of its similar efficacy and significantly reduced cardiopulmonary bypass time. In a non-randomised trial of patients with AF requiring mitral valve surgery, Nakajima et al. (2002) compared the efficacy of cryoablation versus the original "cut and sew" technique in performing the Cox Maze procedure and reported no significant difference in the number of patients in sinus rhythm at discharge: 85% cryoablation vs. 86% 'cut and sew'. The Arctic Front® cryoballoon ablation system (Medtronic Cryocath) (Figure 1.17) was developed as a method of performing pulmonary vein isolation. Liquid nitrous oxide is delivered under pressure to the cryoablation balloon, where it changes into gas, resulting in cooling of the surrounding tissue to temperatures below -40°C.

Figure 1.17: Arctic Front® cryoablation balloon and Achieve™ circular mapping catheter (Medtronic Cryocath)

Tissue freezing, with the creation of intracellular ice crystals, and rewarming results in cell death by disrupting cell membranes and interrupting cellular metabolism and intracellular electrical activity. As with radiofrequency energy, good tissue contact is required to generate effective ablation lesions. Blood flow around the cryoablation balloon counteracts the effects of cooling, thus reducing the likelihood of a transmural ablation lesion. Therefore, complete vein occlusion is required to create circumferential pulmonary vein lesions and durable PVI.

There are several potential advantages with using cryoablation. Balloon adhesion to myocardial tissue during freezing enhances the efficacy of ablation lesions and allows the operator to pivot the balloon on the adhered section to reach other areas of the pulmonary vein ostium which is particular useful when treating large diameter pulmonary veins. Cryoablation also carries a low risk of thrombus formation (Khairy et al., 2003), which potentially reduces the risk of thromboembolic complications.

In a systematic review of the efficacy and safety of cryoballoon ablation in 1298 patients (1211 paroxysmal AF), Andrade et al. (2011) reported that pulmonary vein isolation was achieved in 98.8% of patients. One-year freedom from recurrent AF was 72% in patients with paroxysmal and 45% in patients with persistent AF. Three non-randomised studies comparing cryoballoon versus radiofrequency ablation reported no difference in arrhythmia outcomes (Linhart et al., 2009; Kojodjojo et al., 2010; Kuhne et al., 2010).

1.11.8 Safety

In a worldwide survey on the safety of catheter ablation for AF, Cappato et al. (2010) reported an overall complication rate of 4.5% including vascular complications (1.47%), cardiac tamponade (1.31%), stroke / transient ischaemic attack (0.94%), pulmonary vein stenosis requiring intervention (0.29%) and death (0.15%). It should be highlighted that this data was taken from voluntary surveys and therefore likely underestimates the true complication rates. A systematic review of the safety and efficacy of AF ablation using phased radiofrequency energy and multielectrode catheters reported an acute procedural complication rate (stroke, myocardial infarction, pericardial effusion or tamponade, and vascular access complications) of 2% in 1719 patients from 25 studies (Andrade et al., 2012). However, two separate studies (Herrera Siklody et al., 2011; Gaita et al., 2011) reported a significantly higher rate of silent cerebral ischaemic lesions after PVAC® ablation (37.5 – 45.1%) when compared to irrigated radiofrequency (7.4 – 16.7%) and cryoballoon ablation (4.3 – 5.6%). Importantly, Schwarz et al. (2010) demonstrated that these lesions might be associated with neuropsychological sequelae.

Haines et al. (2013) investigated this further using a porcine model and demonstrated that left atrial ablation using irrigated tip radiofrequency and PVAC® catheters was associated with microbubble and microembolus production. They hypothesised that this could explain the ischaemic cerebral lesions seen on diffusion weighted MRI and reported that bipolar ablation using electrodes 1 and 10 on the PVAC® catheter was associated with the most microbubbles due to electrode overlap. These findings were corroborated by Wieczorek et al. (2013) in a study of 37 patients with paroxysmal AF and this has been addressed in the design of the new PVAC® Gold catheter (Medtronic Ablation Frontiers) which has nine electrodes and therefore eliminates the potential overlap between electrodes 1 and 10.

Regarding the safety of cryoballoon ablation, Andrade et al. (2011) reported that the commonest complication was phrenic nerve paralysis with an incidence of 4.7%. This was transient in the majority of cases with only 0.37% experiencing phrenic nerve paralysis 1 year following ablation. Other complications were less frequent including vascular complications (1.8%), cardiac tamponade / pericardial effusion (1.5%), thromboembolic complications (0.6%), and significant pulmonary vein stenosis (0.2%).

1.11.9 Effect on Stroke Risk and Mortality

Our knowledge of the long-term effects of catheter ablation on mortality and risk of stroke has increased significantly over the past decade. In a retrospective analysis of 775 patients who underwent AF ablation with 2-year follow up, Oral et al. (2006a) demonstrated that patients who maintained sinus rhythm after ablation had the same risk of stroke as patients in the control group from the Framingham study with no history of AF. In an epidemiological study of 4212 patients who underwent AF ablation compared to age and gender-matched controls with and without AF, patients in the AF ablation group had a significantly lower risk of death and stroke in comparison to AF patients who did not receive ablation during a 3-year follow up period (Bunch et al., 2011). Interestingly, the reduction in stroke risk and mortality was not exclusively dependent on maintaining sinus rhythm after ablation in this study. These findings have been corroborated by Lin et al. (2013) who compared long-term outcome and mortality in 384 AF patients with high thromboembolic risk (CHA_2DS_2-VAS_C score ≥ 1) – 174 patients who underwent AF ablation and 174 propensity-matched patients who received antiarrhythmic medication. At 4-year follow up, 90.2% patients maintained sinus rhythm in the ablation group vs. 39.7% patients in the medically treated group ($p<0.001$).

Mortality and stroke rates were significantly lower in the ablation group compared to the medically treated group (2.9% and 2.3% vs. 11.5% and 8.6% respectively). In addition, patients who maintained sinus rhythm after ablation had significantly lower mortality and stroke rates than patients who experienced recurrent AF (1.7% and 0.8% vs. 5.4% and 5.4% respectively). Furthermore, AF recurrence also predicted the future occurrence of a major adverse cardiovascular or vascular event in a multivariate Cox regression analysis of the ablation group. In summary, there is a growing body of evidence that catheter ablation reduces stroke risk and mortality in patients with AF; although, more definitive results are expected from the ongoing prospective CABANA (Catheter ABlation vs. ANtiarrhythmic drug therapy for Atrial fibrillation) and EAST (Early treatment of Atrial fibrillation for Stroke prevention Trial) randomised controlled studies.

I would now like to present the remaining six chapters of my thesis, which focus on the three main studies I completed during my MD research programme. The unifying aim of the thesis was to investigate whether we could predict and improve clinical outcome following ablation in patients with AF using surface AF waveform analysis and multipolar contact mapping respectively. Each chapter is presented in manuscript format with an individual Abstract, Introduction (including specific Aims), Methods, Results and Discussion. In brief, Chapter 2 examines whether the inclusion of posterior ECG leads improves correlation between surface dominant AF frequency (calculated using principal component analysis) and intracardiac measurements from the left atrium. Chapter 3 explores whether acute and 12-month outcome following catheter ablation can be predicted beforehand using clinical and surface AF waveform parameters. Chapter 4 considers the effect of catheter ablation on AF symptoms and quality of life. Chapters 5 and 6 examine the role of multipolar contact mapping in facilitating catheter ablation in patients with persistent AF. Chapter 7 concludes with a final discussion of the main results of the studies including their clinical relevance and directions for future research.

Chapter 2. Principal component analysis of atrial fibrillation: Inclusion of posterior ECG leads does not improve correlation with left atrial activity

2.1 Abstract

Background

Lead V_1 is routinely analysed due to its large amplitude AF waveform. V_1 correlates strongly with right atrial activity but only moderately with left atrial activity. Posterior lead V_9 correlates strongest with left atrial activity.

Aims

[1] To establish whether surface dominant AF frequency (DAF) calculated using principal component analysis (PCA) of a modified 12-lead ECG (including posterior leads) has a stronger correlation with left atrial activity compared to the standard ECG; [2] To assess the contribution of individual ECG leads to the AF principal component in both ECG configurations.

Methods

Patients were assigned to modified or standard ECG groups. In the modified ECG, posterior leads V_8 and V_9 replaced V_4 and V_6. AF waveform was extracted from one-minute surface ECG recordings using PCA. Surface DAF was correlated with intracardiac DAF from the high right atrium (HRA), coronary sinus (CS) and pulmonary veins (PVs).

Results

96 patients were studied. Surface DAF from the modified ECG did not correlate better with left atrial activity compared to the standard ECG. Both ECG configurations correlated strongly with HRA, CS and right PVs ($p<0.01$) but only moderately with left PVs ($p<0.05$). V_1 contributed most to the AF principal component in both ECG configurations.

Conclusion

Surface DAF calculated using PCA of a modified 12-lead ECG (including posterior leads) did not correlate better with left atrial activity compared to the standard ECG. Surface DAF from both ECG configurations correlated strongly with right atrial activity, reflecting the dominance of lead V_1 in the AF principal component.

2.2 Introduction

It is widely accepted that the atrial waveform seen on the surface ECG during AF reflects intracardiac electrical activity (Alcaraz et al., 2011; Petrutiu et al., 2009). The majority of research studies investigating surface ECG analysis in AF employ QRST subtraction as the method of extracting the AF waveform from the surface ECG. The two principal methods of QRST subtraction are average beat subtraction (ABS) and spatiotemporal QRST cancellation. ABS was initially developed to help identify P waves in ventricular tachycardia (Slocum et al., 1985) and involves creation of an average QRST complex from a single ECG lead, which is then subtracted to leave the residual atrial signal (Bollmann et al., 1998; Holm et al., 1998). It relies heavily on the assumption that the average QRST complex reflects each individual QRST complex accurately. However, QRST morphology can vary with the orientation of the heart's electrical axis and therefore, minor axis variations can result in significant QRST residuals appearing in the extracted AF waveform. Spatiotemporal QRST cancellation was developed to address this problem by using a multi-lead ECG (typically leads II, aVF and V_1) to compensate for variations in electrical axis by transferring information between leads (Stridh and Sornmo, 2001). The majority of studies analysing the body surface AF waveform using these techniques have focused on lead V_1 due to the relatively large amplitude AF waveform in this lead. This reliance on lead V_1 detracts from the sensitivity of the results since V_1 has been shown to correlate strongly with right atrial activity (r=0.89) but only moderately with left atrial activity (r=0.62) (Petrutiu et al., 2009). In the same study, posterior lead V_9 had the strongest correlation with left atrial activity (r=0.88) (Petrutiu et al., 2009). Therefore, results obtained using QRST subtraction of V_1 will have an inherent right atrial bias and may not accurately reflect left atrial activity.

As an alternative to template subtraction methods, blind source separation techniques have been applied to extract atrial components from multi-lead recordings of AF by suppressing ventricular complexes (Langley et al., 2006; Raine et al., 2004; Rieta et al., 2004). The main advantage of these techniques is that they derive a 'global' AF waveform that has contributions from all ECG leads. One such method uses principal component analysis (PCA) (Langley et al., 2006; Raine et al., 2004). Using a combination of PCA and Fourier analysis, we have previously shown that surface DAF is reproducible over time and changes appropriately with drug manipulation of the arrhythmia (Raine et al., 2004).

We have also demonstrated a reduction in surface DAF following creation of linear ablation lesions in the left atrium (Raine et al., 2005). So far the focus of this work has been on the standard 12-lead ECG. However, given the evidence that posterior leads may provide a more accurate reflection of left atrial activity (the chamber responsible for the initiation and maintenance of AF in the majority of patients), the **aims** of this study were: [1] To establish whether surface DAF calculated using PCA of a modified 12-lead ECG (including posterior leads V_8 and V_9) had a stronger correlation with left atrial activity compared to the standard 12-lead ECG; [2] To assess the contribution of individual ECG leads to the AF principal component in both ECG configurations.

2.3 Materials

2.3.1 Patient Recruitment and Clinical Characteristics

Study participants were recruited from patients with AF undergoing their first catheter ablation procedure for standard clinical indications. Class I and III antiarrhythmic drugs were discontinued five half-lives prior to ablation. Patients were excluded from the study if they were unable to give written informed consent or were taking amiodarone – because of its long half-life and effects on cardiac electrophysiology. The clinical characteristics of the 96 consecutive patients studied are shown in Table 2.1. Their mean age was 57 ± 10 years and 79% were male. 54% had persistent AF and the mean AF history was 4 ± 4 years.

2.3.2 Ethical Approval

This study complies with the Declaration of Helsinki and was granted a favourable ethical opinion by the National Research Ethics North West Committee (REC reference: 11/NW/0476). Written informed consent was obtained from all patients included in the study.

2.3.3 Study Protocol

Surface ECG and intracardiac recordings were collected simultaneously on a Labsystem Pro™ recording system (Bard EP) at a digital sampling rate of 1000Hz for offline analysis in Matlab®2013. A one-minute recording was collected from patients in AF at the start of the procedure. For patients in sinus rhythm, AF induction was attempted using routine pacing manoeuvres. If AF was successfully induced, a 5-minute recording was collected to allow the arrhythmia to stabilise and AF parameters from the fifth minute were analysed. Patients were excluded from the study if AF could not be initiated or did not sustain for at least 5 minutes.

Intracardiac recordings were collected from the coronary sinus (CS), high right atrium (HRA) and sequentially from each of the pulmonary vein ostia using a decapolar (Livewire™, St. Jude Medical), quadripolar (Josephson, St. Jude Medical) and bipolar irrigated-tip ablation catheter respectively. The distal poles of the CS catheter were positioned on the lateral aspect of the mitral valve ring, with proximal bipole $CS_{9\text{-}10}$ just inside the ostium of the coronary sinus. The HRA catheter was positioned either in the right atrial appendage or high lateral right atrium depending on whether we were able to achieve a stable catheter position in the right atrial appendage.

2.4 Methods

2.4.1 Modified and Standard Surface 12-lead ECG Measurements

The modified surface 12-lead ECG *(where posterior leads V8 and V9 replaced leads V4 and V6)* was used in patients undergoing their AF ablation procedure without electroanatomical mapping guidance. Standard 12-lead ECG placement was used in patients undergoing their procedures with electroanatomical mapping guidance since the external reference patches for the CARTO® 3 (Biosense Webster) and EnSite Velocity™ (St. Jude Medical) systems preclude placement of posterior leads V_8 and V_9. The decision to use electroanatomical mapping was at the discretion of the physician and there were no significant differences in clinical characteristics between the two patient groups (Table 2.1).

2.4.2 Surface AF Waveform Analysis

AF Waveform Extraction – Principal Component Analysis

The continuous AF waveform was extracted from the surface ECG using PCA as previously described by our group (Raine et al., 2004 and 2005 - *Appendix 1*). This is a multi-variable technique commonly used to identify and separate different sources in the data based on their degree of correlation. Mathematically it represents a linear transformation of the data to a new set of variables (principal components (PCs)), which are uncorrelated.

The transformation is described by:

$$PC_1 = c_{1,1}l_1 + c_{1,2}l_2 \cdots c_{1,12}l_{12}$$
$$PC_2 = c_{2,1}l_1 + c_{2,2}l_2 \cdots c_{2,12}l_{12}$$
$$\vdots$$
$$PC_{12} = c_{12,1}l_1 + c_{12,2}l_2 \cdots c_{12,12}l_{12}$$

where PC_i are the principal components, l_j are the ECG leads and $c_{i,j}$ are the transform coefficients derived from the eigenvectors of the covariance matrix of the ECG leads arranged in order of descending eigenvalue. The transform coefficients describe the contribution of each lead to the PCs. In AF waveform analysis, the PCs contain the separated atrial, ventricular and noise components of the ECG signal (Figure 2.1). For subsequent AF waveform analysis, a single PC was identified visually as the one containing the largest amplitude AF waveform (PC_{AF}). To quantify the contribution of each ECG lead to PC_{AF}, we report the absolute value of the transform coefficients ($|c_{AF,j}|$) separately for standard and modified 12-lead ECG configurations.

AF Waveform Extraction – Average Beat QRST Subtraction

As only one ECG configuration (standard or modified) was recorded in each patient, the AF waveform extracted from lead V_1 using ABS (as described in Bollmann et al. and Holm et al. (1998)) was used as a control to allow comparisons of the strength of correlation between surface and intracardiac DAF measurements between the two ECG configurations.

2.4.3 Intracardiac Waveform Analysis

PCA and Fourier analysis were used to calculate the intracardiac DAF from each bipole on the catheters positioned in the CS, HRA and pulmonary vein ostia. The most distal CS bipole (CS_{1-2}) was excluded from the analysis because of the predominant ventricular activity and low amplitude atrial electrograms frequently recorded at this location.

Dominant AF Frequency

Power spectral density of the body surface and intracardiac atrial signals was performed by periodogram and the DAF was defined as the AF frequency with the highest power in the range 3-10Hz (Raine et al., 2004 and 2005). Figure 2.2 shows a 10-second section of ECG lead V_1 with the extracted AF waveform (PCA and ABS) and intracardiac recordings from the HRA and CS. The corresponding frequency spectra and DAF are shown. Surface and intracardiac DAF were analysed in consecutive 10-second sections and mean values across the one-minute recordings are reported.

2.4.4 Statistical Analyses

Continuous variables are expressed as mean ± SD. Patient characteristics were compared between the modified and standard ECG groups using Student's independent *t*-test for continuous variables and Pearson's chi-squared test for categorical variables.

Surface DAF calculated using PCA and ABS from modified and standard ECG configurations was correlated with intracardiac DAF using Pearson's correlation. Fisher r-to-z transformation was used to evaluate the significance of the difference between comparable correlation coefficients. All tests were 2-tailed and $p<0.05$ was considered statistically significant.

2.5 Results

2.5.1 Modified vs. Standard 12-lead ECG

Surface DAF from both modified and standard 12-lead ECG configurations correlated strongly with intracardiac DAF in the HRA, CS and right-sided pulmonary veins with all correlations being significant at the 0.01 level (Tables 2.2 and 2.3). Surface DAF from the standard but not the modified ECG correlated strongly with left upper pulmonary vein (LUPV) DAF (PCA r=0.79; ABS r=0.84, $p<0.01$ vs. PCA and ABS r=0.43, $p<0.05$). In addition, there was only moderate correlation between surface DAF from either ECG configuration and left lower pulmonary vein (LLPV) DAF (modified r=0.43; standard r=0.50, $p<0.05$) (Tables 2.2 and 2.3). In the ABS control group, surface DAF from the standard ECG had a significantly stronger correlation with LUPV DAF compared to the modified ECG (0.84 vs. 0.43; $p<0.01$) (Table 2.4). In addition, surface DAF from the modified ECG had a stronger correlation with intracardiac DAF from HRA (0.91 vs. 0.82) and $CS_{5\text{-}6}$ (0.81 vs. 0.62), although these did not reach statistical significance. Therefore, the only significant difference between modified and standard ECG configurations in the PCA group was observed with $CS_{7\text{-}8}$ where the modified ECG had a stronger correlation with intracardiac DAF compared to the standard ECG (0.89 vs. 0.74; p=0.03) (Table 2.4).

2.5.2 ECG Lead Contribution to AF Principal Component

We assessed the individual ECG lead contributions to the PC_{AF} by plotting the absolute values of the transfer coefficients ($|c_{AF,j}|$) for the modified and standard 12-lead ECG configurations (Figure 2.3). Lead V_1 contributed most to the PC_{AF} in both ECG configurations, with a transfer coefficient typically three times that of the other leads. This is most likely a reflection of the large amplitude AF waveform typically seen in this lead.

2.6 Discussion

To our knowledge, this study is the first to correlate surface DAF measurements calculated using PCA and Fourier analysis of a modified 12-lead ECG configuration (including posterior leads V_8 and V_9) with intracardiac DAF measurements from the high right atrium, coronary sinus and pulmonary vein ostia. As we only recorded one ECG configuration (standard or modified) in each patient, we controlled for comparisons between the two by calculating surface DAF from lead V_1 using ABS and Fourier analysis in all patients. Surface DAF from both modified and standard ECG configurations correlated strongly with intracardiac DAF from the high right atrium, coronary sinus and right-sided pulmonary veins. However, in general, there was only moderate correlation between surface DAF and intracardiac DAF from the left-sided pulmonary veins.

Taking into account the results from the average beat subtraction (ABS) control group, the only significant difference in the strength of correlation with intracardiac DAF between the modified and standard ECG configurations in the PCA group was in a single bipolar recording from the proximal part of the coronary sinus (CS_{7-8}), which is usually more reflective of right atrial activity. Therefore, our results show that surface DAF calculated using PCA of a modified 12-lead ECG configuration (which included posterior leads V_8 and V_9) does not have a stronger correlation with left atrial activity compared to the standard 12-lead ECG. This can be explained by the dominance of lead V_1 in the AF principal component from both ECG configurations (Figure 2.3) on account of its characteristic large amplitude AF waveform. This also explains the stronger correlation between surface DAF and intracardiac frequencies recorded from the right atrium and the strong correlation between surface DAF calculated using PCA (12-lead ECG) and ABS (lead V1) in both ECG configurations (modified: r=0.91; standard: r=0.86). The disparity between our results and the findings of Petrutiu et al. (2009) can be explained by differences in the method used to extract the AF waveform from the surface ECG. They used QRST subtraction on individual ECG leads, whereas we used PCA on 12-lead ECG configurations. Whilst posterior lead V_9 may have the strongest correlation with left atrial activity, its relatively small amplitude AF waveform ensures that it does not contribute significantly to the AF principal component in PCA.

2.7 Limitations

Firstly, we did not record both ECG configurations in each patient. However, we calculated surface DAF from lead V_1 using ABS and Fourier analysis in all patients as a control measure to validate comparisons between the modified and standard ECG groups. Secondly, we only used recordings from the coronary sinus and pulmonary vein ostia to reflect left atrial activity. Previous studies have shown that the physical and electrical connections between the coronary sinus and left atrium can vary between patients (Antz et al., 1998; Chauvin et al., 2000) and so coronary sinus recordings may not reflect left atrial activity accurately in all cases (Ndrepepa et al., 2001). Similarly, other areas of the left atrium such as the left atrial appendage, roof, septum and posterior wall commonly contain high frequency sites and were not sampled in this study. These sites may contribute to the surface DAF and therefore merit further study.

2.8 Conclusions

Surface DAF calculated using PCA and Fourier analysis of a modified 12-lead ECG configuration (which included posterior leads V_8 and V_9) does not have a stronger correlation with left atrial activity when compared to the standard 12-lead ECG. Surface DAF from both modified and standard ECG configurations correlate strongly with right atrial activity, reflecting the dominance of lead V_1 in the AF principal component.

	Whole Group (n=96)	**Modified ECG** (n=51)	**Standard ECG** (n=45)	*P Value**
Age (years)	57.1 ± 10.1	56.1 ± 11.1	58.2 ± 9.1	0.30
Male Gender	76 (79%)	40 (78%)	36 (80%)	1
Persistent AF	52 (54%)	24 (47%)	28 (62%)	0.16
AF History (years)	4.3 ± 4.2	4.0 ± 3.8	4.6 ± 4.8	0.54
LA Volume (ml)	60 ± 21	59 ± 20	61 ± 22	0.75
LVEF (%)	53 ± 5	53 ± 6	53 ± 5	0.77
Hypertension	35 (36%)	14 (27%)	21 (47%)	0.06
Diabetes	8 (8%)	5 (10%)	3 (7%)	0.72

Table 2.1: Patient Characteristics.

* P value from independent t-test (continuous variables) or chi-squared test (categorical variables) comparing modified and standard ECG configurations. LA = left atrial; LVEF = left ventricular ejection fraction.

12-lead ECG Configuration	Surface DAF (Hz) PCA	Surface DAF (Hz) ABS	Surface DAF R Value	Intracardiac DAF (Hz)		R Value PCA	R Value ABS
Modified (n=51)	6.52 ± 1.07	6.51 ± 1.13	0.91	**HRA**	6.54 ± 1.19	0.92[a]	0.91[a]
				CS_{3-4}	6.04 ± 0.97	0.81[a]	0.78[a]
				CS_{5-6}	6.11 ± 0.93	0.87[a]	0.81[a]
				CS_{7-8}	6.06 ± 0.90	0.89 [a]	0.83[a]
				CS_{9-10}	6.01 ± 0.99	0.80[a]	0.76[a]
				LUPV	6.07 ± 0.87	0.43[b]	0.43[b]
				LLPV	6.10 ± 0.83	0.43[b]	0.43[b]
				LCPV	6.75 ± 0.83	0.88[a]	0.73[b]
				RUPV	5.90 ± 0.86	0.69[a]	0.62[a]
				RLPV	5.84 ± 1.00	0.72[a]	0.69[a]

Table 2.2: Surface and Intracardiac DAF Correlation: Modified 12-lead ECG configuration

[a] Correlation is significant at the 0.01 level (2-tailed); [b] Correlation is significant at the 0.05 level (2-tailed)

ABS = average beat subtraction, CS = coronary sinus; DAF = dominant AF frequency; HRA = high right atrium; LCPV = left common pulmonary vein; LLPV = left lower pulmonary vein; LUPV = left upper pulmonary vein; PCA = principal component analysis; RLPV = right lower pulmonary vein; RUPV = right upper pulmonary vein

12-lead ECG Configuration	Surface DAF (Hz) PCA	Surface DAF (Hz) ABS	Surface DAF R Value	Intracardiac DAF (Hz)		R Value PCA	R Value ABS
				HRA	6.28 ± 0.86	0.86[a]	0.82[a]
				CS_{3-4}	5.69 ± 0.57	0.69[a]	0.68[a]
				CS_{5-6}	5.66 ± 0.69	0.69[a]	0.62[a]
				CS_{7-8}	5.65 ± 0.60	0.74[a]	0.73[a]
Standard (n=45)	6.13 ± 0.86	6.24 ± 0.65	0.86	**CS_{9-10}**	5.70 ± 0.71	0.78[a]	0.78[a]
				LUPV	6.07 ± 0.80	0.79[a]	0.84[a]
				LLPV	6.06 ± 0.81	0.50[b]	0.50[b]
				RUPV	5.72 ± 0.64	0.62[a]	0.56[a]
				RLPV	5.60 ± 0.79	0.72[a]	0.71[a]

Table 2.3: Surface and Intracardiac DAF Correlation: Standard 12-lead ECG configuration

[a] Correlation is significant at the 0.01 level (2-tailed); [b] Correlation is significant at the 0.05 level (2-tailed)

Abbreviations as for Table 2.2

Intracardiac Channel	PCA				ABS			
	Modified ECG	Standard ECG			Modified ECG	Standard ECG		
	R Value		Z Value	P Value	R Value		Z Value	P Value
HRA	0.92	0.86	1.33	0.18	0.91	0.82	1.70	0.09
CS_{3-4}	0.81	0.69	1.23	0.22	0.78	0.68	0.99	0.32
CS_{5-6}	0.87	0.69	2.18	0.03	0.81	0.62	1.82	0.07
CS_{7-8}	0.89	0.74	2.19	**0.03**	0.83	0.73	1.15	0.25
CS_{9-10}	0.80	0.78	0.21	0.83	0.76	0.78	-0.31	0.76
LUPV	0.43	0.79	-2.25	0.02	0.43	0.84	-2.80	<0.01
LLPV	0.43	0.50	-0.31	0.76	0.43	0.50	-0.31	0.76
RUPV	0.69	0.62	0.46	0.65	0.62	0.56	0.35	0.73
RLPV	0.72	0.72	0.00	1.00	0.69	0.71	-0.14	0.89

Table 2.4: Correlation Coefficient Comparison: Modified vs. Standard ECG Configuration
Z and P values were calculated using the Fisher r-to-z transformation
Abbreviations as for Table 2.2

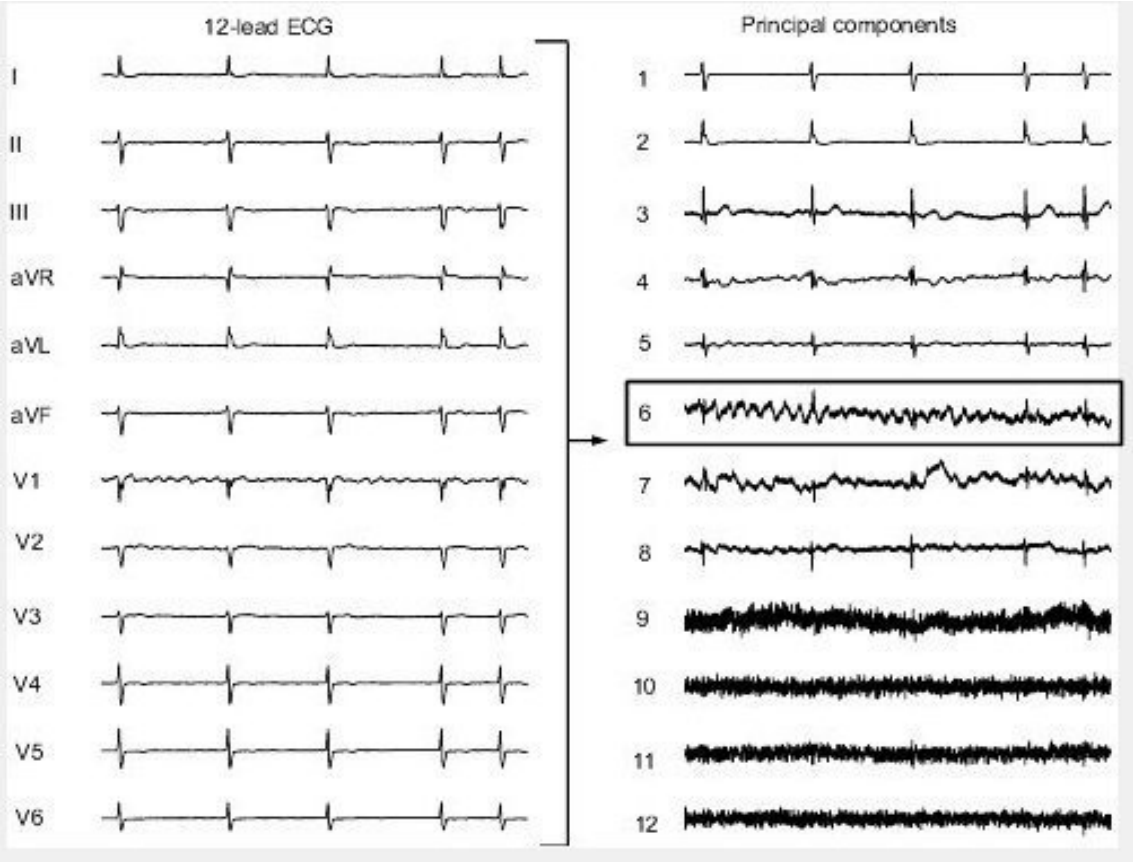


Figure 2.1: Principal Component Analysis. Left panel: 12-lead ECG showing AF. Right panel: Twelve principal components (PCs) derived from the 12-lead ECG. The ventricular components are predominantly contained in the upper PCs (1-3). The largest amplitude AF waveform is seen in PC6 (black box). The lower PCs (9-12) contain electrical noise. The amplitude scale is different for each PC with PC1 having the largest amplitude and PC12 the smallest.

