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CURRENT CHALLENGES IN ATRIAL FIBRILLATION ABLATION

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CURRENT CHALLENGES IN ATRIAL FIBRILLATION
ABLATION

By

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Current Challenges in Atrial Fibrillation Ablation

Abstract

Dr Edward J Davies

The ablative management of atrial fibrillation, despite a number of landmark discoveries, remains one of the most challenging fields in interventional electrophysiology. It is generally accepted that successful isolation of the pulmonary veins is a highly effective way of managing paroxysmal forms of AF. However, despite almost a decade of research into alternative lesion patterns, the solution to persistent AF remains beyond our grasp.

A variety of strategies have been proposed to target key areas in the atria; these use various complex mapping systems, usually based on tailored lesion sets to try and improve outcomes. None have proven to be the golden bullet.

We have investigated the role of a lesion set intended to alter the electrical properties of the posterior wall of the left atrium. Commonly known as the 'box-set', this pattern has shown promise in early studies and may provide some key insights into future developments.

Surgical ablation using the Epicor system aims to deliver the box-set lesion, outcomes have previously been documented but each series has its limitations. In our series, very late outcomes are reported to show an 80% freedom from AF rate in patients with paroxysmal AF pre-operatively and only 20% in those with long-standing persistent forms. The reason behind this dramatic variation is explored through the invasive electrophysiologal assessment of both successful and unsuccessful cases. We report a clear correlation between the successful isolation of the posterior wall and long-term freedom from AF.

Though surgical ablation may be an acceptable approach for some, the ultimate goal is a lesion set that can be delivered purely endocardially. We explore the outcome of one such empirical pattern based on the box-set concept delivered through linear catheter technology and report outcomes broadly similar to alternative patterns.

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ABREVIATIONS

AAD	Antiarrhythmic drug
ACT	Activated clotting time
AF	Atrial fibrillation
AFl	Atrial flutter
AP	Action potential
APD	Action Potential Duration
AT	Atrial tachycardia
ATP	Adenosine triphosphate
AVR	Aortic valve replacement
BMI	Body mass index
bpm	Beats per minute
Ca^{2+}	Calcium
CABG	Coronary artery bypass graft
CFAE	Complex fractionated atrial electrograms
CS	Coronary sinus
CTI	Cavo-tricuspid isthmus
CV	Conduction velocity
DAP	Delayed afterdepolarisation
DCCV	Direct current cardioversion
DF	Dominant frequency
ECG	Electrocardiogram
EF	Ejection fraction
EP	Electrophysiological
ESC	European Cardiac Society
GP	Ganglionic plexi
HIFU	High intensity focussed ultrasound
INR	International normalised ratio
IVC	Inferior vena cava
K^+	Potassium
LA	Left Atrium
LAA	Left atrial appendage
LTCC	L-type calcium channel

LV	Left ventricle
LVA	Low voltage area
MVR	Mitral valve replacement
Na^{2+}	Sodium
NYHA	New York Heart Association
LS PsAF	Long-standing persistent atrial fibrillation
LTCC	L-type Ca^{2+} channel
MAAC	Multi-array ablation catheter
MASC	Multi-array septal catheter
ms	milliseconds
NSR	Normal sinus rhythm
PAF	Paroxysmal atrial fibrillation
PIS	Patient information sheet
PsAF	Persistent atrial fibrillation
PV	Pulmonary vein
PVAC	Pulmonary vein ablation catheter
PW	Posterior wall
RIPV	Right inferior pulmonary vein
RSPV	Right superior pulmonary vein
RP	Refractory period
SA	Sinoatrial
SPSS	Statistical Package for the Social Sciences
SR	Sarcoplasmic reticulum
SVC	Superior vena cava
TV	Tricuspid valve
T-VAC	Tip versatile ablation catheter
WACA	Wide area circumferential ablation
3D	Three dimensional

Current Challenges in Atrial Fibrillation

Ablation

"When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble, but still perceptible, thin like a silk thread), then the impulse of life is small."

Huang Ti Nei Ching Su Wen. *Circa* 220 BC

1   GENERAL INTRODUCTION

1.1   The Normal Heart – Atrium

The normal heart is comprised of two atria and two ventricles (left and right). The atria receive blood from the systemic circulation (right) and lungs (left) and contribute to the active filling phase of the ventricles. Because they operate at a low pressure, the atria are thin walled chambers when compared to the ventricles. Like all chambers of the heart, they are composed of three layers, the epicardium, myocardium and endocardium. All three are electrically active and in the normal healthy heart, function synergistically.

1.1.1   Anatomy of the atrium

The right atrium has three inlets, the inferior and superior vena cava (IVC, SVC) and the coronary sinus (CS). The outlet connects to the right ventricle via the tricuspid valve. The triangle formed by the TV, CS and IVC is referred to as the triangle of Koch.[1] It is an area that conducts relatively slowly and is of significance in the pathogenesis of a right atrial macro-re-entrant circuit – typical (or 'classic') atrial flutter.

The inlet to the left atrium (LA) is typically comprised of four (sometimes 3 or 5) pulmonary veins (PV). There is a blind ending sac arising from the LA known as the left atrial appendage (LAA). In normal sinus rhythm, this appendage is of limited clinical interest; it is sheathed in myocytic tissue and contracts to empty during each atrial systole. Its importance becomes more apparent when viewed under pathological conditions; it is a significant source of thromboembolic particles during certain atrial arrhythmia.

1.1.2   Physiology of The Atrium

1.1.2.1   Action Potentials

The AP is a rapid and temporary change in the electrical property of a cell that is conducted and propagated to the adjacent cells. This results in rapid transmission of electrical signals across tissue. There are 5 phases to the AP: depolarisation, early repolarisation, plateau, repolarisation and resting potential. Depolarisation (phase 0) occurs during a massive influx of Na^+ ions through opened sodium channels. At the same time, the reduced membrane permeability to K^+ is mediated through a drop in passage through the slow K^+ channels.

This depolarisation is maintained through early repolarisation and plateau (phases 1 and 2 respectively) through the increase in influx of Ca^{2+} via slow voltage-gated Ca^{2+} channels. It is this influx of Ca^{2+} that is integral to the contraction of the myocyte. During the plateau phase, the inward current mediated principally through Ca^{2+} is balanced through the outward current from K^+.

Repolarisation (phase 3) is mediated by two mechanisms: i. an increase in the membrane's permeability to K^+ and ii. a decrease in the Ca^{2+} permeability which brings the membrane potential back towards the normal resting membrane potential of around -90mV.

The action potential duration (APD) is split into 2 components: the absolute refractory period (ARP) and the relative refractory period (RRP). The absolute refractory period is the time between phase 0 depolarisation and midway through phase 3 repolarisation. During this phase, a second AP cannot be triggered. Following on from this, the relative refractory is characterised by its ability to trigger a further AP if the stimulus intensity is high enough. The refractoriness of the atrial cell has been found to be in the region of 85 to 100ms during high frequency firing.[2]

1.1.2.2 Electrical Conduction System

The complex synchronised cardiac conduction relies on both a specialist tree of conductive tissue and on conduction from adjacent myocytes via gap junctions.

1.1.2.2.1 Sinoatrial Node

Having the fastest escape rhythm in the heart, the sinoatrial (SA) node, first described anatomically in 1907,[3] is primarily responsible for the regulating the heart rate.[4] Specialist 'pacemaker' cells are located near the junction of the RA and SVC. Though initially thought to be a simple dominate area of pacemaker cells, it has since been found to contain several major pacemaker components (head, centre and tail) surrounded by isolating structures situated all along the cristae terminalis.[5] There are multiple sites within the RA that are able to initiate 'sinus' rhythm.[6]

The sinus node itself has 4 preferential conduction pathways (SACP) which are responsible for conduction of electrical impulses into the surrounding atrial myocardium.[5] The route of exit and propagation depends on the preferential SACP, the excitation wave spreads from the right atria to the left atria through the main intra-atrial musculature: either through Bachmann's bundle and the coronary sinus musculature or through intra-atrial septum connections.[7]

1.1.2.2.2 Crista Terminalis

The cristae terminalis is comprised of cells that conduct electrical impulses from the SA node through the atrium until they reach the AV node. There is a conduction delay inherent to the cristae that can act as a slow pathway – a critical component to re-entrant circuits that may result in organised atrial tachyarrhythmia. The cristae is a rich source of ectopy and that these ectopics may lead to both atrial tachycardia (AT) or AF.[8]

1.1.2.2.3 Atrioventricular Node

The Atrioventricular (AV) node is located at the base of the atrial septum in the triangle of Koch. There are 2 'zones' of cells making up the node, transitional and compact. The cells within the transitional zone are a histological and functional fusion of atrial myocytes and compact zone cells. This compact zone gives way to 3 posterior extensions: one in the direction of the CS (the 'slow pathway'), one anteriorly near the compact zone (the 'fast pathway') and the third towards the mitral annulus (the left atrial extension). There is typically a gap of around 15mm between the putative fast and slow pathways that allows for ablation not resulting in complete AV block.

1.2 Atrial Fibrillation

1.2.1 History

The condition characterized by an irregular pulse has roots in all the main ancient civilizations. Perhaps the earliest recorded description dates from as far back as 250BC given in Huang Ti Nei Ching Su Wen, the Yellow Emperor's Classic of Internal Medicine. In 1628, William Harvey, the first to correctly describe the circulatory system, was likely to be the first to describe fibrillation of the auricles of dying animals.[9] It took a further 150 years for his theory to be replicated by Jean-Baptiste de Senac,[10] described in relation to mitral valve disease. In 1909, Thomas Lewis, a close friend of the inventor of the electrocardiogram, William Einthoven, reported the first electrical description of *pulsus irregularis perpetuus* and correctly ascribed this chaotic rhythm as arising from fibrillation of the auricles.[11] The beneficial effect of digitalis was first reported in the 1930s but the mechanisms and possible consequences of AF remained very much in debate until 1970 when a computer model was used to demonstrate that the irregular ventricular response was

due to "randomly spaced atrial impulses of random strength reaching the atrioventricular node from random directions".[12]

1.2.2   Epidemiology

Atrial fibrillation is a very common condition with a prevalence increasing with age; 8% of the over 75 population are affected.[13] It is responsible for significant morbidity and mortality and as such has major health economic implications. Hypertension, rheumatic heart disease and heart failure were identified as common precursors in the Frammingham study, though in around one-third of patients, no clear cause is found. In 2010, an estimated 33.5 million people were affected worldwide (20.9 million males and 12.6 million females).[14] Traditionally, hypertension has been considered a strong risk factor for AF. The actual relative-risk is between 1.2 and 1.5, but because of the extreme prevalence in the global population, the overall effect is large with estimates suggesting that around 14% of cases are related to hypertension.[15]

1.2.3   Signs and Symptoms

Atrial fibrillation contributes to a patient's morbidity and mortality regardless of symptoms. Many cases of asymptomatic AF are recognised as incidental findings during unrelated consultations with healthcare professionals. Unfortunately, many others present with thromboembolic events, such as stroke. Estimates suggest that between 5% and 35% of all AF cases are asymptomatic.[16–18]

Patients may complain of 'constitutional' symptoms including tiredness and lethargy or others related to a rapid heart rate: palpitations, dyspnoea and chest pain. Some patients only develop symptoms during exertion; others have debilitating symptoms, even at rest.

The only sign of AF is an irregularly irregular pulse. However, there may be other signs pertaining to the underlying condition such as the mid-diastolic murmur of mitral stenosis or proptosis suggesting Grave's disease.

1.2.4   Complications

Though thrombus arising from the LA can embolise to practically anywhere in the body, probably the most significant complication is a cerebral embolism leading to stroke.

AF may lead to a reduced left ventricular ejection fraction; first described a century ago by James Mackenzie,[19] it's prevalence probably remains underestimated to the current day. The exact mechanism of tachycardia or AF mediated cardiomyopathy remains poorly understood. Groups working on animal models have reported myocardial energy depletion, myocardial ischaemia, alterations in the way calcium is regulated and extracellular matrix remodelling as potential theories for the observed effect.[20]

1.2.5   Definitions and Classifications of Atrial Fibrillation

AF is a supraventricular arrhythmia characterised by disorganised, chaotic contraction of the atria. Diagnosis is made when all three of the following surface ECG properties are seen:

1. Irregular RR intervals

2. A lack of distinct p-waves on the surface ECG

3. A variable atrial cycle length of less than 200ms.[21]

AF is classified depending on its temporal characteristics. Paroxysmal AF (PAF) is defined as recurrent ($\geq$2) episodes that each last less than 7 days and terminate spontaneously. Persistent AF (PsAF) is defined as a single episode that lasts greater than 7 days. Should cardioversion be performed within 7 days of onset, it is classed as PAF if cardioversion

occurred within 48 hours of initiation, and PsAF if it was after.[22] A third classification is that of 'longstanding persistent AF' (LS PsAF), a continuous single episode lasting greater than one year. Finally, when a joint decision has been made between the physician and patient to accept AF and make no further attempts at rhythm control, it is termed 'permanent'. Where patients have episodes that fall across categories, it is recommended that the predominant class over the preceding 6 months is used (particularly in relation to the outcomes from ablation procedures).[22]

1.2.6 Mechanisms of Atrial Fibrillation

Characteristics of AF give clues to the underlying pathophysiology. Patients with new onset AF usually have one of 2 main clinical phenotypes; those that have frequent, short lived episodes and those that have episodes that last >48 hours and require either AADs or DCCV to restore sinus rhythm. The former likely arises from the firing of rapid focal triggers, which may or may not arise from the PV. Where the AF lasts greater than 48 hours, there is likely to be electrical and later anatomical remodelling involvement (discussed in 1.2.6.2).

1.2.6.1 Initiation

Initiation of automated activity is thought to be responsible for the triggering of AF. Inward movement of Na^+ or Ca^{2+} can cause depolarisation of the cell. Should this depolarisation reach a threshold potential, automatic activity is produced and the cell will fire. When this process occurs before the next sinus beat (originating from the SA node) a premature atrial complex results.

There are different mechanistic theories as to how these ectopic beats come about, though 'delayed afterdepolarisations' are the predominant mechanism within the atrial tissue.

1.2.6.1.1 Delayed Afterdepolarisations

Ca^{2+} is stored within the cell in an organelle called the sarcoplasmic reticulum (SR). Ca^{2+} entering cardiomyocytes through channels during the AP plateau triggers a massive release of Ca^{2+} from these SR stores via a specialist channel called RyR2. This causes the cell to contract. During the following relaxation phase, this Ca^{2+} is removed from the cytosol back into the SR by an active pump, an ATPase. When there is an abnormality with the RyR2 channel, Ca^{2+} can leak into the cytosol inappropriately. This calcium is handled by a cell membrane Na^+/Ca^{2+} exchanger which will eject one Ca^{2+} ion in exchange for three Na^+ ions; this creates a net depolarisation and subsequently a delayed afterdepolarisation.

1.2.6.1.2 Pulmonary Vein Triggers

The majority of episodes of PAF arise from triggers located within the PVs. This discovery was made in the seminal paper by Haissaguerre.[23] The evidence to back up this theory not only lies in the electrophysiological observations of PV potentials at the time of ablation, but also in the considerable success that PVI has accrued in the ablative management of PAF. Series outcomes from PVI report success rates ranging from 66% to 89% at one-year follow-up.[22] However, there are cases where PAF ablation has failed despite successful, validated PVI. It is in these cases that non-PV triggers should be sought.[8,24–27]

1.2.6.2 Propagation – Remodelling

"AF begets AF", a commonly quoted expression which neatly expresses what was first observed by M. Rosenbaum with the phrase "domestication of atrial fibrillation".[28] It is based not only on anecdotal observation by the physicians, but also on the prevailing disease pattern. Typically, AF will initially exist in the paroxysmal form and will be reliant on triggers for repetitive initiation. This form of AF typically involves episodes the last less than 48 hours. However, after a period of time these episodes become more sustained. There are

four main physiological changes that occur during AF, which may lead to it progressing from paroxysmal to persistent. Some processes are brought on by AF itself and others are related to commonly associated disease processes. Remodelling can be both electrical and/or structural, autonomic changes occur and calcium handling is altered.

1.2.6.2.1 Electrical Remodelling

Like all the cells in the body, ion channels, the properties of which can be altered by atrial remodelling, mediate the electrophysiological properties of atrial cells. There are three main aspects to this:

- Down-regulation of the I_{CaL} channel.

During the action potential depolarisation, Ca^{2+} enters the cell through the L-type Ca^{2+} channel (LTCC). This in turn triggers a release of Ca^{2+} from the SR via the RyR2 channel. It is this large net increase in intracellular Ca^{2+} levels that initiate cellular contraction via myofilament movement.

The levels of Ca^{2+} within the SR are dictated by net Ca^{2+} movement; inward via an active ATPase channel and outward via the RyR2 channel. The ATPase channel is inhibited by a subunit which, when phosphorylated, becomes dissociated. This happens under adrenergic stimulation or increased intracellular Ca^{2+} loading, which also leads to phosphorylation of RyR2 by protein kinase A. This adaptive mechanism responding to adrenergic drive increases the cardiac chronotropic and inotropic response. However, sustained Ca^{2+} loading causes abnormal diastolic RyR2 Ca^{2+} release. This is achieved via a Na/Ca exchange pump responsible for the inward current causing phase 4 membrane depolarisation. These resulting afterdepolarisations have been described previously (see section 1.2.6.1.1).

During rapidly conducted AF there is a sustained increase in the level of intracellular Ca^{2+} which leads to certain self-defence mechanisms designed to defend against chronic Ca^{2+} overload. Ultimately this leads to down regulation in the gene coding for the LTCC[29] resulting in a decrease in the inward calcium current, maintenance of the AP Plateau, shortening of the AP duration and leads to an environment where re-entrant circuits become more likely. These re-entry circuits, particularly in a fibrosed substrate increase the likelihood of AF sustainability.

- Up regulation of I_{K1}

The I_{K1} channel controls the principal background cardiac inward rectifier current and determines the resting potential and terminal phase 3 repolarization. These inward rectifier currents are a particularly important determinant of the putative types of re-entry circuits that maintain AF. Unfortunately I_{K1} is up-regulated during AF.[30]

An alternative inward-rectifier current is responsible for some of the effects of acetylcholine. The I_{KACh} channel is the key to the causative effect of enhanced vagal activation to in the promotion of AF – in part by reduction in the action potential duration, which again leads to an environment of putative rotor stability. Further activation of I_{KAChc} channel results from AF induced atrial tachycardia and enhanced Ca^{2+} loading.

- Up regulation of the small conductance calcium activated potassium channel

Small conductance calcium-activated potassium channels, when activated, may shorten the APD. The genes KCNN1/KCNN2 and KCNN3 encode these channels. A link has been found between *KCNN3* single nucleotide polymorphisms and AF.[31] It has been proposed that rapid atrial activation, typically seen in AF, may up regulate expression of small conductor's calcium activated potassium channels which in turn contributes to AF maintenance and susceptibility.[32]

1.2.6.2.2 Structural Remodelling

Many disease processes associated with AF act by causing atrial enlargement and secondary tissue fibrosis. There are a number of mechanisms by which fibrosis promotes AF; the interaction between cardiomyocyte and fibroblast is potentially arrhythmogenic by causing changes in the cardiomyocyte biochemistry. Also, the interruption of the fibre bundles within the LA wall can alter local conduction. There is a documented association between fibrosis and both AF incidence[30,33,34] and the likelihood of failure of ablation procedures.[35,36]

1.2.6.2.3 Autonomic Regulation

There is a well-recognised pattern of AF, particularly in the young, which sees paroxysms triggering mostly at night. The autonomic nervous system is heavily implicated in both the initiation and propagation of AF.[37] High vagal tone acts to enhance acetylcholine-dependent K^+ currents, which leads to a reduction in the duration of the action potential. This stabilises re-entrant rotors and subsequently AF.[38] In addition, adrenoceptor activation increases diastolic Ca^{2+} leak and promotes DAD related ectopic firing by hyperphosphorylating RyR2 chnnels.[39] This state of atrial sympathetic hyperinnervation can occur in PsAF.[40]

Positive feedback loops may arise through autonomic remodelling and can act to promote AF persistence and recurrence.[40] The role that targeting the ganglionic plexi has in the ablative management of AF is discussed in section 1.3.2.6.

1.2.6.2.4 Calcium handling abnormalities

Abnormal Ca^{2+} handling may be proarrhythmic through the increase in DAD induced ectopy. LS PsAF is associated with an increased incidence of arrhythmogenic DAD triggered activity.[41] Hyperphosphorylation of RyR2 leads to an increase in sarcoplasmic Ca^{2+} leak.[41] Meanwhile, up-regulation in the Na^+/Ca^{2+} exchange increases the magnitude of

delayed afterdepolarisation generating inward currents for any given amount of aberrant Ca^{2+} release, thereby magnifying the effect from the leaked Ca^{2+}. Sustained and rapid atrial activation appears to cause AF induced remodelling through increase in Ca^{2+} cytoplasmic loading.

While LS PsAF is likely maintained by complex multiple circuit re-entry,[30,33,42,43] ectopic activity may contribute by reinitiating AF should it terminate spontaneously or via medical intervention. Recent work points to a predisposition to DADs in patients with PAF that likely plays a more primary role in arrhythmogenesis.[44] The principal underlying mechanisms include increased SR Ca^{2+} load due to hyperphosphorylation of RyR2 and abnormalities with RyR2 itself.[44]

1.2.6.3   Propagation - Theories

The basic mechanistic principles behind the competing AF theories are based around ideas developed nearly a century ago.[45] Three such theories became mainstream: rapidly discharging atrial ectopic foci, single re-entry circuit and multiple functional re-entrant circuits. In the multiple-wavelet model (see 1.2.6.3.1), atrial irregularity is a consequence of the arrhythmia mechanism. For the rapid focal and single-circuit mechanisms, irregularity is proposed to arise from interactions between wavefronts produced by the primary generator (the ectopic focus or primary re-entrant circuit) and the spatially variable refractory properties of atrial tissue ('fibrillatory conduction').

In order to develop effective pharmacological and ablative strategies, an appreciation of the predominant mechanism is paramount.

1.2.6.3.1 Multiple Wavelets

The multiple wavelet theory was the first to become mainstream. The work of Moe *et al.*,[46] emphasized the role of multiple wavelets in the propagation of AF. A familiarity of the 'wavelength of re-entry', developed by Allessie *et al.* is important in understanding the multiple wavelet concept.[47,48]

The wavelength is the distance travelled by an electrical impulse in one refractory period, and is calculated as the product of the refractory period (RP) and the conduction velocity (CV). If the pathlength of a potential circuit is smaller than the wavelength, the impulse will meet its tail in a refractory state and subsequently terminate. Therefore, the wavelength is the shortest pathlength that can sustain re-entry.

According to the 'leading circle' hypothesis of Allessie *et al.*,[47] functional re-entry will naturally establish itself in a pathlength the size of the wavelength. Wavelets behave as reentrant circuits. Therefore, the number of wavelets that can co-exist is proportional to LA size and the wavelength. When the wavelength decreases, so too does the minimum circuit size, which in turn increases the number of circuits that can be accommodated. This favours the formation of multiple wavelets and subsequently AF propagation. Based on this theory, the primary pharmaceutical approach to AF has been to increase the RP (and thereby the wavelength), limiting the number of wavelets to a point whereby AF can no longer be sustained.

Interventions that limit the ability of these multiple wavelets to self-sustain include drugs that increase the RP and surgical division of the atria into electrically isolated areas.

An observation incompatible with leading circle theory is the response of AF to antiarrhythmic drugs that block Na^+ channels. Such agents are effective in terminating AF,

but according to leading circle theory should promote AF because they decrease conduction velocity and thereby decrease the wavelength.

1.2.6.3.2 Focal Discharges

Nearly 2 decades ago, Haissaguerre first reported the prominence of the PVs as dominant sites of ectopy, triggering PAF.[23] To date, the role of PV and non-PV ectopy in PsAF is less certain.[23] Focal impulses are defined by "centrifugal activation contours (isochrones) from an origin".[49] Ectopic mechanisms would be susceptible to drugs that suppress automaticity and to targeted destruction of ectopic foci by surgery or catheter-based approaches.

A recent study looked at the role of 'arrhythmogenic foci' manifest through isoproterenol administration in PsAF ablation cases. They report that in the pre-ablation setting, 89% of their cases had PV foci and 54% non-PV. Following on from an "aggressive" ablative strategy only 41% had demonstrable foci at any site. Those patients with on-going foci had a 50% of AF recurrence at 2.5-year follow-up whereas in those with no foci, the rate was only 26%.

It may be that these ectopic foci encourage PsAF by acting as a driver or by reintroducing it when it terminates.[50] A third possibility however is that these foci are merely a marker of an advanced disease process within the substrate and do not play a mechanistic role.[50] Further work is needed to delineate the importance of these foci in PsAF to guide future ablative strategies.[51]

1.2.6.3.3 Rotors

Rotors are a form of spiral wave and were first described in 'myocardial fibrillation' in the early 1990s,[52] when they were linked to the characteristic ECG changes seen in ventricular fibrillation.[53] They have since been proposed as a driving force behind PsAF. Initial attempts

to use isochronal (activation) mapping did not detect stable rotational circuits in AF[54] until complex signal analysis known as phase mapping was applied.[55]

Several types of reentry exist; spiral waves represent one specific form. The central core from which the spiral waves emanate is termed a 'rotor' and meanders as it pivots around 'unexcited but eminently excitable tissue'.[56] Critical to the action of rotors is the extreme wavefront curvature thet they exhibit. This curvature increases as conduction slows towards the 'core' and the small (curved) excitable gap that exists between head and tail of the wavefront eluding standard entrainment maneuvers.[57] Rotors are thus defined using three key characteristics (Figure 1-1).

- Extreme wavefront curvature at the core where head meets tail.

- An excitable and precessing core.

- A highly variable reentrant wavelength, with a usually undetectable excitable gap.
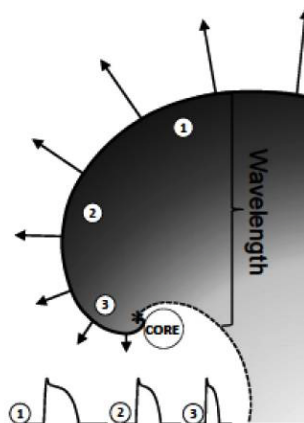
Figure 1-1. Mechanistic theory of rotors. The solid line represents the wavefront, in this case moving anticlockwise. The dashed line is the wave tail. The velocity vector is represented by the solid arrows and the so called 'phase singularity' is shown by *. Reproduced from Pandit *et al.* with permission.[56]

Single-circuit re-entry should be suppressed by drugs that prolong the refractory period and inhibit re-entry, and by ablating key components of the re-entrant pathway. The role of focal impulse and rotor mapping and ablation is discussed in section 1.3.5.

1.2.7   Management of Atrial Fibrillation

The management of AF is a dynamic process which should be discussed and agreed upon between patient and physician. There are several important strands that need to be addressed at varying times throughout the management journey. Symptoms should be assessed and a cause found. For example, palpitations may be as a result of poor rate control; breathlessness could be secondary to impairment of LV function or inappropriate chronotropic responses and poor energy levels may be a 'constitutional' symptom of AF itself. Secondly, an objective assessment of the LV systolic and diastolic function will guide subsequent management decisions. Depressed systolic function may be due to poor rate control, irregular RR intervals or the primary cause for the AF. Thirdly, the individual thromboembolic risk should be assessed and anticoagulants administered where appropriate.

1.2.7.1   Rate vs. Rhythm Control

The decision of rate versus rhythm is complex and dynamic. Experience is needed to formulate and guide patients through appropriate management strategies. Important variants affecting this process include the duration and severity of symptoms, co-morbidities, LV function and other structural abnormalities, and arguably, the thromboembolic risk.

There have been several studies published investigating the advantages of either a rate or rhythm control strategy. The largest of these was the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.[58] Including over 4000 patients, they found no difference in all cause mortality (primary endpoint) or stroke rate between the 2 groups.

Rate control was judged to be non-inferior to rhythm control in the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) trial.[59] The population of patients with PsAF and LV function <35% were investigated in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) study. In patients with AF and congestive heart failure, a routine strategy of rhythm control was not found to reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy.[60]

These three studies were performed between 2002 and 2008 in an era when ablative technologies for managing AF were in their infancy. Furthermore, a subgroup analysis of the AFFIRM trial suggested that the benefit from being in NSR was counterbalanced by the risk of adverse side effects from the AADs.[61] It was proposed that "if an effective method for maintaining NSR with fewer adverse effects were available, it might be beneficial".[61] This statement lends support to the concept of invasive management of AF. These will be discussed in depth in section 1.3.

1.2.7.2 Optimal Rate Control

The optimal rate for a patient in PsAF is often thought to be similar to a person in NSR, i.e. between 60 and 100bpm. However, this is based on little more than intuition. Furthermore, as a result of the loss of atrial systolic contraction, it may well be that a higher than normal heart rate is physiologically appropriate. Through randomisation into either a strict (<80bpm) or lenient (<110bpm) rate control group, the RACE II study investigated this issue in over 600 patients.[62] Strict rate control conferred no advantage in any of the endpoints including mortality, hospitalisation or stroke rate, heart failure progression or, importantly, symptoms.

1.3   Ablative Strategies for Persistent Atrial Fibrillation

Ablative technologies revolutionised the management of many types of cardiac arrhythmia by the mid-1990s. It was only more recently when reliable results were achieved for PAF and to this day, the results from ablation in PsAF remain disappointing.[63]

1.3.1   Local Atrial Activity

The possibility of there being key areas of substrate responsible for AF perpetuation led investigators to look for such critical area markers. In 2004, a study defined Complex Fractionated Atrial Electrograms (CFAE) as "atrial electrograms that have fractionated electrograms composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10s recording period".[27] These have since been further classified into 6 grades of fractionation ranging from grade 1 "uninterrupted fractionated activity (defined as segments ≥70 ms) for ≥70% of recording and uninterrupted ≤1 s" to grade 5 "discrete simple electrograms (≤4 direction changes)", (Figure 1-2).

