INTERVENTIONAL TECHNIQUES

IN THE MANAGEMENT OF ATRIAL FIBRILLATION

A thesis presented for the degree of

Doctor of Medicine (Research) – MD Res

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Declaration

I declare that I am the author of this thesis. The work contained within this thesis is my own original work, and all content by others has been referenced appropriately.

Shouvik Haldar

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with significant morbidity and mortality. Historically, anti-arrhythmic drug (AAD) therapy achieves sub-optimal efficacy. The last two decades have seen major advances in cardiac electrophysiology, with catheter ablation now becoming the treatment of choice for AF. However, although outcomes for paroxysmal AF are excellent, the optimal interventional strategy for patients with long-standing persistent atrial fibrillation (LSPAF) has yet to be determined. Catheter ablation in LSPAF can achieve a modest degree of success, but the majority of patients require more than one procedure. Thoracoscopic surgical ablation, a relatively new technique, with the potential to improve clinical outcomes in AF, has yet to be evaluated in a head-to-head trial in LSPAF.

The ***C***atheter ***A***blation Versus Thoracoscopic ***S***urgical ***A***blation in Persistent ***A***trial ***F***ibrillation (CASA-AF) was a prospective, non-randomised clinical trial, designed to investigate de novo patients with LSPAF and left ventricular ejection fraction (LVEF) of ≥ 40%. Patients underwent either thoracoscopic surgical ablation or catheter ablation. The primary end-point was freedom from atrial arrhythmias after a single procedure without AADs. Secondary end-points included: clinical success (defined as 75% or greater reduction in AF burden), multi-procedure success, change in atrial anatomy and function, and change in AF symptom score (EHRA score) and quality of life assessments (SF-36).

This thesis aims to investigate the interventional techniques used in the management of AF, with the main focus on the CASA-AF study. In addition, the Complex Fractionated Atrial Electrogram sub-study assesses the atrial substrate and its role in AF, whilst the Cardiac

Magnetic Resonance sub-study investigates the changes in atrial and ventricular chambers pre- and post-ablation. The final study presented in this thesis concerns the effects of using exciting new Contact Force technology on the acute efficacy of pulmonary vein isolation in AF ablation.

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Chapter 1

Introduction

1.1 Background

1.1.1 Brief History of Atrial Fibrillation

The earliest historical description of atrial fibrillation (AF) dates back to approximately 4000 years ago from 'The Yellow Emperor's Classic of Internal Medicine' by Huang Ti Nei Ching Su Wen. He wrote: 'When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades'. [1] In 1628, William Harvey observed 'fibrillation of the auricles' in a dying heart, whilst Sir Thomas Lewis in the early 20th Century was the first to document AF on an electrocardiograph, and described the fine diastolic oscillatory activity as fibrillatory activity in the atria.[2 3] Several mechanisms of AF have since been proposed, including excess multiple ectopic activity (Winterberg), single-circuit re-entrant activity (Lewis) and the multiple wavelet hypothesis (Moe). [4] The latter, based on the notion of multiple re-entry circuits with self-perpetuating activation wavelets propagating and colliding on heterogeneous atrial tissue, and supported by his computer modelling work, became the most widely accepted theory underpinning this complex arrhythmia.

1.1.2 Prevalence, incidence and impact of AF

AF is the commonest arrhythmia encountered in modern day clinical practice. The Global Burden of Disease 2010 Study estimated the prevalence of AF worldwide to be approximately 33.5 million with an incidence of 5 million new cases per year.[5] As the prevalence of AF increases with age, an epidemic is predicted as the worldwide population ages, coupled with improved survival from all

major cardiovascular conditions such as ischaemic heart disease and heart failure. Data from US population statistics predicts the prevalence of AF in the US will exceed 12 million by 2050.[6] AF independently increases the risk of stroke 4- to 5-fold in all ages, with at least 15-20% of all debilitating strokes due to underlying AF.[6] In the UK alone the cost implication of AF and its associated morbidity is 0.9-2.7% of the total health-care expenditure.[7] Therefore, the potential future impact on healthcare costs of this arrhythmia should not be underestimated.

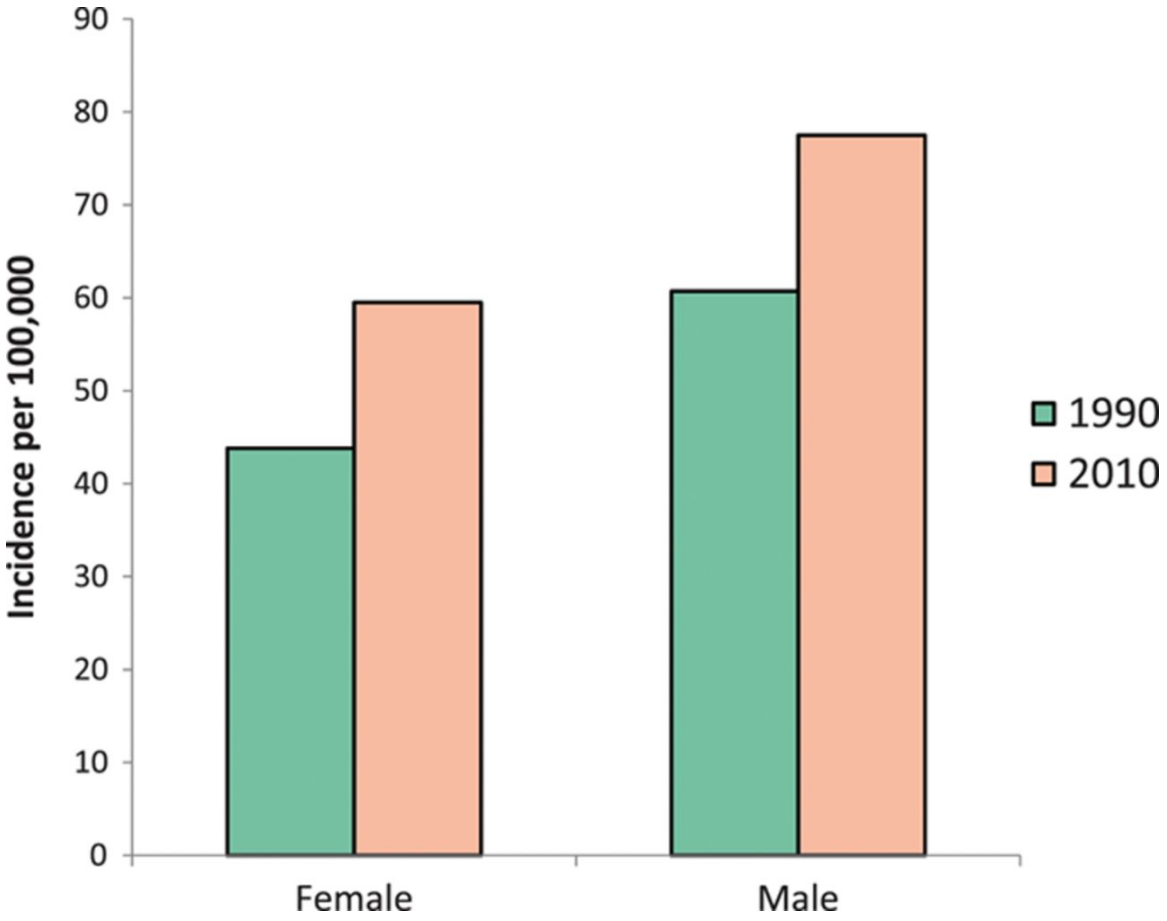


Figure 1.1 Increasing incidence of AF

Incidence of atrial fibrillation: Estimated age-adjusted global incidence (per 100 000 person-years) for women and men at two time points; 1990 and 2010, showing a clear increase. Reproduced with permission. [5]

1.1.3 Aetiology, pathophysiology and mechanisms of AF

The pathophysiology of AF is complex, multifactorial and still not fully understood. AF is associated with numerous medical conditions including ischemic heart disease, hypertension, valvular disease, diabetes and thyroid disease.[1] More recently, life-style related factors have also been implicated, such as excess alcohol consumption, athletic levels of exercise, and obesity in the context of obstructive sleep apnoea.[8] Furthermore, there has been increasing interest in the genetic associations of AF with several epidemiological studies confirming the heritability of AF.[9]

The aforementioned conditions may result in anatomical remodelling of the atria via dilatation and fibrosis, which in turn causes electrical remodelling due to altered atrial (slow) conduction velocities and refractoriness coupled with altered autonomic tone. As the disease progresses, this electroanatomical remodelling provides a 'substrate' for AF maintenance, and the resultant AF becomes more persistent in nature. This observation coined the term 'AF begets AF' and it is this 'substrate' that Moe et al. described in their 'multiple wavelet hypothesis' in 1963.[10] Their use of computer modelling demonstrated that the perpetuation of AF was based on 'fractionation of a grossly irregular wavefront' resulting in 'multiple wavelets colliding with each other'. This hypothesis was subsequently supported by the experimental studies of Wijffels and Allesie.[11 12]

AF generally begins as a paroxysmal rhythm disturbance and evolves with time into a more persistent or permanent state. In the 'early' paroxysmal stages of the disease course, pulmonary vein (PV) focal triggers are thought to play the dominant role in AF causation. This is based on the seminal work by Haissaguerre's group, that showed spontaneous initiation of AF is provoked by rapidly firing ectopic foci located predominantly within the PVs, often referred to as the 'focal source hypothesis'.[13] This discovery prompted the rise in catheter based pulmonary vein isolation (PVI) procedures to treat AF.

In many respects, the chronological order of these mechanistic discoveries was back to front, with AF 'maintenance' being discovered before the concept of AF 'triggers'. If one examines the temporal relationship of these discoveries to treatment strategies, it is clear that this chronological mismatch resulted in confusion. For example, after Haissaguerre's paper, there was a notion that PVI was all that was required to treat all forms of AF. However, the encouraging outcomes from PVI in paroxysmal AF were not translated into non-paroxysmal forms of AF, and it is now widely accepted that PVI alone is an ineffective interventional strategy in non-paroxysmal AF, based on a wealth of evidence from both catheter and surgical ablation studies. [14-16] A number of other mechanisms have since been proposed including; PV and non-PV triggers; the intrinsic cardiac autonomic nervous system and the rotor hypothesis [13, 17-19] Each are likely to be as valid as the other, but the complexity of the arrhythmia would suggest that all these mechanisms co-exist and are interlinked to varying degrees. Furthermore, the purported interplay between them would explain the challenges in treating this arrhythmia, and why one uniform ablation strategy is not sufficient to treat the whole spectrum of AF.

1.1.4 Principles of AF Management

AF is characterised by an irregularly irregular pulse, loss of atrial contractile function with the associated loss of active ventricular filling, and the risk of thromboembolic stroke. In addition to prevention of stroke with anticoagulants (commonly warfarin and more recently the novel oral anticoagulant agents), there are two principal therapeutic strategies for treatment of AF: rhythm control (to restore sinus rhythm) and rate control (to accept AF and simply control the ventricular rate).

Of the two strategies, rhythm control is the desired strategy in symptomatic patients, especially those that are younger and more active with symptoms, despite adequate ventricular rate control.

Although drug therapy for rate control is well established and commonly includes beta-blockers, non-dihydropyridine calcium channel blockers and digoxin, anti-arrhythmic drug (AAD) therapy, such as class I agents (flecainide and propafenone) and class III agents (amiodarone and sotalol), to reduce the burden of AF in 'rhythm-control' strategies, has numerous limitations. First, AADs are only able to control AF in 23-63% of patients, although this figure is significantly lower for those with more longer-standing AF and enlarged atrial dimensions. [20 21] Second, their side-effect profiles and tendency for proarrhythmia are major disadvantages. Overall, the net benefit of AAD therapy is modest at best. Unsurprisingly, the suboptimal efficacy of AADs has been one of the main motivations in the development of non-pharmacological approaches in the management of AF over the last two decades.

1.2 Early open-heart surgical procedures – rationale and lessons learnt

The surgical community must be credited as the first to apply the concepts of the previously discussed 'multiple wavelet hypothesis' therapeutically. The first of these was the description of the 'corridor' procedure by Guiraudon in 1985. [22] The procedure entailed isolating a strip ('corridor') of atrial tissue between the two atria providing a direct link between the sinoatrial node and the atrioventricular node. The rationale of this procedure was to reduce the critical mass of atrial tissue required to sustain the multiple re-entrant wavelets implicated in AF. The procedural results, with respect to freedom from AF were respectable, but there was one major limitation to this technique. Although the 'corridor' was free from AF and permitted sinus node control of the ventricular rate with a degree of atria-ventricular synchrony, the remainder of the atria remained in AF resulting in continued thromboembolic risks, and loss of the 'atrial kick'.

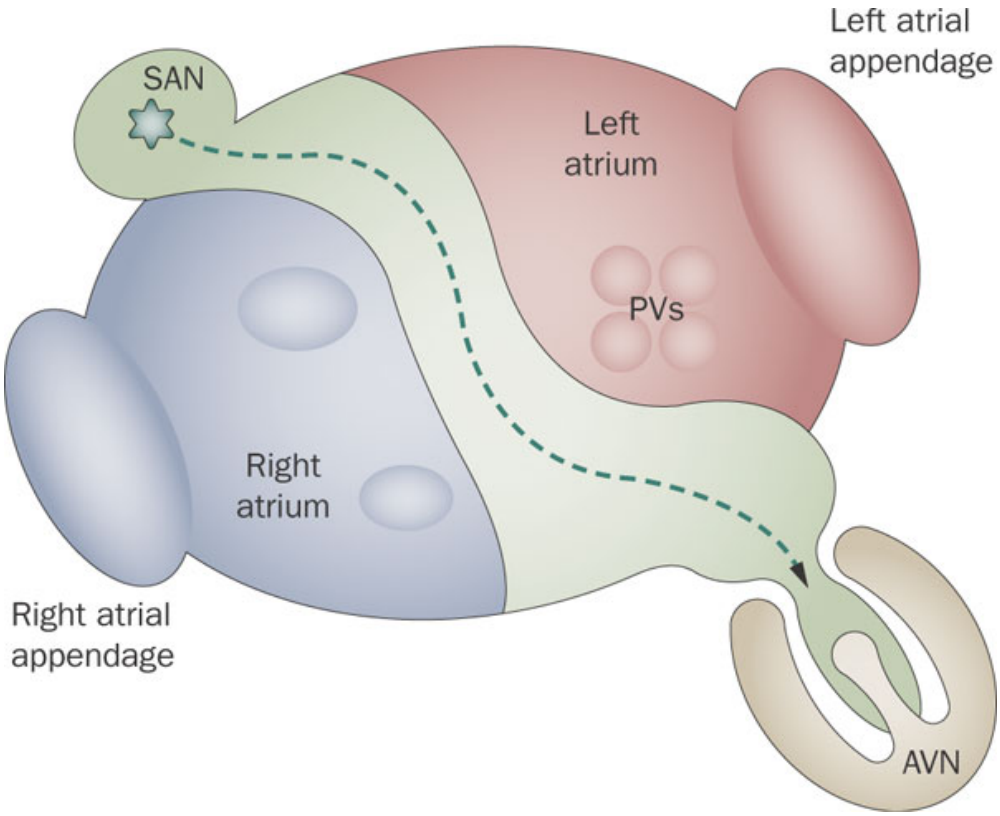


Figure 1.2 Guiraudon's 'corridor' procedure

The above schematic shows the isolation of a strip of tissue that that directs the sinus impulse to the AVN in a small zone which minimises the chance of re-entry and hence AF. The excluded right and left atria still fibrillate and thus the risk of stroke remains. AF= atrial fibrillation; AVN= atrioventricular node; PVs= pulmonary veins; SAN= sinoatrial node. Reproduced with permission. [27]

The late 1980s saw further surgical research involving experimentation with atrial incisions in canine hearts, which led the way for Cox et al. to perform the first human atrial transection procedure in 1986. Using a cut and sew technique they were able to restore sinus rhythm (SR) in the short term and were, therefore, the first group to demonstrate that termination of AF was indeed possible with interventional therapy. [23] The continued efforts of Cox et al., coupled with their appreciation of the inter-relationship between atrial anatomy and electrophysiology, led to the conception of the Maze procedure. [23] The first Maze procedure was performed in 1987 and quickly became known as the Cox-Maze procedure in recognition of their pioneering and visionary work. The procedure involved making multiple atrial incisions to create a series of scars resulting in

atrial compartmentalisation and isolation of the posterior left atrium (LA) and all four PVs. These scars not only isolated the PVs, but also interrupted the macro-re-entrant circuits required by the atrial tissue to maintain AF, thus modifying the atrial substrate. The scars also created a pathway of conduction between the SAN and the AVN, which was similar in principle to Guiraudon's 'corridor' procedure. Early iterations of the procedure were tainted by damage to the intrinsic conduction system (SAN), resulting in a high incidence of pacemaker implantation as well as significant LA dysfunction. [23] The procedure underwent numerous modifications, which culminated in the Cox-Maze III procedure. [24] The long-term follow-up results were exceptional, with SR maintained in 96% of patients beyond 5 years. [25]

Unsurprisingly, the Cox-Maze III became the gold standard for surgical ablation (SA) for over a decade, but there were important caveats to consider. The multiple atrial incisions and cardiopulmonary bypass ensured that the procedure remained long and technically complex whilst retaining a significant risk of morbidity. Thus, although highly effective, the 'Cox-Maze' failed to gain popularity as a treatment modality for standalone AF, and became reserved for those undergoing concomitant cardiac surgery. [25] Furthermore, taking into account contemporary guidelines, questions linger over the true efficacy of the Cox-Maze III procedure, as the follow-up for arrhythmia recurrence was not as rigorous as present day recommendations. [26]

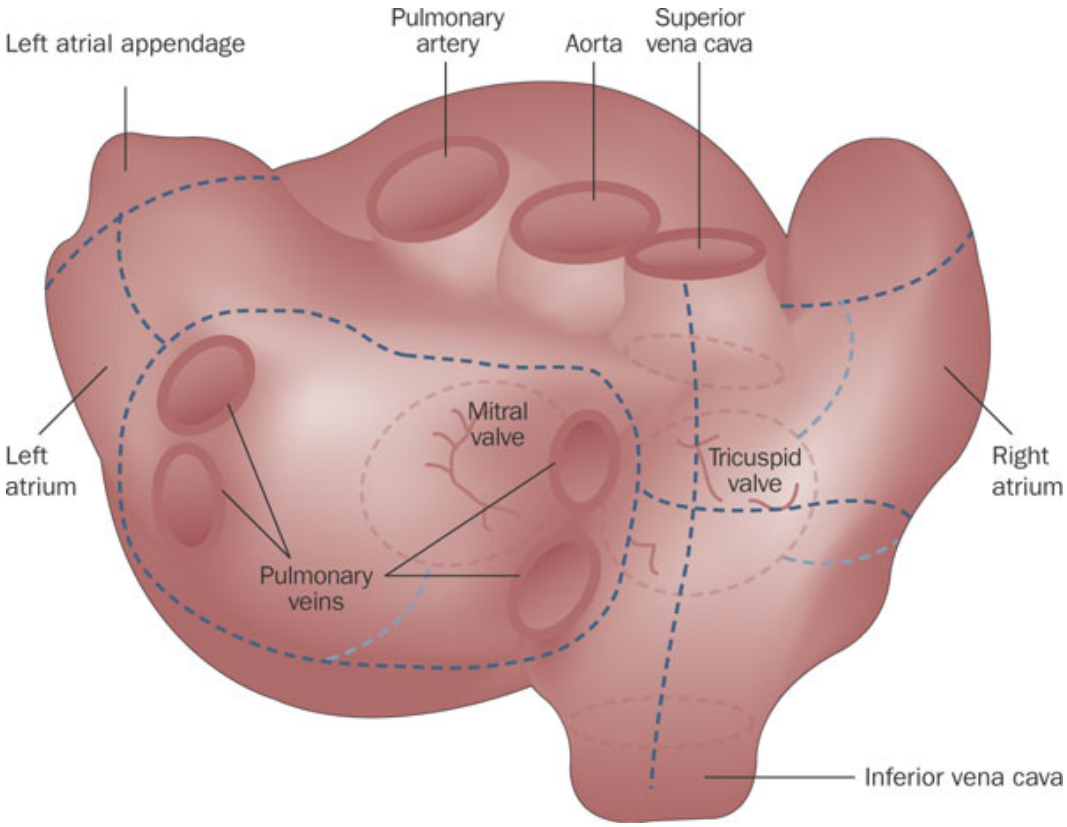


Figure 1.3 The Cox-Maze procedure

The Cox-Maze procedure compartmentalizes both atria by using a cut-and-sew technique to form a series of scars (dashed lines). These scars isolated the pulmonary veins, the posterior wall and the left atrial appendage and created a pathway between the SA node and the AV node. AV= atrioventricular, SA= sinoatrial. Reproduced with permission. [27]

1.3 Catheter ablation – the rationale

In the mid 1990s, electrophysiologists were conducting increasingly inquisitive work with regard to the mechanistic aspects of AF, the consequence of which was the previously mentioned seminal work by Haissaguerre et al. in 1998. [13] They were the first to describe that PV ectopic foci, witnessed during invasive electrophysiological studies, were the triggers of AF in a significant proportion of patients. This finding provided the necessary impetus for electrophysiologists to develop percutaneous techniques to isolate the PVs (PVI) electrically, heralding a new era of catheter-based ablation. The technique of PVI has been refined over the years to concentrate on ablation away from the PV ostia, as this had been associated with significant risks of PV stenosis. [28]

Nowadays, most operators isolate these ipsilateral pairs of PVs with wide area antral encircling ablation lesions.

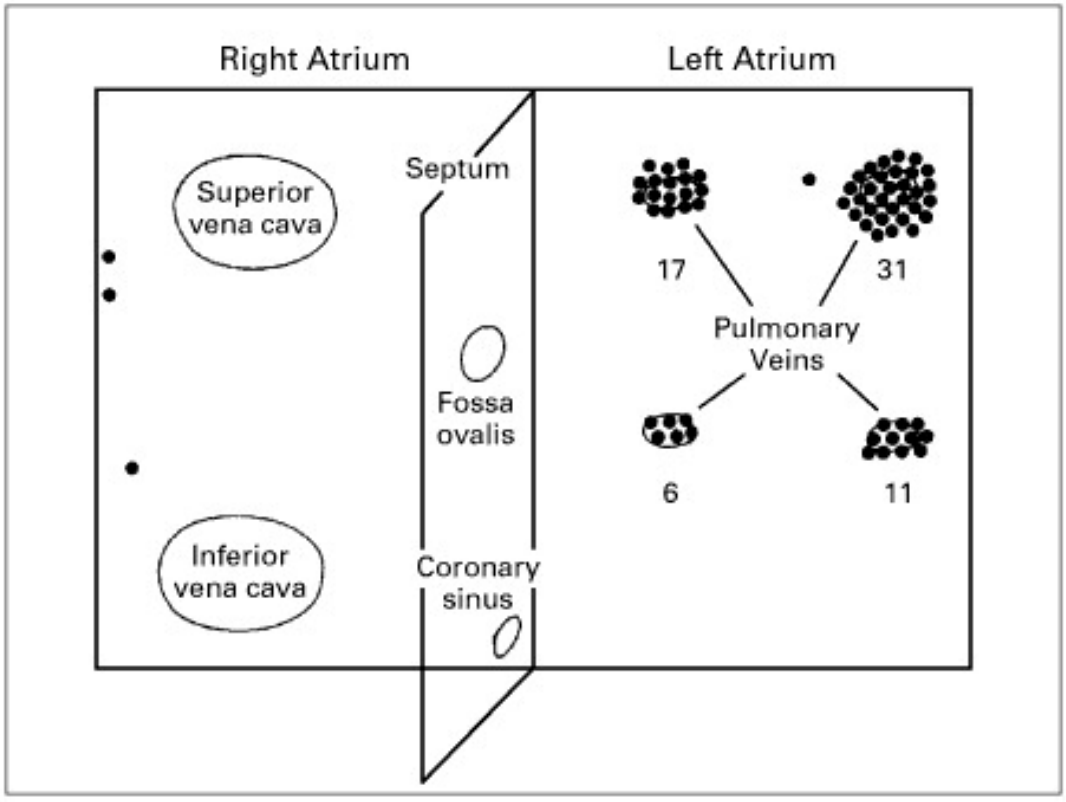


Figure 1.4 Predominance of pulmonary vein focal sites, triggering AF in 45 patients

Distribution (numbered) of focal sites that triggered AF in 45 patients. Clustering was observed, particularly in the upper pulmonary veins. Reproduced with permission. Copyright Massachusetts Medical Society [13]

Despite this discovery, it was quickly realised that achieving PVI alone was not enough to treat AF in all patients. [29-31] It stands to reason that PVI will be of most benefit in paroxysmal patients in whom PV triggers predominate as the main mechanism. However, those with more persistent forms of AF, where time has disrupted the electro-anatomical architecture of the atria, require more than just PVI. Put another way, if the atria are already in a state of persistent fibrillation (with the substrate alone maintaining fibrillation) the importance of PV triggers becomes less important, as it is in these patients where substrate modification, in addition to PVI, is of paramount

importance.

An important technique to modify the LA substrate in non-paroxysmal AF is the creation of linear lesions to interrupt the macro-re-entrant loops that contribute to the maintenance of AF. Commonly used linear lesions include a roof line connecting the left and right superior PVs, and a mitral line connecting the mitral annulus to the left inferior PV. The benefit of such lines in persistent AF has been elegantly highlighted by Willems et al. in a randomised control trial where persistent or permanent AF patients are randomised to either PVI + additional linear lesions (roof and mitral isthmus line) or PVI alone. At 16 months, 20% were free from AF with PVI alone, versus 69% with additional substrate modification. [32] Linear ablation can be technically challenging and if undertaken, the aim must be to achieve and confirm bi-directional block to document the completeness of such lines. Furthermore, it is best not to attempt linear lines than to leave them incompletely blocked, as this can result in a highly pro-arrhythmogenic atrial substrate. In fact the resultant macro-re-entrant atrial tachycardias (AT) can themselves pose significant symptomatic burden to the patient. [32]

Another technique in lieu of, or additional to, PVI which also modifies the substrate has been investigated and advocated by Nadamanee et al. [33] Their group targeted areas exhibiting complex fractionated atrial activity (CFEs), thought to represent areas of slow conduction, colliding waveforms, migration rotors and/or sites of underlying ganglionated plexi (GP) amongst other proposed mechanisms. [34-36] Nademanee demonstrated that this approach was highly effective with 91% of patients (combination of paroxysmal and persistent) free from arrhythmia and symptoms at 1 year. [33] However, the same degree of success has not been replicated by other groups, causing controversy on the merits of CFE ablation. [37 38] Even when combining CFE ablation with PVI, some results have been inconclusive, although a subsequent metanalysis of several randomised control

trials has shown that there is indeed an incremental benefit to CFE ablation when added to PVI. [39] CFE ablation is, therefore, often used as one of the adjunct techniques of substrate modification after PVI in non-paroxysmal AF.

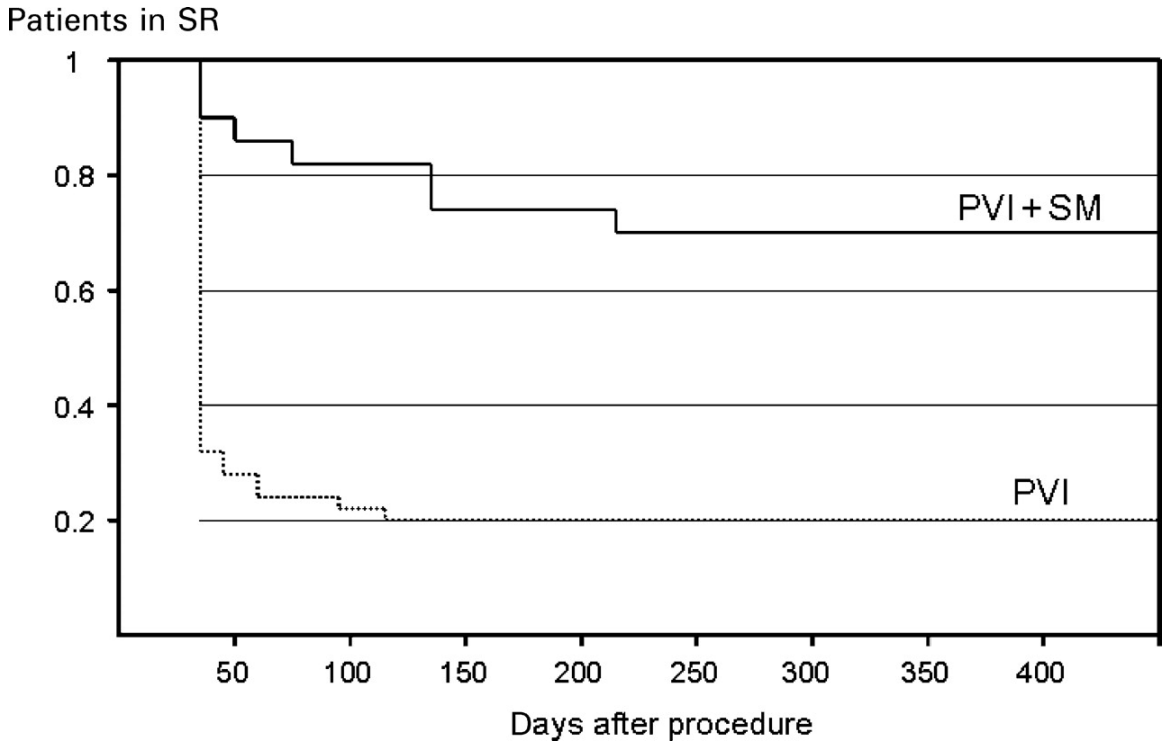


Figure 1.5 Outcome differences when linear lesions added to PVI in non-paroxysmal AF

Kaplan-Meier curves showing freedom from AF after PVI or PVI plus SM (substrate modification via linear lesions); p=0.0001. Reproduced with permission. [14]

Contemporary CA can treat paroxysmal AF with a high degree of success but results remain suboptimal for persistent and long standing persistent AF (LSPAF), with patients often needing multiple procedures. [39] For example, in LSPAF, previous studies show single procedure success of either 27% at 40 months or 32% at just over 12 months' follow-up. [40 41] Therefore, in addition to PVI, linear lesions and/or CFE guided substrate modification are often employed to improve procedural results in this group. [39] The stepwise ablation approach has been championed by

Haissaguerre's group and incorporates PVI, linear ablation, CFE targeted ablation +/- right atrial ablation. The integration of these aforementioned adjunct techniques seems to be a sensible and scientifically sound approach to treat non-paroxysmal AF patients, and many centres have now adopted this strategy. [32, 42 43]

1.4 Advances in surgical ablation

1.4.1 Dawn of a new surgical era – the Cox-Maze IV

With CA for AF gaining momentum in the late 1990s and early 2000s, the surgical community renewed its interest in AF intervention and developed less invasive techniques that could deliver the same efficacy benefits of the Cox-Maze III, whilst offering a viable alternative to catheter based therapy. The need to find an alternative to the cut-and-sew technique led to the development of energy delivering ablation devices. The remit was clear; the device would have to deliver energy that would result in contiguous and transmural ablation lines endo- and epicardially, and be small and flexible enough to use in a minimally invasive thorocoscopic approach.

The use of energy devices began with the first cryomaze procedures in 1999, where cryoenergy ablation lesions completely replaced atrial incisions (entirely non cut-and-sew Maze procedure). [44] This was followed closely by Damiano and colleagues pioneering the use of RF ablation devices with the resultant development of the Cox-Maze IV procedure. [45] They used a bipolar RF device to create two islands that isolated the PVs (equivalent to wide area antral encirclement) but additional cryoablation was also employed to help isolate the posterior LA. Instead of a midline sternotomy, the procedure was done via a smaller right-sided thoracotomy but still required cardiopulmonary bypass, although operating times and hence ischaemic times were significantly shorter. The results of the Cox-Maze IV were very encouraging and demonstrated that replicating

the Maze procedure with an energy enabling ablation device was comparable to the effectiveness of the Cox Maze III procedure at up to 12 months' follow-up. [46]

1.4.2 Thoracoscopic (minimally invasive) surgical ablation

The evolution from the cut-and-sew technique to energy delivering devices heralded the next logical step - to perform SA without a midline sternotomy, on a beating heart. In fact, James Cox had already set the challenge in 2004, proclaiming that the ideal surgical procedure for AF would 'be performed via a minimally invasive incision (endoscopically or robotically), off bypass, in less than 1 hour, with hospital discharge planned for the next morning'. [47]

Thoracoscopic ablation has a number of potential advantages when compared with catheter-based treatments. The ability to visualise directly the target tissue of the LA-PVs junction improves accuracy of lesion delivery with less collateral tissue damage to surrounding structures. Lesions can be visualised in real time, particularly with RF energy, and the risk of PV stenosis is unlikely if PV lesions are placed correctly on the antrum. The option to excise the left atrial appendage (LAA) is also present, which can minimise subsequent thromboembolic risk and may simultaneously eliminate a potential source of trigger in some patients. [48 49] Unlike CA, there are no devices in contact with the endocardium, which eliminates the risks of thrombus formation, and there is no need for fluoroscopy. Disadvantages include the usual risks of surgery, a longer hospital stay (3-5 days), incisional discomfort which may last for a few weeks in some cases and cosmetic issues from thoracoport access sites.

1.4.3 Energy Devices

Numerous energy delivering devices facilitating thoracoscopic ablation have been available on the market including those employing microwave, laser and cryothermal techniques. In the last

decade, bipolar RF devices have become the tool of choice for several reasons. Compared to other energy sources, it has a rich evidence base with animal models demonstrating the bipolar RF clamp's ability to produce both acute and chronic transmural lesions consistently. [50-53] Use of the bipolar RF clamp also minimises collateral tissue damage, by confining the energy between the two electrodes embedded within the jaws of the clamp. This creates a transmural scar, with real time verification of transmurality, via a drop in tissue conductance. In contrast, unipolar RF and cryoablation are unable to create such reliable transmural lesions because of the rapid dissipation of heat energy via conductance to the circulating intracavity blood – a phenomenon known as heat sink. [54]

Other energy sources such as microwave and laser have been shown to be ineffective with regards to PVI and are no longer on the market, whilst high-intensity focussed ultrasound has not met the appropriate safety standards required for AF ablation. [55-57] The paucity of experience with alternatives to bipolar RF renders any meaningful comparison difficult.

In the study presented in this thesis, the Atricure RF surgical ablation system (AtriCure Inc., Westchester, OH, USA) was used due to the fact that there is significantly more data published using this system. However, there are two other RF systems that are currently commercially available and which should be mentioned. Firstly, the COBRA® Surgical System (San Ramon, CA, USA), which is a multi-electrode, temperature controlled epicardial device which is currently being evaluated in clinical trials. The device has a unique suction mechanism that pulls the atrial epicardial tissue to the probe in order to obtain contiguous lesions and to maintain a stable position during RF application. Secondly, the Medtronic Cardioablate systems (Minneapolis, MN, USA) which are low profile RF ablation clamps suitable for thoracoscopic procedures and are also currently being evaluated in clinical

studies. Both

Medtronic and Atricure also have cryothermal energy probes which destroy tissue by freezing rather than by heating. Although this can preserve myocardial tissue architecture it takes longer than RF to create lesions and also has the potential risk of thromboembolism due if intracavity blood freezes as a consequence of ablation.

1.4.4 Ganglionated Plexi Ablation

The intrinsic cardiac autonomic system comprises a complex weave of parasympathetic and sympathetic nerve fibres that interconnect the LA and the PVs. Their neurones cluster in ganglionic plexi (GP) that can be found within the epicardial fat pads that innervate and overlie the myocardial sleeves of the PV-LA junction. GPs have been implicated in the pathogenesis of AF and one of the advantages of the thoracoscopic approach is that GPs can be identified and eliminated quickly alongside PVI.

Experimental data has shown that GP stimulation can convert PV ectopy into AF but also that GP stimulation can instigate this ectopic PV activity in the first place. [58-59] Animal and clinical studies have shown that CA of these GP can prevent AF inducibility and eliminate AF once present, suggesting that GPs have a role in both triggering and the maintenance of AF. [33, 60-64] Scherlag et al. put this into clinical context by demonstrating that the addition of GP ablation to PVI increases the efficacy of ablation (as compared to PVI alone), although study numbers were small with a short follow-up period. [61] In addition, McClelland et al. recognised that 79% of pre-PVI identified GP sites were eliminated via PVI using the RF clamp, suggesting that GP mapping is best undertaken post PVI to reduce both RF applications and overall operating time. [65] The ligament of Marshall (LoM) must also be mentioned here as it is frequently transected and/or ablated during PVI or GP ablation, which is relevant as there is evidence of its role as an AF trigger. [66-68]

At present, the incremental benefits of GP ablation over and above PVI +/- linear lesions remains unclear - particularly when its long-term efficacy has been challenged by an animal study which shows that re-innervation occurs within four weeks of ablation with recurrence of AF within 1 year. [69] Although still widely incorporated in surgical lesion sets, its inclusion remains controversial and needs further robust validation.

1.4.5 Early Experience with Thoracoscopic Surgical AF Ablation

Early thoracoscopic procedures concentrated on a more simplified lesion set than that of the Cox-Maze III. Although earlier reports exist, Wolf et al. were credited as the first to use a minimally invasive, video-assisted, thoracoscopic surgical (VATS) technique to access the heart, and perform epicardial ablation on a beating heart in 2005. Ipsilateral PVs were electrically isolated using a non-irrigated, bipolar RF device and the left atrial appendage (LAA) was excluded using a staple device. Of the twenty-three patients who had more than 3 months' follow-up, more than 90% were free of AF whilst on AAD.

Edgerton et al. then reported a series of thoracoscopic PVI that added targeted GP ablation but did not include LAA exclusion (n=74). At 6-months' follow-up, 70% of patients with paroxysmal AF and 35% of persistent AF patients were off AAD and in SR. [16]

In 2009, Edgerton and colleagues published a further multi-centre series of 114 patients with a mixture of AF classifications who underwent minimally invasive PVI, GP ablation and LAA excision. At 6 months, SR rates off AAD were 71% for paroxysmal, 47% for persistent and 32% for long standing persistent AF patients. [70]

A number of such studies were published between 2005 and 2010, and it became clear that thoracoscopic PVI with or without autonomic denervation and/or LAA exclusion was indeed as

effective as CA in treating paroxysmal AF. [16, 65, 71-76] However, the results for persistent or LSPAF were suboptimal, but not unexpected, given the limited lesion set used. The success from the more extensive lesion set used in the Cox-Maze III, together with CA studies demonstrating increasing efficacy when LA substrate modification is added to PVI, clearly highlighted the need for substrate modification in non-paroxysmal AF patients.

1.5 Totally Thoracoscopic Surgical Ablation

Despite the use of the term 'minimally invasive' in many of the early thoracoscopic SA reports, the majority still used muscle splitting, mini-thoracotomy incisions for instrumentation. Although clearly better than a median sternotomy, this remained too invasive from a patient's perspective.

Efforts to reduce patient morbidity and discomfort, and to facilitate a faster post-operative recovery led to the publication of three reports between 2008 and 2009, detailing a totally thoracoscopic approach to surgical ablation i.e. without the need for mini-thoracotomies or additional incisions.

The first such report in early 2008 was a short series of nine patients with paroxysmal AF. Access in these cases was via three thoracoports bilaterally (one 10mm and two 5mm), without the need for muscle splitting and emphasis on blunt dissection to minimise tissue damage (Figure 1.6). Their experience showed that achieving PVI and LAA exclusion via this technique was both feasible and safe. After a mean follow-up time of greater than 9 months, 78% patients were in SR as per Holter monitoring.[72]

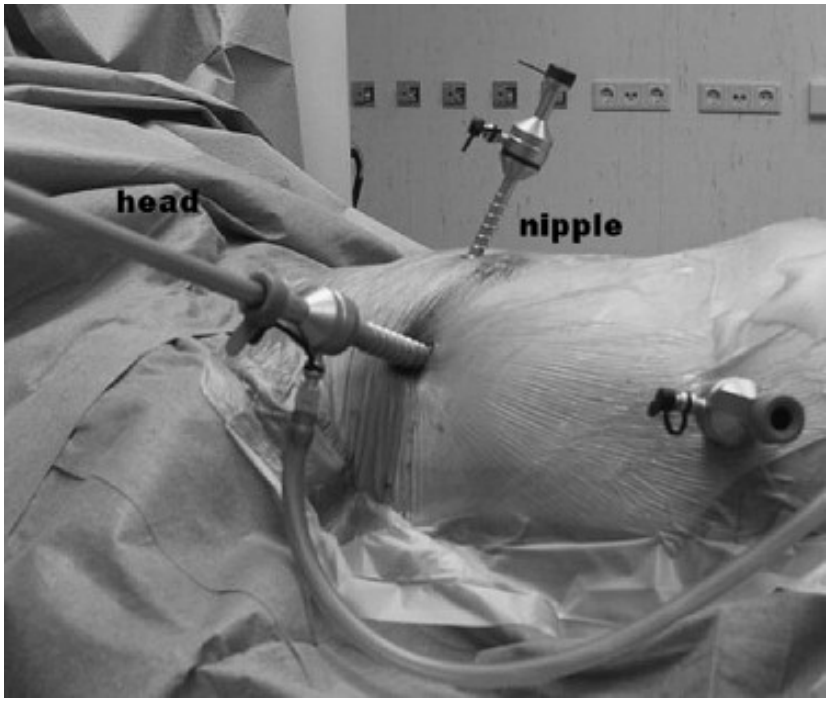


Figure 1.6 Totally thorocoscopic surgical ablation access points

Three thoracoports are used each side. One at the mid-axillary line, a second at the fourth intercostal space and a third inserted between the two other ports at the sixth intercostal space. Reproduced with permission. [72]

Later that year, Sirak et al. published retrospective data on 32 patients who had undergone a totally thoracoscopic approach to surgical AF ablation. [77] Contrary to most surgical ablation studies performed up until then, they conducted these procedures on persistent or LSPAF patients. Hence, in addition to PVI and GP ablation, they uniquely incorporated three connecting linear lesions; a line connecting the superior PVs (roof line); a line connecting inferior PVs (an inferior line); and a line connecting the roof line to the anterior trigone of the mitral valve. A reasonable attempt was made to verify linear lesion continuity via electrocardiographic signal attenuation (>90%) using an EP catheter, but bi-directional block was demonstrated only for the PVI lesions. At 6 months, 87% of patients were off AAD (except low dose beta-blocker) and in SR. It is worth noting that none of the patients in this study were documented to have post-procedural macro-re-entrant tachycardias, which may suggest that the linear lesions were indeed completely blocked.

No doubt spurred on by Sirak's results and in an attempt to improve upon their previous results,

Edgerton et al. studied the use of a more extensive lesion set in their treatment of persistent AF. [78] Their lesion set was designed to replicate the LA lesions used in the Cox-Maze III procedure and included a roof line connecting the superior PVs, a connecting line to the base of the resected LAA, and a line connecting the roof line transversely with the subaortic root. In a more detailed fashion than Sirak, they conducted robust testing of these linear lesions with differential sensing and pacing to confirm conduction block. At 6 months, they achieved 78% and 47% freedom from AF off AAD, in the persistent and LSPAF groups respectively.

1.5.1 Electrophysiological validation of surgical lesions

Further efforts to improve surgical ablation results saw a novel study being published by Krul et al. They combined totally thoracoscopic ablation with thorough electrophysiological confirmation of conduction block. [79] This entailed confirming entrance and exit block of the PVs in all patients, and demonstrating bi-directional block of linear ablation lines in the non-paroxysmal cases. This approach yielded impressive results with a single procedure success rate (defined as freedom from atrial arrhythmias off AAD) of 92% in the paroxysmal group and 80% in the non-paroxysmal group, at 1 year. The addition of robust electrophysiological testing had clearly improved efficacy when compared to previous studies, and further substantiated the results obtained by Sirak and Edgerton who had undertaken a degree of electrophysiological assessment of their linear ablation lesions. [77 78]

1.5.2 Sequential epicardial and endocardial ablation

Sequential thoracoscopic SA followed by CA during the same hospital admission has been recently studied in persistent AF patients by Mahapatra et al. [80] Their rationale was to see if combining these modalities could improve efficacy by eradicating post-surgical macro-re-entrant arrhythmias. Notably, all enrolled patients had previously failed CA. The sequential group (n=15) was matched

to a control group (n=30) who underwent CA alone (more than one procedure allowed). Both SA and CA arms had PVI and additional linear ablation, as now expected in this patient subset. Rhythm assessment was rigorous with the use of both 7-day continuous auto-triggered monitor and 24 hour Holter monitoring. Results were striking with 87% of sequential patients free of atrial arrhythmias and off AAD, compared with 53% of catheter-alone patients after a mean follow-up period of 20.7 ± 4.5 months. This was the first study to achieve the high success rates obtained by Sirak et al. as previously described.

1.5.3 Catheter ablation versus totally thoracoscopic surgical ablation

The end of 2011 yielded the first randomised controlled study - the FAST study - comparing these two techniques. [81] This was a welcome addition to the literature in this arena with the hope that it would clarify the relative positions of these two modalities in the invasive treatment of AF. One hundred and twenty four patients with drug-refractory AF were randomised in a 2-centre study. In the CA arm (n=63), 58.8% were paroxysmal with 41.2% non-paroxysmal, while in the SA arm (n=61), 73.8% were paroxysmal with 26.2% non-paroxysmal. The primary endpoint was freedom from LA arrhythmia at 12 months, off AAD. 36.5% met this endpoint in the CA group, versus 65.6% in the SA group, highlighting a statistically significant difference. The results are striking, but must be interpreted with caution, for several reasons. First, there were significant inequalities with regard to lesion set depending on both modality and site of treatment. This makes the comparison of the two procedures difficult. Second, catheter technology was different between the centres, with one using a 4mm solid-tip whilst the other used a 4mm irrigated-tip. Irrigated tip catheters provide more effective RF lesions which may have contribute to the third point, which was that the efficacy for both modalities was far lower than expected. When examining the CA

group, this is hardly surprising considering that some patients received only PVI regardless of whether they were paroxysmal or persistent AF cases - inconsistent with contemporary practice. In the SA group, when surgical linear ablation was undertaken, verification of conduction block was not sought in all of the lines, which may have reduced the overall efficacy obtained. Finally, major adverse events were significantly higher in the SA group compared to the CA group (34.4% vs. 15.9%; p=0.027), but also of note is that the CA complication is significantly higher than data from the worldwide survey on complications. [30] Although this study concluded that SA was superior to CA, if one analyses the data closely it would appear that the risk-benefit ratio of surgery is unfavourable.