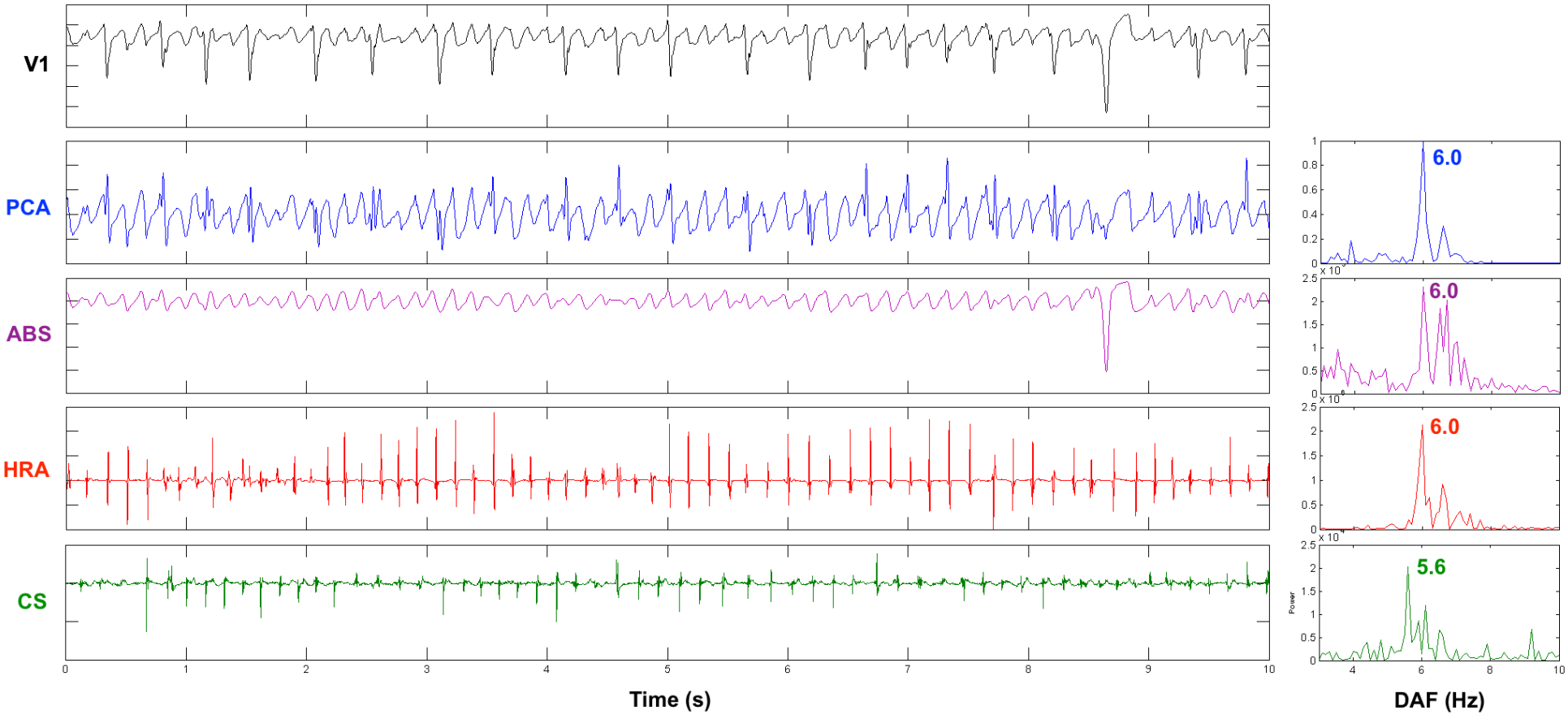
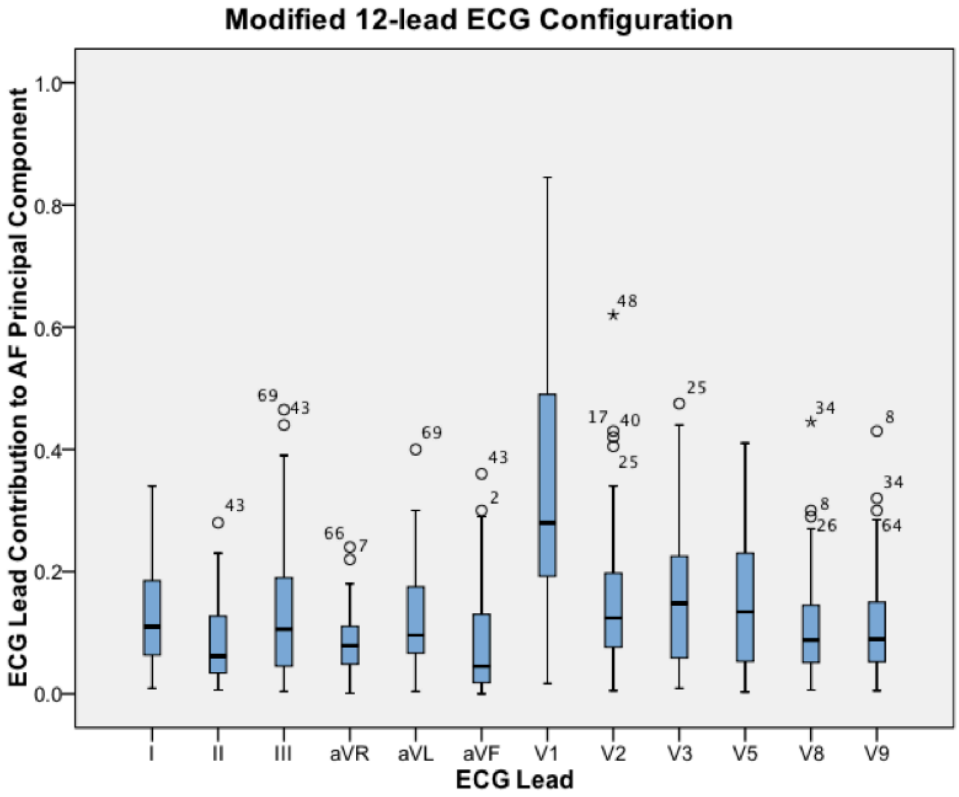


Figure 2.2: Ten-second section of ECG lead V1 with extracted AF waveform (PCA and ABS) and intracardiac recordings from HRA and CS. Corresponding frequency spectra and DAF are shown. Abbreviations as for Table 2.2



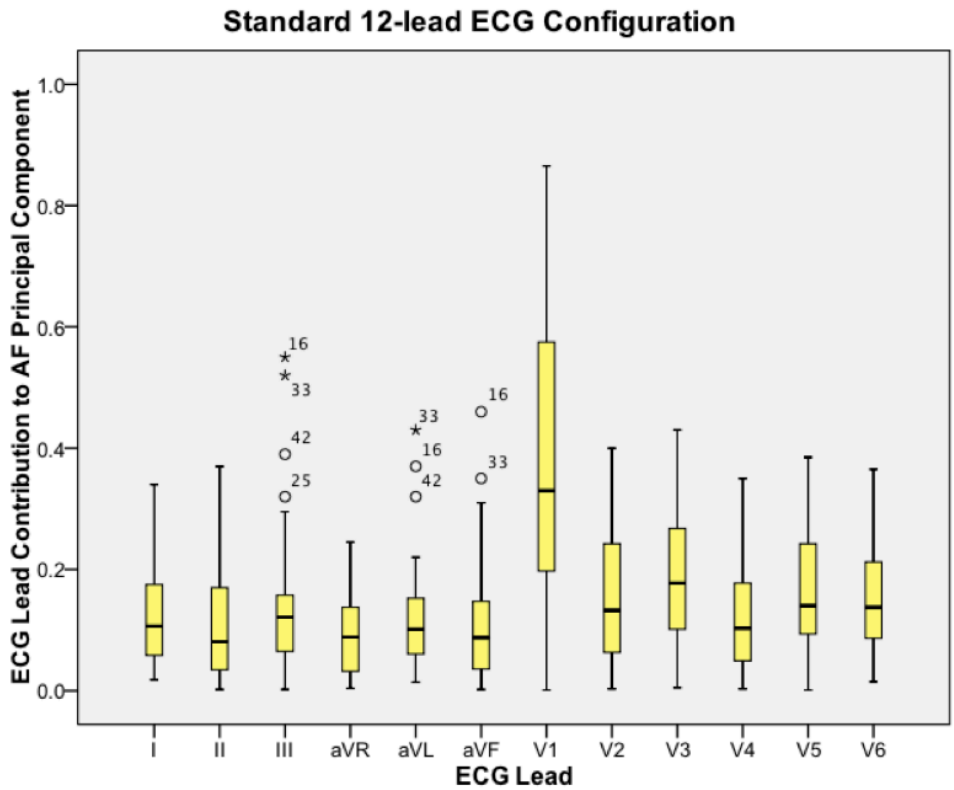


Figure 2.3: ECG Lead contribution to AF Principal Component for Modified and Standard 12-lead configurations. Minimum, first quartile, median, third quartile and maximum principal component contribution are shown for each ECG lead. Outliers and extreme outliers are represented by black circles and stars respectively and are labelled by case number.

Chapter 3. Prediction of catheter ablation outcome using surface ECG waveform and clinical parameters in patients with atrial fibrillation

3.1 Abstract

Background

Previous studies assessing the value of surface AF waveform parameters in predicting ablation outcome have produced conflicting results. The aim of this study was to evaluate whether a combination of surface AF and clinical parameters prior to ablation could predict acute and 12-month outcome afterwards.

Methods

Patients with symptomatic AF undergoing catheter ablation were recruited. Surface ECG recordings were analysed at the start and end of the procedure. The AF waveform was extracted using principal component analysis. Waveform parameters: fibrillatory wave amplitude (FWA), spatial organisation, dominant AF frequency (DAF), spectral concentration and sample entropy were studied. All patients underwent pulmonary vein isolation (PVI). Additional left atrial ablation was considered in patients who remained in AF after PVI. Surface AF and clinical parameters (gender, AF type and history, left atrial volume, LVEF, hypertension and diabetes) were correlated retrospectively with ablation outcomes.

Results

96 consecutive patients (52 persistent AF) were studied. In multivariate analysis, the acute outcome risk score had a predictive accuracy of 93% with paroxysmal AF and spectral concentration both independent predictors of AF termination during ablation ($p<0.001$). Paroxysmal AF ($p<0.01$), lead V9 FWA and male gender ($p=0.02$) were independent predictors of sinus rhythm maintenance 12-months after ablation. Inclusion of the change in lead V9 FWA after ablation ($p=0.02$) increased the predictive accuracy of the 12-month outcome risk score from 79% to 88%.

Conclusion

Multivariate risk scores comprising surface AF and clinical parameters prior to ablation can predict acute and 12-month outcomes in patients with AF.

3.2 Introduction

The threshold for recommending catheter ablation to patients with symptomatic AF has fallen progressively over the past ten years (Wazni et al., 2005; Tanner et al., 2011). Pulmonary vein isolation (PVI) is the mainstay of catheter ablation for AF and can achieve durable sinus rhythm in 59-93% of patients with paroxysmal AF (Oral et al., 2003; Van Belle et al., 2008; Fiala et al., 2008). However, success rates in patients with persistent AF remain significantly lower, despite the development of ablation strategies aimed at modifying the AF substrate more extensively (Brooks et al., 2010).

It is widely accepted that the atrial waveform seen on the surface ECG during AF reflects intracardiac electrical activity (Alcaraz et al., 2011; Petrutiu et al., 2009). Our group has developed and validated a method of extracting the AF waveform from the surface ECG using principal component analysis (PCA) (Langley et al., 2006; Raine et al., 2004 and 2005 - *Appendix 1*). The main advantage of PCA over the more commonly used QRST subtraction method is that it derives a global atrial signal from all 12 ECG leads (Figure 2.1).

To date, several studies have assessed the value of individual surface AF parameters in predicting ablation outcomes with conflicting results. In a study of patients with persistent AF, Matsuo et al. (2009) reported that mean surface AF cycle length >142ms was predictive of AF termination during ablation and longer-term maintenance of sinus rhythm. In contrast, Garibaldi et al. (2012) reported that higher spectral concentration (reflecting a more organised AF waveform) but not DAF (the inverse of mean AF cycle length) was predictive of maintenance of sinus rhythm following ablation. Nault et al. (2009) reported that higher fibrillatory wave amplitude (FWA) predicted AF termination during ablation and longer-term freedom from arrhythmia. However, Meo et al. (2013) reported that AF termination during ablation could be predicted using a logistic regression model combining FWA and AF spatiotemporal variability but not by FWA alone. In light of these discordant results, the **aim** of this study was to establish whether a combination of surface AF and clinical parameters prior to ablation could predict acute and 12-month outcome afterwards.

3.3 Methods

3.3.1 Patient Recruitment and Ethical Approval

This study was based on the same cohort of 96 patients described in Chapter 2 (sections 2.3.1 and 2.3.2).

3.3.2 Study and Ablation Protocol

A surface 12-lead ECG was recorded throughout the ablation procedure on a Labsystem Pro™ system (Bard EP) at a digital sampling rate of 1000Hz for offline analysis in Matlab®2013. At the start of the procedure, a two-minute ECG recording was analysed from patients in AF. For patients in sinus rhythm, AF induction was attempted using routine pacing manoeuvres. If AF was successfully induced, a 5-minute recording was collected to allow the arrhythmia to stabilise and AF parameters from the final two minutes were analysed. Patients were excluded from the study if AF could not be initiated or did not sustain for at least 5 minutes. Additional two-minute ECG recordings prior to AF termination or electrical cardioversion were analysed to assess the effect of ablation on surface AF waveform parameters.

Pulmonary Vein Isolation

All patients underwent PVI using one of three ablation technologies: (1) PVAC™ multielectrode circumferential ablation catheter (Medtronic Ablation Frontiers), (2) Arctic Front® Advance™ cryoballoon (Medtronic CryoCath), or (3) Wide-area circumferential ablation guided by the CARTO® 3 cardiac mapping system (Biosense Webster). Electrical isolation of the pulmonary veins was confirmed using standard pacing manoeuvres.

Left Atrial Substrate Ablation

Additional complex fractionated atrial electrogram (CFAE) and/or linear ablation was added in patients who remained in AF after PVI, according to the degree of signal complexity and fractionation in the left atrium.

CFAE Ablation

A detailed analysis of the left atrium and inter-atrial septum was performed to identify CFAEs (focal sites exhibiting constant electrical activity or multicomponent electrograms with cycle length ≤120ms averaged over a 10-second period), which were then ablated. This process was completed when no residual CFAE sites could be identified or when sinus rhythm was restored by ablation.

Linear Ablation

A combination of 'roof line' (connecting right and left upper pulmonary vein ostia), 'mitral line' (connecting left lower pulmonary vein ostium to mitral valve annulus), and 'inferior line' (connecting right lower pulmonary vein to coronary sinus) were constructed depending on the degree of signal complexity in each region. Linear ablation was performed until electrograms were no longer recordable or double potentials were evident along the length of each line. Differential pacing manoeuvres were not performed routinely to further confirm conduction block. All patients in AF at the end of the ablation procedure underwent electrical cardioversion.

3.3.3 Modified Surface 12-lead ECG Measurements

It was initially planned to record a 15-lead ECG *(including posterior leads V7-9)* since posterior leads have been shown to reflect left atrial activity better than the standard 12-lead ECG configuration (Petrutiu et al., 2009). However, because the amplifier available could only incorporate 12 ECG lead inputs, we opted for a modified surface 12-lead ECG *(where posterior leads V8 and V9 replaced leads V4 and V6)* in patients undergoing their AF ablation procedure when electroanatomical mapping was not being used. Standard 12-lead ECG placement was used in patients undergoing procedures when electroanatomical mapping was deployed, since the external reference patches for the CARTO® 3 (Biosense Webster, Inc.) and EnSite Velocity™ (St. Jude Medical, Inc.) systems preclude placement of posterior leads V_8 and V_9. The decision to use electroanatomical mapping was at the discretion of the physician and there were no significant differences in clinical characteristics between the two patient groups (Table 2.1). As reported in Chapter 2, we observed no difference in the strength of correlation between modified or standard 12-lead ECG configurations and intracardiac recordings from the left and right atrium (Raine et al., 2015).

3.3.4 Surface AF Waveform Analysis

The ECG recordings were analysed for five parameters previously used by others to characterise body surface AF signals: (1) fibrillatory wave amplitude (FWA); (2) spatial organisation; (3) dominant AF frequency (DAF); (4) spectral concentration and (5) sample entropy. FWA and spatial organisation were calculated directly from isolated TQ sections of the ECG, whereas DAF, spectral concentration and sample entropy were calculated from the continuous AF waveform extracted from the 12-lead ECG. The continuous AF waveform was extracted from the surface ECG using PCA as previously described in Section 2.4.2.

3.3.5 AF Waveform Parameters

The five AF waveform parameters included in this study are described below:

1. Fibrillatory Wave Amplitude (FWA)

FWA reflects the mass of atrial tissue activated during AF and is therefore dependent on the amount of viable atrial myocardium. Therefore, patients with more extensive atrial fibrosis would be expected to have lower FWA than those with near normal atria. In this study, AF amplitude was determined from the TQ sections of the ECG - sections containing only atrial activity and free from obscuring ventricular activity. FWA was calculated as the mean peak-to-peak amplitude of the AF waveform in TQ sections containing at least one AF cycle length from all 12 leads in both ECG configurations (Figure 3.1).

2. Spatial Organisation

Spatial organisation quantifies the degree of similarity in AF waveforms measured at different body surface sites (Di Marco et al., 2012; Bonizzi et al., 2010). As previously reported, PCA was applied to TQ sections of the 12-lead ECG recordings and the percentage of AF waveform variability explained by the first three principal components calculated (Di Marco et al., 2012). Recordings with highly correlated AF waveforms across the 12 ECG leads, and hence high spatial organisation, would have a high percentage of variability explained by these three principal components.

3. Dominant AF Frequency (DAF)

Fourier analysis was applied to the continuous AF waveform extracted from the ECG to calculate the power spectral density by periodogram with rectangular window and frequency resolution of 0.1Hz. The DAF was defined as the AF frequency with the highest power in the range 3-10Hz as in our previous studies (Raine et al., 2004 and 2005).

4. Spectral Concentration

Spectral concentration measures the concentration of power around the DAF relative to the whole recorded spectrum. In this study, spectral concentration was calculated from the power spectral density as the ratio of power contained in the interval DAF ± 0.5Hz to the power contained in the interval 3 to 10Hz (Di Marco et al., 2012). A single stable AF source would give rise to an AF spectrum with a single narrow peak, indicating that the majority of spectral energy was concentrated around the DAF (i.e. high spectral concentration).

Conversely, multiple and/or temporally unstable AF sources have AF spectra with multiple peaks or diffuse energy around the dominant peak (i.e. low spectral concentration).

5. Sample Entropy

Sample entropy is a marker of the complexity and irregularity of atrial activity with higher values indicating more disorganised activity (Alcaraz and Rieta, 2009). It is defined as the negative natural logarithm of the conditional probability that two sequences of data values, that are similar for *m* points, will remain similar at the next point in the data sequence, within a tolerance *r*. Thus sample entropy (*r*,*m*) = -ln (A/B), where A and B are the total number of forward matches of length *m*+1 and *m*, respectively. Our approach follows that of Alcaraz and Rieta (2009) who applied sample entropy to the mean atrial waveform, derived by narrow band filtering the continuous AF waveform around the DAF (DAF ± 1.5Hz). Values of m=2 and r=0.25 times the standard deviation of the atrial waveform were used as they have previously produced accurate and reproducible sample entropy results (Alcaraz and Rieta, 2009). Each of the AF waveform parameters were analysed in consecutive 10-second sections and mean values across the 2-minute ECG recordings are reported.

3.3.6 Clinical Parameters

Ablation outcome was correlated with the following clinical parameters: gender, AF type (paroxysmal / persistent), total duration of AF history, left atrial volume, left ventricular ejection fraction (calculated using Simpson's biplane method from apical two and four-chamber views on transthoracic echocardiography performed at the initial outpatient consultation prior to ablation), comorbidities of hypertension and diabetes.

3.3.7 Clinical Outcome following Ablation

Acute Outcome

Acute outcome was assessed by cardiac rhythm at the end of the ablation procedure (prior to electrical cardioversion if performed): (1) Sinus rhythm; (2) AF.

Twelve-month Outcome

Clinical outcome was determined by symptom review, 12-lead ECG and 72-hour Holter monitoring at the twelve month assessment after ablation and was divided into two categories: (1) Sinus rhythm (no arrhythmia symptoms and no documented AF episodes >30 seconds); (2) AF recurrence (documented AF episodes >30 seconds).

3.3.8 Statistical Analyses

Continuous variables are expressed as mean ± SD. Baseline surface AF parameters and clinical variables were compared between acute and 12-month outcome groups using Student's independent t-test for continuous variables and Pearson's chi-squared test for categorical variables. The magnitude of change in surface AF parameters after ablation in those who remained in AF was compared between acute and 12-month outcome groups using independent t-tests. Acute and 12-month outcome were compared between different ablation strategies using Fisher's exact test. All tests were 2-tailed and $p<0.05$ was considered statistically significant.

Parameters with $p\leq0.10$ were entered into a binary logistic regression model using stepwise selection to assess their independent and combined ability to predict acute and 12-month outcome following ablation. After multivariate analysis, parameters with $p\leq0.10$ were retained and risk scores calculated by multiplying the maximum likelihood estimates with the values for each parameter included in the model. Binary values were used for categorical variables. ROC curve analysis was used to evaluate the performance of independent outcome predictors and multivariate risk scores and to select cut-off points with highest sensitivity and specificity.

3.4 Results

Baseline characteristics of the 96 consecutive patients recruited to the study are shown in Table 2.1. There were no significant differences in clinical characteristics between the modified and standard ECG groups. In addition, there were no significant differences in acute procedural outcome between patients treated with PVI alone or additional lesions after pulmonary vein isolation ('PVI-plus') (Table 3.1). In patients with paroxysmal AF, 28/36 (78%) treated with PVI alone maintained sinus rhythm 12-months after ablation compared to 2/8 (25%) treated with more extensive lesion sets. In contrast, there was no significant difference in 12-month outcome in patients with persistent AF treated with PVI alone or PVI-plus (Table 3.1).

3.4.1 Surface AF Waveform & Clinical Parameters and Acute Outcome

Sinus rhythm was restored during ablation in 17/44 (39%) patients with paroxysmal AF but in only one patient with persistent AF ($p<0.001$) (Table 3.2). Left ventricular ejection fraction was significantly higher in those who reverted to sinus rhythm during ablation compared to those who remained in AF (54 ± 2 vs. $53 \pm 6\%$; $p=0.02$).

Spatial organisation (96.6 ± 1.5% vs. 94.3 ± 3.1%; p<0.001), spectral concentration (41.0 ± 7.6% vs. 36.2 ± 8.2%, p=0.03) and FWA in lead II (0.123 ± 0.035mV vs. 0.100 ± 0.036mV; p=0.02) were significantly higher in patients who reverted to sinus rhythm during ablation (Table 3.3). Furthermore, patients who reverted to sinus rhythm during ablation had a significantly greater increase in FWA in lead II compared to those who remained in AF (0.012 ± 0.029mV vs. -0.005 ± 0.021mV; p=0.03) (Table 3.3). Conversely, baseline DAF was significantly lower in patients who reverted to sinus rhythm (5.5 ± 0.6Hz vs. 6.5 ± 1.0Hz, p<0.001).

In multivariate analysis (Table 3.4), paroxysmal AF (OR 0.01, 95% CI <0.01-0.12; p<0.001) and spectral concentration (OR 1.17, 95% CI 1.05-1.31; p<0.001) were independent predictors of AF termination during ablation. The area under the receiver operating characteristic (ROC) curve for the multivariate risk score to predict acute procedural outcome was 0.93 (95% CI 0.87-0.99; p<0.001) (Figure 3.2). There were no significant differences in the other surface AF and clinical parameters studied including the degree of change after ablation between patients who reverted to sinus rhythm and those who remained in AF (Tables 3.2 and 3.3).

3.4.2 Surface AF Waveform & Clinical Parameters and Twelve Month Outcome

Twelve months after ablation, 56 (58%) patients maintained sinus rhythm without further intervention (68% paroxysmal and 50% persistent AF; p=0.10). Men were more likely to maintain sinus rhythm than women (64% vs. 35%; p=0.02). In the modified ECG group, patients maintaining sinus rhythm had significantly greater FWA in posterior lead V9 before ablation (0.052 ± 0.025mV vs. 0.041 ± 0.015mV; p=0.05) and showed a greater reduction in that measure after ablation (-0.004 ± 0.009mV vs. 0.003 ± 0.008mV; p<0.01) compared to those with recurrent AF (Table 3.3).

In multivariate analysis of baseline surface AF and clinical parameters (Table 3.4), paroxysmal AF (OR 0.12, 95% CI 0.03-0.55; p<0.01), FWA in lead V9 (OR >999; p=0.02) and male gender (OR 0.10, 95% CI 0.01-0.75; p=0.02) were independent predictors of maintenance of sinus rhythm after ablation. Furthermore, inclusion of the change in FWA in lead V9 after ablation (OR <0.001; p=0.02) increased the predictive accuracy of the multivariate risk score from 79% to 88% (Table 3.4). ROC curve analyses for the multivariate risk scores to predict outcome 12-months after ablation are shown in Figure 3.3.

3.5 Discussion

3.5.1 Main Findings

To our knowledge, the present study is the most comprehensive evaluation to date of the association between surface AF waveform and clinical parameters prior to ablation and arrhythmia outcomes afterwards in a cohort of patients with either paroxysmal or persistent AF. The main finding is that multivariate risk scores comprising surface AF and clinical parameters prior to ablation can accurately predict acute and 12-month outcome afterwards in this diverse patient group. Paroxysmal AF and spectral concentration were independent predictors of AF termination during the ablation procedure. Paroxysmal AF, FWA in lead V9 and its change after ablation, and male gender were independent predictors of maintenance of sinus rhythm 12 months after ablation.

3.5.2 Ablation Outcome

Ablation Strategy

In this study, 58% of patients maintained sinus rhythm 12 months after a single ablation procedure (68% paroxysmal vs. 50% persistent AF), which is comparable to the results of others (Ganesan et al., 2013). 78% of patients with paroxysmal AF treated with PVI alone maintained sinus rhythm 12 months after ablation compared to 25% of patients treated with PVI and additional left atrial substrate ablation. This supports the strategy, previously advocated by others (Mun et al., 2012; Wu et al., 2013), of performing PVI alone as a first procedure in patients with paroxysmal AF – even if sinus rhythm is not restored during ablation. This contrasts with the lack of difference in 12-month outcome in patients with persistent AF treated with PVI alone or PVI-plus, which concurs with the results of the STAR AF II trial (Verma et al., 2015).

Surface AF Waveform parameters

Spectral concentration was an independent predictor of acute outcome with higher values correlating with AF termination during ablation, as shown by others (Garibaldi et al., 2012). However, Garibaldi et al. also reported an association between spectral concentration and medium term outcome following ablation, not corroborated by our study. Fibrillatory wave amplitude in posterior ECG lead V9 was an independent predictor of 12-month outcome in this study with higher values associated with maintenance of sinus rhythm long-term. This is a novel finding and highlights the benefit of including posterior ECG leads in surface AF waveform analysis on account of their stronger correlation with left atrial activity (Petrutiu et al., 2009).

The association between higher FWA values and freedom from arrhythmia recurrence after ablation has been reported previously by Nault et al. (2009); although, we could not confirm the correlation between FWA in lead V1 and ablation outcome they reported. This may be due to the fact that they calculated FWA manually from a single ECG lead whereas we used a computer assisted algorithm to calculate FWA. In addition, 26% of their patients were taking amiodarone with its associated effects on cardiac electrophysiology. Reduction in lead V9 FWA after ablation was also identified as an independent predictor of maintenance of sinus rhythm at 12 months. This correlation between FWA reduction after ablation and arrhythmia freedom has been previously reported by Meo et al. (2012) and likely reflects successful ablation of atrial myocardium critical to the maintenance of AF.

In this study, baseline DAF was associated with acute but not 12-month outcome with significantly lower values in patients who reverted to sinus rhythm during ablation, as reported by Heist et al. (2012). There was no significant difference in the magnitude of DAF reduction after ablation between patients who maintained sinus rhythm and those with recurrent AF, in contrast to Yoshida et al. (2010) who reported that an 11% reduction in lead V1 DAF predicted maintenance of sinus rhythm after ablation. The discordance in results is likely secondary to the differing study populations, ablation strategy and method of DAF calculation from the surface ECG. Finally, sample entropy was not predictive of acute or 12-month outcome after ablation, corroborating the findings of Garibaldi et al. (2012).

Clinical parameters

In multivariate analysis, paroxysmal AF was an independent predictor of both acute and 12-month outcome following ablation, as shown by other studies (Wokhlu et al., 2010a; Balk et al., 2010; D'Ascenzo et al., 2013). 15/18 (83%) patients with AF termination during ablation maintained sinus rhythm at 12 months, corroborating the findings of Komatsu et al. (2012) that termination of AF during ablation is a predictor of favourable longer-term outcome. In this study, male gender was an independent predictor of sinus rhythm maintenance 12 months after ablation, as shown by Heist et al. (2012). However, there was no significant correlation between left atrial volume and ablation outcome at either time-point, in contrast to D'Ascenzo et al. (2013) and Ejima et al. (2014). This disparity may be due to progressive atrial dilatation occurring in the variable interval between echocardiographic measurement and the ablation procedure itself, particularly in patients with persistent AF.

Finally, there were no significant differences between acute and 12-month outcome groups with respect to duration of AF history, left ventricular ejection fraction and prevalence of treated hypertension and diabetes, as reported by Ejima et al. (2014).

3.6 Limitations

Firstly, our analysis is limited by its relatively small sample size and the offline retrospective nature of the AF waveform analyses. In addition, lead V9 FWA could only be calculated in the modified ECG group and therefore, the positive association between lead V9 FWA and twelve month ablation outcome was based on a smaller number of patients (n=51) rather than the whole cohort (n=96). The predictive accuracy of these findings now needs to be tested prospectively in a separate group of patients. Secondly, although reflective of current clinical practice, the conduct of the AF ablation procedure was not standardised. The optimum ablation strategy and extent of ablation required in patients with persistent AF has yet to be defined. Thirdly, AF recurrence was determined by patients' symptoms, 12-lead ECG and 72-hour Holter monitoring 12 months after ablation and not by continuous ECG monitoring throughout the follow-up period. Although, we cannot completely exclude asymptomatic AF episodes in the 'sinus rhythm' group, we consider this unlikely given the previously high AF symptom burden in those studied.

3.7 Conclusions

Frequency and organisation parameters of AF waveform can readily be measured from the surface ECG and allow objective characterisation of AF. Using routinely available surface AF waveform and clinical parameters, these results show that acute and longer-term outcomes following ablation can be predicted by multivariate individualised patient profiling. Predictive accuracy of ablation outcome was improved by including AF waveform parameters in comparison to when only clinical parameters were studied. If employed routinely, AF-waveform analysis would allow those most likely to benefit from ablation to be identified beforehand and so improve patient selection.