By using electroanatomical mapping systems, it is possible to map and subsequently ablate these CFAEs. The landmark 2004 study by Nademanee *et al.* reported on the outcome from this strategy in a patient group comprising 121 patients. By ablating only on sites of CFAEs (and importantly without performing PVI) they reported a 76% one-year freedom from AF rate after a single procedure and 91% after 2.[27] Subsequent studies have failed to replicate these promising results.[64]
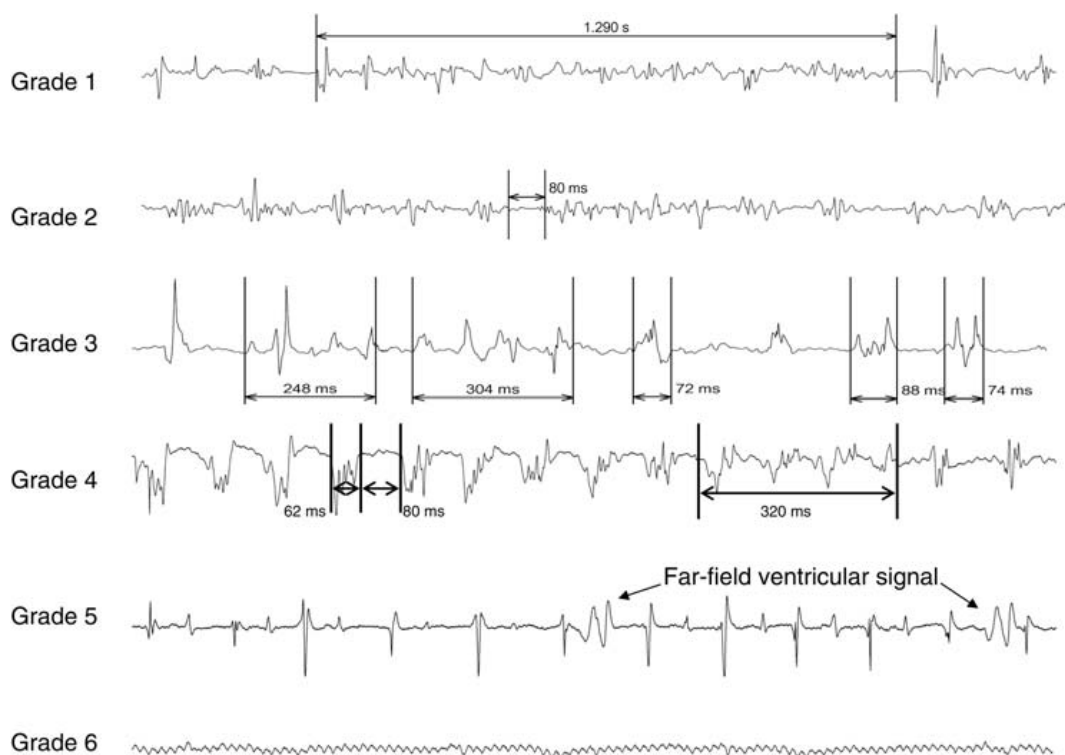
Figure 1-2. Examples of electrograms from the revised grading system. Fractionation ranges from Grade 1 (fractionated activity defined as continuous deflections without pause for ≥70ms occupying >70% of the tracing) to Grade 5 (discrete (<70ms) and simple (≤4 direction changes) electrograms). Grade 6 represents scar with no discernable deflections. Reproduced from Hunter *et al*. with permission.[134]

The exact underlying mechanism responsible for CFAEs remains unclear. Indeed, the presence of fractionated electrograms are normal findings in the left atrium during sinus rhythm owing to wavefront collisions.[65] However, it is clear that ablation at these CFAE sites can result in slowing, termination, and long-term freedom from AF.[64] Although the initial reports of this technique were encouraging, this strategy has not been universally successful. This may in part be due to the widespread distribution of CFAE within the LA, which often requires extensive ablation.[66]

CFAE sites may represent areas of passive atrial activation or collision of wavefronts.[67] As such, some of these sites may represent critical areas for the maintenance of AF whereas others may merely be bystanders.

1.3.2 Linear Lesions

The placement of various linear lesions for the ablative management of PsAF has been studied. The 2 most commonly deployed are the left atrial 'roof line' and 'mitral isthmus line', though others have been applied.[68,69] Though there is some evidence that linear lesions can enhance the outcome for ablative procedures,[70] the evidence is not yet compelling and such a strategy is not without risks.[71] If an incomplete lesion is deployed, it may act as an area of slow conduction leading to the manifestation of macro-reentrant circuits.

In 2015, the STAR-AF 2 study compared the outcome between 3 different ablation strategies; PVI alone, PVI plus CFAE ablation or PVI plus linear lesions (roof and mitral isthmus). At the 18 month follow up, there was no statistical inter-group difference in either the primary outcome of AF recurrence or the secondary outcome of atrial arrhythmia recurrence. Post-hoc analysis analyses showed that the group assigned to PVI plus linear lesions had a significantly higher incidence of arrhythmia recurrence without an AAD compared to PVI alone.[71]

1.3.3 Targeting Ganglionic Plexi

The intrinsic nervous system of the heart is formed by a complex network of nerves which join to form ganglionic plexi (GP) in areas typically sited in the epicardial fat around, but not exclusive to, the LA. The causative association between the autonomic nervous system and AF has long been described.[72] A study looking at the effect of adjunctive complete vagal denervation during PVI procedures found it to significantly reduce AF recurrences at 12 months.[118]

Anatomical studies suggest that the majority of GP either overlay or are adjacent to the PVs.[73] Over the past decade, there have since been many, relatively small studies, looking into the effect of different iterations of PVI and GP ablation. GPs have been identified both

anatomically and through high frequency stimulation techniques.[74–78] PVI ablation alone resulted in a lower recurrence rate of AF compared with the rate after anatomically-guided selective GP ablation.[76,77] By contrast, other studies have found that anatomical GP ablation followed by PVI ablation resulted in better clinical outcomes than with PVI ablation alone.[70,71]

1.3.4 Dominant Frequency Analysis

Dominant frequency (DF) analysis is a mathematical method of identifying areas of substrate critical for the initiation and perpetuation of AF.[81] It can be considered as an extension of CFEA mapping and may mechanistically represent rapid local re-entrant circuits, focal ectopic sources or wavefront collision.[82,83] This process enables the identification of areas which 'fire' at high frequencies in an environment of irregularity. Areas showing a higher dominant frequency are thought to represent areas that are critical to AF maintenance and therefore represent potentially useful ablation sites.

1.3.5 Targeting Rotors

A description of a rotor is provided in section 1.2.6.3.3. These electrical rotors and focal impulses are thought to contribute to AF perpetuation.[43,49,84–87] In experimental models, rotors or focal impulses become disorganized and develop into AF.[43,85] Although the rotor itself may be stable and regular, the heterogenicity of the surrounding substrate causes fibrillatory conduction.[85]

Given these findings, clinical computational approaches to mapping have been developed. These involve the physiological interpretation of fibrillatory wave activity by analysing widely sampled atrial sites through the insertion of a basket catheter placed sequentially in both atria.[49,87] Spatiotemporal analysis can be performed allowing propagation cines to be constructed.[87] These digital electroanatomical atrial maps, created using novel software

mapping systems can help identify localized sources of AF in the form of sustained electrical rotors and repetitive focal impulses in humans.[87] In this study, rotors were defined as "rotational activity around a centre, and focal impulses were defined as a point of origin of AF from surrounding diastole".[87]

In the CONFIRM trial,[49] computational maps were used to demonstrate that ablation of AF-sustaining sources terminated or consistently slowed persistent and paroxysmal AF in 82% of patients after 2 years.[49] Interpretation of the CONFIRM study and other studies using this technology has been challenging because of the heterogeneous patient population. In particular, the cohort was made up of patients with PAF, PsAF or LS PsAF and some patients had previously undergone a LA ablation procedure. Despite the compelling data from the CONFIRM trial, invasive mapping of AF mechanisms has limitations.

Non-invasive electrocardiographic imaging has also been used to investigate the mechanisms underlying AF.[88] One such technique utilizes a jacket that contains 256 body surface electrodes sited around the patient's torso. Each electrode contains a marker which records its location on a CT scan. This data is then digitalized and transferred to one of the commercially available 3D mapping packages.

The first study to report on this non-invasive mapping technique reported on the frequency of each different putative mechanism. The most-common patterns of AF were multiple wavelets (between 1 and 5 wavelets seen in 92% of cases), many of which also had PV (69%) and non-PV (62%) focal sites. Rotor activity was seen infrequently (15% of cases). In patients in whom potential rotor activity was observed, these rarely made one full rotation before breaking into less-organized wavelets.[88] That said, the areas of rotor activity were consistent over multiple mapping attempts. Interestingly, rotors were only seen in patients with PsAF.
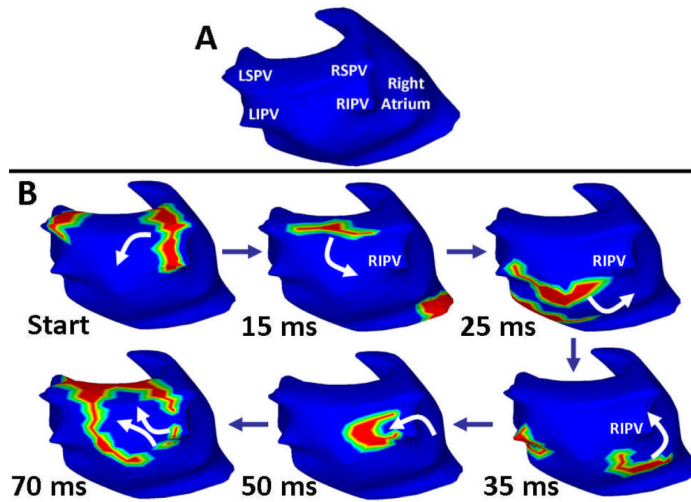
Figure 1-3. Example of rotor pattern and focal site involving RIPV in a patient with persistent AF demonstrated using body surface mapping techniques. A reference showing the posterior wall of the left atrium is provided in panel A. Panel B shows six time-lapse electrocardiographic imaging maps of activation wavefronts (red) in a rotor pattern. In this example, the RIPV acts as a pivot. White arrows show the path of wavefronts down the posterior LA and around the RIPV. Reproduced from Cuculich *et al.* with permission.[88]
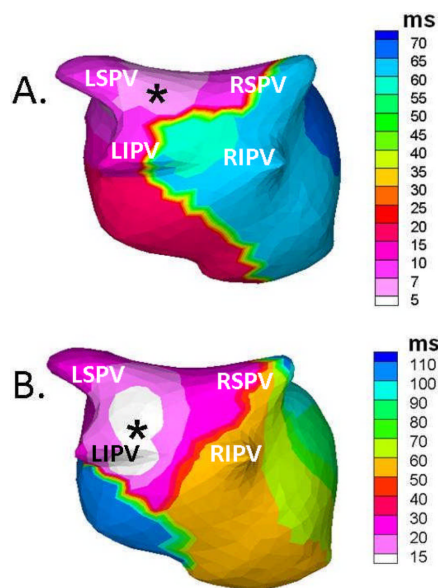
Figure 1-4. Example of left PV focal sites in a patient with paroxysmal AF. Shown are two examples of isochrone maps of both atria (posterior view) at select times during AF. Here, a focal site is seen near the left PVs (*) with radial activation spread. Conduction delay (crowded isochrones) is seen in posterior LA. Reproduced from Cuculich *et al.* with permission. [88]

1.3.6 Targeting Areas of Low Voltage

It has been proposed that diseased myocardium can be identified through areas of low voltage (LVA). Furthermore, it is possible that these areas are important for AF propagation and as such could represent markers for effective ablation targets.[89] The presence of LVA are a significant predictor for AF recurrence following an ablation procedure.[90] There are a number of variables that need to be taken into account when assessing LVA:

- Unipolar / bipolar. Unipolar measurements record signals amplitude between the electrode (local event) and a distant cathode (usually a skin pad). They have the advantages of showing signal direction but suffer significant artefact. Bipolar catheters record the voltage of myocardium between a proximal and distal electrode. As such, the resolution of bipolar mapping is restricted by the spacing between these 2 electrodes, which will range between 3.5 and 7.5mm for a standard mapping catheter depending on the angle of incidence. Smaller spaced catheters are available which may be of use in defining areas of diseased myocardium with a higher resolution, demonstrating areas of heterogenicity which would potentially have been missed.[91] Most centres targeting areas of low voltage will use bipolar mapping. Catheter contact force and orientation will affect recorded voltages. It is possible, especially with multi-electrode catheters, that low voltage will be recorded when in fact there was poor tissue contact. Newer generations of mapping systems attempt to reduce this by utilising the contact force measured by catheter tips to ensure good tissue contact or by only recording voltage samples when the mapping catheter is within 5mm of the anatomy shell.

- Rhythm. Centres predominately map areas of low voltage in NSR. There can be marked variations between voltages obtained while in atrial arrhythmia and

NSR,[92] although a recent study has demonstrated a linear relationship between the voltage measured in NSR and AF; this is an area needing further research.[93]

There is debate in the literature as to the definition of 'low voltage' within the LA. Several studies have used a value of >0.5mV to define normal tissue, diseased myocardium to be between 0.2 and 0.5mV and <0.2mV as likely scar.[90,94–96]

Some studies have reported a relationship between scar identified on gadolinium enhanced CMR and LVA though this remains a controversial area. An interesting study examined the correlation in patients with previous ablation lines and found only a very weak correlation (r=-0.17) between the 2 measurements.[97] Other studies have suggested that the degree of fibrosis in the left atrium can help predict ablation outcome.[89,98,99]

In 2014, Rolf *et al*. described using this technique in 178 patients with PAF or PsAF.[96] Following standard WACA, they identified LVA whilst in NSR and targeted these, either through 'boxing off' or by homogenising with ablation delivered over the whole area.

There are two particularly interesting points to this study. Firstly, is the distribution of the LVA. The LA roof, posterior and antero-septal wall were most commonly affected. Many of these areas are frequently covered by the traditional box-set pattern (described in paragraph 1.3.7) and would have been influenced by this empirical approach; though many of the septal areas may not have. Secondly is this group's assertion that PAF and PsAF should in fact be treated as one and the same with regards to ablation strategy and that these areas of low voltage should be sought in all AF ablation cases regardless of phenotype.

There is a marked discrepancy between LVA and those of focal impulses / rotors suggesting that the 2 techniques are mapping different pathophysiological processes.[100]

1.3.7   Posterior Wall Isolation

The posterior wall of the left atrium has repeatedly been identified as one of the key substrate areas for AF activity.[96,101] Previously, we have discussed the major competing mechanistic theories of AF. Furthermore, we have shown examples of studies where these individual mechanisms have been targeted during ablation procedures. Particularly in the PsAF group, none of these mechanistic strategies have shown significantly superior outcomes.[71]

An entirely different conceptual strategy is to accept the fact that the PW and PVs harbour the bulk of AF substrate. Thus, a potentially effective empirical technique is to isolate this whole area *en bloc*. The first group to attempt this was lead by Karl Heinz Kuch in 1999.[102] They planned to deliver a single ring of ablation scar anterior to the pulmonary veins in 13 patients (Figure 1-5). Unfortunately, the catheter technology at the time was unable to deliver the full lesion set reliably and all 13 patients suffered AF recurrence.

Four years later in 2003, Todd *et al.*, reported on a series of patients in whom the same lesion set was delivered through a combination of surgical (incision) and cryo-ablation.[103] The outcome was much more rewarding; only one of the 14 patients suffered a recurrence of AF. A subsequent EP study in this one remaining patient identified a gap in the cryo line which, when ablated, resulted in AF freedom.
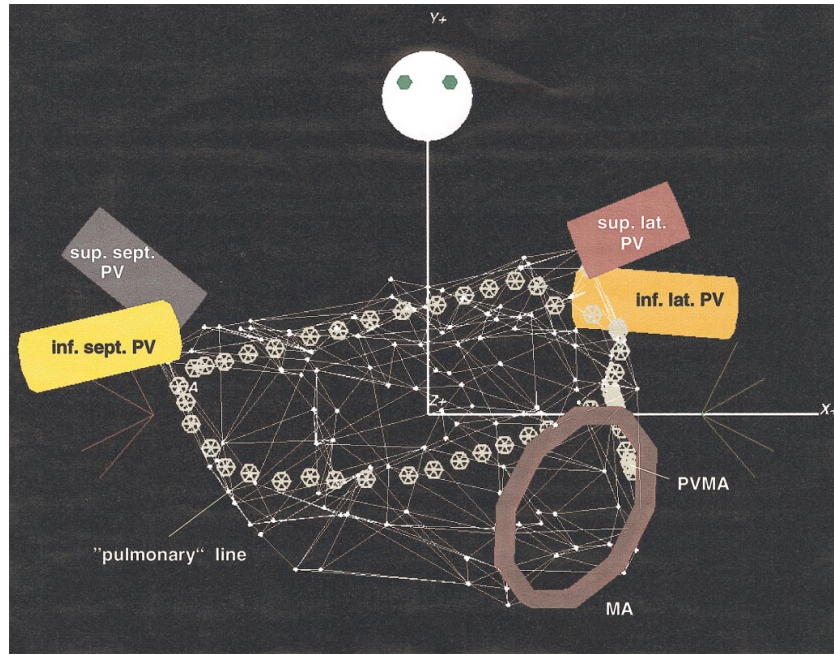
Figure 1-5. 3D anatomical map of the LA showing the intended ablation sites (white dots). Reproduced from Ernst *et al.* with permission.[102]
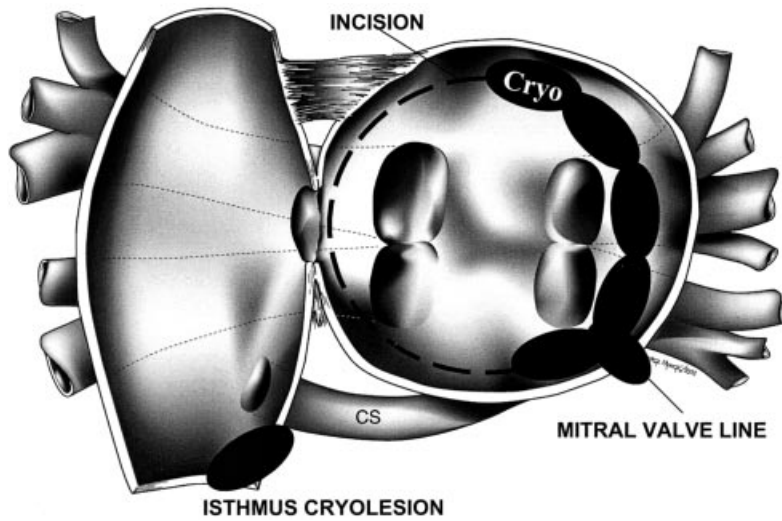
Figure 1-6. Showing the lesion set delivered by Todd *et al.* The incision circumventing the left atrium is shown together with the sites of cyro ablation to complete the electrical isolation of the posterior wall. Reproduced from Todd *et al.* with permission.[103]

More recently, Thomas *et al.* described the feasibility of AF ablation using a pattern similar to that by Todd *et al* using catheter technology only.[104] A study comparing this lesion pattern to 'standard' WACA showed that the single ring patients had significantly fewer recurrences of AF compared at 2 year follow-up.[105] However, when including all atrial arrhythmia, there was no significant difference between the 2 strategies.

The same group have also reported on the arrhythmia mechanism in recurrent cases.[106] In a series of 100 consecutive patients who underwent single ring ablation (66% PAF), 34 went on to a redo procedure. All patients who suffered a recurrence of AF had gaps in their ablation ring. Conversely, recurrences of AFl were found to be due to either peri-mitral circuits or through 2 gaps in the PW ring.

1.3.7.1   Surgical AF Ablation

There are a variety of techniques that can be applied in the open or closed chest for the surgical management of AF.[107] The lesion patterns are variable depending on the device used.

A bipolar clamp can be used in the open chest. This clamp is applied to the epicardial surface of the atrium near each pair of PVs. The clamp action is used to compress the atrial tissue onto the surface of the tool and bipolar RF energy is delivered. This tool causes both tissue damage from the crush effect but more importantly, there is excellent energy delivery to the tissue increasing the chance of a thorough, transmural lesion being delivered (Figure 1-7 A).

Another such technique is to deliver a single-ring lesion set from the epicardial surface of the heart via a minimally invasive thoracoscopic port. This has become known as the 'box-set' pattern. In chapter 2, the reader will be introduced to more about the role of AF ablation during concomitant cardiac surgery and will be presented with the long-term outcomes from a single centre experience in over 100 patients using a form of this ablation. A newer

generation designed to deliver this lesion set is called the Cobra device. It is inserted into the chest 53 minimally invasive Ports. It uses a suction property to enhance the device's adherence to the epicardial surface of the atrium to help ensure transmurality (Figure 1-7 B)

A third novel surgical ablation tool is called nContact. It is applied to the posterior wall of the left atrium via a sub diaphragmatic approach. It can be used both to deliver lesions to the posterior wall and other linear lesions such as a mitral isthmus line. Complete posterior wall 'blanking' can be achieved where not only is the posterior wall isolated in a box fashion, but it is completely ablated in its entirety. This reduces the potential issue of lesion recovery (Figure 1-7 C).

Figure 1-7 has been removed due to Copyright restrictions.

Figure 1-7. (A) The bipolar clamp used to deliver bilateral PV antrial isolation. **(B)** The Cobra device, delivered thoracoscopically to deliver a single ring lesion in a box pattern and **(C)** the nContact tool which is delivered via the sub diaphragmatic approach to deliver sequential linear lesions across the posterior wall **(D)**.

1.3.7.2   Hybrid Ablation Strategies

The series published by Lim *et al.*[106] suggests that early cases of AF recurrence were exclusively due to failure in the adequacy of delivery of the box-set lesion. One possible way to deliver a more durable lesion is to perform both epicardial and endocardial ablation in an attempt to ensure transmurality of the lesion. There have been several commercially available devices designed to deliver this epicardial lesion pattern; one such, Epicor (St. Jude Medical, UK) is discussed in chapter 2.

Atricure, a company who develop novel cardiac systems, have developed a tool which can deliver radiofrequency energy in a box-set pattern on the beating heart via 3 minimally invasive thoracoscopic ports. It has suction properties which help maintain good contact between the device and the epicardial surface, reportedly enhancing the integrity of the lesion delivered. Groups have been using this device in combination with catheter ablation to deliver the box-set pattern. The catheter procedure has been performed either at the same sitting or as part of a staged procedure with a 2 − 3 month interval. The aim is to deliver the epicardial energy first and then map and ablate the gaps via the catheter approach. It is therefore argued that an interval of 2 − 3 months is preferable, as this will allow for any oedema, which may mask incomplete block, to subside.

The group led by Munneretto have led the way in this technique. Their published outcomes from a hybrid strategy, using implantable loop recorders to monitor arrhythmia recurrence, show a freedom from AF rate of 88% at mean follow-up of 28 months (where 25% of the entire group were on an AAD). Five of the 24 patients included in this series required additional catheter ablation at the second stage of the procedure, but the paper does not report the rhythm at time of arrival in catheter laboratory.

One potential key to long term success in PsAF ablation is, in the author's opinion, the development of an effective and readily replicable generic lesion-set that improves on current models and does not rely on the complexities of tailored strategies.

There are very limited cases reported in the literature of isolated LA posterior wall in patients with recurrences of AF. It can thus be hypothesised that:

- Posterior wall isolation is an appropriate lesion set for the ablative management of AF

- Cases of recurrence are predominately due to failures in technology to deliver durable isolation.

1.4   Thesis Outline

1.4.1   Aims

The general aim of this research was to characterise the suitability of posterior wall isolation for the ablative management of AF.

The specific objectives were:

- To investigate the outcome from concomitant epicardial AF ablation at very long-term follow-up.

- To gain an understanding of the difference in the electrical properties of the PW in patients who have historically undergone box-set epicardial ablation in those with freedom from and those with on going AF.

- To investigate the relationship between BMI and LA pressure in an AF ablation population.

- To investigate the long-term outcome from a novel procedure designed on the box-set concept using catheter ablation only.

1.4.2   Overview of The Upcoming Chapters

- **Chapter 2** will report a single centre experience of surgical AF ablation performed on a cohort of 110 patients, the majority during concomitant open chest surgery. This chapter describes the patient mix and provides an analysis of the very-late freedom from AF rates measured by 7-day ambulatory ECG monitoring.

- **Chapter 3** will describe to the reader the electrical properties of the PW in patients who underwent historical epicardial AF ablation. A total of 17 patients are included, 6 of who had excellent outcomes from their original ablation procedure and no further AF at a minimum of 52 months.

- **Chapter 4** explores the possible mechanism of action between BMI and AF burden by investigating the relationship between BMI and LA pressure.

- **Chapter 5** introduces the reader to duty-cycled radiofrequency ablation. The outcome from a novel ablation strategy based on the box-set concept will be reported.

- **Chapter 6** provides a final discussion and conclusion, summarises the limitations of the studies and suggests areas for future development.

2 LATE OUTCOME OF HIGH INTENSITY FOCUSED ULTRASOUND EPICARDIAL ABLATION

2.1 Introduction

Atrial fibrillation is associated with valvular and ischaemic heart disease and as such is commonly found in patients undergoing cardiac surgery.[13] Preoperative AF is an independent risk factor for long-term survival in surgical bypass patients.[108,109] In valvular heart disease patients, those in AF preoperatively are older, have more co-morbidities and poorer left ventricular function than those in NSR. Several small studies have shown survival benefits from being in NSR during valvular heart surgery though it remains unproven whether AF is an independent risk factor for late survival.[110,111]

The ECS consensus expert statement on catheter and surgical ablation for AF supports the use of surgical ablation during concomitant cardiac surgery for patients with PAF, PsAF and LS PsAF.[22] Over 40% of patients with a history of AF who undergo cardiac surgery are offered concomitant AF ablation.[112]

Since the initial introduction of the Cox-Maze procedure over 20 years ago, there have been many developments in the surgical treatment of AF. Currently employed techniques range from the Cox-Maze IV cut-and-sew method to epicardial linear ablation lines delivered through a variety of energy sources. One such energy source is High Intensity Focussed Ultrasound (HIFU). This technology is designed to deliver PV and posterior left atrial wall isolation on the beating heart using an encircling 'cinch' and create left atrial lines using a hand held wand device. By encircling around the pulmonary ostia, it also ablates areas where ganglionic plexi commonly reside and where dense collections of complex fractionated atrial electrograms (CFAEs) are found.

In our centre, we have over 5 years historical experience in using the Epicor HIFU ablation system (St. Jude Medical, UK). Patients with PAF, PsAF and LS PsAF have been treated with this technology, predominantly during concomitant valvular and non-valvular cardiac surgery.

Seven groups have reported outcome data from epicardial AF ablation using the Epicor system in a total of 483 patients summarised in Table 2-1.[113–118] Twenty-four hour ambulatory ECGs have been used in the majority of these previous studies.

Our aim is to assess the safety and efficacy of the Epicor system using 7-day ambulatory ECG monitoring post 2-year follow-up. We present complication rates and follow-up data on our group of patients, with attention to the incidence of AF documented by 7-day ambulatory ECG or pacemaker interrogation.

Study	Number	Event monitor type	Male gender n(%)	Operation Type n(%)	Patient numbers n(%)				NSR n(%)			Device related complications
					PAF	PsAF	LS PsAF	Time of F/U (months)	PAF	PsAF	LS PsAF	
Ninet[113]	103	24 hour holter	59(58)	MV surgery 46(44.6) 2 valve surgery 22(21.3) AVR 17(16.5) CABG 7(6.8) Other 11(10.8)	22(21)	5(5)	76(74)	6	100%		80%	Nil reported
Groh[114]	129	24 hour holter	79(61)	MV surgery 65(50) 2 valve surgery 35(28) CABG (41(32) AVR 20(16) Other 3 (2)	43(33)	20(16)	66(51)	6 12	60(77) 21(90)		39(92) 34(82)	Nil reported
Schopka[115]	110	24 hour holter	66(60)	AVR 30(27) MV surgery 13(11) CABG 37(33) 2 valve surgery 12(10) Other 30(27)	(29)	(31)	(40)	12	(100)	(58)	(44)	Nil reported
Feyrer[116]	103	24 hour holter (at 3 and 6 month)	Not reported	MV surgery 23(22.5) AV surgery (42(41) CABG 11(11) Other 5(5)	37(36)	5(5)	55(53)	6 12 48	(84) (77) (90)	Not reported	(50) (46) (40)	Nil reported
McCarthy[117]	24	30 day (at 6 months)	20(83.3)	MV surgery 5(20.8) AVR 0(0) CABG 5(20.8) Other 1(4.2)	2(8.3)	4(16.7)	18(75)	22	10(35.8)			Nil reported
Mitnovetski[118]	14	24 hour holter	12(86)	MV surgery 3(21) AVR 4(29) CABG 9(64)	4(29)	10(71)		9	4(29)	9(64)		Nil reported
Garcia[119]	30	15 day external loop	21(71)	AVR 15(50) MV surgery 3(10) CABG 10(33) Other 9(30)	4(47)	16(53)		6	5(56)	7(44)		Nil reported

Table 2-1. Summary of previously published series reporting on AF ablation during concomitant cardiac surgery using HIFU (AVR = aortic valve replacement, CABG = coronary artery bypass graft, LS PsAF = long standing persistent atrial fibrillation MI = myocardial infarction, NSR = normal sinus rhythm, PAF = paroxysmal atrial fibrillation, PsAF = persistent atrial fibrillation).

2.2   Methods

2.2.1   The Patients

All patients who underwent an ablation using the Epicor device between the dates of January 2006 and December 2009 were asked to participate in this retrospective study. All patients irrespective of AF classification or LA size were included. Institutional research & development and regional ethics approval was obtained.

A total of 110 patients received an ablation: 76 male and 32 female. The mean patient age was 70. Preoperative AF classification was: PAF 29 (26%), PsAF 37 (34%) and LS PsAF 44 (40%). Forty-eight patients underwent coronary artery bypass grafting, 70 had valve surgery (25 aortic valve replacement, 25 mitral valve replacements, 17 mitral valve repairs and 3 had double valve replacement) and 8 underwent lone epicardial ablation (2 PAF, 3 PsAF and 3 LSPsAF).

2.2.2   Study Design and Investigations

Ninety-three patients retrospectively underwent either a 7-day period of monitoring or pacemaker interrogation, baseline demographics are shown in Table 2-2.