1.5.4 Hybrid thoracoscopic surgical and transvenous catheter ablation

In 2012, Pison et al reported the results of a hybrid ablation approach combining a totally thoracoscopic, off-pump, surgical approach using a bipolar radiofrequency clamp and linear ablation pen with conventional endocardial catheter ablation. [82] Of the 26 patients studied, 11 (42%) had persistent AF and 11 had prior CA for AF or atrial flutter (42%). The ablation strategy included PVI, posterior wall isolation, mitral isthmus line, cavo-tricuspid isthmus line and bi-caval line. However, not all patients received all these lesions, as the strategy was tailored to each individual patient with more extensive ablation conducted in those with more advanced substrates. Endocardial ablation enabled the mitral and cavotricuspid lines to be conducted, and was also used to 'top-up' areas where epicardial ablation had left gaps or was not transmural. Importantly, bi-directional block for PVI was confirmed via using circular catheters within the pulmonary veins and also for linear lesions. The mean follow-up was 470 ± 154 days and 12-month success off AAD was 93% for patients with paroxysmal AF and 90% for patients with persistent AF. The single procedure success rate was 83% and there were no

significant complications reported.

The high success rates in this trial demonstrate the potential of this hybrid approach, however, due to the heterogeneity of the lesion sets used, it is difficult to interpret which lesions are required for which subset of patients. What can be inferred is that more advanced substrates need more extensive ablation, and that underpinning this is the need for meticulous validation of PVI and linear lesions which no doubt contributed to the high success rates. It also of note that the complication rate was very low, in contrast to the FAST study. This highlights, as with catheter ablation, that procedures of this nature need to be conducted by experienced operators in high-volume centres.

1.5.5 Arrhythmia recurrence post-surgical ablation

Most SA studies report upon procedural success rates, but there is a paucity of data regarding the arrhythmias that constitute the 'failures'. A study that investigated this very aspect looked at late (>3 months) recurrence of symptomatic arrhythmia post SA. [83] The index procedures included the Cox-Maze III, IV and left atrial SA and a variety of energy sources were also used. Very few patients had conduction block tested intraoperatively. Of those patients with refractory, symptomatic, post-operative arrhythmias, only 4% (n=16) underwent subsequent EPS - all of whom had persistent forms of AF from study enrolment. Sixteen arrhythmias were identified (including 7 right atrial flutters, 3 left atrial flutters, 1 bi-atrial flutter and 5 left atrial tachycardias), and interestingly all except one of these patients had either the Cox-Maze III or IV. This highlighted the propensity of recurrent macro-re-entrant tachycardias post open-heart Cox-Maze III and IV procedures, if intra-operative conduction testing is not undertaken.[84]

Kron et al then investigated post-surgical arrhythmias in thoracoscopic patients. They offered

an electrophysiological study (EPS) +/- ablation to all those who had 'failed' having had an index procedure of PVI and GP ablation via a mini-thoracotomy. [85] Rhythm recurrence was assessed rigorously by continuous 1-month trans-telephonic monitoring with AF triggering and defined as supraventricular tachycardia of greater than 30 seconds' duration in the follow-up period. Of the 50 patients enrolled, 20 patients (40%) had recurrent documented AT, of whom 13 (65%) chose to undergo EPS. 14 arrhythmias were documented in these patients including AF in 8 patients and atrial flutter in 3 patients. Importantly, despite confirmation of acute entrance and exit block at the index PVI, the commonest finding in those who had recurrent AF was PV reconnection (50% of PVs). These findings with regard to PV reconnection are consistent with that of endocardial ablation, which is why it remains the Achilles' heel of all ablation procedures. [86-88] Although canine models have shown that conduction can break though small gaps (1.1mm) in ablation created by the bipolar RF clamp, epicardial PVI is still thought to provide more reliable transmural conduction block based on animal studies as described earlier in this article.[83 89]

1.6 Conclusion

The contemporary management of AF increasingly includes the use of interventional therapies such as catheter (CA) or surgical ablation (SA). The 2012 international consensus statement from the Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society admits that LSPAF patients are the least studied subset of AF patients, which probably reflects the increased complexity of these advanced atrial substrates. [26]

In lieu of poorly tolerated and ineffective AAD therapies, patients actively seek curative procedures in LSPAF. This demand has driven electrophysiologists to improve their outcomes to give these patients a better quality of life. Thoracoscopic SA has slowly evolved into a potentially promising alternative option for patients who require intervention for AF. Results have shown equivalent success rates to catheter ablation for paroxysmal AF and encouraging results in persistent forms with more extensive lesions sets akin to catheter ablation. However, it is clear that more research is required in this area to delineate precisely where it fits into the armamentarium for AF management. As patients are unlikely to choose a more invasive option of ablation with similar efficacy to catheter ablation, the role of thoracoscopic SA is more likely to lie in those with more advanced substrates where catheter ablation outcomes remain suboptimal.

This concept formed the basis of the ***C***atheter ***A***blation versus ***S***urgical ***A***blation in ***A***trial ***F***ibrillation (CASA-AF) study, which predated the publication of the FAST and the Hybrid studies. The aim of CASA-AF was to compare thoracoscopic surgical ablation with catheter ablation in LSPAF patients, using appropriate lesions sets that incorporated robust electrophysiological confirmation of conduction block of all lesions.

1.7 Main hypothesis

'A thoracoscopic surgical ablation strategy is more effective than a catheter ablation strategy in long standing persistent atrial fibrillation, with regards to freedom from atrial arrhythmia.'

The above hypothesis was investigated in a clinical trial. The methods pertaining to this study are presented in chapter 2 and the results in chapter 6. Two further sub-studies linked to the

main trial are presented in chapter 3 (CFE sub-study) and chapter 4 (MRI sub-study).

1.7.1 Other hypotheses

'The use of contact force sensing technology during pulmonary vein isolation reduces the rate of acute electrical PV reconnection rates by improving endocardial catheter contact and lesion formation.'

The above hypothesis was investigated in a clinical trial, which is presented in chapter 5.

Chapter 2

CASA-AF Clinical trial design and methods

2.1 Introduction

The purpose of this study was to investigate the hypothesis that a thoracoscopic surgical ablation strategy was superior in efficacy to a catheter ablation strategy in patients with longstanding persistent atrial fibrillation (LSPAF). This was a single centre (Royal Brompton & Harefield NHS Foundation Trust), prospective, non-randomised clinical trial to evaluate these two ablation modalities.

The study was commenced in 2011, having gained ethical approval from Oxfordshire Research Ethics Committee A, 11/SC/0032. During the inception and study design phase, detailed and extensive searches through PubMed, Medline and Clinicaltrials.gov showed that there were no published trials comparing these two strategies head-to-head for the management of atrial fibrillation (AF), and certainly none in the LSPAF classification. Of note, there was one randomised controlled clinical trial identified, 'Ablation or Surgery for Atrial Fibrillation Treatment' (FAST), ClinicalTrials.gov Identifier: NCT00662701, which compared the safety and efficacy of these two strategies in a mixed population of AF patients. This randomised controlled clinical trial was stated as being in the recruitment phase, despite being registered in March 2008 with a scheduled completion date of May 2009.

2.2 Study objectives

When preparing for this study, it became clear from the available research that the evidence was somewhat hampered by heterogeneous definitions of both AF classification, and of study endpoints. This inevitably led to a degree of uncertainty in the understanding of the true safety and efficacy of AF ablation. We designed our study carefully to try to overcome these issues. The 2012 Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society (2012 HRS/EHRA/ECAS) consensus document sought to improve the standards for reporting outcomes in clinical trials involving AF ablation via several recommendations.[26] Some of the important recommendations are listed below:

i. Studying a specific subset of the AF population, namely LSPAF, which are a group of patients poorly represented in clinical trials;

ii. Enrolling only one subset of AF patients;

iii. Reporting single procedure outcomes in AF ablation;

iv. Comparing catheter ablation with surgical ablation.

Although published after our study had commenced, our study design had incorporated a number of the aforementioned recommendations, which were not only in keeping with our study rationale, but also validated our study design. Furthermore, the primary endpoint of this study was also in accordance with the 2012 HRS/EHRA/ECAS consensus document as freedom from AF, atrial flutter, or atrial tachycardia (AT) lasting 30 seconds or longer after a 3-months' blanking period.

2.2.1 Primary objective

- Assess freedom from atrial arrhythmias after a single procedure without anti-arrhythmic drugs (AADs) within 9 months (as assessed from the end of the 3 months' blanking period to 9 months).

2.2.2 Secondary objectives

- Assess freedom from atrial arrhythmias after multiple procedures with and without AADs within 9 months (as assessed from the end of the 3 months' blanking period to 9 months);
- Assess clinical (partial) success - defined as a 75% or greater reduction in the number and duration of AF episodes in the presence or absence of previously ineffective antiarrhythmic drug therapy (as assessed from the end of the 3 months' blanking period to 9 months);
- Serious adverse event rates (stroke, MI, emergency surgery, death);
- Major procedural complication rates – defined as complications that result in permanent injury or death or that require emergency treatment or prolongs / requires hospitalisation for more than 48 hours;
- Change in AF symptom score;
- Change in quality of life SF 36 score;
- Change in atrial and ventricular dimensions and in bi-ventricular function as measured by cardiac MRI (Chapter 4).

2.2.3 Other objectives

- Acute procedural success – defined as attaining SR at the end of the procedure either through DC cardioversion or termination to SR through ablation.
- Assessment of intraoperative conduction block testing in the surgical group using the multifunctional ablation and pacing pen and the 20 pole multielectrode EP catheter.

2.3 Trial design

2.3.1 Overall design

The Royal Brompton & Harefield NHS Foundation Trust (RB&HFT) is one of the largest specialist cardiothoracic centres in Europe, which specialises in heart and lung transplants and pioneering minimally invasive surgery, including thoracoscopic techniques. Despite this wealth of thoracoscopic experience, thoracoscopic surgical AF ablation using radiofrequency (RF) was still a relatively new operative procedure in the trust. The research team were keen to investigate this technique using a randomised control trial however, the RB&HFT Clinical Trials Unit felt it was premature to conduct this study using a randomised control design given that the true risks of conducting this procedure at our instituition were unknown. Therefore the study design was a prospective, non-randomised clinical trial but with patients given the choice to select one of the two interventional treatments. This trial design was ratified by RB&HFT Clinical Trials Unit, Imperial College London and the research team. All individuals entering the study had been referred for catheter ablation of their AF, and so theoretically were also suitable for thoracoscopic surgical AF ablation, barring specific contraindications for thoracoscopic surgical AF.

The study was 'open-label', which meant that the investigators were aware of which arm of the study patients were allocated to; however, assessment of the primary endpoint as well as imaging (secondary) endpoints were performed by blinded physiologists and cardiac radiologists respectively.

The study population was defined as patients between the ages of 18-80 with symptomatic, drug-refractory (to at least one anti-arrhythmic drug, or anti-arrhythmic drugs are contraindicated and not tolerated), or DC cardioversion refractory LSPAF, with left ventricular ejection fraction (LVEF) of ≥ 40%. LSPAF was defined as continuous AF of greater than one-year duration in accordance with the 2012 HRS/EHRA/ECAS consensus document.[26]

2.3.2 Rationale - Why long standing persistent AF?

The clinical success rates for catheter ablation in paroxysmal AF (PAF) are high, with single procedure success rates of 67-88%. [90 91] Such procedures used to treat non-paroxysmal AF, in particular LSPAF, are less encouraging with single procedure success rates of ranging from 27-38%.[15 40 92-95] Traditional open heart Cox-Maze procedures have excellent long term results, with one study consisting of mixed paroxysmal (64%) and persistent (36%) patients demonstrating 87.5% freedom from AF at a mean follow-up of 5.4 ± 3 years.[25] Due to the high success rates of catheter ablation in PAF, open-heart surgical ablation with its attendant invasiveness is understandably rarely considered in PAF. However, with the advent of a totally thoracoscopic surgical approach, coupled with encouraging early efficacy data in patients with LSPAF (87% freedom of atrial arrhythmias off AAD at 6 months), this alternative strategy has the potential to confer benefit to these patients.[77] LSPAF patients represent the hardest to treat subset of AF patients and consequently are the least studied. Taking into account all of these aforementioned points, our rationale was to investigate whether this alternative

totally thoracoscopic surgical ablation approach may provide superior single/multiple procedural efficacy, compared with contemporary catheter ablation.

2.3.3 Allocation of index procedure

Under normal clinical care, patients recruited to the study would have been referred for catheter ablation of their AF, and hence theoretically were also suitable for thoracoscopic surgical AF ablation, barring specific contraindications for thoracoscopic surgical procedures. Therefore, assignment of the index procedure was based predominantly on patient preference. Patients were given the REC approved detailed patient information sheet (see appendix), and the opportunity to have all questions answered by the research team (predominantly the Chief Investigator and me) to help facilitate that choice. All information given was factual and was not biased towards either procedure, to enable the choice to be based entirely on patient preference. All patients who chose the surgical option were discussed at an Electrophysiology Multi-Disciplinary team meeting, consisting of at least one electrophysiologist and one cardiothoracic surgeon (and all of these patients were deemed appropriate to proceed with their chosen surgical ablation option).

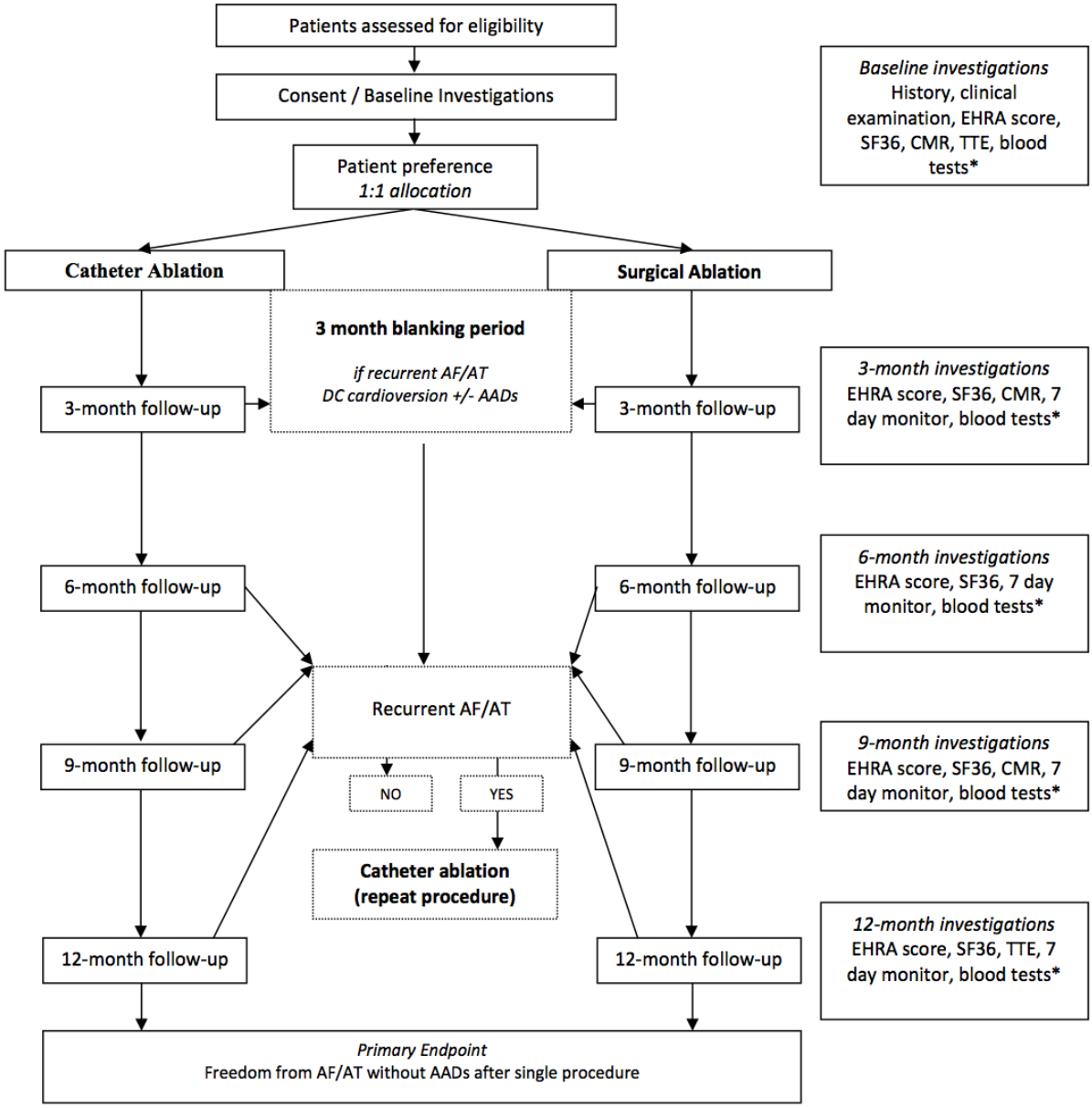


Figure 2.1 Schematic of Trial Design.

Key: AAD = anti-arrhythmic drug; AF = atrial fibrillation; AT = atrial tachycardia; CMR = cardiac magnetic resonance imaging study; ECG = 12-lead electrocardiogram; EHRA = European Heart Rhythm Association; SF36 = Quality of life health questionnaire; TTE = transthoracic echocardiography.

** Comprising: full blood count, urea/creatinine/electrolytes, coagulation profile, liver and thyroid function tests, C-reactive protein.*

2.4 Eligibility Criteria

2.4.1 Inclusion criteria

- Age ≥ 18 years ≤ 80years;
- Symptomatic LSPAF (≥ 12 months);
- Refractory to anti-arrhythmic drugs (or anti-arrhythmic drugs contraindicated/not tolerated), and/or refractory to direct current cardioversion.

2.4.2 Exclusion criteria

- Significant impairment of left ventricular systolic function (LVEF < 40% as determined by baseline cardiac MRI);
- Contraindication to anticoagulation;
- Thrombus in the left atrium (LA) despite anticoagulation;
- Active malignancy;
- Cerebrovascular accident within the previous 6 months;
- Previous thoracic and cardiac surgery (including interventions for AF such as Cox-Maze procedure) if patient wished to have thoracoscopic surgical AF ablation;
- Prior LA catheter ablation with the intention to treat AF;
- Prior AV nodal ablation;
- Contraindication to general anaesthesia;

- Unable to provide written informed consent;
- Patients actively participating in another research study will not be permitted to enrol;
- Patients who have been involved with other research studies will be able to participate after a minimum period of 3 months after completion of prior study follow-up.

2.5 Study approvals and patient recruitment

2.5.1 Ethical and NHS approval

The study was given ethical approval by Oxfordshire Research Ethics Committee A in March 2011. Local institutional NHS Research and Development approval followed in June 2011, with trial registration (CASA-AF Catheter Ablation versus Surgical Ablation in Persistent Atrial Fibrillation) prior to study initiation on ClinicalTrials.gov (ClinicalTrials.gov identifier NCT01385358).

2.5.2 Recruitment

The primary recruitment source was the RB&HFT outpatient arrhythmia clinics, including outreach arrhythmia clinics from nearby district general hospitals. All patients who were being considered for catheter ablation for their LSPAF were deemed as potentially eligible patients, based on a brief assessment of inclusion and exclusion criteria. After verbal discussion, those interested in participating in a research study were given the detailed patient information sheet (see appendix) which provided a full account of its nature, purpose, risks, burdens and potential benefits, either as a hard copy or electronically via email using the secure NHS email system. Patients were asked to take their time to consider the

information, and contact the study coordinator if they were keen to participate. For those who did not make contact, a follow-up telephone call was made at two weeks. For potential study subjects, fully informed consent was obtained only after all the aforementioned information had been given and patients had ample time to deliberate and further opportunity to ask questions. Patients who expressed their wish to participate at periods shorter than 24 hours were permitted if the patient felt that further deliberation would not lead to a change in their decision, and that the researcher seeking consent was satisfied that the patient had fully retained, understood and deliberated on the information given. All patients who were keen to proceed, signed the ethically approved study consent form (see appendix) prior to undergoing their baseline investigations and assessment, and if eligible were enrolled on the RB&HFT site. The number of patients assessed for eligibility through to those allocated to each group is detailed in the Consort diagram (Figure 6.1).

2.6 Baseline Investigations

At the baseline visit, all patients were assigned a patient identification code. This unique code was recorded on all source data worksheets, and used to identify the patient throughout the study.

All patients had a thorough medical history taken and underwent clinical examination, transthoracic echocardiography and routine blood tests. All 51 patients had LSPAF, with the duration of continuous AF estimated from both the history obtained from the patient and the records from the referring cardiologist. If a patient had undergone successful DC cardioversion (attaining sinus rhythm >30 seconds) within 12 months prior to the index ablation procedure, but had had documented early recurrence of AF within 30 days, this did

not alter the classification of AF as LSPAF in accordance with the 2012 HRS/EHRA/ECAS consensus document.[26] The duration of continuous AF was defined as the period of continuous AF that led up to the index ablation procedure. The following research baseline investigations (see below) were conducted prior to enrolment into the study. Data from the baseline visit was entered into the CRF and were then subsequently transferred to an electronic CRF (Microsoft Excel for Mac 2011 spreadsheet), which served as the study database. Both the study database and the patient-participant code list were stored on secure local NHS computer servers.

2.6.1 Cardiac Magnetic Resonance Imaging

2.6.1.1 Acquisition Technique

A 1.5-T MR system with 32-channel cardiac coil (Magnetom Avanto, Siemens Healthcare, Germany) was used to scan patients in this study. The MR acquisition protocol consists of retrospectively gated breath-hold short-axis and trans-axial cine stacks for the measurement of ventricular and atrial function. This was followed by a trans-axial stack of breath-hold T2-weighted turbo spin echo images for the assessment of oedema. A coronal navigator-gated 3D steady state free precession acquisition covering the whole heart was performed in the systolic or diastolic rest period. First-pass gadolinium angiography was also performed. A transaxial navigator gated 3D late gadolinium enhancement dataset of the atria was acquired 15 minutes after gadolinium administration for the assessment of atrial scarring. Sequence parameters included repetition time/echo time of 55/1.7ms, inplane voxel size 1.7x1.7x7.0mm, base resolution 256ms, phase resolution 100ms, slice thickness 7mm, and flip angle 59°.

2.6.1.2 Image Analysis

LA area and length were traced on the atrial systolic and atrial diastolic frames of the complete cine CMR (Steady State in Free Precession, SSFP) acquired in the left ventricular vertical and horizontal long axes. LA maximum volume (ventricular end-systole) was defined as the phase with the largest LA volume on visual assessment and just prior to mitral valve opening. LA minimum volume (ventricular end-diastole) as the phase with the smallest volume/dimension at the point of mitral valve closure. LA maximum and minimum volumes were then calculated using the biplane area-length method for ellipsoid bodies. LA emptying fraction (active LA function) was then calculated: [LA max – LA min / LA max] x 100. RA maximum volume (ventricular end-systole) was defined as the maximal RA volume just prior to the tricuspid valve opening, with RA minimum volume (ventricular end-diastole) defined as the minimal RA volume at the point of tricuspid valve closure.

For LA volumes calculations, the biplane area-length method for ellipsoid bodies was used, but this is not suitable for usage in the RA due to its more complex morphology. RA volumes were instead measured from a stack of contiguous transaxial cines covering the whole of the RA. The right atrial appendage was included, but the coronary sinus ostia were excluded from the RA volumes.

The semi-automated software package (CMR Tools, Cardiovascular Imaging Solutions, London) was used for all atrial and ventricular measurements. Left and right ventricular volumes at end-diastole and end-systole were also determined using this software package. [96] [97]

Finally all atrial and ventricular volumes were indexed to body surface area (BSA). The image measurements were taken by an observer specialising in cardiac MR imaging techniques and were blinded to the ablation modality, the patient's clinical data and rhythm outcomes (see

chapter 4).

2.6.2 SF-36 Short-Form Health Survey Questionnaire (version 2)

The SF-36 is a well validated 36 question short-form health survey, which yields an 8-scale profile of functional health and well-being scores from the patient's point of view.[98] It also provides psychometrically based physical and mental health summary measures. This scoring system was chosen, as it is practical, reliable, and a valid measure of physical and mental health, which can be completed in less than ten minutes. It is a generic health measurement tool, and accordingly has been used in many surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments. Although it has not been specifically designed for arrhythmias, the SF-36 has been used previously to assess health status in a number of AF studies.[98] After answering all the questions, a score out of 100 is obtained which can also be interpreted using the norm-based scoring system (Mean = 50, SD = 10).

2.6.3 EHRA AF Symptom score

The EHRA score of AF-related symptoms is a validated simple clinical tool designed to assess symptoms whilst patients are in AF, which makes it very suitable for LSPAF patients.[99] EHRA class I represents ‘no symptoms’, whilst at the other end of the spectrum EHRA class IV represents ‘disabling symptoms’ such that normal daily activity is discontinued. In essence, the higher the EHRA class the greater the symptoms, and the lower the quality of life. This scoring system only considers symptoms attributable to AF and importantly can be reversed upon restoration and maintenance of normal SR. This scoring system was given to each patient for completion, without additional prompting by the investigator, at the beginning of

each visit prior to clinical interview and/or examination. To reduce the chance of participant bias, patients were not allowed to see their score from previous attendances.

2.7 Pre-Intervention

2.7.1 Assignment of index procedure

After baseline investigations, those patients who were eligible were asked their preference of index procedure. Patients would have typically had 4-6 weeks to consider the detailed patient information sheet, which provided a comprehensive account of the study, its nature, purpose, risks, burdens and potential benefits. At the baseline consultation, patients were given the opportunity to ask any further questions to help aid their decision and additional time was given for those who required it.

If the patient chose catheter ablation they would be placed on the waiting list with the procedure scheduled within 8 weeks of their baseline investigations. If the patient chose surgical ablation, they were discussed at the Electrophysiology Multi-Disciplinary Team meeting consisting of at least 1 electrophysiologist and 1 cardiothoracic surgeon to ensure this was deemed a sensible clinical decision (all were deemed appropriate to proceed with surgical ablation option). Once agreed they were booked to see the cardiothoracic surgeon in outpatients, at which point they were listed for surgical ablation within 8 weeks.

2.7.2 Anticoagulation regime

All patients were already established on oral anticoagulation at the time of enrolment. For patients in both arms of the study, it was mandatory to have 4 consecutive weekly INR

readings in the normal therapeutic range of 2-3 prior to the scheduled date of ablation, with the differences in anticoagulation regime between the two groups immediately before ablation detailed below.

For those undergoing catheter ablation, procedures were performed on uninterrupted warfarin with an INR in the range 2-3.5.

For those in the surgical ablation arm, oral anticoagulation was discontinued 5 days prior to the scheduled date of ablation with patients receiving subcutaneous injections of low molecular weight heparin (1.5mg/kg) until 24 hours prior to ablation. Bridging therapy with concomitant warfarin was resumed at least 6 hours after the ablation procedure in the absence of active bleeding.

2.7.3 Catheter ablation group

Patients enrolled into the catheter ablation group were scheduled to undergo percutaneous radiofrequency (RF) catheter ablation as described in section 2.8 with a provisional date identified at the time of enrolment. No adjustments to medication were made pre-procedurally, unless there was a clear clinical need for optimisation of medical therapy. The follow-up period was protocolled to commence the day index ablation had been completed. This was not to be reset after any repeat procedures.

2.7.4 Thoracoscopic surgical ablation group

Patients enrolled into the thoracoscopic surgical ablation group were scheduled to undergo thoracoscopic surgical ablation as described in section 2.9 with a provisional date identified at the time of the surgical outpatient appointment. No adjustments to medication were made pre-procedurally, unless there was a clear clinical need for optimisation of medical therapy.

The follow-up period was protocolled to commence the day index ablation had been completed. This was not to be reset after any repeat procedures.

2.8 Catheter ablation procedural protocol

In each case, the procedure was performed under general anaesthesia on uninterrupted warfarin therapy in accordance with 2012 HRS/EHRA/ECAS consensus document guidelines. [26] A transoesophageal echocardiogram (TOE) was performed at the start of the case to ensure absence of thrombus in the left atrial appendage (LAA) and LA, assess the interatrial septum and pulmonary venous (PV) anatomy and guide trans-septal puncture. Double trans-septal punctures were used to access the LA via a Brockenburgh needle. Two long sheaths (Preface Biosense Webstar, Diamond Bar, CA, USA) were then placed in the LA to allow the introduction of mapping and ablation catheters. Further anticoagulation in the form of intravenous heparin was given from this point onwards to achieve a target activated clotting time (ACT) > 300 seconds. Multiple ACT measurements were taken thereafter to ensure this target ACT was maintained. The two long sheaths in the LA were also continuously perfused with heparinised saline at 25-50 ml per hour.

The following catheters were then placed in the heart: steerable decapolar catheter (CR Bard, Lowell, MA, USA) into the coronary sinus (CS); quadripolar catheter into the right atrial appendage (RAA) to allow the measurement of the RAA cycle length (CL); duodecapolar high-density mapping catheter AFocus II (St Jude Medical) inserted via one of the long sheaths initially to the right atrium (RA) and then to the left atrium (LA) sequentially; and finally a 3.5mm irrigated-tip D-F SF ablation catheter (Thermocool, Biosense Webster).

After collection of bi-atrial geometry using the EnSite Velocity^{TM} system three-dimensional

cardiac mapping system (St Jude Medical) (Figure 2.2) RF catheter ablation was commenced using a 3.5mm irrigated-tip D-F SF ablation catheter (Thermocool, Biosense Webster). Power was limited to 35W in the anterior LA, 30W on posterior wall, 25W within CS, and 40W in the cavo-tricuspid isthmus (CTI). The following sequence of ablation lesions were conducted in a stepwise fashion:

- Wide area circumferential antral electrical isolation of all four PVs;
- Linear ablation lesion connecting the contralateral superior PVs (roof line);
- Linear ablation lesion connecting the lateral mitral isthmus to the inferior aspect of the left inferior PV (mitral isthmus line);
- Targeted ablation of complex fractionated electrograms (CFE) ablation within the LA;
- DC cardioversion to SR if AF still persisted;
- Cavotricuspid isthmus (CTI) ablation within the RA only if documented evidence of typical or atypical atrial flutter.

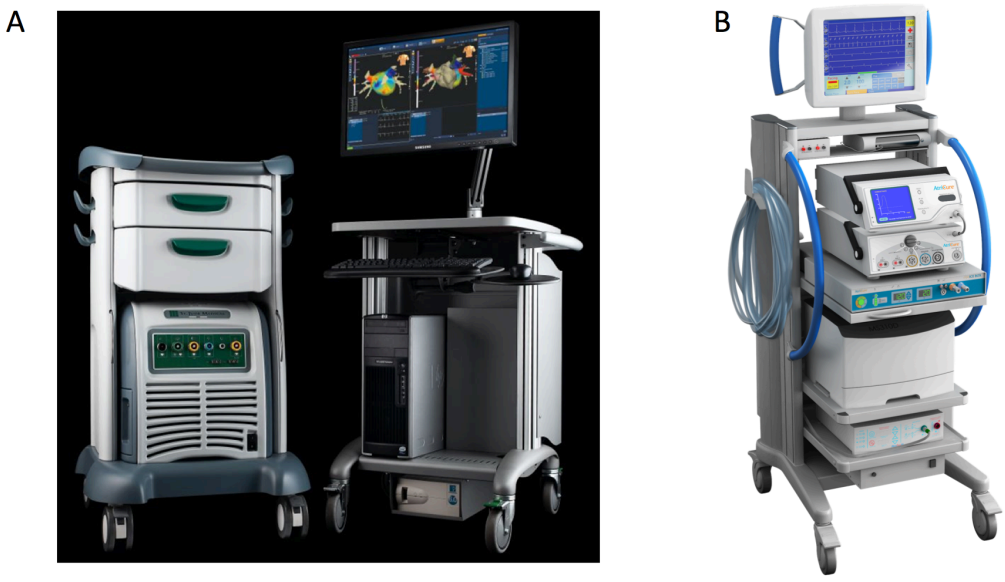


Figure 2.2 Catheter Ablation 3D Mapping System and Thoracoscopic Surgical Ablation System

A = EnSite Velocity™ system three-dimensional cardiac mapping system (St Jude Medical), B = AtriCure Operating Tower including Micropace OR lab intra-operative testing unit and AtriCure Ablation and Sensing Unit. Reproduced with permission from St Jude Medical (source professional.sjm.org) and from AtriCure Inc.

In addition to the aforementioned steps, the electrophysiological properties of both atria were examined immediately before and after each step of ablation. This was achieved firstly by acquiring a CFE map, (via multiple contact points on the internal surface of both atria) with documented mean cycle lengths (CL) of local electrograms using a multipolar mapping catheter, and secondly by recording the AF cycle length (AFCL) within the appendages of both atria (see chapter 3) at each of these stages.

The absolute minimum goal for these catheter ablation procedures was to achieve PVI. If AT ensued before completion of PVI, then PVI would be completed before commencing the ablation treatment of the AT.

After restoration of SR (either by termination of AF through ablation, or by DC cardioversion), all linear lesions were thoroughly assessed for bi-directional block. This was conducted by differential pacing and sensing manoeuvres; from the LAA and posterior wall, to assess the roof and mitral lines, and from the proximal CS to assess the CTI line if deployed.

2.8.1 Immediate post catheter ablation care

Post catheter ablation patients routinely remained in hospital on the night of the procedure, and were discharged the following day in the absence of complications requiring a longer inpatient stay and after satisfactory routine transthoracic echocardiography (i.e. without significant pericardial collection).

2.9 Thoracoscopic surgical ablation procedural protocol

Details of the operation are as described previously by Yilmaz and others.[72 79] In addition we included the presence of a cardiac electrophysiologist to ensure conduction block was tested thoroughly and achieved for all lesions.

The procedure was performed under general anaesthesia with double-lumen endotracheal tube tracheal intubation for selective lung ventilation. The entire procedure was performed on the beating heart without the use of extracorporeal circulation. A TOE was then performed to ensure exclusion of thrombus in the LAA and LA and assess PV anatomy. After appropriate positioning of the patient to facilitate thoracoscopic access, three thoracoports were introduced on the right side (two 5mm ports and one 10mm working port) in a triangular shaped configuration appropriate to the patient's body habitus (Figure 2.3). The right lung was then deflated and maintained using continuous carbon dioxide insufflation into the pleural cavity at 8-10 mmHg. Using endoscissors and the endograsper tools through the working ports, dissection down to the pericardium was performed. A cranio-posterior pericardiotomy was performed anteriorly and parallel to the phrenic nerve, maintaining at least 4-5cm distance from the phrenic nerve, to expose the superior (SVC) and inferior vein cavae (IVC). To aid visualisation, two pericardial retraction sutures were used, taking care not to apply excessive tension to avoid inadvertent phrenic nerve damage. Blunt dissection was performed using the Lumitip dissector (AtriCure Inc., Westchester, OH, USA) (Figure 2.4), which has an illuminated tip and a distal dissection arm.

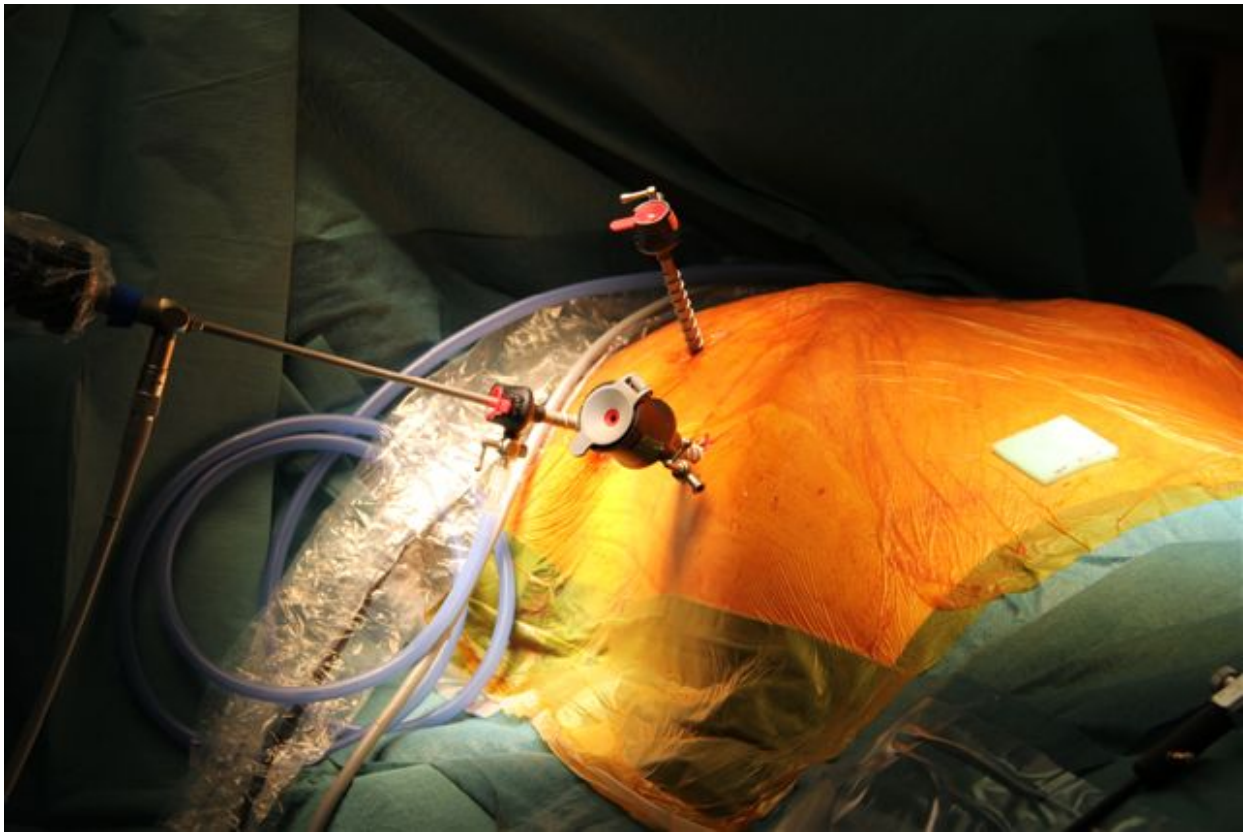


Figure 2.3 Thoracoport access sites on right side of chest for thoracoscopic surgical ablation.

On this right-sided example, one 5mm port is placed 4th intercostal space in mid-axillary line with another 5mm port placed in the 3rd intercostal space anteriorly in the mid-clavicular line. A 10mm port is placed in the 6th/7th intercostal space in the mid-axillary line.

PVI was then performed on the right side from the epicardial surface with the aid of the Lumitip dissector (AtriCure Inc.) and bipolar RF ablation clamp (AtriCure Inc.) (Figure 2.4). Overlapping applications were deployed around each ipsilateral pair of PVs. RF is delivered in bipolar mode at a frequency of 460KHz with power output that ranges form 12 to 30 watts. Using the tissue conductance measurements the Ablation and Sensing Unit (ASU) (AtriCure Inc.) (Figure 2.2) gives an audible and visual warning when transmurality has been reached. PVI was then assessed using the multifunctional ablation and pacing pen and the Micropace OR lab intraoperative testing unit (AtriCure Inc.) (Figure 2.2), initially to ascertain entrance block, and towards the end of the procedure, upon restoration sinus rhythm, to assess exit

block during pacing, (see section 2.9.3). If PVI was incomplete upon initial entrance block testing, further ablation was performed until PVI was achieved. PVI destroys the majority of the epicardial ganglionic plexi (GP) located at the PV antrum. To locate any remaining GP (often found at the inferior aspect of the posterior wall), high-frequency stimulation (1200 bpm, 18 V output, 2 ms pulse width) using the multifunctional ablation and pacing pen (AtriCure Inc.) was used, and if identified, then ablated using the ablation function of the pen with confirmation of abolition by the absence of a vagal response.

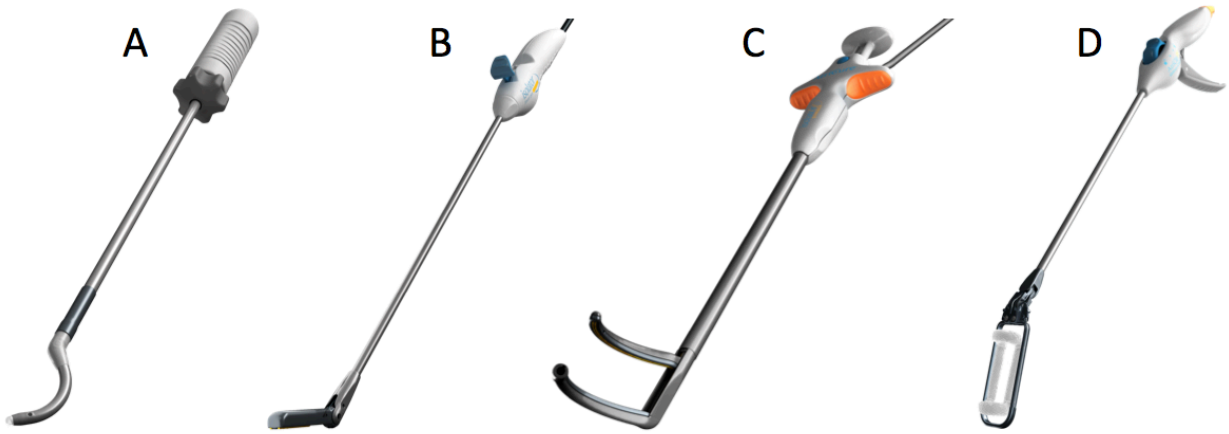


Figure 2.4 Thoracoscopic surgical tools (AtriCure Inc.)

A = Lumitip dissector, B = Coolrail linear pen, C = Bipolar RF ablation clamp, D = AtriClip® LAA occlusion system. Reproduced with permission from AtriCure Inc.

Additional linear lines were then undertaken using the internally irrigated bipolar RF Coolrail® linear pen (AtriCure Inc.) (Figure 2.4) connecting the contralateral superior PVs (roof line) and the inferior PVs (inferior line) to commence a posterior box lesion (Figure 2.5). The linear pen applications were guided by the conductance indicator on the ASU as described earlier for PVI. Lesions were overlapped to ensure contiguous linear lesions were achieved.

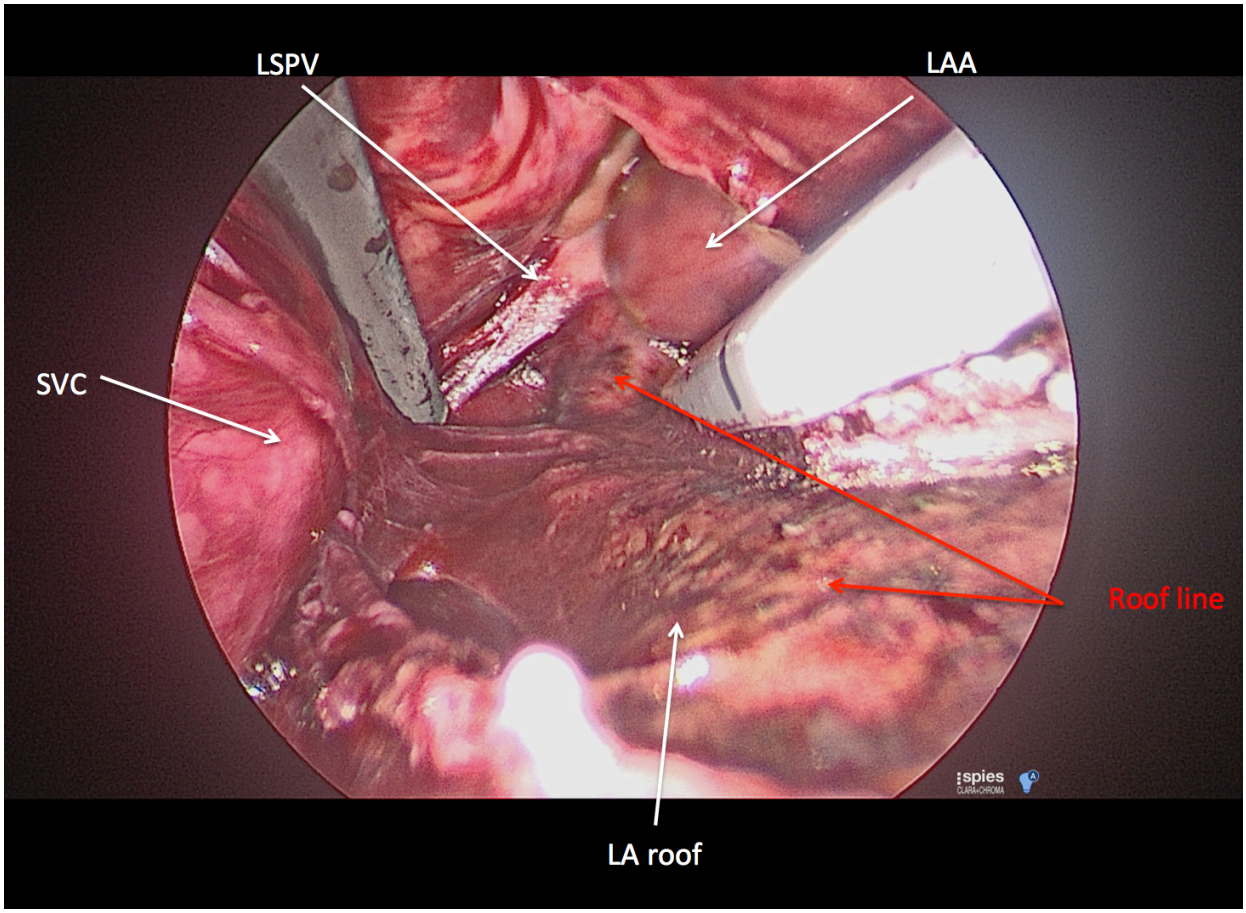


Figure 2.5 Intraoperative image showing surgical linear (roof) line of ablation

Key: LSPV = left superior pulmonary vein, LAA = left atrial appendage, SVC = superior vena cava, LA = left atrium.

The surgical team then switched to the left side with a similar approach as to the right except for some important differences. Firstly, the pericardiotomy was more posterior to the phrenic nerve and secondly the ligament of Marshall (a potential source of adrenergic driven atrial arrhythmias) was dissected. After PVI of the left sided PVs, the posterior box lesion was then complete. This marked the completion of the set of ablation lesions. If AF persisted at this time point, external DC cardioversion was conducted to restore SR and allow for further conduction block testing. Sensing and pacing manoeuvres (see section 2.9.3) were conducted using the multifunctional ablation and pacing pen, as well as the 20 pole multielectrode recording catheter (Bard RADIA™ Bidirectional Diagnostic Catheter) to verify electrical isolation of the posterior box in SR. The LAA was then excluded using either an amputating

thoracoscopic surgical stapler device (Endo GIA, Covidien) or the AtriClip® LAA occlusion system (AtriCure Inc.) (Figure 2.4). The pericardium was closed and a chest drain inserted into the right pleural space with port access closure performed, and local anaesthetic (Lidocaine 1%) applied into the intercostal spaces to relieve postoperative pain.

In summary, the following sequence of thoracoscopic surgical ablation lesions were conducted in a stepwise fashion:

- Pulmonary vein isolation;
- GP ablation;
- Linear ablation connecting the contralateral superior PVs (roofline);
- Linear ablation connecting the contralateral PVs (inferior line);
- DC cardioversion if still in AF;
- LAA exclusion.

2.9.1 Ganglionic plexi ablation

LA GP are autonomic targets for AF ablation, which due to their epicardial location can be targeted by thoracoscopic surgical ablation. The four major LA GP are the superior left GP, the inferior left GP, the anterior right GP and the inferior right GP, which are located within epicardial fat pads at the border zones of the PV antrum. Localisation of these GP is conducted by high frequency stimulation (HFS) and deemed positive when a positive vagal response is elicited (>50% lengthening of R-R interval and/or > 3 seconds of asystole). These are then targeted for ablation and retested until HFS does not elicit a vagal response.