	Acute Outcome			12-month Outcome		
	SR	**AF**	*P Value**	**SR**	**AF**	*P Value**
Paroxysmal AF (n=44)	**17**	**27**		**30**	**14**	
PVI	17	19		28	8	
PVI + Linear Ablation	0	4	0.11	1	3	**0.01**
PVI + CFAE Ablation	0	2		1	1	
PVI + Linear + CFAE Ablation	0	2		0	2	
Persistent AF (n=52)	**1**	**51**		**26**	**26**	
PVI	1	10		5	6	
PVI + Linear Ablation	0	18	0.40	7	11	0.48
PVI + CFAE Ablation	0	13		7	6	
PVI + Linear + CFAE Ablation	0	10		7	3	

Table 3.1: Additional Ablation Strategies and Clinical Outcome

* P value from Fisher's exact test comparing acute and 12-month outcome between the four ablation strategies

	Acute Outcome			12-month Outcome		
	SR	**AF**	*P Value*	**SR**	**AF**	*P Value*
Number of Patients	18	78		56	40	
Age (years)	56.6 ± 13.2	57.2 ± 9.5	0.83	56.7 ± 11.0	57.6 ± 9.0	0.67
Male Gender	14 (78%)	62 (80%)	1	49 (88%)	27 (68%)	**0.02**
Persistent AF	1 (6%)	51 (65%)	**<0.001**	26 (46%)	26 (65%)	0.10
AF History (years)	3.9 ± 2.6	4.4 ± 4.6	0.61	4.2 ± 4.3	4.4 ± 4.3	0.85
LA Volume (ml)	55 ± 22	61 ± 21	0.30	59 ± 19	61 ± 24	0.81
LVEF (%)	54 ± 2	53 ± 6	**0.02**	54 ± 4	52 ± 7	0.07
Hypertension	7 (39%)	28 (36%)	1	20 (36%)	15 (38%)	1
Diabetes	2 (11%)	6 (8%)	0.64	4 (7%)	4 (10%)	0.72

Table 3.2: Univariate Analysis: Clinical Variables and Ablation Outcome

	Acute Outcome			12-month Outcome		
	SR	**AF**	*P Value*	**SR**	**AF**	*P Value*
Number of Patients	18 (n=12)	78 (n=39)		56 (n=31)	40 (n=20)	
Baseline						
Dominant AF Frequency (Hz)	5.5 ± 0.6	6.5 ± 1.0	**<0.001**	6.3 ± 1.2	6.4 ± 0.8	0.94
Spectral Concentration (%)	41.0 ± 7.6	36.2 ± 8.2	**0.03**	37.3 ± 7.8	36.8 ± 9.0	0.80
Spatial Organisation (%)	96.6 ± 1.5	94.3 ± 3.1	**<0.001**	95.2 ± 2.7	94.0 ± 3.3	0.07
Sample Entropy	0.082 ± 0.018	0.087 ± 0.015	0.19	0.088 ± 0.017	0.085 ± 0.014	0.39
Mean 12-lead ECG FWA (mV)	0.101 ± 0.027	0.087 ± 0.029	0.07	0.089 ± 0.028	0.090 ± 0.031	0.91
Lead II FWA (mV)	0.123 ± 0.035	0.100 ± 0.036	**0.02**	0.105 ± 0.035	0.103 ± 0.039	0.75
Lead V1 FWA (mV)	0.142 ± 0.058	0.123 ± 0.056	0.22	0.125 ± 0.051	0.129 ± 0.065	0.80
Lead V9 FWA (mV) (n=51)	0.050 ± 0.018	0.047 ± 0.023	0.60	0.052 ± 0.025	0.041 ± 0.015	**0.05**
Change after Ablation						
Dominant AF Frequency (Hz)	-0.3 ± 0.4	-0.3 ± 0.4	0.92	-0.3 ± 0.4	-0.3 ± 0.4	0.39
Spectral Concentration (%)	2.5 ± 8.2	0.2 ± 6.4	0.29	0.3 ± 6.9	0.6 ± 6.4	0.84
Spatial Organisation (%)	-0.3 ± 1.3	0.1 ± 1.6	0.44	-0.1 ± 1.6	0.2 ± 1.4	0.44
Sample Entropy	-0.001 ± 0.013	0.001 ± 0.011	0.83	-0.001 ± 0.013	0.001 ± 0.009	0.50
Mean 12-lead ECG FWA (mV)	0.001 ± 0.008	-0.004 ± 0.023	0.56	-0.002 ± 0.021	-0.007 ± 0.023	0.35
Lead II FWA (mV)	0.012 ± 0.029	-0.005 ± 0.021	**0.03**	-0.004 ± 0.019	-0.003 ± 0.027	0.82
Lead V1 FWA (mV)	0.005 ± 0.022	-0.001 ± 0.059	0.74	0.004 ± 0.059	-0.006 ± 0.052	0.43
Lead V9 FWA (mV) (n=51)	0.001 ± 0.005	-0.001 ± 0.010	0.71	-0.004 ± 0.009	0.003 ± 0.008	**<0.01**

Table 3.3: Univariate Analysis: Surface AF Parameters and Ablation Outcome. Lead V9 FWA could only be calculated in the Modified ECG group. The number and distribution of patients in this group is highlighted in red.

	Parameter	Maximum Likelihood Estimate	Standard Error	Wald Chi-square	P Value	Odds Ratio Estimate	95% CI for Odds Ratio	Cumulative Predictive Accuracy*
Acute Outcome	Paroxysmal AF	-4.82	1.36	12.49	<0.001	0.01	<0.01 - 0.12	80%
	Spectral Concentration	0.16	0.06	7.87	<0.001	1.17	1.05 - 1.31	92%
	Lead II FWA	17.52	10.25	2.92	0.09	>999.99	0.08 - >999.99	93%
12-month Outcome (Baseline Parameters only)	Paroxysmal AF	-2.09	0.76	7.55	<0.01	0.12	0.03 - 0.55	67%
	Lead V9 FWA	46.75	20.19	5.36	0.02	>999.99	>999.99	74%
	Male Gender	-2.28	1.01	5.05	0.02	0.10	0.01 - 0.75	79%
12-month Outcome (Baseline Parameters and Change after Ablation)	Change in Lead V9 FWA	-270.1	111.7	5.84	0.02	<0.001	<0.001	75%
	Paroxysmal AF	-1.97	0.90	4.84	0.03	0.14	0.02 - 0.81	82%
	Lead V9 FWA	51.64	26.77	3.72	0.05	>999.99	0.44->999.99	88%

Table 3.4: Multivariate Risk Scores to predict Ablation Outcome

* Cumulative Predictive Accuracy = percentage of the study cohort in whom ablation outcome was correctly predicted.

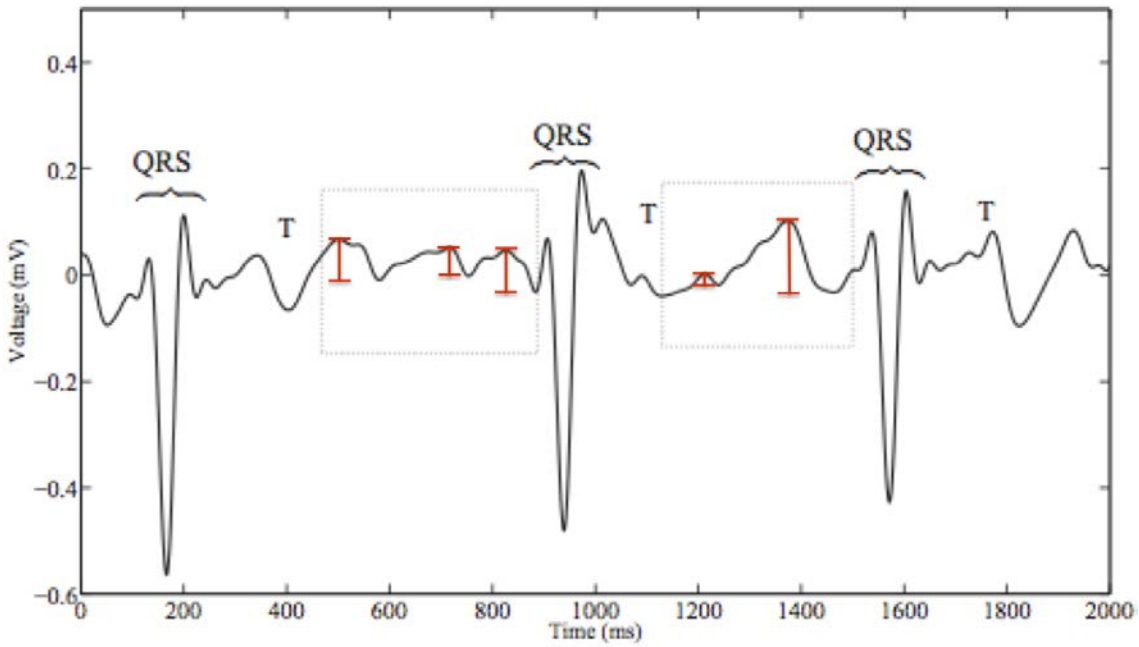


Figure 3.1: Fibrillatory Wave Amplitude (FWA) Calculation. Two-second section of ECG lead V1 showing AF. TQ interval highlighted by the dotted grey box. Peak to peak amplitude measurement of consecutive fibrillatory waves is illustrated by red lines. Mean FWA was calculated for consecutive 10-second sections and averaged over the 2-minute recording for each ECG lead. ms = milliseconds; mV = millivolts.

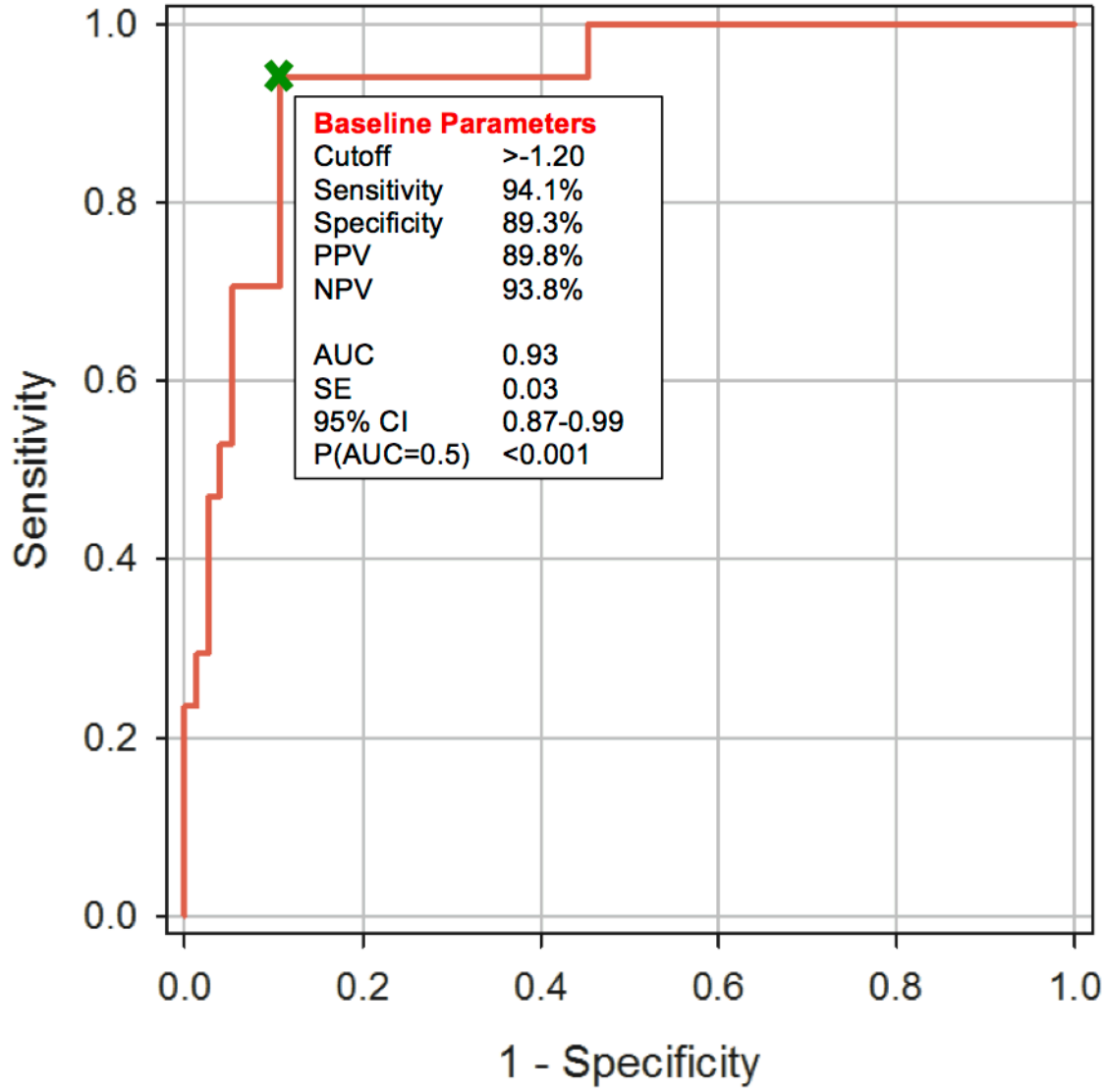


Figure 3.2: ROC Curve – Acute Outcome Risk Score. Green cross indicates optimal cutoff point for sensitivity and specificity. AUC = area under curve; CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value; SE = standard error.

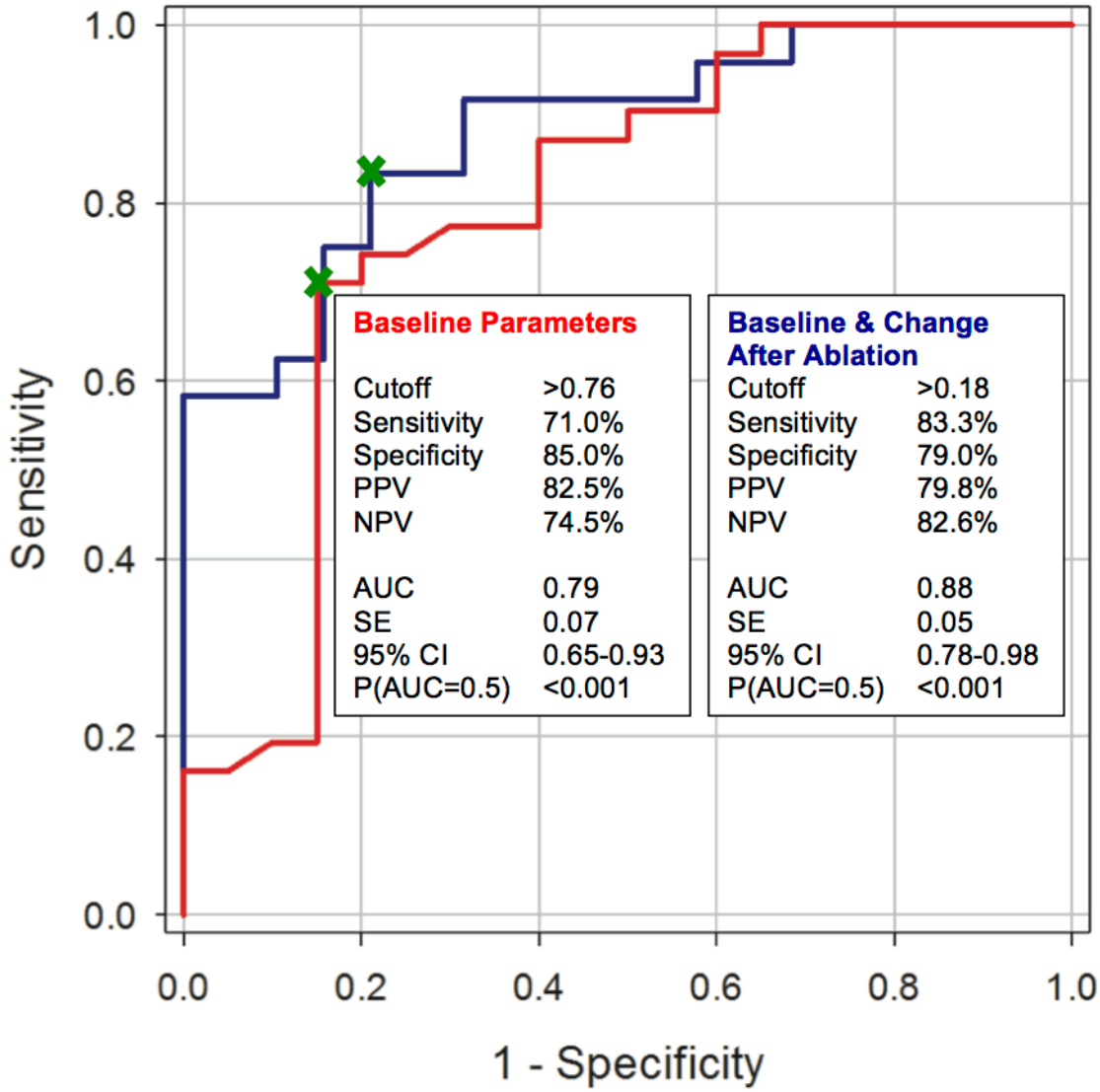


Figure 3.3: ROC Curve – 12-month Outcome Risk Scores. Red line indicates multivariate risk score from baseline surface AF and clinical parameter analysis. Blue line indicates multivariate risk score from baseline surface AF and clinical parameters in combination with the change in surface AF parameters after ablation. Green cross indicates optimal cutoff point for sensitivity and specificity. Abbreviations as for Figure 3.2

Chapter 4. Effect of catheter ablation on quality of life in patients with atrial fibrillation and its correlation with arrhythmia outcome

4.1 Abstract

Objective

To assess the effect of catheter ablation on AF symptoms and quality of life (QoL).

Methods

Patients with AF scheduled for ablation were recruited. Pulmonary vein isolation (PVI) was performed and CFAE ± linear ablation undertaken in patients in AF despite PVI. QoL and AF symptoms were assessed using SF-36 V2 and AFEQT questionnaires before and 3-months after ablation. Change in QoL scores after ablation was correlated with clinical parameters and the extent of ablation. Magnitude of QoL change was compared between AFEQT and SF-36 physical (PCS) and mental (MCS) component scores and correlated with arrhythmia outcome.

Results

80 patients were studied. Summative and individual health scores for both AFEQT (51.5 ± 22.0 vs. 81.3 ± 18.2; $p<0.01$) and SF-36 (PCS 43.3 ± 10.5 vs. 47.9 ± 11.3; $p<0.01$ and MCS 45.0 ± 11.5 vs. 51.5 ± 9.4; $p<0.01$) improved significantly in patients who maintained sinus rhythm after ablation, but not in those with recurrent AF. Improvement in AFEQT (25.4 ± 19) was significantly greater than change in PCS (6.8 ± 6.4; $p<0.01$) and MCS (8.5 ± 7.9; $p<0.01$) scores and correlated more closely with arrhythmia outcome (AFEQT r=0.55; PCS r=0.26; MCS r=0.30).

Conclusions

Patients who maintained sinus rhythm after ablation had a significant improvement in AF symptoms and QoL; however, no improvement was observed in patients with recurrent AF. QoL change after ablation did not correlate with baseline clinical parameters or ablation strategy. AF specific QoL scales are more responsive to change and correlate better with ablation outcome.

4.2 Introduction

Atrial fibrillation is the most common arrhythmia in clinical practice affecting up to 2% of the general population and is associated with significant morbidity and mortality (Camm et al., 2010). Although some patients with AF are asymptomatic, the majority seek treatment to improve symptoms and quality of life (QoL), which is reduced compared to the general population (Dorian et al., 2000; Hagens et al., 2004; Purerfellner et al., 2004). Treatment strategies including antiarrhythmic drugs (Dorian et al., 2002), ventricular rate control (Levy et al., 2001) and catheter ablation (Reynolds et al., 2010) improve QoL particularly if sinus rhythm can be restored and maintained (Singh et al., 2006). However, several studies have reported an improvement in QoL after ablation irrespective of procedural outcome (Wokhlu et al., 2010b; Fichtner et al., 2012; Mantovan et al., 2013). The most widely validated generic QoL scale is the Medical Outcomes Study Short Form Health Survey (SF-36), which has been successfully used to study a range of cardiovascular conditions including AF (Gronefeld et al., 2003). The greatest weakness of generic QoL measures is that, by design, they reflect general health and functioning, and therefore, results are strongly influenced by patient demographics and comorbidity. Therefore, Spertus et al. (2011) developed the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) questionnaire as a disease-specific measure to evaluate QoL in AF patients. The **aim** of this study was to assess the effect of catheter ablation on AF symptoms and QoL in patients with paroxysmal or persistent AF using the AFEQT and SF-36 Version 2 questionnaires.

4.3 Methods

4.3.1 Patient Recruitment

Study participants were recruited from patients scheduled to undergo their first catheter ablation procedure for symptomatic AF. In line with usual practice, class I and III antiarrhythmic drugs were discontinued five half-lives prior to ablation.

4.3.2 Ethical Approval

This study complies with the Declaration of Helsinki and was granted a favourable ethical opinion by the National Research Ethics North West Committee (REC reference: 11/NW/0476). Written informed consent was obtained from all patients recruited to the study.

4.3.3 Quality of Life and AF Symptom Assessment

QoL and AF symptoms were assessed at baseline and three months after ablation using SF-36 V2 and AFEQT questionnaires (*Appendix 2*). Questionnaires were completed without input from study personnel. SF-36 V2 consists of 36 items that assess eight health domains: physical functioning (PF), role limitations because of physical problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations because of emotional problems (RE) and mental health (MH). In addition to these eight subscales, physical (PCS) and mental component summary (MCS) scores are also generated, which are normalised to an overall population mean of 50 ± 10 (Gronefeld et al., 2003). For all subscales, higher scores represent better functioning and QoL. AFEQT is a 20-item questionnaire that assesses four health domains: symptoms (n=4), daily activities (n=8), treatment concern (n=6) and satisfaction (n=2) (Spertus et al., 2011). It combines symptoms, functional status and QoL in a single measure and its results have been shown to be reproducible and responsive to change (Spertus et al., 2011). Patients' responses are scored using a seven-point Likert scoring system and a linear relationship is observed between global AFEQT scores and AF severity, with the most severely affected patients having the lowest scores.

4.3.4 Ablation Protocol

The ablation protocol (PVI ± linear ± CFAE ablation) is described in Chapter 3 (Section 3.3.2).

4.3.5 Clinical Outcome

Clinical outcome was determined by symptom review, 12-lead ECG and 72-hour Holter monitoring three months after ablation and was divided into two categories: (1) Sinus rhythm (no arrhythmia symptoms and no documented AF episodes >30 seconds); (2) AF recurrence (documented AF episodes >30 seconds).

4.3.6 Statistical Analyses

Continuous variables are expressed as mean ± SD. Patient characteristics were compared between paroxysmal and persistent AF groups using Student's independent *t*-test for continuous variables and Pearson's chi-squared test for categorical variables. Baseline QoL scores (AFEQT, PCS and MCS) were compared and correlated with clinical parameters using Pearson's correlation. Individual and summative health domains of the AFEQT and SF-36 V2 questionnaires were compared at baseline and three months after ablation using Student's paired t-tests.

Change in QoL scores after ablation were correlated with clinical parameters using Pearson's correlation (continuous variables) and independent *t*-test (categorical variables) and were compared between different ablation strategies using one-way ANOVA. Parameters with $p<0.05$ were entered into a multivariate linear regression model using stepwise selection to assess their independent and combined ability to predict change in QoL after ablation. After multivariate analysis, parameters with $p<0.10$ were retained. Standardised coefficients (beta) and corresponding p values are reported. The magnitude of QoL change after ablation was compared between AFEQT, PCS and MCS scores using one-way ANOVA and correlation coefficients for the three QoL scores and ablation outcome were compared using Fisher r-to-z transformation. All tests were 2-tailed and $p<0.05$ was considered statistically significant.

4.4 Results

The clinical characteristics of the 80 consecutive patients recruited to the study are shown in Table 4.1. The mean age was 57 ± 10 years and 73% were male. The mean duration of AF history was 4 ± 3 years. Patients with persistent AF (n=36) had a significantly shorter AF history, larger left atrial volume and lower left ventricular ejection fraction than those with paroxysmal AF (n=44). 54/80 (68%) patients (77% paroxysmal; 56% persistent AF) maintained sinus rhythm three months after ablation.

4.4.1 Effect of Ablation on Quality of Life

There was a significant increase in the summative and individual health domain scores for both AFEQT (51.5 ± 22.0 vs. 81.3 ± 18.2; $p<0.01$) and SF-36 V2 (PCS 43.3 ± 10.5 vs. 47.9 ± 11.3; $p<0.01$ and MCS 45.0 ± 11.5 vs. 51.5 ± 9.4; $p<0.01$) questionnaires in patients who maintained sinus rhythm three months after ablation (Figure 4.1A & 4.2A). However, there was no significant change in either summative or individual scores from either questionnaire in patients with recurrent AF (Figure 4.1B & 4.2B). The magnitude of change in AFEQT score (25.4 ± 19) after ablation was significantly greater than the change in PCS (6.8 ± 6.4; $p<0.01$) or MCS (8.5 ± 7.9; $p<0.01$) scores and there was no significant difference observed between PCS and MCS scores ($p=0.14$). Change in AFEQT score after ablation correlated more closely with three-month outcome ($r=0.55$) than PCS ($r=0.26$; $p=0.03$) or MCS ($r=0.30$; $p=0.05$) scores.

In univariate analysis, there was no significant correlation between clinical parameters and change in QoL scores after ablation (Table 4.2).

Of note, there was no difference in the magnitude of change in QoL after ablation between paroxysmal and persistent AF groups (AFEQT 24.3 ± 24.3 vs. 16.3 ± 23.4, p=0.14; PCS 3.0 ± 9.2 vs. 3.1 ± 8.7, p=0.98; MCS 5.8 ± 11.2 vs. 2.6 ± 10.1, p=0.19). However, higher QoL scores at baseline and AF recurrence correlated with smaller changes in QoL scores after ablation for both questionnaires. In multivariate analysis, higher AFEQT, PCS and MCS scores pre ablation and AF recurrence were independent predictors of a smaller change in their respective QoL scores after ablation (Table 4.3).

4.4.2 Change in Quality of Life according to Ablation Strategy

AFEQT scores increased significantly after PVI, PVI + Linear and PVI + Linear + CFAE ablation indicating an improvement in QoL (Table 4.4). AFEQT scores also increased after PVI + CFAE ablation although this did not meet statistical significance (p=0.12). There was a significant increase in PCS and MCS scores after PVI and an increase in MCS score after PVI + Linear ablation. However, there was no significant change in PCS and MCS scores after the other ablation strategies. In addition, there was no significant difference in the magnitude of change in QoL scores between the four ablation strategies (AFEQT p=0.67; PCS p= 0.49; MCS p= 0.29).

4.4.3 Relationship between Clinical Variables and Quality of Life

Baseline AFEQT scores correlated closely with PCS scores (r=0.64, p<0.01) and moderately with MCS scores (r=0.43, p<0.01). However, there was no correlation between PCS and MCS scores (r=0.16, p=0.15). Hypertension was associated with a lower baseline AFEQT score and a trend towards a lower MCS score (Table 4.5). Older age and persistent AF were associated with a lower PCS score. Diabetes was associated with a lower MCS score and a trend towards a lower PCS score. Larger left atrial volume was associated with a higher MCS score, which is unlikely to be clinically meaningful.

4.5 Discussion

4.5.1 Effect of Ablation on Quality of Life

The main finding of this prospective study is the significant improvement in AF symptoms and QoL in patients who maintained sinus rhythm three months after ablation and the contrasting lack of improvement in patients with recurrent AF. This finding was consistent across all individual and summative components of the AFEQT and SF-36 V2 questionnaires. The mean increase in AFEQT score of 30 points in patients who maintained sinus rhythm is consistent with a marked improvement in QoL (Dorian et al., 2013).

The expected lack of QoL improvement in patients with recurrent AF after ablation is clinically coherent and supported by Fiala et al. (2014) and Mohanty et al. (2014). However, other groups have reported significant QoL improvements regardless of arrhythmia outcome. In respective studies of 323 and 100 patients who underwent ablation for symptomatic AF, Wokhlu et al. (2010b) and Mantovan et al. (2013) observed an improvement in QoL in all patients irrespective of ablation outcome. Patients who maintained sinus rhythm following ablation had a greater improvement in generic QoL scores compared to those with recurrent AF; however, this did not reach statistical significance. Wokhlu et al. (2010b) also assessed the impact of ablation on AF symptoms using the Mayo AF Symptom Inventory (Wokhlu et al., 2008) and observed a significant reduction in symptoms following ablation in patients who maintained sinus rhythm compared to those with recurrent AF. Fichtner et al. (2012) reported similar findings in their study of 133 patients (87 paroxysmal) who underwent ablation for symptomatic AF. Improvements in QoL were observed in all patients three months after ablation regardless of AF type and ablation success. In addition, the improvement in QoL was sustained over a 4-year follow up period. Patients who maintained sinus rhythm had a significantly greater improvement in both generic QoL scores and AF symptoms compared to those with recurrent AF; however, in contrast to Wokhlu et al. (2010b), this was statistically significant in both generic and AF-specific assessments. Improvement in QoL irrespective of ablation outcome might be explained by a treatment expectancy effect after ablation, transition from symptomatic to asymptomatic AF, reduction in AF burden short of abolition and the limited sensitivity of generic QoL measurement scales (e.g. SF36 V2) in measuring outcome following a disease specific intervention.

Previous studies have shown that AF specific QoL scales are more responsive to QoL change in this population and correlate better with ablation outcome (Wokhlu et al., 2010b; Spertus et al., 2011). This is corroborated by the greater change in QoL score after ablation and the stronger correlation with ablation outcome observed with the AFEQT questionnaire in this study. There was no significant correlation between the clinical parameters examined (including AF type) and change in QoL scores after ablation, as shown by others (Wokhlu et al., 2010b; Fichtner et al., 2012; Mantovan et al., 2013). However, Bulkova et al. (2014) reported that longstanding persistent AF, younger age and a shorter history of AF were associated with an improvement in QoL three years after ablation. The different patient populations and longer duration of follow up could explain the discordance in results.

In agreement with others, higher QoL scores pre ablation and AF recurrence were independent predictors of a smaller change in the respective QoL score after ablation (Wokhlu et al., 2010b; Mantovan et al., 2013; Dorian et al., 2013). This suggests a ceiling effect, as there is less potential for improvement after ablation in those with preserved QoL beforehand.

4.5.2 Change in Quality of Life according to Ablation Strategy

Mantovan et al. (2013) reported a significant improvement in PCS and MCS scores after PVI, CFAE and PVI + CFAE ablation strategies with the exception of MCS in the CFAE ablation group. In our study, we observed a significant increase in all three QoL scores after PVI; however, there was no significant improvement in PCS and MCS scores after PVI + CFAE ablation. This is likely a chance effect on account of the small number of patients in this subgroup. To our knowledge, the effect of PVI + Linear ablation on QoL has not been previously reported. In this study, PVI + Linear ablation was associated with a significant improvement in AFEQT and MCS scores; however, there was no significant difference in PCS scores. Of note, there was no significant difference in the magnitude of QoL change after ablation between the four ablation strategies.