The primary endpoint was the incidence of AF or AFl at >2-year follow-up as assessed by either a 7-day ambulatory ECG or permanent pacemaker interrogation. The secondary endpoint was the complication rate. Baseline patient demographics including age, sex, NHYA functional class, CHA_2DS_2-VASc score, LVEF, LA diameter (as assessed by long axis parasternal view on transthoracic echo) and history of hypertension, diabetes, renal and pulmonary disease or previous stroke were recorded. The duration of preoperative PsAF was determined by a review of all available previous electrocardiograms (ECGs). Any episode of atrial arrhythmia lasting >30 seconds was recorded as a recurrence.[22] [120]

	PAF	PsAF	LS PsAF	p value
Number	26	34	33	
Age (years)	67.8(9.1)	69.8(11)	70.2(6.8)	0.08
Male (%)	70	74	75	
Diabetic (%)	11.5	5.9	9.1	0.75
CCS (0,I,II,III,IV)	12,1,8,4,1	21,0,11,1,0	15,3,9,5,0	0.26
Previous CVE (%)	3.8	5.9	9.1	0.69
CCF history (%)	3.8	17.6	6.1	0.13
Prev MI (%)	7.7	5.9	3	0.74
Hypertension (%)	65	73.5	48.5	0.10
COPD (%)	3.8	0	3.0	0.55
Renal disease (%)	0	2.9	0	0.41
Cholesterol (%)	55.7	35	33.3	0.15
Smoking history (%)	46	47	42.4	0.98
LVEF (>50%, 30-50%, <30%)	77,15,8	82,15,3	88,6,6	0.68
LA diameter (cm)	4.1(0.5)	4.6(0.6)	4.8(0.9)	0.01
NYHA (mean)	2.1	2.3	2.2	0.39
Pre-Op CHA$_2$DS$_2$-VASc	1.5(1.0)	1.8(1.0)	1.6(0.9)	0.57
BMI (kg/m^2)	28(5.7)	27.1(4.8)	28.6(4.8)	0.73
Crossclamp time (mins)	46(22.1)	50.4(25.8)	55.0(29.3)	0.67
CABG (%)	46	41	30	0.50
AVR (%)	46	9	33	0.01
MVR (%)	19	53	58	0.05
Standalone AF ablation (%)	2	3	3	0.98
Follow-up (months)*	29(29)	25(12)	33(27)	0.54

Table 2-2. Baseline demographics of the surgical AF ablation population. (AVR = aortic valve replacement, BMI = body mass index, CABG = coronary artery bypass graft, CCF = congestive cardiac failure, CCS = Canadian Cardiac Society, COPD = chronic obstructive pulmonary disorder, CVE = cerebrovascular event, LA = left atrium, LS PsAF = long standing persistent atrial fibrillation, LVEF = left ventricular ejection fraction, MI = myocardial infarction, MVR = mitral valve replacement, NYHA = New York Heart Association, PAF = paroxysmal atrial fibrillation, PsAF = persistent atrial fibrillation). *Data expressed as median and (Inter Quartile Range) for non-normally distributed data.
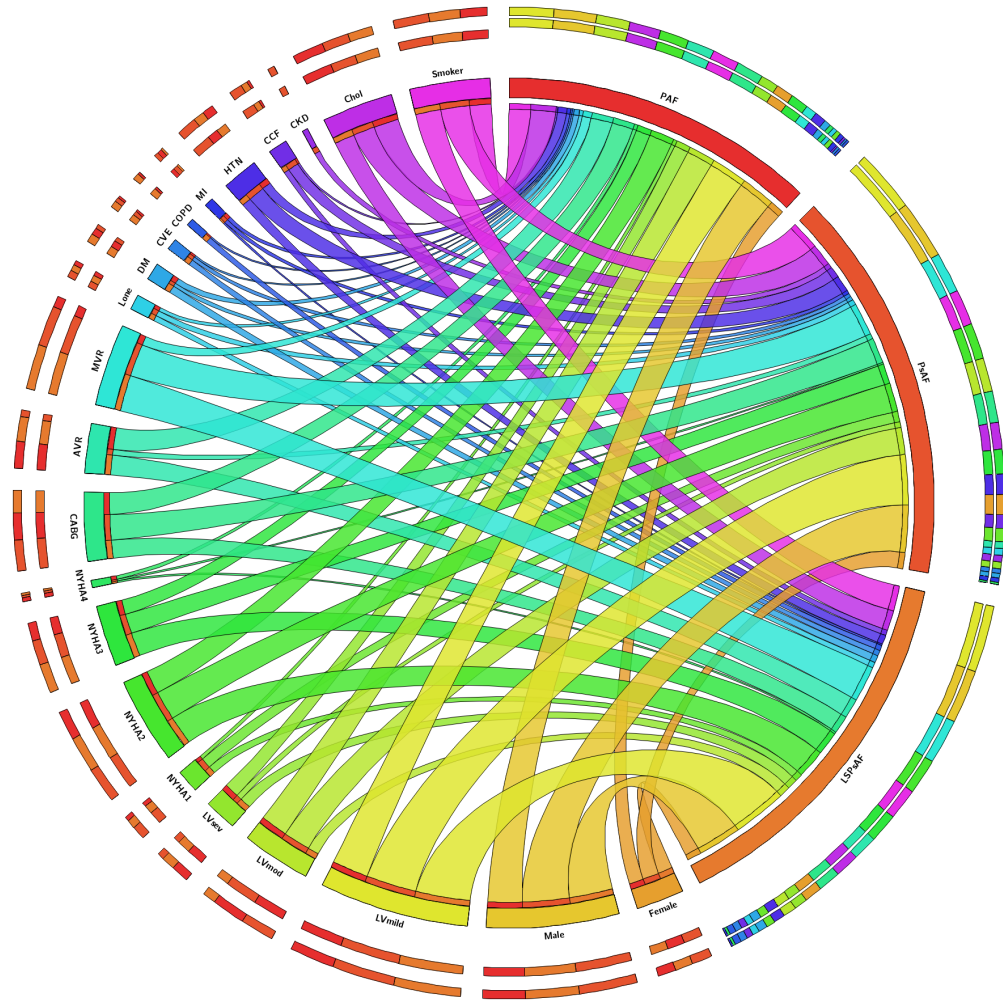
Figure 2-1. Circos plot representing the surgical HIFU ablation cohort.[120] This circular plot shows the relationship between the class of pre-operative AF and specified baseline characteristics. The size of each arc represents group size and the ribbons illustrate relationship size between groups. (AVR = Aortic valve replacement, CABG = Coronary artery bypass graft, CCF = Congestive cardiac failure, Chol = Hypercholesterolaemia, CKD = Chronic kidney disease, COPD = Congestive obstructive pulmonary disease, CVE = Cerebrovascular event, DM = Diabetes mellitus, HTN = Hypertension, LSPsAF = Long-standing persistent atrial fibrillation, LVmild = Normal or mild left ventricular systolic impairment, LVmod = moderate left ventricular systolic impairment, LVsev = severe left ventricular systolic impairment, MVR = Mitral valve repair/replacement, NYHA = New York Heart Association, PAF = Paroxysmal atrial fibrillation, PsAF = Persistent atrial fibrillation).

2.2.3   Surgical Procedure

The surgical ablation technique performed was as previously described.[115] In all cases, the Epicor positioning and sizing system was used. This was passed behind the SVC through the transverse and oblique sinuses and under the IVC. Once sized, the Epicor device was placed in order to create the box-set lesion. HIFU ablation energy was delivered using the UltraCinch device circumferentially around the pulmonary veins on the beating heart before initiation of cardiopulmonary bypass. In all cases a mitral isthmus line was performed using the wand. Acute block was not routinely assessed.

2.2.4   Postoperative Management

All patients received an antiarrhythmic agent (either amiodarone or sotalol) postoperatively for 3 months, along with warfarin, with a target INR of between 2 and 3. The duration of anticoagulation was guided by the individual risk factor profile (based on the CHA_2DS_2-VASc score). Typically, for those patients without a secondary indication for anticoagulation, warfarin was stopped if the score was 0 (or 1 when the only point was for female sex). Patients were reviewed in the outpatient clinic at 3-monthly intervals with standard 12-lead ECG and physical examination.

As part of this retrospective study protocol, a 7-day ambulatory ECG was performed at an interval greater than two-year post procedure. During the blanking period, some patients underwent an electrical cardioversion in an attempt to restore NSR. AF was defined as a period of continuous irregular atrial rhythm on a full disclosure ambulatory holter or permanent pacemaker interrogation lasting greater than 30 seconds.[22] Any atrial arrhythmia reported outside of the study period was recorded as an arrhythmia recurrence.

2.2.5   Statistical Analysis

Continuous variables are expressed as mean ± SD or median and IQR and were compared by one-way analysis of variance. Post hoc analyses were performed with the Tukey test. Categorical variables were compared by chi-square analysis. BMI and LA diameter were analysed as continuous variables, EF was treated as categorical data. Both univariate and multivariate logistic regression analysis was performed to determine the independent predictors of recurrent AF following ablation. A p value of <0.05 indicated statistical significance. All analysis was performed using SPSS version 20.

2.3   Results

There were no statistically significant differences between the three groups at baseline except for LA diameter which was significantly larger in the LS PsAF group. There were significantly fewer patients undergoing AVR in the PsAF group compared to the other two groups. There were no procedural complications or deaths directly related to the ablation procedure. Of the 110 patients treated with HIFU, there were 7 deaths in the follow up period with an in-hospital mortality of 1.8% (n=2) - 4 from post-operative complications unrelated to the AF ablation procedure or use of the Epicor device, 1 died from malignant disease, 1 a traumatic intracerebral bleed and 1 from end-stage heart failure. Patient numbers are illustrated in the CONSORT diagram in Figure 2-2.

Of the 103 surviving patients, 90% (n=93) underwent 7-day ambulatory ECG monitoring greater than 1-year post procedure (median 27 months). For those patients with a permanent pacing system capable of reporting AF burden, this was used instead of a holter (3 patients, 2 confirmed 100% AF and 1 NSR, none of these patients were monitored externally).
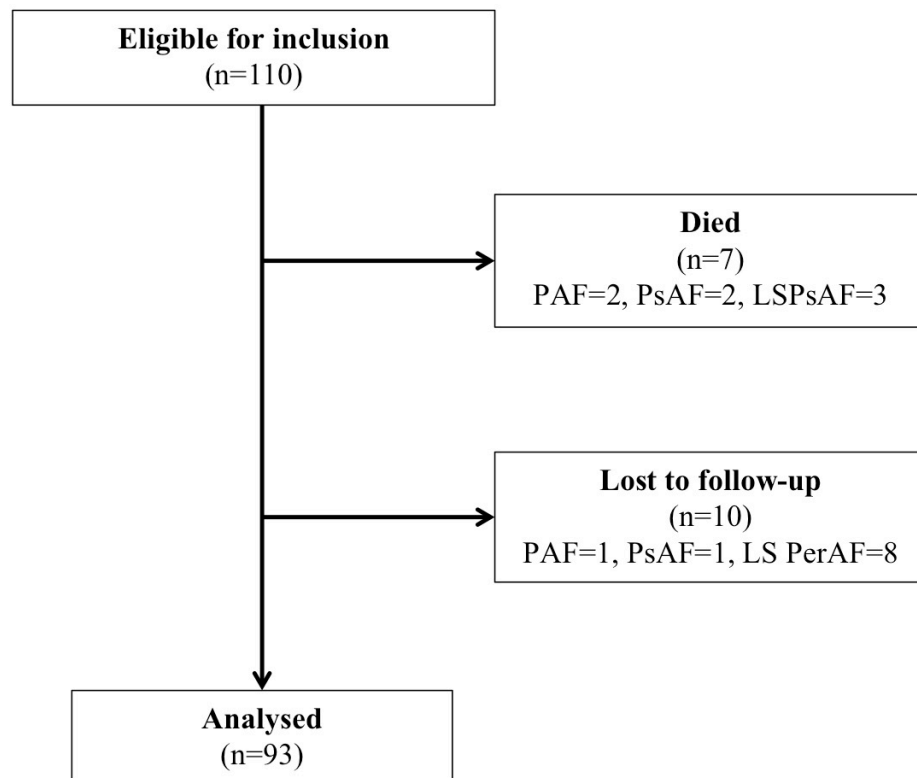
Figure 2-2. CONSORT diagram showing the flow of patients through the study period (LS PsAF = long standing persistent atrial fibrillation, n = number, PAF = paroxysmal atrial fibrillation, PsAF = persistent atrial fibrillation). Reproduced from Davies *et al*. with permission.[132]

The overall results demonstrated that 49% of the patients (n=46) were in sinus rhythm, 1% (n=1) was in an atrial tachycardia, 9% (n=8) were in atrial flutter and 40% (n=38) had evidence of AF. Of the patients in NSR with no evidence of AF recurrence, five were taking an antiarrhythmic drug (AAD) at the time of monitoring (2 on amiodarone, 2 on sotalol and 1 on flecanide). Four patients with evidence of on going AF were on an AAD (1 on amiodarone and 3 on sotalol).

2.3.1 Paroxysmal AF

Of the surviving patients who underwent monitoring, 26 patients had PAF prior to ablation procedure. At >2 year follow up (median 29 months), 81% (21) were demonstrated to be in sinus rhythm on 7-day ambulatory ECG or pacemaker interrogation. The mean LA diameter was 4.1cm and only 11% had any LV impairment. Sixty-five percent were hypertensive, 12% were diabetic and 4% (n=1) had a history of previous cerebrovascular event. The average preoperative CHA_2DS_2-VASc score was 1.5. Of those patients with arrhythmia recurrence, the median number of episodes of AF seen on 7-day holter was 2 and the mean AF burden over 7 days was 78 minutes (SD 61).

2.3.2 Persistent AF

There were 34 surviving patients classified as having PsAF prior to the ablation procedure. At >2-year follow up (median 25 months), 56% had no evidence of AF recurrence on monitoring. The mean LA diameter was 4.6cm, 18% had previous admissions with congestive heart failure, 74% were hypertensive, 6% were diabetic and 3.6% had prior history of cerebrovascular event. The average preoperative CHA_2DS_2-VASc score was 1.8. Only 3 patients with previous PsAF had PAF in the post-operative period. In these 3 patients, the median number of arrhythmic episodes was 4 (mean 7-day arrhythmia burden was 26 hours (SD 14).

2.3.3 Longstanding Persistent AF

Of the 44 patients who underwent ablation for LS PsAF, 33 surviving patients underwent monitoring at >2 year (median 31 months). Only 18% had no evidence of AF recurrence, 65% were in PsAF and 12% were in a persistent atrial flutter (proven to be a left atrial flutter in 2 patients at subsequent electrophysiological study). The mean LA diameter was 4.8cm. Forty-nine percent of patients were hypertensive, 9% had diabetes and 14% had a history of

previous cerebrovascular events. The average CHA_2DS_2-VASc score was 1.6. Twenty-two percent of patients were assessed to have a degree of LV impairment prior to surgery.

Of the patients with recurrence of AF noted on the 7-day holters, 9 (11%) had episodes limited to 1 or 2 of the 7 days. 89% of patients had either normal sinus rhythm or AF throughout their 7-day holter.

Regression analysis was performed to determine factors predicting AF recurrence. All variables were initially tested using univariate analysis. Those with a significance of $p<0.2$ were then tested in a multivariate binary logistic regression model (Table 2-3). AF grade (OR 4.43 (95% CI 2.29-8.58, $p<0.0009$)), and LA size (OR 2.8 (95% CI 1.38-5.7, $p=0.004$)) were significant determinates for AF recurrence. BMI was not a significant determinant under univariate analysis (OR 0.94 (95% CI 0.86-1.02, $p=0.134$)) but when corrected for LA size and AF grade, was found to be significant (OR 0.87 (95% CI 0.78-0.99)). The possible mechanisms by which BMI exerts an effect on AF ablation procedures are discussed in chapter 4.

	Univariate Analysis			Multivariate Analysis		
Variable	Sig	OR	95% CI	Sig	OR	95% CI
AF Grade	0.000	4.43	2.29-8.58	0.001	3.988	1.74-9.10
Sex	0.767	0.87	0.35-2.18			
Age	0.213	1.04	0.99-1.09			
CCF history	0.676	0.74	0.19-2.97			
MI history	0.613	0.62	0.10-3.91			
DM	0.949	0.95	0.22-4.07			
Hypertension	0.873	1.07	0.46-2.50			
Smoker	0.848	0.92	0.41-2.10			
CVE	0.956	0.96	0.18-5.00			
EF >50%	0.906	0.83	0.04-19.99			
EF 30-50%	0.217	0.21	0.02-2.52			
EF <30%	0.875	0.90	0.25-3.22			
AVR	0.767	1.15	0.46-2.88			
MV	0.063	0.44	0.18-1.05			
CABG	0.468	0.74	0.33-1.67			
Standalone	0.483	1.71	0.38-7.60			
BMI (kgm^{-2})	0.134	0.94	0.86-1.02	0.036	0.87	0.78-0.99
Crossclamp time	0.184	1.01	0.99-1.10			
LA Size (cm)	0.004	2.80	1.38-5.70	0.030	2.70	1.10-6.63

Table 2-3. Binary logistic regression showing impact of baseline variables on success rate of surgical ablation. (AVR = aortic valve replacement, BMI = body mass index, CABG = coronary artery bypass graft, CCF = congestive cardiac failure, CVE = cerebrovascular event, DM = diabetes mellitus, EF = left ventricular ejection fraction, LA = left atrial, MI = myocardial infarction, MV = mitral valve surgery)

2.3.4   Additional Interventions

Four patients required permanent pacemaker implantation in the postoperative period (2 patients with CABG, one with AVR and one with AVR plus grafts). 6 patients were cardioverted in the index admission. One patient (lone surgical AF ablation) underwent late catheter ablation. The ablation line was not intact at the time of EP study and further endocardial ablation in an attempt to achieve posterior wall isolation was unsuccessful in maintaining sinus rhythm.

2.4   Discussion

This is the first report of patients undergoing epicardial AF ablation with HIFU with a late follow-up by extended ambulatory monitoring using either a 7-day ambulatory ECG or permanent pacemaker interrogation. Previous groups have reported the recurrence rate of AF post HIFU AF ablation (Table 2-1). Ninet *et al.*[113] reports an overall freedom rate of 85% at 6 months as determined by 24-hour ambulatory ECG monitoring with over 70% of their patient cohort being as described as having permanent AF. They report a 100% sinus rate at 6 months in the combined group of preoperative PAF/PsAF and 80% in those with permanent AF.

Groh *et al.*[114] report outcomes between two classes (a combination of PAF/PsAF and permanent AF) at 6 and 12 months. A significant loss to follow up at 12 months is seen including only 64 of the initial 129 enrolled patients (119 at 6 months). Of the total patients included in follow up, the percentage of patients in NSR are 83%/84% and 86% at 6/12 and 18 months respectively with better results seen in the PAF group (92% vs. 77% at 6 months).

More recently, Feyrer *et al.* reported on the long term outcomes from a similar population, 90% of PAF and 40% of permanent AF maintaining sinus rhythm at 48 months.[116] However, 24 hour holter monitoring was only used at the 3 and 6 month follow up point and for the

late follow up of 4 years, only 30 patients were included with no clear monitoring uniformity. A significant proportion of their patients were on maintenance AADs or betablockers.

An interesting study by McCarthy *et al*. describe the outcomes of 24 HIFU ablation cases.[117] Nine (37%) of these patients who had recurrence of AF underwent an electrophysiological study with view to further ablation. They found absence of intact ablation line in all 9 patients, i.e. it is possible that AF recurrence was due to the inadequacy of the technology to delivery durable lesions.

The study by Garcia *et al*. gives broadly similar outcome rates after the initial ablation using the Epicor device.[119] They go on to provide a description of their patient cohort who underwent an electrophysiological study at 6-months. They found an isolated PW in 38% of cases. They studied 16 patients with successful outcome (i.e. no further atrial arrhythmia) from the initial HIFU ablation and found intact PW isolation in only 4 of them. Unfortunately, the study fails to report the percentage of patients with on going AF in who the PW was isolated. They also do not offer any insight into the conduction times into and out of the box region in either outcome group.

Our results have shown that although freedom from AF can be achieved in over 80% of patients with PAF, in patients with LS PsAF, only 18% have successfully maintained sinus rhythm at >2 year follow up. This contrast to previously published data may in part be explained by our extended monitoring period. Edgerton *et al*. has demonstrated that the reported incidence of AF following surgical ablation is significantly higher when 24-hour holter monitoring is extended to 7-days,[121] and suggested that this is the routine monitoring period following surgical ablation. Our results show that 11% of patients in whom AF was detected may have been misdiagnosed had monitoring been limited to 24 hours.

Another possible explanation for the inferior results seen in our study is the length of follow-up period compared to most outcome series. A natural attrition rate is seen in studies following up AF ablation patients; our median follow-up was 29 months, significantly greater that the majority of previously published data.

There are many possible explanations for the failure to restore NSR in our case series. It is possible that HIFU has not resulted in electrical isolation, or that complete isolation of the posterior wall of the LA is an insufficient lesion set to restore sinus rhythm. Alternatively, it may be that the success Epicor enjoys is not through PWI but through another process such as GP modification or substrate debulking. McCarthy's finding that all patient who underwent late electrophysiological study for AF recurrence had incomplete ablation lines however supports the first explanation. However, without post HIFU ablation invasive EP study data, this issue will remain speculative.

We saw that the outcome of freedom form atrial arrhythmia is dependent on BMI, AF class in the pre-operative period and the LA size. It has long been established in many case series and randomised controlled trials that the LA size is of prognostic relevance with regards to the outcome from an AF ablation procedure.[122,123] Possible mechanisms behind this link are discussed in section 1.2.6.2.2 but include processes such as left atrial fibrosis leading to anatomical and electrical remodelling.

The association between BMI and AF is also well documented, as is the strength of a raised BMI as a poor prognostic marker following an ablation procedure. Perhaps the best study investigating this association is the Legacy Study.[124] This investigated the effect that reducing BMI has on AF burden. It found that in patients with a BMI of 27 or greater, a 9% reduction in BMI lead to a six-fold decrease in AF. Proposed mechanisms of action include a decrease in hypertension driven afterload, reduction in inflammatory responses, a decrease in pericardial fat and prevalence of diabetes. One of the possible mechanisms of action

through which a raised BMI influences AF is through an increase in the mean LA pressure. We investigated this association in chapter 4, but failed to demonstrate any clinically meaningful correlation.

2.4.1 HIFU and Alternative Epicardial Energy Sources

HIFU is an energy source that focuses the ultrasound up to a depth of 1cm. It has the theoretical advantage in that it can be used on the beating heart and can ablate over coronary arteries with minimal risk of compromise to the blood flow. However, the continual washing of the endocardium by blood at 37 degrees and the variable thickness of atria raises the possibility that transmural ablation line integrity cannot be assured. An Italian group have described the histopathological findings following LA surgical HIFU ablation in 2 cases.[125] In both, they found a complete transmural lesion with replacement of the muscle with a fibrous band at 6 and 48 months following ablation.

Besides HIFU, there are several other ablation energy sources available. Radiofrequency (RF) ablation is commonly used during endocardial (catheter) ablation techniques but its use during concomitant surgical procedures gives the operator a method of delivering a continuous transmural lesion set in a rapid and safe setting. However, the PVs must be avoided at the risk of vein stenosis and there remains a possibility of intramural thrombus formation. Oesophageal and circumflex artery damage have been reported. Because of the way the energy is delivered, monopolar RF is not as reliable as HIFU in delivering a transmural lesion. Bipolar RF devices however show better medium term results, particularly in the persistent and long-standing groups.[126] Bipolar energy can be delivered through a variety of different tools and patterns. These are discussed in depth in section 1.3.7.1. Probably the most prevalent in use today include the bipolar clamp which is based on the WACA lesion patters and the Estech Cobra and nContact which delivers patterns based on the box-set.

Cryoablation use helium to cool tissue to around -60°C, eventually resulting in inflammation and fibrosis without loss to stromal integrity.[127] Although results appear similar to RF, cryoablation has certain advantages such as visual confirmation of the ablation integrity, a lower likelihood of causing intramural thrombus and its safety in relation to the pulmonary veins and circumflex artery.

Microwave energy sources have shown poor outcomes though data is lacking. The heat-sink phenomenon resulting from poor tissue contact may result in incomplete ablation lines. Laser ablation uses high-energy optical beams to deliver transmural ablation lines, demonstrated in animal models, though like microwave, there is currently a lack of large-scale human data.

The 2012 consensus guidelines suggest that in patients with LS PsAF, a biatrial procedure should be considered.[22] During the HIFU ablation in this series, no patients received ablation in the right atrium, another factor that perhaps explains why our results from LS PsAF patients were so poor.

2.4.2   Study Limitations

There are limitations to this study. Firstly, although 7-day ambulatory ECG monitoring is considered an acceptable compromise between accurate monitoring and patient inconvenience, it is still possible that periods of AF are going undetected. That said, the aim of AF ablation therapy should be primarily about symptom control and improving disease-related quality of life. Recently, validated AF specific health related quality of life questionnaires have been developed. We would endorse calls for future AF ablation outcome studies to use this as a secondary outcome.

We noted that the majority of surviving patients lost to follow up had LS PsAF. It is possible that this has resulted in a skew in the results. However, the outcome from the longstanding

group is such that it is unlikely to have had a significant impact in the overall conclusion of the study.

The ESC guidelines[22] recommend that PV exit and entry block are assessed at the time of surgical AF ablation; this was not routinely performed in our practise and could possibly have adversely influenced outcome.

2.5   Conclusion

We conclude that high intensity focussed ultrasound surgical ablation for AF using the Epicor system is a safe system. The class of AF prior to surgery, LA size and BMI determine the long-term outcome. Though we saw outcomes for PAF comparable to other ablation systems, the inferior results in the PsAF and LS PsAF groups lead us to suggest that alternative ablation strategies are considered.

3 THE LATE ELECTROPHYSIOLOGICAL CONSEQUENCES OF POSTERIOR WALL ISOLATION IN PATIENTS WITH ATRIAL FIBRILLATION

3.1 Introduction

The mechanism by which AF is initiated and sustained is complex and incompletely understood. It is clear that the majority of triggers for AF reside within the PVs but there are also influential non-pulmonary areas. Though triggers are especially important for PAF, in PsAF a number of different mechanistic theories have been proposed (section 1.2.6.3). Regardless of the mechanism underlying PsAF, some evidence suggests that the bulk of the substrate for these mechanisms resides in the PW of the LA.[81,96,128]

Consistent with these different theories, a wide variety of different ablation techniques are currently being practiced across international centres. The majority of operators rely on a stepwise approach involving PVI followed by further substrate modification. These techniques are sometimes personalised to the individual case.

Alternative ablation techniques rely on the identification and successful ablation of CFAEs, ganglionic plexi (GP), or more novel techniques involved the mapping and ablation of putative rotors[129] or areas of low voltage.[96] These techniques are highly complex, time consuming and rely on the skill of the operator to be able to identify all appropriate electrophysiological targets.

An entirely different strategy is to accept the assumption that the bulk of the substrate on which AF propagates resides within the posterior wall of the LA. Several groups are investigating the application of an empirical ablation strategy that results in posterior wall

isolation.[119,130] There is evidence to suggest that such an end-point may be sufficient in maintaining sinus rhythm in the majority of patients without the complexities involved in other approaches.[119,131]

Once patients have undergone ablation with the box-set, it is unclear whether a successful outcome results from extensive debulking of the LA muscle; GP alteration / destruction; PVI or from isolation of the entire PW and PV substrate.

We wished to determine whether the success of the box-set pattern was due to complete electrical isolation of the PW. One possible model to investigate this was to study the group of patients who had previously undergone AF ablation using epicardial box-set lesions delivered using HIFU as described in chapter 2.[132]

The aim of this study was to characterise the very-late electrical properties of patients in whom the ablation procedure had been a success and compare them to others with on-going AF. We sought to recruit 10 patients from each group for a diagnostic transseptal EP study. This study was performed in accordance with the Declaration of Helsinki and with the approval of the institutional research and development department and of the West of Scotland Regional Ethics Committee. This permission extended to the diagnostic study only; any subsequent ablation procedures were performed as 'usual care' with fully informed written consent being gained prior to the study.

3.2   Methods

3.2.1   The Patients

101 patients who had previously undergone HIFU AF ablation greater than 4 years ago were screened for inclusion in the study (2 of the 103 patients described in chapter 2 died between completion of that study and commencement of this).[132] Seventeen patients agreed to late EP

study, 11 with on going AF and 6 in NSR (Figure 3-1). The studies were conducted at a mean of 65 months post-surgical ablation. Fourteen underwent HIFU concomitantly with cardiac surgery and 3 had surgical AF ablation for lone AF. One patient had a permanent pacemaker in situ (case 5, pre-operative infrequent PAF and in NSR post-operatively).