2.9.2 Left atrial appendage exclusion

The RB&HFT has rigorous safety protocols in place to protect patients when introducing new interventional techniques. The RB&HFT Clinical Practice Committee (CPC) recommended that LAA exclusion could be undertaken after the first ten patients had undergone thoracoscopic surgical ablation. This was adhered to with LAA exclusion undertaken after the tenth thoracoscopic surgical ablation case using either a thoracoscopic surgical stapler or the AtriClip® LAA occlusion system (Figure 2.4).

2.9.3 Intraoperative testing of conduction block

A crucial aspect of the thoracoscopic surgical ablation procedure in terms of achieving success is confirmation of conduction block of the lesions. During the application of ablation lesions using the bipolar RF ablation clamp (AtriCure Inc.) a graph of tissue conductance (current/voltage) versus time is displayed on the ablation and sensing unit (ASU) monitor (AtriCure Inc.) (Figure 2.2). This device produces and delivers RF energy in a bipolar mode, at a frequency of approximately 460 kHz, with a maximum output power ranging from 12 to 30 Watts. Using measurements of conductance, the ASU determines when transmurality has been achieved. Conventional intraoperative surgical testing is undertaken using the multifunctional ablation and pacing pen. The pen is placed sequentially on the superior and inferior PVs after lesions have been delivered using the bipolar RF ablation clamp to show entrance block. The pen is then used to pace the PV side of the PVI lesions to ensure the atrial body does not capture, which confirms exit block. For the success of the procedure, it is essential to assess and confirm bi-directional conduction block of all ablation lines. If conduction block is not confirmed, ablation should be repeated and conduction block reassessed until bi-directional block is achieved.

One of the potential disadvantages of only using the conventional intraoperative surgical multifunctional ablation and pacing pen, is that it may miss regional electrical connections of the PV. An alternative electrophysiological mapping strategy was developed and adopted for this study and involves using a 20 pole multielectrode EP catheter (Bard RADIA™ Bidirectional Diagnostic Catheter), designed primarily for percutaneous endocardial electrophysiological mapping and the EnSite Velocity™ system three-dimensional cardiac mapping system (St Jude Medical). The multielectrode catheter is introduced through one of the ports, visualised by the camera and positioned using standard thoracoscopic instruments. The catheter was then connected to the EnSite Velocity™ system for recording of electrograms. The catheter was wrapped around the entire circumference of each of the ipsilateral pairs of veins and used to map the PVs at multiple locations to provide detailed confirmation of entrance block, akin to the use of the 20-pole circular catheter in conventional catheter ablation. After completion of the box lesion it was also placed within the box lesion on the posterior wall to test for entrance block.

2.9.4 Immediate post thoracoscopic surgical ablation care

Post thoracoscopic surgical ablation patients routinely went to the intensive care unit for 12 hours, before moving to either the high dependency unit or a standard surgical ward depending on the patient's progress. Low molecular weight heparin was commenced six hours after surgery and warfarin commenced once the chest drains were removed. The patient's rhythm was monitored via telemetry and if AF ensued then rate control was initiated, but no AAD drugs were commenced. Patients typically remained in hospital for 3-5 nights, and were discharged following appropriate control of post-operative pain and satisfactory routine clinical investigations (e.g. chest x-ray and transthoracic

echocardiography).

2.10 Post Intervention

2.10.1 Anti-Arrhythmic Drug (AAD) therapy

AAD therapy, defined as class I and III AADs, were discontinued at the time of the index procedure if not already done.

2.10.2 Blanking Period

In accordance with the 2012 HRS/EHRA/ECAS consensus document there was a 3-months' 'blanking' period, during which any recurrence of AF or new onset of AT could be treated by DC cardioversion.[26] ATs after the 'blanking' period generally resulted in the scheduling of a second ablative procedure. Any further intervention and/or anti-arrhythmic drug use after the index ablation procedure and outside the 3-months' blanking period constituted a fail in the primary endpoint.

2.10.3 Repeat ablation procedures

If patients required a repeat procedure, this would always be catheter ablation, as it would be challenging to undergo a repeat thoracoscopic surgical ablation due to fibrosis from the index procedure. Therefore, the catheter ablation protocol for repeat procedures regardless of index ablation modality was as follows:

- Checking integrity of PVI and proceeding to re-isolation if reconnection identified;
- If AT, diagnose mechanism and treat in conventional manner (see Chapter 3);
- Confirmation of integrity of linear lesions in SR. If any linear lesions were deemed

incomplete then further ablation was conducted to re-establish bi-directional block (with a minimum 15 minute waiting time);

- If AF persisted then CFE ablation was conducted within either the LA or RA;
- Other lesions could be added at the discretion of the operator.

2.10.4 Follow-up visits

The onset of the follow-up period was defined as the day of the index ablation procedure in both groups of the study. Thereafter, the follow-up schedule included assessments at 3, 6, 9 and 12 months (Figure 2.6). In addition, patients were brought up for urgent assessment of any symptomatic arrhythmia episodes that were reported between these follow-up time points, to enable accurate assessment of clinical/partial success post ablation. Patients underwent the following assessments at these visits:

- History and clinical examination (all visits);
- EHRA AF symptom score (all);
- SF36 Quality of Life Questionnaire (all);
- 7-day continuous ambulatory rhythm monitor (3, 6, 9 and 12 months);
- Transthoracic echocardiogram for clinical surveillance (baseline and 12 months);
- Cardiac MRI (baseline, 3, and 9 months);
- Blood tests for clinical surveillance: full blood count, urea & electrolytes, liver function tests, thyroid function tests, lipid profile, CRP.

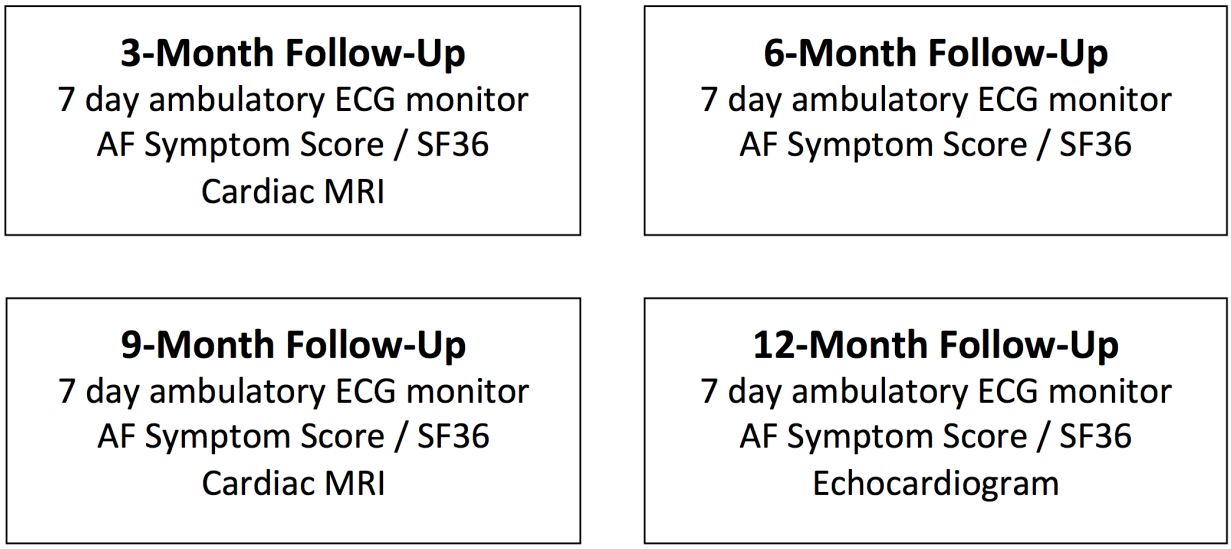


Figure 2.6 – Schedule of follow-up visits

2.11 Statistical analyses

2.11.1 Power Calculation

Due to paucity of data with regards to the primary endpoint, particularly with regards to thoracoscopic surgical ablation outcomes in LSPAF patients, it was difficult to perform robust power calculations. However, an estimated single procedure success rate at 9 months for surgical ablation of 80%, and an estimated single procedure success rate at 9 months for catheter ablation of 40% allowed us to make an estimate of sample size calculation. To achieve this effect size at 80% power and for 5% significance required a sample size of 23 per group (total n=46). The final sample size for the study was 51.

2.11.2 Statistical analysis

All categorical data were presented as proportions and comparisons were made using the chi-squared test or Fisher's exact test. Normally distributed continuous variables were presented as mean ± SD and comparisons made using the 2-sample t-test. Skewed continuous data were presented as the median (interquartile range), with comparisons made using the Wilcoxon

rank sum test and often visually represented using box plots. Outcomes analysis was performed as per intention to treat and by independent comparison of absolute change from baseline where deemed appropriate. Arrhythmia-free survival was analysed by Kaplan-Meier survival curves with log-rank comparisons using the Mantel-Cox test. ROC statistics were used as a measure of model performance for regression modeling.

Statistical significance was defined as $p<0.05$. Data were analysed using GraphPad Prism version 6.00 for Mac (GraphPad Software, San Diego California, USA) and R statistical software (version 3.1.2)

Chapter 3

The CFE sub-study: mechanistic insights into the electrical substrate of long standing persistent atrial fibrillation

3.1 Abstract

3.1.1 Introduction

The interventional treatment of non-paroxysmal (persistent and long standing persistent) atrial fibrillation (AF) remains one of the most intriguing aspects of invasive electrophysiology. In addition to pulmonary vein isolation (PVI), these advanced atrial myopathies require additional substrate modification, which in contemporary practice entails linear lesions and/or ablation of complex fractionated electrograms (CFE). Despite extensive left atrial (LA) ablation via these techniques, single procedure success (defined as freedom from atrial arrhythmia) is at best modest in this group of patients, and often needs repeat procedures. This sub-study was designed to evaluate the effects of a systematic ablation strategy on the advanced electrical substrate found in patients with long standing persistent atrial fibrillation (LSPAF) and preserved left ventricular function, as well as to compare with our previously published data in patients with persistent AF in heart failure.

3.1.2 Methods

The patient enrolment criteria comprised patients undergoing first time ablation for LSPAF with left ventricular ejection fraction of at least 50% or greater. The catheter ablation procedure protocol incorporated the acquisition of multiple high-density CFE maps including the bi-atrial AF cycle length (AFCL) at each stage of the procedure. The sequence of data

acquisition was as follows:

Step 1 - Baseline bi-atrial CFE maps and bi-atrial AFCL;

Step 2 - LA CFE map and bi-atrial AFCL post PVI;

Step 3 - LA CFE map and bi-atrial AFCL post linear lesions (roof and mitral isthmus);

Step 4 - Final bi-atrial CFE maps and bi-atrial AFCL post LA CFE ablation

The CFE area was defined as the surface area of CFE (120ms) that was remote to PVI and linear lesion ablation sites and all of the data was then analysed offline.

In addition, the bi-atrial CFE area, AFCL, and clinical outcome data from these non-heart failure patients (non-HF group) were then compared with previously published data in a heart failure cohort (HF group) from our institution, in order to understand the differences in substrate between the two groups.

3.1.3 Results

CFE data was available from 158 maps from 30 patients. In response to LA ablation, baseline LA CFE area decreased post PVI (27.6±11.8 to 21.6±12.5 cm^2; $p<0.001$); post linear lesions (21.6±12.5 to 16.5±9.8 cm^2; $p=0.002$); and post CFE ablation (16.5±9.8 to 7.8±8.7 cm^2; $p<0.001$). LA ablation also resulted in decreased final RA CFE area (39.8±19.3 to 24.1±12.9 cm^2; $p=0.0003$). Overall, the mean LA AFCL prolonged (153±18 to 173±29 ms; $p<0.0001$), but the mean RA AFCL did not prolong as a result of LA ablation (163±18 to 168±24 ms; $p=0.26$), resulting in a final mean RA AFCL that was shorter than the final mean LA AFCL (168±24 vs. 179±42 ms; $p=0.70$). Primary roof block predicted reduction in remote RA CFE area (coefficient 23.2 cm^2, 95% CI (3.2-43.2, $p=0.03$). The duration of radiofrequency (RF) time

spent ablating CFE was an independent predictor of single procedure arrhythmia-free survival at 1 year.

Comparison of this with data from our previously published data in a HF cohort showed that: RA surface areas were larger, baseline and final bi-atrial CFE areas were higher, and there were different patterns of bi-atrial AFCL prolongation in the non-HF group post LA ablation. The Kaplan-Meier, single procedure, arrhythmia-free survival estimation at 1 year was significantly lower in the non-HF group compared with the HF group (41% vs. 72%, log rank p=0.03).

3.1.4 Conclusions

The sequential reduction in remote LA and overall reduction in RA CFE-area, observed post PVI and LA linear lesions, confirms that a significant proportion of CFE are likely to represent passive bystander activity. The fact that RF time targeting CFE ablation is an independent predictor of clinical outcome highlights the importance of incorporating CFE ablation within the ablation strategy for LSPAF patients. The significant difference in clinical outcome between the non-HF and HF groups may be explained by important differences in the substrate. Firstly, the non-HF LSPAF group had larger RA surface areas and higher proportions of bi-atrial baseline and post ablation CFE. Secondly, the divergent pattern in AFCL prolongation resulting in a RA to LA frequency gradient, in the non-HF group, implies that this may represent a more complex primary atrial myopathy than that when AF occurs secondary to HF. The correct identification of functionally important CFE drivers, and/or patients that may benefit from additional RA ablation, may well be the key to improving clinical outcomes in LSPAF.

3.2 Introduction

Contemporary catheter ablation of paroxysmal AF via wide area circumferential pulmonary vein isolation (PVI) is highly effective, with single procedure success rates of 67-88%.[91 101] However, results for those with non-paroxysmal forms of AF remain suboptimal, ranging from 38-62% single procedure success off AAD.[39] Although PVI is now regarded as the cornerstone of all AF ablation procedures, PVI alone has been demonstrated to be inadequate with regards to maintenance of sinus rhythm in non-paroxysmal AF.[15 90] In these patients, additional substrate modification is required over and above PVI to improve ablation outcomes, although despite these additional ablation lesions, patients often need multiple procedures to increase success rates.[39] Substrate modification can entail targeted ablation of CFEs and conducting linear lesions, both of which have shown variable outcomes in randomised controlled studies.[39] Areas of CFEs have been postulated to represent critical regions that can maintain AF although their exact significance remains debated, and their existence may be heterogeneous in origin (e.g. slow conduction zones, pivot points, anisotropy that can facilitate localised re-entry).[33 62 101 -103]

Previous studies have shown that in mixed classifications of AF (paroxysmal, persistent and LSPAF), PVI does reduce the amount of CFE both in the vicinity of the PVs and at sites that are remote to PVI.[104 105] It has been postulated that this reduction in CFE represents either passive CFE activity secondary to PV activity or the disruption of PV region ganglionated plexi (GP) which are known to fractionate AF electrograms when stimulated.[104 106] More recently, PVI and linear ablation has been shown to reduce LA CFE, whilst work from our group has shown reduction in bi-atrial CFE in persistent AF and heart failure. [107 108]

If CFE are indeed important mechanistically in non-paroxysmal AF then the present, widely

used, stepwise approach which combines all of the aforementioned techniques (PVI + linear ablation + CFE), advocated by the Bordeaux group, seems to be a reasonable strategy to adopt for non-paroxysmal AF.[109] It is the predominant strategy undertaken at our institution, but it is important to note that no large multi-centre RCTs have been performed comparing the safety and efficacy of these different strategies in non-paroxysmal AF.

The aim of this study was firstly to examine the effect of stepwise ablation on the quantitative and qualitative distribution of bi-atrial CFE in non-heart failure LSPAF patients, and secondly to compare the CFE and AFCL data with our previously published study of persistent AF patients with heart failure.

3.3 Methods

3.3.1 Study population

Thirty patients with symptomatic LSPAF were recruited from the Royal Brompton and Harefield NHS Foundation Trust (RB&HFT) outpatient arrhythmia service. A proportion of the patients were from the CASA-AF study [73% (22/30)]. All patients were deemed suitable for an interventional strategy and had been clinically referred for de novo catheter ablation. All patients had a left ventricular ejection fraction ≥ 50%, and are therefore referred to as the non-heart failure (non-HF) group.

Table 3.1 Baseline population demographics

	NON-HF GROUP (N=30)
Age (y), mean ± SD	66 ± 9
Sex (male), n (%)	23 (48)
AF duration (months), mean ± SD	21 ± 16
LA size, mean ± SD	44 (5)
LVEF (%), mean ± SD	60 ± 8
Hypertension, n (%)	21 (72)
Coronary artery disease, n (%)	9 (31)
Diabetes Mellitus, n (%)	1 (3)
Beta-blocker, n (%)	18 (72)

Key*: n = 30. AF = atrial fibrillation, LA = left atrial, LVEF = left ventricular ejection fraction*

3.3.2 Mapping and Identification of CFEs

The EnSite Velocity™ system cardiac mapping system (version 4 St Jude Medical; St Paul, MN, USA), and the multi-electrode high density AFocus II™ (St Jude Medical) mapping catheter were used to create discrete three-dimensional (3D) bi-atrial geometries. Additional colour-coded segmental geometries were assigned for each of the pulmonary veins (PV) and both of the atrial appendages, to help delineate important structures. Upon completion of the 3D bi-atrial geometries, the mapping process was initiated with the acquisition of sequential CFE maps at the following stages:

i) Baseline (RA and LA);

ii) Post PVI (LA only);

iii) Post linear lesions (roof and mitral lines) (LA only);

iv) Post LA CFE ablation (RA and LA).

At each of these stages the AFCL at the right atrial appendage (RAA) and the left atrial appendage (LAA) were recorded from bipolar signals (averaged over 10 cycles) from catheters in each respective appendage.

To create the CFE maps, the mapping catheter was rested at a location with good contact with the endocardium (waiting 5 seconds), to allow acquisition of multiple points from all of the bipoles of the mapping catheter. This process was repeated until the mapping catheter had been swept sequentially around the entire internal surface of the chamber. At any given acquired point, there were 19 simultaneous electrograms from which CFEs were identified using a semi-automated detection algorithm (CFE tool), which determines CFE by the mean interval between deflections. The algorithm defines CFE as those with CFE mean ≤120ms over

a 5 second analysis period and annotates electrograms. It should be noted that the 5 second sampling period is used routinely in our centre, as published data has demonstrated the reproducibility of data using this time frame. [110 111] Any points which were inappropriately collected, as well as those which corresponded with electrical interference were manually deleted. Other important settings used in this CFE analysis are given below:

i. Scar threshold defined as < 0.05mV;
ii. Signal sampling frequency 1200Hz – band pass filter 32-300Hz;
iii. Electrogram width 10ms (to abolish far-field signals);
iv. Refractory period 30ms (threshold for non-physiologic re-activation);
v. Interpolation 10mm;
vi. Surface projection 10mm;
vii. Points >10mm from the geometry surface were omitted;
viii. CFE-mean colour map set to display CFE between 30-120ms with areas of CFE mean >120ms denoted as purple; 30>CFE mean <80ms denoted by white; and within the range 80>CFE mean <120ms denoted as per the colour spectrum.

3.3.3 Catheter ablation procedure

The catheter ablation procedure is described in detail in chapter 2. In brief, under general anaesthesia, trans-septal access was gained to permit LA access. The following catheters were then placed in the heart: steerable decapolar catheter (CR Bard, Lowell, MA, USA) into the coronary sinus (CS); quadripolar catheter into the RAA to allow the measurement of the RAA cycle length (CL); duodecapolar high-density mapping catheter AFocus II^{TM} (St Jude Medical) inserted via one of the long sheaths (Preface, Biosense Webster, Diamond Bar, CA, USA),

initially to the right atrium (RA) and then to the left atrium (LA) sequentially; and finally a 3.5mm irrigated-tip D-F SF ablation catheter (Thermocool, Biosense Webster, Diamond Bar, CA, USA).

3.3.4 Catheter ablation and bi-atrial mapping protocol (Figure 3.1)

The procedure commenced with the acquisition of baseline bi-atrial CFE maps. Circumferential radiofrequency ablation lesions in a wide area (WACA) around each pair of ipsilateral PVs were undertaken using the ablation catheter. To achieve PVI (entrance block), additional intervenous ablation was required in some instances. After confirmation of PVI, an LA CFE map was acquired.

Linear ablation was then conducted (roof and mitral isthmus) following which a further LA CFE map was acquired. This map represented the remaining CFE sites after PVI and linear ablation and, therefore, was used for direct-targeted ablation of CFEs. The endpoint of CFE ablation was either eradication or significant organisation into more stable electrograms at all identified CFE sites (with the exception of the LAA). LAA ablation was avoided to prevent unintentional electrical isolation and/or perforation of this structure, but CFE located outside the LAA at its base were targeted. After targeted LA CFE ablation, the final phase of the mapping protocol was undertaken with the acquisition of the final bi-atrial CFE map. In the absence of AF termination to this point, DC electrical cardioversion was then used (up to maximum 360J biphasic energy) to restore sinus rhythm (SR). Once SR was attained and all lesions sets were completed, the lesion assessment phase of the protocol was commenced. PVI was assessed for bidirectional block. Entrance block has already been described earlier, with exit block proven by one or more of the following methods:

1. Pacing within one of the PVs showing local ipsilateral PV capture without capturing the

atrium;

2. Maximum output pacing within the PVs without capturing the atrium.

The next step was the assessment of linear lesions, with bi-directional block again being the defined endpoint. Differential pacing and sensing were undertaken from the LAA, CS and posterior wall. If the linear ablation lines were blocked bi-directionally at this stage, they were defined as either primary roof or primary mitral isthmus block. If linear lesions were not blocked, and additional ablation was undertaken to achieve bi-directional block (e.g. epicardial CS ablation to block mitral isthmus line), then this was defined as secondary block.

Cavo-tricuspid isthmus ablation was only conducted if there was documented evidence of typical or reverse typical atrial flutter pre- or intra-procedurally. This was done whilst pacing the proximal CS with the defined endpoint being bi-directional block.

If AF terminated to atrial tachycardia (AT), the CFE mapping and stepwise ablation protocol was terminated, and the AT mapped and ablated to SR, with confirmation of PVI.

3.3.4.1 Strategy for Atrial Tachycardia ablation

The strategy used to treat AT follows contemporary techniques. The first step was to ascertain whether the tachycardia was focal in origin or due to macro re-entry. This was done by using a combination of intra-cardiac recordings and the surface ECG P wave to assess the direction of its activation and temporal stability, using the CS or LAA as a timing reference. Subsequent assessment at the anterior, posterior and inferior LA was performed to ascertain whether macro re-entry was responsible for the arrhythmia. If a macro re-entrant tachycardia appeared likely, pacing manoeuvres were undertaken to determine concealed entrainment sites, thereby directing radiofrequency ablation to terminate the arrhythmia. Macro re-entry

sites encountered were LA roof dependent, mitral isthmus dependent or cavo-tricuspid isthmus dependent. If the arrhythmia was thought to be focal in its initiation, a 3D local activation map was performed with either the AFocus II™ or mapping/ablation catheter.

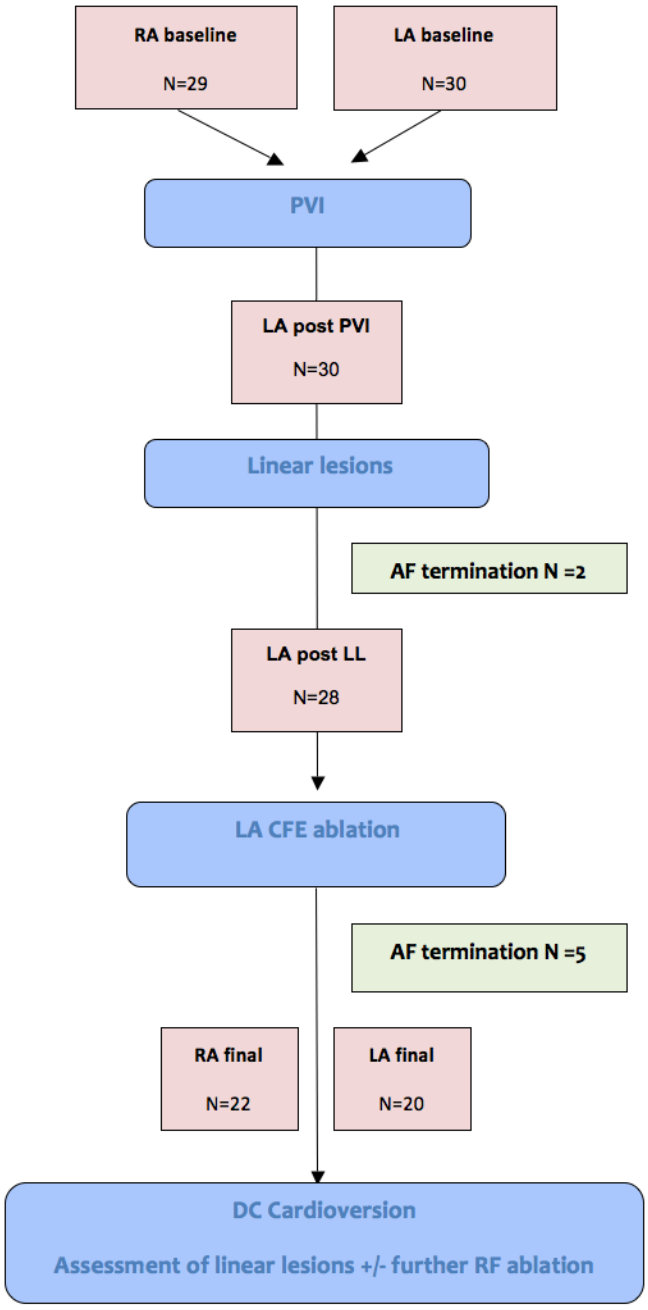


Figure 3.1 Procedural protocol - sequence of treatment and mapping

The protocol is summarised in the diagram above. The number of maps at each stage is shown in red boxes. The ablation and DC cardioversion stages are shown in blue boxes. Number of AF termination is shown in green boxes. Technical software failure resulted in the loss of 1 baseline, 2 final RA maps and 3 final LA maps. RA = right atrium, LA = left atrium, PVI = pulmonary vein isolation, CFE = complex fractionated electrograms, LL = linear lesions.

3.3.5 Pre-analysis CFE data cleaning

Each patient's 3D electroanatomical mapping data was recorded onto DVD and stored under a unique study code. Subsequent offline analysis was conducted on the Ensite Velocity™ Workstation (St Jude Medical).

Before the detailed analysis of each map, the CFE data was examined and cleaned using the following steps:

i. All acquisitions were displayed in order of CFE-mean.
ii. High frequency electrical or mechanical artefacts were removed.
iii. The peak-peak voltage/amplitude threshold to detect CFE was adjusted to minimise background noise, although to ensure standardisation of measurement, this threshold was fixed for all maps within each atrium in individual patients throughout the study.

3.3.5.1 Segmentation of atria

The LA and RA were each segmented into 3 regions to allow categorisation of the distribution of CFE. [108 112] The LA regions were anterior, posterior and appendage. The RA regions were lateral, septal and appendage (Figures 3.2 and 3.3).

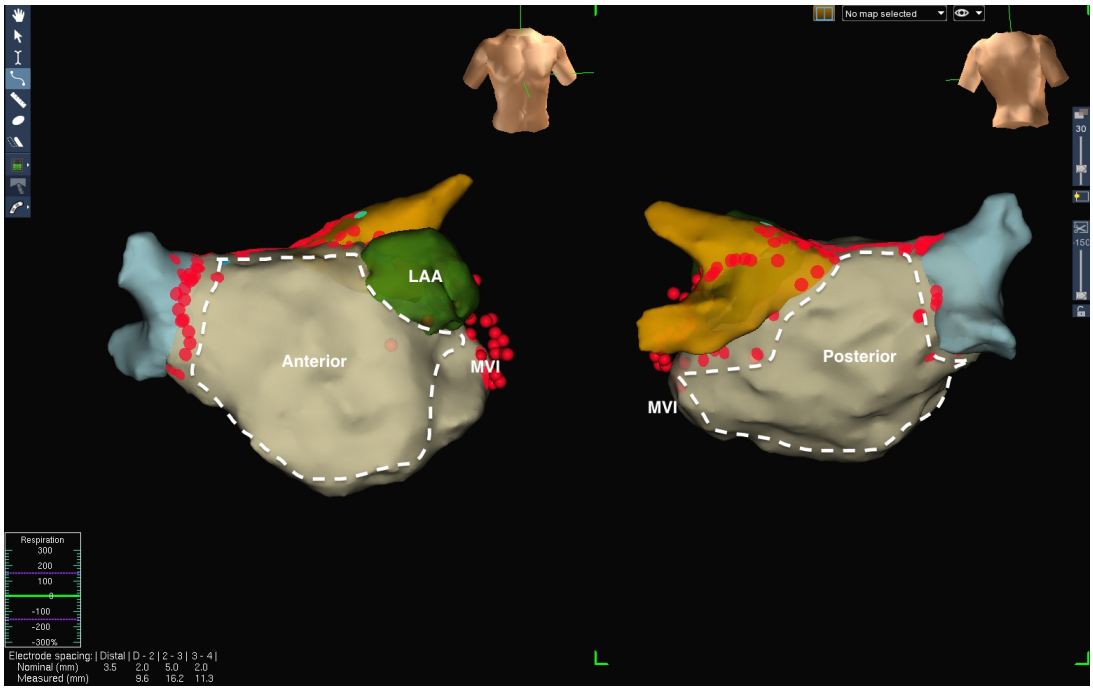


Figure 3.2 Left atrial segmentation

The following segmentation method is based on that of Singh et al. (19) *and segments the LA into three regions. The roof line connects the left (LSPV) and right superior pulmonary veins (RSPV) and demarcates the anterior and posterior walls superiorly, whilst laterally they are demarcated by the mitral isthmus (MVI) line in AP and PA views respectively. The LAA was defined as an extension from the LA body (geometry) as shown in the figure above.*

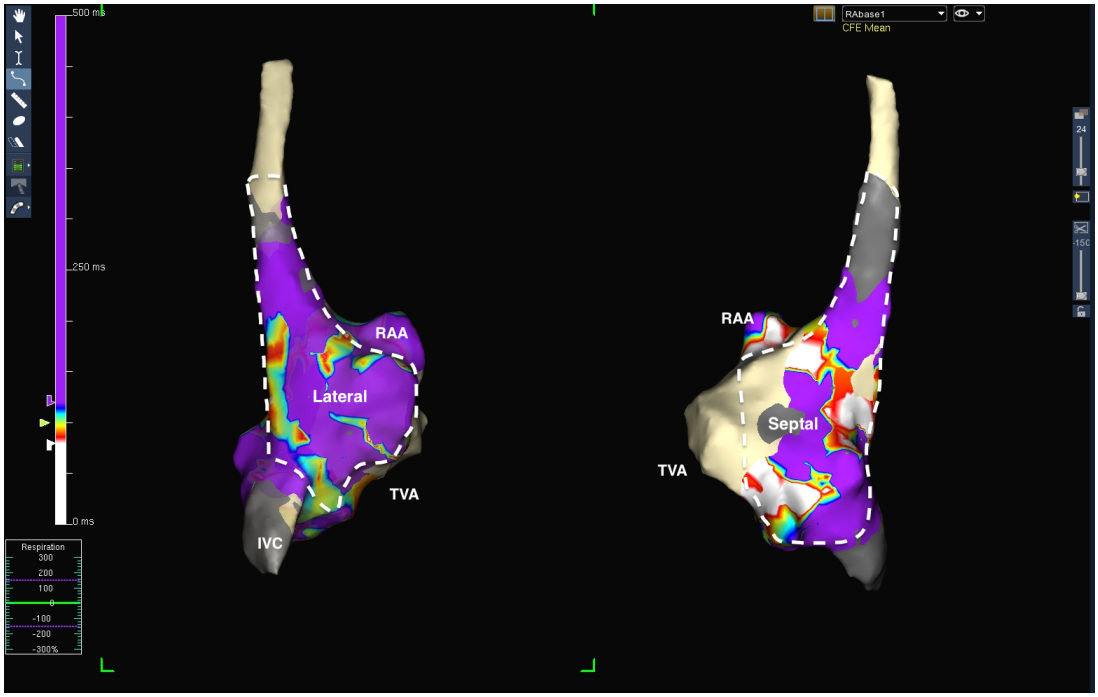


Figure 3.3 Right atrial segmentation

Segmentation of the RA into 3 regions: lateral, septal and appendage. The tricuspid valve annulus (TVA) demarcates the anterior perimeter of both the lateral and septal regions with the midline of that structure dividing the two regions. The RAA was defined by its typical extension from the anteromedial aspect of the RA body (geometry). The left image (right anterior oblique projection) shows the lateral aspect of the RA. The right image (left posterior oblique projection) shows the septal aspect of the RA. IVC = inferior vena cava.

3.3.5.2 Analysis of bi-atrial CFE area

To appreciate the remote effect of both PVI and linear lesions sets on remote LA CFE accurately, it was important to ensure those areas circumscribed by these lesion sets (to within 5mm from PVI and linear lesions) were excluded from the analysis zone. The remainder of the geometry by default became the LA denominator area i.e. the LA CFE analysis zone.

The Ensite Velocity™ surface marker tool (Figure 3.4) was used to delineate the following areas with the Ensite Velocity™ field-scaling algorithm applied, and with standardised projection and interpolation settings as defined previously:

i. The LA area, after exclusion of the PVI encircling lesions, linear lesions (within 5mm), and mitral valve annulus was defined the LA CFE analysis zone (cm^2);
ii. The exclusion zones, consisting of right/left PV and linear lesion area.
Therefore, the addition of i+ii equated to the total (baseline) LA surface area (cm^2);
iii. The sum total of all regions within (i) with CFE-mean ≤120ms, as denoted by white-blue colour annotation, is defined the LA CFE area.

The final LA CFE map assessed the impact of direct-targeted CFE ablation as guided by the

post-linear lesion map.

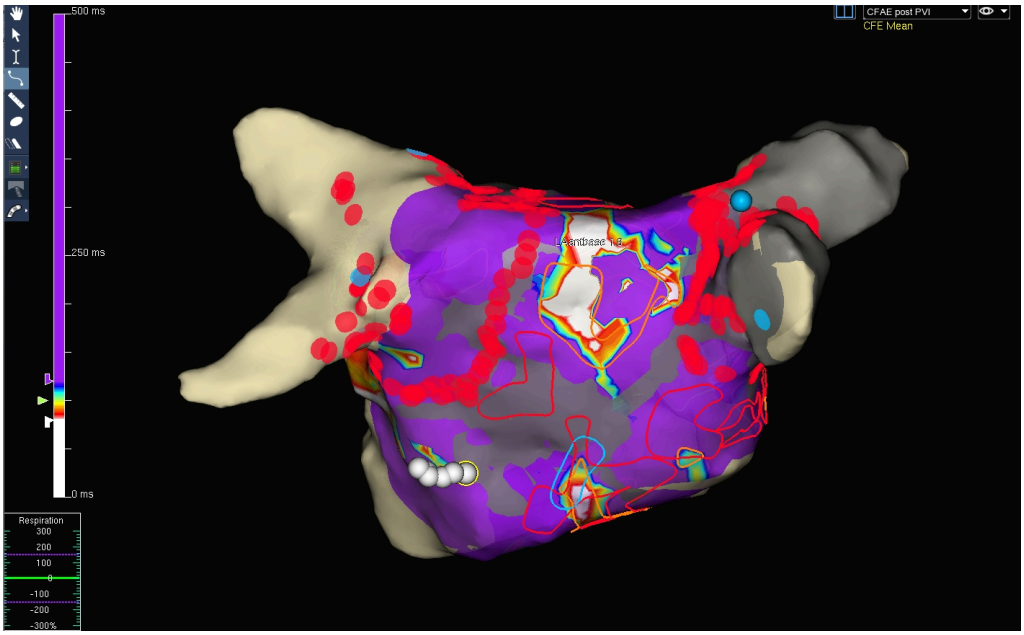


Figure 3.4 CFE-mean map with surface markings of CFE distribution

Posterior aspect of LA geometry with CFE-mean map. The map shown is after pulmonary vein isolation, however the surface annotation tool is used to annotate CFE areas with colour coded annotation schema: baseline (red), post-PVI (amber), post-linear lesions (green), final post CFE ablation (blue). These are projected onto the map surface.

A visual representation of progressive reduction in CFE via sequential LA-CFE mean maps with each step of ablation is shown in Figure 3.5.

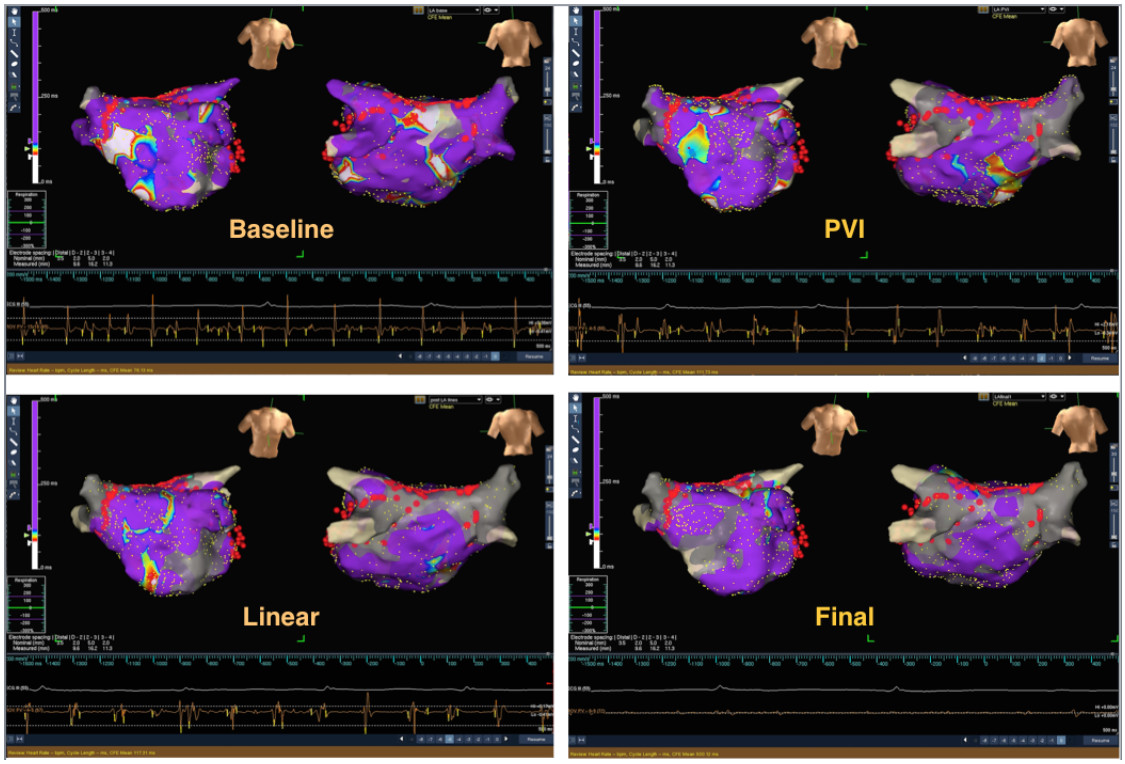


Figure 3.5 Post stepwise ablation CFE maps

High-density CFE maps acquired using the AFocus II (St Jude Medical; St Paul, MN, USA) catheter shown at each stage of the procedural protocol.

The RA denominator area was defined by the final RA map, acquired immediately after the final LA CFE map. This map enabled analysis of the remote effect of all LA ablation lesions (PVI, linear, and direct targeted CFE ablation) on the RA. To ensure the highest degree of accuracy and prevent confounding from LA ablation lesions, all RA projecting lesions from the LA (i.e. within 10mm of the RA geometry) were excluded. As before, the Ensite Velocity™ surface marker tool (Figure 3.4) was used to delineate the following areas with the Ensite Velocity™ field-scaling algorithm applied, and with standardised projection and interpolation settings as defined previously:

i. The RA area after exclusion of all projected septal LA lesions (within 10mm); the tricuspid valve annulus; the CS ostia; and superior and inferior vena cavae;

ii. All regions within (i) with CFE-mean ≤120ms as denoted by white-blue colour annotation, the sum total of which defined right atrial CFE area.

3.3.6 Statistical analysis

Continuous data are presented as mean (SD) or median (IQR), and categorical data as number and percentage. Paired t tests (within group) and unpaired t tests (between groups) were used to analyse change in CFE-area (absolute and percentage coverage of atrial surface area). Linear regression modelling was undertaken to assess predictors (age, gender, LA diameter, LVEF, baseline AFCL, and duration of AF) of baseline CFE areas, reduction of remote RA CFE area (adding RF duration and primary linear lesion block as explanatory variables), and the reduction of remote LA CFE area (by PVI and linear lesions). Arrhythmia-free survival was analysed by Kaplan-Meier survival curves with log-rank comparisons using the Mantel-Cox test. Cox regression was used to assess predictors of arrhythmia-free survival and only variables that had $p<0.25$ were included in the multivariable model. Throughout the analysis, p values < 0.05 were considered statistically significant. Data were analysed using GraphPad Prism version 6.00 for Mac (GraphPad Software, San Diego California, USA) and R statistical software (version 3.1.2).

3.3.7 Follow-up

All class I and III antiarrhythmic drugs were discontinued at the time of ablation if this had not already been done. Patients were followed up in at 3, 6, 9 and 12 months with 7-day ambulatory monitoring at each time point. Reported symptoms outside of these were followed up immediately either locally or at the RB&HFT, with a minimum of a 12-lead ECG.

Arrhythmia recurrence was defined in accordance with the 2012 Heart Rhythm Society, European Heart Rhythm Association, and European Cardiac Arrhythmia Society consensus document as freedom from AF, atrial flutter, or atrial tachycardia lasting 30 seconds or longer after a 3-months' blanking period to the 12 months' follow-up period.[26]

3.4 Results

3.4.1 Catheter ablation procedure

The total procedural duration for catheter ablation was 271±55 mins, fluoroscopy time was 52±16 mins, and total RF ablation time 58±15 mins. During linear lesion assessment post DC cardioversion, primary roof block was demonstrated in 93% (28/30) patients and primary mitral isthmus block in 37% (11/30) patients. Secondary roof block was achieved in the remaining 2 patients with 7.4±6.1 mins of RF ablation. Secondary mitral isthmus block was achieved in the remaining 19 patients, with an additional 6.5±6.0 mins of RF ablation.

3.4.2 CFE Mapping

158 CFE maps were acquired in total (Figure 3.1), of which 108 were LA maps (475±191 points per map) and 50 RA maps (410±161 points per map). The total surface area included for sequential CFE area analysis was 114±30 cm^2 in the LA (after exclusion of 96±25 cm^2 area from PVI and linear lesions).

3.4.2.1 Impact of catheter ablation on remote LA CFE area

The following results demonstrate the impact of catheter ablation upon the CFE area in both atria. The results for each chamber are further sub-divided into their constituent segments,

and are also shown as the percentage of analysed LA surface (Figure 3.6).

At baseline, the LA CFE area was 27.6±11.8 cm^2 (24.4±10.2% of analysed LA surface). This encompassed 11.7±7.0 cm^2 (10.1±5.9%) anteriorly, 12.1±8.1 cm^2 (10.3±5.8%) posteriorly and 5.3±3.8 cm^2 (4.8±3.5%) in the LAA. After PVI, there was a reduction in CFE-area to 21.6±12.5 cm^2 (18.6±10.4%, p=0.002 vs. baseline). This encompassed 9.3±5.9 cm^2 (8.1±5.3%, p=0.1 vs. baseline) anteriorly, 7.1±5.7 cm^2 (6.0±4.5%, p=0.0006) posteriorly, and 5.1±3.7 cm^2 (4.5±3.1%, p=1.0) in the LAA. After addition of linear lesions and compared with post-PVI analysis, total LA CFE-area had further reduced to 16.5±9.8 cm^2 (14.8±9.5%, p=0.008 vs. post-PVI). This encompassed 8.0±5.2 cm^2 (7.1±4.9%, p=1.0) anteriorly, 4.7±3.9 cm^2 (4.3±3.7%, p=0.03) posteriorly, and 3.7±2.9 cm^2 (3.4±2.9%, p=0.27) in the LAA. As expected, direct CFE ablation significantly reduced final LA CFE-area, compared with post-linear lesion analysis, to 7.8±8.7 cm^2 (6.7±6.6%, p=0.001 vs. post-linear lesion). This encompassed 2.8±3.4 cm^2 (2.5±2.7%, p<0.0001) anteriorly, 1.7±3.5 cm^2 (1.3±2.5%, p=0.006) posteriorly, and 3.3±3.1 cm^2 (2.9±2.7%, p=1.0) in the LAA.