4.5.3 Relationship between Clinical Variables and Quality of Life

This study showed no correlation between gender and QoL, in contrast to Reynolds et al. (2006) who reported that female patients were more symptomatic from AF with an associated reduction in QoL. In addition, they reported that older patients (>65 years) had fewer AF symptoms than their younger counterparts, which was not observed in this study. The disparity in results may be explained by different patient populations and eras of AF management as they studied patients with new-onset AF who were managed pharmacologically prior to the development of AF ablation; whereas, we studied patients referred for ablation who, by their very nature, have a high AF symptom burden and reduced QoL. Hypertension was associated with a higher symptom burden and reduced QoL secondary to AF in this study, which has not been previously reported. Persistent AF was associated with lower physical health scores than paroxysmal AF, as shown by Bulkova et al. (2014). However there was no difference in AF symptom burden between the two groups, which contradicts the common belief that symptoms regress as AF progresses from paroxysmal to persistent forms. Finally, diabetes was associated with lower mental health and a trend towards lower physical health scores in this study, which supports its negative impact on quality of life.

4.6 Limitations

Firstly, the choice of ablation strategy after PVI was not randomised and was dependent on the operator and the degree of signal complexity in the left atrium. Secondly, this was a prospective cohort study without a randomised control group comparing AF ablation to best non-ablative management (rate vs. rhythm control). However, the superiority of ablation over antiarrhythmic drugs in improving QoL has been demonstrated consistently. Thirdly, AF recurrence was determined by patients' symptoms, 12-lead ECG and 72-hour Holter monitoring three months after ablation and not by continuous ECG monitoring. Although, we cannot completely exclude asymptomatic AF episodes in the 'sinus rhythm' group, we consider this unlikely given previous AF symptoms. Fourthly, change in QoL was assessed 3 months after ablation in line with the first outpatient clinic review and therefore, the longer-term effect of ablation on QoL is unknown. Finally, patients enrolled in this study had been referred for catheter ablation and therefore, represent a select cohort with a high AF symptom burden. Extrapolation of the benefits demonstrated to a wider population requires caution.

4.7 Conclusions

Patients who maintained sinus rhythm after ablation had a significant improvement in AF symptoms and QoL. No improvement was observed in patients with recurrent AF. QoL did not correlate with either baseline clinical parameters or extent of ablation. AF specific QoL scales are more responsive to change than generic measures and correlate better with arrhythmia outcome.

	Paroxysmal AF (n=44)	**Persistent AF** (n=36)	*P Value*
Age (years)	56.9 ± 10.5	58.2 ± 9.5	0.58
Male Gender	30 (68%)	28 (78%)	0.45
AF History (years)	4.4 ± 3.4	2.9 ± 2.7	**0.04**
LA Volume (ml)	53 ± 17	65 ± 20	**<0.01**
LVEF (%)	54 ± 2	51 ± 8	**0.02**
Hypertension	12 (27%)	14 (39%)	0.34
Diabetes	2 (5%)	5 (14%)	0.23
Smoking	22 (50%)	17 (47%)	0.83

Table 4.1: Patient Characteristics

		AFEQT	PCS	MCS
		R/T (P)	*R/T (P)*	*R/T (P)*
Age		-0.02 (0.87)	0.05 (0.70)	-0.16 (0.15)
Female Gender		0.28 (0.78)	-1.14 (0.26)	1.31 (0.19)
Persistent AF		1.48 (0.14)	-0.03 (0.98)	1.33 (0.19)
AF History		-0.09 (0.44)	-0.18 (0.11)	-0.01 (0.96)
LA Volume		<-0.01 (0.98)	0.06 (0.63)	-0.34 (<0.01)
LVEF		0.06 (0.61)	-0.05 (0.68)	0.10 (0.38)
Hypertension		-0.57 (0.57)	-0.01 (0.99)	-0.49 (0.63)
Diabetes		1.31 (0.20)	0.95 (0.34)	-0.23 (0.82)
Smoking		-1.96 (0.05)	-0.40 (0.69)	-0.67 (0.51)
Baseline	AFEQT	**-0.47 (<0.01)**	-0.10 (0.37)	-0.13 (0.25)
	PCS	**-0.22 (0.05)**	**-0.34 (<0.01)**	0.20 (0.08)
	MCS	-0.12 (0.30)	0.16 (0.17)	**-0.54 (<0.01)**
Three Month Outcome		**-5.79 (<0.01)**	**-2.39 (0.02)**	**-2.72 (<0.01)**

Table 4.2: Change in QoL Scores after Ablation: Relationship with Clinical Parameters and Ablation Outcome

* R values from Pearson's correlation (continuous variables) and T values from independent t-tests (categorical variables) are shown

	Parameter	Standardised Coefficient (Beta)	P Value
AFEQT	AF Recurrence	0.57	<0.01
	Baseline AFEQT	-0.56	<0.01
PCS	Baseline PCS	-0.40	<0.01
	Baseline MCS	0.25	0.02
	AF Recurrence	0.23	0.03
MCS	Baseline MCS	-0.68	<0.01
	AF Recurrence	0.28	<0.01
	Baseline PCS	0.27	<0.01

Table 4.3: Multivariate Predictors of Change in QoL Scores after Ablation

	AFEQT			PCS			MCS		
	Baseline	3 months	*P*	Baseline	3 months	*P*	Baseline	3 months	*P*
PVI (n=45)	53.4 ± 22.3	76.7 ± 20.9	<0.01	43.8 ± 10.7	47.0 ± 11.0	0.02	44.3 ± 12.1	49.8 ± 9.1	<0.01
PVI + Linear (n=17)	47.6 ± 23.0	62.7 ± 25.5	0.04	44.5 ± 98	44.9 ± 10.4	0.82	45.4 ± 10.5	50.9 ± 9.4	0.04
PVI + CFAE (n=8)	39.2 ± 15.3	56.9 ± 22.3	0.12	38.2 ± 12.5	43.2 ± 11.7	0.26	44.1 ± 13.8	47.0 ± 11.6	0.46
PVI + Linear + CFAE (n=10)	52.1 ± 23.2	72.5 ± 29.0	0.02	43.0 ± 13.0	48.2 ± 15.8	0.14	49.5 ± 8.3	48.0 ± 14.1	0.65

Table 4.4: Change in QoL Scores according to Ablation Strategy

	AFEQT *R/T (P)*	**PCS** *R/T (P)*	**MCS** *R/T (P)*
Age	-0.14 (0.22)	**-0.35 (<0.01)**	0.05 (0.69)
Female Gender	1.01 (0.31)	1.13 (0.26)	-0.14 (0.89)
Persistent AF	1.64 (0.10)	**2.05 (0.04)**	0 (1)
AF History	0.14 (0.22)	0.20 (0.09)	-0.04 (0.76)
LA Volume	-0.03 (0.82)	-0.20 (0.09)	0.33 (<0.01)
LVEF	-0.01 (0.96)	0.12 (0.29)	-0.08 (0.47)
Hypertension	**2.22 (0.03)**	1.43 (0.16)	1.93 (0.06)
Diabetes	1.38 (0.17)	1.81 (0.07)	**2.64 (0.01)**
Smoking	1.21 (0.23)	0.35 (0.73)	0.96 (0.34)

Table 4.5: Baseline QoL Scores and Clinical Parameters

* R values from Pearson's correlation (continuous variables) and T values from independent t-tests (categorical variables) are shown

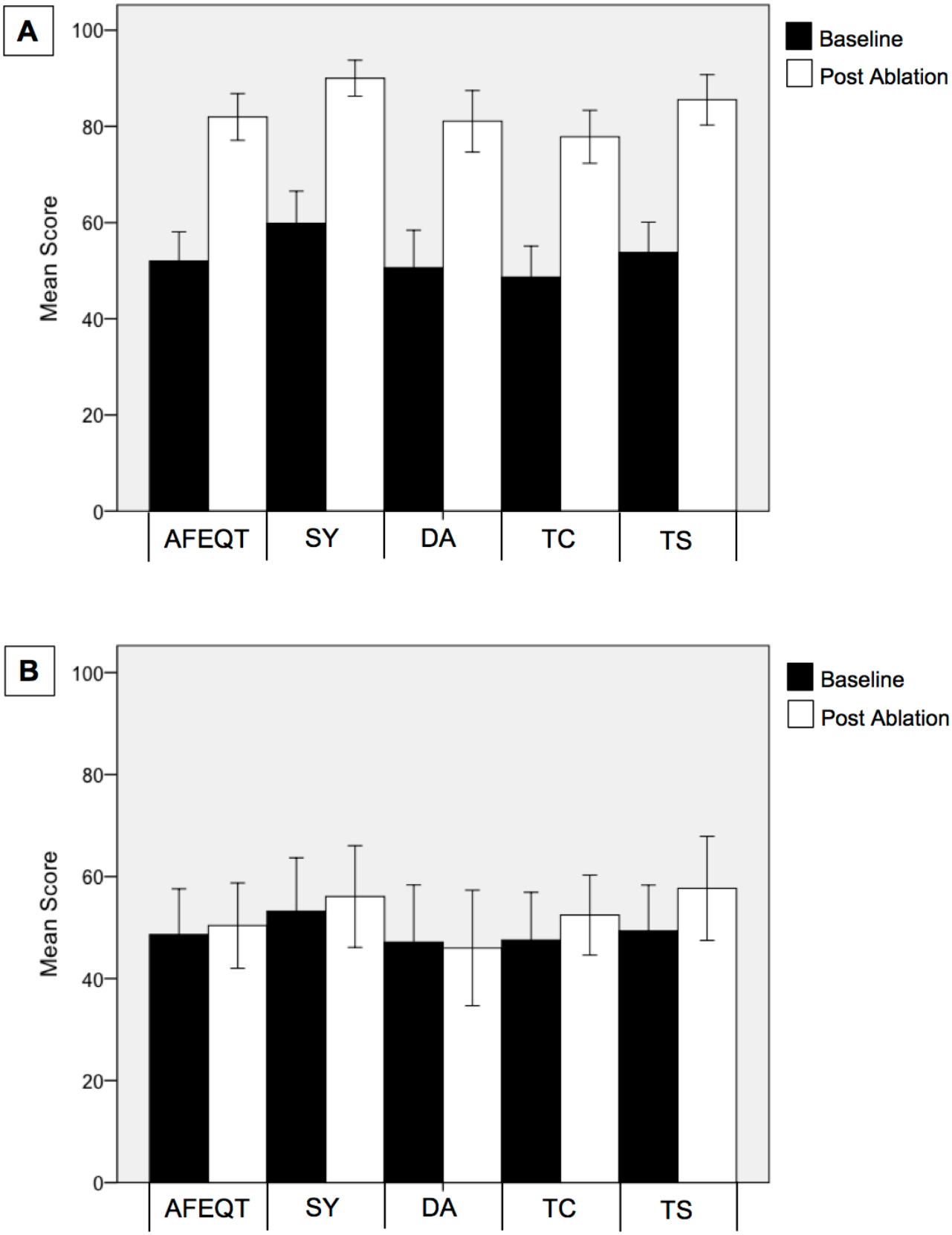


Figure 4.1: Mean individual and summative AFEQT scores before and three months after ablation. Figure 4.1A = patients who maintained sinus rhythm post ablation; Figure 4.1B = patients with recurrent AF. AFEQT = overall AFEQT score; DA = daily activities; SY = symptoms; TC = treatment concern; TS = treatment satisfaction.

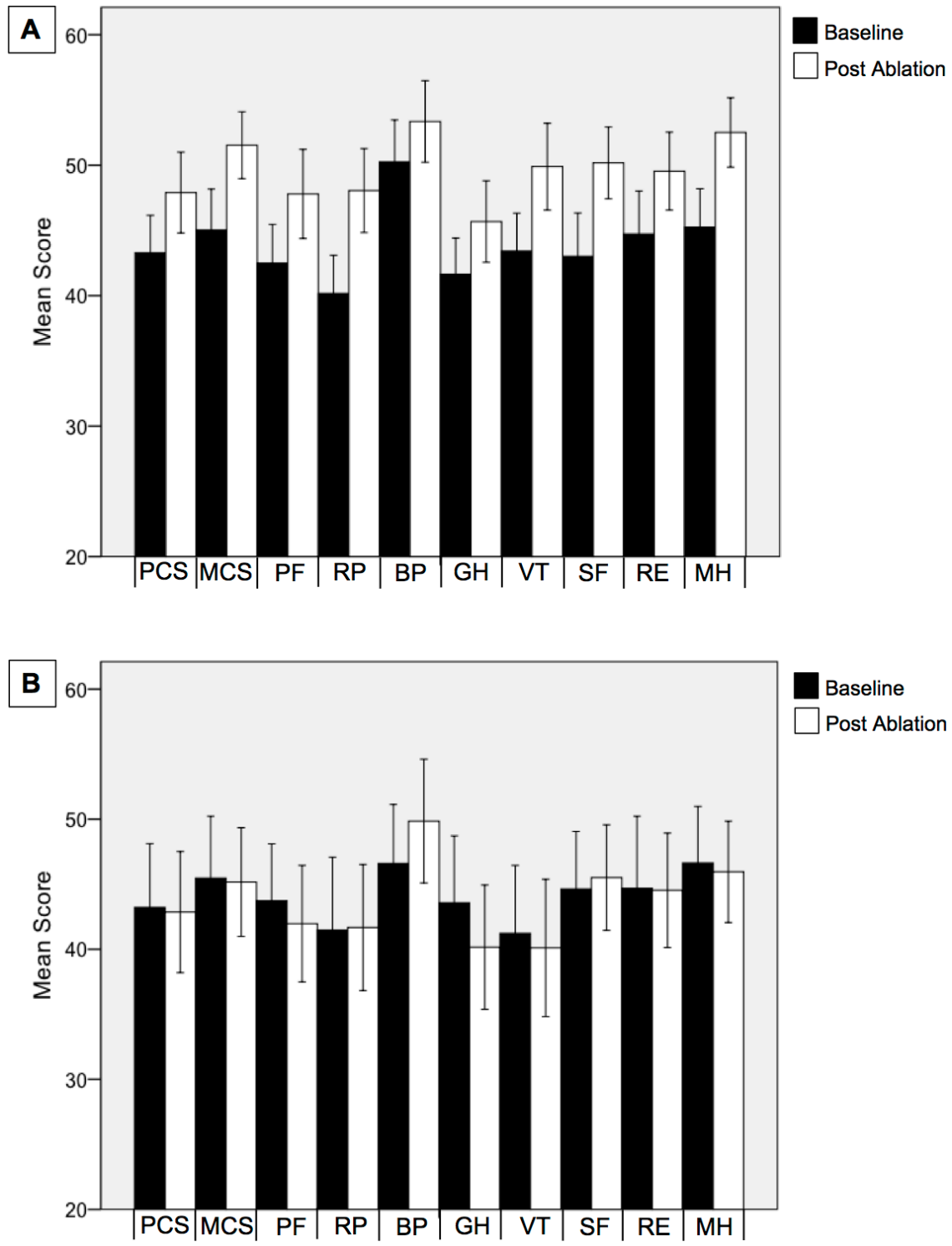


Figure 4.2: Mean individual and summative SF-36 V2 scores before and three months after ablation. Figure 4.2A = patients who maintained sinus rhythm post ablation; Figure 4.2B = patients with recurrent AF. PCS = physical component summary; MCS = mental component summary; PF = physical functioning, RP = role limitations because of physical problems, BP = bodily pain, GH = general health perception, VT = vitality, SF = social functioning, RE = role limitations because of emotional problems; MH = mental health.

Chapter 5. Inter-atrial frequency gradients and dominant frequency variability in patients with persistent atrial fibrillation: Insights from multipolar contact mapping

5.1 Abstract

Introduction

In an observational study, the majority of patients with persistent AF had a 'right-to-left' atrial frequency gradient with a significantly higher dominant frequency (DF) in the right atrium compared to the coronary sinus and pulmonary veins. The aim of this study was to investigate inter-atrial frequency gradients and DF variability in patients with persistent AF using a basket catheter to collect data simultaneously from multiple atrial sites.

Methods and Results

Twelve patients were studied. The basket catheter was deployed sequentially in the right and left atrium and 1-minute recordings were collected from one/two positions in each chamber. Separate recordings were collected from the coronary sinus and pulmonary veins. Mean DF was calculated for each bipole using Fourier analysis. Five patients had a 'left-to-right' (LA 7.3 ± 0.7Hz vs. RA 6.7 ± 0.7Hz; $p<0.001$) and three patients had a 'right-to-left' atrial frequency gradient (RA 6.9 ± 1.2Hz vs. LA 6.2 ± 0.9Hz; $p<0.001$). The location of DF_{MAX} (highest frequency site) remained stable throughout the 1-minute recording in all patients. Mean temporal coefficient of variation for DF in the whole group was 4.5 ± 2.1% and was significantly higher in the right compared to the left atrium (4.9 ± 2.1% vs. 4.4 ± 2.1%; $p<0.001$).

Conclusions

A proportion of patients with persistent AF have a 'right-to-left' atrial frequency gradient implying that their arrhythmia is maintained by high frequency sources in the right atrium. These sources are anatomically stable over a 1-minute period. The effectiveness of ablating these sites warrants further investigation.

5.2 Introduction

A left-to-right atrial frequency gradient during AF was first described by Mansour et al. (2001) using high-resolution optical and electrode-based mapping of isolated sheep hearts. AF was induced using a combination of burst pacing and increasing concentrations of acetylcholine and dominant frequency (DF) maps were created using fast Fourier transform (FFT) algorithms. They reported that left atrial DF was consistently higher than in the right atrium and hypothesised that high-frequency sources in the left atrium were responsible for maintaining AF (Mansour et al., 2001). Lazar et al. (2004) corroborated these findings by demonstrating a left-to-right atrial frequency gradient in patients with paroxysmal AF. They also found that patients with left-to-right atrial frequency gradients had better clinical outcomes following pulmonary vein isolation but that the majority of patients with persistent AF did not have an inter-atrial frequency gradient (Lazar et al., 2004 and 2006). Interestingly, none of their AF patients had a right-to-left atrial frequency gradient, which is at odds with our own experience. In an observational study of 41 patients with persistent AF (Raine et al., 2013), we observed a right-to left atrial frequency gradient in 63% of patients with a significantly higher DF recorded in the high right atrium compared to the coronary sinus and pulmonary vein ostia prior to ablation (Table 5.1). The remaining patients had a left-to-right atrial frequency gradient with a significantly higher DF in the pulmonary vein ostia compared to the coronary sinus and high right atrium (Table 5.1). The presence of a right-to-left atrial frequency gradient implies that the arrhythmia is being maintained by high frequency sources in the right atrium. This has profound implications for ablation strategies since currently the right atrium is largely ignored and considered a bystander chamber not critical to the maintenance of AF. The obvious limitation of the observational study was the small number of atrial sites sampled simultaneously for electrogram analysis. Therefore, the **aim** of this study was to investigate inter-atrial frequency gradients and temporal and spatial variability of DF in patients with persistent AF using a 64-electrode contact mapping catheter (Constellation®, Boston Scientific) to record simultaneous electrograms from multiple sites in the left and right atria.

5.3 Methods

5.3.1 Patient Recruitment

Study participants were recruited from patients with persistent AF (AF episode duration >7 days (Camm et al., 2010)) undergoing their first catheter ablation procedure for standard clinical indications. Class I and III antiarrhythmic drugs were discontinued five half-lives prior to ablation. Patients were excluded from the study if they were unable to give written informed consent or were taking amiodarone – because of its long half-life and effects on cardiac electrophysiology. Transverse and longitudinal right and left atrial measurements were obtained from apical two and four-chamber views on transthoracic echocardiography two weeks prior to the ablation procedure to enable appropriate sizing of the Constellation® catheter.

5.3.2 Ethical Approval

This study complies with the Declaration of Helsinki and was granted a favourable ethical opinion by the West of Scotland Research Ethics Committee (REC reference: 13/WS/0141). Written informed consent was obtained from all patients included in the study.

5.3.3 Study Protocol

At the start of the ablation procedure, electroanatomical maps of both atria were created using a bipolar irrigated-tip ablation catheter and the EnSite Velocity™ cardiac mapping system (St. Jude Medical). A Constellation® catheter was then deployed sequentially in the right and left atrium (Figure 5.1) and one-minute intracardiac recordings were collected from one or two catheter positions in each atrium to ensure satisfactory coverage of the chamber. If satisfactory contact with all areas of the atria could not be achieved using Constellation®, a bipolar ablation catheter was used to collect sequential 1-minute recordings from these inadequately covered sites to complete high-resolution DF maps of both atria. Intracardiac recordings were also collected simultaneously from the coronary sinus (CS) (steerable decapolar catheter) and sequentially from each of the pulmonary vein ostia (ablation catheter). The distal poles of the CS catheter were positioned on the lateral aspect of the mitral valve ring, with proximal bipole $CS_{9\text{-}10}$ just inside the ostium of the coronary sinus.

5.3.4 Intracardiac Data Analysis

All intracardiac signals were filtered using a standard bandpass of 30-250Hz and recorded on a Labsystem Pro™ recording system (Bard EP) at a digital sampling rate of 1000Hz for offline analysis in Matlab® 2013.

To preserve signal integrity, no additional filtering was applied. The 64 electrodes on the Constellation® catheter were employed in an overlapping format to record 56 bipolar electrograms. Power spectral density (PSD) of consecutive 10-second sections of bipolar electrograms was estimated by periodogram with rectangular window and frequency resolution of 0.1Hz. For each section, DF was identified as the intracardiac frequency with the highest power in the range 3-10Hz as previously defined (Raine et al., 2004 and 2005). DFs were verified to be in close agreement with the number of electrogram activations per second by plotting the electrograms and corresponding PSDs as illustrated in Figure 5.2. Mean and SD values of DF from the one-minute recordings are reported.

5.3.5 Statistical Analyses

Continuous variables are expressed as mean ± SD. Mean DF from each atrium were compared using Student's independent t-tests to identify significant inter-atrial frequency gradients. DF_{MEAN} from different atrial and CS sites were compared to DF_{MAX} in the corresponding atrium or coronary sinus using a one-sample t-test and correction for multiple comparisons was performed using the sequential Bonferroni method. Temporal and spatial variability of DF were quantified using the coefficient of variation, which is a normalised measure defined as the ratio of the SD to the mean. Temporal coefficients of variation were compared between different atrial sites and between patients using a one-way ANOVA. Spatial coefficients of variation were compared between left and right atria using a paired t-test. All tests were 2-tailed and $p<0.05$ was considered statistically significant.

5.4 Results

Characteristics of the 12 consecutive patients recruited to the study are shown in Table 5.2. Ten of the 12 patients had longstanding persistent AF (AF episode duration ≥1 year (Camm et al., 2010)). 60mm Constellation® catheters (5mm inter-electrode spacing) were used in eight patients and 48mm catheters (4mm inter-electrode spacing) in the remaining four patients based on their atrial dimensions on transthoracic echocardiography. All patients required two Constellation® catheter positions in the left atrium and 7/12 patients required two catheter positions in the right atrium. The number of Constellation® catheter bipoles with electrograms suitable for FFT analysis (i.e. containing atrial activity without significant artefact or noise) was 2034/2688 (76%) – RA 1179/1344 (88%) vs. LA 855/1344 (64%).

5.4.1 Inter-Atrial Frequency Gradients

Five patients (42%) had a 'left-to-right' atrial frequency gradient (LA DF_{MEAN} 7.3 ± 0.7Hz vs. RA DF_{MEAN} 6.7 ± 0.7Hz; $p<0.001$) (Figure 5.3). In these, DF_{MAX} was located in the lateral left atrium (n=2), roof (n=1), left lower pulmonary vein (n=1) or distal CS (n=1). Three patients (25%) had a 'right-to-left' atrial frequency gradient (RA DF_{MEAN} 6.9 ± 1.2Hz vs. LA DF_{MEAN} 6.2 ± 0.9Hz; $p<0.001$) with DF_{MAX} located at superior vena cava (SVC) / RA junction (n=1), right atrial appendage (RAA) ostium (n=1) or posterior right atrium (n=1). The remaining four patients (33%) had no significant inter-atrial frequency gradient (LA DF_{MEAN} 6.4 ± 0.4Hz vs. RA DF_{MEAN} 6.5 ± 0.5Hz; $p=0.22$). Inter-atrial frequency gradients and the location of DF_{MAX} remained stable throughout the 1-minute recordings in all patients (temporal coefficient of variation 4.1 ± 0.8%). In addition, the site with the second highest DF was located in the same atrium as DF_{MAX} in all patients.

5.4.2 Dominant Frequency Distribution

The distribution of dominant frequencies according to intracardiac site is shown in Table 5.3. In the right atrium, the RAA ostium had a significantly higher DF (7.0 ± 1.0Hz) compared to the floor (6.5 ± 0.6Hz; $p<0.001$) and septum (6.6 ± 0.8Hz; $p<0.001$). In the left atrium, the lateral wall (6.9 ± 1.0Hz), left atrial appendage (LAA) ostium (6.9 ± 1.0Hz) and roof (6.9 ± 0.9Hz) had significantly higher DF compared to the floor (6.6 ± 0.7Hz; $p<0.001$). In the coronary sinus, the highest DF was found in the distal electrode pair CS_{3-4} (6.7 ± 1.1Hz); however, this was not significantly higher than the other electrode pairs.

5.4.3 Temporal and Spatial Variability of DF

The mean temporal coefficient of variation for DF in the whole group was 4.5 ± 2.1% (range 0–12.8%). Temporal variability of DF was significantly higher in the right atrium (4.9 ± 2.1%) compared to the left atrium (4.4 ± 2.1%; $p<0.001$). In contrast, temporal variability of DF was significantly lower in the CS (3.4 ± 1.4%) compared to the right atrium (4.9 ± 2.1%; $p<0.001$), left atrium (4.4 ± 2.1%; $p<0.001$) or pulmonary veins (4.6 ± 1.6%; $p<0.01$). Significant differences in temporal variability of DF in both atria were observed between patients ($p<0.001$) (Figure 5.4) and between different intracardiac sites ($p<0.001$) (Figure 5.5). The highest temporal variability of DF was observed in the right lower pulmonary vein (5.8 ± 1.6%) and right atrial septum (5.7 ± 3.0%) and the lowest temporal variability of DF observed in the left atrial septum (1.3 ± 1.1%) and inferior vena cava (1.4 ± 1.7%).

The mean spatial coefficient of variation for DF in the whole group was 7.0 ± 2.7% (range 3.8–13.7%). In contrast to temporal variability, there was no significant difference in spatial variability of DF between right and left atria (6.2 ± 2.6% vs. 4.7 ± 1.5%; p=0.14).

5.5 Discussion

This study is the first to investigate inter-atrial frequency gradients in patients with persistent AF using the simultaneous multipoint recording capability of the Constellation® catheter. To optimise fidelity of recordings, mean DF for each bipolar electrogram was calculated over one-minute rather than sequentially over 6.82 seconds as used by EnSite Velocity™ for creation of its automated DF maps. The longer recording negated the impact of transient high frequency sites and facilitated the creation of high-resolution frequency maps of both atria. This study is also the first to investigate temporal and spatial variability of DF in the right atrium in patients with persistent AF, building on the work of Habel et al. (2010) who investigated DF variability in the left atrium using multipolar recordings in a cohort of patients with paroxysmal or persistent AF.

5.5.1 Inter-Atrial Frequency Gradients

Consistent with the results of Lazar et al. (2004 and 2006), five of the 12 patients in this study had a left-to-right atrial frequency gradient and four patients had no inter-atrial frequency gradient. However, the remaining three patients (25%) had a right-to-left atrial frequency gradient with DF_{MAX} located at the SVC/RA junction, RAA ostium or posterior right atrium. This implies the arrhythmia in these patients is maintained by high frequency sources in the right atrium and therefore, they would not be expected to maintain sinus rhythm following conventional left atrial ablation procedures. Our results are in agreement with those of Narayan et al. (2012) who reported that 24% of patients enrolled in their CONFIRM trial had AF sources (electrical rotors and/or focal impulses) located in the right atrium. The fact that Lazar et al. (2004 and 2006) did not find right-to-left atrial frequency gradients in any of their patients may be explained by differences in the methods used to collect intracardiac electrograms. Whereas, they recorded electrograms simultaneously from decapolar catheters in the coronary sinus and posterior right atrium and a circular mapping catheter in the posterior left atrium, we ensured more comprehensive coverage of both atria using a Constellation® catheter positioned in one/two locations in each chamber and a decapolar catheter in the coronary sinus.

Another key finding from this study is that inter-atrial frequency gradients and the location of DF_{MAX} remained stable throughout the 1-minute recording in all patients. Stability of high frequency sites over a 30-second period in patients with persistent AF has been reported recently by Salinet et al. (2014) using non-contact mapping. Longer-term stability over a 1-minute recording has not been reported and supports the hypothesis that DF_{MAX} sites are important to the maintenance of AF and therefore should be targeted with ablation.

5.5.2 Dominant Frequency Distribution

In their study of 50 patients with persistent AF, Lin et al. (2010) investigated the spatial distribution of DF_{MAX} sites in the left atrium using high-density frequency mapping. They reported that DF_{MAX} was most commonly found in the left atrial septum (32%), LAA ridge (19%), posterior wall (19%) or pulmonary vein antrum (14%). In the five patients in our study with left-to-right atrial gradients, DF_{MAX} was located in the lateral left atrium (n=2), roof (n=1), left lower pulmonary vein (n=1) or distal CS (n=1). The discordance in results may again be explained by differences in the methods of data collection. Lin et al. (2010) created high-density frequency maps of the left atrium using the automated DF software in EnSite Velocity™ as previously discussed. We calculated mean DF for each catheter bipole from each 1-minute recording to provide a global assessment of atrial frequencies and to negate the impact of transient high-frequency activity.

To our knowledge, the distribution of dominant frequencies in both atria has not been previously studied using multipolar recordings. In this study, the highest mean left atrial DF was found in the lateral wall and LAA ostium, which were significantly higher than the left atrial floor. In the right atrium, the RAA ostium had a significantly higher DF compared to the floor and septum. The identification of high frequency activity – likely contributing to the maintenance of AF – in the atrial appendages is of particular interest since these sites have traditionally been unattractive regions for ablation because of their complex thin-walled structure, contribution to atrial contractility and role in thromboembolism. However, evidence that electrical isolation of the left atrial appendage abolishes its contractile function and exposes the patient to a higher risk of thromboembolism is lacking. In a study of 987 patients (71% persistent AF), Di Biase et al. (2010) reported a significant improvement in ablation outcome in patients with documented high frequency LAA activity who underwent circumferential LAA isolation.

In addition, LAA mechanical function was maintained in 53% of these patients and no LAA thrombus was observed (including in those with poor LAA contractility).