3.2.2 Recruitment

At routine follow up, patients were introduced to the study and invited to participate. Those who expressed an interest were given a patient information sheet (PIS) and were contacted by telephone to confirm willingness to participate 2-days later. NSR was confirmed by the absence of symptoms, a 7-day full disclosure ambulatory electrocardiogram (ECG) confirming absence of AF (and other atrial arrhythmia) and a 12-lead ECG at time of recruitment. The AF group contained those patients having any documented recurrence of AF following a 3-month blanking-period post surgical ablation. Patients with recurrences solely of AFl were included in the NSR group but described separately. The patient demographics (as at time of epicardial AF ablation) are shown in Table 3-1.
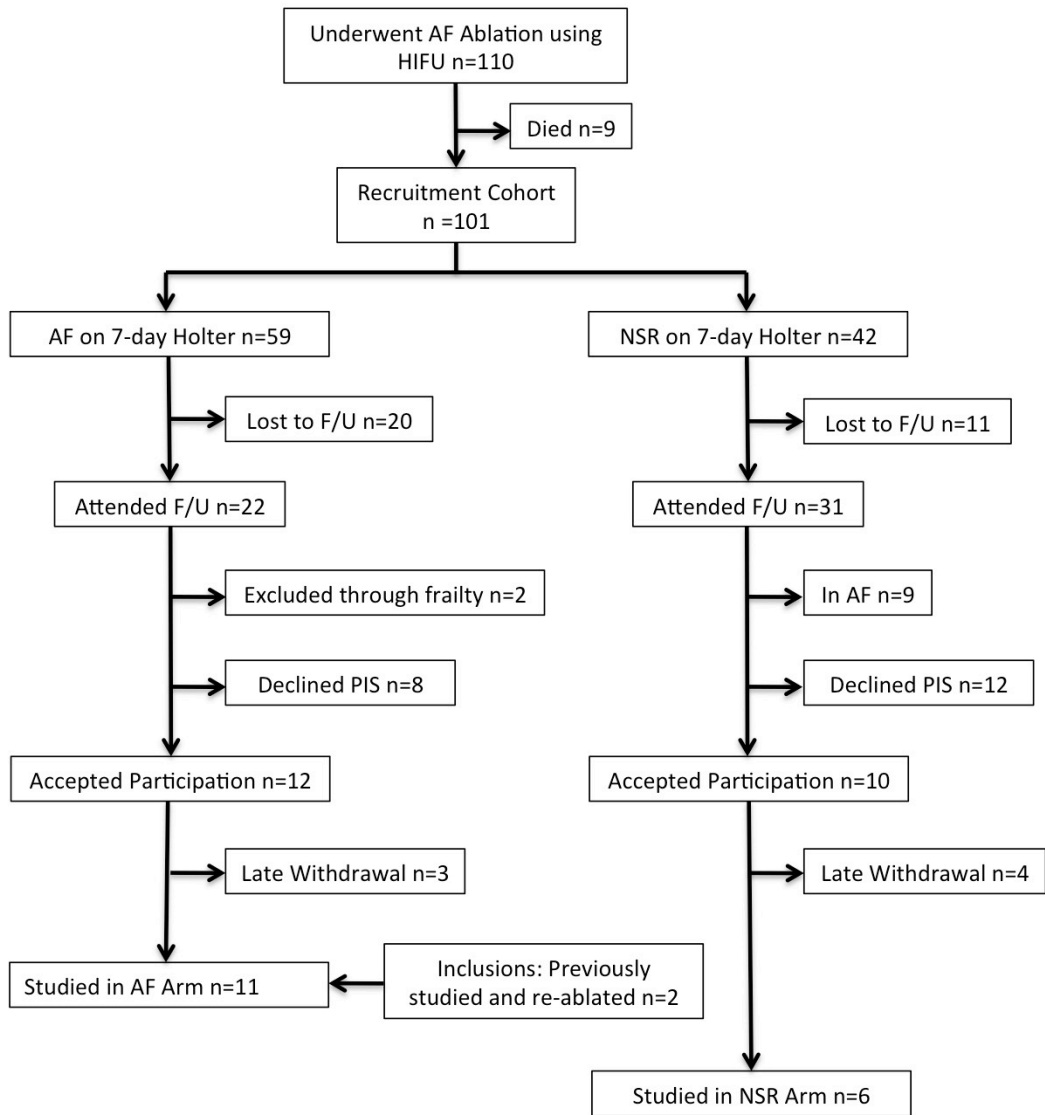
Figure 3-1. Flow diagram showing the journey through the post-operative electrophysiological study. (AF = Atrial fibrillation, F/U = Follow-up, HIFU = High intensity focussed ultrasound, n = Number, NSR = Normal sinus rhythm, PIS = Patient information sheet)

Participant Number	Pre-op AF category	Pre-op AF duration (months)	Pre-op DCCV	Pre-op AAD failed	Operation	Op to EP duration (months)	LA size (AP) / (cm)	EF (%)	PPM	NTH	CAD	Post-op rhythm
01	LSP	14	1	-	CABG	60	4.0	20	-	-	Yes	NSR
02	LSP	36	0	-	MVR	54	4.6	60	-	-	-	NSR
03	LSP	30	0	Flec	MV Repair	96	5.2	70	-	-	-	AF
04	LSP	30	1	-	AVR/MVR	82	2.8	60	-	-	-	NSR
05	PAF	24	0	-	CABG	84	4.6	45	Yes	Yes	Yes	PAF
06	PsAF	6	1	-	CABG/ AVR	52	3.8	45	-	-	Yes	NSR
07	LSP	50	0	Flec, Sot, Amio	Lone	56	4.2	58	-	-	-	NSR
08	LSP	14	1	-	MV Repair	70	5.3	52	-	-	-	NSR
09	PsAF	5	0	-	CABG	63	5.1	35	-	-	Yes	NSR
10	LSP	15	1	Amio	CABG	71	5.1	50	-	Yes	Yes	AF
11	LSP	60	1	-	MV Repair	51	6.2	60	-	Yes	Yes	AF
12	LSP	54	1	-	Lone	17	5.1	60	-	-	-	AF
13	LSP	10	0	-	AVR	98	3.8	45	-	-	-	NSR
14	LSP	48	2	Amio	Lone	13	5.4	30	-	-	-	AF
15	LSP	144	0	-	MVR	83	5.2	55	-	-	-	AF
16	LSP	18	0	-	MVR	60	3.8	60	-	-	-	NSR
17	LSP	24	3	Sot	CABG	43	4.2	60	-	Yes	Yes	NSR

Table 3-1. Post-operative electrophysiological study participant demographics and operative data (AAD = Antiarrhythmic drug, Amio = Amiodarone, BMI = Body Mass Index, CAD = Coronary Artery Disease, CTI = Carvotricuspid Isthmus Ablation, CVE = Cerebrovascular Event, DCCV = DC Cardioversion, Flec = Flecanide, LA = Left Atrial, AF = Atrial Fibrillation, AP = Anterioposterior, cm = centimetre, DM = Diabetes Mellitus, EF = Ejection Fraction, HTN = Hypertension, LSP = Longstanding Persistent Atrial Fibrillation, PPM = Permanent Pacemaker, Pre-op = Preoperative, PsAF = Persistent Atrial Fibrillation, Sot = Sotalol)

	LUPV		LLPV		RUPV		RLPV		PW		Arrhythmia following HIFU	Additional Ablation at EP study?	Endocardial ablation strategy	PWI achieved?
	Exit	Entry	Exit	Entry	Exit	Entry	Exit	Entry	Exit	Entry				
01	192	194	200	190	160	166	166	172	190	226	AF	No	N/A	N/A
02	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Flutter	No	N/A	N/A
03	80	128	No capture	54	152	126	106	132	108	106	AF	Yes	Linear ablation to PW	No
04	270	226	196	192	272	304	220	284	260	252	Flutter	No	N/A	N/A
05	102	92	No capture (no muscle)		176	118	No capture (no muscle)		98	98	NSR	No	N/A	N/A
06	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	NSR	No	N/A	N/A
07	Rapid reversion to AF following DCCV – proceeded onto additional ablation										AF	Yes	Bilateral WACA and roof line	Yes
08	No capture (no muscle)								136	104	AF	Yes	Roof and floor line	Yes
09	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	NSR	No	N/A	N/A
10	Reversion to AF				118	106	Reversion to AF				AF	No	N/A	N/A
11	Reversion to AF following PW testing				145	152	Reversion to AF		120	118	AF	No	N/A	N/A
12	Rapid reversion to AF following DCCV – proceeded onto additional ablation										AF	Yes	Linear ablation to posterior wall.	No
13	Reversion to AF following PW testing – proceeded onto additional ablation								42	40	AF	Yes	Bilateral WACA	Yes
14	Rapid reversion to AF following DCCV – proceeded onto additional ablation										AF	Yes	Linear ablation to posterior wall	No
15	Unsuccessful DC Cardioversion – CFAE throughout PW and PVs										AF	No	N/A	N/A
16	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Blocked	Flutter	Yes	Mitral isthmus	N/A
17	160	138	194	204	148	200	190	186	158	154	AF	Yes	Completion of box-set.	No

Table 3-2. Invasively assessed conduction times in milliseconds (ms) expressed as exit and entry between the pulmonary veins / posterior wall and coronary sinus. (AF = Atrial fibrillation, CFAE = Complex fractionated atrial electrogram, DCCV = Direct current cardioversion, EP = Electrophysiological, HIFU = High intensity focussed ultrasound, PV = Pulmonary veins, PW = Posterior wall, WACA = Wide area circumferential ablation).

3.2.3   The diagnostic study

A transseptal EP study was performed in all patients. Patients with a CHA_2DS_2-VASc of >1 and on-going atrial arrhythmia were anticoagulated with either warfarin (target INR 2.0-3.0) or dabigatran (150mg bd) for a minimum of 3 weeks prior to the study.[133] All diagnostic studies were performed as a day-case using IV sedation (diazemuls and diamorphine titrated to response). Access was gained via the right femoral and subclavian/internal jugular vein. A decapolar catheter was placed in the coronary sinus (CS) and a quadripolar catheter in the right ventricle.

Using a standard Brockenbrough needle, a transseptal puncture was performed to allow passage of a steerable sheath - Channel, (BARD Electrophysiology) or Agilis® (St. Jude Medical) into the LA. Puncture was facilitated using a combination of contrast injection and pressure monitoring. IV heparin was administered to maintain the ACT at >300s for the duration of LA instrumentation. Pulmonary venography was performed for all PVs. A circular mapping catheter (Expandable Lasso or AFocus II, St. Jude Medical) was sequentially placed in all four PVs and flat on the PW.

For patients in NSR at the time of the study, we tested for exit and entry block and recorded the conduction times between CS and PV/PW. Those in AF at the time of the study were cardioverted (200J biphasic AP pad position) on a maximum of two occasions to allow conduction to be assessed.

In selected cases of apparent PW isolation (defined as the absence of electrical activity, or evidence of spontaneous isolated atrial complexes), we tested for pace/detect within the PW. A passed a second catheter alongside the steerable sheath and used it alongside the mapping catheter to test for conduction contained within the isolated PW.

3.2.4   Additional ablation

Further ablation was performed with 4mm irrigated-tip ablation catheters (Smarttouch; Biosense-Webster or TactiCath; St. Jude Medical) facilitated by the use of a steerable sheath (Agilis; St. Jude Medical). The standard ablation settings consisted of an upper temperature limit of 45°C, radiofrequency power of 25 to 40W, and a flow rate of 17 to 30 mL/min. Power delivery was reduced to 25W near the oesophagus. A voltage map was produced using either CARTO (Biosense-Webster) or NavX (St. Jude Medical). Additional ablation was performed in 7 patients with symptomatic drug refractory atrial arrhythmia: 5 cases for AF and 2 for AFl. Additional lesions were delivered either around the pulmonary vein ostia and/or LA roof and floor to complete the existing lines created by the HIFU procedure. The ablation goal was validated PWI in the cases of AF recurrence and termination of marco-reentrant circuits in the case of flutter.

3.3   Results

3.3.1   Free from Atrial Fibrillation – NSR

Of the six patients who had an absence of AF, only 3 were completely free from any atrial arrhythmia recurrence the remaining 3 had experienced episodes of documented AFl. Of the 3 patients where no atrial arrhythmia had occurred since surgical ablation, two had originally experienced PsAF pre-operatively (cases 6&9) and the other infrequent PAF pre-operatively only (case 5).

In cases 6&9, there was no conduction into or out of the PW during capture pacing from the CS together with isolated potentials throughout the PVs and the PW (Figure 3-2).
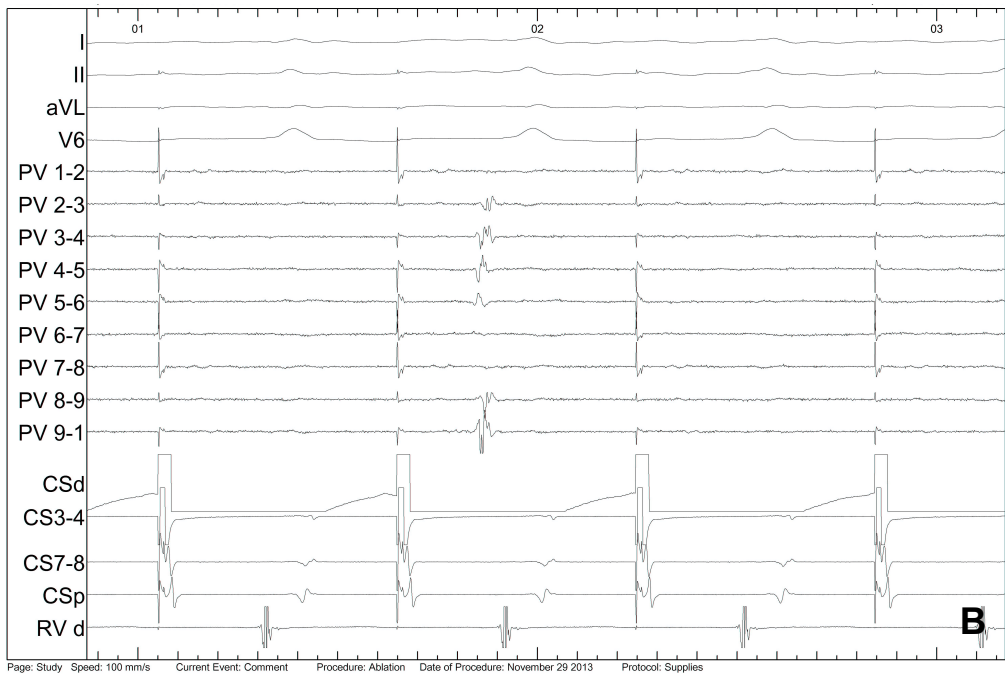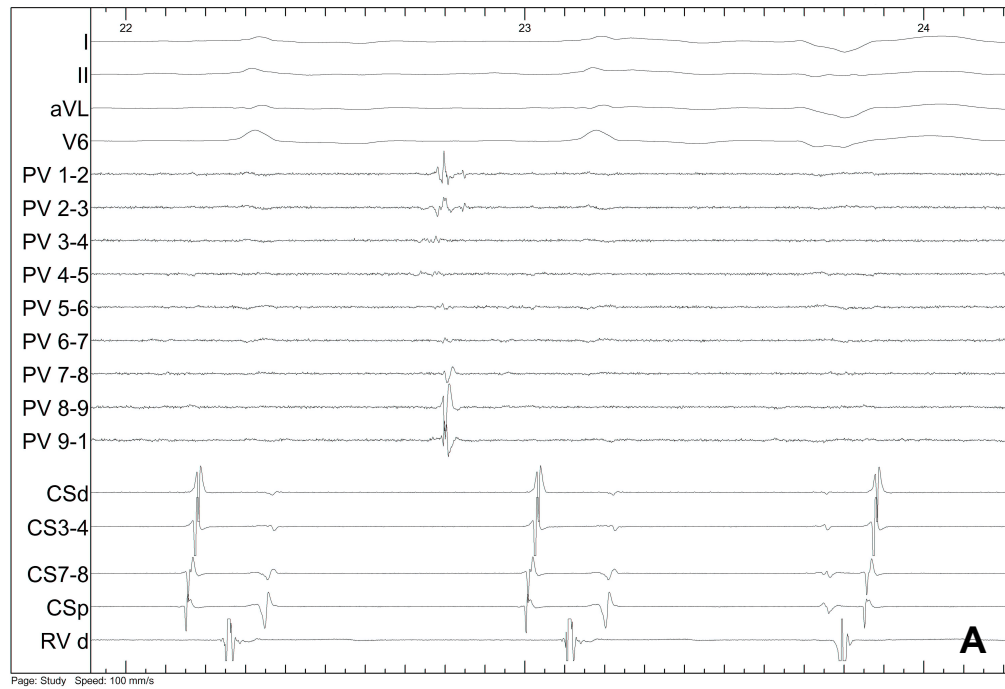
Figure 3-2(A). With the circular mapping catheter (PV) placed flat on the posterior wall, an isolated premature atrial beat is seen showing electrical isolation of this region during sinus rhythm. **(B)** Circular mapping catheter (PV) in the right upper pulmonary vein and capture pacing from the coronary sinus, there is no evidence of conduction into the vein. Also seen is a non-conducted pulmonary vein potential (case 9).

In the patient with prior pre-operative infrequent PAF (case 5), there was no evidence of either exit or entry block from the posterior region (Figure 3-3).
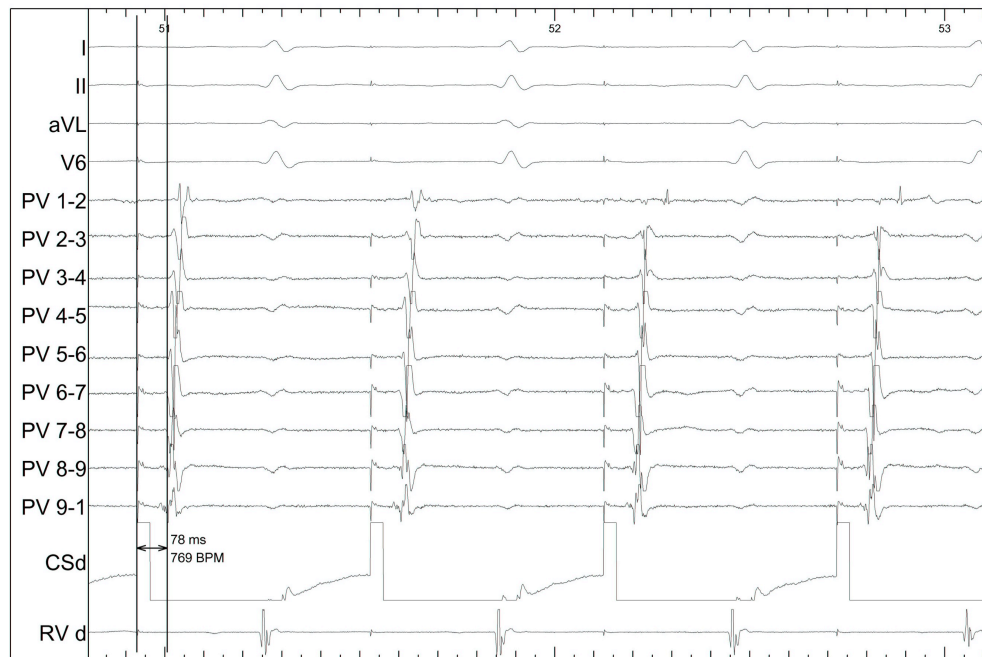
Figure 3-3. In a patient with preoperative PAF and freedom from any recurrent atrial arrhythmia. Pacing from CS distal demonstrates intact conduction between the coronary sinus and the posterior wall with a conduction time of 78ms (case 5).

3.3.2   Free from Atrial Fibrillation – Atrial Flutter

Of the 6 patients with freedom from AF, 3 have experienced documented recurrences of atypical paroxysmal atrial flutter. In 2 cases, the PW was found to be silent with intact block throughout the veins and posterior LA. The other one case had very delayed conduction between the PW and the CS (case 4). The area of conduction gap is identified near the RSPV (Figure 3-4).
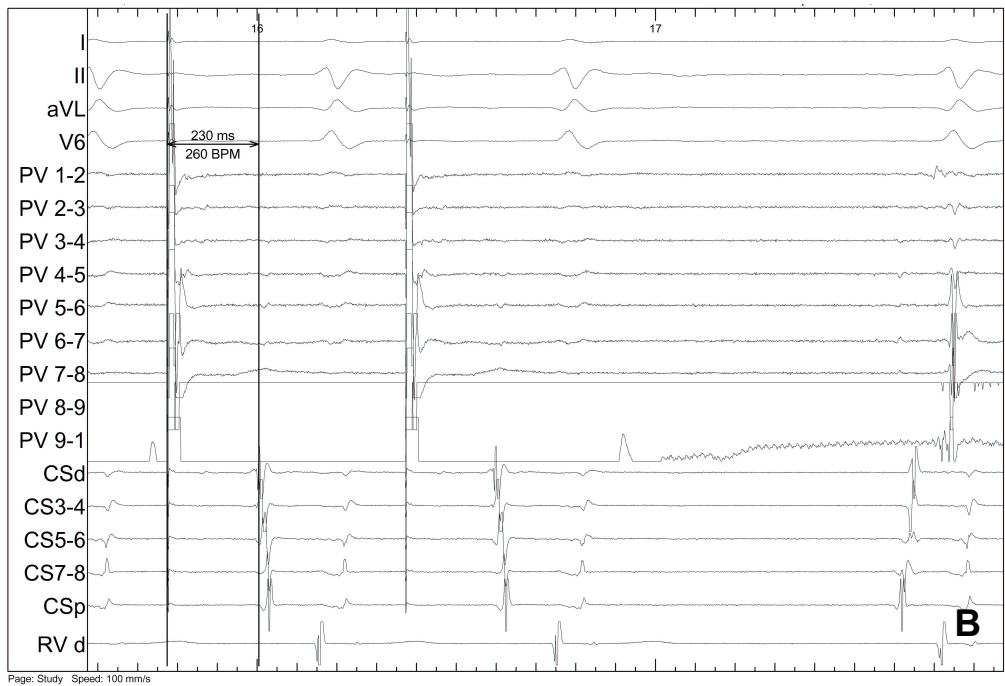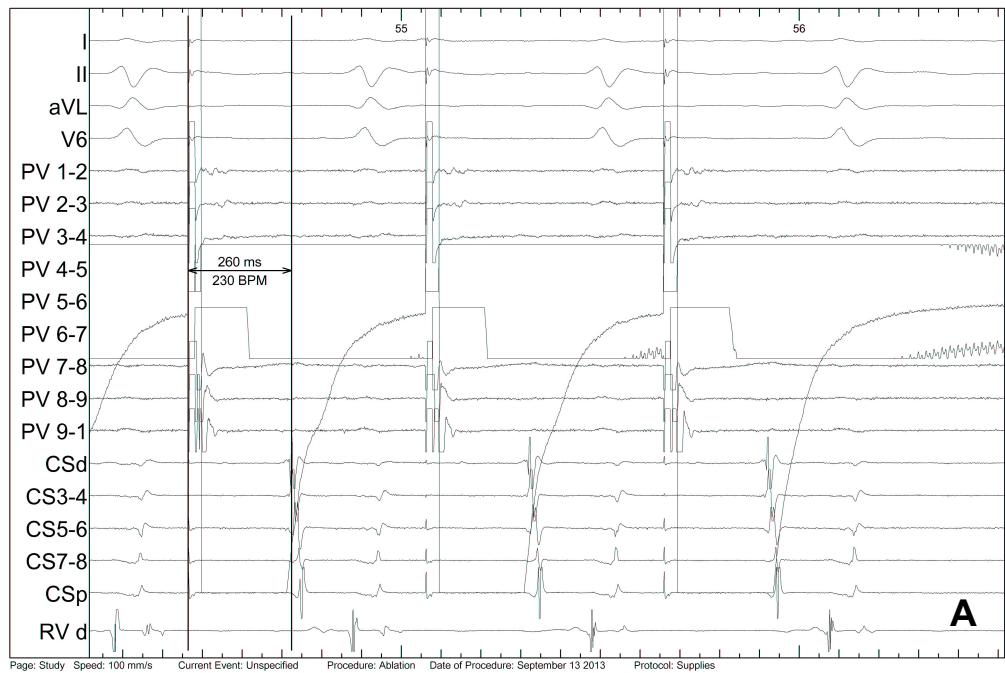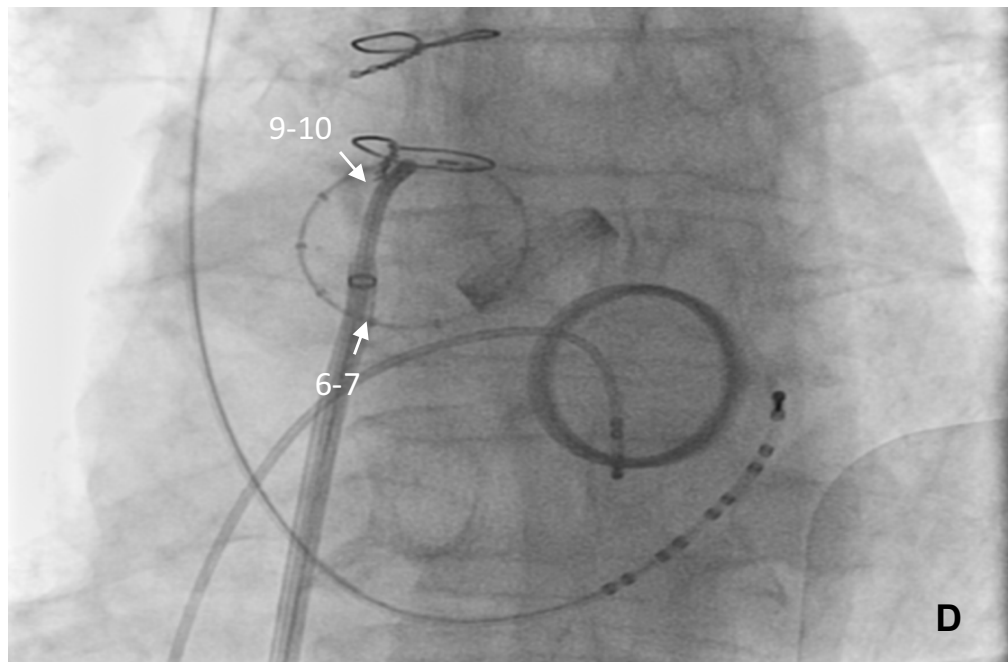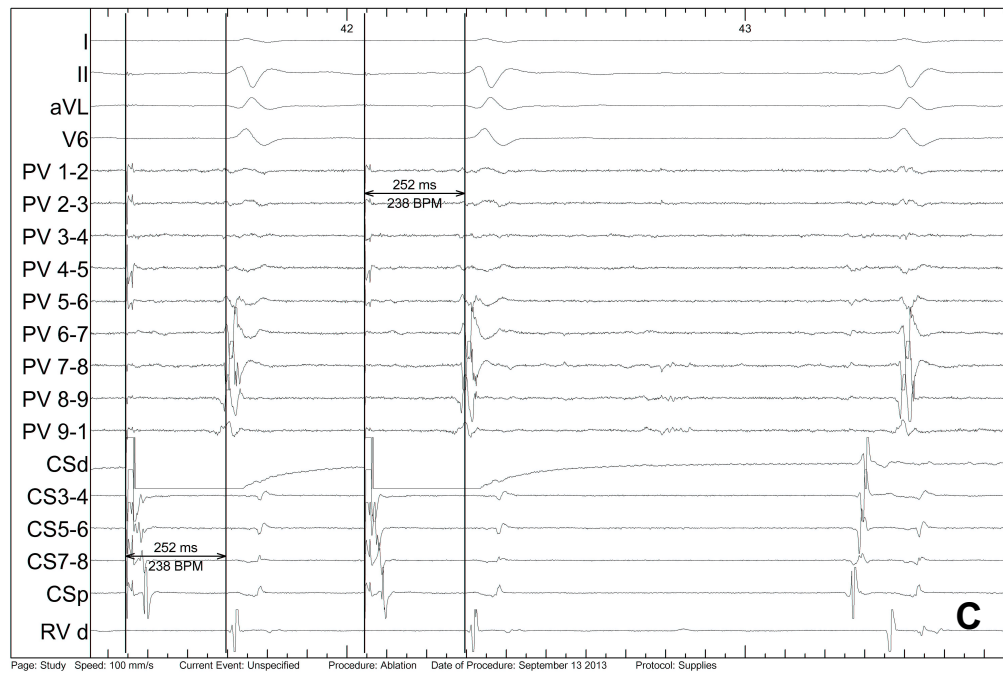
Figure 3-4. In a patient with recurrence of paroxysmal left atrial flutter but freedom from atrial fibrillation. **(A)** Pacing from PV9-10 (on the posterior wall) to the CS has a conduction time of 230ms **(B)** whereas 6-7 to CS is 260ms. **(C)** Earliest signal from CS pacing is seen in 9-10. **(D)** Posterior-anterior fluoroscopy image showing the circular mapping catheter on the posterior wall. The lesion gap was localised to the left side of the roof line (case 4).

In one of the cases of post-operative AFl, the patients remained symptomatic and we proceeded on to ablate a peri-mitral flutter circuit (case 16, Figure 3-5).
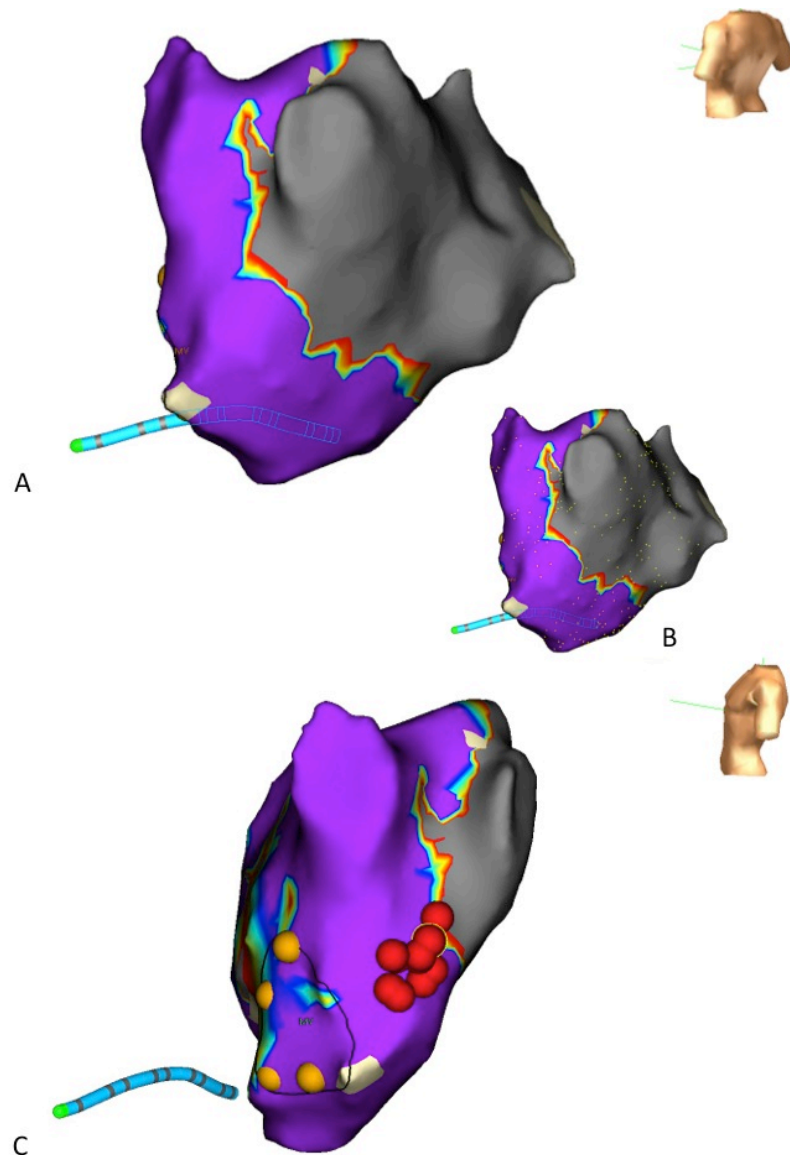
Figure 3-5. In a patient with mitral valve replacement, pre-operative longstanding persistent atrial fibrillation and on-going symptomatic paroxysms of an atypical atrial flutter. **(A)** NavX voltage map (bipolar peak to peak) illustrates the border of the scar delivered by the HIFU device and the electrically silent posterior wall. **(B)** Surface marking show density of recordings over the posterior wall. **(C)** A peri-mitral flutter was successfully entrained by pacing manoeuvres from the coronary sinus catheter and ablated back to sinus rhythm by joining the mitral annulus to the adjacent inferior border of the HIFU scar. Colour coding: <0.2 mV=scar (grey), 0.2 to 0.5 mV=altered atrial tissue (red, yellow), >0.5 mV=healthy atrial myocardium (purple)[90] (case 16).