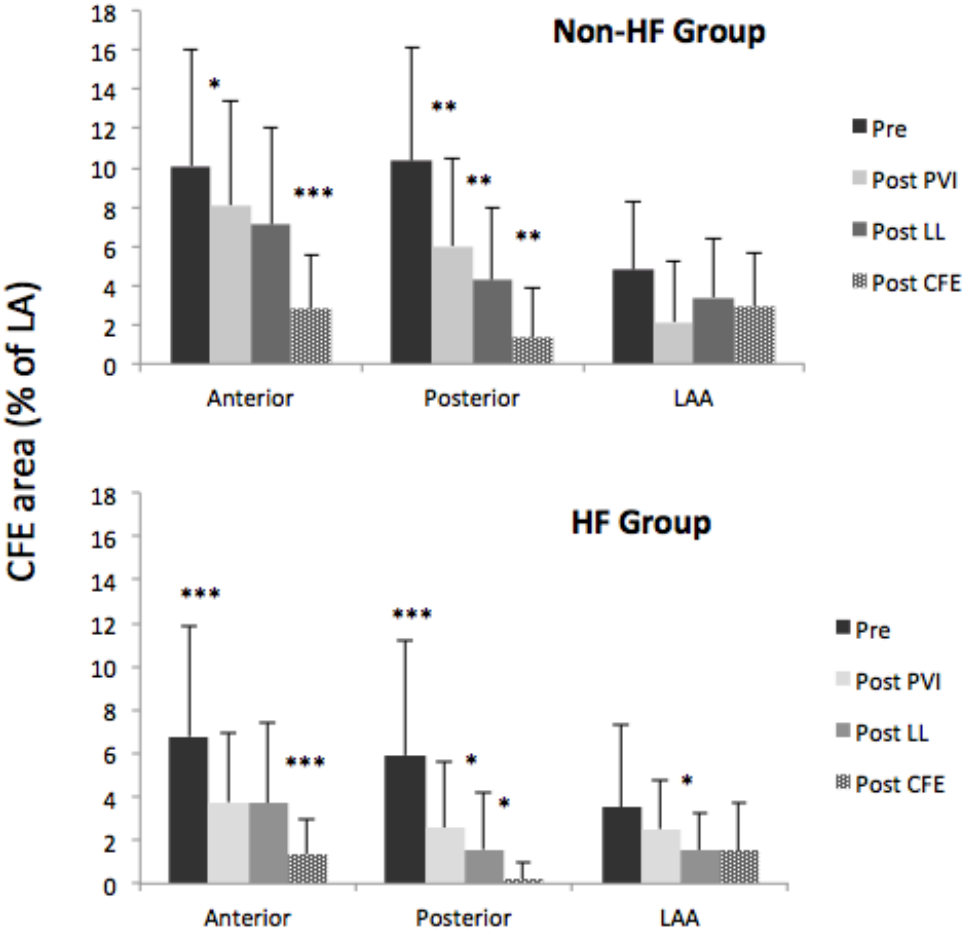


Figure 3.6 Sequential impact of stepwise LA ablation on left atrial CFE area

*The graphs above show the percentage (mean±SD) coverage of CFE of the atrial surface (after exclusion of PVI and linear lesions), within the segmented LA at baseline and after each stage of ablation. The first graph is of the Non-HF group from this study and the second of the HF group from our previously published data allowing for comparison between the two groups. P values are shown for comparisons between steps of ablation, and denoted * <0.05, ** <0.01, and *** <0.001.*

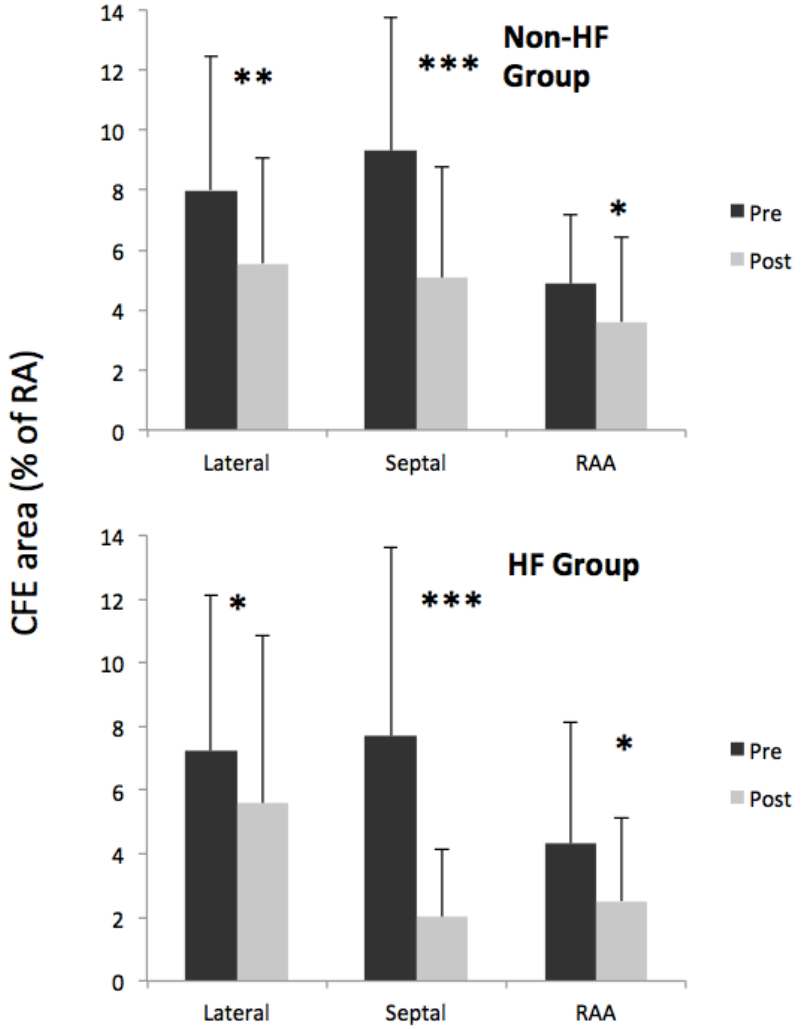


Figure 3.7 Impact of LA ablation on right atrial CFE area

*The graphs above show the percentage (mean±SD) coverage of CFE of the atrial surface within the segmented RA at baseline (pre) and after the completion of all the steps of LA ablation (post). The first graph is of the Non-HF group from this study and the second of the HF group from our previously published data allowing for comparison between the two groups. P values are shown for comparisons between steps of ablation, and denoted * <0.05, ** <0.01, and *** <0.001.*

3.4.2.2 Impact of catheter ablation on remote RA CFE area

At baseline, RA CFE-area was 39.8±19.3 cm^2 (22.1± 9.2% of the RA surface). This encompassed 14.7±9.1 cm^2 (7.9±4.4%) laterally, 16.6±9.2 cm^2 (9.3±4.8%) septally, and 8.6±4.5 cm^2 (4.9±2.3%) RAA. Final RA CFE-area after LA ablation was reduced to 24.1±12.9 cm^2

(13.3±8.1%, p=0.0001 vs. baseline). This encompassed 10.0±6.4 cm^2 (5.6±3.5%, p=0.009) laterally, 8.9±6.6 cm^2 (5.1±3.7%, p=0.0001) septally, and 6.1±4.2 cm^2 (3.6±2.8%, p=0.02) in the RAA. (Figure 3.7).

3.4.2.3 Impact of catheter ablation on AF cycle length

LAA and RAA AFCL were used as the measure of LA and RA AFCL respectively. LA AFCL at baseline was 153±18 ms. After PVI, there was prolongation to 161±23 ms (p=0.02 vs. baseline). LA AFCL after linear lesions was 161±22 ms (p=1 vs. post-PVI). LA AFCL further prolonged after LA CFE ablation to 179±42 ms (p=0.04 vs. post-linear lesions). RA AFCL at baseline was 163±18 ms. It increased after PVI to 171±29 ms (p=0.25 vs. baseline). It was 167±26 ms (p=1 vs. post-PVI) after linear ablation, prolonging to 168±24 ms (p=1 vs. post-linear lesions) after completion of LA CFE ablation. Hence in the LA, the AFCL prolonged significantly after PVI and CFE ablation, but was not impacted independently by linear ablation, whilst in the RA the AFCL was not significantly impacted upon by LA ablation. Overall, the mean LA AFCL prolonged (153±18 to 173±29 ms; p<0.0001) but the mean RA AFCL did not prolong as a result of LA ablation (163±18 to 168±24 ms; p=0.26) resulting in a final mean RA AFCL that was shorter than the final mean LA AFCL (168±24 vs. 179±42 ms; p=0.70).

Additional analysis of correlation between change in LA/RA AFCL and change in LA/RA CFE area (cm^2) between baseline and final CFE map was undertaken. No significant correlation was seen between these two parameters in the LA (r = 0.14, coefficient of determination r^2 = 0.02; p=0.50), or in the RA LA (r = -0.27, coefficient of determination r^2 = 0.07; p=0.29).

3.4.2.4 Predictors of baseline CFE area

Linear regression modelling was used to determine predictors for baseline RA and LA CFE areas. The following explanatory variables were included in the model; age, sex, LA diameter, EF, AFCL and AF duration. In multivariable analysis, male gender was the only strong risk factor for a higher baseline LA CFE area (coefficient 12.7 cm^2, 95% CI 1.9-23.4, p=0.02) and higher RA CFE area (coefficient 18.5 cm^2, 95% CI 4.1-32.9, p=0.01), although EF showed a trend towards a small effect on RA baseline CFE area (coefficient -0.68 cm^2, 95% CI -1.4-0.1, p=0.09).

3.4.2.5 Predictors of remote RA CFE area reduction

Linear regression analysis was used to identify determinants of remote RA CFE reduction. The following explanatory variables were included in the initial univariable model; age, sex, LA diameter, EF, AFCL, AF duration, radiofrequency time, primary roof block and primary mitral isthmus block. Multivariable analysis revealed that primary roof block exerted significant influence in the reduction in remote RA CFE area (coefficient 23.2 cm^2, 95% CI (3.2-43.2, p=0.03) with left ventricular EF exerting lesser effect (coefficient 0.9 cm^2, 95% CI 0.1-1.7, p=0.03).

3.4.2.6 Predictors of remote LA CFE area reduction

Linear regression analysis was used to identify determinants of remote LA CFE reduction. The following independent explanatory variables (age, sex, LA diameter, EF, AFCL, AF duration, radiofrequency time) were included in the model for remote LA CFE reduction after PVI, after linear ablation (adding both primary roof and mitral isthmus block as explanatory variables to the model), and after direct-targeted LA CFE ablation (adding radiofrequency time for CFE

ablation to the model). In univariable analysis, none of the above exerted any effect on the remote reduction of LA CFE area.

3.4.2.7 Predictors of final CFE area

Linear regression modelling was used to determine predictors for final LA and RA CFE areas. The following independent explanatory variables (age, sex, LA diameter, EF, AFCL, AF duration, radiofrequency time, primary roof and mitral isthmus block, radiofrequency time for CFE ablation) were included in the model. LA AFCL (coefficient -0.2 cm^2, 95% CI -0.4-0.01, p=0.06) and primary roof block (coefficient -12.2cm^2, 95% CI -24.8-0.5, p=0.06) showed a trend towards smaller LA final CFE area in univariable analysis and in multivariable analysis (coefficient -0.2 cm^2, 95% CI -0.4-0.03, p=0.09 and coefficient -10.3 cm^2, 95% CI -22.5-1.9, p=0.09) respectively.

3.4.2.8 Termination of AF

Termination of AF was defined as termination to SR without DC cardioversion, and was observed in 5 cases. In 2 patients, direct termination to SR occurred at the end of the roof linear lesion. In 2 patients, termination to SR occurred during direct-targeted CFE ablation with subsequent ablation of focal right atrial AT to SR. In 1 patient during direct CFE ablation, AT ensued which was terminated at ablation at the ostium of the coronary sinus. In 2 other patients although termination of AF to AT occurred, SR was not achieved through ablation of the AT and required DC cardioversion to SR. Therefore, these 2 events were not recorded as AF termination.

To investigate potential predictors of AF termination, a logistic regression model analysis was conducted incorporating the following explanatory variables: age, AF duration, RF time,

baseline CL, change in AFCL, bi-atrial CFE area, primary roof and mitral isthmus block. AF duration and baseline LA CFE area were individually associated with a higher chance of AF termination, although in multivariable analysis AF duration only showed a trend towards this finding (OR 1.2, 95% CI 1.0-1.6, p=0.07).

3.4.3 Clinical outcome - Single procedure arrhythmia free success

In this study consisting of non-HF patients with LSPAF, the single procedure, atrial arrhythmia free success rate at 300±257 days' follow-up, was 40% (12/30 patients). The Kaplan-Meier arrhythmia-free survival estimation 1 year, off antiarrhythmic drugs, after a single ablation procedure was 41% (Figure 3.8).

In the 17 patients who had a documented recurrence of symptomatic arrhythmia, 9 had AF, 5 had AT and 2 had both AF and AT. There were no deaths during follow-up, although one patient had a primary intra-cerebral event in the context of a supra-therapeutic INR level within the 3 months' blanking period, with a recurrence of documented AF whilst an in-patient. Due to the residual neurological deficit, the patient was unable to attend follow-up, although it had been documented that the patient remained in AF and was treated with anticoagulation and a rate control strategy.

3.4.3.1 Predictors of clinical outcome

Cox regression analysis was undertaken to assess the effect of single procedure catheter ablation on arrhythmia-free survival after adjustment of several explanatory variables (Table 3.2). The following explanatory variables were incorporated into the model: age, male sex, LA size (diameter on M-mode transthoracic echocardiography), LV ejection fraction, AF duration, baseline LA and RA CFE- areas, change in LAA AFCL, total change in LA CFE, AF termination,

total RF time and total CFE RF time. AF termination and CFE RF duration per 5 mins were individually associated with a higher chance of single procedure atrial arrhythmia-free survival at 1 year. In multivariable analysis AF termination showed a trend towards this finding (OR 0.1, 95% CI 0.01-1.3, p=0.08), but CFE RF duration per 5 mins was associated with a higher arrhythmia-free survival at 1 year (OR 1.6, 95% CI 1.03-2.4, p=0.04).

Table 3.2 Cox regression analysis model for single procedure atrial arrhythmia-free survival n=30

	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
	HR (95% CI)	**P - VALUE**	**HR (95 CI)**	**P - VALUE**
Age/yr	0.97 (0.92-1.03)	0.36		
Male	0.75 (0.24-2.37)	0.62		
LA size/5mm	0.96 (0.79-1.16)	0.64		
LV EF/5%	0.71 (0.34-1.49)	0.36		
AF, duration/mo	1.01 (0.95-1.06)	0.84		
Baseline LA CFE area/cm2	0.99 (0.96-1.04)	0.88		
Baseline RA CFE area/cm2	1.00 (0.97-1.03)	0.94		
Change in LAA AFCL/5ms	0.99 (0.86-1.13)	0.85		
Change in LA CFE area/cm2	0.98 (0.92-1.04)	0.46		
AF termination	0.28 (0.04-2.16)	0.22	0.13 (0.01-1.26)	0.08
Total RF, duration/10 min	0.87 (0.63-1.21)	0.41		
CFE RF duration/5 min	1.23 (0.93-1.69)	0.13	1.57 (1.03-2.40)	0.04

Key

HR = Hazard Ratio, CI = confidence interval, AF = atrial fibrillation, CFE = complex fractionated electrogram, AFCL = cycle length, HF = heart failure, LA = left atrial, LL = linear lesion, LV = left ventricular, RA = right atrial, RF = radiofrequency ablation. Note there were no unblocked linear lesions in this group of patients.

3.5 Comparison of Non-Heart Failure with Heart Failure group

The following results compare this data in non-HF patients with that of our previously published data in persistent AF and heart failure (HF). The baseline characteristics of these two groups are shown below (Table 3.3). The LA size, as measured by LA diameter on transthoracic echocardiography (TTE), was smaller, and hypertension was more prevalent in the non-HF group. Although the non-HF group consisted solely of LSPAF and the HF group included both LSPAF and persistent AF, the mean AF duration in the overall population was 21 months, suggesting that they were indeed comparable.

Table 3.3 Baseline population demographics of both non-HF and HF groups

	All Patients	Non-HF	HF	p-value
Age (y), mean ± SD	64±9	66±9	63±9	0.09
Sex (male), n (%)	48 (80)	23 (48)	25 (52)	0.51
AF duration (months), mean ± SD	21±16	19±4	24±8	0.28
LA size, mean ± SD	44 (7)	44 (5)	50 (7)	<0.001
LVEF (%), mean ± SD	47±20	60±8	25±11	<0.001
Hypertension, n (%)	31 (53)	21 (72)	10 (33)	0.004
Coronary artery disease, n (%)	21 (36)	9 (31)	12 (40)	0.59
Diabetes Mellitus, n (%)	8 (14)	1 (3)	7 (23)	0.05
Beta-blocker, n (%)	46 (84)	18 (72)	28 (93)	0.06

3.5.1 Procedural data (Table 3.4)

The procedural time (271±55 vs. 331±55 mins; p<0.001), fluoroscopy time (52±16 vs. 79±18 mins; p<0.001), total RF time (58±15 vs. 82±19 mins; p<0.001, and PVI RF time (28±10 vs. 46±17 mins; p<0.001) were all shorter in the Non-HF group. With regards to baseline chamber areas, the only major difference was that the total RA surface area was significantly higher in the Non-HF group (178±41 vs. 136±33 cm^2; p<0.001). Although LA diameter on TTE was smaller in the non-HF group, the LA surface area readings measured on the 3D mapping system were similar between the two groups.

3.5.2 CFE data (Table 3.4)

In the LA of the non-HF patients, the CFE areas were all higher than in the HF group respectively. Baseline total CFE area (27.6±11.8 vs. 18.3±12.0 cm^2; p=0.004), post PVI total CFE area (21.6±12.5 vs. 10.2±7.1 cm^2; p=0.001), post LL total CFE area (16.5±9.8 vs. 7.7±6.5 cm^2; p<0.001), and final total CFE area (7.8±8.7 vs. 3.1±3.5 cm^2; p=0.018),

In the RA of the non-HF patients, the baseline total CFE area (39.8±19.3 vs. 25.9±14.1 cm^2; p=0.002) and final total CFE area (24.1±12.9 vs. 12.9±11.8 cm^2; p=0.003) were also significantly higher than in the HF group respectively.

Table 3.4 Comparison of procedural and CFE data between non-HF and HF groups

PARAMETER	NON-HF	HF	P-VALUE
Total procedural time (mins)	271 (±55)	331 (±55)	0.001
Fluoroscopy time (mins)	52 (±16)	79 (±18)	<0.001
Total RF time (mins)	58 (±15)	82 (±19)	<0.001
PVI RF time (mins)	28 (±10)	46 (±17)	<0.001
Roof line RF time (mins)	3.4 (±1.4)	3.3 (±1.7)	0.97
Mitral isthmus line RF time (mins)	4.9 (±2.4)	4.0 (±2.4)	0.16
CFE RF time (mins)	9.4 (±7.0)	12.1 (±7.7)	0.17
LA points per map	475 (±191)	479 (±99)	0.92
RA points per map	410 (±161)	373 (±96)	0.14
LA CFE area analysis zone (cm^2)	114 (±30)	117 (±24)	0.62
Total LA surface area (cm^2)	210 (±38)	213 (±43)	0.75
Total RA surface area (cm^2)	178 (±41)	136 (±33)	<0.001
Baseline (non PV) LA CFE area (cm^2):	27.6 (±11.8)	18.3 (±12.0)	0.004
- Baseline anterior LA CFE area (cm^2)	11.7 (±7.0)	7.9 (±6.0)	0.03
- Baseline posterior LA CFE area (cm^2)	12.1 (±8.1)	6.6 (±5.8)	<0.001
- Baseline LAA CFE area (cm^2)	5.3 (±3.8)	3.8 (±4.1)	0.16
Post PVI LA CFE area (cm^2):	21.6 (±12.5)	10.2 (±7.1)	0.001
- Post PVI anterior LA CFE area (cm^2)	9.3 (±5.9)	4.5 (±4.0)	<0.001
- Post PVI posterior LA CFE area (cm^2)	7.1 (±5.7)	2.8 (±3.2)	0.006
- Post PVI LAA CFE area (cm^2)	5.1 (±3.7)	2.8 (±2.5)	0.006
Post LL LA CFE-area (cm^2):	16.5 (±9.8)	7.7 (±6.5)	<0.001
- Post LL anterior LA CFE area (cm^2)	8.0 (±5.2)	4.2 (±4.2)	0.004
- Post LL posterior LA CFE area (cm^2)	4.7 (±3.9)	1.7 (±2.8)	0.001
- Post LL LAA CFE area (cm^2)	3.7 (±2.9)	1.7 (±1.8)	0.002
Final LA CFE-area (cm^2):	7.8 (±8.7)	3.1 (±3.5)	0.018
- Final anterior LA CFE area (cm^2)	2.8 (±3.4)	1.4 (±2.0)	0.08
- Final posterior LA CFE area (cm^2)	1.7 (±3.5)	0.2 (±0.9)	0.06
- Final LAA CFE area (cm^2)	3.3 (±3.1)	1.6 (±2.1)	0.03
Baseline RA CFE area (cm^2):	39.8 (±19.3)	25.9 (±14.1)	0.002
- Baseline lateral RA CFE area (cm^2)	14.7 (±9.1)	9.6 (±6.8)	0.002
- Baseline septal RA CFE area (cm^2)	16.6 (±9.2)	10.1 (±7.2)	0.004
- Baseline RAA CFE area (cm^2)	8.6 (±4.5)	6.2 (±5.8)	0.08
Final RA CFE area (cm^2):	24.1 (±12.9)	12.9 (±11.8)	0.003
- Final lateral RA CFE area (cm^2)	10.0 (±6.4)	7.0 (±7.1)	0.14
- Final septal RA CFE area (cm^2)	8.9 (±6.6)	2.5 (±2.8)	0.0001
- Final RAA CFE area (cm^2)	6.1 (±4.2)	3.6 (±3.9)	0.04

3.5.3 AFCL data

3.5.3.1 Stepwise change in AFCL with intergroup analysis

In terms of AFCL, the pattern of prolongation in the LA was similar (AFCL prolonged significantly after PVI and CFE ablation, but there was no impact from the linear ablation lesions) in both Non-HF and HF groups. No significant difference was seen at any stage of AFCL measurement between the two groups (Table 3.5).

3.5.3.2 Overall change in AFCL with intragroup analysis

When analysing the overall impact of LA ablation on bi-atrial AFCL within each group, two different patterns of change emerged (Table 3.6). In the HF group, baseline LA AFCL was 161±27 which prolonged to 180±42 in the final CFE map (p=0.004); baseline RA AFCL was 167±33 prolonging to 178±40 in the final CFE map (p<0.001). In contrast, in the Non-HF group, the RA AFCL did not significantly prolong as a result of LA ablation (163±18 to 168±24; p=0.26) resulting in a final mean RA AFCL that was shorter than the final mean LA AFCL (168±24 vs. 179±42; p=0.70), although this did not reach statistical significance.

Table 3.5 Comparison of AFCL at each stage of procedure between non-HF and HF groups

AFCL at each stage of Procedure (ms)	Non-HF	HF	p-value
Baseline LA AFCL	153±18	161±28	0.19
Post PVI LA AFCL	161±23	170±37	0.26
Post LL LA AFCL	161±22	174±34	0.08
Final LA AFCL	173±29	180±42	0.98
Baseline RA AFCL	163±18	167±32	0.61
Post PVI RA AFCL	171±29	175±33	0.69
Post LL RA AFCL	167±26	173±30	0.41
Final RA AFCL	168±24	178±40	0.31

Table 3.6 Comparison of overall change in AFCL pre- and post-LA ablation in the non-HF and HF groups (intragroup analysis)

	NON-HF		HF	
	AFCL (MS)	**P-VALUE**	**AFCL (MS)**	**P-VALUE**
RA BASELINE	163±18	0.26	167±32	0.004
RA FINAL	168±24		178±40	
LA BASELINE	153±18	<0.0001	161±28	<0.0001
LA FINAL	173±29		180±42	

3.5.3.3 Clinical outcome - Single procedure arrhythmia free success

In the non-HF group, the single procedure, atrial arrhythmia free success rate at 300±257 days' follow-up, was 40% (12/30 patients). When compared with our previously studied group of HF patients, 63% (19/30 patients) at 494±259 days' follow-up were arrhythmia free after a single procedure (p=0.07). The Kaplan-Meier arrhythmia-free survival estimation (Figure 3.8), for this non-HF group at 1 year, off anti-arrhythmic drugs, after a single ablation procedure was 41% vs. 72% for the HF group (log rank, p= 0.03).

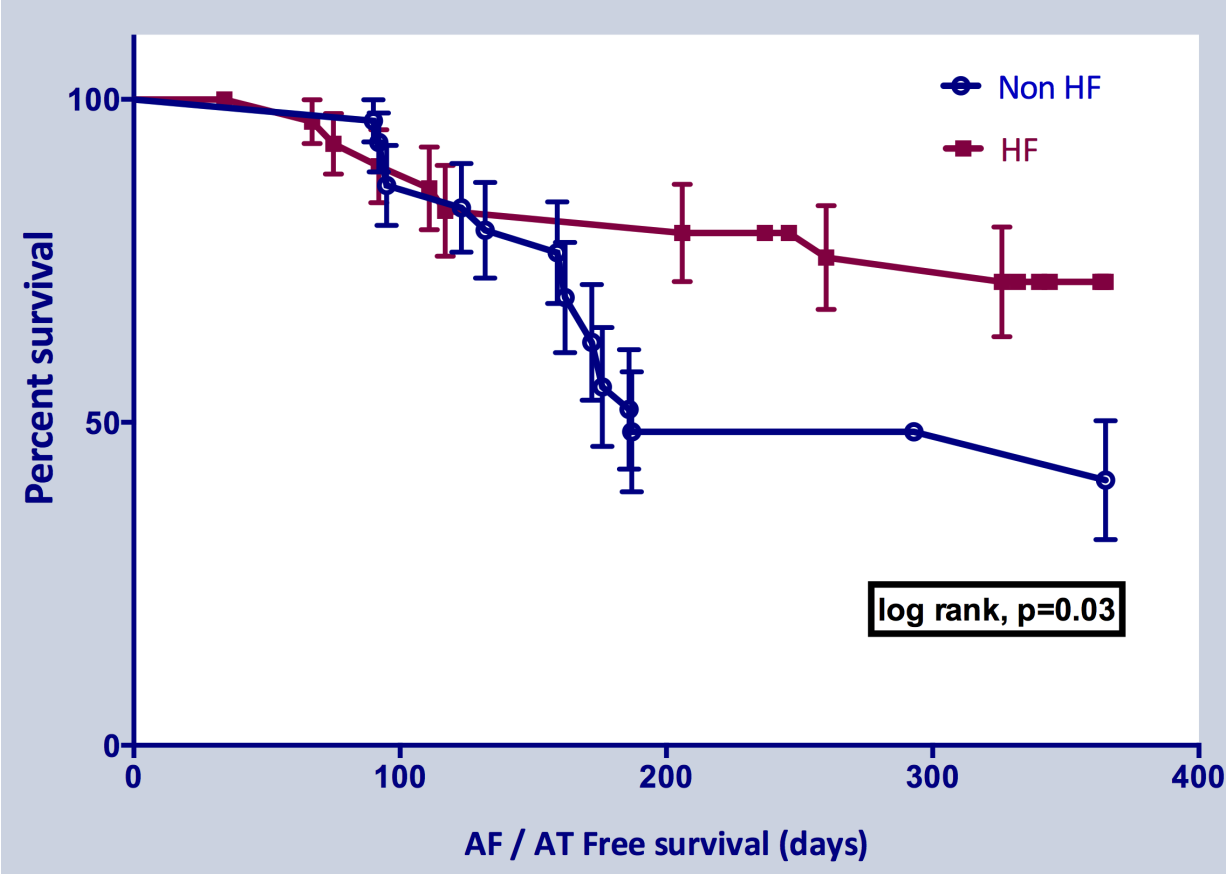


Figure 3.8 Freedom from atrial arrhythmias (single procedure) at 12 months

Non-HF versus HF groups, single procedure Kaplan-Meier curves of atrial arrhythmia-free survival off AAD (censored at 365 days). Note success is defined as freedom from atrial arrhythmia after a 3 month blanking period. The two survival curves were compared using the log-rank (Mantel-Cox) test.

3.6 Discussion

This study has demonstrated that CFE-area is reduced at remote sites in both atria after PVI and linear ablation lesions, in patients with LSPAF and preserved LV systolic function. The fact that this observation is consistent with previous data from our group and other investigators is crucial to understanding the mechanistic importance of CFE. [104 105 107 108]

3.6.1 Non-Heart Failure Group

The use of adjunctive CFE ablation in AF has been a source of controversy for many years with

conflicting reports as to its efficacy.[95 113 114] In this study the importance of CFE ablation is clearly highlighted by the fact that the greater the RF time targeting CFE, the greater the chance of clinical success. This is in keeping with a recent metanalysis that has shown greater atrial arrhythmia free survival when CFE ablation is added to PVI in non-paroxysmal patients.[115] These observations suggest that CFE plays an important mechanistic role in these patients. The major limitation of CFE ablation, however, is that we, as electrophysiologists, lack the ability to differentiate between fractionation representing high-frequency sources that may perpetuate AF (drivers) and those that are passively activated (bystander), for example by wavefront collision, during AF. This is demonstrated by the fact that PVI and linear ablation reduces the extent of CFE area at sites remote from ablation, shown in this study and in others, adding weight to the hypothesis that these CFE are likely to represent passive (bystander) activity. Therefore, an ablation strategy based solely on CFE ablation clearly cannot be justified until electrophysiologists are able to make this differentiation confidently. This in turn vindicates the commonly used strategy of stepwise PVI and linear lesions followed by targeted CFE ablation which is supported by superior outcome data, but also that it may reduce unnecessary ablation of non-critical CFE which are in fact simply bystander phenomena.[39 104]

3.6.2 Non-Heart Failure versus Heart Failure groups

The comparison of this data with that of our previously published CFE data in persistent AF and heart failure (HF) is noteworthy. Although the two groups were not investigated at the same time, the catheter ablation protocol, operators, data collection and analysis were very similar.

The first observation is that the pattern of findings with respect to change in CFE is very

similar in both groups. For example, in both HF and non-HF groups, there is sequential reduction in remote LA CFE-area post PVI and linear lesions, with the exception of the LAA segment in the non-HF group (Figures 3.6 and 3.7) whilst in the RA, remote CFE-area reduction also occurs as a result of isolated LA ablation. The second observation is that the two groups exhibit 2 different patterns of AFCL prolongation in response to LA ablation. The third observation is the difference in RF ablation times between the two groups. The fourth and most striking difference between the two groups, however, is the difference in clinical outcome. The Kaplan-Meier, single procedure, arrhythmia-free survival estimation at 1 year (Figure 3.8) is significantly lower in the non-HF group (41% vs. 72%, log rank p=0.03). This result goes against the widely accepted notion that heart failure confers additional complexity to the atrial substrate in AF rendering it more difficult to achieve SR through catheter ablation compared to non-heart failure AF.[116]

Current thinking suggests the longer the duration of AF and the larger the LA, the more complex the AF substrate. Furthermore, it is accepted that AF is driven predominantly by the LA, supported by the fact that contemporary practice and guidelines concentrate predominantly on LA ablation procedures for AF. Although early data shows conflicting results on the efficacy of bi-atrial ablation in persistent forms of AF from both surgical and catheter ablation, there is now increasing evidence to show that the RA is important to outcomes in a significant proportion of patients with non-paroxysmal forms of AF.[117 118] Rostock et al. found in their study of chronic AF patients, RA ablation terminated AF in 26% of patients.[92] More recently, Narayan et al. published a novel computational mapping technique, which identified drivers of AF in the form of rotors and focal impulses.[119] In a predominantly persistent AF population, 24% of these drivers were located in the RA and ablation of these sources resulted in excellent freedom from arrhythmia rates at 9 months. Ravelli et al. used another

novel technique combining analysis of AFCL and fibrillatory wave analysis to show that in their cohort of persistent AF patients, 23% of potential AF rotors were found in the RA.[120] These and other recent studies adopt a more pragmatic, patient-specific approach, targeting drivers, which are deemed to be relevant for arrhythmia termination. Intuitively, this seems to be a sensible approach, as it should minimise unnecessary ablation whilst simultaneously improving outcomes.[119 121]

In our study, the non-HF LSPAF group had significantly larger RA surface areas in conjunction with higher RA CFE areas observed at both baseline and after remote LA ablation. In the context of poorer outcomes in this group, this is highly suggestive of a more advanced atrial substrate than the HF group. The other important observation was the pattern of AFCL prolongation. In the HF group there was a parallel increase in the AFCL in the LA ($p=0.004$) and RA ($p<0.001$), when comparing baseline to final CFE map. This implies that LA ablation had a significant impact on the LA substrate, which in turn manifested in the corresponding RA AFCL changes, reflecting its likely bystander role. In contrast, in the non-HF group, there was a divergent pattern of AFCL change with a significant change in AFCL from baseline to final CFE map, in only the LA (Table 3.6). This resulted in a RA to LA AFCL frequency gradient at the final bi-atrial map (after completion of LA ablation) indicating that the RA may well have been driving the AF in a significant proportion of patients, although the small sample size was not powered to detect this as a statistically significant difference ($p=0.70$). This is in keeping with data from Hocini et al., whose group demonstrated that in LSPAF patients, where LA ablation failed to terminate AF but resulted in an RA to LA AFCL frequency gradient, RA ablation terminated AF in 50% of patients.[122] One more potentially important observation from the non-HF group should be discussed. The fact that remote CFE in the LAA did not reduce in response to LA ablation does raise the possibility that in some of these patients the

LAA may well have been the driver. Indeed, the incidence of LAA drivers has been shown to be in the region of 20% so this is certainly a plausible reason for the lower degree of success in this group.[120]

The other interesting observation is the fact that less RF time (both total RF time and PVI RF time) was spent ablating the non-HF group compared with the HF group in order to obtain the same endpoints. This cannot be explained by a difference in LA chamber size between the two groups as this was not the case. Plausible explanations for this observation are that it was easier to obtain the endpoints in the non-HF group and/or that this may simply reflect the increasing experience of the operators who have become more adept at conducting catheter ablation.

These aforementioned differences focussing on the RA are certainly plausible arguments to explain the discrepancy in outcome between the two groups. Indeed, it emphasises the fact that perhaps more importance should be given to the bi-atrial aspect of the substrate in LSPAF patients whose primary atrial myopathy (i.e. without concomitant left heart disease) may well be more severe and hence difficult to treat than those with a secondary atrial myopathy, for example, secondary to HF. It is worth mentioning at this point the opinion of the pioneer of cardiac arrhythmia surgery, Professor James Cox. He has previously proposed a different classification for AF based on underlying cause. He described *primary* AF as those without another cardiac co-morbidity serious enough to warrant concomitant surgical intervention, and *secondary* AF as AF that is due to another left heart condition (e.g. ischaemia, heart failure and valvular heart disease). Based on surgical outcomes he postulated that primary non-paroxysmal AF harboured a very abnormal bi-atrial substrate, which mandated bi-atrial surgical lesions to achieve similar efficacy to that of secondary AF

treated by surgical procedure confined to the left atrium.[123]

Despite the fact that Cox-regression analyses of baseline CFE did not predict clinical outcome, the overall findings from this study suggest that non-HF LSPAF may well be a more advanced primary atrial myopathy with a complex bi-atrial substrate consisting of extensive CFE, compared with the secondary atrial myopathy found in persistent AF and HF. Furthermore, the outcome data suggest that LA only ablation – albeit with a similarly extensive lesion set in both non-HF and HF groups – may not be as effective in patients with advanced primary atrial myopathies. This study once again brings to the fore the difficulties in achieving SR in LSPAF, and the potential importance of the RA in non-paroxysmal AF patients. Looking forward to the future, electrophysiologists need to be able to identify accurately which non-PAF patients will benefit from RA ablation, to prevent a blanket strategy of subjecting all such patients to extensive bi-atrial radiofrequency lesions. This would reduce unnecessary ablation, with the inherent implications on post ablation atrial transport function and increased procedural times and complications.

3.7 Limitations

The main limitation of this study is the small sample size, which may have precluded the detection of small but important differences in parameters such as changes in the AFCL. Another limitation was the fact that RA CFE maps were not taken in parallel with the LA CFE maps at all time points. The reason for this was to prevent the total procedure duration from being too long which could have adverse effects on the patient. In doing so the stepwise effect of LA ablation on RA CFE cannot be ascertained, although the overall effect of LA ablation is of course discussed.

With regards to the second part of the study comparing the non-HF and HF cohorts, it is important to note that these two groups were studied at different time points and thus may incorporate unmeasured differences to account for the contrast in clinical outcome. With regards to the intensity of arrhythmia follow-up, the non-HF group presented in this chapter had more rigorous follow-up, encompassing 3, 6, 9 and 12-month 7-day ambulatory monitoring, whereas in the previous HF group a 3-month ECG was followed with a 48 hour Holter monitor at 6 and 12 months. In both groups, symptomatic recurrences also prompted further investigation. It is possible that this discrepancy may account for the differences in arrhythmia free success, although it was clear from the non-HF group that patients with persistent forms of AF predominantly have a binary outcome, either success with SR or recurrence with persistent AF/AT. Therefore, documented SR at several time points is highly indicative of clinical success.

3.8 Conclusion

In non-HF patients with LSPAF, LA ablation (post PVI and linear lesions) sequentially reduces CFE at remote sites in both the LA and RA. This reproducible phenomenon, confirmed in this and other studies, strongly suggests that these abolished CFE represent passive bystander activity.[104 105 108] The RF time spent ablating CFE was also an independent predictor of single procedure arrhythmia-free survival at 1 year. This highlights the importance of incorporating CFE ablation within the ablation strategy for LSPAF patients. The significant difference in clinical outcome between the non-HF and HF groups may be explained by differences in the substrate. The non-HF LSPAF group had larger RA surface areas, higher proportions of bi-atrial baseline and post ablation CFE, and a divergent pattern in AFCL prolongation, resulting in a RA

to LA frequency gradient which implies a more complex primary atrial myopathy than that which occurs when AF occurs secondary to HF. The correct identification of functionally important CFE drivers, and/or patients who may benefit from additional RA ablation, may well be the key to improving clinical outcomes in LSPAF. Further research should, therefore, focus on patient-tailored ablation strategies to optimise outcomes in those with complex atrial substrates.

Acknowledgements

This work was conducted in sequence from previous work published from our group investigating CFE in persistent AF patients with heart failure (see below).

I would like to specifically thank Dr David Jones for his expert guidance and support in conducting this CFE sub-study.

Paper

Impact of Stepwise Ablation on the Biatrial Substrate in Patients with Persistent Atrial Fibrillation and Heart Failure. Jones DG, Haldar SK, Jarman JWE, Johar S, Hussain W, Markides V, Wong T. Circ Arrhythm Electrophysiol. 2013; 6:761–8.

Chapter 4

Left atrial structural changes in long standing persistent atrial fibrillation are not irreversible: a pre- and post-ablation cardiac magnetic resonance sub-study

4.1 Abstract

4.1.1. Introduction

The use of interventional ablation treatments has grown in line with the increasing incidence and prevalence of atrial fibrillation (AF).[124] [125] Long standing persistent atrial fibrillation (LSPAF) is the most difficult type of this arrhythmia to treat, due to the extensive electrical and anatomical remodelling that occurs with time. The effect of ablation on the atria in LSPAF has yet to be fully understood. The aim of this study was to examine the effect of left atrial (LA) ablation on atrial volumes and emptying fractions, in addition to ventricular volumes and ejection fractions, using cardiac magnetic resonance (CMR).

4.1.2 Methods

Forty-eight patients (63 ± 9 years, 29 males) underwent either thoracoscopic surgical ablation or catheter ablation for de novo LSPAF. Left and right atrial (LA/RA) volumes and emptying fractions and left and right ventricular volumes and ejection fractions were measured at baseline, 3 and 9 months post ablation using CMR. LA remodelling was defined as ≥15 % decrease in maximum LA volume (LAmax) during follow-up. Follow-up also included the assessment of arrhythmia recurrence.

4.1.3 Results

The mean duration of follow-up was 267 ± 16 days. There was significant reduction in the following volumes at 9 months when compared to baseline: LAmax (59.4±14.8 vs. 47.9±13.0; p<0.001); minimum LA volume (LAmin) (49.9±13.2 vs. 36.6±12.3; P<0.001); and minimum RA volume (RAmin) (63.7±20.9 vs. 45.3±22.7; p<0.0001). LA (16.5±9.2 vs. 25.7 ±12.1; p=0.001) and RA (13.1±7.9 vs. 32.6±14.7; p<0.0001) emptying fractions increased in tandem at 9 months when compared to baseline. Both left ventricular ejection fraction (LVEF) (59.2±9.7 vs. 65.5±8.8; p=0.003) and right ventricular ejection fraction (RVEF) (52.0±10.9 vs. 59.1±8.0; p=0.001) also increased at 9 months. LA reverse remodelling occurred in 60% of patients. In patients that remodelled, there was a higher percentage of AF recurrence (48%) than those that had not remodelled (18%) (p=0.04). Ablation modality did not have an influence on any of the atrial and ventricular parameters but post ablation maintenance of SR improved LVEF and LA emptying fractions at 9 months. LAmax volume at baseline was the only independent predictor of LA reverse remodelling in multivariable analysis [OR 1.08 (1.02-1.16); p=0.01]. None of the atrial volume parameters were predictive of clinical outcome.

4.1.4 Conclusion

This study using CMR shows that ablation therapy in LSPAF, irrespective of clinical outcome, results in LA (and RA) reverse remodelling and improvement in biventricular ejection fractions. LAmax volume at baseline was an important predictor of LA reverse remodelling. Structural changes in LSPAF are, therefore, not irreversible.

4.2 Introduction

AF is the commonest arrhythmia encountered in the general population. Its prevalence increases with age, from 0.5% at 40-50 years to 5-15% at 80 years. With an ageing population worldwide, AF will affect an increasing proportion of the population.[124] AF can cause significant symptoms for patients and confers a significant cardiovascular morbidity and mortality risk, including a four-fold increase in stroke risk.[125-128]

Despite the availability of several anti-arrhythmic drugs (AADs), their use is limited due to the combination of suboptimal efficacy and side-effect profiles. This has driven the increasing use of interventional treatments, namely catheter ablation, over the last decade for the treatment of patients with symptomatic, drug-refractory AF. Pulmonary vein isolation (PVI) is the cornerstone of all these procedures, but ablation techniques for persistent forms of AF often involve additional LA substrate modification in addition to PVI, reflecting the remodelled atrial substrate associated with non-paroxysmal AF as described above.[26] Ten randomised controlled trials can now be found confirming that catheter ablation is superior to AADs with regards to maintenance of normal sinus rhythm (SR). [129-138] Although the majority of these trials studied paroxysmal AF patients, there is one notable multicentre randomised control trial confirming the superiority of catheter ablation over medical therapy (70.4% vs. 43.7%, p=0.002) in persistent AF over a 12-month follow-up period.[138]

LA enlargement has been shown to be associated with AF in many studies and is also associated with stroke, heart failure and an increased mortality risk.[139] LA enlargement has also been demonstrated to be an important prognostic predictor of success post AF ablation.[140] Furthermore, there are data to show that post-ablation maintenance of SR allows for atrial reverse remodelling with significant LA volume reduction, (using echocardiography, computed tomography and magnetic resonance imaging).[141-147] LA volume is a recognised

measurement of LA size and in routine clinical practice this is commonly done by echocardiography. The limitation with echocardiographic techniques lies with the fact that image quality is operator dependent, which in turn has a bearing on the geometric assumptions that are required to enable LA volume to be calculated. In contrast, due to the high spatial and temporal resolution three-dimensional reconstructions that cardiovascular magnetic resonance (CMR) can produce, the accuracy of LA volume and other cardiac chamber volume measurements are greater although geometric assumptions are also made with the commonly used biplane area-length method. Therefore, at present, CMR is deemed to be the gold standard imaging modality for LA volume assessment.[148]

In general, and despite the technical and technological advances over the last decade, ablation strategies to restore SR in persistent, and in particular LSPAF, have been controversial in their efficacy and clinical benefit, particularly in view of the extensive ablation that is often required. In these patients, the chronicity of AF invariably leads to significant electrical and structural remodelling of the atria through progressive dilatation with or without accompanying fibrosis. The current paradigm is that the greater the extent of progressive atrial dilatation with its consequent architectural changes, the lower the chance of restoration of SR through ablation. It is not uncommon for the decision not to pursue an interventional strategy in otherwise symptomatic patients, to be based on LA chamber parameters. If indeed there is the potential for reverse atrial remodelling post ablation in these patients, then this may translate into significant clinical benefit to patients.

The following sub-study of the CASA-AF trial was, therefore, designed to assess LA reverse remodelling and other associated structural changes that may occur in conjunction with reverse remodelling in LSPAF patients undergoing either catheter ablation or thoracoscopic surgical ablation, using pre- and post-procedural CMR. In addition, analysis of predictors of

outcome with respect to LA reverse remodelling and clinical outcome was undertaken.

4.3 Methods

4.3.1 Study population

This prospective sub-study imaged patients with symptomatic drug-refractory LSPAF, referred for ablation therapy using either catheter or thoracoscopic surgical modalities.

4.3.2 MRI Protocol

A 1.5-T MR system with 32-channel cardiac coil (Magnetom Avanto, Siemens Healthcare, Germany) was used to scan 48 patients (mean age 65±9 years) with LSPAF at baseline and then at 3 and 9 months post ablation therapy. Images of the atria were acquired in the two-chamber and four-chamber orientation using a breath-hold ECG-gated steady state free precession cine sequence. Sequence parameters included repetition time/echo time of 55/1.7ms, inplane voxel size 1.7x1.7x7.0mm, base resolution 256ms, phase resolution 100ms, slice thickness 7mm, and flip angle 59°.

4.3.3 Assessment of Atrial Volumes and Emptying Fraction

LAmax was defined as the maximal LA volume just prior to the mitral valve opening (ventricular end-systole) with LAmin defined as the minimal LA volume at the point of mitral valve closure (ventricular end-diastole) (Figure 4.1). RA maximum volume (RAmax) was defined as the maximal RA volume just prior to the tricuspid valve opening (ventricular end-systole) with RAmin defined as the minimal RA volume at the point of tricuspid valve closure (ventricular end-diastole) (Figure 4.2). A semi-automated software (CMR Tools, Cardiovascular Imaging Solutions, London) was used for all atrial and ventricular

measurements.

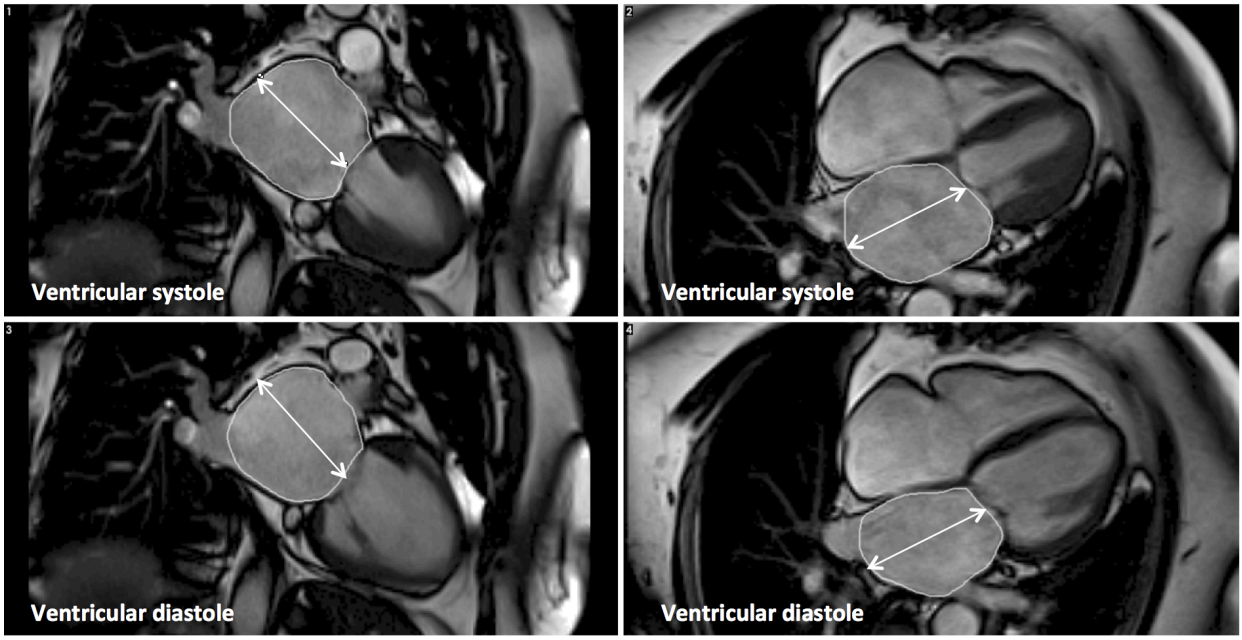


Figure 4.1 Biplane method for LA volume measurements.