5.5.3 Temporal and Spatial Variability of DF

In this study, the mean temporal and spatial coefficients of variation for DF were 4.5 ± 2.1% and 7.0 ± 2.7%, which are significantly lower than the 22.7 ± 5.4% and 26.9 ± 6.6% reported by Habel et al. (2010). The differing results may be explained by the shorter duration of recording (1-minute vs. 5-minute) and longer analysis sections (10-second vs. 5-second). Furthermore, we recorded data from additional intracardiac sites including the right atrium, CS and pulmonary veins and ensured complete coverage of both atria by supplementary recordings using a bipolar ablation catheter in areas of inadequate endocardial contact with Constellation®. Interestingly, temporal variability of DF was significantly lower in the left atrium compared to the right atrium. This reflects more organised activity in the left atrium, which in turn could represent rotors and/or focal AF drivers responsible for maintaining AF. Another possible explanation for the higher temporal variability of DF in the right atrium is its' more complex anatomical structure. In agreement with Habel et al. (2010), we observed significant differences in temporal variability of DF between patients and between different atrial sites ($p<0.001$). In the right atrium, the lowest temporal variability of DF was observed in the IVC, SVC, crista terminalis and roof. Conversely in the left atrium, the septum, roof, anterior, posterior and lateral walls had the lowest temporal variability of DF. High frequency activity in these areas is likely to represent an AF source on account of the inherent low temporal variability. Finally, despite an average 7% variation in DF across both atria, there was no significant difference in the degree of spatial variation of DF between the left and right atrium.

5.6 Limitations

Firstly, the findings need to be interpreted cautiously since only 12 patients were studied. Secondly, only one Constellation® catheter was deployed per patient, which, theoretically, meant that the size of catheter could not be optimised to the individual dimensions of either atrium. However, this did not result in a significant compromise in this study as all of the patients had similar sized right and left atria. Thirdly, we collected data sequentially from one or two catheter positions in each atrium to ensure optimum coverage of the chamber. This meant a compromise between maximising the number of atrial sites recorded and the degree to which all electrograms were recorded simultaneously. In light of the above, we were unable to collect true simultaneous inter- and intra-atrial recordings in all patients.

This was due primarily to limitations in the ability of the Constellation® catheter to provide comprehensive coverage of either atria from one position. This was most apparent in the left atrium where only 64% of the Constellation® catheter bipoles contained electrograms suitable for FFT analysis despite being deployed through a steerable sheath. The Constellation® catheter had greatest difficulty in achieving endocardial contact with the left atrial floor and septum; therefore, a bipolar ablation catheter was needed to record electrograms from these sites when necessary. Nevertheless, we were able to record data from the left atrial septum in 9/12 patients using Constellation® by flexing the sheath around the left atrium and deploying the catheter with its' tip pointing towards the right upper pulmonary vein. However, this manoeuvre can only be performed in patients with a significantly dilated left atrium. Finally, with regard to spectral DF analysis, potential limitations include: (1) overestimation of DF due to double counting; (2) impact of far-field ventricular depolarisations and noise; (3) significant DF variability with short recording durations (Narayan et al., 2006; Ng et al., 2007). We attempted to address these limitations by using bipolar recordings to reduce the impact of far field ventricular depolarisations and by ensuring that any potential sources of electrical noise were removed from the recording apparatus. We also used a frequency range of 3-10Hz to extract the atrial DF and calculated mean DF from consecutive 10-second sections across the 1-minute recording to negate the impact of transient high frequency activity. In addition, we plotted the electrograms and corresponding PSDs to verify that the calculated DF was in close agreement with AF cycle length.

5.7 Conclusions

High-density frequency analysis of both atria showed that 25% of the patients with persistent AF studied had a 'right-to-left' atrial frequency gradient. This implies that their arrhythmia is maintained by high frequency sources in the right atrium. These sources were anatomically stable over a one-minute period and typically exhibited organised activity with low temporal variability. The effectiveness of targeting these sites with ablation warrants further investigation.

Atrial Frequency Gradient	Mean ± SD Intracardiac Dominant Frequency (Hz)		
	High Right Atrium	**Coronary Sinus**	**Pulmonary Vein with highest DF**
Right-to-Left (n=26; 63%)	6.89 ± 0.82	6.08 ± 0.71 (p<0.001)	6.37 ± 0.55 (p<0.001)
Left-to-Right (n=15; 37%)	6.45 ± 1.10 (p=0.013)	6.23 ± 1.07 (p=0.005)	7.11 ± 0.86

Table 5.1: Inter-Atrial Frequency Gradients. The proportion of patients with right-to-left and left-to-right atrial frequency gradients from the observational study (Raine et al., 2013) is shown. Respective intracardiac dominant frequencies from the high right atrium, coronary sinus and highest frequency pulmonary vein and the P values from the inter-site comparisons are quoted.

Age (years)	56 ± 8
Male Gender	10 (83%)
AF Duration (months)	21 ± 11
LA Volume (ml)	119 ± 37
RA Volume (ml)	128 ± 59
LVEF (%)	52 ± 5
Hypertension	6 (50%)
Diabetes	1 (8%)

Table 5.2: Patient Characteristics

	Intracardiac Site	DF_{MEAN} (Hz)	P Value*
Right Atrium (DF_{MAX} 7.0Hz)	RAA	7.0 ± 1.0	N/A
	SVC	6.9 ± 0.9	0.68
	Crista Terminalis	6.9 ± 0.9	0.45
	Roof	6.8 ± 0.8	0.17
	Posterior	6.7 ± 0.8	0.04
	Anterior	6.7 ± 0.8	0.02
	IVC	6.6 ± 0.8	0.07
	Septum	6.6 ± 0.8	**<0.001**
	Floor	6.5 ± 0.6	**<0.001**
Left Atrium (DF_{MAX} 6.9Hz)	Lateral	6.9 ± 1.0	N/A
	LAA	6.9 ± 1.0	0.99
	Roof	6.9 ± 0.9	0.94
	LUPV	6.8 ± 0.6	0.64
	LLPV	6.8 ± 0.7	0.60
	Posterior	6.8 ± 0.9	0.39
	Anterior	6.7 ± 0.9	0.17
	Floor	6.6 ± 0.7	**<0.001**
	Septum	6.5 ± 0.8	0.07
	RLPV	6.5 ± 0.6	0.09
	RUPV	6.4 ± 0.7	0.05
Coronary Sinus (DF_{MAX} 6.7Hz)	CS 3-4 (Distal)	6.7 ± 1.1	N/A
	CS 7-8	6.5 ± 1.1	0.50
	CS 5-6	6.3 ± 1.1	0.37
	CS 9-10 (Proximal)	6.2 ± 1.0	0.17

Table 5.3: Mean Dominant Frequencies (Hz) by Intracardiac Site

* P value from one-sample t-test comparing DF_{MEAN} at each site with DF_{MAX} in the corresponding atrium or coronary sinus. P values highlighted in bold remain significant after correcting for multiple comparisons using sequential Bonferroni method.

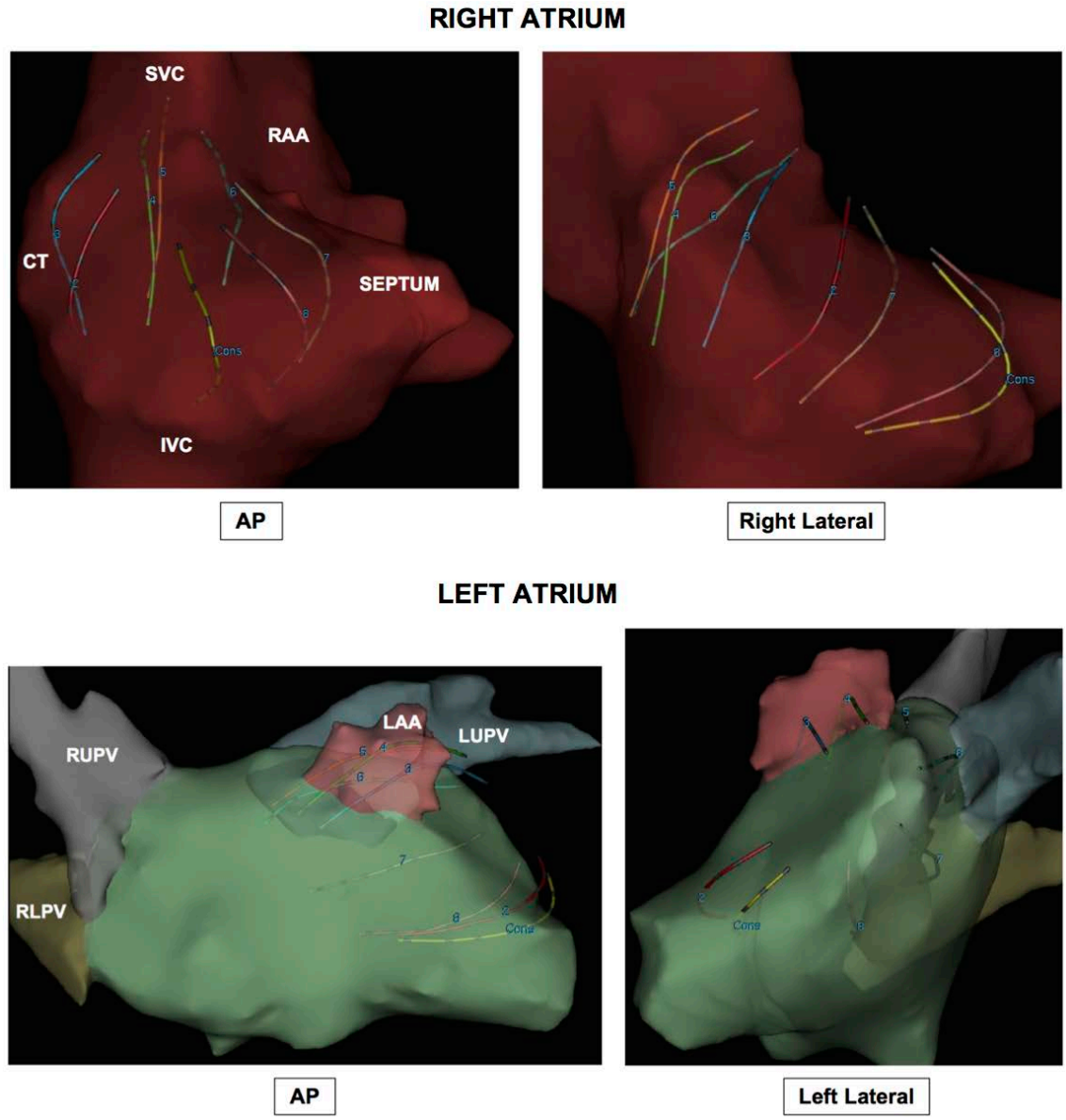


Figure 5.1: Constellation® catheter deployed in the right atrium (top panel) **and left atrium** (bottom panel) **with guidance from the EnSite Velocity™ cardiac mapping system.** The eight catheter splines are labelled and shown in different colours. AP = anteroposterior; CT = crista terminalis; IVC = inferior vena cava; LAA = left atrial appendage; LUPV = left upper pulmonary vein; RAA = right atrial appendage; RLPV = right lower pulmonary vein; RUPV = right upper pulmonary vein; SVC = superior vena cava.

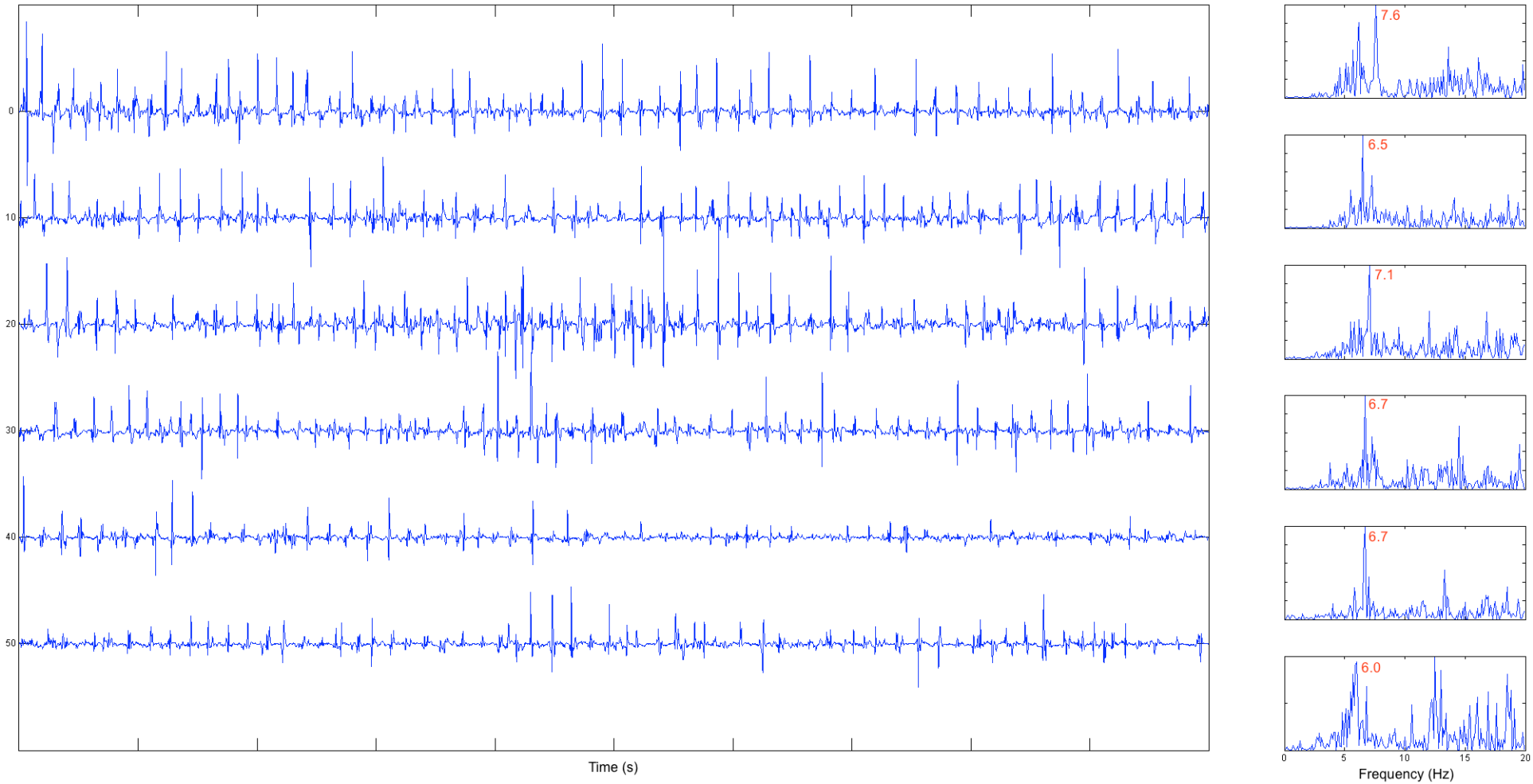


Figure 5.2: Bipolar intracardiac electrograms and dominant frequency spectra. Each 1-minute recording is divided into six 10-second sections and the corresponding frequency spectrum for each 10-second section displayed. Dominant frequency is highlighted in red.

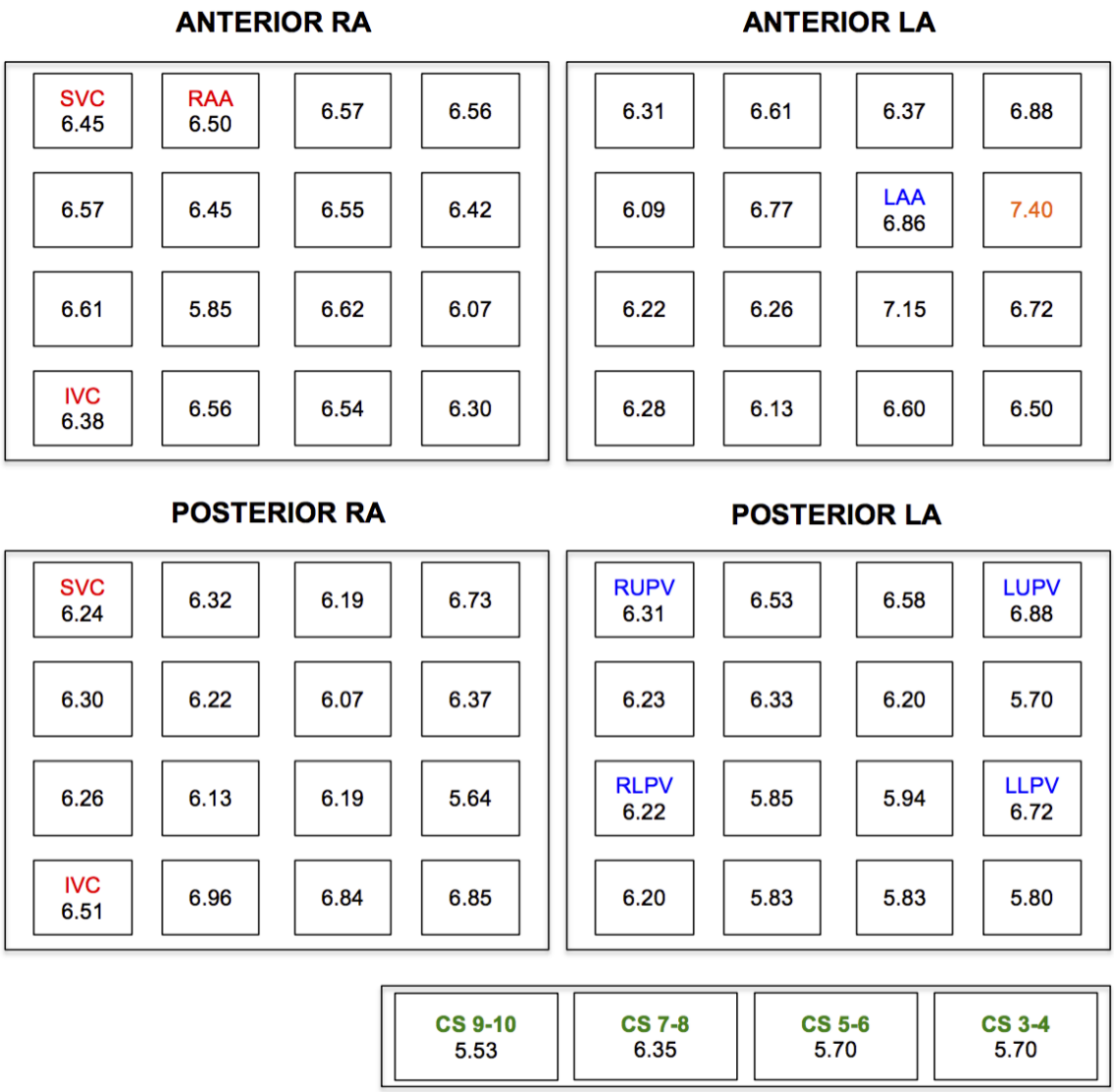


Figure 5.3: Bi-atrial dominant frequency map illustrating a left-to-right atrial frequency gradient. Each atrium is divided into 32 sectors (16 anterior and 16 posterior). The highest dominant frequency is highlighted in orange and located in the anterolateral left atrium.

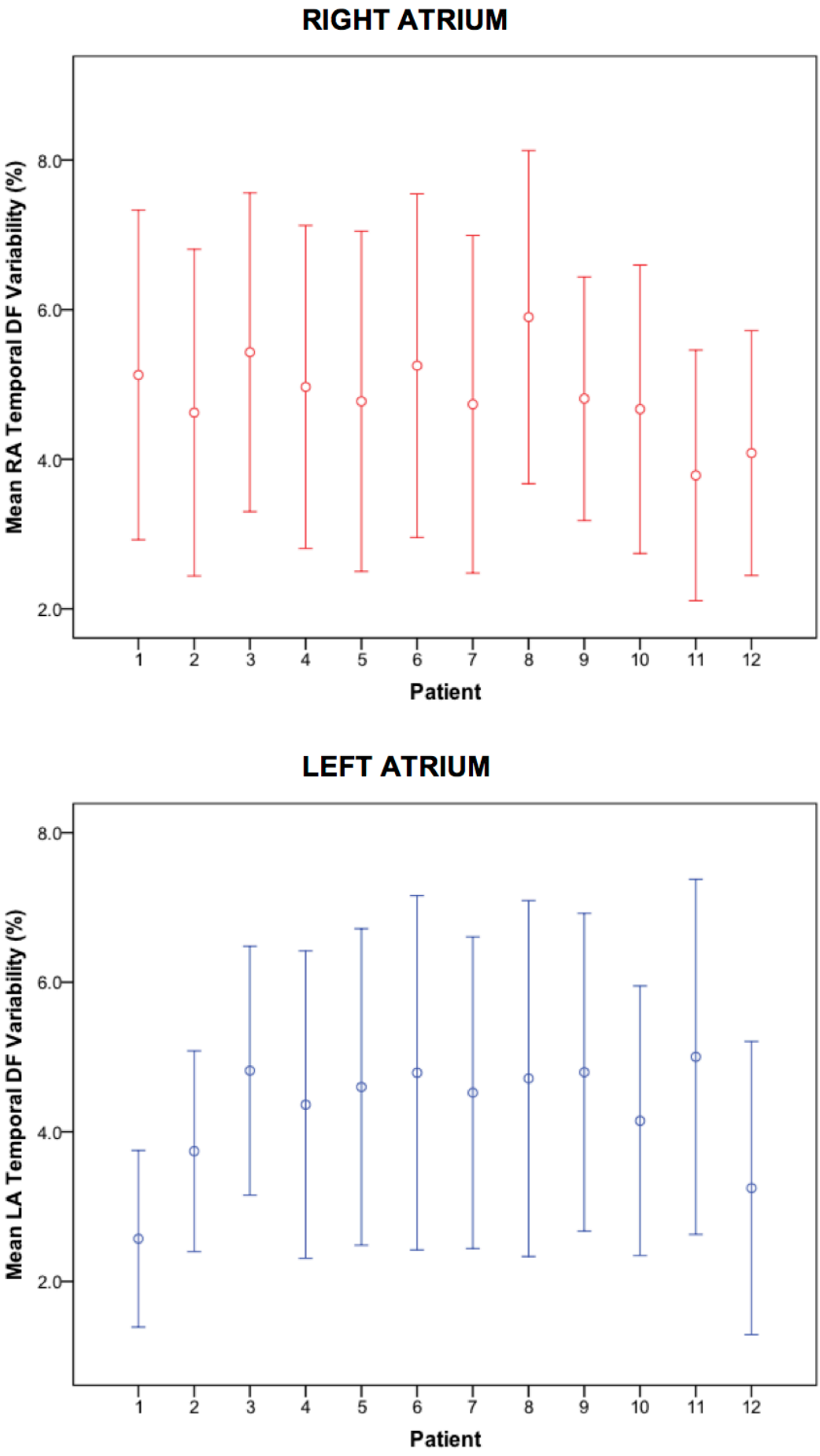


Figure 5.4: Mean temporal variability of DF in the right atrium (top panel) **and left atrium** (bottom panel) **for each patient.** The circles indicate the mean value and the error bars represent one standard deviation from the mean.

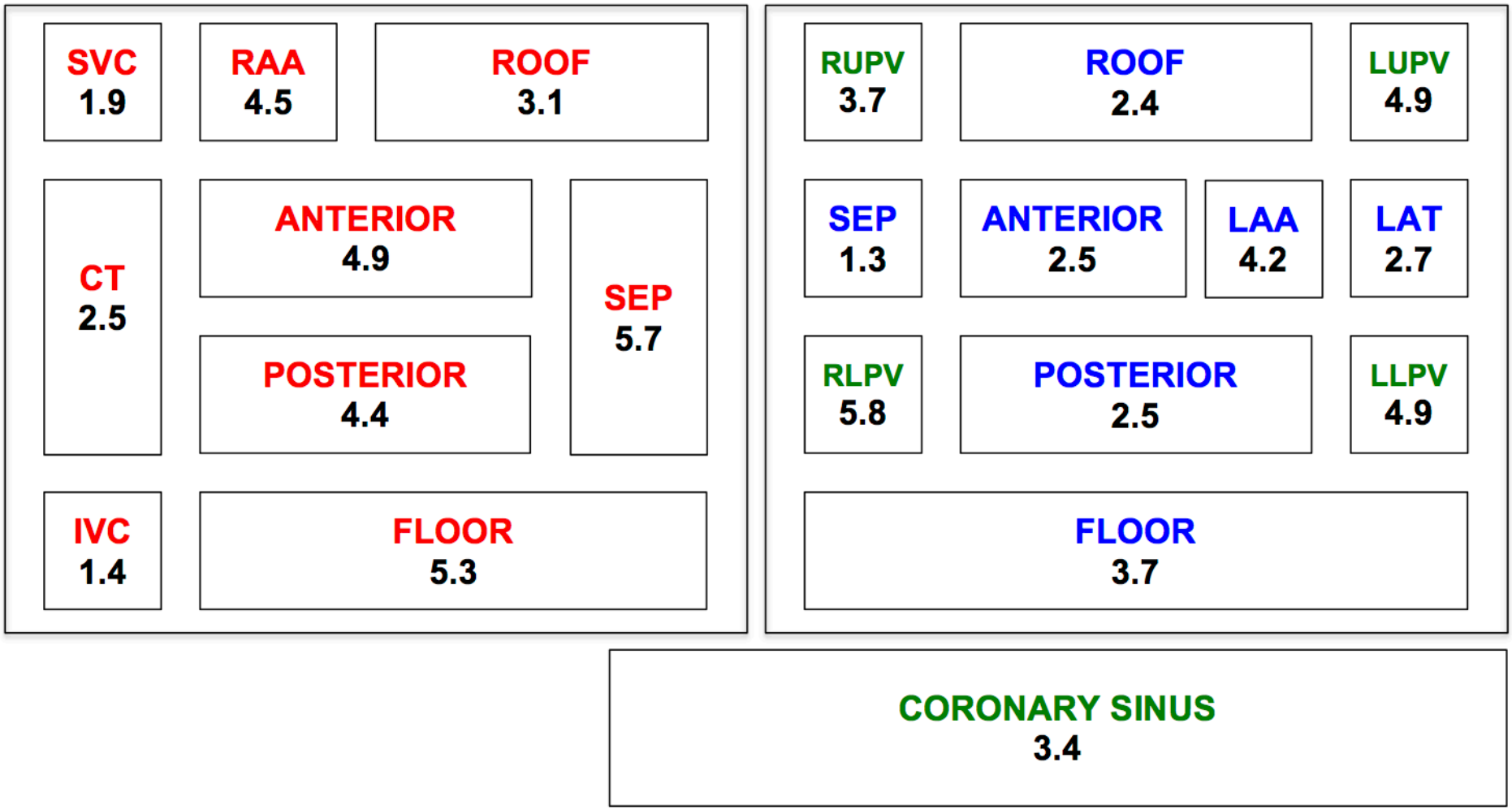


Figure 5.5: Temporal variability of DF (%) according to intracardiac site. LAT = lateral wall; SEP = septum. Other abbreviations as for Figure 5.1

Chapter 6. Multipolar contact mapping guided ablation of temporally stable high frequency and complex fractionated atrial electrogram sites in patients with persistent atrial fibrillation

6.1 Abstract

Introduction

Previous studies of high frequency and CFAE site ablation have produced conflicting results. The aims of this study were: (1) To investigate the distribution and effectiveness of ablating high frequency (≥8Hz) and highly repetitive CFAE (interval confidence level ≥120) sites in patients with persistent atrial fibrillation (AF) using a basket catheter to collect data simultaneously from multiple atrial sites; (2) To assess the utility of intra-procedural flecainide in identifying critical AF sites.

Methods and Results

Twelve patients were studied. The basket catheter was deployed sequentially in both atria and 1-minute recordings collected from one/two positions in each chamber. Separate recordings were collected from the coronary sinus and pulmonary veins. Sites that exhibited high frequency and/or fractionated activity throughout the recordings were identified. All patients underwent pulmonary vein isolation and the eleven who remained in AF received flecainide. Further recordings from both atria were collected. High frequency and highly repetitive CFAE sites were ablated.

High frequency sites were found in 4/12 patients: 32 right atrium (RA) and 31 left atrium (LA). Highly repetitive CFAEs were more commonly identified (RA 377; LA 296). Flecainide reduced CFAE burden significantly (85% RA; 79% LA). No patient cardioverted to sinus rhythm during high frequency or CFAE ablation. 5/12 (42%) patients were free of AF at 12-months.

Conclusions

Highly repetitive CFAEs are distributed throughout both atria in persistent AF. High frequency sites (≥8Hz) are less commonly identified. Flecainide does not help identify critical sites. Twelve-month outcome was similar to that reported after other ablation techniques.

6.2 Introduction

High-frequency microreentrant sources perpetuating AF were initially described by Mandapati et al. (2000) using high-resolution optical mapping in a sheep model. These findings were corroborated in humans by Sanders et al. (2005) using spectral analysis and frequency mapping. They observed that ablation of high frequency sites in both atria and the coronary sinus terminated AF in 17/19 patients with paroxysmal AF but did not restore sinus rhythm in any patient with persistent AF. More recent studies on the ablation of high frequency sites have produced conflicting results. Complex fractionated atrial electrogram (CFAE) ablation was first proposed by Nademanee et al. (2004). In their study of 121 patients (64 persistent AF), 110 (91%) patients were free from AF at 12 months following bi-atrial CFAE ablation. However, other groups have been unable to replicate their findings (Estner et al., 2008b; Oral et al., 2009). In the aforementioned studies, high frequency and CFAE sites were identified using automated algorithms based on short (3 to 7 second) electrogram recordings collected sequentially using a roving catheter. The validity of the resulting DF and CFAE maps is based on the assumption that these sites remain stable over time. However, Habel et al. (2010) reported significant temporal and spatial variability of both high frequency and CFAE sites with sequential mapping failing to detect 93% and 36% of the high frequency and CFAE sites identified from simultaneous multielectrode recordings in the left atrium.

Singh et al. (2010) investigated the use of ibutilide in guiding CFAE ablation and identifying critical AF sites in 11 patients with persistent AF. They reported a significant reduction in left atrial CFAE burden after ibutilide administration and that AF termination was achieved in 10/11 (91%) patients following pulmonary vein isolation and ablation of residual CFAEs after ibutilide. To our knowledge, the utility of flecainide in this context has not been studied.

The **aims** of this study were: (1) To investigate the distribution and effectiveness of ablating stable high frequency (≥8Hz) and highly repetitive CFAE (interval confidence level ≥120) sites in patients with persistent AF identified using a 64-electrode contact mapping catheter (Constellation®, Boston Scientific Inc.) to record simultaneous electrograms from multiple sites in the left and right atria; (2) To assess the utility of administering intravenous flecainide during the procedure to reduce CFAE burden and identify sites critical to the maintenance of AF.

6.3 Methods

6.3.1 Patient Recruitment and Ethical Approval

This study was based on the same cohort of 12 patients described in Chapter 5 (Sections 5.3.1 and 5.3.2).

6.3.2 Electrophysiological Study

Once femoral venous access had been achieved, a deflectable decapolar catheter was positioned in the coronary sinus (CS) under fluoroscopic guidance. The distal poles of the CS catheter were positioned on the lateral aspect of the mitral valve ring, with proximal bipole $CS_{9\text{-}10}$ just inside the ostium of the coronary sinus. A single transseptal puncture was used to gain access to the left atrium and heparin anticoagulation was administered to maintain an activated clotting time >300 seconds. Electroanatomical maps of both atria were created using a 3.5mm irrigated-tip bipolar ablation catheter (2mm inter-electrode spacing) and the EnSite Velocity™ cardiac mapping system (St. Jude Medical). The Constellation® catheter was then deployed sequentially in the right and left atrium using a fixed curve (Heartspan™, Boston Scientific) and steerable sheath (Agilis™, St. Jude Medical) respectively. One-minute intracardiac recordings were collected from one or two catheter positions in each atrium to ensure satisfactory coverage of the chamber. If satisfactory contact with all areas of the atria could not be achieved using Constellation®, a bipolar ablation catheter was used to collect sequential 1-minute recordings from these inadequately covered sites. Intracardiac recordings were also collected simultaneously from the CS (steerable decapolar catheter) and sequentially from each of the pulmonary vein ostia (ablation catheter).