Figure 3-6. In a patient with aortic valve replacement, pre-operative long-standing persistent atrial fibrillation and on-going symptomatic paroxysms of atrial fibrillation. The circular mapping catheter is on the posterior wall. Capture pacing from the coronary sinus shows rapid conduction to the posterior wall around 40ms.

We studied a total of eleven participants with AF following the ablation procedure. In all instances, persistent atrial electrograms were present throughout the PW and PVs, ranging from grade 1 to 5 in degree of fractionation.[134] DCCV was performed to restore NSR and allow for the conduction between the CS and the PW/PV to be assessed; rapid reversion back to AF limited assessment in 7 patients (cases 7, 10-15). Where tested, the conduction times between the PW/PVs and the CS are shown in Table 3-2. There were no instances of conduction block or PW isolation in any of the persisting AF cases.
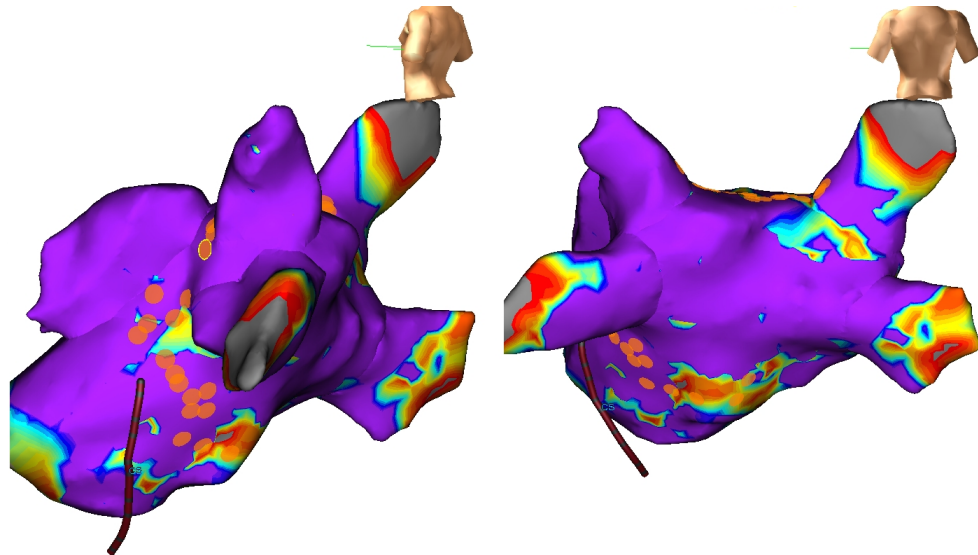
Figure 3-7. In a patient with previous coronary artery bypass grafting, pre-operative longstanding persistent atrial fibrillation and on-going persistent atrial fibrillation. The NavX voltage map (bipolar, peak to peak) shows minimal evidence of scar delivered by the HIFU apparatus and an electrically active posterior wall. The additional endocardial ablation points delivered to complete the box are shown as red dots and the CS catheter is shown in red. Colour coding: <0.2 mV=scar (grey), 0.2 to 0.5 mV=altered atrial tissue (red, yellow), >0.5 mV=healthy atrial myocardium (purple)[90] (case 17).

In summary, of the 11 patients with post-operative AF, none showed any evidence of PW isolation. Conversely, of the 6 patients with absence of post-operative AF, 4 had electrically isolated PW, one had delayed conduction between PW and CS and one (post-operative infrequent PAF only) had intact conduction.

3.3.4   Additional Findings During AF Ablation

3.3.4.1   Example 1 (Case 13)

Though in NSR at the start of the procedure, instrumentation of the LA initiated AF with organised grade 5 fractionated electrograms throughout the PW. Voltage mapping showed established transmural scar line along the left atrial roof and floor. We proceeded to isolate the right PV pair using a standard wide area circumferential ablation approach resulting in rhythm organization (cycle length of 250ms). Following completion of the left PV-encircling lesion set continuous with the roof-line, spontaneous resolution of SR occurred. The PW is shown to contain a marcoreentrant circuit while surface ECGs show NSR (Figure 3-8). This PW block persisted during the administration of 15mg of adenosine, sufficient to caused AV block.
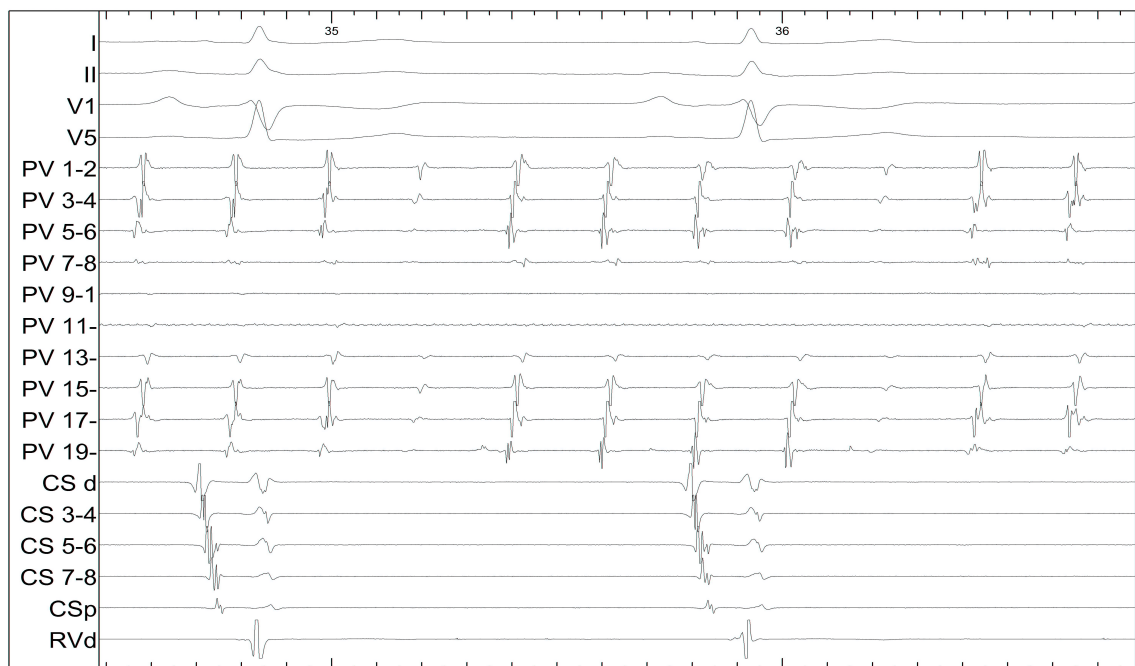
Figure 3-8. Following successful ablation back to sinus rhythm, the circular mapping catheter on the posterior wall demonstrates an enclosed circuit most likely an atypical macro-reentrant in the presence of normal sinus rhythm on the surface electrograms.

3.3.4.2 Example 2 (Case 7)

DC cardioversion resulted in non-sustained sinus rhythm; no conduction intervals were obtained during this short window but the circular mapping catheter on the posterior wall showed fractionated signals. During AF, a voltage map was constructed using CARTO (Figure 3-10); established transmural scar is evident along the floor of the left atrium but was incomplete on the roof and anterior to both pairs of pulmonary veins. Spontaneous return of sinus rhythm resulted from bilateral PV-encircling lesions together with the completion of a roof-line (Figure 3-11).
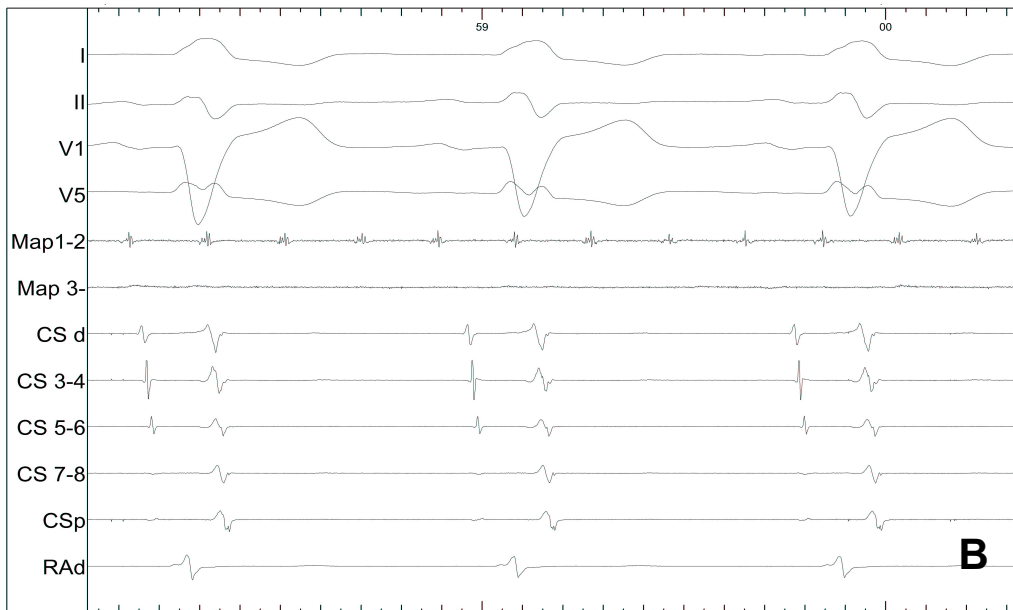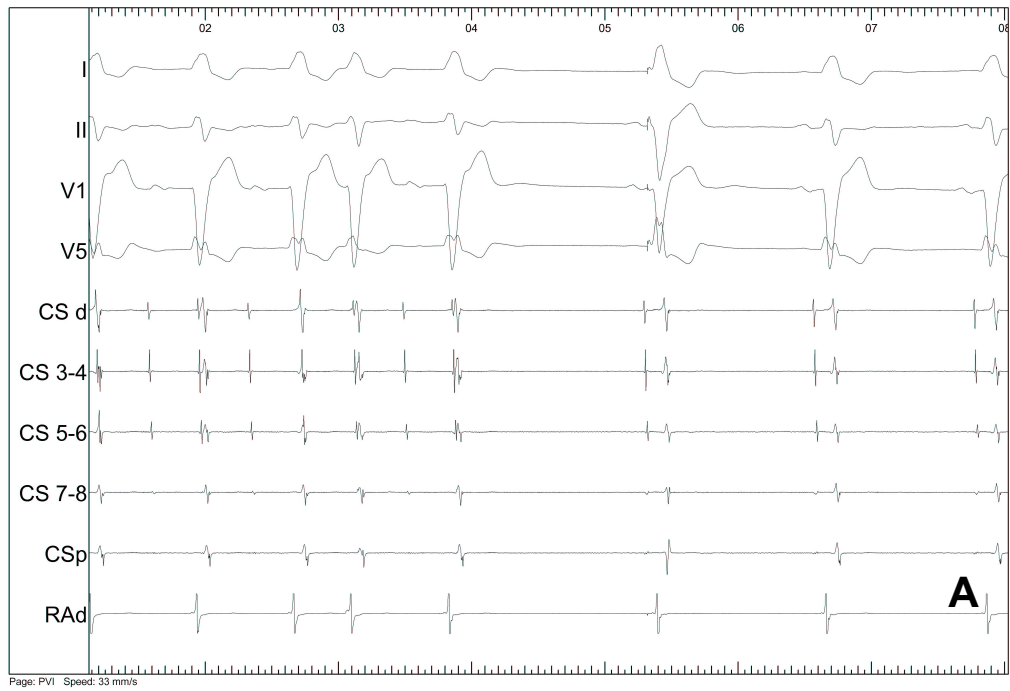
Figure 3-9(A). Completion of the WACA lesion encircling the right-sided veins to join the roof line resulted in reversion to sinus rhythm. **(B)** Following completion of the bilateral PV-encircling lesions joining to the HIFU roof and floor lines, sinus rhythm is seen on the surface electrodes while the PW (here demonstrated through the ablation catheter, Map 1-2) shows the PW to persist in flutter (case 13).
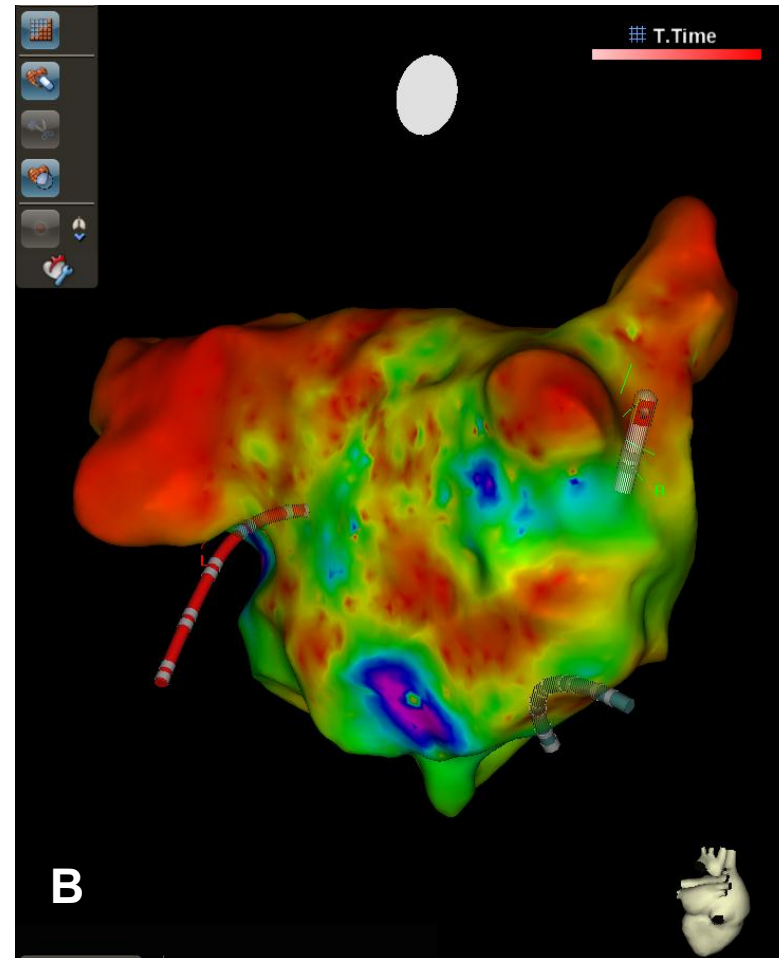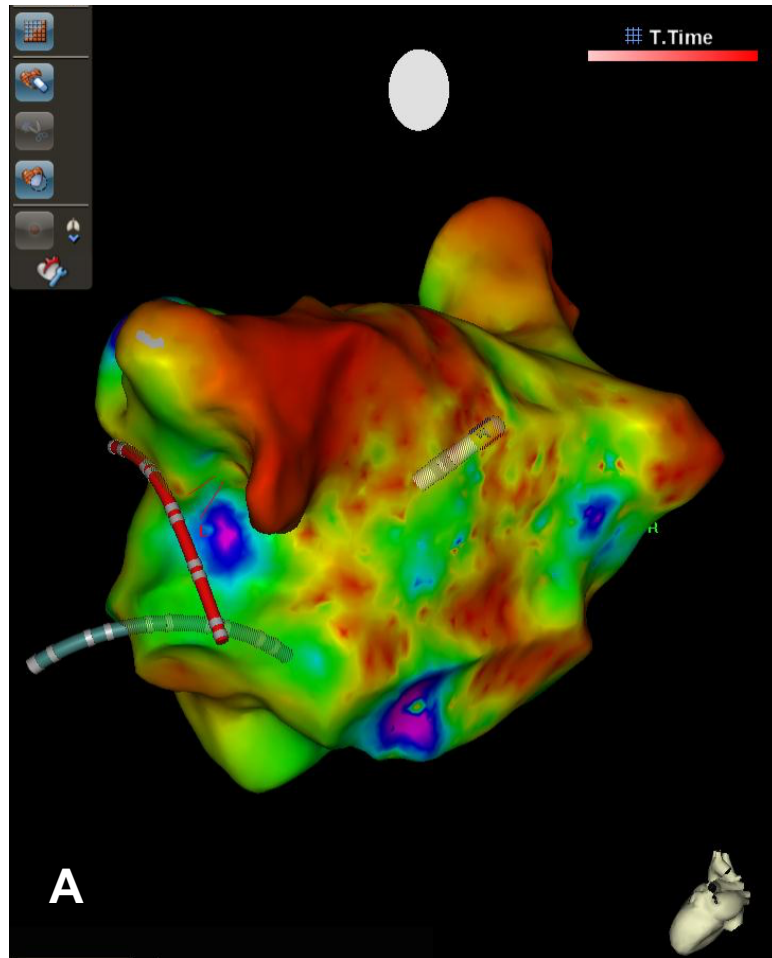
Figure 3-10. CARTO voltage map prior to catheter ablation energy delivery (scale 0.01 to 2.3mV). The red depicts areas of low voltage (i.e. Scar) purple/blue are areas of relative high voltage. We view the posterior wall from the left posterior oblique view **(A)** and right posterior oblique **(B)**. Clearly visible is the scar in red running across the floor of the left atrium which has been previously delivered by the Epicor apparatus.
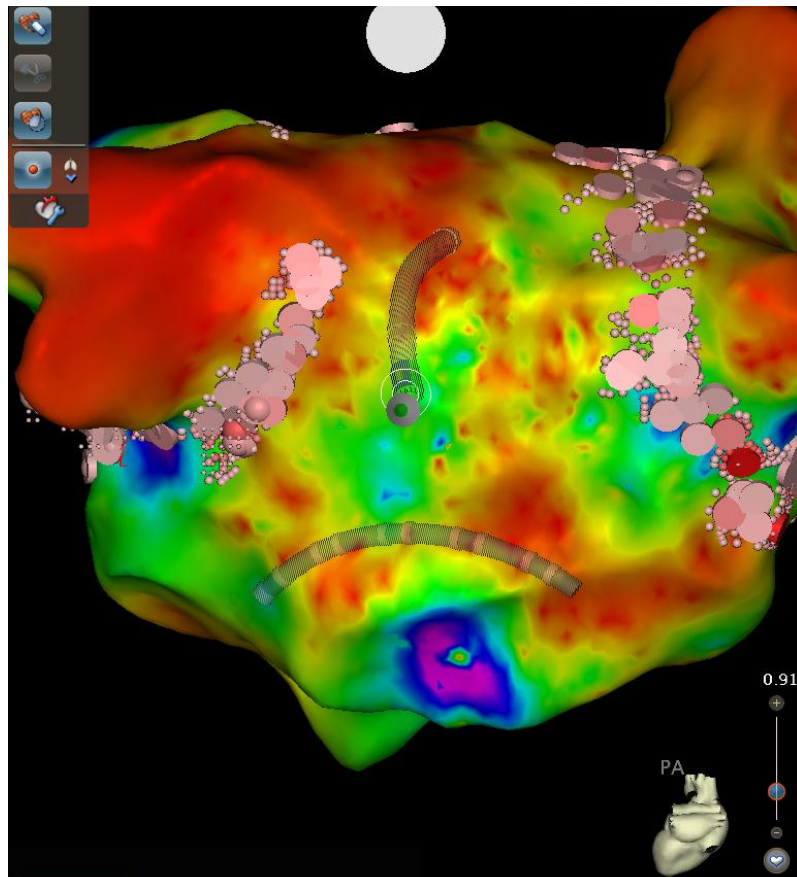
Figure 3-11. CARTO voltage map and superimposed catheter ablation energy delivery markers, here depicted as pink dots (scale 0.01 to 2.3mV). Complete WACA lesion set encircling the right-sided pulmonary veins is viewed. On the left we see the ablation lesions running up the posterior aspect of the left pulmonary vein pair to join the scar previously delivered by Epicor (in red). The ablation catheter is seen here touching the middle of the posterior wall and suggests that there is an enclosed flutter circuit persisting in this region, where the surface ECG showed the patient to be in sinus rhythm (Figure 3-9 B).

3.3.5   Outcome from Additional Ablation Cases

All cases in whom additional ablation was performed remain now in sinus rhythm at minimum of 6-month follow-up (one on a class 3 antiarrhythmic) except one (case 17) in whom the PW was not successfully isolated due to the patient poorly tolerating the catheter ablation procedure under conscious sedation.

3.4   Discussion

Although several groups have reported on the invasive electrophysiological findings following ablation,[119,135] to the best of our knowledge, this is the first study aiming to describe the association between PW isolation and long-term (>4 years) freedom from AF. A summary of the previous knowledge gained from such studies is provided in Table 3-3, most of which is obtained from studies involving redo procedures. As such, there is a skew against reporting what constitutes a successful outcome.

Study	Number	Lesion pattern / Energy	Validated PWI?	Follow-up findings	Conclusions	Complications
Catheter Based						
Ernst *et al.*[102] Case series	13	RF; Box, MI	0%	100% AF recurrence but no prior PWI.	Failure to deliver intended lesion set resulted in 100% AF recurrence.	Nil reported.
Tamborero *et al*[136] RCT	60: 35 PAF, 13 PsAF and 12 LS PsAF	RF; BiWACA, roof and floor line	100%	67% of initial PWI group with recurrent arrhythmia had reconnected roof-line and electrical activity on PW.	"LA posterior wall isolation does not improve the outcome of CPVA"	1 TIA 1 inf. STEMI.
Kumagai *et al*[137]	91 PAF	RF; Box	90%	6 redo cases (3 AFl/AT, 3 AF); all had reconnection – none had intact PWI	"86 (95%) of the 91 patients were free of AF, including six patients after the second procedure without antiarrhythmic drugs. The remaining five patients were arrhythmia-free but required drugs."	Nil reported.
Lim *et al.*[106] Case series	100: 66 PAF, 18 PsAF, 16 LS PsAF.	RF; Box ± MI ± CTI	96%	"30 of 34 patients had breaches in the single ring of lesions that led to resumption of electrical activity in the previously isolated PLA." "… none of the 4 patients who still had intact isolation of the PLA had recurrence of AF after their first procedure…"	"Recurrence of atrial arrhythmias after single-ring isolation of the PLA and pulmonary veins is usually associated with reconnection across the ring of ablation lesions…"	Nil reported.
Sanders *et al.*[138] Case series	27 "chronic" AF	RF; BiWACA, roof and floor line, CTI	Yes	One case of PWI with AF recurrence.	"Isolation of the posterior-LA in patients with chronic AF is associated with prolongation of the AFCL, incremental to the effect of PV isolation, and termination of AF in ≈20%."	1 tamponade 1 temporary phrenic nerve injury.
Chen *et al.*[139] Case series	42: 18 PAF, 14 PsAF and 10 LS PsAF	BiWACA, roof and floor line	100%	6 cases of redo for AF; all had reconnection of PW.	"Silencing electrical activity in the PIA is feasible, and capable of decreasing the rate of AF recurrence."	Nil reported.

Study	Number	Lesion pattern / Energy	Validated PWI?	Follow-up findings	Conclusions	Complications
Surgical based						
Todd *et al.*[103] Case series	14; 11 PAF, 3 PsAF/LS PsAF	Incision and cryo; Box, MI, CTI		100% isolated at 6-day EP study. One late recurrence of AF – gap in cryo line.	"The unique data collected from these patients support the principle of isolation of the pulmonary veins and posterior LA as a curative therapy, regardless of the method used"	1 pleural effusion
Sueda *et al.*[140] Case series	49 LS PsAF	Incision and cryo/RF	Not stated	30% AF recurrence. No EP findings provided.	Nil relevant.	Nil
Garcia *et al.*[119] Case series	30: 14 PAF, 16 PsAF / LS PsAF	HIFU	Not checked	40% arrhythmia recurrence (AF n=6, left atrial flutter n=4, typical flutter n=2). Of those with arrhythmia freedom, 25% had isolated PW at EP study	Gaps tended to be near the RSPV where the HIFU device is closed and are globally more prevalent when a larger cinch device was used.	Nil
Hybrid Based						
Pison *et al.*[141]	23; 1 LSP AF, 9 PsAF, 13 PAF	RF: WACA, roof and floor line	100%	2 patients redo: one with flutter and one AF (gap in ring)	"A combined transvenous endocardial and thoracoscopic epicardial ablation procedure for paroxysmal and recent persistent AF resistant to AADs has a single-procedure success rate of 83% at 1 year."	1 pleural effusion 1 hospitalized for 13 days - chest pain at the insertion sites
Bisleri et al.[131] Case series	45 LS PsAF	Epicardial RF: Box	100% exit block 91.1% entrance block	No correlation made between rhythm and EP findings at time of second stage.	92.6% freedom from AF in those with documented PW isolation at 28-month follow-up.	Nil

Table 3-3. Summary of the previous studies reporting invasive electrophysiological findings following ablation strategies intending to achieve posterior wall isolation. (AFl = Atrial flutter, AT = Atrial tachycardia, Box = Box-set lesion, Cryo = Cryoablation, CTI = Carvotricuspid isthmus, EP = Electrophysiology, HIFU = high intensity focussed ultrasound, LSP AF = Long-standing persistent atrial fibrillation, MI = Mitral isthmus, PAF = Paroxysmal atrial fibrillation, PsAF = Persistent atrial fibrillation, PWI = Posterior wall isolation, RF = Radiofrequency, RSPV = right superior pulmonary vein, WACA = Wide area circumferential ablation).

Possibly the first published attempt a box pattern using catheters was Ernst *et al*. in 1999.[102] Unfortunately, the limited technology available at that time resulted in failure to achieve PWI in all of their cases. Todd *et al*. describes the initial 2003 experience following the combined open-chest surgical and catheter cryoablation box pattern for AF.[103] At 6-days post procedure, all cases had persistently intact posterior wall isolation, determined through epicardial wires. Late recurrent of atrial arrhythmias in one patient resulted in electrophysiological restudy; a gap was found in the posterior wall isolation, closure of which restored sinus rhythm. Todd demonstrated that the isolated PW was able to sustain atrial arrhythmia independent of the remaining atria; a finding that has been replicated in our study (3.3.4.1, 3.3.4.2).

Lim *et al.* provides a comprehensive assessment of the mechanisms of arrhythmia recurrence following single ring ablation delivered by catheter.[106] In 100 patients with an end-point of validated PWI, 69% experienced recurrence of an atrial arrhythmia (35% AF and 34% flutter). In those patients that underwent a redo procedure for recurrent AF, all had gaps in the ablation ring with conduction in and out of this region. In six of the patients, a flutter circuit was established through two gaps in the ring. Four patients had atrial flutter without evidence of AF and were found to have intact isolation of the posterior wall. The authors concluded that "electrically isolating the posterior LA may thus prevent the initiation and perpetuation of AF". This agrees with the findings in our patients to mean follow-up of 63-months.

Tamborero *et al*.[136] randomised patients undergoing AF ablation to receive PV-encircling lesions and roof-line alone or supplemented with a floor line to complete the box-set. A redo procedure was performed in 20% of their patients, and in 67% of initial PWI group, conduction across the roof-line was seen, suggesting that failure of the PWI model was in

part due to reconnection. They found no advantage to PWI attempted through the addition of a floor line compared to PV-encircling lesions and roof-line only.

Sanders *et al.* provide a rare example of AF recurrence in one of 27 patients following box isolation in whom the PWI remained intact at restudy.[138] That index patient required additional "substrate modification" to restore sinus rhythm.

Kumagi *et al.*[137] studied a purely paroxysmal group who, at mean follow-up of 13 months following catheter box-set ablation, showed a 95% rate of freedom from AF. Six of these patients required a redo procedure, three for recurrences of AF and the others from organised/focal arrhythmia. In all cases of recurrence, gaps in the lesions lines were seen. In none of these cases of recurrence was the PW found to be isolated.

A recent resurgence in interest in the box pattern has come about as a result of the development of hybrid AF ablation techniques. These studies have the potential to offer some further insight into the electrical consequences of a single ring approach.[131] To date, little has been published on the association between on-going AF prior to the second (catheter) stage of the hybrid pathway and the subsequent EP findings. As technology matures, this is a key opportunity to gaining a greater appreciation into the mechanisms of PsAF.

3.5   Findings of This Study

Although the EP findings in patients with recurrent atrial arrhythmia following box isolation have previously been described (Table 3-3), much less is known about long term invasive findings, especially in the group of patients with no recurrent arrhythmia. The bulk of the previous data comes from reports of patients undergoing transseptal procedures for organised atria arrhythmias. In the six patients free from AF in this present study, 4 had complete isolation of the PW, one had very delayed conduction through one gap near the

right upper PV and one (who had experienced very little AF prior to surgery) had a non-isolated PW. The only patient who was AF free and was found to have a non-isolated PW was the only patient in the study with infrequent paroxysmal AF prior to surgery. This is maybe the reason for the clinical success despite the apparent electrophysiological failure. It may be that in such patients it is sufficient merely to modify the conduction without necessarily achieving complete PWI for successful outcome.

Perhaps more interesting is our observation that in none of the patients with post-operative AF was the PW isolation found to be intact. It can thus be reasoned that the primary reason for failure to secure sinus rhythm is the failure of the technology used to deliver a complete transmural ablation ring, rather than the inappropriateness of the lesion pattern itself.