Areas were measures in the two (left panel) and four (right panel) chamber views in both ventricular end-systole (maximum atrial volume) and end-diastole (minimum atrial volume) with exclusion of the atrial appendage and the ostia of the pulmonary veins. Longitudinal diameter was measured in both views and the maximum value was used for calculation of the atrial volumes.

For LA volumes calculation the biplane area-length method was used, but as the RA morphology is complex this method was not appropriate. [149 150] RA volumes were, therefore, measured from a stack of contiguous transaxial cines encompassing the entire RA. The RA volumes included the right atrial appendage but the ostium of the coronary sinus was excluded (Figure 4.2).

LA emptying fraction was defined as [LAmax – LAmin / LAmax], and RA emptying fraction as [RAmax – RAmin / RAmax]. Baseline transthoracic echocardiography (TTE) was also conducted the same day of the baseline CMR scan, and correlation analysis between baseline LA diameter obtained by M-mode TTE and baseline LAmax volume was conducted (Figure 4.3).

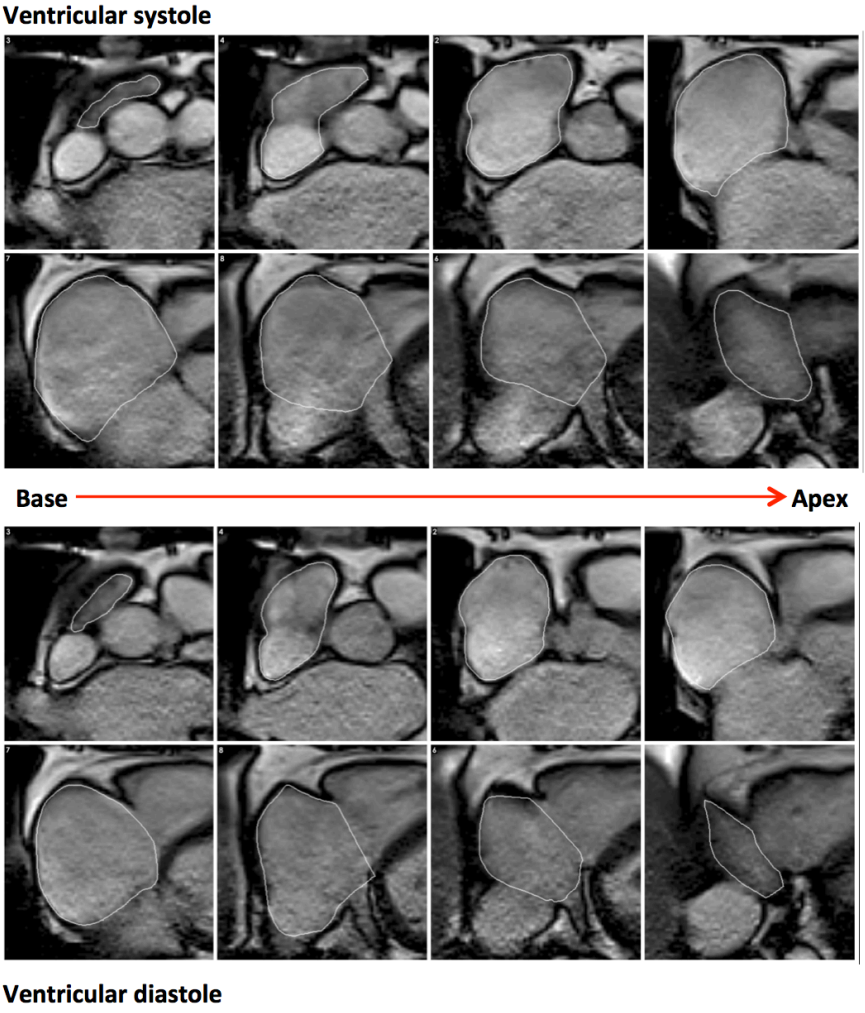


Figure 4.2 Example of transaxial RA stack cines used to calculate RA volumes.

Right atrial endocardial borders were delineated in all slices in both ventricular end-systole (maximum atrial volume) and end-diastole (minimum atrial volume) with inclusion of the atrial appendage and exclusion of the cava veins and the coronary sinus orifice.

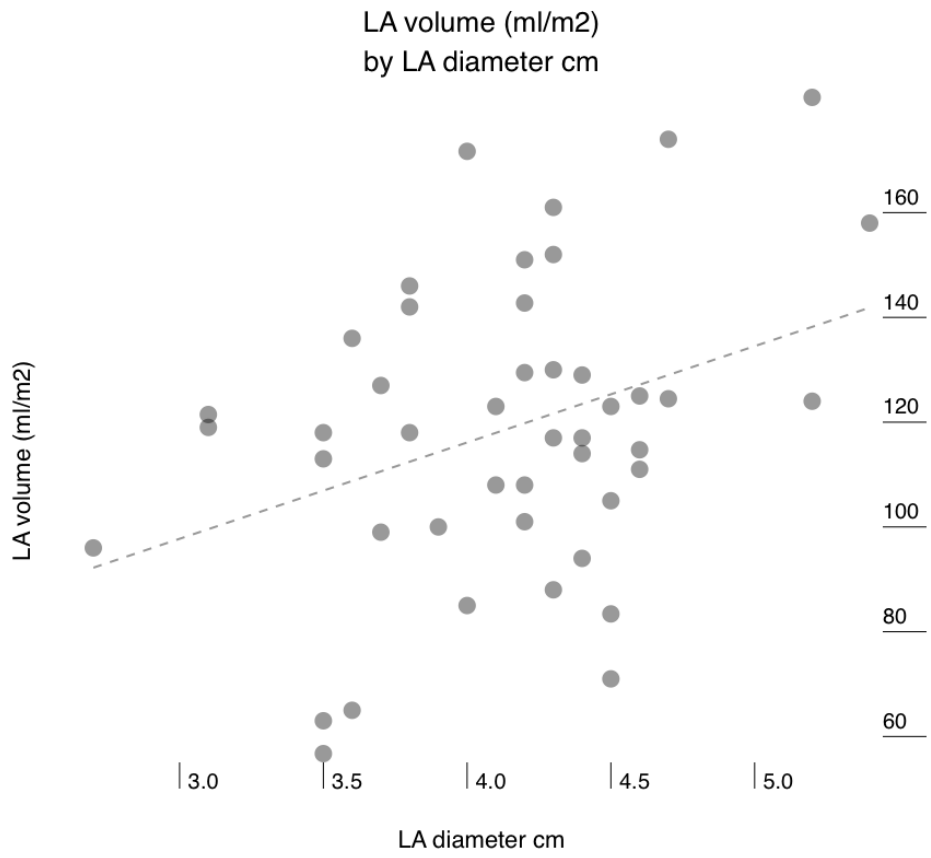


Figure 4.3 Correlation analysis of LA volume (ml/m^2) as measured by CMR and LA diameter as measured by M-mode TTE.

The correlation coefficient (r) is 0.35, the coefficient of determination (r^2) is 0.12 and the p value = 0.02.

4.3.4 Assessment of Ventricular Volumes and Ejection Fraction

Left and right ventricular volumes at end-diastole and end-systole were determined using semi-automated CMR tools (Cardiovascular Imaging Solutions, London, UK) as previously described (see Figure 4.4). [96-97]All atrial and ventricular volumes were indexed to body surface area, and measurements were undertaken by an observer, blinded to patient's clinical data, ablation procedure, and rhythm outcomes.

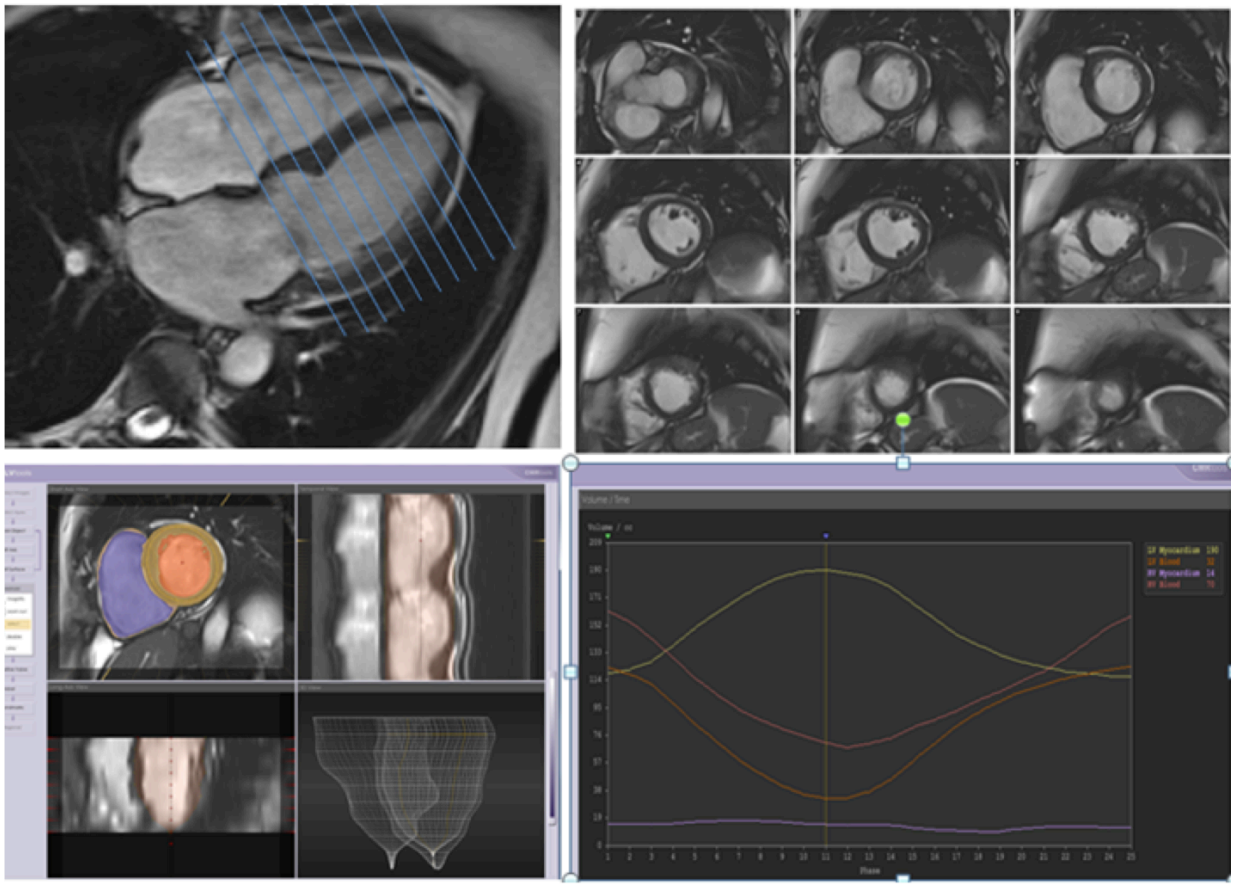


Figure 4.4 Ventricular volumes and mass using CMR tools.

Top panel - The short axis stack is shown relative to four-chamber view

Bottom panel - CMR Tools volumetric analysis: endo- and epicardial surfaces are delineated by manually placing points on the cardiac borders in short axis images. An interactive thresholding tool is applied to subjectively define solid structures. Blood volumes, ejection fraction and ventricular mass are automatically calculated and displayed graphically.

4.3.5 Assessment of intraobserver and interobserver variability

The intraobserver and interobserver variability of the atrial and ventricular indexed measurements was assessed in a random sample of 10 patients. Two observers with more than 3 years of CMR experience were employed. To assess intra-observer variability, the same observer measured atrial and ventricular volumes from each data set, with a minimum 2-week interval between repeat analyses, and were blinded to the index values for each

parameter when repeating measurements. The second independent blinded observer analysed atrial and ventricular volumes to provide a measure of interobserver variability. Results were analysed with the Bland-Altman method (MedCalc software, version 13.3). Intracorrelation coefficient value, mean bias and standard deviation of bias were assessed for the purpose of inter- and intra-observer agreement.

Table 4.1 Intraobserver and interobserver variability

	Intraobserver				**Interobserver**			
	ICC*	**p-value**	**Mean bias**	**SD of bias**	**ICC***	**p-value**	**Mean bias**	**SD of bias**
LAmax (ml/m^2)	0.92	0.0003	-0.55	8.47	0.91	0.0002	-2.26	5.19
LAmin (ml/m^2)	0.90	0.0008	0.58	6.64	0.90	<0.0001	-2.65	4.82
LAEF (%)	0.77	0.01	-1.03	5.03	0.65	0.04	2.89	9.81
RAmax (ml/m^2)	0.82	0.006	-2.44	11.9	0.75	0.01	-5.88	14.35
RAmin	0.84	0.0041	-1.25	12.26	0.86	0.001	-6.6	8.69
RAEF (%)	0.77	0.01	-1.09	10.47	0.80	0.005	3.04	9.57
LVEDV (ml/m^2)	0.95	0.0001	-0.61	4.08	0.87	0.0009	-15.45	21.61
LVESV (ml/m^2)	0.90	0.0008	-1.02	2.73	0.96	<0.0001	-4.2	2.4
LVEF (%)	0.90	0.0008	0.67	2.69	0.90	<0.0001	1.2	2.74
RVEDV (ml/m^2)	0.96	<0.0001	2.25	3.45	0.76	0.01	8.9	9.67
RVESV (ml/m^2)	0.90	0.0007	-0.28	4.07	0.75	0.01	-6	6.43
RVEF (%)	0.77	0.02	2	5.26	0.80	0.0098	1.9	5.97

*Key: * ICC = intra– or inter– correlation coefficient, SD = standard deviation.*

4.3.6 Ablation procedures

Anti-arrhythmic drugs (class IC and III) were stopped before or on the day of the ablation procedure. The catheter ablation technique has been previously described in detail (see Chapter 2).[151] In brief, under general anaesthesia, using the EnSite Velocity™ 3D electroanatomical mapping system (version 4.0.1/4.0.2, St Jude Medical), all four pulmonary veins (PVs) were electrically isolated, with additional substrate modification encompassing roof and mitral isthmus linear lesions and ablation of complex fractionated atrial

electrograms. Endocardial mapping was performed using a duodecapolar high-density mapping catheter AFocus II (St Jude Medical) and ablation with an irrigated-tip F-curve 3.5mm ablation catheter (Thermocool, Biosense Webster, Diamond Bar, CA, USA) for ablation with a power limit of 35W in the anterior LA, 30W on posterior wall, 25W within CS, and 40W in the cavotricuspid isthmus (CTI).

Surgical ablation was performed using the bilateral video assisted thoracoscopic surgical technique under general anesthesia, with double-lumen endotracheal tube placement for selective lung ventilation. On the right side, a 10mm camera port and two 5mm working ports were used to allow opening of the pericardium with subsequent blunt dissection to the right-sided PVs. Pulmonary vein isolation (PVI) was then conducted on the right side from the epicardial surface with a bipolar radiofrequency ablation clamp (AtriCure Inc., Westchester, OH, USA) using overlapping applications around each ipsilateral pair of PVs. Additional linear ablation lines were then undertaken connecting the contralateral superior PVs (roof line) and the inferior PVs (inferior line) to commence a posterior box lesion, before switching to the left side with a similar approach to conduct left PVI to complete the lesion set. Finally, the left atrial appendage was excluded using the AtriClip LAA excluder system (AtriCure Inc.).

4.3.7 Definition of atrial reverse remodelling

The goal of this study was to investigate LA reverse remodelling in LSPAF patients undergoing either catheter or surgical ablation. Accordingly, the study population was divided into 2 groups according to whether they reverse remodelled or not. The remodellers were defined as those with a ≥ 15% decrease in LAmax during follow-up. The non-remodellers were defined as those who demonstrated a <15% decrease or an increase in LAmax during follow-up. The baseline characteristics of these 2 groups are detailed in Table 4.2.

Table 4.2 Baseline Patient Characteristics

	All Patients	Remodelled	Non-remodelled	p-value
Age (y), mean ± SD	63 ± 9	66 ± 8	60 ± 10	0.03
Sex (male), n (%)	29 (69)	17 (68)	12 (71)	0.86
AF duration (months), median (IQ range)	22 (16,30)	23 (15,28)	18 (16,30)	0.64
CVD, n (%)	2 (5)	2 (12)	0 (0)	0.16
Hypertension, n (%)	27 (64)	18 (72)	9 (53)	0.21
Dyslipidaemia, n (%)	9 (21)	4 (16)	5 (29)	0.30
Diabetes Mellitus, n (%)	4 (10)	2 (8)	2 (12)	1.00
Smoking, n (%)	20 (48)	11 (44)	9 (53)	0.57
CHA2DS2-VASc, median (IQ range)	2 (1,3)	3 (1,3)	1 (0,2)	0.04
Beta-blocker, n (%)	34 (81)	18 (72)	16 (92)	0.07
ACEI and /or ARBs, n (%)	26 (62)	16 (64)	10 (59)	0.74
Diuretic, n (%)	11 (26)	9 (36)	2 (12)	0.08
Body Surface Area, mean ± SD	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.1	0.41
LAmax (ml/m2), mean± SD	60 ± 15	65 ± 13	52 ± 13	0.003
LVEF (%), mean± SD	59 ± 10	60 ± 9	58 ± 10	0.51
LVEDV (ml), mean± SD	60 ± 12	62 ± 13	57 ± 8	0.13
LVESV (ml), mean± SD	25 ± 8	25 ± 8	25 ± 9	0.87

4.3.8 Follow-Up

Seven-day ambulatory monitoring was used to assess patients' rhythm post-ablation at 3 and 9 months. 48 patients underwent either surgical or catheter ablation therapy successfully, achieving SR post procedure. 3 patients subsequently had pacemakers implanted precluding further CMR scans, 1 patient did not attend follow-up post ablation due to a neurological event, and 2 had incomplete atrial data sets. A complete CMR dataset at all of the follow-up time points was available for the remaining 42 patients.

4.3.9 Statistical analysis

Baseline data were presented as number and percentage for categorical variables, and comparisons done using the chi-squared or Fisher's Exact Test, while numeric data were presented as mean (SD) or median (IQR) and comparisons done using the 2 sample independent t-test or the Mann-Whitney test.

To assess any differences between the 3 time points in the CMR parameters, one-way ANOVA or the Kruskal-Wallis test was used, and the p-values adjusted using the Bonferroni correction for multiple comparison.

To assess the change in CMR parameters between time points in relation to the effect of remodeller status, catheter/surgery and SR/AF recurrence, a series of t tests or Mann-Whitney tests were done with the p-values obtained adjusted for multiple comparisons using the Bonferroni correction.

Univariable and multivariable logistic regression was done to determine the predictors of a remodeller and of clinical success from ablation. Only variables that had $p < 0.25$ were included in the multivariable model. ROC statistics were used as a measure of model performance and were within the acceptable range. Throughout the analysis, p values < 0.05 were considered statistically significant.

4.4 Results

48 LSPAF patients underwent either surgical (22) or catheter (26) ablation for AF, with acute procedural success achieved in 97% (47/48) of patients who were in SR at the end of the

procedure. Recurrence of AF occurred in 27% (13/48), and all those patients underwent repeat ablation, via catheter ablation regardless of the modality of index ablation. Mean duration of follow-up was 267 ± 16 days.

4.4.1 Intraobserver and interobserver variability

Excellent intraobserver agreement with a low mean bias was seen for the following parameters: LAmax, LAmin, LVEDV, LVESV, LVEF, RVEDV and RVESV (Table 4.1). LAmax, LAmin, LVESV and LVEF also demonstrated excellent interobserver agreement with low mean bias of values.

The intra- and inter-observer ICC values for LVEF and LA emptying fraction were greater than the right-sided values. This reflects the irregularity of the right heart anatomy (shape and trabeculated regions) which limit both endocardial and epicardial definition. Furthermore, clinicians are comparatively less familiar with the right heart as compared to the left heart. Despite this, the intra and inter-observer agreements remain excellent for both RV and RA measurements, and are comparable to previous studies. [152 153]

4.4.2 Change in atrial and ventricular parameters at follow-up

In the overall study population (Table 4.3), the absolute change (Δ), as compared with baseline, was significant in the following parameters: LAmax; LAmin; RAmin; RAEF; LVEDV; and RVEF at both the 3 month and 9 month time point. The change in LAEF, RVEDV and LVEF was only significant at 9 months when compared with baseline. There were no significant changes in any of the parameters between 3 and 9 months. A visual example of pre- and post-ablation LAmax volume reduction is shown in Figure 4.4.

Table 4.3 Values at baseline, 3 and 9 months and change between time points for MRI parameters for overall study population

	Baseline	3 months	9 months	Δ0-3 months	Δ3-9 months	Δ0-9 months
LAmax (ml/m^2)	59.4 (±14.8)	51.0 (± 13.5)	47.9 (±13.0)	-8.5 (P=0.01)	-3.1 (p=0.92)	-11.5 (P<0.001)
LAmin (ml/m^2)	49.9 (±13.2)	39.6 (±14.4)	36.6 (±12.3)	-10.2 (P=0.002)	-3.0 (p=0.92)	-13.3 (P<0.001)
LAEF (%)	16.5 (±9.2)	22.9 (±12.7)	25.7 (±12.1)	6.4 (P=0.03)	2.8 (p=0.82)	9.2 (P=0.001)
RAmax (ml/m^2)	71.7 (±24.0)	70.4 (±28.0)	65.1 (±21.4)	-1.3 (P=1)	-5.3 (p=1)	-6.5 (P=0.668)
RAmin (ml/m^2)	61.0 (51.5-79.1)	42.0 (34.0-59.0)	41.6 (30.3, 49.4)	P=0.0006*	p=0.57*	P<0.0001*
RAEF (%)	13.0 (7.8, 16.5)	31.8 (22.0, 41.3)	30.9 (25.1, 44.3)	P<0.0001*	(p=1) *	P<0.0001*
LVEDV (ml/m^2)	59.1 (±11.9)	67.1 (±13.7)	68.6 (±11.7)	8.0 (P=0.011)	1.4 (p=1)	9.4 (P=0.002)
LVESV (ml/m^2)	25.0 (±8.4)	25.3 (±8.2)	22.9 (±6.4)	0.3 (P=1)	-2.4 (p=0.5)	-2.1 (P=0.61)
LVEF (%)	59.2 (±9.7)	62.8 (±7.8)	65.5 (±8.8)	3.6 (p=0.18)	2.6 (p=0.5)	6.2 (P=0.003)
RVEDV (ml/m^2)	67.2 (±12.9)	74.4 (±15.8)	76.8 (±16.9)	7.1 (p=0.10)	2.4 (p=1)	9.5 (p=0.01)
RVESV (ml/m^2)	31.6 (±9.0)	30.9 (±9.0)	33.4 (±10.3)	-0.6 (p=1)	2.4 (p=0.76)	1.8 (p=1)
RVEF (%)	52.0 (±10.9)	58.0 (±8.1)	59.1 (±8.0)	6.0 (p=0.009)	1.1 (p=1)	7.1 (p=0.001)

Key: *Values are given either as mean ± SD or median (interquartile range), *Kruskal-Wallis test.*

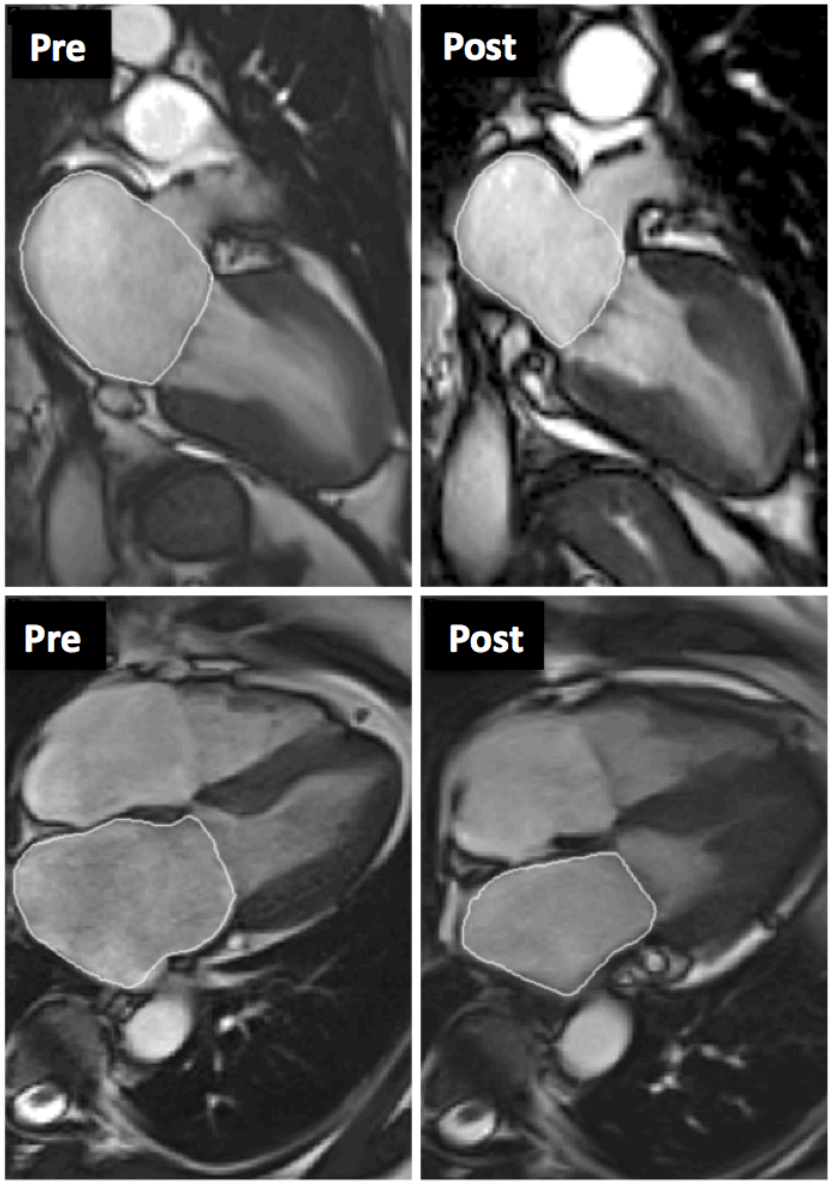


Figure 4.5 Atrial remodelling

Key: LAmax volume before (left panel) and 3 months post ablation (right panel).

4.4.3 Reverse remodelling

Over the 9 months' follow-up period, 25/42 (60%) of patients demonstrated reverse remodelling (remodellers) whilst 17/42 (40%) did not reverse remodel (non-remodellers). Those that remodelled were older [66±8 vs. 60±10; p=0.03], had a larger LAmax [65±13 vs. 51±13; p=0.003], and had a higher CHA2DS2-VASc score [3(1,3) vs. 1(0,2); p=0.04] at baseline when compared to the non-remodeller group respectively (Table 4.2). There were no

differences in baseline measures of LV dimensions and ejection fraction between the 2 groups.

4.4.4 Remodellers versus Non-remodellers

The change in biatrial and biventricular parameters between baseline and 9 months was analysed, and compared between the two groups (Table 4.4). The change in LAmax

[-20.9 (±9.9) vs. 1.7 (±7.2); p<0.0001] and LAmin [-18.6 (±7.5) vs. -4.4 (±7.7); p<0.0001] was significantly greater in the remodeller group compared to the non-remodeller group as would be expected. Figure 4.5 shows examples of pre- and post-ablation LAmax volumes whilst Figure 4.6 shows the mean LAmax at different time points for the two groups. Interestingly, within the follow-up period, 12/25 (48%) patients in the remodeller group had AF recurrence compared with only 3/17 (18%) patients in the non–remodeller group (p=0.04).

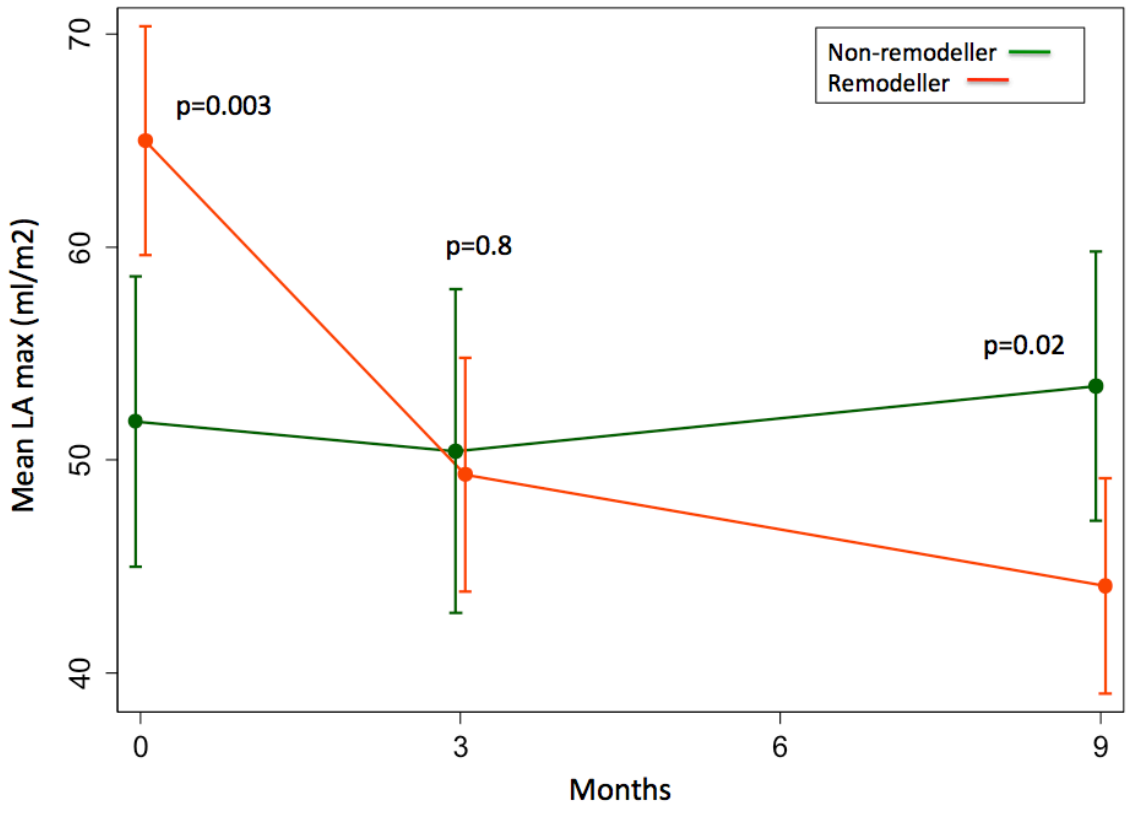


Figure 4.6 – LAmax for remodeller vs. non-remodeller plotted over time

Table 4.4 Changes in MRI parameters over time for non-remodellers vs. remodellers and AF recurrence vs. SR subgroup analyses

	Δ 0-3 months [mean ± sd or median (IQR)]			Δ 3-9 months [mean ± sd or median (IQR)]			Δ 0-9 months [mean ± sd or median (IQR)]		
	Non-Remodeller	**Remodeller**	**p - value**	**Non-Remodeller**	**Remodeller**	**p - value**	**Non-Remodeller**	**Remodeller**	**p - value**
iLAmax	-3.72 (±15.7)	-31.0 (± 23.1)	0.0003	1.7 (±9.1)	-5.2 (±8.2)	0.05	1.7 (±7.2)	-20.9 (±9.9)	<0.0001
iLAmin	-9.96 (±14.5)	-29.0 (±18.3)	0.004	-0.1 (±5.8)	-4.9 (±7.0)	0.13	-4.4 (±7.7)	-18.6 (±7.5)	<0.0001
LAEF	7.7 (1.2 - 19.0)	2.7 (-0.7 - 10.4)	1.00	-0.64 (-7.3 - 5.9)	2.82 (-1.3 - 8.3)	1.00	9.0 (0.8 - 12.9)	3.55 (-5.7, 14.9)	1.00
iRAmax	2.25 (±23.6)	2.29 (±33.6)	1.00	-4.8 (±13.5)	-6.0 (±13.9)	1.00	-3.7 (±20.8)	-7.4 (±27.0)	1.00
iRAmin	-11.9 (±19.4)	-6.63 (±38.3)	1.00	-5.6 (±13.5)	-4.4 (±15.1)	1.00	-20.4 (±16.9)	-17.2 (±28.3)	1.00
RAEF	18.4 (9.85 - 27.6)	23.4 (12.1 - 29.0)	1.00	1 (-4.1 - 14.6)	0 (-12.0 - 13.9)	1.00	21.2 (13.4 - 31.2)	21.05 (5.70 - 30.6)	1.00
iLVEDV	10.9 (±8.3)	4.2 (±12.7)	0.33	1.6 (±9.7)	0.2 (±12.1)	1.00	13.9 (±9.5)	5.8 (±12.2)	0.09
iLVESV	3.2 (±10.4)	-1.3 (±8.2)	0.37	-4.1 (±9.6)	-0.7 (±4.5)	0.46	-2.1 (±6.6)	-2.4 (±8.4)	1.00
LVEF	6.2 (±8.0)	3.4 (±8.4)	1.00	2.7 (±3.5)	0.8 (±9.6)	1.00	8.4 (±9.0)	4.7 (±11.7)	0.82
iRVEDV	5.2 (±8.9)	4.0 (±15.7)	1.00	9.3 (±8.4)	-1.2 (±23.6)	0.40	15.5 (±11.5)	3.3 (±21.1)	0.11
iRVESV	-1.7 (±4.3)	-2.6 (±9.0)	1.00	4.7 (±3.8)	3.9 (±13.2)	1.00	2.0 (±5.1)	1.3 (±14.9)	1.00
RVEF	5.9 (±7.1)	7.0 (±13.7)	1.00	-1.1 (±4.5)	-0.2 (±6.3)	1.00	6.8 (±7.6)	7.0 (±14.0)	1.00
	AF Recurrence	**Sinus**	**p - value**	**AF Recurrence**	**Sinus**	**p - value**	**AF Recurrence**	**Sinus**	**p - value**
iLAmax	-9.9 (±18.2)	-7.5 (± 11.9)	1	-5.3 (±9.1)	-1.0 (±8.9)	0.51	-17.5 (±14.6)	-8.6 (±13.3)	0.15
iLAmin	-9.1 (±10.3)	-9.8 (±9.8)	1	-4.2 (±7.9)	-2.3 (±6.4)	1	-13.5 (±9.7)	-12.5 (±10.8)	1
LAEF	-5.3 (-9.3 - 8.7)	7.8 (1.3 - 19.0)	0.09	0.5 (3.0 - 7.0)	2.2 (-3.0 - 7.8)	1	-1.3 (-6.4 - 7.5)	12.0 (2.9 - 18.9)	0.03
iRAmax	6.8 (±29.7)	-4.3 (±29.6)	0.81	-9.4 (±13.7)	-3.0 (±13.2)	0.54	-1.8 (±24.7)	-8.7 (±24.6)	1
iRAmin	-0.6 (±36.6)	-17.8 (±25.5)	0.36	-9.6 (±18.3)	-1.7 (±10.0)	0.39	-10.1 (±27.7)	-23.8 (±20.5)	0.27
RAEF	13.0 (3.4 - 25.2)	22.9 (12.8 - 32.3)	0.99	-2.7 (-12.5 -	1.3 (-4.1 - 13.0)	1	10 (0.6 - 24.2)	26.2 (18.9 - 38.3)	0.09
iLVEDV	5.1 (±13.1)	8.2 (±11.5)	1	-0.2 (±14.4)	1.3 (±9.1)	1	6.6 (±14.5)	10.5 (±10.0)	1
iLVESV	1.4 (±5.1)	-0.5 (±9.5)	1	-0.5(±3.9)	-2.6 (±7.9)	1	-0.6 (±7.5)	-3.2 (±7.7)	0.90
LVEF	-0.1 (±8.1)	7.0 (±8.0)	0.03	-0.2 (±12.7)	2.4 (±3.8)	1	-0.3 (±11.5)	9.8 (±8.5)	0.006
iRVEDV	6.2 (17.4)	3.6 (±9.8)	1	-6.8 (±29.8)	7.5 (±9.8)	0.12	1.0 (±22.7)	12.7 (±14.6)	0.15
iRVESV	0.4 (±8.5)	-3.2 (±6.7)	0.48	5.3 (±16.8)	3.6 (±5.6)	1	4.4 (±16.3)	0.04 (±7.9)	0.81
RVEF	1.9 (±6.6)	9.3 (±12.9)	0.15	-0.2 (±7.1)	-0.6 (±4.9)	1	2.7 (±7.5)	9.2 (±13.0)	0.24

Table 4.5 Changes in MRI parameters over time for surgery vs. catheter subgroup analysis

	Δ 0-3 months [mean ± sd or median (IQR)]			Δ 3-9 months [mean ± sd or median (IQR)]			Δ 0-9 months [mean ± sd or median (IQR)]		
	Surgery	**Catheter**	**p - value**	**Surgery**	**Catheter**	**p - value**	**Surgery**	**Catheter**	**p - value**
iLAmax	-12.7 (±15.1)	-4.1 (± 12.6)	0.15	-3.3 (±8.6)	-1.8 (±9.7)	1	-14.6 (±15.5)	-8.6 (±12.4)	0.54
iLAmin	-11.2 (±10.7)	-7.8 (±8.9)	0.84	-2.4 (±6.0)	-3.7 (±7.9)	1	-13.7 (±9.9)	-11.9 (±10.9)	1
LAEF	8.7 (-3.70 - 20.2)	-0.2 (-5.8 - 8.0)	0.78	-0.8 (-3.0 - 6.6)	2.1 (-3.0 - 7.8)	1	8.5 (1.2 - 16.3)	3.8 (-4.9 - 13.3)	1
iRAmax	9.2 (±33.3)	-8.6 (±23.0)	0.21	-6.0 (±16.1)	-5.1 (±10.7)	1	0.1 (±25.5)	-13.5 (±21.6)	0.27
iRAmin	-6.6 (±32.6)	-13.6 (±31.4)	1	-2.2 (±14.0)	-7.6 (±14.5)	0.9	-14.5 (±25.2)	-23.2 (±22.8)	0.84
RAEF	15.1 (7.7 - 22.9)	25.2 (13.0 - 32.3)	1	-0.18 (-3.6 - 14.9)	1.2 (-12.3 - 10.3)	1	21.2 (15.1 - 26.0)	23.5 (5.4 - 37.3)	1
iLVEDV	8.5 (±11.6)	5.4 (±12.6)	1	2.7 (±10.2)	-1.7 (±12.1)	0.75	13.1 (±9.2)	4.4 (±12.9)	0.06
iLVESV	2.3 (±9.0)	-2.1 (±6.5)	0.27	-2.2 (±8.3)	-1.5 (±4.7)	1	-0.4 (±5.4)	-4.4 (±9.2)	0.27
LVEF	2.4 (±8.4)	6.4 (±8.7)	0.45	1.6 (±10.2)	1.3 (±4.6)	1	6.0 (±10.9)	6.5 (±10.8)	1
iRVEDV	9.4 (11.9)	-0.5 (±12.6)	0.06	1.3 (±23.2)	4.0 (±16.3)	1	12.3 (±18.4)	4.3 (±18.3)	0.51
iRVESV	-0.6 (±6.0)	-3.2 (±8.9)	0.9	5.8 (±13.1)	2.5 (±7.1)	1	4.4 (±13.2)	-1.1 (±9.4)	0.42
RVEF	7.8 (±13.5)	5.2 (±8.8)	1	-0.1 (±6.4)	-1.0 (±4.8)	1	9.2 (±14.3)	4.4 (±7.5)	0.57

4.4.5 Procedural success subgroup analysis - SR versus AF recurrence

The difference in change of all parameters throughout the follow-up period was also analysed and compared between patients who maintained SR or had an AF recurrence post ablation (Table 4.4). LAEF [12.0 (2.9, 18.9) vs. -1.3 (-6.4, 7.5); p=0.03] showed improvement in the SR group at 9 months, whilst RAEF showed a trend towards improvement at 9 months [26.2 (18.9, 38.3) vs. 10 (0.6, 24.2); p=0.09). LVEF increased in the SR group, but conversely decreased in the AF recurrence group [9.8 (±8.5) vs. -0.3 (±11.5); p=0.006]. There were no differences in change in any of the other parameters at any of the time points between the 2 groups.

4.4.6 Ablation modality subgroup analysis - Catheter versus surgical ablation

Patients were also analysed as per their ablation modality. There were no differences in change in any of the parameters at any of the time points between the 2 groups (Table 4.5).

4.4.7 Atrial Volume and drug therapy

Cardiovascular drugs such as angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and diuretics can affect atrial remodelling, loading conditions and atrial chamber volume respectively.[154] The effects of these drugs were investigated by analysing those treated and not treated with these drugs throughout the study period, with respect to change in biatrial volume between baseline and at 9 months follow-up. The reduction in LAmax volume in patients treated with either ACEI/ARB or diuretic therapy was compared with those without, was [13.0 ± 15.5 vs. 9.7 ± 12.0; p=0.48] and [17.5 ± 18.1 vs. 9.7 ± 12.3; p=0.12], respectively. The reduction in RAmax volume in patients treated with either ACEI/ARB or diuretic therapy compared with those without was [0.8 ± 28.7 vs. 8.6 ± 22.2;

p=0.36] and [2.8 ± 26.6 vs. 13.5 ± 17.2; p=0.22], respectively. Therefore, the use of ACEI/ARB and diuretic therapy did not have any significant impact in the reduction in LA and RA volumes in our population.

4.4.8 Clinical predictors of LA reverse remodelling and of SR maintenance

Univariable and subsequent multivariable logistic regression analysis were performed to determine the clinical predictors of LA reverse remodelling. The results are shown in Table 4.6 and 4.7. The univariable analysis showed age and baseline LAmax to be associated with LA reverse remodelling. At multivariable analysis, the only independent predictor of LA reverse remodelling was baseline LAmax [1.08 (1.02-1.16); p=0.01]. For clinical success of the ablation procedure, univariable analysis showed age, CHA2DS2-VASc and baseline LVEF to be significant but at multivariable analysis, there were no independent predictors.

Table 4.6 Univariable and multivariable logistic regression analysis for predictors of LA reverse remodelling

	Univariable analysis		**Multivariable analysis**	
	OR (95% CI)	**p - value**	**OR (95 CI)**	**p - value**
Age	1.09 (1.00-1.18)	0.04	1.07 (0.96-1.21)	0.24
Sex - Male	0.89 (0.23-3.38)	0.86		
AF duration (> 24 months)	1.35 (0.36-5.08)	0.66		
LAmax	1.08 (1.03-1.14)	0.003	1.08 (1.02-1.16)	0.01
Hypertension	2.29 (0.63-8.32)	0.21	1.03 (0.14-7.33)	0.98
CHA2DS2-VASc	5.06 (1.16-22.06)	0.03	1.00 (0.51-2.03)	0.99
LVEF	1.02 (0.96-1.09)	0.50		
Surgery	0.47 (0.13-1.61)	0.23	0.44 (0.08-2.13)	0.31

Table 4.7 Univariable and multivariable logistic regression analysis for predictors of clinical success of ablation procedure (SR maintenance)

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age	0.97 (0.91-1.03)	0.32		
Sex - Male	2.83 (0.82-9.76)	0.10	1.76 (0.45-6.90)	0.42
AF duration (> 24 months)	0.99 (0.94-1.03)	0.56		
LAmax	0.98 (0.94-1.02)	0.26		
RAmax	0.99 (0.97-1.02)	0.82		
Hypertension	0.58 (0.17-2.08)	0.41		
CHA2DS2-VASc	0.72 (0.49-1.05)	0.09	0.74 (0.48-1.13)	0.16
LVEF	0.93 (0.87-0.99)	0.04	0.93 (0.87-1.00)	0.06

4.5 Discussion

This study is the first prospective CMR study demonstrating significant and progressive LA (and RA) reverse remodelling, with improvement in biventricular ejection fraction in medium-term follow-up of post ablation LSPAF patients. In addition, this is the first cardiac remodelling study to include both catheter and thoracoscopic surgical ablation treatment modalities. The results are striking, as they corroborate the previously observed phenomenon of post-ablation LA reverse remodelling, seen predominantly in paroxysmal AF patients, but now importantly, this extends to LSPAF patients. This challenges the widely held notion that the progressive structural remodelling that occurs in LSPAF is irreversible. Furthermore, our data shows that the reverse remodelling group had a significantly higher proportion of AF recurrences (p=0.04) showing that complete ablation success is not a prerequisite for LA reverse remodelling.

The clinical implications of these findings are crucial as they suggest that even though it may be difficult to maintain SR long-term post ablation, the anatomical changes that occur in LSPAF can be reversed irrespective of clinical outcome. This may reflect the fact that even in patients with AF recurrences, the overall net reduction in AF burden as a result of ablation facilitates reverse remodelling, although this study does not specifically explore this relationship (reduction in AF burden with regards to reverse remodelling). In this study, baseline LA (and RA) atrial volumes were not predictive of clinical success, which is interesting given that LA size has been previously shown to be an important predictor.[140] Perhaps atrial volume (as opposed to antero-postero LA diameter on M mode echocardiography) is not as clinically important although the more likely explanation is that perhaps different geometric types of dilatation, (for example anteropostero vs. longitudinal dilatation), may predispose to different clinical outcomes. Further studies are needed to examine this aspect of remodelling in more detail.

In the overall study population, there was significant change between baseline and 9 months in LAmax, LAmin and RAmin, demonstrating biatrial reverse remodelling (albeit more pronounced in the LA volumes as both maximum and minimum volumes decreased), as well as improvement in biatrial emptying fractions. Importantly, biventricular ejection fractions also improved significantly between baseline and 9 months, accompanied, somewhat counter-intuitively, by an increase in biventricular EDV, although this increase may simply reflect increased atrial contribution to ventricular filling, post ablation. Sub-group analysis showed those who maintained SR demonstrated significant improvement in LA emptying fraction and LV ejection fraction.

The lesions sets for both catheter and surgical ablation were extensive, in keeping with the challenging substrate posed by these LSPAF patients. Interestingly, however, the modality of ablation had no impact on any of the atrial or ventricular parameters measured. This suggests that it is the extent, integrity and outcome of the ablation lesions sets that facilitates the cardiac remodelling, rather than whether the lesions were epicardial or endocardial. It has been previously postulated that LA volume reduction can be as a consequence of post ablation contraction due to scarring, however, this is refuted to some extent by our data showing remote RA volume reduction in patients who have only had LA ablation.[144] As previously mentioned, subgroup analysis also showed that LA reverse remodelling is not limited to those with procedural success, but also occurs in those who have documented AF recurrence.[143-145] This is likely to reflect the reduction in AF burden post ablation in both groups of patients, taking into account the fact that even those patients deemed to have complete procedural success are still likely to have a degree of asymptomatic, undetected AF. Maintained SR does, however, confer an improvement in LAEF and importantly LVEF.