6.3.3 Intracardiac Data Analysis

Intracardiac data was collected using the same filter settings and electrode format described in Chapter 5 (Section 5.3.4).

Dominant Frequency

Power spectral density (PSD) of consecutive 10-second sections of bipolar electrograms was estimated by periodogram with rectangular window and frequency resolution of 0.1Hz. For each section, dominant frequency (DF) was identified as the intracardiac frequency with the highest power in the range 3-10Hz as previously defined (Raine et al., 2004 and 2005). Sites with mean DF ≥8Hz from the one-minute recording were identified and tagged on the electroanatomical map. The DF threshold of ≥8Hz was chosen in line with previous studies (Verma et al., 2011; Kumagai et al., 2013)

Complex Fractionated Atrial Electrograms

We developed an automated CFAE detection algorithm to identify highly repetitive CFAE sites, which exhibited fractionated activity throughout the 1-minute recordings. This was based on the CFAE detection software embedded in the CARTO®3 mapping system (Biosense Webster) (Scherr et al., 2007) and is illustrated in Figure 6.1. Firstly, bipolar electrogram peaks greater than or equal to ±0.05mV (green horizontal lines) are identified. The peaks that fall within the voltage window of 0.05 to 0.15mV are tagged with black crosses, and those exceeding ±0.15mV (red horizontal lines) are tagged with red crosses. Secondly, intervals between two successive peaks falling within the voltage window (0.05-0.15mV) were determined. Thirdly, the number of intervals between 70 and 120ms during the 1-minute recording was determined as the interval confidence level (ICL). Scherr et al. (2007) reported that an ICL≥5 (in a 2.5-second recording) was consistent with a highly repetitive CFAE. As the focus of this study was on sites that exhibited fractionated activity throughout the 1-minute recording, we extrapolated their ICL recommendation and required an ICL≥120 (per 1-minute recording) to reflect a highly repetitive CFAE. The highly repetitive CFAE sites identified were manually verified by analysis of the bipolar electrograms and tagged on the electroanatomical map.

6.3.4 Catheter Ablation

All patients underwent PVI by wide-area circumferential ablation, which was confirmed using standard pacing manoeuvres. After PVI, 11/12 patients remained in AF and received intravenous flecainide (2mg/kg up to maximum dose of 150mg) as per study protocol (Figure 6.2). The Constellation® catheter was then redeployed and additional 1-minute recordings were collected from the original catheter positions in each atria. Sites with mean DF ≥8Hz and/or highly repetitive CFAE activity after flecainide were tagged on the electroanatomical map and targeted with ablation. If sinus rhythm was not restored, ablation was performed at the high frequency and highly repetitive CFAE sites identified prior to flecainide administration. The procedure was curtailed when all identified high frequency and highly repetitive CFAE sites had been ablated. Patients who did not revert to sinus rhythm during ablation underwent electrical cardioversion at the end of the procedure.

6.3.5 Clinical Outcome

Clinical outcome was assessed 12 months after ablation by symptom review, 12-lead ECG, and 72-hour Holter recordings. AF recurrence was defined as the presence of arrhythmia symptoms with documented AF on a 12-lead ECG and/or AF episodes >30 seconds on Holter monitoring. In line with other studies, AF recurrences in the 3-month blanking period after ablation were excluded from the analysis.

6.4 Results

Characteristics of the 12 consecutive patients recruited to the study are shown in Table 5.2. Ten of the 12 patients had longstanding persistent AF (AF episode duration ≥1 year (Camm et al., 2010)). 60mm Constellation® catheters (5mm inter-electrode spacing) were used in eight patients and 48mm catheters (4mm inter-electrode spacing) in the remaining four patients. All patients required two Constellation® catheter positions in the left atrium and 7/12 patients required two catheter positions in the right atrium. The number of Constellation® catheter bipoles with electrograms suitable for analysis (i.e. containing atrial activity without significant artefact or noise) was 2034/2688 (76%) – right atrium (RA) 1179/1344 (88%) vs. left atrium (LA) 855/1344 (64%). Mean procedure duration was 219 ± 31 minutes.

6.4.1 High Frequency Site Distribution

High frequency sites (DF≥8Hz) were identified in 4/12 patients (33%) with a similar number in both atria: RA (n=32) and LA (n=31) (Figure 6.3). In the right atrium, the majority of high frequency sites were located in the crista terminalis (n=13) and right atrial appendage (n=10). In the left atrium, high frequency sites were more evenly distributed between the left sided pulmonary veins, left atrial appendage, roof and posterior wall.

6.4.2 Highly Repetitive CFAE Distribution

Highly repetitive CFAEs (ICL≥120) were observed in all 12 patients and were more commonly found in the right (n=377) than the left atrium (n=296) (Figure 6.4). The 16 CFAEs in the left upper pulmonary vein and 28 in the left lower pulmonary vein were successfully abolished with PVI leaving 252 CFAEs in the left atrium prior to flecainide. In the right atrium, the commonest locations for highly repetitive CFAEs were the anterior wall (n=75), superior vena cava (n=62) and crista terminalis (n=61). In the left atrium, the majority of highly repetitive CFAEs were located in the posterior wall (n=76), anterior wall (n=46) and roof (n=42).

6.4.3 Utility of Flecainide in identifying critical AF sites

Intravenous flecainide resulted in a general reduction in atrial frequencies to between 3 and 4 Hz; therefore, no high frequency (DF≥8Hz) sites were observed in either atrium after flecainide administration. In addition, there was a significant reduction in the number of highly repetitive CFAEs after flecainide: RA 58 (85% reduction) and LA 54 (79% reduction) (Figure 6.5). In the right atrium, the commonest locations for highly repetitive CFAEs after flecainide were the superior vena cava (n=18) and right atrial appendage (n=15). In the left atrium, highly repetitive CFAEs were most commonly found in the left atrial floor (n=16) and appendage (n=11). None of the patients cardioverted to sinus rhythm during high frequency and/or highly repetitive CFAE site ablation.

6.4.4 Twelve Month Outcome

Of the 12 patients studied, three (25%) maintained sinus rhythm at 12-month follow-up without further intervention. Two patients developed atypical left atrial flutter successfully treated by a second ablation procedure. The remaining seven patients (58%) experienced recurrent AF and six underwent a second ablation procedure. All six patients had evidence of pulmonary vein reconnection and had their pulmonary veins re-isolated. Additional linear lesions were constructed to consolidate the previous high frequency ± CFAE ablation. The remaining patient had minimal symptoms despite AF recurrence and opted for a rate control strategy.

6.5 Discussion

The main findings of this study are: (1) Multipolar contact mapping guided ablation of temporally stable high frequency (≥8Hz) and CFAE sites does not improve 12-month outcomes in patients with persistent AF; (2) Flecainide significantly reduces CFAE burden but does not identify sites critical to the maintenance of AF; (3) Stable high frequency and highly repetitive CFAE sites are distributed throughout both atria in patients with persistent AF with highly repetitive CFAEs more commonly identified; (4) The primary limitation of the Constellation® catheter is its inability to provide comprehensive coverage of particularly the left atrium from one position.

6.5.1 High Frequency and Highly Repetitive CFAE Site Distribution

In this study, high frequency sites in the right atrium were most commonly identified in the crista terminalis and right atrial appendage. Okumura et al. (2012) identified high frequency and CFAE sites in the right atrium in 58% and 68% of patients respectively who remained in AF after PVI, but did not report their distribution within the right

atrium. In agreement with previous studies (Okumura et al., 2012; Nakahara et al., 2013), high frequency sites in the left atrium were more evenly distributed between the left sided pulmonary veins, left atrial appendage, roof and posterior wall. Interestingly, more highly repetitive CFAEs were found in the right than the left atrium in this study, which is in contrast to Solheim et al. (2010) who, aside from the right atrial septum, observed significantly fewer CFAEs in the right compared to the left atrium. The differing results may be explained by differences in data collection and CFAE analysis. Solheim et al. (2010) used a 3.5mm irrigated ablation catheter to record sequential 8-second electrograms from multiple atrial sites analysed using the CFAE mapping software in the EnSite™ NavX™ system (St. Jude Medical); whereas, we used Constellation® to collect simultaneous multipoint recordings from one or two positions in each atria and identified highly repetitive CFAEs which exhibited fractionated activity throughout the one-minute recordings using customised software. In our study, highly repetitive right atrial CFAEs were most commonly found in the anterior wall, superior vena cava and crista terminalis; however, CFAEs were identified in all sections of the right atrium (Figure 6.4). Chen et al. (2013) also observed CFAEs throughout the right atrium but reported that the commonest sites for conversion to atrial tachycardia or sinus rhythm were the crista terminalis, followed by the right atrial appendage and septum. In agreement with previous studies (Nakahara et al., 2013; Solheim et al., 2010), the majority of highly repetitive left atrial CFAEs were located in the posterior wall, anterior wall and roof in this study.

6.5.2 Utility of Flecainide in identifying critical AF sites

The number of highly repetitive CFAEs reduced significantly after flecainide administration, although, none of the patients cardioverted to sinus rhythm during ablation of these sites. Flecainide does not appear to be useful therefore in identifying sites critical to the maintenance of AF. This is in contrast to the aforementioned study of Singh et al. (2010) who reported AF termination in 91% of patients after PVI and ablation of CFAEs remaining after ibutilide. The differing results could be explained by the different pharmacological mechanism of action (Class 3 (ibutilide) vs. Class 1C (flecainide)) and the low dose of ibutilide (0.25mg) used compared to our higher relative dose of flecainide (2mg/kg).

6.5.3 Effectiveness of High-Frequency and CFAE Site Ablation

Of the 12 patients studied, five (42%) were free of AF at 12-month follow up. This included two patients who developed atypical left atrial flutter successfully treated by a second ablation procedure. Our results are comparable to the 47% mean success rate for substrate ablation techniques reported by Brooks et al. (2010) in their systematic review. In agreement with Kumagai et al. (2013), none of the patients cardioverted to sinus rhythm during high frequency or CFAE ablation, despite focusing on sites that exhibited high frequency and/or fractionated activity throughout the one-minute recordings. In their study which included 27 patients with persistent AF, only 1 patient cardioverted to sinus rhythm during a stepwise ablation protocol including PVI, hierarchical high frequency site (DF>8Hz) and continuous CFAE (fractionated interval <50ms) ablation and 13/27 (48%) patients were free of AF without antiarrhythmic drugs at 12-month follow up. Our results support the view that CFAE sites are not critical to the maintenance of AF and are more likely explained by wavefront collision and breakout in areas of tissue heterogeneity or at the boundaries of fixed high-frequency rotors (Oral et al., 2008; Lin et al., 2010).

Regarding high frequency site ablation, the use of a DF threshold of 8Hz significantly reduces the number of high frequency sites identified as sites with DF≥8Hz were only found in 4/12 (33%) patients in this study (Chapter 5). Interestingly, the two other studies in which DF sites ≥8Hz were also targeted with ablation reported low AF termination rates (Verma et al., 2011; Kumagai et al., 2013); whereas, Atienza et al. (2009) reported that ablation of sites with the highest frequency (DF≥20% higher than surrounding points) in individual patients was associated with a higher likelihood of maintaining sinus rhythm at 12-month follow up.

6.5.4 Inter-Atrial Frequency Gradients and their Relationship to Ablation Outcome

Of the five patients who maintained sinus rhythm 12-months after ablation, three had a ‘left-to-right’ atrial frequency gradient, one had a ‘right-to-left’ atrial frequency gradient and the remaining patient had no atrial frequency gradient (Chapter 5). All patients with inter-atrial frequency gradients received CFAE ± high frequency site ablation in the dominant atrium. On first inspection, these results appear disappointing with respect to the role of high frequency sites in the right atrium maintaining AF in patients with a right-to-left atrial frequency gradient. However, in the remaining two patients with right-to-left atrial frequency gradients, one had a right atrial DF_{MAX} <8Hz which was therefore not ablated and the other had a right atrial DF_{MAX} ≥8Hz adjacent to the sinus node which was not ablated due to the risk of significant complication.

Of the four patients who underwent ablation of high frequency sites (DF ≥8Hz), three maintained sinus rhythm 12-months after ablation and the remaining patient had high frequency sites throughout both atria with no clear DF_{MAX} responsible for maintaining the arrhythmia. These results support the need for further studies investigating the role of high frequency site ablation targeting DF_{MAX} of the individual patient rather than an arbitrary cutoff of ≥8Hz.

6.6 Limitations

Firstly, the findings are based on only the 12 patients studied. Secondly, only one size of Constellation® catheter was used per patient, which meant that contact could not be optimised to the individual dimensions of either atrium in some cases. Thirdly, data was collected sequentially from one or two catheter positions in each atrium, which meant a compromise between maximising the number of atrial sites recorded and the degree in which all electrograms were recorded simultaneously. However, we do not believe that this significantly affected our findings. The primary limitation in this methodology is the inability of the Constellation® catheter to provide comprehensive coverage of particularly the left atrium from one position despite deployment via a flexible sheath. The left atrial floor and septum were the most difficult areas to achieve contact with using Constellation® and bipolar electrograms had to be collected from these sites using the ablation catheter in several patients. This highlights the difficulty in developing a multipolar mapping catheter with adjustable dimensions and manoeuvrability to allow tissue contact and coverage from one position. Finally, due to a lack of parallel processing capability and consequent real-time analysis, the high frequency ablation strategy targeted sites with DF ≥8Hz rather than the DF_{MAX} of the individual patient. This is likely to have underestimated the effectiveness of high frequency site ablation and warrants further study as detailed above.

6.7 Conclusions

Highly repetitive CFAEs are distributed throughout both atria in patients with persistent AF. High frequency (≥8Hz) sites are also found in both atria but are less frequently observed. Flecainide administration significantly reduces CFAE burden but does not help identify sites critical to the maintenance of AF. None of the patients cardioverted to sinus rhythm during high frequency or CFAE ablation and 12-month outcome was comparable to other substrate ablation techniques.

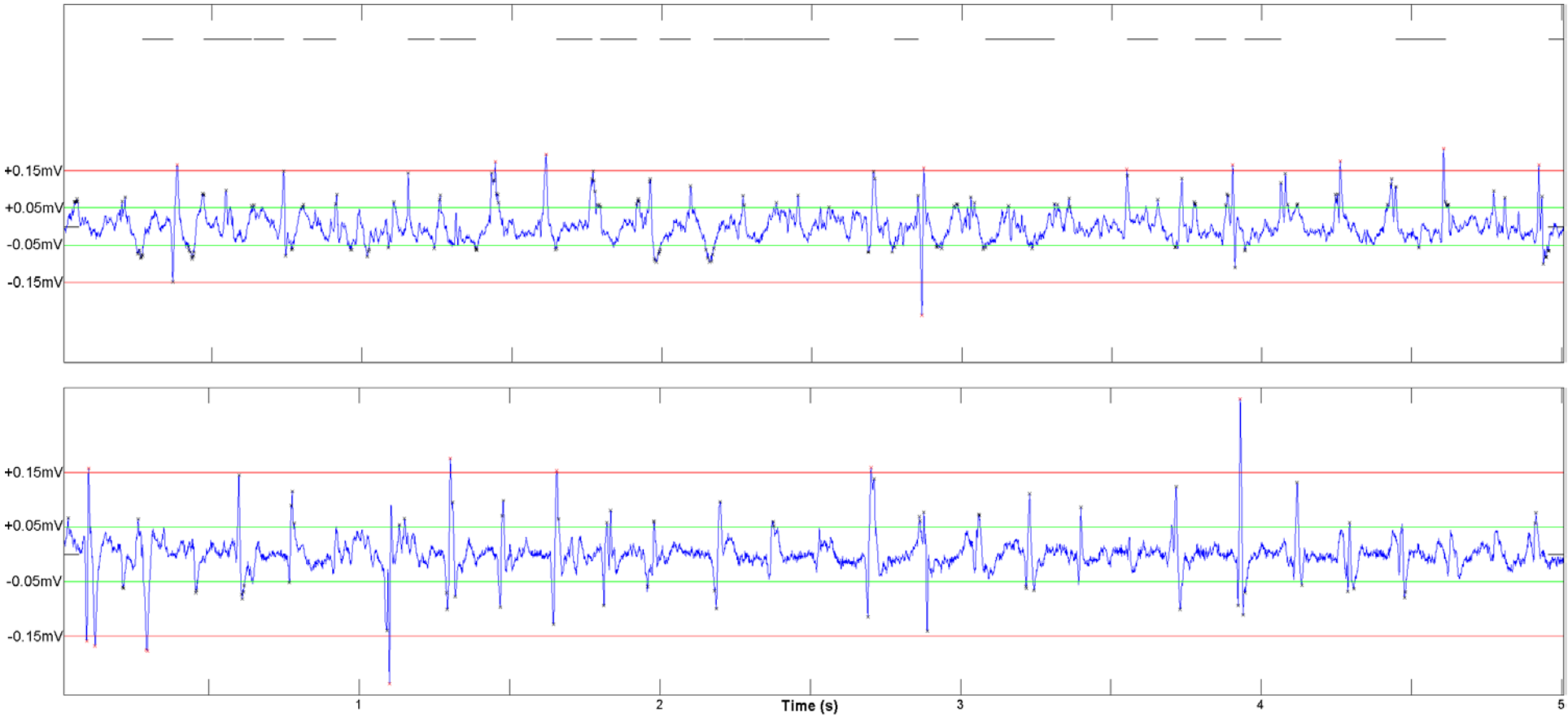


Figure 6.1: CFAE Detection Algorithm. Each panel illustrates a 5-second section of atrial electrogram recorded using the Constellation® catheter. The top panel contains complex fractionated activity throughout the recording as illustrated by the solid black lines at the top of the panel. The bottom panel does not contain any complex fractionated activity and therefore, there are no solid black lines above the recording. See text for highly repetitive CFAE detection criteria.

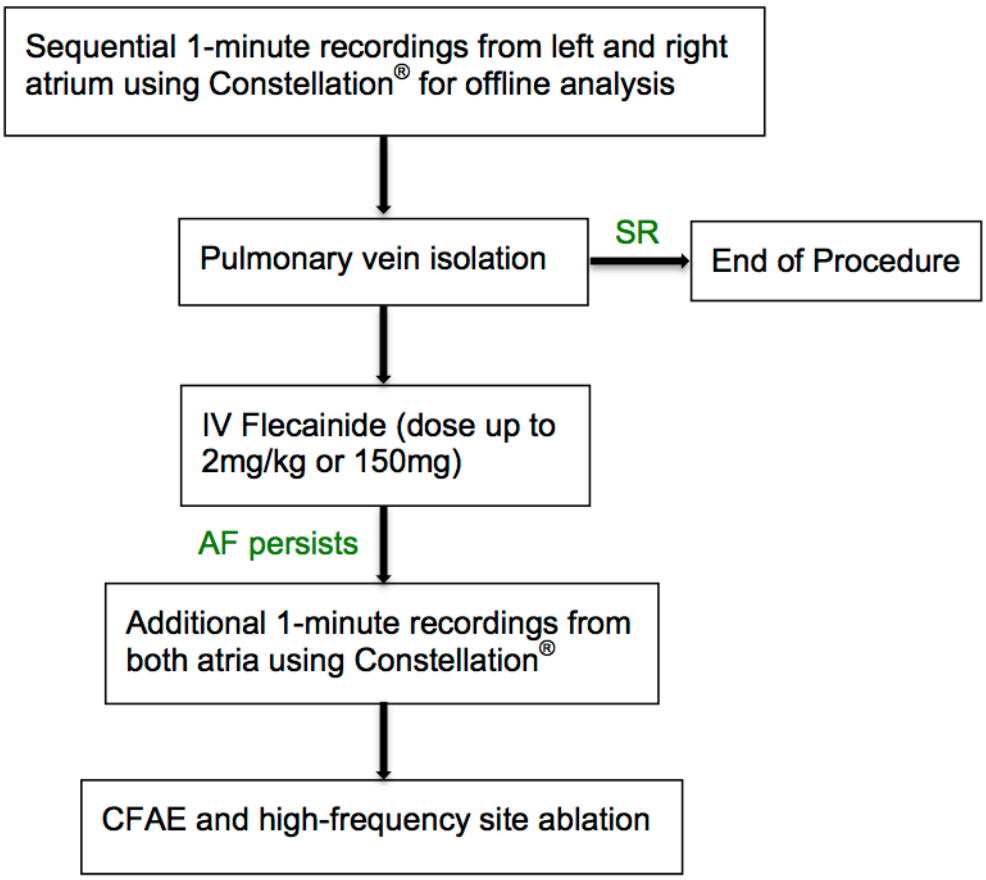


Figure 6.2: Study Protocol. SR = sinus rhythm.

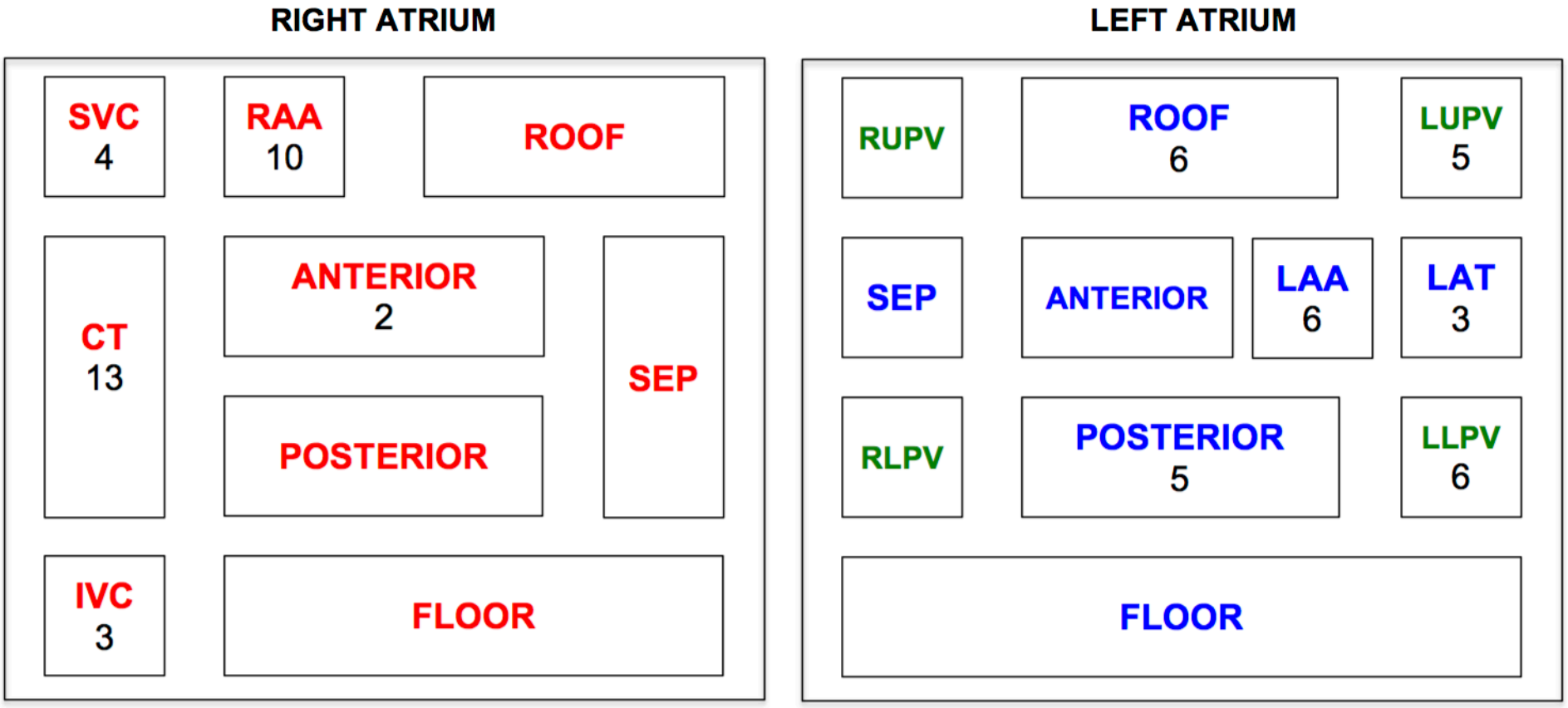


Figure 6.3: Distribution of High Frequency Sites (DF≥8Hz). The number of high frequency sites identified in each atrial location is shown. CT = crista terminalis; IVC = inferior vena cava; LAA = left atrial appendage; LAT = lateral left atrium; LLPV = left lower pulmonary vein; LUPV = left upper pulmonary vein; RAA = right atrial appendage; RLPV = right lower pulmonary vein; RUPV = right upper pulmonary vein; SEP = septum; SVC = superior vena cava.

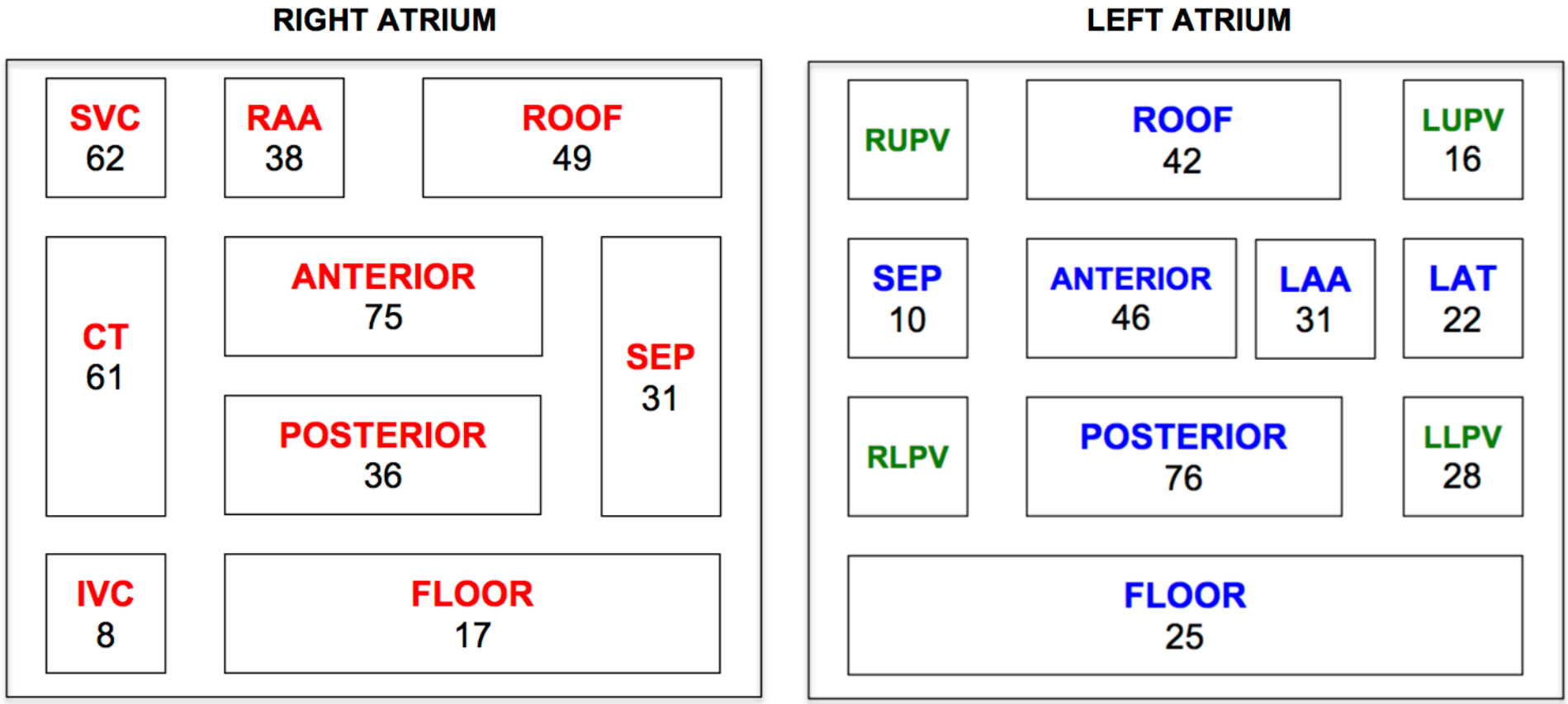


Figure 6.4: Distribution of Highly Repetitive CFAEs (ICL≥120). The number of highly repetitive CFAEs identified in each atrial location is shown. Abbreviations as for Figure 6.3.

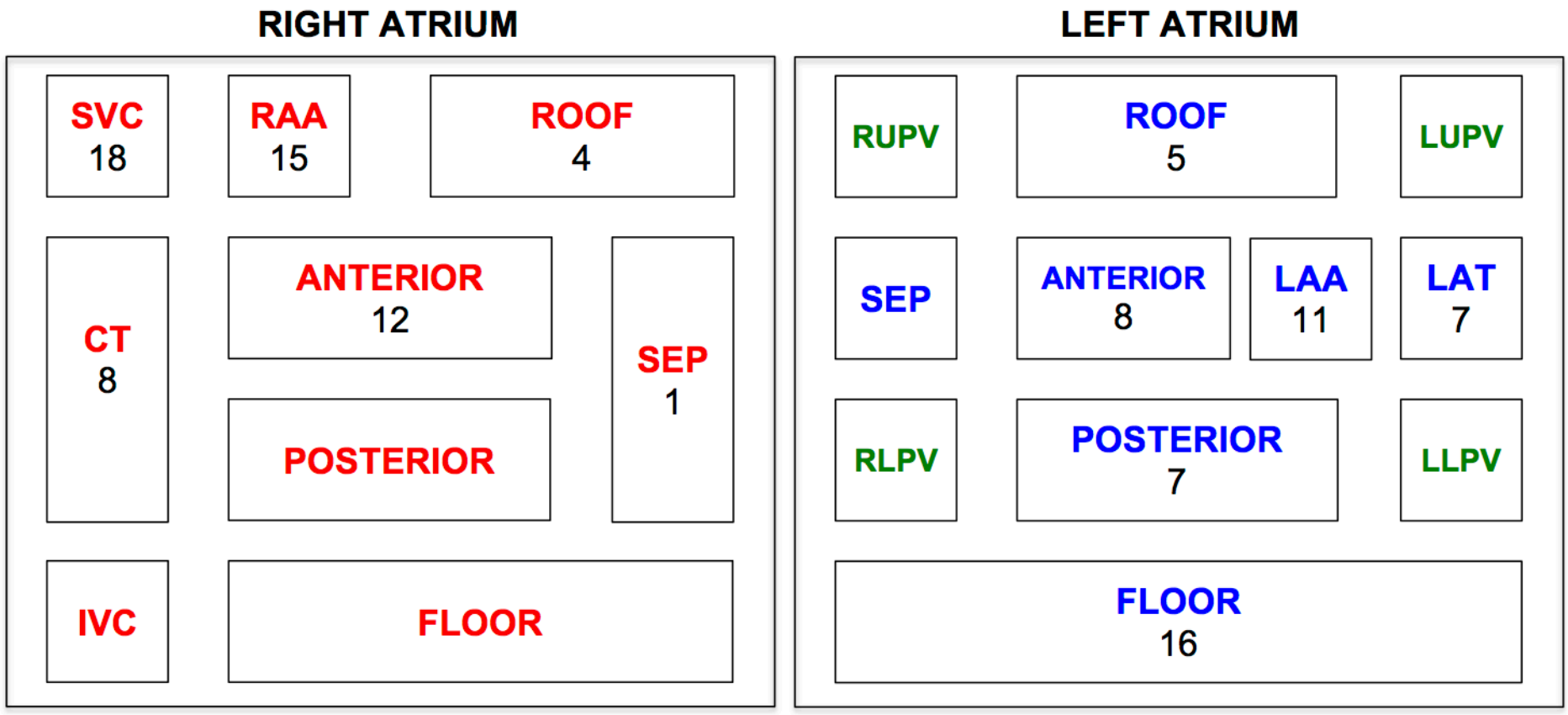


Figure 6.5: Distribution of Highly Repetitive CFAEs after Flecainide. The number of highly repetitive CFAEs identified in each atrial location after flecainide administration is shown. Abbreviations as for Figure 6.3.