3.6   Limitations of Study

The aim of this study was to correlate the late clinical outcome with the electrical properties of the PW. The study achieved this endpoint. However, there are several limitations. Most significant is the low numbers included; a total of 17 patients of which only 6 had freedom from AF. This is in part due to the reluctance of patients with a clinically excellent outcome to undertake a further invasive procedure for no personal gain. The patient information provided was necessarily very comprehensive in describing potential adverse outcomes from what was on their part an entirely altruistic agreement to be studied. We observed a significant attrition rate during the waiting period between agreeing to enter the study and planned study date. All 31 patients who were contactable and eligible for inclusion in the sinus rhythm group were approached.

Secondly, we would have hoped to gain an appreciation of the role of the ganglionic plexi (GP) in AF propagation post epicardial HIFU ablation. GP stimulation was excluded from the present study protocol. No initial 'roadmap' of their location had been made at time of

surgery to guide which sites to address with high frequency stimulation. To attempt to stimulate all potential areas to would have prolonged the procedure beyond what was reasonable for these patients who had agreed to be studied under conscious sedation.

3.7   Conclusions

At long term follow-up, the decisive feature determining whether PW isolation results in freedom from recurrence of AF appears to be either intact isolation of the area or extreme functional delay of conduction into and out of the box-set.

4 THE RELATIONSHIP BETWEEN LEFT ATRIAL PRESSURE AND BODY MASS INDEX

4.1 Introduction

There are many diseases processes associated with an increase in prevalence of AF. It was generally thought that these were processes that tended to alter the pressure load on the LA, leading to an increase wall stress, fibrosis and ultimately fibrillation. Common examples include mitral valve and hypertensive heart disease. Other conditions act through more refined pathways; 15% of patients with hyperthyroidism develop AF.[142] Proposed mechanisms for this include elevation of LA pressure secondary to increased left ventricular mass and impaired ventricular relaxation,[143] ischemia resulting from raised resting heart rate, and increased atrial ectopic activity.[144]

For a long time, obesity has been considered by many to be an independent risk factor for the development of AF. The mechanism of action is likely to be complex and involve multiple pathways. Conditions associated with obesity are themselves recognized risk factors for AF; hypertension, diabetes and obstructive sleep apnoea to name a few.

The LEGACY study investigates the relationship between BMI and AF burden.[124] The authors offered 415 patients with a BMI of >27kg/m^2 and AF the chance to participate in a weight reduction program. Outcomes are reported in three main groups; less than 3% weight reduction, 3 to 9% weight reduction and greater than 10%. They reported a statistically significant reduction in AF burden with weight loss.

Pathak *et al.* provide a comprehensive discussion on possible mechanisms of action of the link between BMI and AF. Factors such as obstructive sleep apnoea, inflammation,

pericardial fat and diabetes are all suggested as associated co-morbidities. In section 2.3.3 we report that the BMI of the HIFU cohort was an independent risk factor for AF recurrence following ablation when analysis was corrected for both LA size and AF grade (p=0.036, OR 0.87 (0.78-0.99)). We hypothesised that this effect was mediated, at least in part, through an elevation in the LA pressure.

To investigate this, we aimed to assess the relationship between mean LA pressure and BMI in an AF ablation cohort. We hypothesised that there would be a positive correlation between the two variables. In this two centre retrospective study, we collected data from transseptal studies in patients who have undergone AF ablation and compared them with the BMI at time of procedure.

4.2   Methods

156 consecutive patients from two high-volume sites (Derriford Hospital Plymouth and the Bristol Heart Institute) were included in the study. BMI data was retrospectively collected from the electronic databases. Mean LA pressure was determined using data recorded on Mac Lab following successful transseptal puncture. Readings was taken when clear steady-state pressure have been achieved. An example is shown in Figure 4-1. As the interpretation of pressure tracings was subjective, pressures was recorded independently by two experienced observers. Both took readings from the same set of pressure tracings and recorded them without collaboration. We performed intra class correlation analysis to check for observer reliability.

4.2.1   Statistical Analysis

A scatter plot was produced charting LA pressure and BMI. Visual assessment identified outliers in both data points; we elected to use Spearman's Rank correlation for analysis. A $p < 0.05$ was considered statistically significant.   Subgroup analysis was performed by

selectively running analysis excluding patients with specific characteristics (on ACE inhibitors, type of sedation and hypertension). Intra-observer reliability was assessed using Cronbach's alpha.
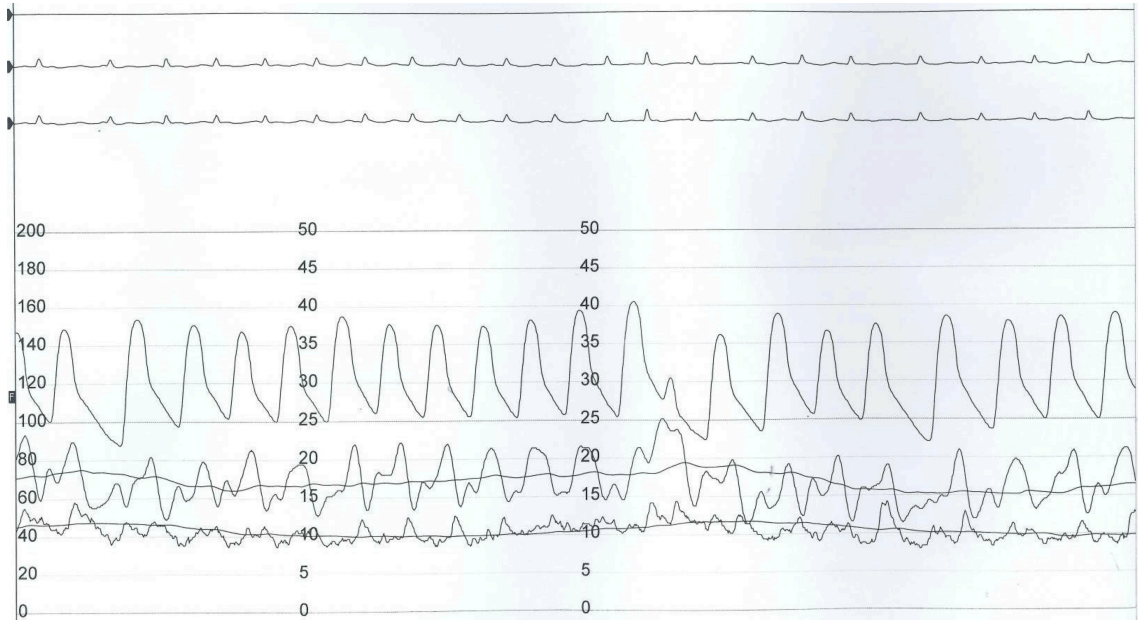
Figure 4-1. Example of a pressure tracing taken during AF ablation. The top tracing depicts the arterial waveform. The left atrial pressure is shown on the middle curve with both a real-time and mean trace. The bottom curve illustrates the real-time and mean pressure of the right atrium. In this example, the men left atrial pressure was judged to be 17mmHg by one observer and 18mmHg by the second.

4.3   Results

A total of 156 patients were included in the study. The procedures were performed between 2009 and 2015. Patient baseline demographics are shown in Table 4-1. Additional analysis was performed by excluding certain individual patient groups; these also failed to show any clinically meaningful correlation. These results are shown in Table 4-2.

Analysis of intra-observer variability was used to check for the reliability of the left atrial pressure recordings. Cronbach's alpha was 0.993, showing an excellent degree of agreement between the 2 independent observers.

Demographic	N (%)
Age/years	60.0 (9.2)
Male: Female	
BMI	28.5 (4.0)
OSA	27 (17.3)
Hypertension	95 (61)
Diabetes	14 (9)
Smoker	32 (21)
ACEi	56 (36)
Betablockers	93 (60)

Table 4-1. Baseline demographics of study patient population (ACEi = Angiotensin Converting Enzyme Inhibitor, BMI = Body mass Index, OSA = Obstructive Sleep Apnoea).

Excluded Parameter	Spearman's Rank Correlation	p Value
ACEi	0.146	0.155
Betablocker	0.276	0.036
OSA	0.136	0.139
Smoker	0.157	0.090
Hypertension	0.227	0.081
Normotensive	-0.020	0.854

Table 4-2. Correlation values with the exclusion of specified patient groups (ACEi = Angiotensin Converting Enzyme Inhibitor, OSA = Obstructive Sleep Apnoea)
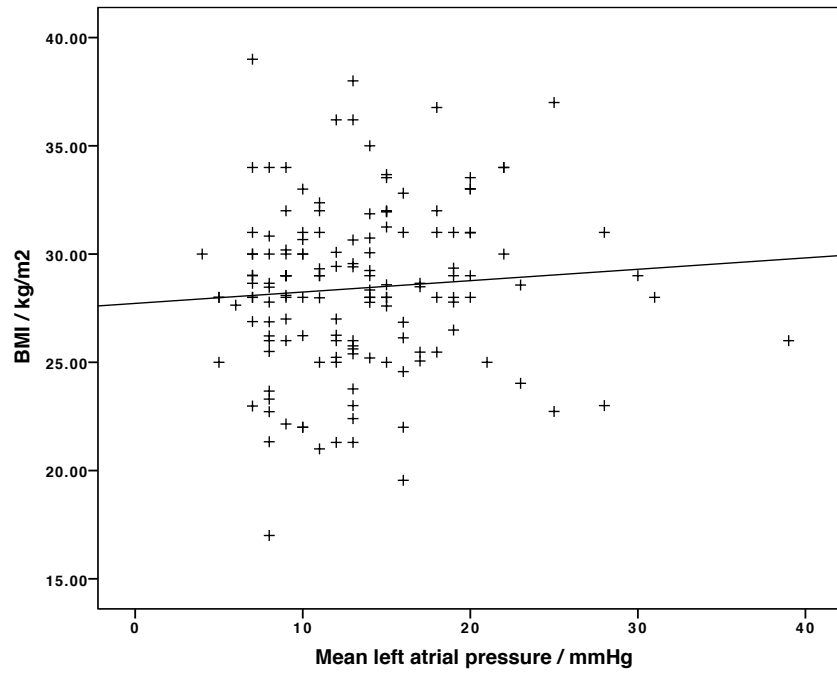
Figure 4-2. Scatterplot representation of the association between BMI and mean LA pressure. A line of best fit is shown (BMI = Body mass Index)

4.4   Discussion

The improvement in outcomes from invasive AF management has resulted not only from a better appreciation of what constitutes an appropriate lesion set, but also from an improved understanding of the importance of patient selection. Patient characteristics that confer a poor outcome from medical and ablative strategies have been well-documented and there are a multitude of prognostic markers for the success of ablative procedures. Age, AF phenotype, LV impairment, dilated LA, comorbidities such as sleep apnoea, obesity, hypertension, LA fibrosis, and inflammatory markers have all been shown to be independent markers for a poor outcome.[145–147]

 Not only does obesity convey a risk of recurrence following an AF ablation procedure, but it is also an independent risk factor for *de novo* AF onset. A recent population study of over 18,000 patients showed that every 1 kg/m^2 reduction in BMI during follow-up was associated with a 7% reduction in the risk of first time AF occurrence.[148]

The link between obesity and AF is complex. Some theories suggest that is mediated primarily through an elevation in the LVEDP which in turn causes an increase in the mean LA pressure. This small study aimed to investigate whether the association between BMI and AF was mediated through an increase in LA pressure. Through the analysis of 156 consecutive patients, we have failed to demonstrate any such meaningful correlation between the two parameters.

It is likely that the mechanistic link is far more complex. For example, another well-established comorbidity is obstructive sleep apnoea (OSA), which is itself closely correlated with BMI. It may be that OSA acts directly through elevation in LA pressure or through persistent hypoxemia, hypercapnia and surges in sympathetic tone.[149] Pericardial fat which increases in obesity has also been associated with AF, both in the pre- and post ablation

setting. Again, the mechanism by which pericardial fat becomes pro-arrhythmic is unclear but may involve adipose infiltration of the myocardium or more complex inflammatory pathways.[150] The GPs which supply the autonomic control to the myocardium are encased in epicardial fat. It has been suggested that increase in fat coverage enhances proarrhythmic behaviour mediated by both the sympathetic and parasympathetic systems, but much work is needed to clearly define these pathological processes.

It is possible that our findings have failed to detect a genuine association. Haemodynamics during an ablation procedure differ to those during 'real life'; the patients are either heavily sedated or under a general anaesthetic. Both anaesthesia delivered through propofol or sedation via benzodiazepines can lead to a decrease in the systemic vascular resistance resulting in a drop in afterload with usually little or no compensatory increase in stroke volume or heart rate.[151]

There are weaknesses in this analysis. Most importantly, we have failed to take into account the degree of mitral valve disease, the severity of which will tend to increase mean LA pressure, independent of BMI. That said, very few patients with haemodynamically significant MR are accepted for AF ablation, so this should not have exerted a great skew effect on our analysis. Correlation analysis through Spearman's rank will also tend to account for this small number of potential outliers.

Based on these findings, it is likely that the mechanism of influence between BMI and AF is mediated through more complex pathways than merely elevation in mean LA pressure, though this may still play some part.

5 PERSISTENT ATRIAL FIBRILLATION ABLATION USING THE TIP-VERSATILE ABLATION CATHETER

5.1 Introduction

For patients with PsAF, the debate over the optimal ablative lesion set continues. PVI alone may be an inadequate solution with only 48% arrhythmia free off AAD at 18 follow up in the recently reported STAR AF II trial.[71] There is a spectrum of additional approaches currently being deployed to achieve the substrate modification required to improve PsAF ablation outcomes (section 1.3).[22] Strategies have been combining PVI with roof and mitral isthmus lines, targeting putative rotors, CFAEs or areas of low voltage, or ablating the GP.[22,71] All have been reported to give largely similar success rates.[71,152]

Surgical (epicardial) ablation is being revisited, particularly in selected patients with unfavourable anatomy or during concomitant cardiac surgery. Many of these surgical approaches aim to deliver the box-set lesion pattern. There is a growing body of evidence to suggest that this empirical pattern is effective in abolishing PsAF.[153] Groups are now examining the role that this lesion pattern has to play in catheter ablation.[105,154,155]

Between 2009 and 2013, we investigated deploying lesions in a box-set pattern from a purely endocardial approach using a combination of the Pulmonary Vein Isolation Catheter (PVAC) and the Tip-Versatile Ablation Catheter (T-VAC, Medtronic, Inc.). Here, we report our experience to date including a comprehensive description of the technique, complication rate, long-term (>1 year) outcome and procedural limitations. Outcomes from first time ('*de novo*') and all including redo procedures ('all procedures') are reported.

5.2   Methods

5.2.1   The Patients

Forty consecutive patients with symptomatic, drug resistant PsAF who had undergone 44 ablation procedures between the years of 2009 and 2013 at our institution were retrospectively entered onto a database. Eligible procedures were identified by a data search through the local procedure database. PsAF was defined as any single episode that lasted greater than 7 days.[22] Characteristics such as LA size and duration of AF had been considered when selecting patients for an ablation procedure, though no formal parameters were applied. Baseline characteristics are shown in Table 5-1.

The primary endpoint was freedom from atrial arrhythmia (all arrhythmia and AF only) at late (>1 year) follow-up off AAD. Secondary endpoints were time to first arrhythmia recurrence post 3-month blanking period, freedom from atrial arrhythmia on and off AAD, procedural and fluoroscopy duration and complication rate.

The study was performed in accordance with the Declaration of Helsinki and with the approval of the local research and development department and Queen's Square ethics committee. The written informed consent of the participants who required further rhythm monitoring as part of the study was obtained.

	All procedures (n=44)	*de novo* (n=27)	p value
Age/years	56 (11)	57 (12)	0.77
Male	37 (84)	21 (78)	0.62
BMI	28.6 (4.0)	28.1 (3.6)	0.66
Diabetes	2 (4.5)	2 (7.4)	0.63
CAD	2 (4.5)	1 (3.7)	1.00
SHD	4 (9.1)	3 (11.1)	1.00
Hypertension	17 (38.6)	9 (33.3)	0.65
Stroke	3 (6.8)	1 (3.7)	1.00
OSA	1 (2.5)	1 (3.7)	1.00
Amiodarone refractory AF	16 (36.4)	11 (40.7)	0.71
Duration of AF/months*	62 (66.5)	41 (30.7)	0.18
LA Vol / cm^3	148 (44.3)	150 (44)	0.89

Table 5-1. Baseline demographics of the T-VAC 'de novo' and 'all procedure' groups with inter group differences. (AF = Atrial fibrillation, BMI = Body Mass index, CAD = Coronary artery disease, LA Vol = Left atrial volume, OSA = Obstructive sleep apnoea, SHD = Structural heart disease). *Data expressed as median and (Inter Quartile Range) for non-normally distributed data.

5.2.2 Ablation Procedures

Historic ablation was performed under either general anaesthesia or with IV sedation. Access was obtained via the right femoral and subclavian / internal jugular vein. Anticoagulation was delivered by either warfarin discontinued and bridged by low-molecular weight heparin (pre-2010), or uninterrupted oral anticoagulation with a target INR of 2.0 to 3.0. Heparin was administered intravenously following successful transseptal puncture to maintain the activated clotting time (ACT) at >300 seconds. Transseptal sheaths were continually flushed with heparinised saline (2 ml/min). Procedural duration was defined as the time between first needle insertion and final sheath removal. Cumulative fluoroscopy duration and radiofrequency energy dose and duration were recorded at the end of the procedure.

5.2.2.1 Multielectrode Ablation Catheter (T-VAC) Technique

Pulmonary vein isolation (PVI) using PVAC has been described previously.[156] Briefly, following successful transseptal puncture, a 9F sheath (Channel, Bard Electrophysiology) was positioned into the left atrium to allow selective venography of all four pulmonary veins (PV). The PVAC catheter was deployed via the channel sheath to sequentially isolate all 4 PVs; catheter was placed 1.0cm into the PV and baseline PV electrogram recordings were made (5 bipolar recordings, 16 x amplification and filter settings 100-500Hz). This was repeated during coronary sinus (CS)-pacing. The pacing threshold for capture via the PVAC catheter within the PV was measured prior to ablation. The PVAC was then placed on the antrum of the PV and the optimal rotational position was found to maximise contact. Energy was applied over a 60 second period with a target temperature of 60°C. Applications were made using 4:1 mode. In general, 4 applications were made per vein rotating the catheter to ensure arcs of ablation overlapped around the circumference of the PV antrum. Entry block was indicated by abolition of the pulmonary vein potentials (PVPs) observed prior to ablation within the vein. When all PVs appeared isolated the PVAC catheter was removed.

Following removal of the PVAC catheter, the T-VAC catheter was inserted into the LA via the steerable sheath. The T-VAC catheter is a steerable linear ablation catheter with 6 electrodes capable of independently delivering unipolar or bipolar energy. Starting at the junction of the right upper pulmonary vein, sequential linear lesions were made in a sweep across the left atrial roof to the left sided veins. The catheter was then deployed at the lateral LA wall with the tip extending to the isolated area of the left lower pulmonary vein and applications made in a line directed towards the coronary sinus. Here, the catheter was directed parallel to the CS and then across the LA floor to the right sided PVs before being brought up to complete the encircling of the PVs and the PW via the interatrial septum anterior to the right sided veins (Figure 5-1). In 3 cases the lesion pattern was mapped using the LocaLisa 3D mapping system (Figure 5-2). Each application was for 60 seconds using a 2:1 mode and a target temperature of 60°C. The empirical deployment of T-VAC was guided purely by single plane fluoroscopy. Total energy delivery durations are shown in Table 5-2.

Complete electrical isolation of the PW was not validated in any of the cases. Additional ablation was performed in areas with dense CFAE (defined visually as local continuous deflections with multiple components crossing the baseline) where these were observed during catheter movements.

In cases where typical right atrial flutter had previously been documented, a carvotricuspid isthmus (CTI) line was performed in the RA. This was done in most cases using the T-VAC catheter in a reverse configuration.

PV isolation was then re-checked and additional ablation delivered as required. In addition to confirming absence of conducted PVPs in NSR, exit block was confirmed by pacing via the PVAC catheter within the PV. Acute procedural success was defined as exit and entry block

from the pulmonary veins together with the empirical deployment of T-VAC linear lesions. Electrical isolation of the PW was not sought as a procedural endpoint.
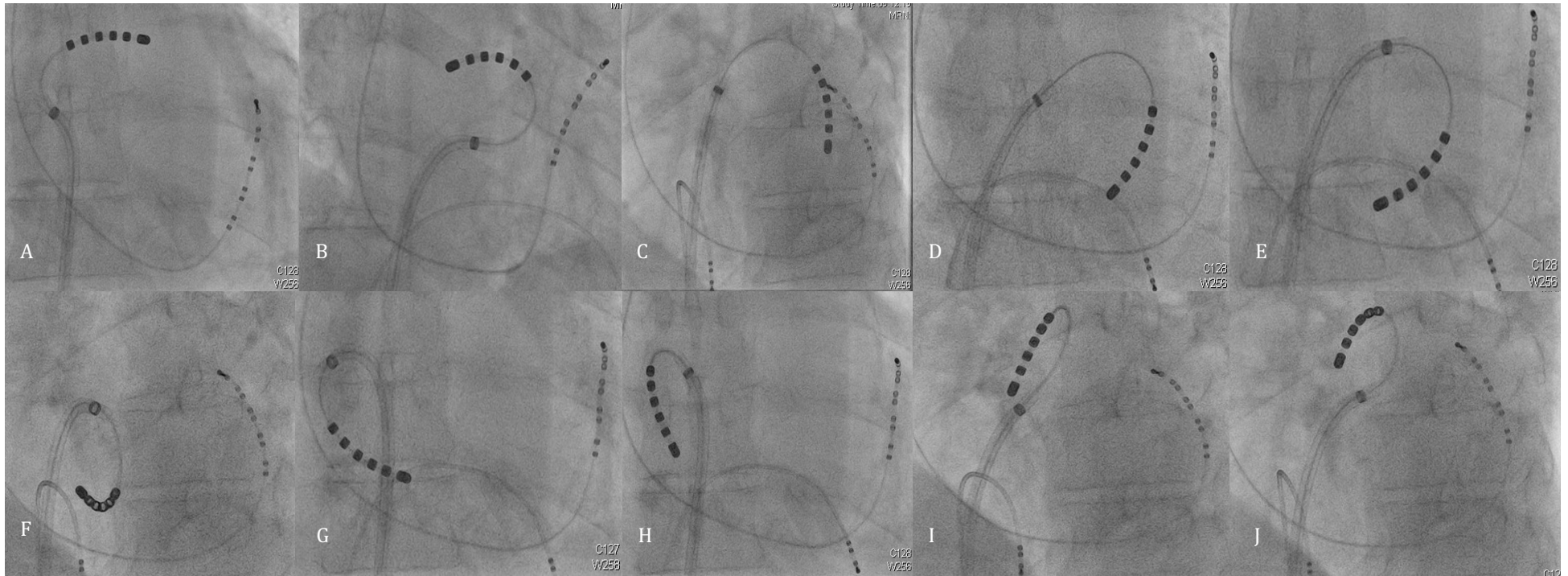
Figure 5-1. Fluoroscopy images of the T-VAC deployment: left atrial roof to the left sided veins **(A, B)**; lateral LA wall to the isolated area of the left lower pulmonary vein directed towards the coronary sinus **(C-E)**; directed parallel to the CS **(F)** and then across the floor of the LA to the right sided veins **(G)** before **(H)** being brought up to complete the encircling of the PVs and the posterior wall via the interatrial septum anterior to the right sided veins **(I&J)**. Reproduced from Davies *et al.* with permission.[157]
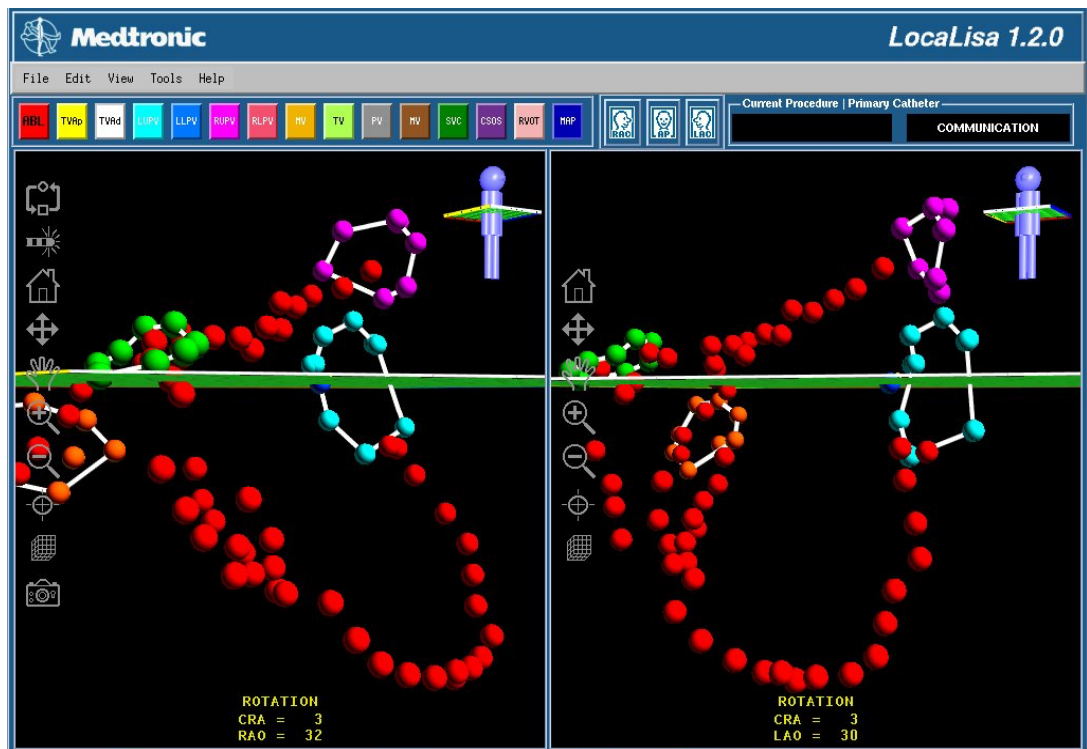
Figure 5-2. PVAC and T-VAC lesion patterns displayed using LocaLisa 3D system. Although we were able to use the software to depict the T-VAC catheter, the red lesions were added manually. In this case, the integrity of the box-set appears complete but posterior wall isolation was not achieved. Reproduced from Davies *et al*. with permission.[157]

5.2.3   Post Procedural Management

AADs were continued throughout the 3-month blanking period and then withdrawn at the discretion of the managing physician. DCCV was offered for sustained symptomatic arrhythmia throughout the blanking period; these were not recorded as procedural failure. Follow-up was performed at 3, 6 and 12 months with a standard 12-lead electrocardiogram and additional symptom driven ambulatory monitoring where required. During the late follow-up visit, those patients in NSR were asked to undergo a 6-day period of ambulatory monitoring (Spiderflash, Sorin) to exclude atrial arrhythmia. NSR was defined as freedom from AF or AFl lasting >30 seconds.[22] The follow-up restarted when a patient underwent a

redo ablation procedure and in the further follow-up they were recorded as single-procedure failures.

5.2.4   Follow-up and Data Capture

The data was collected retrospectively. A database was constructed to capture all case variables. The cases were identified as described in 5.2.1. All 40 patients remained under active follow-up. If an existing clinic appointment was scheduled for within 6 months, this was kept; otherwise patients were invited to be reviewed in an additional research clinic. During this clinic visit, the accuracy of the baseline demographic data was checked, drug history was recorded (including details on all AADs) and symptoms were investigated. A 12-lead ECG was used to check the heart rhythm. Any patient in NSR at this clinic appointment was invited to undergo a 6-day ambulatory ECG to confirm the absence of atrial arrhythmia.

Final outcomes were recorded according to the following definitions:

- AF: In AF on the 12 lead ECG with no electrocardiographic evidence of or symptoms suggesting NSR in the past 6 months.

- PAF: In NSR at the time of clinic ECG but with evidence of >30 seconds of AF on the ambulatory event monitor[22] or in NSR in clinic but with ECG evidence of AF within the past 6 months.

- AFl: Any ECG evidence of atrial flutter or atrial tachycardia within 6 months of follow-up.

- NSR: Both in NSR at the time of clinic and with no evidence of atrial arrhythmia on 6-day ambulatory event monitor.

In addition to taking a comprehensive symptom history, all available records were searched for evidence of arrhythmia. This included, but was not limited to, the hospital notes from Derriford and surrounding DGHs, all electronic notes and GP records (enquired via telephone). This data was used to record the time to first atrial arrhythmia recurrence.

5.2.5   Statistical Analysis

Categorical variables are presented by percentages. Numerical variables were tested for normality using Shapiro-Wilk and are expressed either as mean and standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normal data. Between group differences were assessed by independent samples t-test, Chi squared (Fischer's exact test when any cell number was ≤ 5) or Mann-Whitney where appropriate. The Kaplan–Meier method was used for the event-free survival curve; follow-up was censored at the first arrhythmia recurrence or last arrhythmia-free clinic visit, whichever came first. A p value <0.05 was considered statistically significant. Data analyses were performed using the IBM SPSS v21.

5.3   Results

5.3.1   'De novo' and 'all procedures'

Between 2009 and 2013, 44 procedures were performed on 40 patients; 27 procedures were *de novo* cases, the other 17 had previously undergone AF ablation using a variety of technologies (9 wide area circumferential ablation, 1 surgical HIFU, 3 duty cycled RF PVI and 4 PVAC & T-VAC redos). All had documented PsAF prior to the procedure. The baseline demographics for the '*de novo* only' and 'all procedures' are shown in Table 5-1. Follow-up data is available on all 40 patients eligible for inclusion in the study.