The other important aspect of this study is the use of CMR, which is deemed to be the gold standard of cardiac chamber volume and function quantification.[141-145] Previous cardiac remodelling studies have relied upon echocardiography as the predominant imaging tool used, and although echocardiography is commonly used in clinical practice, it has limitations. These include the fact that image quality is very operator dependent and often suboptimal in those with poor acoustic windows (e.g. patients with raised body mass index and chronic obstructive pulmonary disease). For example, Natale et al. have shown that severely dilated LA in non-paroxysmal AF exhibit reverse remodelling after catheter ablation, using simply LA diameter on 2D-TTE.[155] However, our data clearly highlights the fact that LA diameter correlates poorly to MRI assessment of LA volume ($r=0.35$, $p=0.02$) (Figure 4.3) whilst other

studies have shown that echocardiography underestimates LA size as compared with computed tomography and CMR.[156]

Another advantage of CMR is the high interstudy reproducibility due to the fact it is not significantly operator dependent, unlike in echocardiography. This is particularly relevant to this study as chamber measurements were compared longitudinally. [157 158]

Finally our study has demonstrated that baseline LAmax is an independent predictor of LA reverse remodelling. The odds ratio (1.08) suggests the higher the baseline LAmax volume, the more chance of reverse remodelling, in keeping with data from Fredersdorf et al.[159] This challenges the notion of irreversibility of structural changes associated with LSPAF, and suggests that it is indeed possible for those with LSPAF and significantly enlarged atria to reverse remodel in the context of ablation treatments.

4.5.1 Limitations

One of the unique aspects, and perhaps a limitation, of the study is that baseline CMR scans were conducted with patients in AF, typical of LSPAF patients. These patients were not electrically cardioverted immediately before CMR scans as these patients often fail to restore and maintain SR long enough to conduct these CMR scans, and because this does not reflect real world clinical practice. Imaging the atria in AF is technically challenging and poses challenges with regards to image quality. However, in addition to optimising ventricular rate control prior to the scan, technical adjustments to exclude heart beats that lie outside the main average range of R-R interval were used for image acquisition to improve image quality in some patients. Retrospective imaging was typically used with the exception of some patients with faster heart rates where prospective imaging was utilised. The last limitation is with regards to the definition of LA reverse remodelling and the regression analyses. There is

no formal evidence base on which to base this 'cut off' figure. In the absence of a consensus figure, the ≥ 15% decrease was chosen in line with previously published studies. Clearly a higher or lower cutoff would have an impact on the results in this study. [160] [161] The regression model presented above should be treated with caution, as it incorporates the baseline LAmax volume as well as the fact that LAmax defines reverse remodeling. [162] One probable approach to solve this is to use an instrumental variable. However, the fact that this model is underpowered using the methodology of Demidenko means that this approach is impractical. [162] [163]

4.6 Conclusion

CMR imaging shows that ablation therapy in LSPAF, irrespective of clinical outcome, results in favourable LA (and RA) reverse remodelling and improvement in biventricular ejection fractions. LAmax volume at baseline is an important predictor of LA reverse remodelling. This provides important evidence that the structural changes that accompany LSPAF are not irreversible, and that an interventional approach in these patients should be considered.

Acknowledgements

The above work has been presented in modified format as an abstract as listed below:

Abstract

Preliminary results accepted as an abstract (poster presentation) at the ECAS 9th Annual Congresss, April 2013, Paris, France.

Left Atrial Ablation & its Impact on Left Atrial Remodelling and Cardiac Function in LSPAF. Haldar S, Nyktari E, Panikker S, Jones D, Jarman J, Keegan J, Wage R, Hussain W, Markides V, Mohiaddin R, Wong T. J Interv Card Electrophysiology 2013; 36: S89 (Abstract 15).

Chapter 5

The impact of using contact force technology during catheter ablation of atrial fibrillation

5.1 Abstract

5.1.1 Introduction

Pulmonary vein reconnection after pulmonary vein isolation (PVI) is one of the key weaknesses of contemporary of atrial fibrillation (AF) ablation procedures. The acute reconnection of pulmonary vein (PV) is a common occurrence post PVI, and has been demonstrated to be a negative predictor of long-term success in AF ablation. This has driven the quest to improve the durability and longevity of radiofrequency (RF) lesions and has resulted in ongoing advances in the tools used by electrophysiologists. Recently a new generation of catheters has emerged with inbuilt contact force (CF) sensing technology, enabling real-time catheter tip-to-tissue CF analysis during ablation. It was postulated that the use of CF technology might improve the efficacy of PVI by reducing acute PV reconnection rates.

5.1.2 Methods

Forty patients with symptomatic AF were sequentially recruited and divided into two groups – first ‘unblinded’ and then ‘blinded’. Twenty patients in each group underwent PVI using an irrigated tip catheter providing real-time analysis of catheter tip-to tissue CF. RF energy was applied at 30W with a temperature limit of 48°C. The operator was only blinded to the CF sensor values in the blinded group. After PVI confirmation, exit and entrance block were re-tested after 1 hour, including the use of intravenous adenosine challenge to awaken any

dormant PV sleeve connections.

5.1.3 Results

Acute electrical isolation was successfully achieved in all 80 PVs (100%) in each group of 20 patients (age 62±13 yrs, 26 male). Baseline characteristics (no statistical difference) and the type of AF (35% paroxysmal, 65% persistent) were well matched between the two groups. In the blinded group, acute PV reconnection rates were significantly higher than in the unblinded group: 17/80 (21%) vs. 3/80 (4%); p=0.001 respectively. Blinding the operator resulted in lower mean CF overall (11.6g (10.5,12.9g) vs. 14.4g (13.3,15.7g); p=0.002). Regions where the CF applied was lower than others, correlated to regions that were most prone to reconnection, i.e. the ridge between the left atrial appendage (LAA) and the left upper PV, and at the right carina.

5.1.4 Conclusion

This prospective, non-randomised clinical study demonstrated that the use of real time CF data during PVI significantly lowers acute PV reconnection rates. Furthermore, CF technology identified low CF regions which correlated with reconnection areas. The use of this technology may translate into superior long-term success rates from AF ablation, although clearly formal long-term data in larger studies are required to verify this.

5.2 Introduction

In 1998, Haissaguerre's seminal paper reported that ectopic activity from pulmonary vein (PV) foci played a significant role in the initiation of AF.[13] Subsequent catheter ablation strategies to electrically isolate the PVs, thereby eliminating the triggering of AF, have been developed and used to treat AF effectively. The last decade has seen PVI become the foundation of all contemporary catheter ablation procedures for AF, and has rapidly evolved into a safe and increasingly efficacious procedure. [26]

However, the one crucial limitation of catheter ablation is the recurrence of atrial arrhythmias. This is, in part, related to the recovery of conduction in previously ablated tissue, resulting in the electrical reconnection of the PVs.[15 88 164] Studies have shown that acute electrical reconnection rates of PVs after PVI (i.e. within 60 mins), range from 33% to as high as 93%, whilst longer-term reconnection rates (4 months post-PVI) have been shown to be 80%.[165 166] Furthermore, there is data to support the hypothesis that elimination of acute PV reconnections may improve long-term success rates. [167 168] Therefore, strategies that seek to create more effective radiofrequency (RF) lesions from the outset (both transmural and permanent), are desirable in the quest to improve both acute and long-term success rates.

As the adoption and application of catheter ablation for AF has increased over the last decade, so the associated technologies have evolved and improved in tandem. For example, irrigated-tip catheters are now the tool of choice in AF ablation, as these catheters allow the use of increased power outputs to increase lesion size and depth, although this is at the cost of accurate catheter tip temperature monitoring. With regards to the size and volume of RF lesions formed during ablation, there are several factors that collectively interact to influence the resultant lesion during ablation. These include the duration and power of RF application,

the size and temperature of the electrode, catheter tip irrigation, the surrounding local blood flow and finally the contact and stability at the catheter tip-tissue interface.[169]

From this list, the contact force (CF) between the catheter tip and tissue seems intuitively to be a vital parameter to monitor during catheter ablation, but until now it has not been possible to measure it directly.[169 170] Historically, the CF has always been gauged subjectively by the operator using indirect methods such as tactile feedback from catheter, X-ray position of the catheter tip, and continuous monitoring of changes in intracardiac electrograms and impedance.[169 170] However, it is important to note that these surrogate methods have not been validated, and as such their accuracy remains uncertain with some postulating that they in fact correlate poorly with contact force.[171 172]

This has driven the development of a novel CF sensing technology for use in catheter ablation. These special catheters can measure the CF between the catheter tip and the target myocardium via a unique sensor located at the distal tip of an irrigated RF catheter (ThermoCool® SmartTouch™, Biosense Webster, USA). Pre-clinical data in animal studies using CF technology has demonstrated that CF is directly related to the size of RF ablation lesions created, and that its use can reduce the incidence of steam pops and thrombus formation, with subsequent data verifying its safety in humans.[170 172 173] From the clinical perspective, real time CF information has a number of potential benefits. It could unmask known hotspots of poor catheter tip-tissue contact, allowing targeted ablation at these sites with appropriate levels of contact force to produce durable transmural lesions. This in turn this could reduce rates of acute electrical re-connection and potentially improve clinical outcome. This idea formed the basis of this study.

The main hypothesis was that suboptimal endocardial catheter tip contact with the

endocardium during PVI contributes to suboptimal lesion formation, and hence a greater potential for acute electrical re-connection. A further hypothesis was that areas with low CF are likely to correlate with regions of acute reconnection.

5.3 Methods

5.3.1 Study population

Forty patients consecutive patients between the ages of 18 and 80 who were referred for and due to undergo de novo AF ablation at our tertiary cardiac centre were enrolled into this prospective non-randomised study. All procedures were performed after obtaining written informed consent in accordance with local institutional guidelines at the Royal Brompton & Harefield NHS Foundation Trust (RB&HFT). An ethical review committee granted approval for the study (London-East NRES REC 11/LO/1954).

5.3.2 Clinical trial design

Patients were sequentially recruited into an 'unblinded group' and then into a 'blinded group'. Both groups consisted of twenty patients each, all of whom underwent AF ablation conducted by experienced operators at our high volume centre using the CF sensing catheter.

5.3.3 CF catheter technology

The CF sensing catheter used in this study is the SmartTouch^{TM} catheter developed by Biosense Webstar in the USA, which is designed to be fully integrated with its existing CARTO 3 electroanatomical mapping system. The catheter itself is 7.5F with a 3.5mm externally irrigated electrode, which is connected to a tiny spring in the shaft, which has 3 location sensors (Figure 5.1). The sensors measure each deformation of the spring with a resolution of

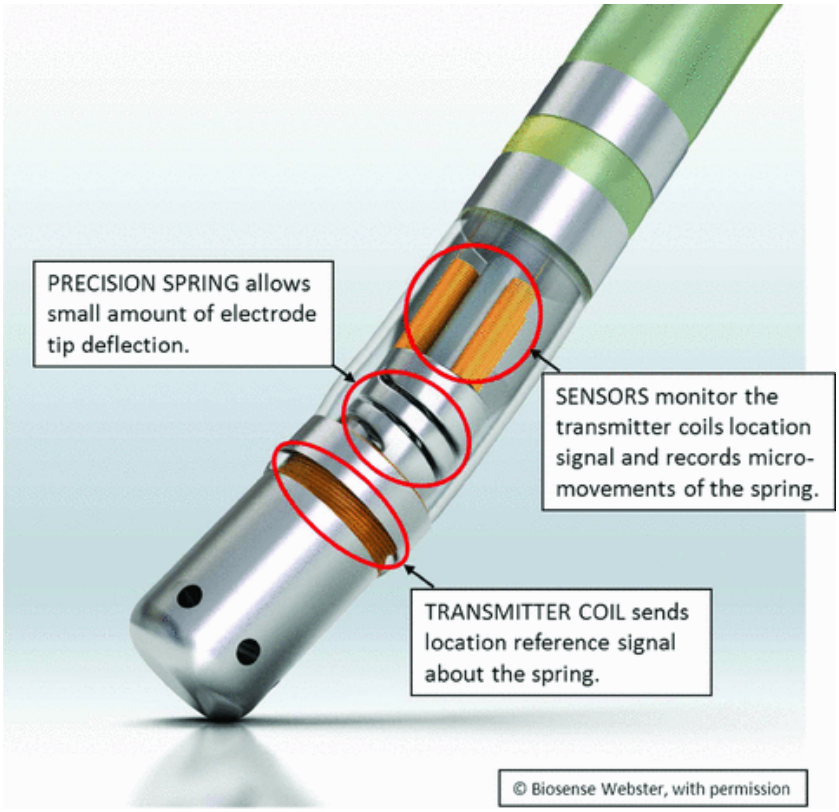


Figure 5.1 SmartTouch™ catheter (Biosense Webster, USA).

Reproduced with permission from Biosense Webster.

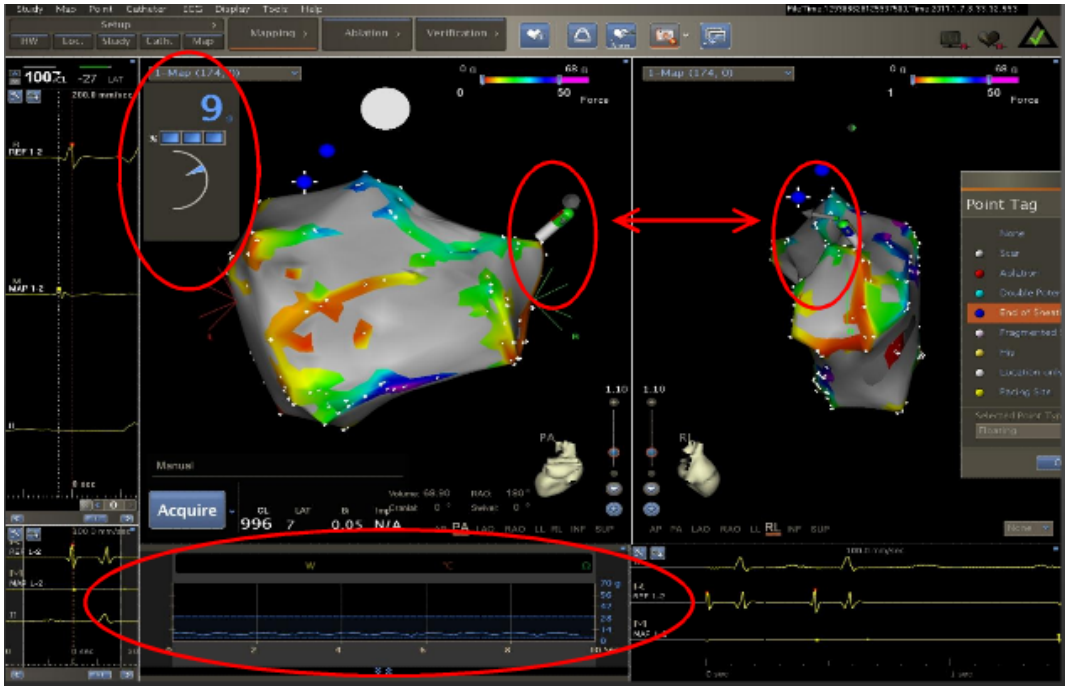


Figure 5.2 CARTO 3 SmartTouch Software Module (CARTO 3 System, Biosense Webster, USA)

This module shows graphical and numerical displays of CF and the force vector in real time. Reproduced with permission from Biosense Webstar.

1g, and transmit this information every 50ms, allowing both graphical and numerical displays of CF and the force vector in real time (Figure 5.2).

5.3.4 Catheter ablation protocol

The AF ablation procedures were conducted according to standard clinical practice guidelines in all aspects except for the use of the SmartTouch™ 4mm catheter with the accompanying SmartTouch module on the CARTO 3 electroanatomical mapping system (Biosense Webster, USA). The SmartTouch™ catheter is a modification of a commonly used existing AF ablation catheter, the EZ Steer ThermoCool® Nav, which was very familiar to the operators in the study and importantly has very similar handling characteristics. Furthermore, all of the operators in the study had extensive experience of using the SmartTouch™ catheter prior to commencement of the clinical trial.

The catheter ablation procedure was performed on uninterrupted warfarin therapy in accordance with 2012 guidelines.[26] Transoesophageal echocardiography was undertaken immediately after induction of general anaesthesia to exclude thrombus in the LAA, assess patency of the interatrial septum, delineate left atrial and PV anatomy, and thereafter to guide the trans-septal puncture alongside fluoroscopy in order to enter the left atrial (LA) chamber. Trans-septal access was then gained using a Brockenburgh needle, and two long sheaths (Preface Biosense Webster, Diamond Bar, CA, USA) were placed in the LA to allow introduction of the catheters. At this point, additional anticoagulation in the form of unfractionated heparin was given to achieve a target activated clotting time (ACT) >300 seconds, with dosing judged by the operator based on patient BMI and pre-procedural INR. The ACT was then measured at frequent intervals thereafter to ensure the target time >300

seconds was maintained. In addition, the long sheaths in the LA chamber were continuously flushed (via side-arm) trans-septal sheaths with heparinised saline at 25-50ml per hour to minimise LA thrombus formation on either the sheaths or mapping and ablation catheters.

With access to the LA secured, PV venograms were obtained to delineate PV and LA anatomy. LA geometry was collected using the CARTO 3 three-dimensional electroanatomical mapping system with a twenty pole circular mapping catheter (LASSO 2515 NAV, Biosense Webster, USA). The mapping system was able to show the force sensor value which reflected the applied CF between the catheter tip-tissue interface in real time. Each pair of ipsilateral PVs were then isolated by circumferential ablation at their antra, with additional intervenous ablation performed if necessary. RF energy was delivered at 30W and temperature limited to 48°C. The differences in the two groups were as follows. In the un-blinded group, operators were able to view the force sensor value on the 3D electroanatomical map in real time during all phases of the procedure (mapping and ablation) with the aim of applying between 10-30g of CF during ablation.[170 172]. In the blinded group, the operator was blinded to this force sensor value during the procedure, although this data was recorded for the purpose of offline analysis.

5.3.4.1 Acute PV reconnection testing protocol

One hour after wide area circumferential ablation and PVI was achieved, electrical conduction was re-assessed in two stages. First, entrance block was tested with placement of a circular catheter in each of the individual PVs to ensure electrical disconnection and then exit block (during sinus rhythm) for each PV was checked by pacing within one of the PVs showing local ipsilateral PV capture without capturing the atrium or by maximum output pacing within the PVs without capturing the atrium. The second stage was the administration of an adenosine

challenge of 12mg given intravenously for each PV in order to reveal any sites of reconnection. Adenosine is used frequently in clinical practice to assess for dormant PV conduction after PVI, due to its ability to hyperpolarise the resting membrane potential of dormant PVs. [174] If reconnection was demonstrated, further ablation was applied to achieve PVI.

5.3.4.2 Analysis of CF data

Post-procedural analysis of all 11,304 ablation points used to achieve PVI in all 40 patients was performed offline. Using CARTO 3 software (Figure 5.3) each ipsilateral pair of PV antra was divided into seven segments and the CF and Force Time Integral (FTI) data for each lesion were then analysed. FTI was defined as the integral of the CF-time curve during the ablation period in which the catheter was located within the segment of interest.

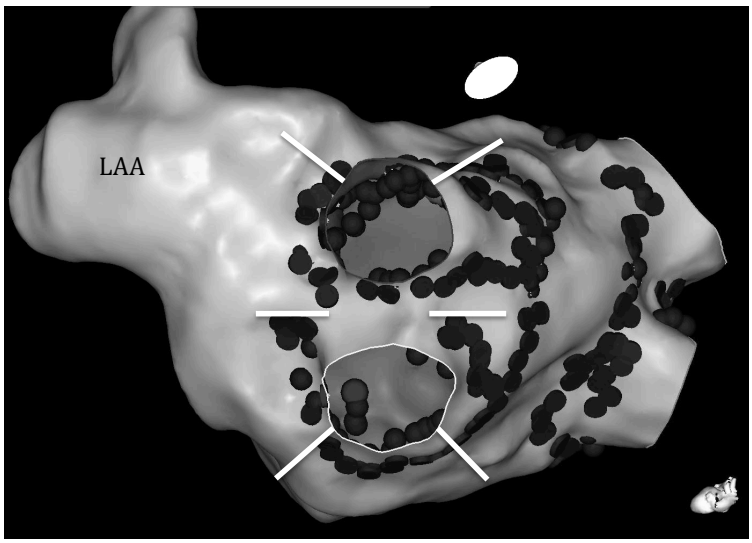


Figure 5.3 Segmentation of left pulmonary vein into 7 segments.

5.3.5 Statistical analysis

Normally distributed continuous variables were presented as mean ± SD and comparisons made using the 2-sample t-test. Categorical data were presented as proportions, and comparisons made using the chi-squared test. Skewed continuous data were presented as the median (interquartile range (IQR)) and comparisons made using the Wilcoxon rank sum test.

To determine the effect of several variables on PV reconnection, generalised linear models were used assuming gamma distribution with the logarithm as the link function. For these analyses, the ratio of the arithmetic means between pairs of groups was reported for statistical significance, full details of which are shown in Tables 5.2-5.4. For clinical applicability, these ratios, where relevant, are reported as arithmetic mean values in the text. Statistical significance was defined as $p<0.05$ and data were analysed using Stata 12 (Statacorp,Texas,USA).

5.4 Results

5.4.1 Baseline characteristics

Twenty patients were enrolled sequentially into each of the two groups, starting with the un-blinded group. The baseline characteristics for each of the two groups, un-blinded and blinded, were analysed and detailed in Table 5.1 below. There were no statistically significant differences observed.

Table 5.1 Baseline characteristics

Parameter	Un-blinded Group (n=20)	Blinded Group (n=20)	p-value
Age (y)			
Mean ± standard deviation	63 ± 14	60.7 ± 12	0.58
Sex, n (%)			
Male	15 (75)	11 (55)	0.19
Cardiovascular co-morbidities			
Coronary artery disease, n (%)	2 (10)	1 (5)	1
Heart failure, n (%)	6 (30)	2 (10)	0.24
Valvular disease, n (%)	1 (5)	0 (0)	1
Hypertension, n (%)	7 (35)	6 (30)	0.74
Dyslipidaemia, n (%)	7 (35)	10 (50)	0.34
Left atrium diameter (mm)			
Mean ± standard deviation	42 ± 8	41 ± 5	0.83
Ejection fraction (%)			
Mean ± standard deviation	57 ± 12	59 ± 10	0.56
Type of AF			
Paroxysmal, n (%)	7 (35)	7 (35)	1
Persistent, n (%)	13 (65)	13 (65)	1

5.4.2 Procedural results

The total procedure time in the un-blinded group compared with the blinded group was 209±65 vs. 207±59 mins; p=0.92. The total radiofrequency time in the un-blinded group compared with the blinded group was 3641±1233 vs. 3113±1387s; p=0.29.

5.4.3 Rates of acute PV reconnection

Twenty consecutive patients in each group underwent successful PVI for symptomatic drug-refractory AF. In both groups, all 4 PVs per patient (total n=80) were successfully electrically isolated. In the un-blinded group, acute reconnection of 3/80 PVs (4%) occurred in 3/20 patients (15%) (Figure 5.4). In the blinded group, the rate of acute reconnection was significantly higher, with reconnection occurring in 17/80 PVs (21%; p=0.001) amongst 14/20 patients (70%; p=0.001). Out of all the reconnections, 19/20 (95%) occurred spontaneously, with the use of intravenous adenosine unmasking only 1/20 of these reconnections.

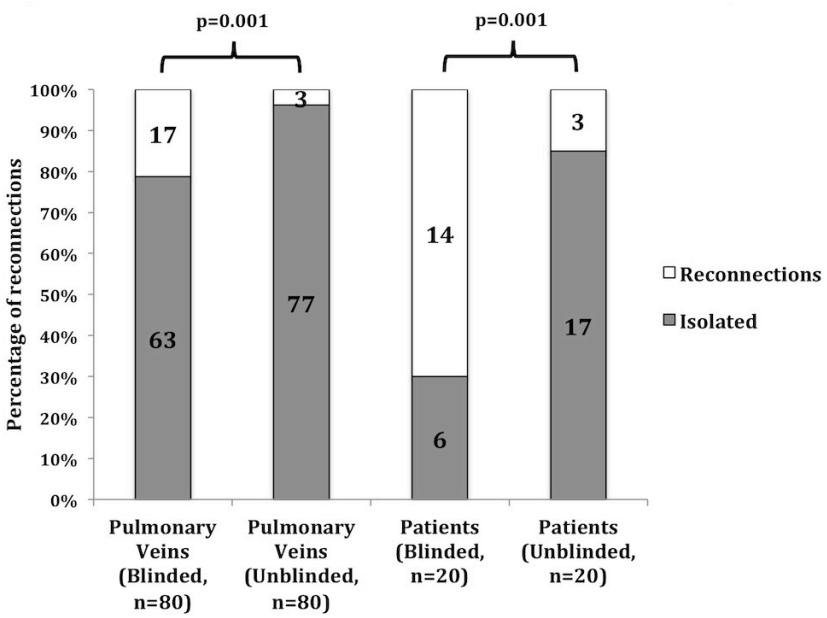


Figure 5.4 - Number of acute PV reconnections at PV at patient level

Reproduced with permission. [188]

5.4.4 Regional sites of PV reconnections

The regional distributions of all the acute PV reconnections are shown in Figures 5.5 and 5.6. As previously mentioned, the blinded group had the greatest number of acute PV reconnections. Further investigation showed that of the left PV reconnections, 7/9 (77%) were located in the left anterior-superior and left superior segments, whilst of the right PVs, the commonest segment for reconnection 3/8 (38%) was the carina (intervenous region). In both groups, the posterior wall accounted for only 4/20 (20%) of reconnections, which were all near the right PVs. In comparison, the rate of reconnections in the un-blinded group was far less at 3/20 (15%), with none located in the superior segments.

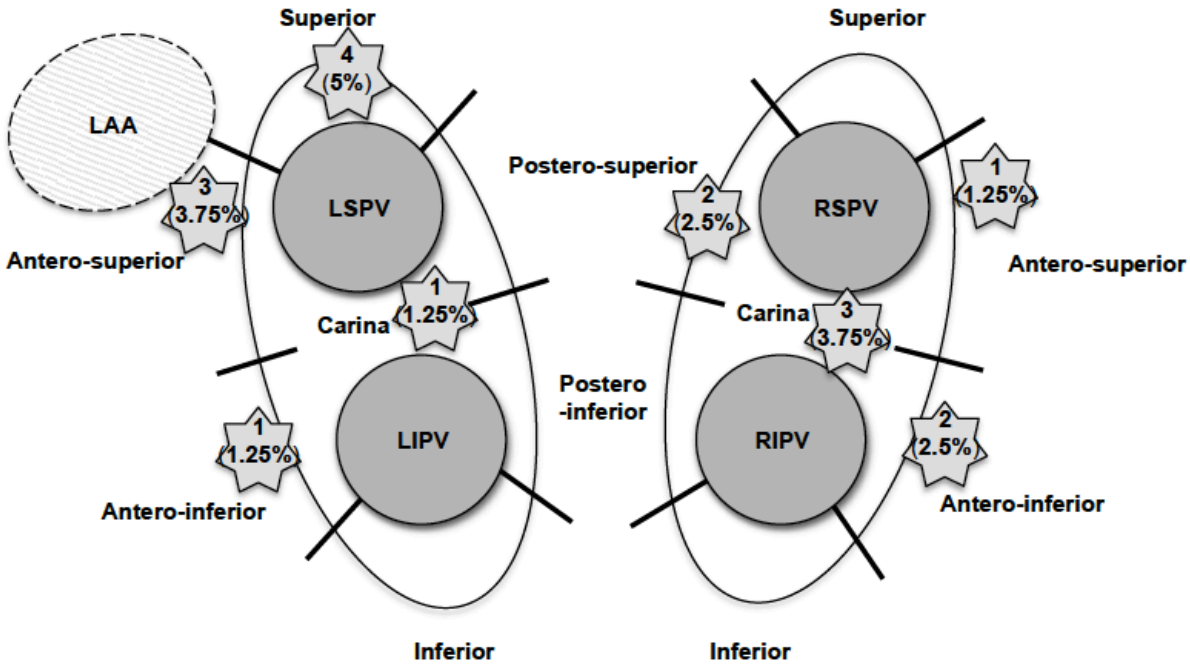


Figure 5.5 Segmented PV model showing regions of acute reconnection— blinded group.

Key: n=80, total 17 acute reconnections, 21% reconnection rate. Reproduced with permission. [188]

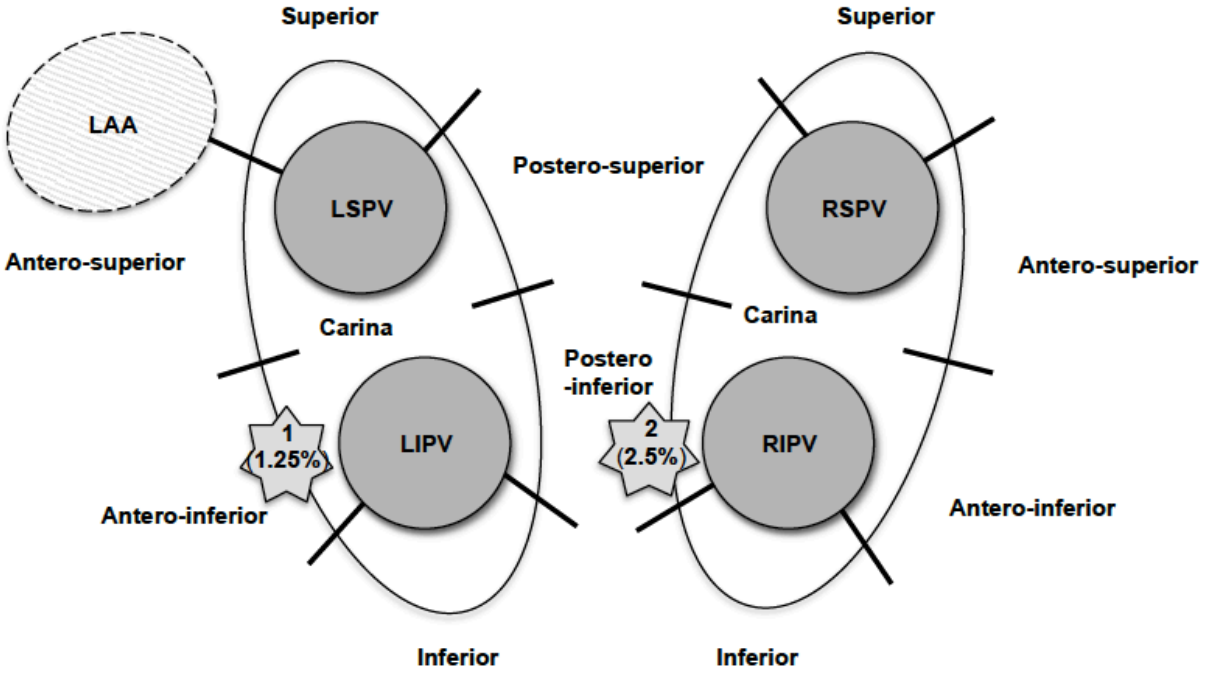


Figure 5.6 Segmented PV model showing regions of acute reconnection— un-blinded group.

Key: n=80, total 3 acute reconnections, 4% reconnection rate. Reproduced with permission [188]

5.4.5 Intergroup CF analysis (blinded vs. un-blinded) at segmental level

A comparison was then made between the two groups with regards to the ratios of the overall mean CF and overall mean total FTI. This demonstrated significant differences with the blinded group showing significantly lower overall mean CF values (11.6g (10.5,12.9g) vs. 14.4g (13.3,15.7g); p=0.002, and significantly lower overall mean total of FTI 1819g/s ((1620, 2042g/s) vs. 3055g/s (2662, 3506g/s); p<0.0001), compared with those in the un-blinded group respectively.

At segmental level, analysis of the mean CF ratio between these two groups (Table 5.2 and Figure 5.7) showed that the left antero-superior (8.7g (6.8,10.98g) vs. 12.6g (10.4,15.4g); p=0.02) and the left superior (9.5g (7.7,11.7g) vs. 14.6g (12.8,16.7); p=0.001) segments had significantly lower mean CF ratio values in the blinded group. Interestingly, these were also the two commonest areas of reconnection in the left PVs, which all occurred in the blinded

group. Similarly, on the right-sided PVs, the right carina which was the commonest site of reconnection in the blinded group showed a lower mean CF, however this did not reach statistical significance (6.4g (3.9, 10.5g) vs. 10.5g (7.6,14.6g); p=0.1).

Table 5.2 - Regions of differential mean CF between groups in segmented PV model

Segment	Mean CF ratio (CI) Grams	p-value	Blinded Group Arithmetic Mean CF (CI) Grams	Un-blinded Group Arithmetic Mean CF (CI) Grams
Left carina	0.9 (0.5-1.8)	0.8	8.2 (5.0-13.5)	8.8 (5.9-13.2)
Right carina	0.6 (0.3-1.1)	0.1	6.4 (3.8-10.6)	10.5 (7.6-14.6)
Left inferior	0.9 (0.7-1.1)	0.19	10.9 (9.0-13.1)	12.7 (11.1-14.6)
Right inferior	0.8 (0.6-1.1)	0.1	11.2 (8.4-15.0)	14.6 (13.1-16.3)
Left superior	0.7 (0.5-0.8)	0.001	9.5 (7.7-11.7)	14.6 (12.8-16.7)
Right superior	0.8 (0.6-1.1)	0.2	14.4 (11.5-18.0)	17.2 (14.6-20.3)
Left antero-inferior	1.0 (0.7-1.4)	0.92	12.1 (9.2-15.9)	12.3 (10.4-14.6)
Right antero-inferior	0.8 (0.6-1.1)	0.1	13.5 (10.6-17.3)	17.4 (14.7-20.6)
Left antero-superior	0.7 (0.5-0.9)	0.02	8.7 (6.8-11.0)	12.6 (10.4-15.4)
Right antero-superior	0.8 (0.6-1.0)	0.1	14.1 (11.5-17.4)	17.7 (15.0-21.0)
Left postero-superior	0.9 (0.7-1.2)	0.55	13.8 (12.0-15.9)	14.8 (12.4-17.7)
Right postero-superior	0.8 (0.5-1.1)	0.17	14.9 (10.6-20.9)	19.4 (16.7-22.4)
Left postero-inferior	0.9 (0.6-1.3)	0.54	12.0 (8.9-16.2)	13.4 (11.5-15.5)
Right postero-inferior	0.8 (0.6-1.1)	0.11	13.0 (10.5-16.2)	16.1 (14.0-18.5)

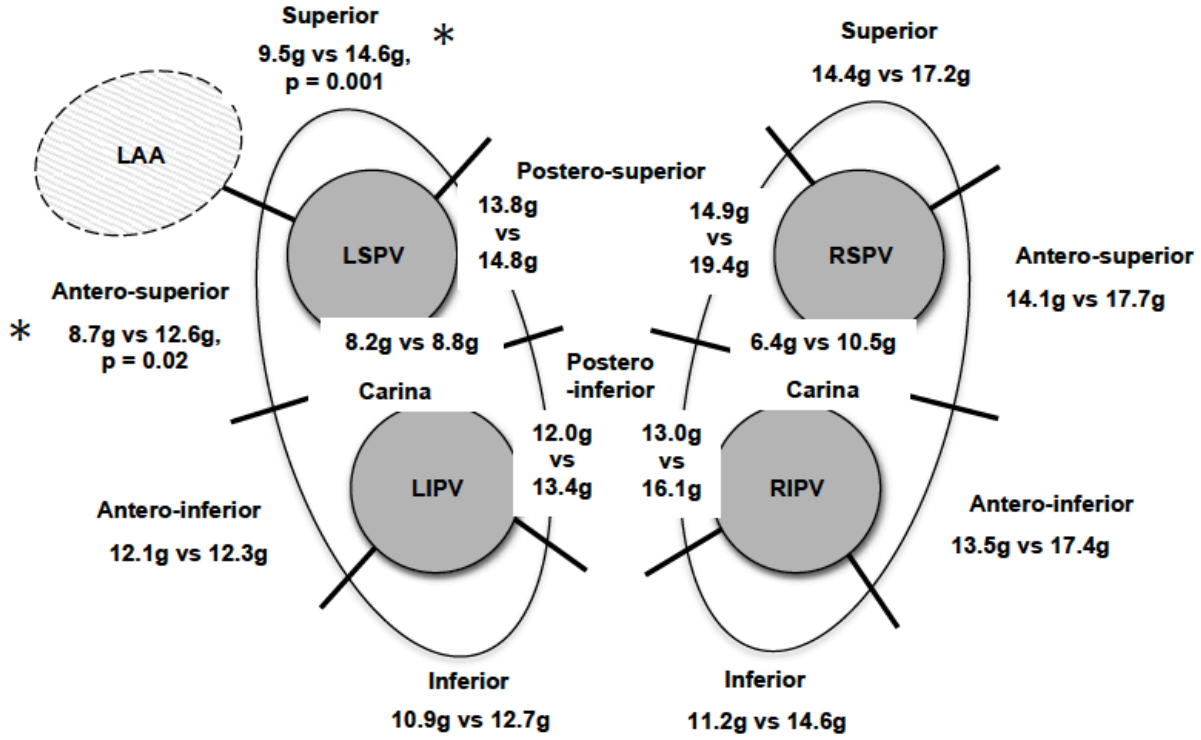


Figure 5.7 Regions of differential mean CF between groups in segmented PV model. Segments demonstrating significant difference between groups are highlighted with an asterisk.

Key: LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein. Reproduced with permission [188]

5.4.6 Intragroup mean CF analysis at segmental level

To examine the potential impact of real time CF at different regions of PVs, each segment was analysed in comparison to all other segments in each of the two groups. In the blinded group (Table 5.3*)*, three segments were found to have significantly lower mean CF when compared with all other segments: left superior segment (9.5g (7.6, 11.7g) vs. 11.8g (13.2,15.8g); p=0.04), left antero-superior segment (8.7g (6.8,11.0g) vs. 11.8g (10.6, 13.3g); p=0.02) and right carina segment (6.4g (3.8,10.6) vs. 12.0g (10.8,13.5g); p=0.02). These three segments correlated to segments with a high predilection of reconnection.

Table 5.3 - Blinded intragroup segmental mean CF analysis

	Blinded Intragroup Segmental Mean CF Analysis		
Segment	**Mean CF ratio (CI) of segment vs. all other segments Grams**	**p-value**	**Corresponding Arithmetic Mean CF values (CI) Grams**
Left carina	0.7 (0.4-1.1)	0.15	8.2 (5.0-13.6) vs. 11.9 (10.7-13.2)
Right carina	0.5 (0.3-0.9)	0.02	6.4 (3.8-10.6) vs. 12.0 (10.8-13.5)
Left inferior	0.9 (0.8-1.1)	0.43	10.8 (9.0-13.1) vs. 11.7 (10.5-13.0)
Right inferior	1.0 (0.7-1.3)	0.8	11.2 (8.4-15.0) vs. 11.6 (10.4-13.0)
Left superior	0.8 (0.6-1.0)	0.04	9.5 (7.6-11.7) vs. 11.8 (10.5-13.2)
Right superior	1.3 (1.0-1.5)	0.02	14.4 (11.5-18.0) vs. 11.4 (10.3-12.7)
Left antero-inferior	1.0 (0.8-1.4)	0.79	12.1 (9.1-16.0) vs. 11.6 (10.3-13.0)
Right antero-inferior	1.2 (0.9-1.5)	0.17	13.5 (10.5-17.3) vs. 11.5 (10.3-12.8)
Left antero-superior	0.7 (0.6-1.0)	0.02	8.7 (6.8-11.0) vs. 11.8 (10.6-13.3)
Right antero-superior	1.2 (1.1-1.5)	0.01	14.1 (11.5-17.4) vs. 11.4 (10.3-12.7)
Left postero-superior	1.2 (1.0-1.4)	0.03	13.8 (12.0-16.0) vs. 11.4 (10.2-12.8)
Right postero-superior	1.3 (0.9-1.8)	0.11	15.0 (10.6-21.0) vs. 11.4 (10.2-12.6)
Left postero-inferior	1.0 (0.8-1.4)	0.8	12.0 (8.9-16.3) vs. 11.6 (10.5-12.8)
Right postero-inferior	1.1 (0.9-1.4)	0.27	13.0 (10.4-16.2) vs. 11.5 (10.3-12.8)

Table 5.4 - Unblinded intragroup segmental mean CF analysis

	Unblinded Intragroup Segmental Mean CF Analysis		
Segment	**Mean CF ratio (CI) of segment vs. all other segments Grams**	**p-value**	**Corresponding Arithmetic Mean CF values (CI) Grams**
Left carina	0.6 (0.4-0.9)	0.01	8.8 (5.9-13.3) vs. 14.9 (13.7-16.1)
Right carina	0.7 (0.5-1.0)	0.05	10.5 (7.5-14.6) vs. 14.7 (13.5-16.0)
Left inferior	0.9 (0.8-1.0)	0.06	12.7 (11.0-14.6) vs. 14.6 (13.4-15.9)
Right inferior	1.0 (0.9-1.1)	0.78	14.6 (13.0-16.3) vs. 14.4 (13.3-15.7)
Left superior	1.0 (0.9-1.2)	0.87	14.7 (12.8-16.7) vs. 14.4 (13.2-15.8)
Right superior	1.2 (1.1-1.4)	0.01	17.2 (14.6-20.3) vs. 14.2 (13.1-15.4)
Left antero-inferior	0.8 (0.7-1.0)	0.01	12.3 (10.4-14.6) vs. 14.6 (13.5-15.8)
Right antero-inferior	1.2 (1.0-1.4)	0.02	17.4 (14.7-20.6) vs. 14.2 (13.0-15.5)
Left antero-superior	0.9 (0.7-1.1)	0.17	12.6 (10.4-15.4) vs. 14.6 (13.4-15.8)
Right antero-superior	1.2 (1.1-1.5)	0.01	17.7 (14.9-21.0) vs. 14.2 (13.1-15.4)
Left postero-superior	1.0 (0.9-1.2)	0.73	14.8 (12.4-17.7) vs. 14.4 (13.3-15.7)
Right postero-superior	1.4 (1.2-1.6)	0.001	19.4 (16.7-22.5) vs. 14.1 (12.9-15.3)
Left postero-inferior	0.9 (0.8-1.1)	0.27	13.3 (11.5-15.5) vs. 14.5 (13.3-15.8)
Right postero-inferior	1.1 (1.0-1.3)	0.08	16.1 (14.0-18.7) vs. 14.3 (13.1-15.6)

In the un-blinded group (Table 5.4), the only segment that demonstrated a significantly lower mean CF when compared to all other segments was the left antero-inferior segment (12.3g (10.4,14.6g) vs. 14.6 (13.5, 15.8g); p=0.01). In this group, this was one of only two segments to host a reconnection.

5.4.7 Regions exhibiting reconnections

The next stage of the analysis concentrated on comparison of the mean CF at segments experiencing reconnection (the blinded group accounting for the majority of these), with the

mean CF at segments which did not experience reconnection in the un-blinded group. The hypothesis for this analysis was based on the assumption that segments may have avoided reconnection via the availability and use of real time CF data. Indeed, the statistical analysis showed that at the segments that had a predilection for reconnections, the mean CF was significantly lower (14.5g (13.3,15.7g) vs. 19.6 (14.6, 26.3g); p=0.02).

5.4.8 Clinical predictors of reconnection

Univariable analysis of clinical variables did not show any statistically significant association with reconnections (Table 5.5). Multivariable analysis therefore was not indicated.

Table 5.5 Univariable analyses of clinical predictors of reconnection

	Univariable Analysis of Clinical Predictors of Reconnection		
Parameter	**Reconnection**	**Non-reconnection**	**p-value**
Age (y) Mean ± SD	63 (11)	61 (14)	0.72
Sex, n (%) Male	10/17 (59)	16/23 (70)	0.48
Cardiovascular co-morbidities			
Coronary artery disease, n (%)	2/17 (12)	1/23 (4)	0.57
Heart failure, n (%)	4/17 (24)	4/23 (17)	0.70
Valvular disease, n (%)	0/17 (0)	1/23 (4)	1.00
Hypertension, n (%)	5/17 (30)	8/23 (35)	0.72
Dyslipidaemia, n (%)	8/17 (47)	9/23 (39)	0.62
Left atrium diameter (mm) Mean ± SD	42 (41-44)	43 (39-49)	0.67
Ejection fraction (%) Mean ± SD	57 (13)	59 (9)	0.52
Type of AF Persistent, n (%)	12/17 (71)	14/23 (61)	0.52

5.4.9 Procedural complications

The only peri-procedural complication sustained in either group was that of a one femoral pseudoaneurysm in the un-blinded group which was managed conservatively with a thrombin injection and which resolved clinically without long-term sequelae.

5.5 Discussion

The key findings of this study examining the impact of contact force sensing during PVI were as follows:

(1) The use of real time CF data during PVI resulted in very low rates of acute PV reconnection. Acute PV reconnection rates were statistically much lower than that observed when the operator was blinded to the CF data.

(2) The resultant effect of blinding the operator were that of significantly lower values of mean CF overall.

(3) Finally, the segments in the blinded group where mean CF was significantly lower than at other segments, or significantly lower than in the un-blinded group, correlated to the commonest sites of reconnection.

5.5.1 Importance of PVs in AF

The PVs are known to play a critical role in the pathophysiology of AF. PV ectopics are implicated in the mechanisms of both paroxysmal and persistent AF. Mechanistically, in paroxysmal AF the PVs are predominantly a trigger for AF, whilst in persistent forms it may act as a rapid driver that sustains the arrhythmia, alongside several other postulated mechanisms. [13 175 176] It is, therefore, unsurprising that after Haissaguerre's seminal paper, PVI

subsequently became the cornerstone of catheter ablation therapy of AF, and is deemed an effective form of therapy for those with drug-refractory paroxysmal AF or as part of a more extensive ablation strategy in persistent forms of AF. [26]

5.5.2 Relevance of acute PV reconnection

PVI, however, has an Achilles' heel. This is the reconnection of previously ablated and isolated PVs. Following successful PVI, patients who experience a recurrence of AF or atrial tachycardia have a very high likelihood of PV reconnection, with previously published data documenting this figure to be over 80%.[15 88 164] What is interesting is that the converse is found amongst patients who do not experience a recurrence of atrial tachyarrhythmia following PVI i.e. the rate of PV reconnection found on re-studying the LA is much lower at 19-32%. This is highly suggestive of the fact that PV reconnection plays an important mechanistic role in these recurrences. [86 177]

The published rates of acute electrical reconnection within 60 minutes of PVI range widely from 33% to as high as 93%. [165 166 178] Unsurprisingly, the higher figure of above 90% rate of acute PV reconnection is found in a study with a waiting time of 60 minutes.[165] Importantly, the early recurrence of AF has been demonstrated to predict recurrences at a later date, and overall is associated with lower long-term success rates of catheter ablation.[179-181] However, there is data supporting the aggressive identification and re-isolation of acute reconnected PVs which translates into higher long-term success rates.[167 168] Thus, technologies such as CF sensing catheters, which can reduce the rate of acute PV reconnection, may have the potential to improve long-term procedural success rates.

5.5.3 Mechanisms of acute PV reconnection

PV reconnection is thought to occur at sites post-ablation where there is non-transmural and non-permanent myocardial tissue damage. There is histologic and ultrasound data supporting the concept that this is caused by reversible tissue oedema, which in itself is due to poor stability and contact between catheter tip-myocardial tissue during ablation.[182 183] To avoid the potential for reversibility of PV electrical isolation, it is of paramount importance to achieve optimal RF lesions at the first sitting. This requires stable and appropriate levels of contact force between catheter tip-myocardial tissue to result in permanent myocardial tissue damage. The use of real time CF data during RF ablation may in part help to achieve this goal.