Chapter 7. Final Discussion

The unifying aim of this thesis was to investigate whether we could predict and improve clinical outcome following ablation in patients with AF using surface AF waveform analysis and multipolar contact mapping respectively. The results from Chapter 3 show that we can accurately predict acute and more importantly 12-month outcome following ablation using a combination of clinical and surface AF waveform parameters. Paroxysmal AF, male gender and fibrillatory wave amplitude in posterior ECG lead V9 were independent predictors of sinus rhythm maintenance 12-months after ablation. Fibrillatory wave amplitude in lead V9 has not been previously studied and our results highlight the benefit of analysing posterior ECG leads in this context. The utility of surface AF waveform analysis in predicting 12-month outcome following ablation is particularly relevant in the selection of patients for ablation of persistent AF as it could be used to guide the decision regarding rhythm vs. rate control at the initial outpatient consultation. Patients with a low likelihood of maintaining sinus rhythm longer term could be recommended a rate control strategy and so avoid the need for multiple, ultimately unsuccessful, ablation procedures with their associated risks. Future research should focus on prospectively testing the multivariate risk scores derived from this study by comparing predicted versus observed outcome 12 months after ablation in a new cohort of patients with persistent AF. An important precursor to this is to test the efficacy of extracting AF waveform parameters from Holter ECG recordings (including posterior leads) prior to the initial outpatient review.

Chapter 4 highlights the importance of maintaining sinus rhythm following ablation to improve quality of life and AF symptoms. Similar improvements in quality of life were observed in patients with paroxysmal and persistent AF, which is an important observation in the current climate of NHS Commissioning as it supports the benefits of ablation for patients with persistent AF. Further research in this area should focus on assessing quality of life and AF symptoms 12-months after ablation and compare rhythm vs. rate control strategies in patients with persistent AF using AF-specific quality of life scales.

Chapters 5 and 6 examine the role of multipolar contact mapping in identifying inter-atrial frequency gradients and facilitating high frequency and highly repetitive CFAE ablation in patients with persistent AF. A quarter of the patients studied had right-to-left atrial frequency gradients, which implies that their arrhythmia is maintained by high frequency sources in the right atrium.

The presence of right-to-left atrial frequency gradients and the stability of high frequency sources over a one-minute period have not been previously reported. Highly repetitive CFAEs were distributed throughout both atria in all of the patients studied. High frequency (DF ≥8Hz) sites were also found in both atria but were only identified in a third of patients. None of the patients cardioverted to sinus rhythm during high frequency or CFAE ablation and 12-month outcome was comparable to other substrate ablation techniques in this patient cohort (42% success after a single AF ablation procedure).

The results from Chapters 5 and 6 are interesting for a number of reasons. Firstly, they add support to the growing body of evidence that CFAE sites are not critical to the maintenance of AF and are more likely explained by wavefront collision and breakout in areas of tissue heterogeneity or at the boundaries of fixed high-frequency rotors. Secondly, of the four patients who underwent ablation of high frequency sites (DF ≥8Hz), three maintained sinus rhythm 12-months after ablation and the remaining patient had high frequency sites throughout both atria with no clear site responsible for maintaining the arrhythmia. These results support the role of high frequency site ablation and the need for further studies targeting DF_{MAX} in the individual patient rather than an arbitrary cutoff of ≥8Hz. Thirdly, this study highlighted an important technical limitation of the Constellation® catheter which is its inability to provide comprehensive coverage of particularly the left atrium from one position. This prevents collection of truly simultaneous recordings from both atria, which, in my opinion, is the crucial next step in developing our understanding of the pathophysiology of AF and refining the ablation strategy in patients with persistent AF. Development of a multipolar contact mapping catheter with adjustable dimensions and improved manoeuvrability to enable comprehensive coverage of each atrium from one position is a key component needed for future AF research.

I would like to close by discussing my thoughts with respect to AF ablation. When I started this MD research project, I was a firm believer of pulmonary vein isolation (PVI) alone for patients with paroxysmal AF and PVI plus left atrial substrate ablation in patients with persistent AF as a first ablation procedure. However, the results of Chapters 3 and 6 together with the recently published STAR AF II trial (Verma et al., 2015), which showed no benefit of adding CFAE and linear left atrial ablation to PVI as a first ablation procedure in patients with persistent AF, have changed my opinion.

I now advocate PVI alone as a first procedure for all patients with AF (irrespective of AF type) with the Arctic Front Advance® cryoballoon being my ablation technology of choice on account of its high rate of durable pulmonary vein isolation and lower risk of complications. I would then consider linear left atrial ablation in addition to re-isolation of the pulmonary veins (when required) for patients with recurrent AF. This is based on the meta analysis by Wynn et al. (2014) who reported that patients with persistent AF who underwent PVI and limited linear left atrial ablation had a significantly lower incidence of AF recurrence compared to other ablation strategies. In this context, the efficacy of high frequency site ablation focused on DF_{MAX} in the individual patient warrants further study as previously discussed. I would like to conclude by stressing the importance of tackling the risk factors for AF including obesity, hypertension, diabetes mellitus, hyperlipidaemia and obstructive sleep apnoea to further reduce AF burden and improve the likelihood of maintaining sinus rhythm after ablation in line with the results of the ARREST-AF study (Pathak et al., 2014).

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Appendix 1

Surface Atrial Frequency Analysis in Patients with Atrial Fibrillation: A Tool For Evaluating the Effects of Intervention

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Atrial Fibrillation Frequency Analysis. ***Introduction:*** **The aims of this study were to evaluate (1) principal component analysis as a technique for extracting the atrial signal waveform from the standard 12-lead ECG and (2) its ability to distinguish changes in atrial fibrillation (AF) frequency parameters over time and in response to pharmacologic manipulation using drugs with different effects on atrial electrophysiology.**

Methods and Results: **Twenty patients with persistent AF were studied. Continuous 12-lead Holter ECGs were recorded for 60 minutes, first, in the drug-free state. Mean and variability of atrial waveform frequency were measured using an automated computer technique. This extracted the atrial signal by principal component analysis and identified the main frequency component using Fourier analysis. Patients were then allotted sequentially to receive 1 of 4 drugs intravenously (amiodarone, flecainide, sotalol, or metoprolol), and changes induced in mean and variability of atrial waveform frequency measured. Mean and variability of atrial waveform frequency did not differ within patients between the two 30-minute sections of the drug-free state. As hypothesized, significant changes in mean and variability of atrial waveform frequency were detected after manipulation with amiodarone (mean: 5.77 vs 4.86 Hz; variability: 0.55 vs 0.31 Hz), flecainide (mean: 5.33 vs 4.72 Hz; variability: 0.71 vs 0.31 Hz), and sotalol (mean: 5.94 vs 4.90 Hz; variability: 0.73 vs 0.40 Hz) but not with metoprolol (mean: 5.41 vs 5.17 Hz; variability: 0.81 vs 0.82 Hz).**

Conclusion: **A technique for continuously analyzing atrial frequency characteristics of AF from the surface ECG has been developed and validated.** *(J Cardiovasc Electrophysiol, Vol. 15, pp. 1021-1026, September 2004)*

principal component analysis, frequency analysis, atrial fibrillation, electrocardiography

Introduction

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice, and its incidence increases with age.[1] It is responsible for considerable morbidity and medical costs, is the major determinant of stroke in the elderly, and may increase mortality, particularly in patients with congestive heart failure.[2-4]

Traditionally, AF has been diagnosed clinically based on an "irregularly irregular" pulse and thus in terms of its ventricular consequences rather than in its own right. On ECG, AF is confirmed by the replacement of consistent P waves with rapid fibrillatory waves of varying frequency, amplitude, and morphology. Even from surface ECG recordings, however, varying degrees of atrial electrical disorganization are apparent during AF in different patients and at different times within the same patient. To date, this information has not been put to clinical use, yet it is likely that parameters of atrial waveform frequency and amplitude contain information relevant to the clinical management of these patients.

A technique of QRST cancellation has been applied to the analysis of atrial signal parameters, and the effects of various drugs on AF frequency have been reported.[5-9] In pilot studies, we have compared a new algorithm for extracting the atrial electrical waveform using principal component analysis (PCA) with a QRST cancellation algorithm and have shown that for estimating the AF frequency these agree.[10,11] However, these comparisons are limited because QRST subtraction derives a lead specific atrial waveform, whereas PCA derives a global atrial waveform with contributions from all leads. Previous applications of PCA to ECG analysis include the separation of maternal and fetal ECG.[12]

The aims of the present study were to evaluate PCA as a technique for extracting the atrial signal waveform from the standard 12-lead ECG and its ability to distinguish changes in AF frequency parameters over time and in response to pharmacologic manipulation using drugs with different effects on atrial electrophysiology.

Methods

Patients and Data Collection

Patients with persistent AF of any etiology who were scheduled for elective day-case direct-current cardioversion under general anesthesia at the Freeman Hospital or the Royal Victoria Infirmary, Newcastle-upon-Tyne, were approached and invited to participate in the study.

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Patients were excluded if they had a history of left ventricular failure or an ejection fraction <35%, asthma, hypotension (<100 mmHg systolic), significant renal impairment (serum creatinine more than twice upper limit of normal), hypokalemia (<3.5 mmol/L), uncontrolled hyperthyroidism, or previous adverse reaction or allergy to any of the study drugs. In addition, patients were excluded if they were on maintenance amiodarone, flecainide, or sotalol therapy prior to admission. However, to maintain ventricular rate control, patients continued other rate control medications such as digoxin, calcium channel blockers, or beta-blockers.

On admission, patients suitable for enrollment were informed of the study, provided with an information summary document to supplement a comprehensive verbal explanation, and invited to consent for study inclusion. Individuals who gave informed consent were fitted with a simultaneous 12-lead ECG Holter recorder (H-12™ digital recorder, Mortara®, Milwaukee, WI, USA) capable of storing up to 24 hours of high-quality ECG data.

Ethical Approval

This study complies with the Declaration of Helsinki, and ethical approval for the study was granted by the Newcastle and North Tyneside Joint Ethics Committee. Informed consent was obtained from all patients.

Data Recordings

Sixty minutes of continuous 12-lead ECG data were first recorded at baseline with the patients on their regular ventricular rate control medications. Patients were then sequentially allotted to receive a single intravenous loading dose of 1 of the 4 drugs being used in the study: amiodarone (7 mg/kg), flecainide (1.5 mg/kg), sotalol 1.5 (mg/kg), or metoprolol (5–15 mg). At the time of drug administration, patients were monitored continuously with ECG, heart rate, and blood pressure recordings. Five patients were recruited for each drug treatment in a prospective, unblinded study.

Amiodarone, flecainide, and sotalol are known to slow ventricular rate and reduce the frequency and variability of the atrial waveform.[13-16] Metoprolol slows ventricular rate but has no effect on atrial frequency.[17] Each drug was chosen based on its different effects on atrial electrophysiology to determine whether the analysis technique would be capable of detecting the changes anticipated.

Holter recordings were continued after drug administration until direct-current cardioversion was performed on the afternoon of admission in all patients.

Data Storage and Handling

Simultaneous 12-lead Holter ECG data were stored directly onto a 40-MB flash memory card at a digital sampling rate of 180 Hz per channel. This sampling frequency is suitable for clinical evaluation given that AF frequencies generally are below 10 Hz.[18]

Software to convert from the manufacturer's proprietary data format for off-line computer storage was provided by Mortara (H-Scribe™ 12-lead Holter system, Mortara®).

Waveform analysis was performed by computer using principal component and fast Fourier transform algorithms.

Atrial Frequency Analysis

PCA is a multivariable technique that is commonly used to reduce the dimensionality of data based on the degree of correlation between variables.[19] Conversely, the transformed variables (principal components) are uncorrelated, and this characteristic can be used to identify and separate different sources in the data. Mathematically, it represents a linear transformation of the data to a new set of data variables (principal components), which are uncorrelated. The transformation is described by Equation 1:

$$s_i = \sum_{j=1}^{12} A_{i,j} l\,(j)\,(i = 1:12) \qquad (1)$$

where A is a matrix of transform coefficients derived from the eigenvalues of the covariance matrix of the ECG leads, $l(j)$ represents the j^{th} lead from the 12-lead ECG, and s_i are the principal components.

In the context of atrial waveform extraction from the 12-lead ECG, PCA separates atrial and ventricular features into different principal components. The resulting atrial signal represents global atrial activity as seen on the body surface since intracardiac atrial electrical activity contributes to each surface ECG lead. Figure 1 illustrates the results of applying the technique to a section of 12-lead ECG from a patient in AF.

To investigate the time course of atrial waveform frequency during AF (AF frequency), all ECGs were subdivided into 20-second sections, and PCA was applied to each section. The principal component with the largest contribution from lead V_1 was selected automatically, because this is generally the lead with the most dominant atrial activity.

Fourier analysis [periodogram; no windowing; length = 20 s/180 Hz (sample rate)] was used to determine the peak frequency of the extracted atrial signal in each 20-second section. For the purposes of this study, the data were not analyzed for the presence of multiple peaks.

AF frequencies generally lie within a window from 4 to 10 Hz.[18] Therefore, for this study, a sampling window between 3 and 10 Hz was used to allow sufficient scope for any changes in AF frequency to be recorded accurately.

The atrial waveform extraction and frequency analysis was performed off-line using principal component and fast Fourier transform algorithms implemented in MATLAB® R12 (Natick, MA, USA). Two parameters of AF frequency were measured in this study: (1) mean AF frequency and (2) variability derived as the standard deviation of AF frequency.

Intergroup Differences and Intrapatient Variability of AF Frequency

A 60-minute baseline recording was used to determine the chronic AF frequency in these patients. To ensure stability of the frequency measurements, the 60-minute baseline period was divided into two 30-minute periods. Mean and variability of AF frequency were then compared for each 30-minute period by analyzing sequential 20-second sections (i.e., 90 separate sections per 30-minute period). Subsequently, mean and variability of AF frequency calculated in this way from the 60-minute baseline recording were compared with a similar analysis of the hour after drug administration to assess the ability of the analysis technique to detect changes in atrial frequency parameters. In addition, mean and variability of

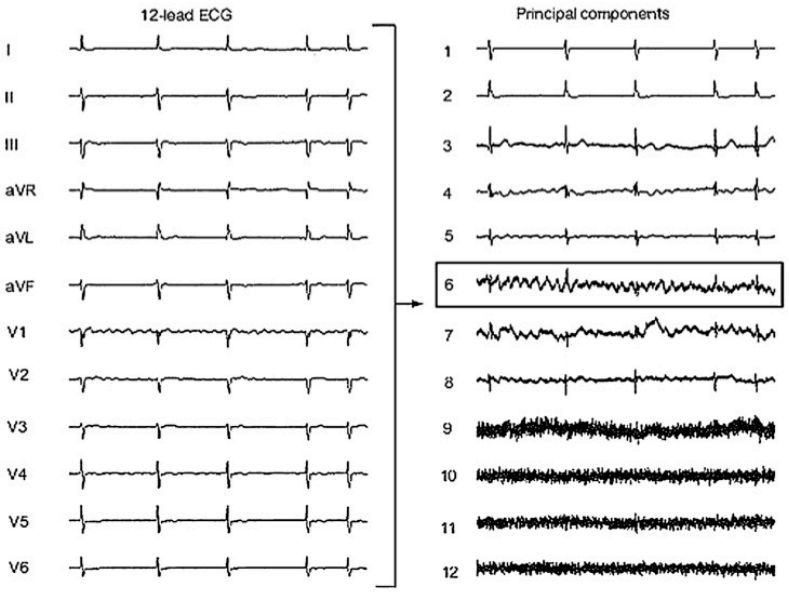

Figure 1. *Left: Twelve-lead ECG of a patient in atrial fibrillation (AF). Right: Twelve principal components (PCs) derived from the 12-lead ECG. Large ventricular components are contained in the upper PCs (1–3). The most dominant AF (atrial) signal in seen in PC6 (black box). The lower PCs (9 to 12) contain noise. Note that the amplitude scale is different for each PC: PC1 has the largest amplitude and PC12 the smallest.*

AF frequency calculated (as described earlier) from the 60-minute baseline recording were compared between patients in the four drug treatment groups to determine intergroup variability.

Statistical Analysis

Statistical analysis was performed using the SPSS 11.0 for Windows package. Continuous variables are expressed as mean values. Differences in mean AF frequency and its variability within patients and after drug administration were compared using the Student's paired *t*-test. Comparability of mean AF frequency and its variability (calculated from the 60-minute baseline recording) between the four drug treatment groups and between patients receiving different rate control medications was assessed using one-way ANOVA.

For all comparisons, statistical significance was assessed at the 0.05 level using two-tailed P values, and 95% confidence intervals (CI) of the difference between the mean values are given where appropriate.

Results

The clinical characteristics (including contributors to AF, left atrial size, and left ventricular function) of the 20 patients (15 men; age 69 ± 11 years) studied are summarized in Table 1. Patients were recruited and studied over a 10-month period.

Although no patients were taking amiodarone, flecainide, or sotalol, the following ventricular rate control medications had been taken by patients on the morning of admission and would have been active throughout the study recordings: digoxin alone (4), beta-blocker alone (6), diltiazem alone (1), digoxin + diltiazem (1), and digoxin + beta-blocker (6). Two patients were not taking rate slowing medications. There were no significant differences in mean AF frequency between patients taking different or no rate control medications calculated from the 60-minute baseline recording (digoxin alone 5.45 Hz, beta-blocker alone 5.20 Hz, diltiazem alone 5.85 Hz, digoxin + diltiazem 5.71 Hz, digoxin + beta-blocker 6.17 Hz, no rate control medication 5.34 Hz; P = 0.124).

Intergroup and Intrapatient Variability of AF Frequency

There were no significant differences in either mean or variability of AF frequency within patients between the first and second 30-minute sections of the 60-minute baseline recording before drug administration (mean 5.61 vs 5.61 Hz; P = 0.986, 95% CI: −0.092 to 0.090; variability: 0.71 vs 0.74 Hz; P = 0.368, 95% CI: −0.089 to 0.035].

Even though patients were taking different ventricular rate control medications, there were no significant differences at baseline in either mean or variability of AF frequency between patients in each of the four drug treatment groups (mean: amiodarone 5.77 Hz, flecainide 5.33 Hz, sotalol 5.94 Hz, metoprolol 5.41 Hz; P = 0.36; variability: amiodarone 0.55 Hz, flecainide 0.71 Hz, sotalol 0.73 Hz, metoprolol 0.81 Hz, P = 0.072).

Effect of Drug Administration on AF Frequency

Amiodarone, flecainide, and sotalol all reduced mean and variability of AF frequency over time from the start of drug administration. Metoprolol did not change either mean or variability of AF frequency. Acute drug treatment did not restore sinus rhythm in any of these patients with chronic AF, and all patients underwent direct-current cardioversion

TABLE 1
Characteristics of the Twenty Patients Studied

Sex/Age (Years)	Drug Administered	Duration of AF History (Months)	Comorbidity	LAD	LVEF
M52	Amiodarone	16	Mitral valve prolapse	Mild–moderate dilation	Good
M72		3 weeks	IHD/AVR	Normal	Good
M69		2	Hypertension	Mild–moderate dilation	Good
F70		9	None	N/A	N/A
M58		32	Thyrotoxicosis	Normal	Good
M85	Flecainide	6	Hypertension	Normal	Good
F84		3	Hypertension	Normal	Good
M80		5	Hypertension	Mild–moderate dilation	Good
M62		4	Hypertension	Normal	Good
M74		9	Thyrotoxicosis	Normal	Good
M49	Sotalol	3	HCM	Normal	Good
F81		9	Hypertension/LV impairment	Mild–moderate dilation	Good
M54		30	Alcohol excess	Normal	Good
M58		8	Hypertension ± alcohol	Mild–moderate dilation	Good
F79		4	Hypertension	Normal	Good
M72	Metoprolol	4	IHD	Mild–moderate dilation	Mildly impaired
F66		8	IHD/hypertension	Normal	Good
M62		6	Hypertension	Normal	Mildly impaired
M68		3	None	Normal	Good
M63		2	Hypertension ± alcohol	Normal	Good

AF = atrial fibrillation; AVR = aortic valve replacement; HCM = hypertrophic cardiomyopathy; IHD = ischemic heart disease; LAD = left atrial transverse dimension [normal ≤45 mm (male), ≤40 mm (female); mild–moderate dilation ≤55 mm (male), ≤50 mm (female)]; LVEF = left ventricular ejection fraction [good >50%, mildly impaired 30%–50%].

as planned. The magnitude of the changes observed within each group are summarized in Table 2 and Figures 2 and 3. Changes observed in individual patient examples are shown in Figure 4.

Discussion

The main findings of this initial study were as follows. First, atrial frequency parameters could be recorded and extracted from simultaneous 12-lead commercially available Holter recordings using fast Fourier and PCA techniques. Second, within an individual patient in chronic persistent AF, at least over a short-term recording, measurements of waveform frequency and variability were consistent. This means that the technique should be capable of detecting and quantifying changes induced by therapies. Third, although measures of atrial frequency varied between patients, these differences were not as large as might have been anticipated. This interpatient variability is consistent with the observation from intracardiac mapping of AF that the mean number of reentrant wavelets in the atria varies between patients, but that as long as the number of active wavelets is above a critical number (between three and six), the arrhythmia is likely to perpetuate.[20,21]

Effect of Different Drugs on Atrial Frequency

In the second phase of this research, antiarrhythmic drugs with differing effects on atrial electrophysiology were administered to determine if the recording and analysis technique could detect the changes reliably.

A single dose of intravenous amiodarone, flecainide, or sotalol each reduced both mean and variability of AF frequency progressively over time. This would be anticipated, because each agent prolongs action potential duration and thereby increases the degree of refractoriness in the atria.[13–16] However, given the time frame of the observed amiodarone effect, this probably relates more to its Class I and II rather than to its Class III pharmacologic action.[16] These intracardiac effects are manifest as a reduction in both the frequency and the variability of atrial waveform on surface ECG. Conversely, metoprolol, with no direct effects on atrial

TABLE 2
Mean and Variability of AF Frequency Before and After Drug Administration in the Four Treatment Groups

		Amiodarone (7 mg/kg; 30-Minute Infusion)	Flecainide (1.5 mg/kg; 10-Minute Infusion)	Sotalol (1.5 mg/kg; 10-Minute Infusion)	Metoprolol (5–15 mg; 10-Minute Infusion)
Mean AF frequency (Hz)	Before Drug	5.77	5.33	5.94	5.41
	After Drug	4.86	4.72	4.90	5.17
	P value	0.002	0.01	0.029	0.146
	95% CI	0.55–1.27	0.23–0.99	0.17–1.91	−0.13–0.62
Variability of AF frequency (Hz)	Before Drug	0.55	0.71	0.73	0.81
	After Drug	0.31	0.31	0.40	0.82
	P value	0.006	0.0001	0.001	0.769
	95% CI	0.11–0.36	0.31–0.48	0.22–0.44	−0.074–0.059

95% CI = 95% confidence interval of the difference between the two means.
AF = atrial fibrillation.

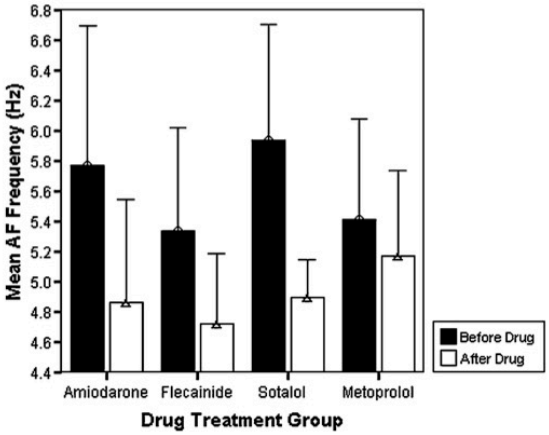

Figure 2. *Mean atrial fibrillation (AF) frequency before and after drug administration in the four drug treatment groups. Error bars indicate the 95% confidence interval of the mean.*

conduction or refractoriness, did not induce changes in either of these measures.[17]

The results from this acute drug administration phase of the study support the concept that frequency parameters derived from the surface 12-lead ECG are able to detect changes corresponding to drug administration from random variations in baseline recordings. Although differences in the effects of the different drugs on atrial frequency were observed, the study was neither designed nor powered for the data to be used to compare relative drug potencies against AF.

Clinical Relevance of the Findings

Management of AF currently is under intensive study, and novel drug, pacing, and ablation therapies are under evaluation.[22-24] The main mode of evaluation of any of these treatment modalities until to now has been whether and how

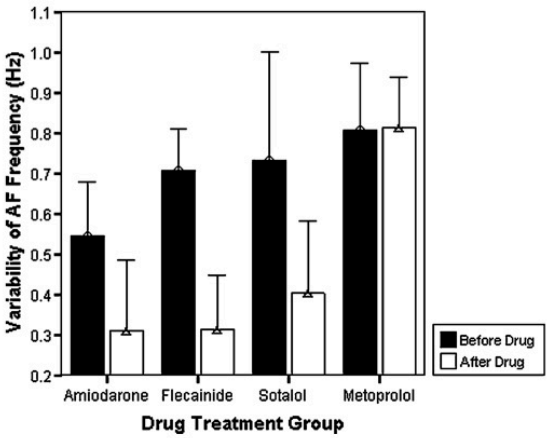

Figure 3. *Variability of atrial fibrillation (AF) frequency before and after drug administration in the four drug treatment groups. Error bars indicate the 95% confidence interval of the mean.*

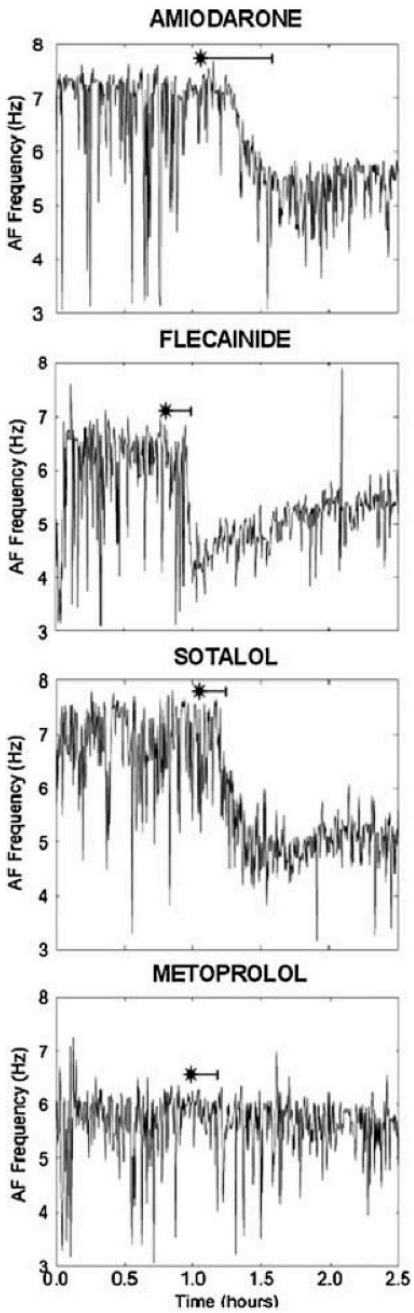

Figure 4. *Atrial frequency (AF) frequency trends for one representative patient from each of the drug treatment groups. Black asterisks and lines indicate commencement and duration of the drug infusion. Mean and variability of AF frequency are reduced after administration of amiodarone, flecainide, and sotalol but not with metoprolol.*

often sinus rhythm is restored and maintained in different clinical situations. When an intervention does not restore sinus rhythm, it has traditionally been considered ineffective.

However, many interventions may help "organize" AF and contribute to its termination, and it is increasingly relevant to separate them from those that do not have such effects. It is a limitation of this study that it was not designed to and does not establish that a reduction in the mean and variability of AF frequency inevitably leads to AF termination. However, it is reasonable to suggest that a continuing reduction in the mean and variability of AF frequency might lead to termination of AF. Serial measures of atrial frequency from the surface ECG in patients who continue to have AF might be useful clinically to distinguish whether a particular drug or line of ablation lesions, for example, has had a measurable antiarrhythmic effect from those that do not, even though AF persists.

Study Limitations

The results are based on analysis of recordings from only 20 patients. Before the technique is implemented clinically, it would be necessary to confirm the results in a larger population of subjects. Second, reproducibility was tested only over a 60-minute period, analyzed in two 30-minute sections. Consistency of frequency measurements over longer periods of time and identifying any diurnal variation in these measures would be prerequisites for using the technique to assist in clinical decision making. Third, only patients with chronic AF were studied. Whether the findings apply to patients with acute-onset AF or paroxysmal AF needs to be tested separately. Fourth, although it would have been preferable methodologically to study all patients in the drug-free state, this would have been ethically difficult, and we do not believe that the continuance of rate slowing medications had any significant effect on the results obtained.

Conclusions

Atrial frequency parameters in patients with AF can be obtained from simultaneous 12-lead Holter ECG recordings, using a combination of principal component and fast Fourier transform algorithms. The measurements of atrial waveform frequency and variability are reproducible and were shown in this study to change in response to drug manipulation of the arrhythmia. The technique warrants further study to determine if the potential applications of this form of analysis can assist in clinical decision making.