Outcome	All procedures (n=44)	De novo (n=27)	p value
NSR	23 (52)	16 (60)	
NSR off AAD	22 (50)	16 (60)	
PAF	7 (16)	4 (15)	
PAF off AAD	5 (11)	4 (15)	
PsAF	11 (25)	5 (19)	
PsAF off AAD	11 (25)	4 (15)	
Atrial Flutter	3 (7)	2 (7)	
Atrial Flutter off AAD	2 (5)	2 (7)	
Follow-up / months	38 (13)	37 (14)	0.95
DCCV during blanking period	7 (16)	5 (19)	0.75
CCV during blanking period	2 (5)	2 (7)	0.63
DCCV following blanking period	13 (30)	8 (30)	1.00
CCV following blanking period	4 (9)	3 (11)	1.00
AAD post blanking period	12 (27)	10 (37)	
Total energy time / seconds	2190 (931)	2239 (883)	0.82
Total fluoro time / minutes	60.6 (11.7)	60.2 (10.0)	0.88
Catheter procedure duration / minutes	193 (35)	191 (25)	0.80

Table 5-2. '*De novo*' and '*all procedures*' outcomes (data expressed at n (%)). (AAD = Antiarrhythmic drugs, NSR = Normal sinus rhythm, AF = Atrial fibrillation, AFl = Atrial flutter, AT = Atrial tachycardia, CCV = Chemical cardioversion, DCCV = DC cardioversion, NSR = Normal sinus rhythm, PAF = paroxysmal atrial fibrillation, PsAF = Persistent atrial fibrillation)

5.3.1.1 Procedural Data

There was no difference in the type of anaesthesia between the '*de-novo*' and 'all procedures' groups (44.4% vs 43.2% general anaesthesia, p=0.92).

Procedure time was 193 ± 35 minutes (192 ± 25 minutes *de novo*, p=0.81), total energy delivered 2190 ± 931 seconds (2239 ± 883 *de novo*, p=0.82) and fluoroscopy time was 61 ± 12minutes (60 ± 10 *de novo*, p=0.87). Twenty-four (54.5%) of the procedures included a concomitant CTI line (52% *de novo*, p=1.00).

5.3.1.2 Long-term Outcome

The mean follow duration was 33 (range 24-63) months. The absolute freedom from any atrial arrhythmia recurrence off AAD was 45% in the *de novo* group and 47% in all procedures group.

All patients in symptom free NSR for at least three months at late follow-up underwent a six-day event-monitor.[22] Late follow-up outcomes are shown in Table 5-2. At mean follow-up, 60% (52% of group 2) of patients remained in sustained NSR (60 and 50% respectively off AAD). A further 15% (16% of group 2) reported only occasional paroxysms of AF (15 and 11% respectively off AAD). Overall, 75% of group one had either AF freedom or a change from persistent to paroxysmal following a single ablation procedure off AAD. Of the four cases that underwent two T-VAC procedures, two remain in AF and two now have PAF. Of the 17 cases that had previously undergone a LA ablation for AF, only 41% were free from AF at late follow-up.

5.3.1.3 Time to First Event

Following a blanking period of 3 months, the first documented arrhythmia recurrence was recorded (Figure 5-3 & 5-4). Univariate analysis showed no effect of LA size or total duration of AF on likelihood of event free survival (OR 0.99 (0.98-1.01, p=0.64 and 1.0 (0.99-1.01), p=0.58 respectively).
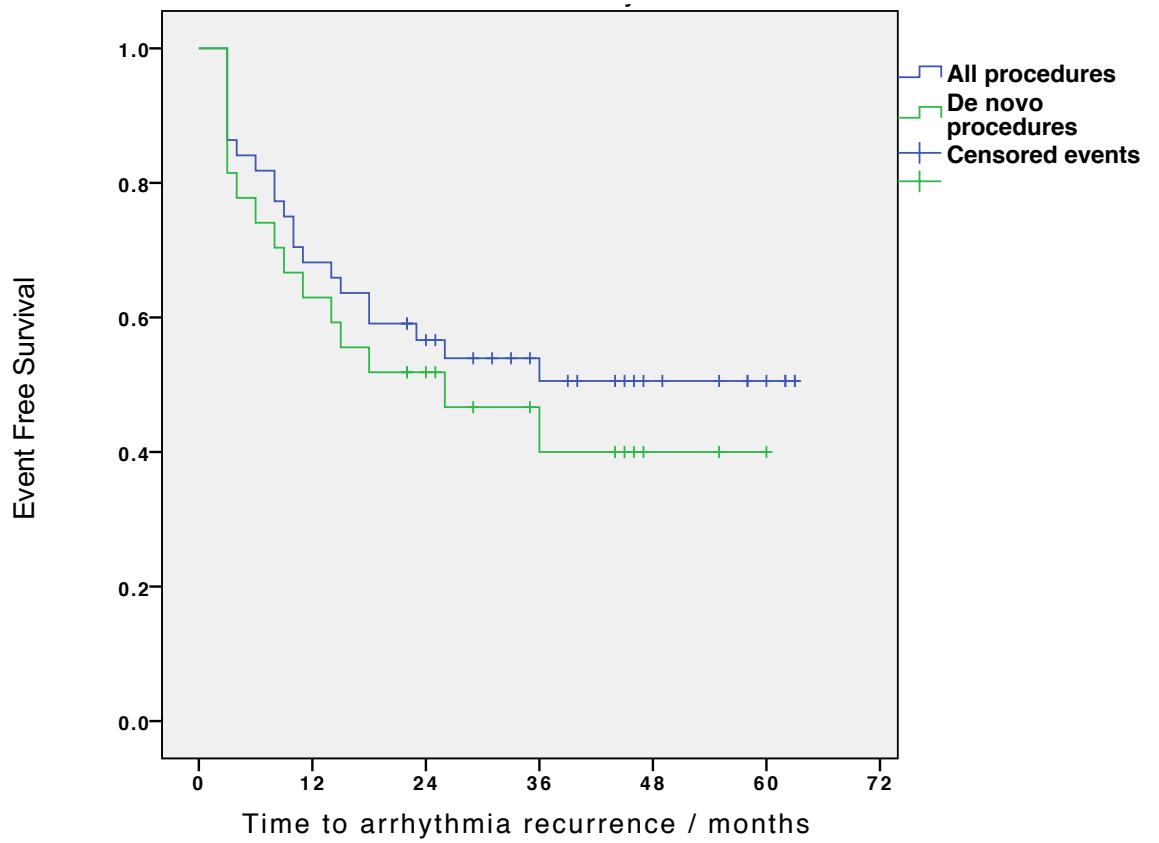
Figure 5-3. Kaplan-Meier plot showing the event free survival from all atrial arrhythmia between the all T-VAC procedures versus the *de novo* T-VAC group. Reproduced from Davies *et al.* with permission.[157]
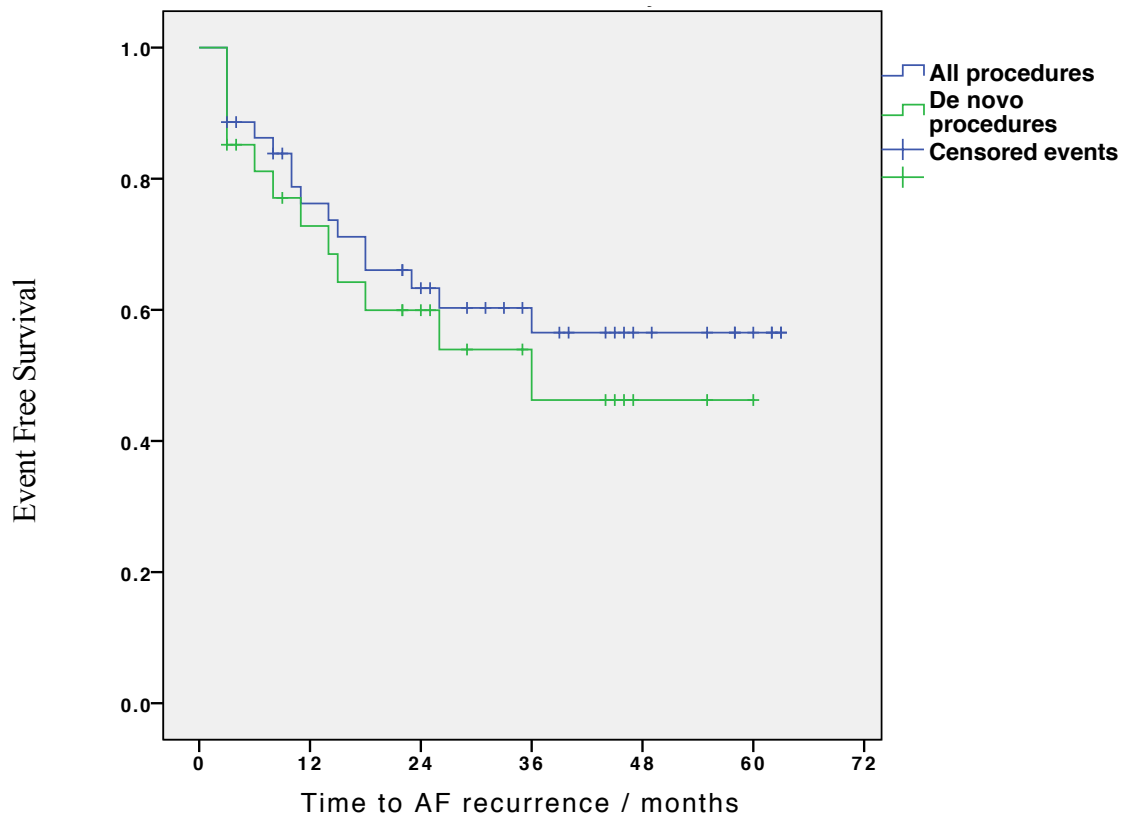
Figure 5-4. Kaplan-Meier plot showing the atrial fibrillation free survival of all T-VAC procedures versus the *de novo* group. Reproduced from Davies *et al.* with permission.[157]

5.3.1.4   Redo Study Findings

9 patients had previously undergone WACA ablation using point-by-point techniques and 3 had PVI with the PVAC catheter. In all cases except 2, there was evidence of reconnection in between 1 and 4 PVs. Ablation strategy remained to re-isolate the veins before completing the T-VAC catheter sweep. In the two cases where all 4 veins were isolated at the start of the procedure, the operator proceeded directly onto posterior wall ablation. In one of these cases, confirmed posterior wall isolation was achieved with the T-VAC; this patient was in NSR at long-term follow-up. In the other, confirmed PW isolation was not achieved; the patient suffered a relapse into PsAF.

Of the 4 patients who underwent a redo procedure where the initial procedure was with T-VAC, all 4 had at least one PV reconnected.

5.3.2   Complications and Procedural Safety

There were no major procedural related 30-day complications. In particular, no atrio-esophageal fistulae, thromboembolic events or phrenic nerve paralyses were reported in any of the 44 ablation procedures.

5.4   Discussion

These results show that PsAF ablation can be performed quickly and safely with the PVAC and T-VAC catheter combination with a long-term freedom from AF rate of around 60% of cases.

5.4.1   Duty-cycled Radiofrequency in Persistent AF

The efficacy of duty-cycled technology in paroxysmal AF ablation is proven.[158] The limited work into it's use in PsAF to date is summarised in Table 5-3. The only randomised controlled trial (TTOP-AF) compares duty-cycled ablation to medical management in PsAF patients.[159] Their ablation technique employed three multi-electrode catheters: Multi-Array Ablation Catheter (MAAC), Multi-Array Septal Catheter (MASC) in addition to the PVAC catheter. They report a reduction in AF (defined as a reduction in AF burden of >90%) in around 71% of cases at 6-month follow-up in a cohort of patients broadly similar to ours but with a shorter history of AF (0.9 ± 0.9 vs. 38.5 ± 27.7 months).

Mulder *et al.* reported 50 of 89 (56%) patients with PsAF were free from AF/AFl lasting >30 seconds after 1.2 procedures without AAD at 12-month follow-up using a 7-day ambulatory ECG.[160] Similarly, Scharf *et al.* reported an 66% success rate (defined as a >80% reduction in AF burden) at 20 months, though 50% of patients required 2 procedures.[161] Tivig *et al.* report a single procedure success rate of 46% at >1 year follow-up using the PVAC, MAAC and MASC combination, rising to 73% after multiple procedures.[162]

Study, design	Number	Ablation catheters / technique	Comparator	Follow-up period/Method	AF Outcome	Complications
TTOP-AF[159] **International, multicentre RCT.**	138 DC Ablation, 72 Medical management	PVAC, MAAC & MASC. PVI and CFAE targeted ablation	Medical Management (43 cross-over to ablation)	6 months 7-day holter monitor	>90% AF reduction: Ablation, 67.4%; Control, 26.4%	12.3% acute complication rate (2.9% stroke, 1.4% tamponade)
Scharf et al.[161] **Multicentre, single arm.**	50 (100% LS PsAF)	PVAC, MAAC & MASC. PVI and CFAE targeted ablation	None	6±1 months 7-day holter monitor	*>80% reduction in AF;* 64% off AAD, 80% on AAD. *Free of AF;* 54% off AAD, 70% on AAD.	8% (2% haematoma, 2% AV fistulae, 2% tamponade & 2% stroke)
				20±4 months 7-day holter monitor	*>80% reduction in AF;* 47% off AAD, 66% on AAD *Free of AF;* 45% off AAD, 60% on AAD.	
Tivig et al.[162] **2006-8 Non-randomized, single centre.**	209 (143 PAF, 66 PsAF) DC Ablation, 211 (155 PAF, 56 PsAF)	PVAC, MAAC & MASC. CFAE targeted ablation ± PVI	Conventional 3D guided point-by-point ablation.	>6 months	1 procedure success; 51% (57% control)*	2.6% total (0.5% stroke in DC arm, 0.5% AV fistulae and 0.7% tamponade)
				>12 months	1 procedure success; 46% (61% control)*	
Mulder et al.[160] **Single arm, single centre.**	89 (100% LS PsAF)	PVAC, MAAC & MASC. PVI and CFAE targeted ablation	None	12 months 7-day holter monitor	*Free of AF;* 36% off AAD, *On-going PAF;* 17%	*Within 24 hours;* 1 STEMI & 1 haematoma *>1 month;* 1 TIA and 1 pericardial effusion.

Table 5-3. Summary of case series reporting outcomes from persistent atrial fibrillation ablation using duty-cycled radio-frequency ablation. *Quoted data is for PsAF cases only. (AAD = Anti-arrhythmic drugs, AF = Atrial fibrillation, AV = Arterio-venous, CFAE = Complex fractionated atrial electrograms, DC = Duty-cycled, LSP = Long-standing persistent atrial fibrillation, MAAC = multiarray ablation catheter, MASC = multiarray septal catheter, PAF = Paroxysmal atrial fibrillation, PVAC = Pulmonary vein ablation catheter, PVI = Pulmonary vein isolation, STEMI = ST elevation myocardial infarction, TIA = Transient ischaemic attack, TTOP-AF = Tailored Treatment of Persistent Atrial Fibrillation, 3D = 3-dimentional, PsAF = Persistent atrial fibrillation)

5.4.2 Posterior Wall Ablation

The lesion set used in this case series is based on the previously described concept of the 'box-set' lesion pattern. Published evidence, both from surgical and catheter based series, have shown that the box-set is an effective lesion set for ablative management of PsAF. Sanders *et al.* report a 63% 2-year freedom from AF rate when combining WACA with a left atrial roof and floor line to produce validated PW isolation.[138] Hybrid approaches, designed to deliver the box-set via both an epi- and endocardial approach in a staged fashion have reported freedom from AF outcomes as high as 89%.[131]

Evidence from studies reporting redo procedures following previous catheter delivered single ring PW isolation showed that in patient with a recurrence of AF, all were found to have reconnection of ablation lines and an un-isolated PW.[106] Furthermore, in all the studied patients with freedom from AF (and a recurrence of an organised atrial tachycardia) all were found to have an intact ablation ring. This finding suggests at the importance of PW isolation in delivering freedom from AF.

Our technique does not deliver validated PW isolation. It is possible therefore, that the observed outcome is due to conduction delay rather than complete isolation, though this would perhaps lead to more recurrences of atypical flutter than we observed. More work is required to ascertain the exact properties of the box-set required for successful outcome. One such randomised study comparing PVI alone to PVI plus PW isolation is due to complete in 2016 and should help define box-set requirements.[154]

5.4.3 Pulmonary Vein Isolation

PVI alone is generally considered insufficient to successfully ablate PsAF - further substrate modification is needed.[22] However, several series looking at the importance of PVI in this tandem approach suggests that it is an important component of the overall procedure. One

such study reported the electrophysiological findings at redo procedure following previous PVI and substrate modification.[163] In all cases of AF recurrence, at least one of the PVs had reconnected, and following re-isolation, good long-term outcomes were seen. The fact that in our series, validated block of all 4 PVs was achieved is likely to be an imported aspect of our lesion pattern.

5.4.4   Ganglionic Plexi

Though more work has yet to be done in the area, there is growing evidence to support the role of the ganglionic plexi (GP) in the initiation maintenance of PsAF.[164] There is evidence to suggest that wide area circumferential or single ring ablation techniques can alter those GP adjacent the pulmonary veins.[165] Furthermore, bilateral GP ablation can positively affect procedural outcomes.[166] Previous groups have established the common anatomical sites for these GPs.[167] There are clusters in the right atrium that will remain unaffected by our technique, but other areas in the left atrium tend to cluster along those areas empirically ablated using the T-VAC technique.[78,163] We did not map out the GPs or intentionally target them during our approach, but it is possible that the irreversible alteration or destruction of GPs positively influences the long-term outcome of our procedure.[78,165] Further work is required to compare residual autonomic function between the 2 groups.

5.4.5   Comments of Technique

The empirical pattern delivered in this study was reproducible under fluoroscopic guidance and used only 2 multi-electrode ablation catheters compared to 3 in the PVAC, MAAC and MASC series;[159,161,162] an important consideration in the current economical climate.

The T-VAC catheter is not currently supported by any of the current 3D imaging technologies such as CARTO™ (Biosense Webster) or Ensite-NavX™ (St. Jude Medical). This means that ensuring continuity of the individual lines into a continuous box lesion is

problematic. In 3 T-VAC cases, we trialled the use of the first generation LocaLisa 3D-mapping system (Medtronic Inc., Figure 5-2). Though we were able to track the catheter movement and mark areas of ablation delivery, overall the system resolution was not sufficient to reliably ensure integrity of the box-set.

Because our novel technique does not utilise a mapping system, it is inherently more suitable for sedation cases compared to point-by-point techniques which conversely rely heavily on the patient remaining static throughout the procedure. Cases performed under sedation are, in our experience, less expensive than those involving general anaesthesia, an important economic consideration.

One significant problem with deployment of the T-VAC catheter was that in several positions where the operator intended to deploy the catheter, it was impossible to achieve sufficient catheter stability needed to guarantee contact across multiple ablating electrodes. Furthermore, there was a tendency for the catheter to slip down towards the floor of the left atrium around right septal positions and away from the posterior wall towards the mitral valve in left sided and central positions.

Patient selection for PsAF ablation is of paramount importance. It is important that various factors are taken into account when selecting a suitable patient cohort. Strong predictors of procedural success include body mass index, absence of underlying disorder (i.e. lone AF), LA atrial diameter, fibrosis and duration of AF.[152] Though we did not assess for fibrosis, the patients in this series were relatively favourable with a mean LA volume of 146cm^3 (normal approximately 88cm^3).[168] It is likely that this patient selection accounts at least in part for the favourable outcomes. This suggests that it may be possible to define a group of patients with PsAF that in combination with a suitable technique can give single procedure success rates in the region of 75%.

5.4.6 Study Limitations

This study was neither prospective nor randomised in design. However, the patients included had characteristics similar to other series describing PsAF ablation techniques.[138,161,162] While a combination of 12-lead ECG and intermittent monitoring was used throughout routine follow-up, prolonged ambulatory monitoring was only performed at the index follow-up in those patients in NSR. The timing of this follow-up was highly variable which significantly degrades the comparability between this and other case series. Given the natural attrition rate of normal sinus rhythm following an ablation procedure, the heterogenicity of the follow-up period may furthermore weaken the strength of these results. Furthermore, as a result of this monitoring schedule, it is possible that some patients with PAF were incorrectly coded as PsAF. However, this would only serve to give a negative skew to the reported success rate.

5.5   Conclusion

Using this novel duty-cycled technique in patients with persistent AF, it is possible to achieve first time success rates commonly achieved using a 3-catheter approach, with a low complication rate.

6   DISCUSSION

6.1   Original Findings

In section 1.4, the reader was introduced to the stated aims of this thesis. These 4 main aspects have been reported in the preceding chapters.

- The very long-term outcome from surgical AF ablation using the Epicor HIFU device has been found to be 81% for PAF, 56% in PsAF and 18% for LS PsAF.

- There appears to be a link between long-term electrical isolation of the PW and freedom from AF.

- There is no clear correlation between BMI and LA pressure suggesting a more complex mechanism of action.

- Using this novel duty-cycled technique in patients with persistent AF, it is possible to achieve first time success rates commonly achieved using a 3-catheter approach, with a low complication rate.

6.1.1   Outcomes from HIFU Surgical Ablation

In line with other published data, the long-term outcome from AF ablation using the Epicor HIFU device was found to be dependent on the classification of pre-operative AF. For PAF, freedom from atrial arrhythmia was in the region of 80% whereas for those with LS PsAF, the figure was closer to 20%. This remarkable discrepancy is difficult to explain. By isolating the PVs and PW *en bloc*, the vast majority of what was traditionally considered the substrate for PAF and PsAF was isolated from the remainder of the heart. Only one ablation ring was delivered. Thus, an incompletely delivered lesion should have been equally

detrimental for all preoperative classes of AF; triggers would still be conducted from the PV to the PW substrate and AF would be conducted to the remained of the heart.

The study by Todd *et al.*[103] suggests that the box-set is an effective lesion pattern for ablative management of AF, yet in our cohort we report a relatively disappointing outcome. There are several possible reasons behind this observed effect; these can be thought of as either a failure of the lesion to control AF, or a failure of the technology to deliver the transmural lesion. Though groups have reported on the effectiveness of the lesion pattern, this is usually through observations made at the time of redo procedures and as such concentrates predominately on cases involving arrhythmia recurrence.

In the second stage of this thesis, we aimed to study patients with both recurrence and freedom from AF in an attempt to delineate the relationship between the integrity of the box-set pattern and procedural outcome.

6.1.2 *Effectiveness of Box-set Patterns*

Patients comprising the cohort described in chapter 2 (Table 2-2) were invited back for an invasive electrophysiological assessment. The electrical characteristics of the PW and PVs were reported. A total of 17 patients were studied: 11 with on-going AF and 6 with AF freedom. This ambitious study has several significant limitations but does lend support to the effectiveness of the box-set pattern. In none of the cases of AF recurrence was the PW found to be isolated; in the patients with long-term freedom from AF, four out of six had complete isolation of the posterior wall and a fifth patient had marked conduction delay in and out of the posterior wall. The remaining patient had shown relatively little AF prior to surgery.

6.1.2.1   Study Challenges

6.1.2.1.1   Recruitment

The numbers in this study were smaller than initially planned, exclusively due to difficulties in recruiting in the sinus rhythm arm. Patients with sinus rhythm were understandably reluctant to participate in this study, as the consent process included a thorough and extensive explanation dwelling on the small chance of serious complications from invasive studies. Some hesitated through the inherent risk of the study and the trans-septal puncture. Others held the belief that the study may initiate refractory AF and some did not wish to be restarted on anticoagulation.

The sinus rhythm pool was also found to be smaller than initially thought as a result of the attrition rate inherent in many AF ablation outcome studies; freedom from AF 4 years following ablation is no guarantee of on-going freedom. Some of those reported to be in NSR in the study reported in chapter 2 were found to have relapsed into AF when the screening was performed for chapter 3; there was approximately 12-18 months between these 2 time points. This delay was in part due to the challenges in securing appropriate funding for the study and also due to the necessary restrictions put in place by the regional ethics committee. As part of their agreement for us to perform this trial, the REC required all 20 patients to be recruited (10 with on-going AF and 10 with normal sinus rhythm) before the first underwent the invasive study. Though we were able to satisfy this requirement with at one point having successfully recruited 21 patients, there was a significant dropout rate between the time of recruitment and study; 6 patients withdrew in this timeframe. We found that the dropout rate was significantly lower when this timeframe was reduced. It appeared that the longer asymptomatic patients were given to reflect on study participation, the more likely they were to withdraw.

6.1.2.1.2   Electrophysiological Assessment

In order to assess the electrical properties of the left atrium, we used 3 main technology platforms; assessment of electrograms via a circular mapping catheter with or without voltage maps obtained using either CARTO or NavX. Due to cost implications we were only able to use the complex 3D mapping strategies in cases where we intended to perform further ablation. Although the use of only a circular mapping mapping catheter cannot allow for scar mapping *per se,* it was certainly sufficient to describe the electrical properties of the posterior wall and pulmonary veins with a clarity sufficient for our purpose.

Our use of the voltage mapping system had limitations and certain flaws. Firstly, inherent in all pre-contact force catheter era studies, the specificity of low voltage areas is reduced due to the issue of contact. We did not routinely use contact force mapping catheters due to the cost implications for the study. Secondly, some of our voltage maps were produced during AF. The general consensus of opinion is that these should ideally be produced during NSR.[96] The theoretical downside of using such techniques whilst mapping during AF is that the scar volume will be overestimated. While we recognise this potential flaw in our methodology, many of our patients had refractory AF (see Table 3-2) which prohibited optimal mapping.

Lessons were learnt in those cases where further ablation was performed. There was one case of an atypical flutter that was found to be peri-mitral and in another case AF organised into a flutter on re-isolation of the pulmonary veins which subsequently terminated on completion of the roofline. Unfortunately one of the well described potential drawbacks of the box-set pattern is that it is potentially proarrhythmic for macro re-entrant circuits.[106] A validated mitral isthmus line should be considered in all cases.

6.1.3 Linear Catheter Ablation

6.1.3.1 Study Design and Recruitment

PsAF ablation using T-VAC catheter has been performed in our centre since 2009. Our initial plan to investigate the effectiveness of this technique was to perform a prospective non-randomised pilot study in around 20 patients. However, with the introduction of contact force feedback catheters and the technological advancement of 3-D mapping systems, it was felt that these were potentially superior platforms with which to perform prospective box-set lesion studies. Subsequently, after discussion with the institutional research and development department, together with the regional ethics committee, it was considered ethically appropriate to use a retrospective design allowing a higher number of participants to be enrolled in a shortened and more feasible timeframe.

6.1.3.2 Ablation Using T-VAC

The T-VAC catheter has specific strengths and weaknesses for this role. Although in theory it is potentially able to deliver a full box lesion with 8 to 10 energy applications, catheter stability, manipulation and tissue contact were found to be suboptimal. There were many occasions where the catheter could not be placed as desired onto the floor of the left atrium and tended to slip into the mitral orifice. Anchoring of the catheter tip was impossible.

There was also the issue of mapping. The T-VAC catheter is not compatible with either CARTO or NavX; all cases were performed using fluoroscopy guidance only (except 2 where we trialled the compatibility with the LocaLisa system, Figure 5-2). This meant that delivering a continuous single ring with no gaps was challenging. Indeed, true PW isolation was not obtained in any of the cases as far as we observed, nor was it an end-point of the procedure.

We have described a case in the previous chapters in whom PsAF was successfully treated by achieving only a significant conduction delay of the PW and not true isolation (case 5, Table 3-2). It is therefore possible that our T-VAC technique was successful in treating some cases of PsAF by delivering significant functional block only. It is equally a possibility however that there are other mechanisms explaining its limited success. For example, the paper by Rolf *et al.* describes the mapping and subsequent box ablation of areas of low voltage (scar).[96] It is possible that chance ablation across these areas of low voltage is the mechanism of action in our successful cases. It is equally possible that we inadvertently modified the ganglionic plexi preferentially with the T-VAC catheter. The study by Garcia *et al.* also describes freedom from AF in patients treated with the Epicor system in who the posterior wall was found to be non-isolated.[119] Much work is needed to determine the true part these factors have to play in the outcome of an AF ablation procedure.

6.2   Future Directions of Study

The three main projects in this thesis view the box-set lesion pattern from different angles. Though a clear link between PW isolation and freedom from AF has been observed, our work does not lend support to any of the competing mechanistic theories. During the completion of this thesis, hybrid AF ablation has become a mainstream ablation technique for patient with PsAF. Involving staged epicardial and endocardial procedures, this exciting technique should be viewed as an opportunity for further investigating the effect of PW isolation.

The T-VAC catheter has been shown to be at least partially successful in delivering a lesion pattern based on the concept of the box-set. Further work is required in the development of more stable linear ablation catheters that are compatible with 3D mapping systems. Once this is available, a randomised prospective trial comparing box-set lesions delivered by linear or point-by-point with contact force mapping should more accurately assess these 2 techniques.

7 REFERENCES

1. Koch W. Weiter mitteilungen uber den sinusknoten des Herzens. *Verh Dtsch Ges Pathol* **13,** 85–92 (1909).

2. Winfree, A. in *Computational biology of the heart* (eds. Panfilov, A. V. & Holden, A. V.) (John Wiley & Sons Ltd, 1997).

3. Keith, A. & Flack, M. The Form and Nature of the Muscular Connections between the Primary Divisions of the Vertebrate Heart. *J. Anat. Physiol.* **41,** 172–89 (1907).

4. Kodama, I., Honjo, H., Dobrzynynski, H. & Boyett, M. in *Cardiac electrophysiology: from cell to bedside.* (eds. Alife, J. & Zipes, D.) (Saunders, 2004).

5. Fedorov, V. V, Glukhov, A. V & Chang, R. Conduction barriers and pathways of the sinoatrial pacemaker complex: their role in normal rhythm and atrial arrhythmias. *Am. J. Physiol. Heart Circ. Physiol.* **302,** H1773–83 (2012).

6. Meek, W. & Eyster, J. Experiments on the origin and propagation of the impulse in the heart. *Heart* (1914).

7. Sakamoto, S., Nitta, T. & Ishii, Y. Interatrial electrical connections: the precise location and preferential conduction. *J Cardiovasc Electrophysio* **16,** 1077–86 (2005).

8. Chen, S. A. *et al.* Right atrial focal atrial fibrillation: electrophysiologic characteristics and radiofrequency catheter ablation. *J. Cardiovasc. Electrophysiol.* **10,** 328–35 (1999).

9. McMichael, J. History of atrial fibrillation 1628-1819 Harvey - de Senac - Laënnec. *Br. Heart J.* **48,** 193–7 (1982).

10.   de Senac, J.-B. *Traits des maladies du coeur*. (Mtquignon l'aine, 1783).

11.   Lewis, T. Report CXIX. Auricular Fibrillation: A Common Clinical Condition. *Br. Med. J.* **2,** 1528 (1909).

12.   Bootsma, B. K., Hoelsen, A. J., Strackee, J. & Meijler, F. L. Analysis of R-R intervals in patients with atrial fibrillation at rest and during exercise. *Circulation* **41,** 783–94 (1970).