The findings from this study show that significantly lower rates of PV reconnection can be achieved with the use of CF data during ablation. Furthermore, areas of reconnection are associated with lower CF values in the blinded group. These observations are in keeping with our original hypothesis that inadequate endocardial contact during PVI contributes to suboptimal lesion formation and hence a greater potential for acute electrical reconnection.

5.5.4 Acute PV reconnection sites

In this study, the majority of the reconnections occurred in the blinded group. In the left PVs reconnections occurred in the left superior and left antero-superior segments which correlate with the region of the PV-LAA ridge, whilst the carina (intervenous ridge) was the commonest region of right PV reconnections. The posterior wall accounted for a smaller proportion of all reconnections in both groups and it is interesting to note that none of the reconnections in the un-blinded group occurred in the superior segments. This latter point perhaps confirms the fact that operators make a concerted effort to make their ablation lesions more effective

(optimal FTI) at these known 'hotspots' of reconnection.

Overall this data correlates well with previously published data, demonstrating that the PV-LAA ridge and the right carina (intervenous ridge) are the key sites which have a predilection for acute reconnection after PVI.[166] As these regions are known to have a propensity to reconnection, it may be postulated that the availability of real time CF data is helpful to the operator with regards to achieving durable lesions.[166]

5.5.5 Other CF technologies

There are currently two other tools available commercially to measure CF on different platforms. The TactiCath™ Quartz ablation catheter (Endosense, SA) uses proprietary fibre optic sensor technology mounted on a 3.5mm open irrigated-tip ablation catheter, which has a 75 or 65mm deflectable curve. The CF measurements created by deformation of the optical fibres in the tip of the catheter are analysed on a dedicated separate workstation, and the need for such hardware is its main drawback. The sensitivity is less than 1g, which is similar to that of the SmartTouch™ catheter. The TactiCath catheter has a wealth of clinical data demonstrating its safety and efficacy in human subjects.[173 184 185]

IntelliSense® (Hansen Medical Inc., Mount View CA, US), uses a robotic catheter navigation module, incorporating a system-based force sensing technology, and is described in the first follow-on study [Section 5.6]. It comprises an inner and outer sheath, each containing a system of pull wires enabling deflection of the sheaths. A conventional ablation catheter is passed through the inner sheath and the Intellisense CF system pulses the catheter proximally at 4Hz and extrapolates the distal catheter CF by the resistance to catheter movement. This provides visual and vibration feedbacks to the operator, and also has published data of its successful usage in human paroxysmal AF.[185 186] The main practical limitation of the

IntelliSense technology is that it can only be used as part of the robot system. The SmartTouch™ system has several advantages over the alternative technologies available. Firstly, the CF data is directly integrated into the Carto 3 workstation without the requirement of additional hardware. Secondly, the ability to visualise the force vector with other essential information such as the catheter position within the 3D anatomical map and the real time CF values, on one screen, is invaluable to the operator in assimilating lots of information in a timely manner.

5.5.6 Limitations

This study has several limitations. As a non-randomised study there may be unmeasured systematic differences between patient groups, although no differences were detected between the demographics of the two groups (Table 5.1). There is a theoretical possibility that during the study the operators became more adept at handling the catheter and in performing PVI during the initial un-blinded phase. If this were the case, the increased rate of reconnection observed when subsequently blinded would only underestimate the benefits of the CF catheter. Furthermore, all operators were very experienced and the SmartTouch™ catheter was similar in handling to a previous generation of catheter used widely by these electrophysiologists. The small sample size potentially limits the power to detect differences between groups, although statistically meaningful differences were still observed with these small numbers, suggesting that CF technology conferred a genuine and substantial effect. Finally, the study was limited to observing the impact of this technology on short-term acute PV reconnection rates. Although it may be extrapolated that these findings are likely to impact upon the long-term clinical outcomes, these data cannot confirm or refute this.

5.6 Follow-on Study 1 – Comparison of Robotic and Manual Persistent AF Ablation using Contact Force

5.6.1 Introduction

Following on from this study, prospective registry data was collected on the use of robotic and manual ablation for de novo persistent AF patients using CF technology. The key objective of this study was to compare remote robotic navigation (RRN) CF ablation with Manual CF ablation. The secondary objective was to compare the use of CF with non-CF ablation for both navigation modes.

5.6.2 Methods

Prospective registries of consecutive cases undergoing de novo ablation for persistent AF from six centres in the UK and South Africa were included for analysis. The Royal Brompton & Harefield NHS Foundation Trust (RB&HFT) was one of the centres that contributed data to this international multi-centre registry study. Study data from this chapter were included as was additional data from the trust. In total 50 Manual/CF and 50 RRN/CF cases were included. For the control arms, historical non-CF ablation patients were matched by propensity score to give a total patient cohort of 200. In addition to CF data, total procedure time, time taken to complete right and left PVI, fluoroscopy time, fluoroscopy dose and rhythm outcome data was collected.

5.6.3 Results

There were no significant differences in the baseline characteristics of the patients in the four groups. The combination of RRN/CF demonstrated superior single procedure 12-month success rates (64% vs. 36%, $p=0.01$) and shorter fluoroscopy times (41% reduction, $p<0.0005$)

than compared with Manual/CF ablation, although there was no difference in procedure times (p=0.8). Mean CF values were higher in the RRN/CF group than in the Manual/CF group (16 (15-18g) vs. 13 (12-15g) respectively, p=0.003). The use of CF technology conferred higher 12-month success rates for RRN when compared with control (historical) non-CF cases (64% vs. 36%, p=0.01) but this was not the case with Manual ablation (36% vs. 38%, p=1). CF cases demonstrated shorter procedural times (20%, p<0.005 for both ablation modalities), and fluoroscopy times (Manual: 43%, RRN 83%, p<0.005 for both). Complication rates were similar between all groups (p>0.5).

5.6.4 Conclusion

This multi-centre registry study of persistent AF ablation suggests that combined RRN and CF can achieve superior success rates at one year and reduced fluoroscopy times, as compared with compared with Manual ablation and non-CF RRN ablation. Further evaluation of this technique in a randomised control trial would be recommended.

5.7 Follow-on Study 2 – Medium Term Outcome for AF ablation using Contact Force Technology

5.7.1 Introduction

The index study detailed in this chapter had shown that CF technology improved acute PV isolation rates. However, its impact upon longer-term clinical outcome remains unknown. The key objective of this study was to assess the impact of CF on freedom from atrial tachyarrhythmia in medium term follow-up. The secondary objective was to assess the impact of CF on fluoroscopy time.

5.7.2 Methods

Registry data of de novo AF ablation procedures utilising CF technology, conducted at four UK centres, were matched 1:2 to non-CF controls by classification of AF (paroxysmal, persistent, long-standing persistent). The RB&HFT was one of the centres that contributed data to this national multi-centre case-control study, including study data from this chapter. In addition to the use of CF technology, nineteen other potential predictors of outcome were analysed.

5.7.3 Results

In total, six hundred de novo AF ablation cases (two hundred CF cases and four hundred non-CF cases) were analysed of which 46% were paroxysmal, 36% persistent, and 18% long-standing persistent. The mean follow up duration was 11.4 ± 4.7 months - paroxysmal AF CF 11.2 ± 4.1 CF vs. 11.3 ± 3.9 paroxysmal AF non-CF (p=0.745) - non-paroxysmal AF CF 10.4 ± 4.5 CF vs. 11.9 ± 5.4 non-paroxysmal AF non-CF (p=0.015). CF technology independently predicted clinical success in the ablation of paroxysmal AF (HR 2.24 (95% CIs 1.29-3.90); p=0.004), however, it did not predict clinical success in the ablation of non-paroxysmal AF (HR

0.73 (0.41-1.30); p=0.289) in a detailed multivariate analysis, which included duration of follow-up. The use of CF technology also demonstrated reduced fluoroscopy time in multivariate analysis (reduction by 7.7 (5.0-10.5) minutes; p<0.001). There were no differences in complication rates between groups (p=0.163).

5.7.4 Conclusion

This large registry based study has interestingly shown that CF technology is associated with a superior medium term clinical outcome in only de novo paroxysmal AF. CF technology was also shown to reduces fluoroscopy times when compared to non-CF technology in all classifications of AF.

5.8 Overall conclusion

The main study demonstrated a significantly lower acute PV reconnection rate with the use of real time contact force information during PVI compared to the rate in a control group, which was blinded to real time CF information. This difference may be due to improved index lesion formation resulting in permanent myocyte injury, particularly in regions prone to reconnection where operators would find the real time CF information invaluable in ensuring that good contact force was achieved. These results may have important implications if, as previous studies have shown, reduced acute PV reconnection translates into better long term clinical outcomes for patients.

The two follow-on studies also highlight that CF technology confers improved efficacy in de novo paroxysmal cases as well as when combined with RRN. In addition, CF technology reduces fluoroscopy times conferring significant safety benefits for both patients and

operators.

CF technology is still a relatively young technology but these early results have shown that it can improve both efficacy and safety of ablation procedures for AF. What is needed now is larger scale randomised clinical trials with long-term follow-up to evaluate this promising new technology robustly.

Acknowledgements

The above work has been presented in a number of abstracts and scientific papers in modified form as listed below:

Abstracts

The Use of Contact Force Data During Pulmonary Vein Isolation Translates into Improved Clinical Outcomes for Atrial Fibrillation Ablation patients.
Haldar S, Jarman J, Panikker S, Jones DG, Salukhe T, Hussain W, Markides V, Wong T.
Circulation 2012; 126:A17218.

Does the Interplay of Contact Force and Force Time Integral Impact on Acute PVI?
Haldar S, Jarman J, Panikker S, Jones DG, Salukhe T, Hussain W, Markides V, Wong T. J Interv Card Electrophysiol 2012; 33:335 (Abstract 18-50).

Papers

The main study presented in Chapter 5 - Contact Force Sensing Technology Identifies Sites of Inadequate Contact and Reduces Acute Pulmonary Vein Reconnection: A Prospective Case Control Study.
Haldar S, Jarman J, Panikker S, Jones D, Salukhe T, Gupta D, Wynn G, Hussain W, Markides V, Wong T. Int J Cardiol 2013;168:1160-1166

Follow-on study 1 - Comparison of Robotic and Manual Persistent AF Ablation Using Catheter Contact Force Sensing An International Multicenter Registry Study.
Ullah W, Hunter R, Haldar S, Mclean A, Dhinoja M, Sporton S, Earley M, Lorgat F, Wong T, Schilling. *Pacing Clin Electrophysiol* 2014; **37**:1427–1435.

Follow-on study 2 - Relationship Between Contact Force Sensing Technology and Medium Term Outcome of Atrial Fibrillation Ablation: A Multicenter Study of 600 Patients.
Jarman J, Panikker S, Das M, Wynn G, Ullah W, Kontogeorgis A, Haldar S, Patel P, Hussain W, Markides V, Gupta D, Schilling RJ, Wong T. J Cardiovasc Electrophysiol. 2014 Dec 27. doi: 10.1111/jce.12606.

Chapter 6

CASA-AF trial results

6.1 Abstract

6.1.1 Introduction

The optimal interventional management strategy for those patients with long standing persistent atrial fibrillation (LSPAF) has yet to be determined. Catheter ablation can achieve modest degrees of success, but the majority of patients require multiple procedures. Thoracoscopic surgical ablation is a relatively new technique for treating AF that has yet to be evaluated in a head-to-head prospective clinical trial in LSPAF.

6.1.2 Methods

Prospective de novo patients with LSPAF and left ventricular ejection fraction (EF) of 40% or more (on cardiac MRI) were recruited and assigned, according to patient preference, to undergo either thoracoscopic surgical ablation or catheter ablation. The primary endpoint was freedom from atrial arrhythmias after a single procedure without anti-arrhythmic drugs (AADs) within 9 months (as assessed from the end of the 3 months' blanking period to 9 months). Secondary endpoints were clinical success (defined as 75% or greater reduction of AF burden), freedom from atrial arrhythmia after multiple procedures, atrial anatomy and function following ablation as assessed by CMR, change in AF symptom score (EHRA score) and quality of life assessments (SF36). Although this was a non-randomised study, the results were analysed by intention-to-treat.

6.1.3 Results

As per intention to treat, 51 patients with an EF of 59±9% and median duration of AF of 22 months were recruited, with 26 consecutive patients undergoing thoracoscopic surgical ablation and 25 consecutive patients undergoing catheter ablation. The primary endpoint was assessed at 9 months' follow-up. Single procedure success (freedom from atrial arrhythmia) in the thoracoscopic surgical ablation arm was 81%, with multiple-procedures conferring no additional benefit to the outcome. In the catheter ablation control arm, single procedure success (freedom from atrial arrhythmia) was 44% (p=0.007), which increased with multiple-procedures to 60% (p=0.10). Major complication rates were 30% vs. 8% (p=0.04), surgical vs. catheter respectively.

6.1.4 Conclusion

This is the first prospective clinical trial comparing thoracoscopic surgical ablation with catheter ablation focusing on de novo LSPAF patients. It shows that thoracoscopic surgical ablation can be performed safely with superior single procedure efficacy, but this is tempered by a higher risk of non-fatal complications. As thoracoscopic surgical techniques and technologies evolve, this may develop to become a viable and more efficacious alternative to catheter ablation in the treatment of LSPAF.

6.2 Introduction

See Chapter 1

6.3 Methods

See Chapter 2

6.4 Results

A total of 74 patients were referred for consideration for the study, of whom 11 (14.9%) were unsuitable as they did not fit the definition of LSPAF as defined by the 2012 Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society consensus document.[26] Of the remaining 63 patients, 54 (86%) gave informed consent and underwent baseline assessment tests.

Of these 54 patients, one patient was found to have concomitant severe mitral regurgitation and was therefore excluded as he required open-heart mitral valve surgery; another patient was found to have concomitant severe coronary artery disease and hence was excluded as he required coronary artery bypass surgery. One other patient was found to have severe left ventricular dysfunction (EF=30%) and angina, and was excluded from the study as per exclusion criteria. 51 patients underwent an ablation procedure, of whom 26 had thoracoscopic surgical ablation whilst 25 had catheter ablation as per their preferences (Figure 6.1).

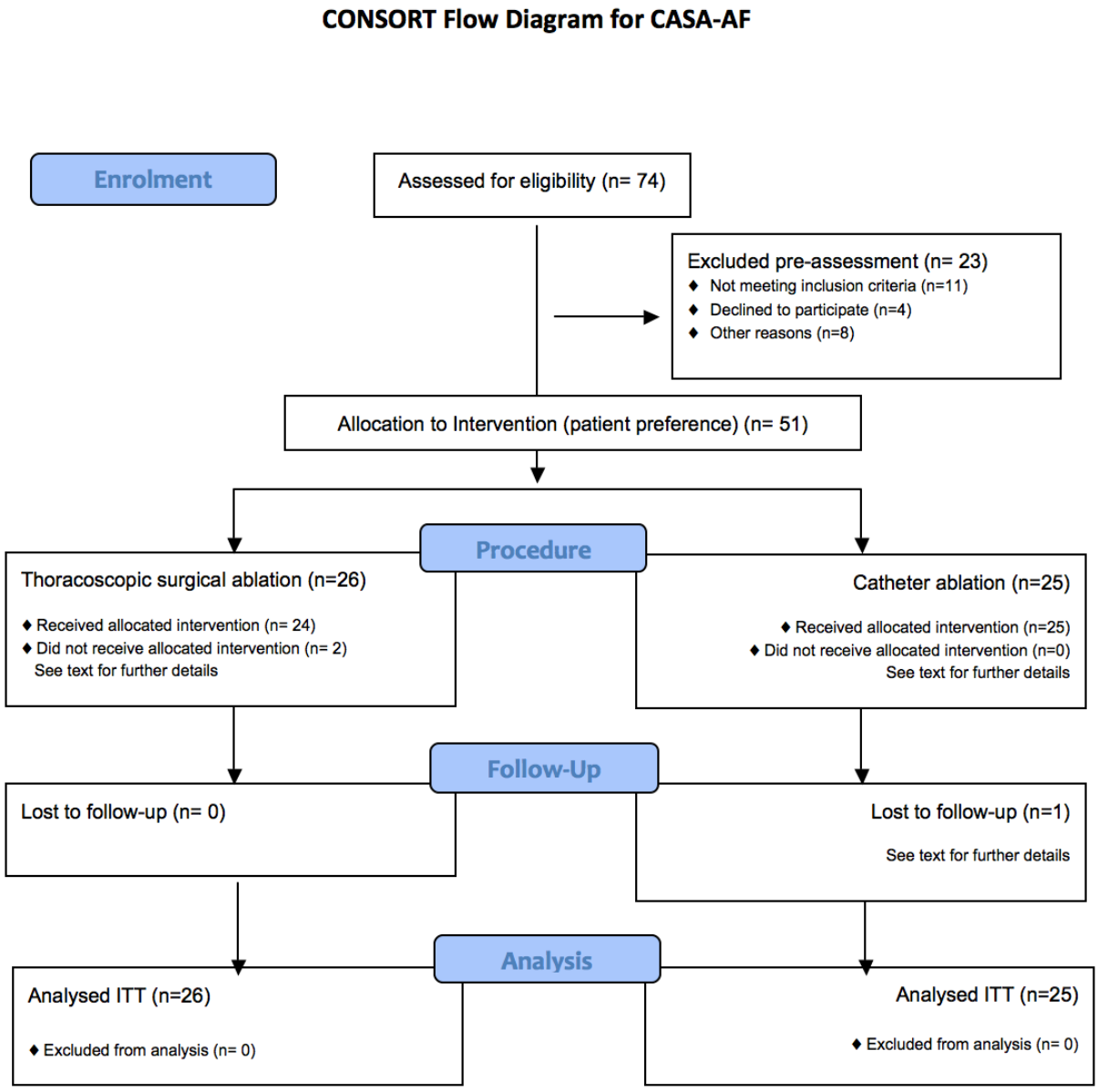


Figure 6.1 CASA-AF CONSORT diagram

Key: AF = atrial fibrillation; ITT = intention-to-treat.

The mean age of the population was 65±10 years, and 34 (67%) of the patients were male. All 51 (100%) patients had LSPAF as defined by the 2012 HRS/EHRA/ECAS consensus document.[26] There was no difference in baseline characteristics between the two groups, except for duration of continuous AF, which was greater in the surgical group (24 vs. 18 months, p=0.04), and there were more hypertensive patients in the catheter group (20 vs. 13%,

p=0.03). Baseline characteristics are summarised in Table 6.1.

Table 6.1 Baseline characteristics (intention to treat)

Parameter	All Patients	Catheter Ablation (n=25)	Surgical Ablation (n=26)	p-value
Age (y) Mean ± standard deviation	65±10	67±11	64±9	0.20
Sex, n (%) Male	34 (67)	17 (68)	17 (65)	0.84
Duration of continuous AF (months) Median (IQR)	22 (16,30)	18 (15,28)	24 (18,30)	0.04
Left atrial volume - index BSA (ml/m^2) Mean ± standard deviation	59.4±14.8	60.0±15.7	58.8±14.1	0.77
Left ventricular ejection fraction (%) Mean ± standard deviation	59.2±9.5	60.9±9.9	57.5±8.9	0.21
Co-morbidities / CV Risk Factors				
Coronary artery disease n (%)	10 (20)	7 (28)	3 (12)	0.14
Cerebrovascular disease n (%)	4 (8)	2 (8.0)	2 (8)	1
Valvular heart disease, n (%)	0 (0)	0 (0)	0 (0)	-
Hypertension, n (%)	33 (65)	20 (80)	13 (50)	0.03
Dyslipidaemia, n (%)	13 (26)	6 (24)	7 (27)	0.81
Diabetes Mellitus, n (%)	5 (10)	1 (4)	4 (15)	0.35
Smoking History	27 (53)	12 (48)	15 (58)	0.49
CHA2DS2-VASc score	2 (1,3)	3 (1,3)	1.5 (1,3)	0.16

6.4.1 Procedural results

The mean surgical ablation procedural time was 242±64 vs. 259±70 mins in the catheter ablation group (p=0.43). Acute procedural success was achieved in 22/26 (85%) surgical ablation patients, compared with 24/25 (96%) of all catheter ablation patients (p=0.97). There were no procedural deaths, strokes or conversion to sternotomy in the surgical or catheter ablation group. Inpatient stay for surgical patients was 7.4±3 vs. 4.1±3 days in the catheter ablation group (p<0.001).

6.4.2 Catheter ablation

6.4.2.1 Index procedure

25 patients chose to undergo catheter ablation. The mean catheter ablation procedural time was 259±70 minutes and fluoroscopy time was 49±17 minutes. Total RF ablation time was 54±15 minutes which incorporated: PVI RF time of 26±10 minutes; roof RF time of 208±86 seconds (additional 447±368 seconds of roof RF ablation required in 2 patients to achieve bidirectional block post DC cardioversion); 290±143 seconds ablation at the mitral isthmus (additional 595±508 seconds in 16 patients requiring additional ablation to achieve bidirectional block post DC cardioversion); and 597±384 seconds of ablation of CFE in the 20/25 (80%) patients who remained in AF after linear lesion deployment. All 25 (100%) patients had bi-directional block of the LPV, RPV, roof and mitral isthmus lines at the end of the procedure.

Intra-procedural termination of AF (defined as termination to SR without DC cardioversion) occurred in 6/25 (24%) patients. In 2 patients, direct termination to SR occurred at the end of the roof linear lesion. In 2 patients, termination to SR occurred during direct-targeted CFE

ablation with subsequent ablation of focal (micro re-entrant) right atrial tachycardia (AT) to SR. In the final 2 patients, AF terminated to AT during CFE ablation with focal ablation at the coronary sinus ostium which terminated to SR.

7/25 (28%) patients underwent DC cardioversion within the 3 months' blanking period, with 3 of these patients remaining atrial arrhythmia free at 9 months after a single procedure (off AAD).

6.4.2.2 Redo procedure

The rigorous follow-up schedule followed the 3 months' blanking period, during which 14 (56%) patients had a recurrence of atrial arrhythmia, 12 of whom (48%) underwent a redo catheter ablation for recurrent symptomatic atrial arrhythmias. Of these patients, 7 had AT whilst 5 had AF. Of the patients who did not have a redo procedure, one had had a recurrence of AF but had suffered a primary intracerebral event at day 60 precluding redo ablation, whilst the other had a low burden of minimal symptomatic atrial arrhythmias (16% at 3 months, <10% at 6 months, <6% at 9 months and <1% at 12 months, with data derived from a dual chamber pacemaker implanted for sino-atrial disease post index ablation). The mean time to occurrence of the first arrhythmia in these 14 patients was 113 (CI 91-135) days (median 96, IQR 92-160).

6.4.3 Surgical ablation

26 patients chose to undergo surgical ablation. The total surgical procedure duration was 242±64 mins. The right PVs had 8.3±2.5 clamp applications with a total 148.0± 61.2 secs of RF ablation. The left PVs had 7.8±3.6 clamp applications with a total 127.9±56.3 secs of RF ablation. Post PVI GP mapping was positive in 22/26 (85%) of patients with 14.1±11.2 RF

applications, and a total of 212.5±179.7 secs of RF during GP ablation. Post GP ablation mapping was negative in 23/26 (88%) of patients, with the remaining patient requiring further RF at already ablated GP sites to abolish the autonomic response. The superior (linear lesion) line connecting the contralateral superior PVs had 34.3±23.1 RF applications with a total of 540.8±487.5 secs of ablation, whilst the inferior (linear lesion) line connecting the contralateral inferior PVs had 38.8±27.6 RF applications with a total of 628.0±490.6 secs of ablation. The first ten surgical patients did not have LAA exclusion (this was a safety measure imposed by the RB&HFT Clinical Practice Committee).

Acute procedural success was achieved in 22/26 (85%) patients, with one patient terminating directly to SR during superior line ablation. Entrance block for both RPV and LPV was demonstrated in 24/26 (92%), and 20/26 (77%) patients had exit block of the PVs and the posterior wall box lesion demonstrated post successful DC cardioversion to SR. 2 patients did not have exit block in the posterior wall box lesion, and although the equipment precluded electrophysiological testing to localise the 'ablation gap' precisely, as in endocardial ablation, visual assessment of the ablation lesions directed further 'top-up' ablation to the junction of the superior line and PVI line of the LSPV in one patient; whilst in another, there was further 'top-up' ablation at both superior and inferior line resulting in exit block of the box lesion. Two further patients had entrance block of both LPV and RPV (shown on surgical pen and EP catheter testing), but were subsequently refractory to DCCV and consequently exit block testing of the PVs and the posterior wall box lesion could not be conducted. One of these patients reverted to SR just after wound closure, whilst the other remained in AF throughout the 12 months' follow-up period, despite a further catheter ablation procedure where once again the patient was refractory to multiple attempts of both external and internal DCCV. The other patient repeatedly went into pacing-induced paroxysmal AT precluding exit block

testing of the PVs and the box lesion, but DCCV at the end of the procedure after wound closure achieved SR.

8 (31%) patients underwent DC cardioversion within the 3 months' blanking period. 5 of these patients remained atrial arrhythmia free at 9 months after a single procedure (off AAD).

6.4.3.1 Intraoperative testing of conduction block

In order to ensure robust assessment of conduction block of surgical lesion sets, both the multifunctional surgical ablation and pacing pen and the 20 pole multielectrode EP catheter was used to test for conduction block (figure 6.2).

Due to technical challenges in positioning, it was not possible to use the EP catheter for entrance block testing for ipsilateral PVs in 2 patients, and box lesion testing in 2 further patients. Of the 22 patients who had both surgical and EP catheter testing for conduction block, 3 patients were found to have PV connections on the EP catheter post PV clamp isolation deemed to be isolated on surgical pen testing. Therefore, EP catheter testing prompted further ablation to achieve conduction block in 14% (3/22) of patients.

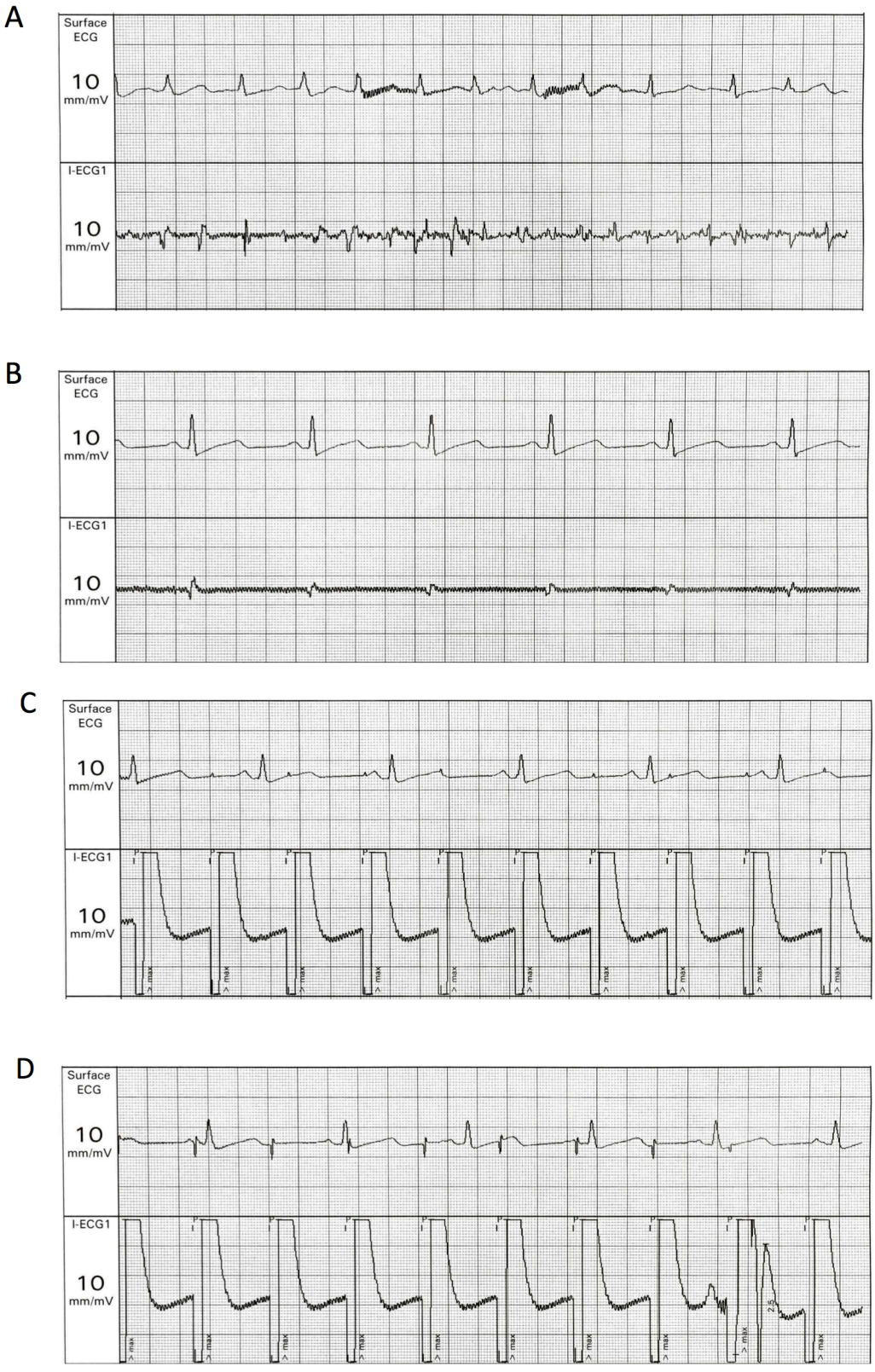


Figure 6.2 Surgical intraoperative conduction testing

Each strip shows the surface ECG on the top with either the sensing/pacing strip below.

A = Baseline sensing of the RPV antrum, B = Post PVI sensing of the RPV antrum – entrance block, C = Pacing within the posterior wall box lesion without capture of the atrium - exit block, D = Pacing PV side of the PVI line on RPV antrum without capture of the atrium - exit block.

6.4.3.2 Redo procedure

During the rigorous follow-up period, which followed the 3 months' blanking period, 5/26 (19%) patients had a recurrence of atrial arrhythmias, of whom 3/26 (12%) patients underwent a redo catheter ablation for recurrent symptomatic AF. One patient had several (mildly symptomatic) short runs of paroxysmal AT and AF lasting less than 1 minute, but as the overall arrhythmia burden was very low, the patient was managed conservatively without the addition of AADs. Another patient had a recurrence of AF at 3 months but did not wish to have another interventional ablation procedure. In the 3 patients who had redo catheter ablation, all had AF as recurrence, and no gaps were found in the surgical lesion set except for in 1 patient where there was an unblocked superior line. Furthermore, in these 3 patients despite additional catheter based ablation including CFE ablation and the addition of mitral isthmus and cavotricuspid linear lesions, 2 patients went on to have a recurrence of AF. The mean time to occurrence of the first arrhythmia in these 5 patients was 128 days (CI 66-190) (median 95, IQR 90-180).

6.4.4 Follow-Up

The mean follow-up duration was 8.8±0.5 months. There were no deaths during the follow-up. Of the whole study population, only one patient (catheter ablation group) could not attend for follow-up due to having a primary intracerebral event in the context of supratherapeutic INR levels within the 3 months' blanking period (day 60). The patient remained as an inpatient for a number of weeks and had documented recurrence of AF after the blanking period. Due to the residual neurological deficit, the patient was unable to attend follow-up, but failed the primary outcome as it had been documented that the patient remained in AF and was treated with anticoagulation and a rate control strategy.

6.5 Primary and secondary end-point results

6.5.1 Primary end-point

Freedom from atrial arrhythmia, off AADs, after a single procedure at 9 months occurred in 21/26 (81%) of patients in surgical ablation groups, versus 11/25 (44%) patients in the catheter ablation group (p=0.007). Sub-analysis of the surgical group with and without LAA exclusion showed no significant difference in primary outcome at 9 months [79% (11/14) vs. 80% (8/10); p = 0.94] respectively.

6.5.1.1 Survival analysis

As per intention-to-treat, Kaplan-Meier survival analysis from a single ablation procedure off antiarrhythmic drugs was conducted for the two groups. The 9 months' (270 days) arrhythmia-free survival was 81% in the surgical ablation groups versus 42% in the catheter ablation group. The survival curves were significantly different between the two groups; log-rank (Mantel-Cox test) p=0.006 (Figure 6.3).

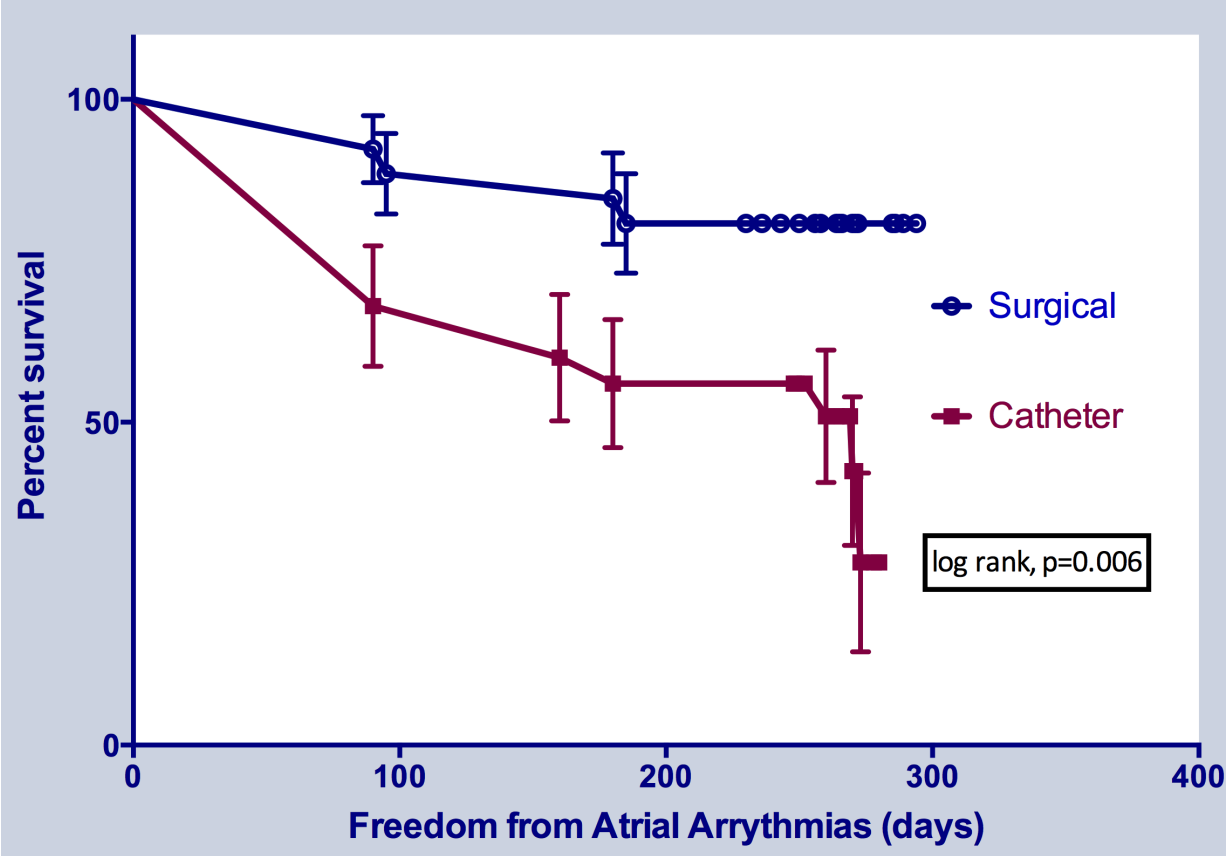


Figure 6.3 Freedom from atrial arrhythmias (single procedure) at 9 months (270 days)

Surgical versus catheter ablation single procedure Kaplan-Meier curves of atrial arrhythmia-free survival off AAD. Note success is defined as freedom from atrial arrhythmia after a 3 months' blanking period. The two survival curves were compared using the log-rank (Mantel-Cox) test.

6.5.2 Secondary end-points

6.5.2.1 Multi-procedure success

Freedom from atrial arrhythmia, off AADs, after multiple-procedures at 9 months occurred in 21/26 (81%) of patients in surgical ablation groups versus 15/25 (60%) patients in the catheter ablation group (p=0.10). The mean number of procedures in the surgical ablation group was 1.04±0.34, and 1.44±0.51 in the catheter ablation group.

The use of AADs was limited to only 3 patients in the catheter ablation arm, who had very advanced substrates based on electrophysiological findings at the index catheter ablation

procedure, and despite undergoing two procedures, required AAD usage (amiodarone) to minimise the subsequent atrial arrhythmia burden.

6.5.2.2 Clinical (partial) success

Clinical success, as defined by a 75% or greater reduction in AF burden (number and duration of AF episodes) with or without AADs, after a single procedure at 9 months, occurred in 23/26 (88%) of patients in surgical ablation group, vs. 17/25 (68%) patients in the catheter ablation group (p=0.07).

6.5.2.3 Serious adverse events

There were no serious adverse events (stroke, MI, emergency surgery or death) in either group.

6.5.2.4 Major procedural complications

In the surgical group, eight major complications occurred in 7/26 patients (31%) post-operatively, compared with two major complications in 2/25 (8%) patients in the catheter ablation group (p=0.04) (Table 6.2).

Each of the complications with the number of days post-intervention are given below:

Surgical Group

In the surgical ablation group, the adverse events reported at patient level were as follows:

- One patient had a large right-sided pleural effusion, which required admission for drainage (day 42);
- One patient had a hospital-acquired pneumonia (HAP) and also, in addition, significant symptomatic (breathlessness) and left upper and left lower pulmonary vein stenosis

(greater than 70%). The symptoms were necessitating PV angioplasty, which was only successful in the left lower PV, with full resolution of symptoms (day 4 and then day 90);

- One patient had right phrenic nerve paralysis (day 14);
- One patient had HAP (day 14);
- Two further patients had significant PV stenosis of the left lower PV, but neither was symptomatic and hence did not require intervention (both day 90);
- One patient had evidence of left phrenic nerve damage (day 94).

Catheter Group

In the catheter ablation group, the adverse events reported at patient level were as follows:

- One patient had asymptomatic left lower PV stenosis (day 90), whilst another was admitted to hospital shortly after discharge with pulmonary oedema (day 2).

Over the course of the 9 months' follow-up, the only other adverse event to note was a primary intra-cerebral haemorrhage in a patient 60 days post index procedure. The event occurred in the context of initial admission to hospital with unidentified source of infection and supra-therapeutic INR. The atypical presentation raised the possibility of atrio-oesophageal fistula and this was examined in detail by a multi-disciplinary team using multiple imaging modalities, but ultimately proved inconclusive. This complication was adjudicated to be unrelated to the index catheter ablation procedure.

Table 6.2 Major complications in catheter and surgical ablation groups

Major Complications	Catheter (n=25)	Surgical (n=26)	p-value
Pneumonia	-	2	
Pleural effusion	-	1	
Pulmonary vein stenosis	1	3	
Phrenic nerve palsy	-	2	
Vascular access complications	-	-	
Acute pulmonary oedema	1	-	
Cardiac tamponade	-	-	
Sternotomy for complication	-	-	
Stroke	-	-	
Death	-	-	
Total	**2 (8.0%)**	**8 (30.7%)**	**p=0.04**

Composite End-point for Major Adverse Clinical Events

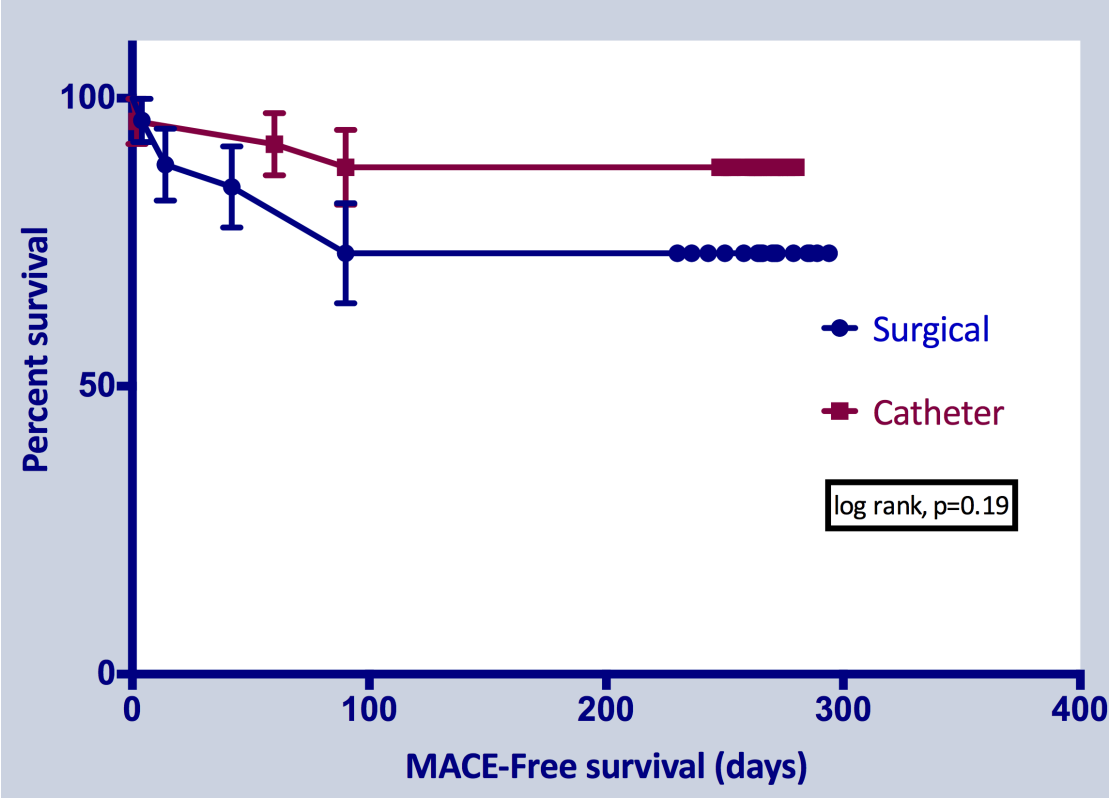


Figure 6.4 MACE-free survival by treatment group

Surgical versus catheter ablation single procedure Kaplan-Meier curves of Major Adverse Clinical Event (MACE - free survival. The two survival curves were compared using the log-rank (Mantel-Cox) test.

6.5.2.5 Change in AF symptom score

Figure 6.5 shows the baseline distribution of AF symptom scores between the catheter and surgical group, which were not significantly different (p=0.30). The median AF symptom score in the catheter ablation group was 3 with 2 outliers, and in the surgical group 3 (2.5,3).

Figure 6.6 shows the change in AF symptom score between 0 and 9 months. There was a median reduction of 2 [2,1] in both groups and again the distribution of the change in AF symptom scores was not significantly different between the 2 groups (p=0.87).

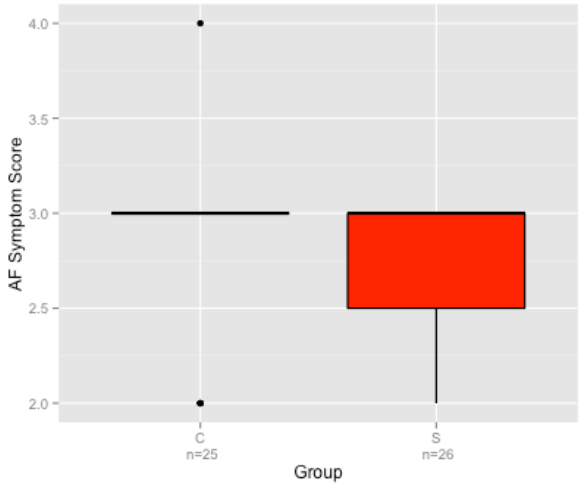


Figure 6.5 Baseline AF Symptom Score by treatment group

Visual representation of baseline AF symptom scores in each group, using box plots. Boxplots splits the data into quartiles. The "box" extends from the first quartile (Q1) to the third quartile (Q3) and hence represents the interquartile range. Within the box, a vertical line is drawn at the Q2, which represents the median of the data set.

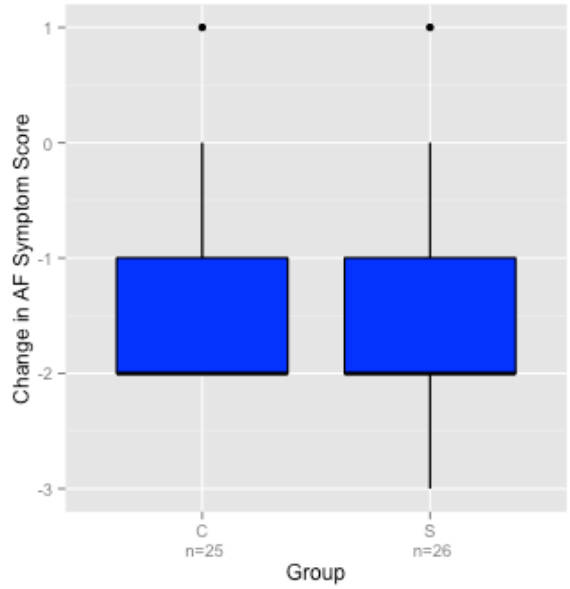


Figure 6.6 Change in AF Symptom Score by treatment group

Visual representation of change in AF symptom scores in each group, using box plots.

6.5.2.6 Change in SF-36 quality of life score

The SF-36 quality of life (QoL) questionnaires were obtained from all 51 patients (100%) at baseline, and 48 (94%) patients at 9 months' follow-up. The scores for baseline and at 9 months are shown side by side in Figure 6.7.

Figure 6.8 shows that at baseline, there was no difference in the distribution of each of the 10 QoL domain scores between the two groups.