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Surface Atrial Frequency Analysis in Patients with Atrial Fibrillation: Assessing the Effects of Linear Left Atrial Ablation

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Atrial Fibrillation Frequency Analysis. ***Introduction:*** **Our group has shown previously that measurements of atrial frequency can be obtained from surface 12-lead ECG recordings of patients during atrial fibrillation (AF), using a combination of principal component and Fourier transform algorithms. Such measurements are reproducible over time and change with drug manipulation of the arrhythmia.**

Aims: **To determine whether linear left atrial ablation, using a combination of "roof" and "mitral isthmus" lines results in changes in surface atrial frequency during AF and to assess the contribution of each individual line when sited sequentially.**

Methods and Results: **Computerized recordings from 26 patients, who had undergone linear ablation procedures for AF, were reviewed. The atrial signal was extracted from the 12-lead ECG data by principal component analysis and the main frequency component identified using Fourier analysis. Atrial frequency before and after these two standard ablation lines was compared. Atrial frequency decreased significantly after the combination of roof and mitral isthmus lines (5.66 vs 5.15 Hz) and when either roof (5.61 vs 5.13 Hz) or mitral isthmus (5.89 vs 5.75 Hz) lines were sited first. However, only the roof line led to a significant reduction in atrial frequency when sited second (5.64 vs 5.49 Hz).**

Conclusions: **Measurements of atrial frequency can be obtained from surface 12-lead ECG recordings during AF and change as predicted in response to linear left atrial ablation. This technique may be useful in assessing antiarrhythmic treatments for AF.** *(J Cardiovasc Electrophysiol, Vol. 16, pp. 1-7, August 2005)*

principal component analysis, frequency analysis, atrial fibrillation, ECG

Introduction

Atrial fibrillation (AF) is the commonest arrhythmia in clinical practice and its incidence increases with age.[1] It is responsible for considerable morbidity and medical costs, is the major determinant of stroke in the elderly, and may increase mortality particularly in patients with congestive heart failure.[2-4]

Only in recent years, however, has this arrhythmia come under intense scrutiny by electrophysiologists. Various drug and catheter or surgical ablation procedures have now been developed to control or abolish AF.

One crucial advance in our understanding of this arrhythmia is the way triggering and substrate factors interact in precipitating and perpetuating AF. A persistently rapid rate of atrial excitation results in a progressive shortening of the atrial effective refractory period and promotes the perpetuation of AF, hence the concept that "AF begets AF."[5,6] Conversely, surface and intracardiac analyses of atrial fibrillation cycle length (AFCL) have shown an increase in AFCL prior to pharmacological cardioversion of AF with Class I and Class III antiarrhythmic agents.[7-9]

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Previous work from our group[10] has shown that atrial frequency parameters in patients with AF can be obtained from simultaneous 12-lead Holter ECG recordings, using a combination of principal component and fast Fourier transform algorithms. Measurements of atrial frequency and variability, obtained using this technique, are reproducible and have been shown to change in response to drug manipulation of the arrhythmia.

Traditionally, the only curative treatment for AF has been surgical, with extensive incisions used to divide the atria into small, electrically insulated compartments,[11,12] thereby reducing the atrial mass below that critical for perpetuation of the arrhythmia.[13,14] More recently, catheter deployed linear ablation lesions are being sited in left and/or right atria to replicate some parts of the surgical approach, in patients with paroxysmal or persistent AF.[15,16]

Right atrial lesions alone have yielded disappointing results in terms of abolishing AF.[17] However, linear lesions in the left atrium have been reported by several groups to organize AF, shorten the duration of arrhythmia episodes and facilitate spontaneous termination.[18,19]

Haissaguerre et al.[20] recently evaluated the effect of catheter ablation for AF on intracardiac AFCL. They observed an increase in AFCL after both pulmonary vein isolation and left atrial linear ablation (using either "roof" or "mitral isthmus" lines) that varied depending on the ablation site and individual patient. They also noted that the magnitude of increase in AFCL correlated with termination and subsequent noninducibility of AF.

Our study had two aims: (1) To determine whether linear left atrial ablation, using a combination of "roof" and "mitral isthmus" lines, results in changes in surface atrial frequency

during AF; (2) To assess the contribution of each individual line when sited sequentially.

Methods

Patients

Patients who had already undergone left atrial linear ablation procedures for paroxysmal/persistent AF in the period January 2001 to April 2004 at Freeman Hospital, UK, were identified retrospectively from case notes and computerized electrophysiological study (EPS) records.

Electrophysiological Study and Ablation Procedure

As reported previously, patients had been selected for catheter ablation of AF during this period on the basis of having highly symptomatic, drug-resistant AF.[21] Linear lesions were sited in patients with a history of persistent AF or long paroxysms of AF with large AF burden. Antiarrhythmic drug therapy was withdrawn 48 hours prior to the procedure in all patients.

Linear Ablation Design

Lesions were sited with the help of X-ray screening and the LocaLisa intracardiac catheter guidance system (LocaLisa®, Medtronic, Inc., Minneapolis, MN). Individual lesions were performed using a 7-Fr, 4-mm-irrigated tipped ablation quad-polar catheter. Lesions were performed using 50 W with temperature limited to 50°C and an irrigation flow rate of 600 mL normal saline per hour. A "burn-mark" was indicated on the LocaLisa map at each site where catheter stability had allowed energy delivery for a minimum of 30 seconds. The catheter was dragged from point to point along the line until it was completed. Thereafter, split electrograms along the line were sought and additional lesions sited at gaps, identified by the presence of single large-amplitude local electrograms. Whether complete bi-directional block had been achieved after siting of the lines could not be confirmed, however, because most patients remained in persistent AF throughout the procedure.

The two ablation lines evaluated in this study were: (1) the "roof" line aiming to create electrical conduction block between the right and left upper pulmonary vein ostia in the posterior left atrium and (2) the "mitral isthmus" line to block conduction between the left lower pulmonary vein ostium and the mitral annulus. Figure 1 shows an example of both lines of lesions from an individual patient as visualized on the LocaLisa system. The order in which the two lines were sited during the procedure was not standardized.

Ethical Approval

This study complies with the Declaration of Helsinki and ethical approval for the study was granted by Newcastle and North Tyneside Joint Ethics Committee.

Data Recordings

The computerized EPS records of patients whose data set included periods of AF before and after completion of the ablation lines were analyzed.

Measurements of atrial frequency were obtained retrospectively from the surface 12-lead ECG data recorded during the ablation procedure on a Prucka Cardiolab® EP system

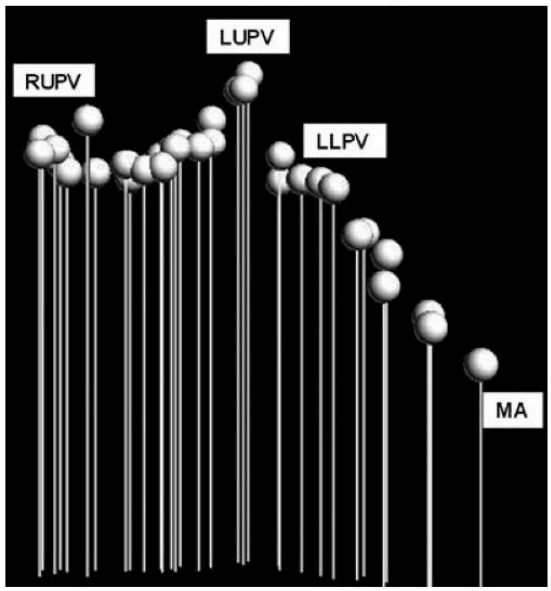

Figure 1. *Image from the LocaLisa intracardiac catheter guidance system showing the position of the roof (RUPV to LUPV) and mitral isthmus (LLPV to MA) lines sited in the left atrium. Each white sphere represents an individual radiofrequency lesion. MA = mitral annulus; LLPV = left lower pulmonary vein; LUPV = left upper pulmonary vein; RUPV = right upper pulmonary vein.*

(digital sampling rate of 979 Hz per channel) and analyzed off-line using a combination of principal component and fast Fourier algorithms implemented in MATLAB® R13. The duration of recordings varied between patients with a median of 141 (range: 23–627) seconds before, 75 (range: 7 to 344) seconds between individual lines, and 115 (range: 16 to 587) seconds after both ablation lines were sited.

Atrial Frequency Analysis

Principal component analysis (PCA) is a multivariable technique that is commonly used to reduce the dimensionality of data based on the degree of correlation between variables.[22] Conversely, the transformed variables (principal components) are uncorrelated and this characteristic can be used to identify and separate different sources in the data.

Mathematically PCA represents a linear transformation of the data to a new set of data variables (principal components), which are uncorrelated. The transformation is described by

$$s_i = \sum_{j=1}^{12} \mathbf{A}_{i,j} l(j) \quad (i = 1 : 12)$$

where **A** is a matrix of transform coefficients derived from the eigenvalues of the covariance matrix of the ECG leads, l(j) represents the jth lead from the 12-lead ECG, and s_i are the principal components.

In the context of atrial waveform extraction from the 12-lead ECG, PCA separates atrial and ventricular features into different principal components.[23] The resulting atrial signal represents global atrial activity as seen on the body surface since intracardiac atrial electrical activity contributes to

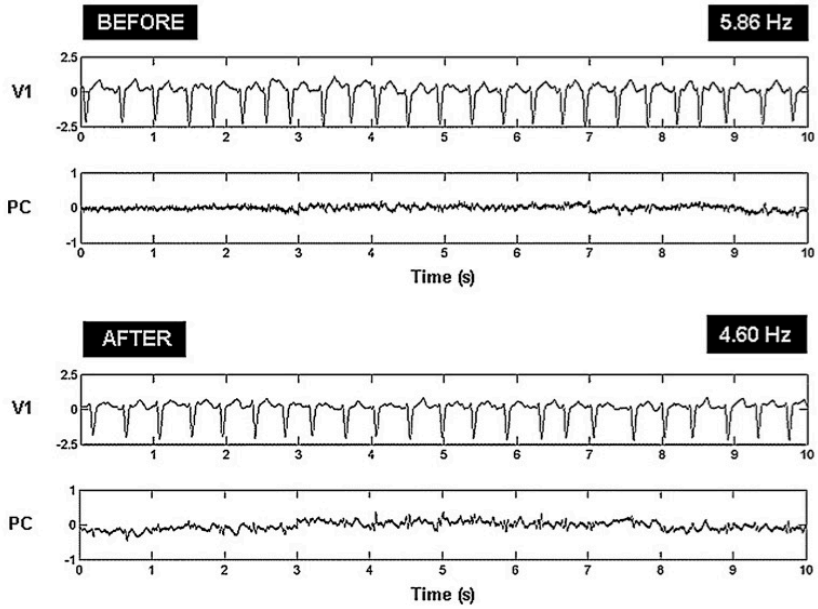

Figure 2. *Example from a single patient of a 10-second section of ECG lead V1 and the corresponding principal component (PC) containing the atrial fibrillatory waveform from before and after both left atrial linear lesions were sited. The corresponding AF frequencies calculated from the principal component using Fourier analysis are quoted.*

each surface ECG lead. Figure 2 shows an example from a single patient of a 10-second section of ECG lead V1, and the corresponding principal component containing the atrial fibrillatory waveform from before and after both left atrial linear lesions were sited, allowing a visual comparison of the atrial waveform before and after the ablation procedure.

AF frequencies generally lie within a window of 4–10 Hz.[23] Therefore, for this study, a window of between 3–10 Hz was used to allow sufficient scope for any changes in AF frequency to be recorded accurately.

To investigate the time course of atrial frequency during AF (AF frequency), all available 12-lead ECG data recorded intraoperatively on the Prucka Cardiolab® EP system from immediately before and after ablation lines were subdivided into 1-second sections and PCA applied to each section.

The principal component containing the atrial fibrillatory waveform was selected and Fourier analysis (periodogram; no windowing; length = 1 second/979 Hz (sample rate)) used to determine the peak frequency of the extracted atrial signal in each 1-second section.

Selection of the principal component for analysis was done visually and was straightforward, as the atrial fibrillatory waveform dominated a single principal component with the remaining components containing ventricular complexes and electrical noise. For the purpose of this analysis, the data were not analyzed for the presence of multiple peaks. The peak AF frequency values for all 1-second sections were averaged to give a mean frequency for each patient both before and after the ablation lines were sited.

AF Frequency Prior to Commencement of the Ablation Procedure

A preliminary analysis of baseline AF frequency prior to commencement of the ablation procedure and its relationship to previous ablation procedures, left atrial volume, and AF type was performed. Left atrial volume was calculated using an ellipsoid method:[24] $\pi/6(L*D1*D2)$, where L is the anteroposterior end systolic dimension from the parasternal long axis view and D1 and D2 are the superior–inferior and medial–lateral end systolic dimensions from the apical four-chamber view.

Effects of Roof and Mitral Isthmus Lines on AF Frequency

Mean AF frequency before and after completion of both left atrial linear lesions were compared to assess the combined effect of roof and mitral isthmus lines.

To assess the individual effect of each linear lesion, mean AF frequency before and after completion of each line were compared in a subgroup of patients, for whom these data were available, and a comparison of the relative effect of each line on AF frequency was also performed.

AF Frequency and Its Relationship to the Antiarrhythmic Success of the Procedure

Mean AF frequency before and after completion of both roof and mitral isthmus lines and the difference between pre- and postablation frequencies were compared between procedures with differing grades of antiarrhythmic success. For the purpose of this analysis, the antiarrhythmic success of the procedure was assessed at 4 months after the ablation procedure and defined as complete (restoration and maintenance of sinus rhythm), partial (change from persistent to paroxysmal AF behavior), and failure (no change in AF behavior).

Statistical Analysis

Statistical analysis was performed using the SPSS 11.0 for Windows package. Continuous variables were expressed as mean values. Comparisons of mean AF frequency at the start of the ablation procedure between first and repeat procedure patients, normal versus enlarged left atria, and paroxysmal versus persistent AF behavior were performed using

a univariate analysis of variance (ANOVA). Differences in mean AF frequency after completion of both and individual roof and mitral isthmus lines were compared using Student's paired *t*-test. The relative effect of each line on AF frequency was assessed using Student's independent *t*-test comparing the differences in mean AF frequency before and after completion of individual lines. A comparison of the mean AF frequency before and after completion of both roof and mitral isthmus lines (and the difference between pre- and postablation frequencies) between procedures with differing grades of antiarrhythmic success was performed using a one-way ANOVA. For all comparisons, statistical significance was assessed at the 0.05 level using 2-tailed P values, and 95% confidence intervals of the difference between the mean values were quoted where appropriate.

Results

The computer recordings of 26 patients (24 men with mean age 53 ± 7 years) were studied. The ablation procedure was their first for AF in 18 and a repeat procedure in 8 patients. None of the eight patients undergoing a repeat AF ablation had had linear lesions sited in the left atrium during their first ablation session.

Four months following the procedure, rhythm status was determined on the basis of symptoms since discharge and rhythm on that occasion from a 12-lead ECG; as such, eight patients were in sinus rhythm, four patients had experienced a positive change in AF behavior (i.e., converted from persistent to paroxysmal AF), ten patients had experienced no change in AF behavior, and follow-up was not available for four patients.

Whether antiarrhythmic and anticoagulant treatment was maintained or withdrawn during follow-up was decided on the basis of rhythm status and the patient's wishes; as such, 13 patients remained on the same antiarrhythmic treatment, two patients did not restart antiarrhythmic treatment after the ablation procedure, three patients started antiarrhythmic treatment after the procedure having been on no treatment beforehand, and four patients changed to a more potent antiarrhythmic treatment after the procedure.

Clinical details including duration of AF history, pre- and postoperative AF behavior and symptoms, contributors to AF, left atrial size, and antiarrhythmic success of the procedure for the 26 patients are summarized in Table 1. Although, five patients had a history of hypertension controlled by two agents (n = 2), three agents (n = 2), and four agents (n = 1), none of these had evidence of left ventricular hypertrophy on ECG or echocardiography. Rather surprisingly, two patients had an episode of rheumatic fever in childhood, one of whom had evidence of rheumatic heart disease.

Fourteen patients had sufficient information in their computerized procedure logs to be included in the individual roof and mitral isthmus line analyses. In the remaining 12 patients, only analysis of frequency changes from before the first to after both lines had been sited could be performed.

AF Frequency Prior to Commencement of the Ablation Procedure

In the 26 patients studied, AF frequency, prior to commencement of the ablation procedure, ranged from 4.79 to 6.75 Hz with a mean of 5.73 ± 0.41 Hz. There were no significant differences in mean AF frequency between patients undergoing their first versus repeat procedure (5.73 vs 5.72 Hz; P = 0.939), between those with normal versus enlarged left atria (5.76 vs 5.61 Hz; P = 0.364), or between those with paroxysmal versus persistent AF behavior (5.59 vs 5.89 Hz; P = 0.06).

Combined Effect of Roof and Mitral Isthmus Lines on AF Frequency

Twenty-two patients had both roof and mitral isthmus ablation lines sited. Mean AF frequency decreased significantly from before to after this combination of lesions (5.66 vs 5.15 Hz; P = 0.0001, 95% confidence interval of the difference 0.39–0.64 Hz).

Individual Effect of Roof and Mitral Isthmus Lines on AF Frequency

Of the 14 patients who had sufficient information to be included in the individual roof and mitral isthmus line analyses, 10 had both lines sited, 2 had only a roof line, and 2 had only a mitral isthmus line.

A significant reduction in AF frequency was observed when either roof or mitral isthmus line was sited first. Adding a roof line to a mitral isthmus line led to a significant further reduction in AF frequency. However, adding a mitral isthmus line to a roof line did not change AF frequency significantly. The magnitude of the changes observed in AF frequency after first and second lines are summarized in Table 2.

Relative Effect of Roof and Mitral Isthmus Lines on AF Frequency

A collective analysis of both lines showed that the roof line led to a significantly greater reduction in mean AF frequency when compared with the mitral isthmus line (0.31 vs 0.10 Hz; P = 0.015, 95% confidence interval of the difference 0.05–0.38 Hz).

Subgroup analysis showed that the roof line led to a greater reduction in mean AF frequency when drawn first (0.48 vs 0.15 Hz; P = 0.004, 95% confidence interval of the difference 0.13–0.54 Hz) and second (0.15 vs 0.02 Hz; P = 0.075, 95% confidence interval of the difference −0.03 to 0.30 Hz) compared to the mitral isthmus line. However, only the first line comparison reached statistical significance.

Figures 3A and B show the individual changes in mean AF frequency observed in patients after siting the roof and mitral isthmus lines first and second in the ablation procedure. There was a consistent reduction in AF frequency observed when roof lines were sited first, and a lesser but consistent reduction when roof lines were sited second.

Conversely, the effect of mitral isthmus lines on AF frequency when sited first was more variable. Overall, mitral isthmus lines had a consistently smaller effect on AF frequency when sited second.

AF Frequency and Its Relationship to the Antiarrhythmic Success of the Procedure

Although there was a trend for patients whose ablation was successful at 4 months to have a lower baseline AF frequency (5.67 Hz (complete success) vs 5.70 Hz (failure); P = 0.899), acute postablation frequency (5.06 Hz vs 5.23 Hz; P = 0.552) and a greater drop in frequency from before to after (0.60 Hz vs 0.47 Hz; P = 0.389), this did not reach statistical significance.

TABLE 1

Summary Details of the 26 Patients Studied

Sex/Age (Years)	AF Duration (Months) and Behavior	Contributors to AF	Pre-RFA Antiarrhythmic Drug Therapy	Left Dimension (cm)	Left Atrial Volume (mL)	Linear Atrial Lesions Sited	Post-RFA Rhythm at 4 Months	Post-RFA Antiarrhythmic Drug Therapy	Antiarrhythmic Success at 4 Months
F/71	31 (Ps)	None	Flecainide	3.3	31.1	**Both**	Px AF	Flecainide	Partial
M/47	24 (Px)	None	Sotalol	3.8	41.6	**Both**	SR	Sotalol	Complete
F/61	84 (Ps)	None	Sotalol	4.1	N/A	**Both**	Px AF	None	Partial
M/49	120 (Px)	Moderate MS (RHD)	Sotalol	5.6	107.2	**Both**	SR	Sotalol	Complete
M/40	9 (Px)	None	Flecainide	4.5	N/A	**Both**		No follow-up data available	
M/58	41 (Ps)	Hypertension	Atenolol	5.1	N/A	**Both**	SR	Amiodarone Atenolol	Complete
M/46	240 (Ps)	None	Flecainide	4.5	46.9	**Both**	SR	Flecainide	Complete
M/48	24 (Px)	None	Flecainide	4.5	N/A	**Both**	Ps AF	Flecainide	Failure
M/47	108 (Px)	None	None	4.8	57.8	**Both**		No follow-up data available	
M/54	108 (Px)	Hypertension	Sotalol	4.5	N/A	**Both**	SR	Sotalol	Complete
M/63	36 (Ps)	Thyrotoxicosis	Flecainide Atenolol	3.7	67.5	**Both**	Px AF	Flecainide Atenolol	Partial
M/46	76 (Px)	None	Flecainide	4.6	N/A	**Both**	SR	None	Complete
M/60	123 (Ps)	MR, Alcohol XS	None	4.7	92.1	**Both**	Px AF	Flecainide	Partial
M/54	66 (Ps)	Alcohol Excess	Bisoprolol	4.7	73.1	**Both**	Ps AF	Bisoprolol	Failure
M/53®	72 (Ps)	None	None	2.6	36.3	**Both**	Ps AF	Flecainide	Failure
M/58®	41 (Ps)	Hypertension	None	4.5	53.4	**Both**	Ps AF	None	Failure
M/52®	48 (Px)	None	Flecainide	5.0	110.9	**Both**	Px AF	Flecainide	Failure
M/51®	60 (Px)	None	None	4.1	48.4	**Both**	Px AF	Flecainide	Failure
M/57®	104 (Ps)	None	Flecainide	3.7	67.5	**Both**	Ps AF	Amiodarone	Failure
M/55®	156 (Px)	None	Flecainide Bisoprolol	3.6	47.8	**Both**	Px AF	Flecainide Bisoprolol	Failure
M/60®	39 (Px)	Hypertension	Sotalol	4.3	96.5	**Both**	Ps AF	Amiodarone	Failure
M/49®	26 (Ps)	None	Flecainide Metoprolol	4.7	N/A	**Both**		No follow-up data available	
M/51	12 (Px)	None	Bisoprolol	3.6	29.7	**Mitral Isthmus Only**	Ps AF	Bisoprolol	Failure
M/36	120 (Px)	None	Flecainide	2.9	33.1	**Mitral Isthmus Only**	SR	Flecainide	Complete
M/47	48 (Px)	None	Digoxin Verapamil	4.3	71.6	**Roof Only**		No follow-up data available	
M/55	16 (Ps)	Hypertension	Digoxin Metoprolol	4.3	67.7	**Roof Only**	SR	Amiodarone Metoprolol	Complete

The items in bold were included in the individual roof and mitral isthmus line analyses. AF = atrial fibrillation; MR = mitral regurgitation; MS = mitral stenosis; Ps = persistent, Px = paroxysmal; ® = repeat ablation procedure; RFA = radiofrequency ablation; RHD = rheumatic heart disease. Antiarrhythmic success: complete = restoration and maintenance of sinus rhythm; partial = change from persistent to paroxysmal AF behavior; failure = no change in AF behavior. Normal values for left atrial dimension (measured as the anteroposterior end systolic dimension from the parasternal long axis view) ≤4.5 cm (male) and ≤4.0 cm (female) and left atrial volume ≤61.2 mL (male) and ≤54.5 mL (female).

Discussion

In our initial study, we reported that atrial frequency parameters could be obtained in patients with AF from simultaneous 12-lead Holter ECG recordings, using a combination of principal component and fast Fourier transform algorithms, and that these measurements were reproducible and changed as predicted in response to drug manipulation of the arrhythmia.[10] The results of this present study demonstrate that this form of analysis can also measure changes in atrial frequency brought about by specific left atrial linear ablation lesions, known to organize AF and facilitate its spontaneous termination.

Combined, Individual, and Relative Effects of Roof and Mitral Isthmus Lines

As might have been anticipated, the combination of roof and mitral isthmus lines led to a significant reduction in mean AF frequency, confirming the observation that linear ablation lesions have an important antiarrhythmic effect on persistent AF. The greatest effect was seen after the combination of both lines.

Either line performed alone reduced AF frequency significantly—indicating an organizing effect on AF. However, the roof line led to a greater degree of organization of AF than the mitral line, both when performed alone and when added to a mitral line.

Indeed, contrary to expectations, adding a mitral line to a roof line did not organize AF significantly in this analysis. However, the roof line had a far more consistent effect on AF frequency than the mitral isthmus line, which could suggest that a greater proportion of the roof lines were electrically intact.

Whether the roof line is really more powerfully antiarrhythmic than the mitral isthmus line as these results suggest or whether the results simply reflect the difficulty in achieving a complete mitral isthmus line cannot be determined from this study. The roof line is undoubtedly technically easier to construct and probably, therefore, more likely to be electrically intact. Indeed, monitoring of AF frequency might have a role in determining the completeness of ablation lines intraoperatively.

AF Frequency and Its Relationship to the Antiarrhythmic Success of the Procedure

Although there was a trend for patients whose ablation was successful at 4 months to have a lower baseline AF frequency, acute postablation frequency and a greater drop in frequency from before to after, in line with our hypothesis that the lower the baseline and acute postablation frequency, the greater the chance of AF termination, this did not reach statistical significance and merits further investigation in a larger prospective study.

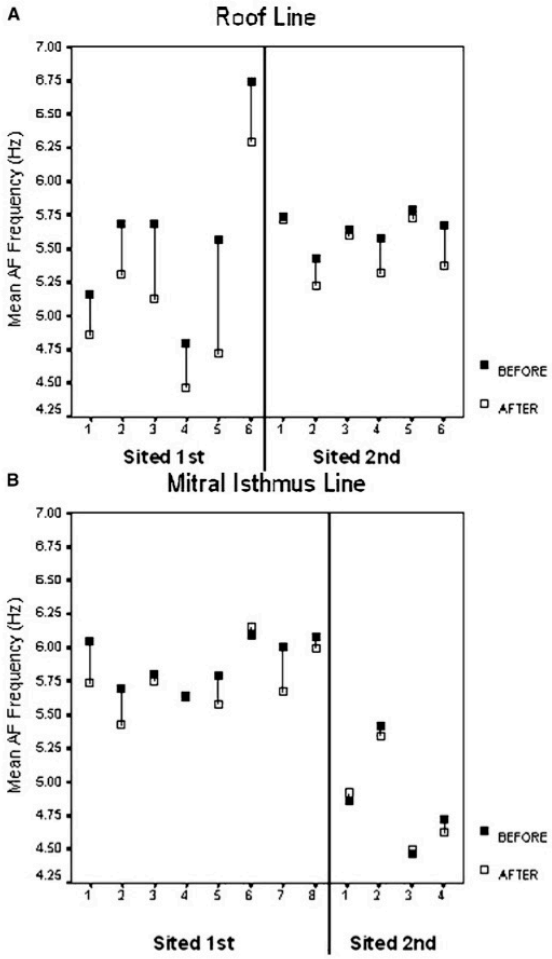

Figure 3. *(A) Individual changes in mean AF frequency observed in patients after siting the roof line first (n = 6) and second (n = 6) in the ablation procedure. (B) Individual changes in mean AF frequency observed in patients after siting the mitral isthmus line first (n = 8) and second (n = 4) in the ablation procedure.*

TABLE 2
Mean AF Frequency Before and After Individual Roof and Mitral Isthmus Line Completion

		Mean AF Frequency (Hz)			
		Before Line	**After Line**	**P Value**	**95% CI**
Roof line	Total (n = 12)	5.62	5.31	0.001	0.17–0.46
	Sited 1st (n = 6)	5.61	5.13	0.002	0.27–0.69
	Sited 2nd (n = 6)	5.64	5.49	0.033	0.02–0.28
Mitral isthmus line	Total (n = 12)	5.55	5.45	0.032	0.01–0.19
	Sited 1st (n = 8)	5.89	5.75	0.032	0.02–0.27
	Sited 2nd (n = 4)	4.86	4.85	0.717	−0.11–0.14

The P values and 95% confidence interval of the difference between the mean values (95% CI) are included.

Study Limitations

The study can be criticized for its retrospective design, for the small number of patients included, and for the lack of randomization to the order in which ablation lines were sited.

However, the consistency of the results overall argue against any of these factors materially affecting the validity of the results and conclusions.

A potentially more serious limitation is that complete conduction block was not confirmed electrically after the ablation lines were sited. However, if the lines in this study were incomplete, then the antiarrhythmic effect of complete lines would be expected to be even greater than that documented. In this event, the results underestimate the real benefit of these particular ablation lesions. Confirming line integrity would also be necessary before concluding that roof lines have greater antiarrhythmic efficacy than mitral isthmus lines.

Conclusions

These results establish that measurements of atrial frequency can be obtained from surface 12-lead ECG recordings during AF and change as predicted in response to linear left atrial ablation. Combining the results of this with our earlier study,[10] we have now validated the robustness of this frequency measure in response to drug and ablation interventions. This technique may be useful in assessing antiarrhythmic treatments for AF.

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Appendix 2

SF36v2® Health Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

Section 1. **Occurrence of atrial fibrillation** **Name or ID:**_____

Are you currently in atrial fibrillation? ☐ Yes ☐ No

If **No**, when was the last time you were aware of having had an episode of atrial fibrillation? (Please check one answer which best describes your situation)

__earlier today
__within the past week
__within the past month
__1 month to 1 year ago
__more than 1 year ago
__I was never aware of having atrial fibrillation

Section 2. **The following questions refer to how atrial fibrillation affects your quality of life.**

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered Or I did not have this symptom	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your: (Please circle one number which best describes your situation)

	Not at all limited	Hardly limited	A little limited	Moderately limited	Quite a bit limited	Very limited	Extremely limited
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in: (Please circle one number which best describes your situation)

	No difficulty at all	Hardly any difficulty	A little difficulty	Moderate difficulty	Quite a bit of difficulty	A lot of difficulty	Extreme difficulty
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7

Developed by AFEQT Core Team-John Spertus, MD, Mid America Heart Institute, Kansas City, MO; Paul Dorian, MD, St. Michaels Hospital, Toronto, ON; Rosemary Bubien, RN, University of Alabama, Birmingham, AL; Caroline Burk, Pharm D. M.S; Steven Lewis, PhD; Donna Godejohn, BSN, St. Jude Medical, St. Paul, MN.

Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire

On a scale of 1 to 7, over the past 4 weeks as a result of your atrial fibrillation, how much did the feelings below bother you? (Please circle one number which best describes your situation)

	Not at all Bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
13. Feeling worried or anxious that your atrial fibrillation can start anytime	1	2	3	4	5	6	7
14. Feeling worried that atrial fibrillation may worsen other medical conditions in the long run	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation treatment, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
15. Worrying about the treatment side effects from medications	1	2	3	4	5	6	7
16. Worrying about complications or side effects from procedures like catheter ablation, surgery, or pacemakers therapy	1	2	3	4	5	6	7
17. Worrying about side effects of blood thinners such as nosebleeds, bleeding gums when brushing teeth, heavy bleeding from cuts, or bruising.	1	2	3	4	5	6	7
18. Worrying or feeling anxious that your treatment interferes with your daily activities	1	2	3	4	5	6	7

On a scale of 1 to 7, overall, how satisfied are you **at the present time** with:
(Please circle one number which best describes your situation)

	Extremely satisfied	Very satisfied	Somewhat satisfied	Mixed with satisfied and dissatisfied	Somewhat dissatisfied	Very dissatisfied	Extremely dissatisfied
19. How well your current treatment controls your atrial fibrillation?	1	2	3	4	5	6	7
20. The extent to which treatment has relieved your symptoms of atrial fibrillation?	1	2	3	4	5	6	7

Name or ID:_____

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