13.   Davis, R. C. *et al.* Prevalence of atrial fibrillation in the general population and in high-risk groups: the ECHOES study. *Europace* **14,** 1553–9 (2012).

14.   Chugh, S. S. *et al.* Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* **129,** 837–47 (2014).

15.   Kannel, W. B., Wolf, P. A., Benjamin, E. J. & Levy, D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am. J. Cardiol.* **82,** 2N–9N (1998).

16.   Healey, J. S. *et al.* Subclinical atrial fibrillation and the risk of stroke. *N. Engl. J. Med.* **366,** 120–9 (2012).

17.   Samol, A. *et al.* Prevalence of unknown atrial fibrillation in patients with risk factors. *Europace* **15,** 657–62 (2013).

18.   Cotter, P. E. *et al.* Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. *Neurology* **80,** 1546–50 (2013).

19.   Mackenzie, J. *Diseases of the Heart*. (Oxford Medical Publications, 1914).

20.   Shinbane, J. S. *et al.* Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *J. Am. Coll. Cardiol.* **29,** 709–15 (1997).

21.   Camm, a J. *et al.* Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur. Heart J.* 2369–2429 (2010).

22.   Calkins, H. *et al.* 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. *Europace* 528–606 (2012).

23.   Haïssaguerre, M. *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N. Engl. J. Med.* **339,** 659–66 (1998).

24.   Lin, W.-S. *et al.* Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. *Circulation* **107,** 3176–83 (2003).

25.   Hwang, C., Wu, T. J., Doshi, R. N., Peter, C. T. & Chen, P. S. Vein of marshall cannulation for the analysis of electrical activity in patients with focal atrial fibrillation. *Circulation* **101,** 1503–5 (2000).

26.   Katritsis, D. *et al.* Identification and catheter ablation of extracardiac and intracardiac components of ligament of Marshall tissue for treatment of paroxysmal atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **12,** 750–8 (2001).

27.   Nademanee, K. *et al.* A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. *J. Am. Coll. Cardiol.* **43,** 2044–53 (2004).

28.   Wijffels, M., Kirchhof, C., Dorland, R. & Allessie, M. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation* (1995).

29. Qi, X. Y. *et al.* Cellular signaling underlying atrial tachycardia remodeling of L-type calcium current. *Circ. Res.* **103,** 845–54 (2008).

30. Wakili, R., Voigt, N., Kääb, S., Dobrev, D. & Nattel, S. Recent advances in the molecular pathophysiology of atrial fibrillation. *J. Clin. Invest.* **121,** 2955–68 (2011).

31. Ellinor, P. T. *et al.* Common variants in KCNN3 are associated with lone atrial fibrillation. *Nat. Genet.* **42,** 240–4 (2010).

32. Qi, X.-Y. *et al.* Role of small-conductance calcium-activated potassium channels in atrial electrophysiology and fibrillation in the dog. *Circulation* **129,** 430–40 (2014).

33. Nattel, S., Burstein, B. & Dobrev, D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ. Arrhythm. Electrophysiol.* **1,** 62–73 (2008).

34. Yue, L., Xie, J. & Nattel, S. Molecular determinants of cardiac fibroblast electrical function and therapeutic implications for atrial fibrillation. *Cardiovasc. Res.* **89,** 744–53 (2011).

35. McLellan, A. J. A. *et al.* Diffuse Ventricular Fibrosis Measured by T1 Mapping on Cardiac MRI Predicts Success of Catheter Ablation for Atrial Fibrillation. *Circ. Arrhythm. Electrophysiol.* (2014).

36. McGann, C. *et al.* Atrial fibrillation ablation outcome is predicted by left atrial remodeling on MRI. *Circ. Arrhythm. Electrophysiol.* **7,** 23–30 (2014).

37. Chou, C.-C. & Chen, P.-S. New concepts in atrial fibrillation: neural mechanisms and calcium dynamics. *Cardiol. Clin.* **27,** 35–43, viii (2009).

38. Kneller, J. *et al.* Cholinergic atrial fibrillation in a computer model of a two-dimensional sheet of canine atrial cells with realistic ionic properties. *Circ. Res.* **90,**

E73–87 (2002).

39. Dobrev, D., Voigt, N. & Wehrens, X. H. T. The ryanodine receptor channel as a molecular motif in atrial fibrillation: pathophysiological and therapeutic implications. *Cardiovasc. Res.* **89,** 734–43 (2011).

40. Gould, P. A. *et al.* Evidence for increased atrial sympathetic innervation in persistent human atrial fibrillation. *Pacing Clin. Electrophysiol.* **29,** 821–9 (2006).

41. Voigt, N. *et al.* Enhanced sarcoplasmic reticulum Ca2+ leak and increased Na+-Ca2+ exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. *Circulation* **125,** 2059–70 (2012).

42. Nattel, S. New ideas about atrial fibrillation 50 years on. *Nature* **415,** 219–26 (2002).

43. de Groot, N. M. S. *et al.* Electropathological substrate of longstanding persistent atrial fibrillation in patients with structural heart disease: epicardial breakthrough. *Circulation* **122,** 1674–82 (2010).

44. Voigt, N. *et al.* Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. *Circulation* **129,** 145–56 (2014).

45. Garrey, W. Auricular fibrillation. *Physiol Rev* (1924).

46. Moe, G., Rheinboldt, W. & Abildskov, J. A computer model of atrial fibrillation. *Am. Heart J.* (1964).

47. Allessie, M., Bonke, F. & Schopman, F. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The' leading circle' concept: a new model of circus movement in cardiac tissue without the. *Circ. Res.* **41,** 9–18 (1977).

48. Rensma, P. & Allessie, M. Length of excitation wave and susceptibility to reentrant

atrial arrhythmias in normal conscious dogs. *Circ. J.* **62,** 395–410 (1988).

49.   Narayan, S. M. *et al.* Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. *J. Am. Coll. Cardiol.* **60,** 628–36 (2012).

50.   Nattel, S. Atrial ectopic activity in long-standing persistent AF: An unanticipated, potentially important role? *Can. J. Cardiol.* (2014). doi:10.1016/j.cjca.2014.10.019

51.   Di Biase, L., Burkhardt, J. D. & Mohanty, P. Effect of empirical left atrial appendage isolation on long-term procedure outcome in patients with long-standing persistent atrial fibrillation undergoing catheter ablation: Results of the BELIEF randomized trial. in *European Society of Cardiology Congress* (2015).

52.   Pertsov, A. M., Davidenko, J. M., Salomonsz, R., Baxter, W. T. & Jalife, J. Spiral waves of excitation underlie reentrant activity in isolated cardiac muscle. *Circ. Res.* **72,** 631–50 (1993).

53.   Gray, R. A. *et al.* Mechanisms of cardiac fibrillation. *Science* **270,** 1222–3; author reply 1224–5 (1995).

54.   Gray, R. A., Pertsov, A. M. & Jalife, J. Incomplete reentry and epicardial breakthrough patterns during atrial fibrillation in the sheep heart. *Circulation* **94,** 2649–61 (1996).

55.   Skanes, A. C., Mandapati, R., Berenfeld, O., Davidenko, J. M. & Jalife, J. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. *Circulation* **98,** 1236–48 (1998).

56.   Pandit, S. V & Jalife, J. Rotors and the dynamics of cardiac fibrillation. *Circ. Res.*

112, 849–62 (2013).

57.   Pandit, S. V *et al.* Ionic determinants of functional reentry in a 2-D model of human atrial cells during simulated chronic atrial fibrillation. *Biophys. J.* **88,** 3806–21 (2005).

58.   Wyse, D. G. *et al.* A comparison of rate control and rhythm control in patients with atrial fibrillation. *N. Engl. J. Med.* **347,** 1825–33 (2002).

59.   Van Gelder, I. C. *et al.* A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N. Engl. J. Med.* **347,** 1834–40 (2002).

60.   Roy, D. *et al.* Rhythm control versus rate control for atrial fibrillation and heart failure. *N. Engl. J. Med.* **358,** 2667–77 (2008).

61.   Corley, S. D. *et al.* Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation* **109,** 1509–13 (2004).

62.   Van Gelder, I. C. *et al.* Lenient versus strict rate control in patients with atrial fibrillation. *N. Engl. J. Med.* **362,** 1363–73 (2010).

63.   Dewire, J. & Calkins, H. Update on atrial fibrillation catheter ablation technologies and techniques. *Nat. Rev. Cardiol.* **10,** 599–612 (2013).

64.   Hayward, R. M. *et al.* Pulmonary vein isolation with complex fractionated atrial electrogram ablation for paroxysmal and nonparoxysmal atrial fibrillation: A meta-analysis. *Heart Rhythm* **8,** 994–1000 (2011).

65.   Saghy, L. *et al.* Is there a relationship between complex fractionated atrial electrograms recorded during atrial fibrillation and sinus rhythm fractionation? *Heart Rhythm* **9,** 181–8 (2012).

66.   Roux, J.-F. *et al.* Effect of pulmonary vein isolation on the distribution of complex fractionated electrograms in humans. *Heart Rhythm* **6,** 156–60 (2009).

67.   Rostock, T. *et al.* High-density activation mapping of fractionated electrograms in the atria of patients with paroxysmal atrial fibrillation. *Heart Rhythm* **3,** 27–34 (2006).

68.   Hocini, M. *et al.* Techniques, evaluation, and consequences of linear block at the left atrial roof in paroxysmal atrial fibrillation: a prospective randomized study. *Circulation* **112,** 3688–96 (2005).

69.   Jaïs, P. *et al.* Technique and results of linear ablation at the mitral isthmus. *Circulation* **110,** 2996–3002 (2004).

70.   Kottkamp, H. *et al.* Specific linear left atrial lesions in atrial fibrillation: intraoperative radiofrequency ablation using minimally invasive surgical techniques. *J. Am. Coll. Cardiol.* **40,** 475–80 (2002).

71.   Verma, A. *et al.* Approaches to catheter ablation for persistent atrial fibrillation. *N. Engl. J. Med.* **372,** 1812–22 (2015).

72.   Coumel, P. *et al.* [The atrial arrhythmia syndrome of vagal origin]. *Arch. Mal. Coeur Vaiss.* **71,** 645–56 (1978).

73.   Lemery, R., Birnie, D., Tang, A. S. L., Green, M. & Gollob, M. Feasibility study of endocardial mapping of ganglionated plexuses during catheter ablation of atrial fibrillation. *Heart Rhythm* **3,** 387–96 (2006).

74.   Pokushalov, E. *et al.* Ganglionated plexi ablation directed by high-frequency stimulation and complex fractionated atrial electrograms for paroxysmal atrial fibrillation. *Pacing Clin. Electrophysiol.* **35,** 776–84 (2012).

75. Pokushalov, E. *et al.* Selective ganglionated plexi ablation for paroxysmal atrial fibrillation. *Heart Rhythm* **6,** 1257–64 (2009).

76. Scanavacca, M. *et al.* Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal atrial fibrillation. *Circulation* **114,** 876–85 (2006).

77. Katritsis, D. *et al.* Anatomic approach for ganglionic plexi ablation in patients with paroxysmal atrial fibrillation. *Am. J. Cardiol.* **102,** 330–4 (2008).

78. Po, S. S., Nakagawa, H. & Jackman, W. M. Localization of left atrial ganglionated plexi in patients with atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **20,** 1186–9 (2009).

79. Katritsis, D. G. *et al.* Rapid pulmonary vein isolation combined with autonomic ganglia modification: a randomized study. *Heart Rhythm* **8,** 672–8 (2011).

80. Katritsis, D. G. *et al.* Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. *J. Am. Coll. Cardiol.* **62,** 2318–25 (2013).

81. Morillo, C. A., Klein, G. J., Jones, D. L. & Guiraudon, C. M. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. *Circulation* **91,** 1588–95 (1995).

82. Nishida, K., Datino, T., Macle, L. & Nattel, S. Atrial fibrillation ablation: translating basic mechanistic insights to the patient. *J. Am. Coll. Cardiol.* **64,** 823–31 (2014).

83. Jarman, J. W. E. *et al.* Organizational index mapping to identify focal sources during persistent atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **25,** 355–63 (2014).

84. Calkins, H. Hybrid thoracoscopic and transvenous catheter ablation of atrial

fibrillation: is this the answer we are searching for? *J. Am. Coll. Cardiol.* **60,** 62–3 (2012).

85. Sahadevan, J. *et al.* Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. *Circulation* **110,** 3293–9 (2004).

86. Chou, C.-C. *et al.* Epicardial ablation of rotors suppresses inducibility of acetylcholine-induced atrial fibrillation in left pulmonary vein-left atrium preparations in a beagle heart failure model. *J. Am. Coll. Cardiol.* **58,** 158–66 (2011).

87. Narayan, S. M., Krummen, D. E. & Rappel, W.-J. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **23,** 447–54 (2012).

88. Cuculich, P. S. *et al.* Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. *Circulation* **122,** 1364–72 (2010).

89. Mahnkopf, C. *et al.* Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI: implications for disease progression and response to catheter ablation. *Heart Rhythm* **7,** 1475–81 (2010).

90. Verma, A. *et al.* Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. *J. Am. Coll. Cardiol.* **45,** 285–92 (2005).

91. Anter, E., Tschabrunn, C. M. & Josephson, M. E. High-Resolution Mapping of Scar-Related Atrial Arrhythmias Using Smaller Electrodes With Closer Interelectrode Spacing. *Circ. Arrhythmia Electrophysiol.* **8,** 537–545 (2015).

92. Bradfield, J. S. *et al.* Tissue voltage discordance during tachycardia versus sinus

rhythm: implications for catheter ablation. *Heart Rhythm* **10,** 800–4 (2013).

93. Yagishita, A. *et al.* Correlation of Left Atrial Voltage Distribution between Sinus Rhythm and Atrial Fibrillation : Identifying Structural Remodeling by 3-D Electroanatomic Mapping Irrespective of the Rhythm. *J. Cardiovasc. Electrophysiol.* (2016). doi:10.1111/jce.13002

94. Sanders, P. *et al.* Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation* **108,** 1461–8 (2003).

95. Kistler, P. M. *et al.* Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J. Am. Coll. Cardiol.* **44,** 109–16 (2004).

96. Rolf, S. *et al.* Tailored atrial substrate modification based on low-voltage areas in catheter ablation of atrial fibrillation. *Circ. Arrhythm. Electrophysiol.* **7,** 825–33 (2014).

97. Harrison, J. L. *et al.* Repeat Left Atrial Catheter Ablation: Cardiac Magnetic Resonance Prediction of Endocardial Voltage and Gaps in Ablation Lesion Sets. *Circ. Arrhythmia Electrophysiol.* **8,** 270–278 (2015).

98. Akoum, N. *et al.* Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: a DE-MRI guided approach. *J. Cardiovasc. Electrophysiol.* **22,** 16–22 (2011).

99. Daccarett, M., McGann, C. J., Akoum, N. W., MacLeod, R. S. & Marrouche, N. F. MRI of the left atrium: predicting clinical outcomes in patients with atrial fibrillation. *Expert Rev. Cardiovasc. Ther.* **9,** 105–11 (2011).

100. Schade, A. *et al.* Spatial Relationship of Focal Impulses, Rotors and Low Voltage Zones in Patients With Persistent Atrial Fibrillation. *J. Cardiovasc. Electrophysiol.* **27,** 507–14 (2016).

101. Wu, T.-J. *et al.* Simultaneous biatrial computerized mapping during permanent atrial fibrillation in patients with organic heart disease. *J. Cardiovasc. Electrophysiol.* **13,** 571–7 (2002).

102. Ernst, S. *et al.* Modification of the substrate for maintenance of idiopathic human atrial fibrillation: efficacy of radiofrequency ablation using nonfluoroscopic catheter guidance. *Circulation* **100,** 2085–92 (1999).

103. Todd, D. M. *et al.* Role of the posterior left atrium and pulmonary veins in human lone atrial fibrillation: electrophysiological and pathological data from patients undergoing atrial fibrillation surgery. *Circulation* **108,** 3108–14 (2003).

104. Thomas, S. P., Lim, T. W., McCall, R., Seow, S.-C. & Ross, D. L. Electrical isolation of the posterior left atrial wall and pulmonary veins for atrial fibrillation: feasibility of and rationale for a single-ring approach. *Heart Rhythm* **4,** 722–30 (2007).

105. Lim, T. W. *et al.* Single-ring posterior left atrial (box) isolation results in a different mode of recurrence compared with wide antral pulmonary vein isolation on long-term follow-up: longer atrial fibrillation-free survival time but similar survival time free of any atri. *Circ. Arrhythm. Electrophysiol.* **5,** 968–77 (2012).

106. Lim, T. W. *et al.* Atrial arrhythmias after single-ring isolation of the posterior left atrium and pulmonary veins for atrial fibrillation: mechanisms and management. *Circ. Arrhythm. Electrophysiol.* **1,** 120–6 (2008).

107. Harling, L., Athanasiou, T., Ashrafian, H., Nowell, J. & Kourliouros, A. Strategies in

the surgical management of atrial fibrillation. *Cardiol. Res. Pract.* **2011,** 439312 (2011).

108. Ngaage, D. L. *et al.* Does preoperative atrial fibrillation influence early and late outcomes of coronary artery bypass grafting? *J. Thorac. Cardiovasc. Surg.* **133,** 182–9 (2007).

109. Quader, M. A. *et al.* Does preoperative atrial fibrillation reduce survival after coronary artery bypass grafting? *Ann. Thorac. Surg.* **77,** 1514–22; discussion 1522–4 (2004).

110. Ngaage, D. L. *et al.* Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic valve replacement: is there an argument for concomitant arrhythmia surgery? *Ann. Thorac. Surg.* **82,** 1392–9 (2006).

111. Ngaage, D. L. *et al.* Influence of preoperative atrial fibrillation on late results of mitral repair: is concomitant ablation justified? *Ann. Thorac. Surg.* **84,** 434–42; discussion 442–3 (2007).

112. Gammie, J. S. *et al.* Atrial fibrillation correction surgery: lessons from the Society of Thoracic Surgeons National Cardiac Database. *Ann. Thorac. Surg.* **85,** 909–14 (2008).

113. Ninet, J. *et al.* Surgical ablation of atrial fibrillation with off-pump, epicardial, high-intensity focused ultrasound: results of a multicenter trial. *J. Thorac. Cardiovasc. Surg.* **130,** 803–9 (2005).

114. Groh, M. a, Binns, O. a, Burton, H. G., Ely, S. W. & Johnson, A. M. Ultrasonic cardiac ablation for atrial fibrillation during concomitant cardiac surgery: long-term clinical outcomes. *Ann. Thorac. Surg.* **84,** 1978–83 (2007).

115. Schopka, S. *et al.* Ablation of atrial fibrillation with the Epicor system: a prospective observational trial to evaluate safety and efficacy and predictors of success. *J. Cardiothorac. Surg.* **5,** 34 (2010).

116. Feyrer, R., Ballazhi, F., Seitz, T., Weyand, M. & Harig, F. Impact of Medical Treatment on Long-Term Results after Surgical Ablation of Atrial Fibrillation in Cardiac Surgical Patients. *Ann. Thorac. Cardiovasc. Surg.* (2013).

117. McCarthy, P. M. *et al.* Where does atrial fibrillation surgery fail? Implications for increasing effectiveness of ablation. *J. Thorac. Cardiovasc. Surg.* **139,** 860–7 (2010).

118. Mitnovetski, S., Almeida, A. a, Goldstein, J., Pick, A. W. & Smith, J. a. Epicardial high-intensity focused ultrasound cardiac ablation for surgical treatment of atrial fibrillation. *Heart. Lung Circ.* **18,** 28–31 (2009).

119. Garcia, R. *et al.* Electrophysiological study 6 months after Epicor™ high-intensity focused ultrasound atrial fibrillation ablation. *J. Interv. Card. Electrophysiol.* **41,** 245–51 (2014).

120. Krzywinski, M. I. *et al.* Circos: An information aesthetic for comparative genomics. *Genome Res.* (2009). doi:10.1101/gr.092759.109

121. Edgerton, J. R., Mahoney, C., Mack, M. J., Roper, K. & Herbert, M. a. Long-term monitoring after surgical ablation for atrial fibrillation: how much is enough? *J. Thorac. Cardiovasc. Surg.* **142,** 162–5 (2011).

122. Zhuang, J. *et al.* Association between left atrial size and atrial fibrillation recurrence after single circumferential pulmonary vein isolation: a systematic review and meta-analysis of observational studies. *Europace* **145,** 638–45 (2012).

123.   Jeevanantham, V. *et al.* Meta-analysis of the effect of radiofrequency catheter ablation on left atrial size, volumes and function in patients with atrial fibrillation. *Am. J. Cardiol.* **105,** 1317–26 (2010).

124.   Pathak, R. K. *et al.* Long-Term Effect of Goal Directed Weight Management in an Atrial Fibrillation Cohort: A Long-term Follow-Up StudY (LEGACY Study). *J. Am. Coll. Cardiol.* **65,** 2159–69 (2015).

125.   Vanelli, P. *et al.* Chronic histological transmurality of high-intensity focused ultrasound ablation. *Ann. Thorac. Surg.* **93,** 2053–6 (2012).

126.   La Meir, M. *et al.* Minimally invasive thoracoscopic hybrid treatment of lone atrial fibrillation: early results of monopolar versus bipolar radiofrequency source. *Interact. Cardiovasc. Thorac. Surg.* **14,** 445–50 (2012).

127.   Comas, G. M., Imren, Y. & Williams, M. R. An overview of energy sources in clinical use for the ablation of atrial fibrillation. *Semin. Thorac. Cardiovasc. Surg.* **19,** 16–24 (2007).

128.   Cox, J. L. *et al.* The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. *J. Thorac. Cardiovasc. Surg.* **101,** 569–83 (1991).

129.   Shivkumar, K., Ellenbogen, K. a, Hummel, J. D., Miller, J. M. & Steinberg, J. S. Acute termination of human atrial fibrillation by identification and catheter ablation of localized rotors and sources: first multicenter experience of focal impulse and rotor modulation (FIRM) ablation. *J. Cardiovasc. Electrophysiol.* **23,** 1277–85 (2012).

130.   Bai, R. *et al.* Proven isolation of the pulmonary vein antrum with or without left atrial posterior wall isolation in patients with persistent atrial fibrillation. *Hear. Rhythm* **13,** 132–140 (2016).

131. Bisleri, G., Rosati, F., Bontempi, L., Curnis, A. & Muneretto, C. Hybrid approach for the treatment of long-standing persistent atrial fibrillation: electrophysiological findings and clinical results. *Eur. J. Cardiothorac. Surg.* **44,** 919–23 (2013).

132. Davies, E. J., Bazerbashi, S., Asopa, S., Haywood, G. & Dalrymple-Hay, M. Long-term outcomes following high intensity focused ultrasound ablation for atrial fibrillation. *J. Card. Surg.* **29,** 101–7 (2014).

133. Bin Abdulhak, A. A. *et al.* Safety and efficacy of interrupted dabigatran for peri-procedural anticoagulation in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Europace* **15,** 1412–20 (2013).

134. Hunter, R. J. *et al.* Validation of a classification system to grade fractionation in atrial fibrillation and correlation with automated detection systems. *Europace* **11,** 1587–96 (2009).

135. Huo, Y. *et al.* Atrial arrhythmias following surgical AF ablation: electrophysiological findings, ablation strategies, and clinical outcome. *J. Cardiovasc. Electrophysiol.* **25,** 725–38 (2014).

136. Tamborero, D. *et al.* Left atrial posterior wall isolation does not improve the outcome of circumferential pulmonary vein ablation for atrial fibrillation: a prospective randomized study. *Circ. Arrhythm. Electrophysiol.* **2,** 35–40 (2009).

137. Kumagai, K., Muraoka, S., Mitsutake, C., Takashima, H. & Nakashima, H. A new approach for complete isolation of the posterior left atrium including pulmonary veins for atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **18,** 1047–52 (2007).

138. Sanders, P. *et al.* Complete isolation of the pulmonary veins and posterior left atrium in chronic atrial fibrillation. Long-term clinical outcome. *Eur. Heart J.* **28,** 1862–71

(2007).

139. Chen, J. *et al.* Treatment of atrial fibrillation by silencing electrical activity in the posterior inter-pulmonary-vein atrium. *Europace* **10,** 265–72 (2008).

140. Sueda, T. *et al.* Midterm results of pulmonary vein isolation for the elimination of chronic atrial fibrillation. *Ann. Thorac. Surg.* **79,** 521–5 (2005).

141. Pison, L. *et al.* Hybrid thoracoscopic surgical and transvenous catheter ablation of atrial fibrillation. *J. Am. Coll. Cardiol.* **60,** 54–61 (2012).

142. Sawin, C. T. *et al.* Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N. Engl. J. Med.* **331,** 1249–52 (1994).

143. Fazio, S., Palmieri, E. A., Lombardi, G. & Biondi, B. Effects of thyroid hormone on the cardiovascular system. *Recent Prog. Horm. Res.* **59,** 31–50 (2004).

144. Sgarbi, J. A., Villaça, F. G., Garbeline, B., Villar, H. E. & Romaldini, J. H. The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities. *J. Clin. Endocrinol. Metab.* **88,** 1672–7 (2003).

145. Aytemir, K. *et al.* Safety and efficacy outcomes in patients undergoing pulmonary vein isolation with second-generation cryoballoon†. *Europace* **17,** 379–87 (2015).

146. Arya, A. *et al.* Long-term results and the predictors of outcome of catheter ablation of atrial fibrillation using steerable sheath catheter navigation after single procedure in 674 patients. *Europace* **12,** 173–80 (2010).

147. Gurses, K. M. *et al.* Red blood cell distribution width predicts outcome of cryoballoon-based atrial fibrillation ablation. *J. Interv. Card. Electrophysiol.* **42,** 51–8 (2015).

148. Berkovitch, A. *et al.* Body mass index and the risk of new-onset atrial fibrillation in middle-aged adults. *Am Hear. J.* **173,** 41–8 (2016).

149. Jongnarangsin, K. *et al.* Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. *J. Cardiovasc. Electrophysiol.* **19,** 668–72 (2008).

150. Wong, C. X., Ganesan, A. N. & Selvanayagam, J. B. Epicardial fat and atrial fibrillation: current evidence, potential mechanisms, clinical implications, and future directions. *Eur. Heart J.* 1–11 (2016). doi:10.1093/eurheartj/ehw045

151. Claeys, M. A., Gepts, E. & Camu, F. Haemodynamic Changes During Anaesthesis Induced And Maintained With Propofol. *BJA Br. J. Anaesth.* **60,** 3–9 (1988).

152. Arbelo, E. *et al.* The Atrial Fibrillation Ablation Pilot Study: an European Survey on Methodology and Results of Catheter Ablation for Atrial Fibrillation: conducted by the European Heart Rhythm Association. *Eur. Heart J.* **35,** 1466–78 (2014).

153. Sternik, L. *et al.* Box lesion in the open left atrium for surgical ablation of atrial fibrillation. *J. Thorac. Cardiovasc. Surg.* **147,** 956–9 (2014).

154. Natale, A., Bai, R., Di Biase, L. & Tondo, C. Outcome of Atrial Fibrillation Ablation After Permanent Pulmonary Vein Antrum Isolation With or Without Proven Left Atrial Posterior Wall Isolation - Full Text View - ClinicalTrials.gov. (2014).

155. Saad, E. B. & Slater, C. Complete Isolation Of The Left Atrial Posterior Wall (Box Lesion) To Treat Longstanding Persistent Atrial Fibrillation. *JAFIB* **7,** (2014).

156. Wieczorek, M. *et al.* Pulmonary vein isolation by duty-cycled bipolar and unipolar antrum ablation using a novel multielectrode ablation catheter system: first clinical

results. *J. Interv. Card. Electrophysiol.* **27,** 23–31 (2010).

157. Davies, E. J., Clayton, B., Lines, I. & Haywood, G. A. Persistent Atrial Fibrillation Ablation using the Tip-Versatile Ablation Catheter. *Heart. Lung Circ.* **25,** 645–51 (2016).

158. McCready, J. *et al.* Safety and efficacy of multipolar pulmonary vein ablation catheter vs. irrigated radiofrequency ablation for paroxysmal atrial fibrillation: a randomized multicentre trial. *Europace* **16,** 1145–53 (2014).

159. Hummel, J. *et al.* Phased RF ablation in persistent atrial fibrillation. *Hear. Rhythm* **11,** 202–9 (2014).

160. Mulder, A. W., Wijffels, M. C., Wever, E. F. & Boersma, L. V. A. Pulmonary vein isolation and left atrial complex-fractionated atrial electrograms ablation for persistent atrial fibrillation with phased radio frequency energy and multi-electrode catheters: efficacy and safety during 12 months follow-up. *Europace* **13,** 1695–702 (2011).

161. Scharf, C. *et al.* Ablation of persistent atrial fibrillation using multielectrode catheters and duty-cycled radiofrequency energy. *J. Am. Coll. Cardiol.* **54,** 1450–6 (2009).

162. Tivig, C. *et al.* Duty-cycled unipolar/bipolar versus conventional radiofrequency ablation in paroxysmal and persistent atrial fibrillation. *Int. J. Cardiol.* **157,** 185–91 (2012).

163. Dixit, S. *et al.* Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation: RASTA Study. *Circulation* **5,** 287–94 (2012).

164. Nakagawa, H. *et al.* Pathophysiologic basis of autonomic ganglionated plexus ablation in patients with atrial fibrillation. *Heart Rhythm* **6,** S26–34 (2009).

165. Yamaguchi, Y., Kumagai, K., Nakashima, H. & Saku, K. Long-term effects of box isolation on sympathovagal balance in atrial fibrillation. *Circ. J.* **74,** 1096–103 (2010).

166. Lemola, K. *et al.* Pulmonary vein region ablation in experimental vagal atrial fibrillation: role of pulmonary veins versus autonomic ganglia. *Circulation* **117,** 470–7 (2008).

167. Pappone, C. *et al.* Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. *Circulation* **109,** 327–34 (2004).

168. Honoris, L. *et al.* Evaluation of left atrial volume and diameter by 64-slice multi detector computer tomograhy. *J. Am. Coll. Cardiol.* **59,** E1203 (2012).