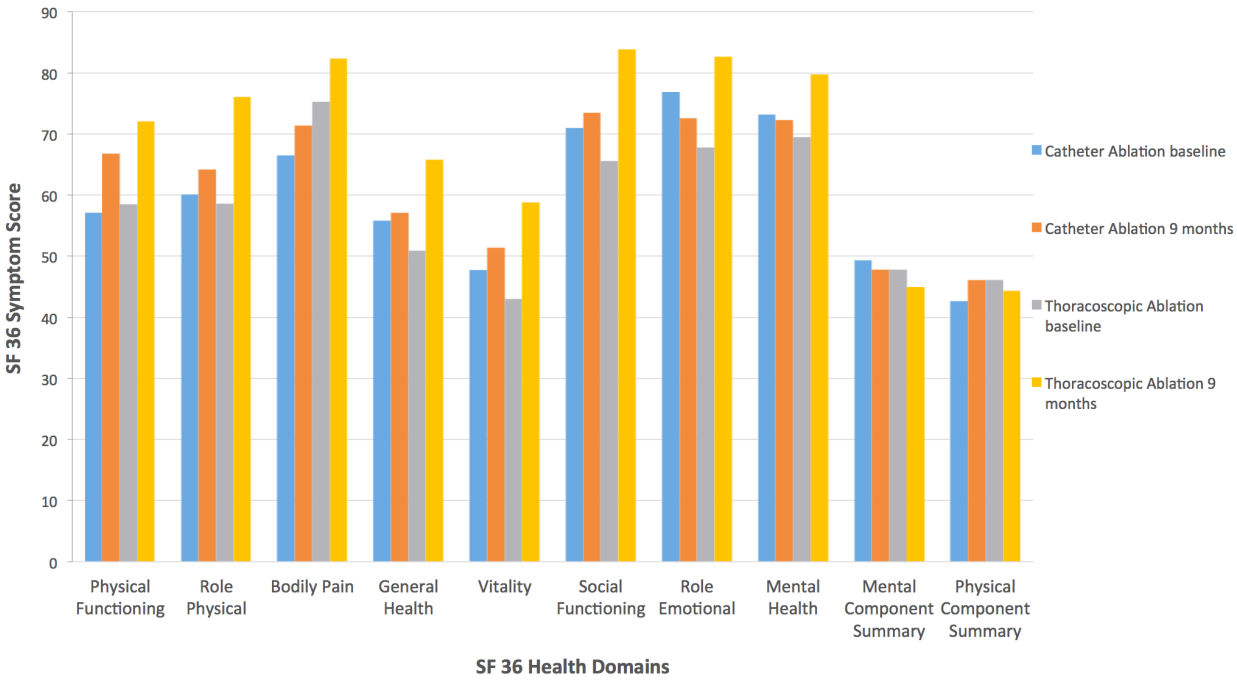


Figure 6.7 SF-36 QoL scores at baseline and 9 months by treatment group

SF-36 quality of life scores at baseline and 9 months' follow-up comparing surgical versus catheter ablation.

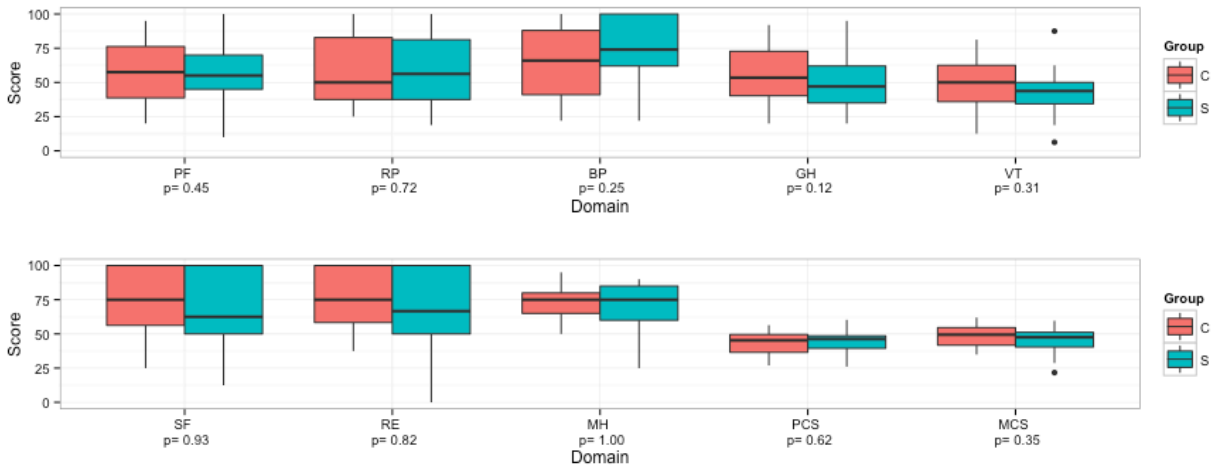


Figure 6.8 Baseline distributions of scores for all 10 domains of SF-36 QoL questionnaire by treatment group

Visual representation of baseline distribution scores for all 10 components of SF 36 QoL questionnaire by treatment group using box plots.

Figure 6.7 visually shows an increase in QoL in 7/10 domains in the catheter group and 8/10 domains in the surgical group. This was examined in more detail in Figure 6.8, which shows box plot representation of the change in the QoL SF-36 score between baseline and 9 months. The amount of change was significantly higher in the surgical group when compared with the catheter group in 3 out of the 10 domains; general health (GH), vitality (VT) and MCS (mental component score). This shows that the surgical group fared better from the QoL perspective in these 3 health domains with equivalence in the other 7 domains.

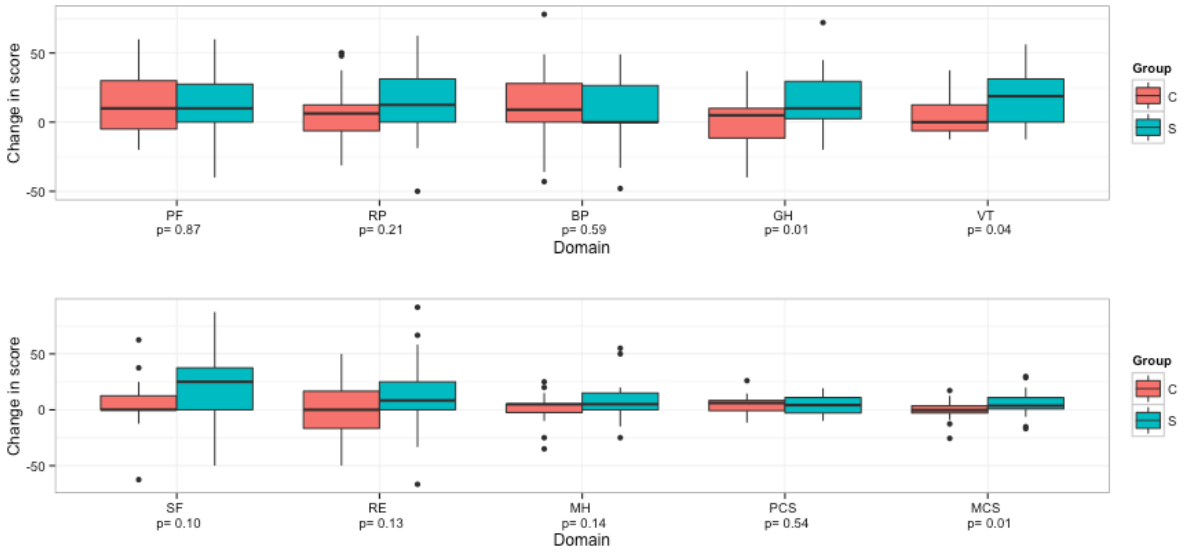


Figure 6.9 Change in scores for all 10 domains of SF-36 QoL questionnaire by treatment group

Visual representation of absolute change in scores for all 10 components of SF 36 QoL questionnaire by treatment group using box plots. P values indicate comparison of change between the two groups.

Figure 6.10 and 6.11 shows the surgical and the catheter intragroup analysis at 9 months. In the surgical group there were significant increases in QoL in 9/10 domains (when compared to baseline) compared with only 2/10 QoL domains in the catheter group.

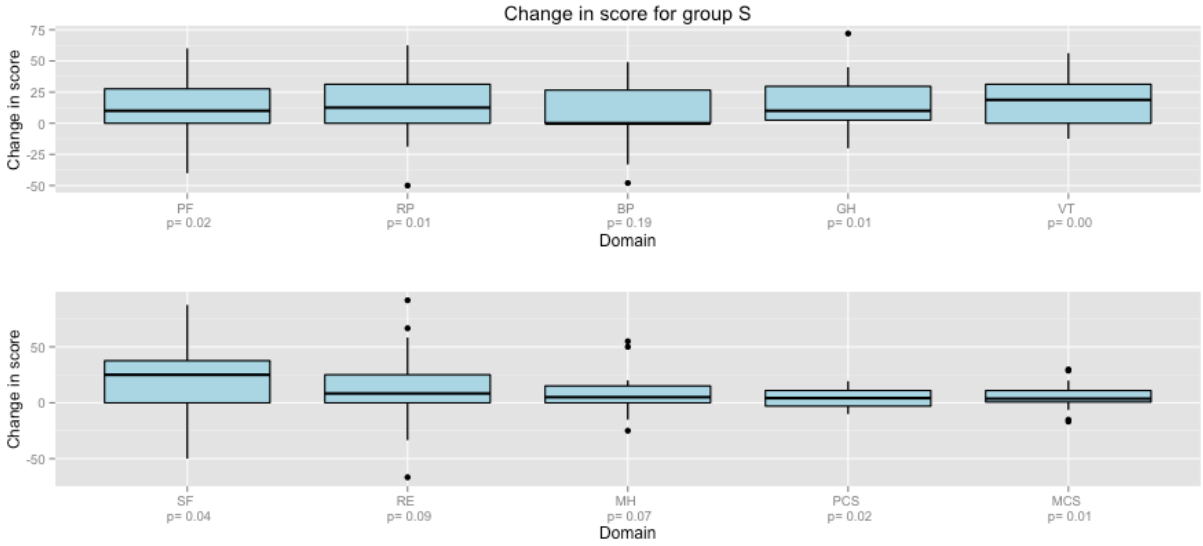


Figure 6.10 Change in scores for all 10 components of SF-36 QoL questionnaire for surgical group

Visual representation of absolute change in scores for all 10 components of SF-36 QoL questionnaire, with p-values indicating comparison of change to baseline value.

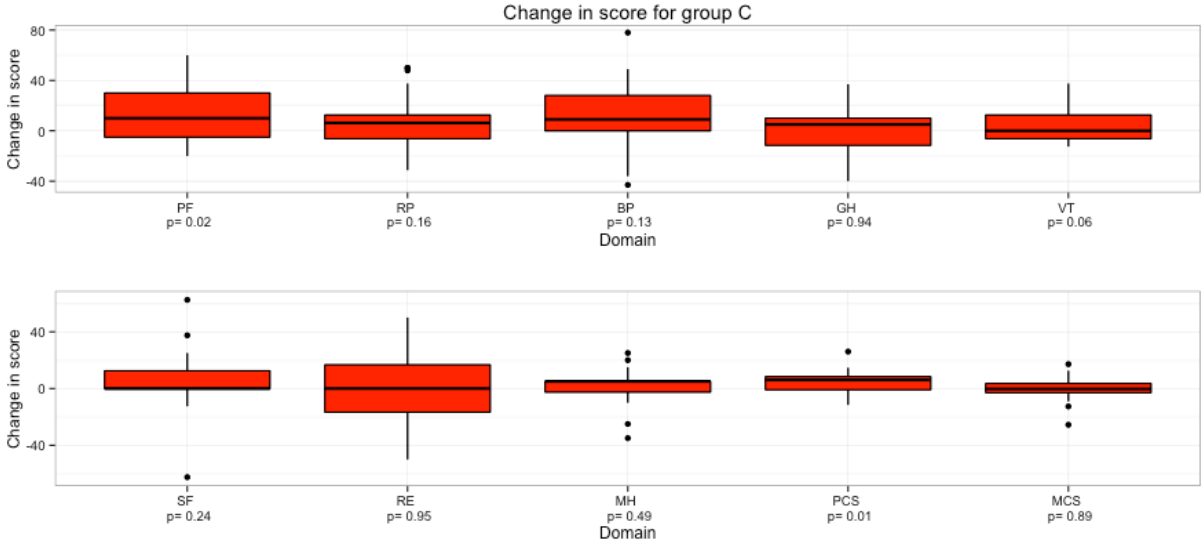


Figure 6.11 Change in scores for all 10 components of SF-36 QoL questionnaire for catheter group

Visual representation of absolute change in scores for all 10 components of SF-36 QoL questionnaire, with p-values indicating comparison of change to baseline value.

6.5.2.7 Change in atrial and ventricular dimensions

See Chapter 4.

6.6 As-treated analysis

2 patients who had chosen surgical ablation had their surgical intervention abandoned at an early stage in the procedure due to anatomical abnormalities leading to significant technical challenges. The risk was deemed too high for the surgeon to continue, and therefore these 2 patients crossed over to the catheter ablation group. All of the analyses thus far have been as per 'intention to treat'.

However, to assess the true efficacy of the procedures as received by patients an 'as-treated' analyses was also conducted for rhythm and major complications outcomes and is shown below.

6.6.1 'As-treated' - Primary end-point

Freedom from atrial arrhythmia, off AADs, after a single procedure at 9 months occurred in 19/24 (79%) of patients in surgical ablation groups, versus 13/27 (48%) patients in the catheter ablation group (p=0.02).

6.6.2 'As-treated' - Multi-procedure success

Freedom from atrial arrhythmia, off AADs, after multiple-procedures (1.03±0.35) at 9 months occurred in 19/24 (79%) of patients in surgical ablation groups versus 17/27 (63%) patients in the catheter ablation group (p=0.20).

6.6.3 'As-treated' - Clinical (partial) success

Clinical success, as defined by a 75% or greater reduction in AF burden (number and duration of AF episodes) with or without AADs, after a single procedure at 9 months, occurred in 21/24 (88%) of patients in surgical ablation group, vs. 19/27 (70%) patients in the catheter ablation group (p=0.14).

6.6.4 'As-treated' - Major procedural complications

In the surgical group, eight major complications occurred in 7/24 patients (33%) post-operatively, compared with two major complications in 2/27 (7%) patients in the catheter ablation group (p=0.04) (see table 5.2). 2 patients who had chosen surgical ablation had their surgical intervention abandoned at an early stage in the procedure due to anatomical abnormalities leading to significant technical challenges. The risk was deemed too high for the surgeon to continue, and therefore these 2 patients crossed over to the catheter ablation group and the primary rhythm outcome was analysed as per intention to treat.

6.7 Discussion

See Chapter 7 for discussion of the CASA-AF trial results.

Acknowledgements

CASA-AF investigators:

Chief Investigator: Dr Tom Wong

Investigators: SK Haldar, DG Jones, V Markides, T Bahrami, A De Souza, and R Mohiaddin.

The above work has been presented in an abstract in modified form as listed below:

Abstract

The preliminary results were accepted as an abstract (poster presentation) at the 35th Annual Scientific Sessions, May 2014, San Francisco, USA.

Catheter Ablation vs. Thoracoscopic Surgical Ablation for Long Standing Persistent Atrial Fibrillation. **Haldar S**, Jones DG, Bahrami T, DeSouza A, Yadav R, Jarman J, Panikker S, Papasavvas I, Hussain W, Salukhe T, Markides V, Wong T.

Chapter 7
Discussion

7.1 Introduction

Atrial fibrillation (AF) can be symptomatically debilitating and can cause significant morbidity and mortality. The worldwide incidence is growing fast with data from a recent epidemiological survey in 2010 showing that at least 30 million people worldwide currently suffer with this arrhythmia, with another 5 million newly diagnosed cases every year.[5] If one also considers that many people with AF are yet undiagnosed, the scale of the problem can only be even greater.[188 189] Although a relatively simple diagnosis to make, the complexity of the aetiology and management of AF has demanded extensive research in an attempt to treat and cure this challenging condition.

Long standing persistent atrial fibrillation (LSPAF) is not only the least studied category of AF, but also the hardest to treat effectively. There are no epidemiological estimates as to the proportion of AF that constitutes LSPAF. Whilst single procedure success rates after catheter ablation in paroxysmal AF rates are consistently high, in LSPAF they remain suboptimal, with previous studies showing success of 27% at 40 months or 32% at just over 12 months' follow-up.[40 41] It is, therefore, conventional practice for electrophysiologists to counsel patients embarking on an interventional strategy of the likely success rates and the potential need for multiple procedures to improve the overall success. Despite the modest figures quoted to patients, many patients remain keen to embark on this 'journey' in the hope of attaining SR. It is this suboptimal efficacy in non-paroxysmal AF that has been the driver for research in this area and underpins the rationale for the CASA-AF study design.

In the late 1990s, at around the time of Haissaguerre's seminal findings documenting the importance of PV triggers in AF, the original cut-and-sew surgical Cox-Maze-III procedure was already declining in popularity. Although efficacious, its highly invasive nature, technical complexity and significant complication rates made it increasingly difficult to justify for patients requiring stand alone intervention for AF. However, the last decade has seen a steady resurgence in surgical AF ablation procedures. Thoracoscopic surgical AF ablation (using a mini-thoracotomy) was first described in 2005, followed by a totally thoracoscopic approach in 2008. [72] [190] In late 2012, the FAST study was published, a landmark trial, as it was the first head-to-head study of thoracoscopic surgical ablation with catheter ablation albeit in a mixed cohort of AF patients. The results showed surgical superiority with respect to freedom from AF, offset by a higher complication rate. [81]

Early thoracoscopic surgical data came from small series, and had shown that results matched that of catheter ablation for PAF, but were more promising in non-paroxysmal AF. At the time of the CASA-AF study inception in late 2010, there had not yet been a head-to-head comparison.[77] [78] From both electrophysiological and patient perspectives, when given the choice between catheter and thoracoscopic ablation, those with paroxysmal AF will typically choose the least invasive option when outcomes are equivalent. The CASA-AF study investigators felt that the most logical (and justifiable) group in which to study an alternative ablation strategy was patients with LSPAF, who were more likely to consider a more invasive technique, particularly if it were to provide improved single procedure outcomes. CASA-AF, albeit non-randomised, was therefore designed to compare these two modalities of ablation in a thorough and robust manner. Only de novo LSPAF patients were studied, as too often surgical ablation studies recruit patients who have previously failed catheter ablation, which confounds the true outcome. The index procedure lesion sets were chosen to allow

comparison (as far as possible given the different approaches) between the two modalities with patients following a standardised follow-up schedule post index procedure. Despite predating the 2012 Heart Rhythm Society, European Heart Rhythm Association and European Cardiac Arrhythmia Society (2012 HRS/EHRA/ECAS) international consensus document and the aforementioned FAST study, the study design addressed many of the consensus document recommendations for AF study design, as described in Chapter 2, and indeed some of the limitations of the FAST study. [26 81]

7.2 CASA-AF trial

In this first, prospective, non-randomised, head-to-head study in LSPAF alone, a thoracoscopic surgical ablation strategy was found to be superior to catheter ablation in the primary end-point of single procedure freedom from atrial arrhythmia off AAD (p=0.007), although this was offset by a higher rate of major (non-fatal) complications (p=0.04). Despite this, the surgical ablation group also had greater improvement in SF-36 QoL scores at 9 months.

7.2.1 Primary End-point

The difference in the primary end-point result at 9 months is striking. Achieving 81% success off AADs in patients where the mean duration of continuous AF was longer than in the catheter ablation comparator group (24 vs. 18 months; p=0.04) is impressive, and corroborates surgical data from Sirak (retrospective data) and Edgerton (prospective data).[77] [78] It is worth pointing out that the one unifying theme in the surgical lesions sets in these studies and in CASA-AF is the inclusion of thorough electrophysiological validation of both PVI and linear ablation lesions, consolidating the need for substrate modification in addition to

PVI in non-paroxysmal patients. The catheter ablation results, however, were not wholly surprising and were in keeping with previous reports in LSPAF patients.

It is widely accepted that the longer the duration of AF, the more advanced and complex the atrial substrate will be, due to the fact atria have had more time to remodel both electrically and anatomically. The lesion sets were therefore chosen to reflect this complex substrate in order to achieve pulmonary vein isolation (PVI), substrate modification and a degree of parity to allow comparison between the two treatment modalities, despite the different approach (endocardial vs. epicardial). With this in mind, there are three potential reasons that could explain this stark difference in outcome:

1. Epicardial surgical lesions applied under direct vision are more contiguous, transmural and durable, particularly if validated conduction block is demonstrated;
2. Ganglionated plexi ablation has a significant impact upon the substrate and hence outcome;
3. LAA exclusion has a significant impact upon the substrate and hence outcome.

In addressing the first point, rigorous electrophysiological validation of bi-directional block was conducted for all lesions in both groups. In the catheter ablation group, 83% (10/12) of the recurrences of AF/AT had documented PV reconnections and 67% (8/12) had one or more linear lesions unblocked at redo catheter ablation. Conversely, only five surgical patients had a recurrence, all of which were AF only. Of those, only three warranted redo catheter ablation, where endocardial assessment of the index surgical lesions showed two patients had intact PVI and posterior wall isolation while the other had an unblocked superior line.

Second, ganglionated plexi ablation may have contributed to the superior outcome in the surgical group. PVI itself transects many of the autonomic ganglia located around the PV antrum, but 92% still required additional targeted ablation of GP positive sites (commonly at the infero-postero floor region close to the coronary sinus) with abolition of the autonomic response attained in 100% of these patients.[191] The literature has been controversial with regards to GP ablation, in part because data has shown the effects of GP fat pad ablation are not durable, with reversal of autonomic denervation at 4 weeks.[69] A surgical review paper from La Meir et al. questioned the value of GP ablation, as studies with GP ablation had lower success rates than those studies without, although they warned that the studies in question were small, and that more GP ablation data was required.[192] Although it is difficult to distinguish what effect it had in our surgical group, the importance of GP ablation should not be dismissed and needs to be examined in detail (see 7.6 Future Directions).

Third, the exclusion of the LAA may have contributed to the improved outcomes, although it should be noted that the first ten surgical patients did not have LAA exclusion, and sub-analysis of the surgical group with and without LAA exclusion showed no significant difference in primary outcome at 9 months [79% (11/14) vs. 80% (8/10); p= 0.94]. Interestingly there were two surgical ablation patients that did not have the LAA excluded who went onto have redo catheter ablation. In both of these patients the entire surgical lesion set was intact and so it is possible that these recurrences may have been driven by a LAA source although this could also be true of any non-PV source. In the absence of any data to support that the LAA was the driver in these cases, these are merely observations, but worth considering given that LAA has been shown to account for 20% of the drivers in non-paroxysmal AF.[120 121] However, although the subgroup analysis showed no difference in outcome between the two groups, these numbers are clearly small and do not have sufficient power to detect the true effect of

LAA exclusion, whilst interpretation of subgroup analyses must always be treated with caution.

Overall, the rate of recurrence in the catheter ablation group, and the fact that surgical lesions were mostly intact in those that required a restudy, provides compelling evidence that the surgical lesions were superior in terms of durability. Animal and clinical studies have previously shown that that the bipolar radio-frequency (RF) clamp and the linear ablation device are able to create robust transmural lesions.[50-53] These data suggest that well placed and validated surgical lesions are more durable, contiguous and permanent than those created by a point-by-point catheter approach. This is likely to account for the significant difference in clinical outcome.

7.2.2 Secondary End-points

7.2.2.1 Multi-procedure success

In the catheter ablation group, when multi-procedure success is considered, there was an increase in success from 41% to 60%. In the four patients that had successful redo procedures, the mode of recurrence was symptomatic AT (with one patient having both AT and AF). PV reconnection was found in all four patients, and additionally in two of these, an unblocked linear lesion was documented. 'Top-up' ablation to correct these reconnections and gaps led to freedom from arrhythmia. Once again, this highlights the shortcomings of index catheter-RF lesions in terms of durability. Contact force sensing catheters were not yet available at the time of this study, and hence were not used, but this new technology has shown reduction in acute PV reconnections which may translate into better longer term outcomes by achieving permanent, transmural RF lesions. [187]

For the three surgical ablation patients in whom there was a recurrence requiring subsequent catheter ablation, the surgical lesion sets were intact except for one patient with an unblocked superior line. In the two patients where the surgical lesions were fully intact, despite extensive additional ablation at the second sitting (catheter ablation redo), atrial arrhythmias still recurred and the patients failed the multi-procedure secondary end-point. This suggests that in these patients, the atrial substrate was too far advanced to respond to interventional therapy. Identifying these refractory patients upfront would be invaluable but no prediction criterion is ever likely to be 100% accurate, and consequently there will always be a certain cohort of patients who will be refractory to interventional therapy.

7.2.2.2 Clinical (partial) success

It is very important to consider this aspect of the study's success, as there is a significant cohort of patients who, whilst failing to achieve the stringent criterion of arrhythmia recurrence (>30 seconds of atrial arrhythmia), may still have derived enormous clinical benefits and an improved quality of life. Indeed, the 2012 HRS/EHRA/ECAS consensus document has acknowledged this by defining clinical success as a 75% reduction in AF burden, with respect to either number or duration of AF episodes.[26]

In the catheter ablation group, the clinical success criterion after a single procedure captured an additional six patients, improving the outcome to 68%. In the surgical group an additional two patients were included who had had only minor self-limiting episodes of AF (fewer than 5 minutes' duration), which increased the clinical success rate to 88%. In this study, clinical success was assessed with 3-monthly 7-day ambulatory recordings as per the follow-up protocol, with any additional symptomatic recurrences captured on an emergency 12-lead ECG. As the definition of clinical or partial success focusses on symptomatic relief, this follow-

up schedule is sufficient. For a fully accurate assessment of AF burden, a continuous recording from a device such as an implantable loop recorder would be necessary. The inclusion of this end-point in all future ablation trials would be a welcome development, although it does commit patients to a small implantable device. The clinical success figures have particular relevance to patients and as such should be the figures used when counselling patients contemplating an interventional strategy.

7.2.2.3 Major complication rates

The benefit in freedom from arrhythmia derived from thoracoscopic surgical ablation comes at the cost of a higher major complication rate. This is in line with data from other reports, including a recent review paper which highlighted that the commonest complications were related to lung issues, phrenic nerve dysfunction and bleeding. [81 192]

In our cohort, bleeding was not an issue, but phrenic nerve dysfunction occurred in three patients. This was not due to direct trauma, as the pericardiotomy was deliberately performed 4-5cm anterior to the nerve's course. It was felt that perhaps indirect trauma via the tension from the pericardial retraction sutures might have been the cause. In latter cases, this tension was relaxed and subsequently there have been no further cases of phrenic nerve dysfunction.

The other complication that merits discussion was the four cases of severe PV stenosis (1 in the catheter ablation group, 3 in the surgical ablation group). In both catheter and surgical ablation, PVI was undertaken at the PV antrum to reduce the risk of PV stenosis, and to modify more of the atrial substrate. In the catheter ablation case, the LLPV was affected but as the patient was asymptomatic, the management was conservative. Examination of the RF distribution sites for this catheter ablation PV stenosis case showed that the PVI lesions were

indeed antrally placed, although there were a few lesions within the PVI line at sites necessary to achieve PVI. It is possible that either the 3D electroanatomical map was inaccurate, and hence the true ostium of the PV was misjudged, or the patient had an idiosyncratic (disproportionate) reaction to nearby ablation lesions, resulting in PV stenosis. In the surgical ablation group, only 1 of the 3 patients with PV stenosis was symptomatic, and required intervention by PV angioplasty. In this case, both the LUPV and LLPV had stenosed, with two possible reasons for this occurrence (Figure 7.1). First, there were anatomical difficulties in achieving reasonable contact with the linear ablation pen at the epicardial junction of left PVI line and the superior line. This resulted in several overlapping lesions being placed at this site, which may have reached the ostium of the PV. Second, the number of RF clamp applications (7) at this site may have been excessive for this patient. In the other two patients, again the only viable explanation was the number of RF clamp applications, which were 8 and 7. This led to a change in the surgical protocol, with a target of 3-5 overlapping applications at the PV antrum, and since this change there have been no further PV stenoses. Routine screening post ablation is seldom conducted, with active investigation for PV stenosis prompted only by suggestive symptoms. However, patients may have significant PV stenosis and be asymptomatic and the prognostic benefits of treatment in this scenario remain unknown.[26] In our patients, symptoms were only apparent when more than 1 PV was stenosed, which is consistent with prior data from other studies, where the authors hypothesised this may be due to compensatory ipsilateral pulmonary venous and therefore alveolar drainage.[193 194] This study highlights the benefit of pre-and post-imaging via MRI in identifying (symptomatic and asymptomatic) PV stenosis, particularly in the surgical ablation group, as it prompted a change in technique. It seems prudent to have a programme of pre-

and post-ablation imaging whenever a new modality or a change in ablation technique is instituted, to assess for this recognised complication of AF ablation.

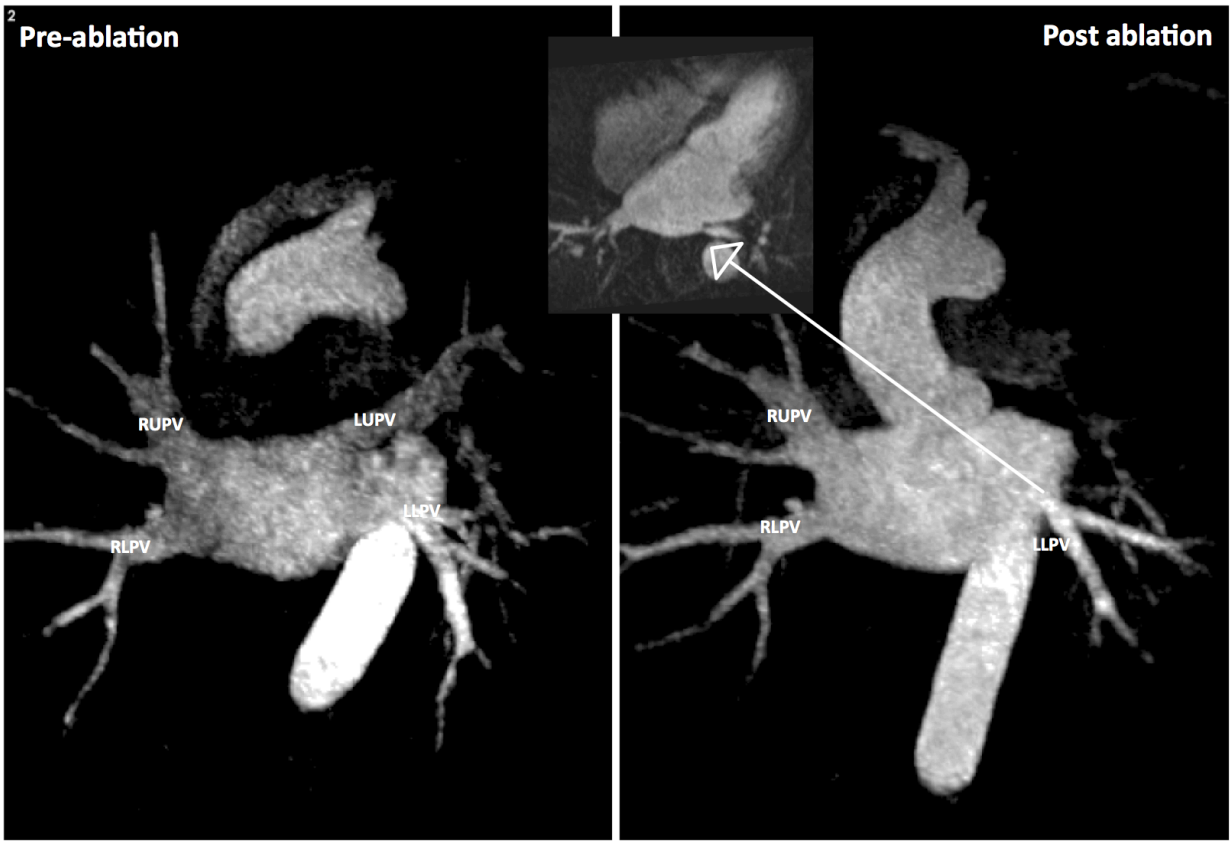


Figure 7.1 Example of left pulmonary vein stenosis post thoracoscopic surgical ablation

Pre- and post-ablation MRI images showing normal calibre left upper and lower pulmonary veins pre-ablation, followed by occlusion of the left upper pulmonary vein and severe (>70%) stenosis of the left lower pulmonary vein.

The final area of complications was from the lung, which is often a by-product of the double lumen endotracheal intubation technique used in thoracoscopic surgical procedures that enable selective lung ventilation. Post-operative pneumonia and atelectasis are not uncommon sequelae and can potentially be avoided with prophylactic antibiotics and meticulous attention to post-operative pain management (to facilitate deep inspiration) and early mobilisation on the ward.

In the catheter ablation group, the only other complication of note was that of acute pulmonary oedema within 48 hours of discharge. This was in the context of preserved left ventricular systolic function, and was likely due to a relative excess of intra- and peri-procedural fluid administration for the patient's body weight. The patient was treated and successfully discharged after 2 days in a district general hospital. In retrospect, perhaps closer monitoring of fluid balance in the immediate post ablation phase may have prevented this re-admission.

Finally, it is important to note that despite the difference in major complications between the two groups, there was no significant difference between the Major Adverse Clinical Event (MACE)-free survival curves (see Figure 6.4) (log rank, p=0.19). This highlights the key point of using Kaplan-Meier for analysis as it focuses on the entire survival curve rather than MACE events at any one-time point. It is debatable whether survival curves are of clinical importance in this context.

7.2.2.4 Intraoperative testing of conduction block

In this study two tiers of conduction block testing were employed for the thoracoscopic surgical ablation group. The results were interesting in that it showed that the addition of testing with the 20 pole EP catheter for entrance block of the PVs and the box lesion increased the pick up rate of acute non-isolated lesions, as compared with the multifunctional surgical ablation and pacing pen. An additional 3/22 patients required further ablation to isolate lesions that were deemed blocked by the multifunctional surgical ablation and pacing pen. This is clearly important, as had it not been for the additional EP catheter testing these 3 patients (14%) may have failed the primary end-point. In this hypothetical scenario and under the intention to treat analysis the thoracoscopic surgical success rate would have been 69%

(18/26) vs. 44% (11/25); p=0.06. It is clear, therefore, that if surgical testing alone is to be used in these procedures then more testing at various regions circumferentially around the PVs must be undertaken to ensure regional areas of PV conduction are identified and then re-isolated with further RF clamp applications. Alternatively, more sophisticated testing using multipolar EP catheters such as those used in this study may be employed, although there are inherent technical difficulties in positioning these catheters to ensure full circumferential coverage around the PV antrum.

7.2.2.5 Quality of life scores

The analysis of quality of life (QoL) data is of particular importance when comparing a new technique to an established technique. The increased complication rate in thoracoscopic surgical ablation would intuitively suggest that perhaps QoL measures would suffer in this group. However, intragroup analysis showed that the surgical patients had significant improvement in 9/10 QoL domains compared with baseline (Figure 6.10). In contrast the catheter group showed significant improvement in only 2/10 QoL domains. Furthermore, the change in QoL was significantly greater in the surgical group for general health, vitality and mental well-being. Despite the higher rate of complications in surgical ablation the net impact on QoL was positive. This is an important aspect of ablation treatment that deserves to be highlighted, as ultimately the aim is to improve patients' symptoms and hence QoL. The AF symptom score, which is a 4-point scale, in this study was not sensitive enough to show a difference in change in score between the two groups. This may be a reflection of the small sample size or its limitation for use in such a manner.

7.2.2.6 Reverse remodelling

The MRI sub-study is important as it is the first prospective study to show that LA (and RA) reverse remodelling, with its associated improvement in biventricular ejection fraction, can occur even in LSPAF patients. The only prior report examining reverse remodelling in LSPAF used LA diameter obtained from 2D M-mode echocardiography as a measure of LA size, and our data clearly shows this correlates poorly with actual 3D LA volume.[155]

These findings challenge the notion that progressive structural remodelling changes associated with LSPAF are irreversible. Furthermore, the baseline LA volume has been shown to be an independent predictor of LA reverse remodelling with an odds ratio of 1.08, suggesting that the higher the baseline LAmax volume, the more chance of reverse remodelling. Another interesting point is that even in those patients who have recurrences post ablation, reverse remodelling still occurs, presumably because the overall burden of AF has been significantly reduced.

Given that there are studies that show LA size as an important predictor of arrhythmia free outcome post ablation, many patients with LSPAF are not offered interventional therapy based on the fact their baseline LA size is too large (often using LA diameter obtained from 2D M-mode echocardiography). [41] Perhaps this latter practice should change as our data clearly shows poor correlation of this parameter with LA volume, although atrial volumes may themselves be less important, as our study showed that they were not predictive of clinical success. This raises the possibility of defining the geometric aspects of atrial enlargement and whether this has relevance in predicting clinical outcome. Overall, the clinical implications of these findings, however, are more profound as they suggest that LSPAF patients should be considered for ablation therapy irrespective of baseline LA size. Clearly, if these patients are

considered for ablation, they will be still be counselled to the possibility of multiple procedures (particularly with catheter ablation), but even if only clinical success (see chapter 6.5.2.2) is obtained this may be enough for the atria to reverse remodel, and hence offer protection from future arrhythmia recurrences and confer physiological advantages to the patient.

7.3 CFE sub-study

The CFE sub-study brings the discussion back to the mechanistic aspects of AF, and the techniques used in catheter ablation to address these. A recent 5 year outcomes paper in LSPAF showed that PVI alone achieved long term SR in only 24% patients.[31] There is now overwhelming evidence to show that PVI alone is not sufficient, and that additional substrate modification is required, and consequently numerous adjunct strategies have been detailed. These include linear lesions and CFE ablation, both of which have been documented to improve outcomes.[195 196 197] The use of linear ablation in catheter ablation originally stemmed from the highly efficacious cut-and-sew Cox-Maze procedures, where a series of linear incisions were used to compartmentalise and debulk the atria. In doing so, it is postulated that many triggers and drivers were also eliminated. CFE are thought to arise from areas of slow conduction, functional conduction block or tissue anisotropy, and may represent passive bystander activity or drivers of AF.[33 198] The elimination of CFE remote to sites of PVI and linear lesion RF application has now been documented in this and other studies, including in both heart failure and non-heart failure models. These consistent observations provide significant evidence that these abolished CFE are passive phenomena, which may explain the conflicting results seen when CFE only ablation strategies are used in AF ablation procedures. Furthermore, the CFE sub-study showed that the length of RF time during CFE ablation was

shown to predict arrhythmia free survival. Therefore, there is little doubt that targeting CFE are important, but the key question is how to differentiate accurately between those CFE that are active drivers, and those that are passive. The answer is that it is currently not possible to do so, and hence this remains one of the main limitations of employing CFE ablation. The accurate identification of functionally important CFE would enable targeted ablation of drivers, which would in theory improve outcomes, reduce unnecessary ablation and possibly reduce procedure times. An exciting development in this area has been the computational mapping and subsequent ablation of drivers, which has led to impressive results in non-paroxysmal forms of AF. This work is in its infancy, but could prove to be revolutionary if the technique is reproducible as it would tailor the ablation procedure to concentrate on patient specific driver mechanisms, and in doing so could improve outcomes whilst shortening procedure times.

7.4 Contact Force study

Despite the huge advances made in catheter ablation since the seminal paper by Haissaguerre et al. in 1998, there remains one fundamental limitation, namely PV reconnection. This limitation is once again highlighted by the CASA-AF data, where in all catheter ablation repeat procedure cases, PV reconnections ± linear lesion conduction recovery was found. The cornerstone of AF ablation may well be PVI, but the Achilles' heel remains the recurrence of atrial arrhythmias, predominantly due to a recovery in PV conduction.[15 88 164 199] Over the last decade, the desire to overcome this and hence improve outcomes in AF ablation, has driven both the electrophysiological community and industry to improve both tools and techniques to enable longer lasting RF lesions. Developments have included; irrigated-tip catheters; the

use of general anaesthesia to minimise patient movement intraprocedurally; use of steerable sheaths to help maintain better contact between catheter tip-tissue; and catheter shaft visualisation. However, these developments still require the operator to use a combination of surrogate markers (catheter stability on fluoroscopy, impedance drop, and electrogram attenuation) to judge appropriate contact with the endocardium. This was until the recent advent of contact force (CF) sensing catheters, which can provide the operator real time CF values during RF ablation.

The CF study presented in Chapter 5 was one of the first to show that this new technology could have a revolutionary impact in AF ablation. The study demonstrated that the use of real time CF not only reduced acute PV reconnections, but could also minimise PV reconnections at known hotspots when using appropriate CF. It also confirmed that if operators were blinded to CF data, they would obtain insufficient CF values to prevent subsequent reconnection. More recent data from another group has shown that one of the commonly used surrogates of CF, electrogram attenuation, actually correlates poorly with CF, although another surrogate, impedance drop, fared better.[200] Overall these data highlight the inadequacy of traditional surrogate measures for tissue CF, and also that CF-directed ablation can improve outcomes for patients.

The follow-on studies presented in Chapter 5 go on to provide further evidence for this latter point. The first study showed that CF in association with robotic navigation was shown to be superior to manual ablation without the use of CF in one-year clinical outcomes, whilst the second follow-on study demonstrated superior medium term (mean follow up 11.4±4.7 months) outcomes in paroxysmal AF.[201 202] Both studies highlighted an additional benefit in

the reduction in fluoroscopy times, which is likely to reflect greater operator confidence in catheter position and stability that real-time CF readings provide.

The improved safety that CF data provides must also be addressed. The LA wall thickness is heterogeneous and the surface of the LA endocardium can be irregular. This can in turn affect the positional stability of the catheter tip and in turn the force between the catheter tip and the myocardium. CF data is invaluable to highlight suboptimal contact in regions known to be difficult (e.g. ridge between left upper PV and left atrial appendage) to facilitate better lesion formation. Conversely, high CF values can prompt a timely response from the operator to adjust catheter orientation or pressure to reduce CF, and potentially prevent serious complications such as a steam pop or cardiac perforation resulting in tamponade.

This promising technology has been heralded by some as the missing link in AF ablation and although relatively new, there is a rapidly growing evidence to highlight the advantages of real time CF sensing. However, there is still more work to be done in this arena, including reaching a consensus as to the optimal target CF required to achieving long-lasting, transmural RF lesions. This technology has the potential to improve outcomes in AF ablation significantly, and may well provide the efficacy that has eluded electrophysiologists since the inception of catheter ablation.

7.5 Limitations

The limitation of the CASA-AF study was the non-randomised study design, which inherently does predispose to unmeasured systematic differences between the patient groups. However, patients were well matched with regards to baseline characteristics, and to

minimise the potential for referral bias, the modality of ablation was determined by patient choice. Furthermore, the analysis of the primary outcome data was carried out as an intention to treat analysis in keeping with a randomised control trial model.

Although the sample size was small, the effect size was significantly different between the two groups meaning that the study was not underpowered.

The SF-36 quality of life questionnaire used was a general health assessment, but perhaps inclusion of an additional disease specific questionnaire such as the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) Questionnaire would have provided additional insight.

Finally, the rhythm monitoring could have missed those with asymptomatic atrial arrhythmia episodes despite the fact the rigour of the monitoring schedule was greater than the minimum requirements set out by the 2012 HRS/EHRA/ECAS International Consensus document. [26]

7.6 Future Directions

During my MD Res studentship, I took the opportunity to develop this investigation into the next phase. I developed a randomised control trial protocol, based on the foundations laid by the CASA-AF study presented in this thesis. I concurrently applied for a £1.2 million NIHR research grant, which was successful.

The forthcoming CASA-AF RCT (due to commence in June 2015) seeks to provide a robust assessment of the differences between thoracoscopic and catheter ablation techniques in LSPAF. It is an industry-independent, multi-centre randomised controlled trial. The primary hypothesis is that thoracoscopic surgical ablation is more effective than percutaneous

catheter ablation in LSPAF with regards to freedom from atrial arrhythmia at 12 months' follow-up after a single procedure without antiarrhythmic drugs. The study will also evaluate, in detail: the effect on LA anatomy and function; safety; change in patients' quality of life using validated general and disease-specific tools; and perform a comprehensive health economic assessment.

To answer the question about the importance of ganglionated plexi (GP) ablation in thoracoscopic surgical procedures, an additional sub-study is planned using nuclear MIBG scanning to identify pre-and post-ablation GP distribution and their correlation with clinical outcomes.

7.7 CASA-AF Conclusions

Data from this prospective, non-randomised study indicates that thoracoscopic surgical ablation achieves superior outcomes with respect to freedom for atrial arrhythmia at 9 months. However, there is an increased risk of major (non-fatal) complications with thoracoscopic surgical ablation, which may have adverse effects on patients' quality of life. Further refinement in surgical tools and techniques is required to reduce complication rates and capitalise on the advantages to make it a viable alternative to catheter ablation. Larger scale and more detailed studies are required to evaluate these two modalities in more detail. CASA-AF provides the framework to base future rigorous assessment of these strategies with the hope that better outcomes can be achieved for LSPAF patients.

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Appendix

Royal Brompton & Harefield NHS
NHS Foundation Trust

A Study to Assess ***C***atheter ***A***blation Versus Thoracoscopically Assisted ***S***urgical ***A***blation in Persistent ***A***trial ***Fi***brillation (CASA-AF)

PATIENT INFORMATION SHEET

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We invite you to consider taking part in a research project
We would like to invite you to consider taking part in a research study at the Royal Brompton & Harefield NHS Foundation Trust. Before you decide it is important for you to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
Atrial fibrillation (AF) is a common heart condition where the heart does not beat in a regular rhythm. This can cause unpleasant symptoms, and can increase the risk of stroke. Traditionally, AF has been treated with medication and/or electrical therapy, with limited success. Two newer, different procedures that are used to treat AF are *catheter ablation* and *thoracoscopically assisted surgical ablation*. At present it is not yet certain which is the more effective treatment. This study is part of a postgraduate higher degree research project, and its aim is to identify the better treatment for this important medical condition. People with AF, including you, could potentially be eligible for either procedure, but you will be offered one of the procedures after careful consideration of your individual medical details. The effects of each treatment will be assessed after the treatment, by considering any improvement in your symptoms, your heart pump function and how regular your heart rhythm is.

Why have I been invited?
You are being asked to participate in this research study because you have symptoms (e.g. palpitations) due to a condition called atrial fibrillation (AF) and you have been identified as a potential candidate. This study will involve a total of 60 participants.

Background to the research study

What is atrial fibrillation?
Normal heart rhythm (known as sinus rhythm) depends on regular electrical activity of your natural pacemaker cells – the sinus node, which usually 'fires' at about 60-100 beats per minute. The impulse spreads to create a coordinated contraction of the heart and the heart rate responds appropriately to the needs of the body. This allows the heart to speed up with activity and slow down on resting. In AF, however, the normal sinus rhythm (SR) is lost due to abnormal electrical activity initiated from the main veins that drain blood back into the heart. This results in the upper collecting chambers (atria) having a completely chaotic rhythm (fibrillation), which no longer pumps blood effectively. At the connection to the lower pumping chambers, the heart 'filters out' many of the impulses so the heart still pumps – but with an irregular, often fast, heart beat which may respond poorly to the needs of the body.

How is atrial fibrillation treated in patients?
There are two alternative treatment strategies for AF (rhythm control and rate control) which doctors may use to try to improve the symptoms related to it, as well as longer-term health:

Rhythm-control – This approach attempts to restore and maintain normal SR. This can be by means of electric shock treatment (DC cardioversion*)* together with long-term tablet medication, or by more recently available 'cauterisation' therapy (catheter or thoracoscopic surgical ablation)*.*

Rate-control - Heart rates in AF can be very variable and generally tend to be too fast putting long term 'stress' on the heart. Rate-control requires patients to take heart-rate slowing tablets to prevent very fast heart rates and allow the heart to pump more efficiently. AF itself is 'accepted' as the long-term heart rhythm.

In this study we will be looking at patients with long standing AF, who have tried and failed tablet and/or electrical therapy to control AF and remain symptomatic. It is in these patients where the need to restore normal SR is very important and this study will concentrate on ***investigating different rhythm-control strategies*** to achieve this.

How might this study help identify the optimal treatment?
As doctors still do not know what the best approach is in treating long-standing persistent AF there is a lot of ongoing research in this area. Catheter ablation – a fairly recent mode of treatment - has been shown to achieve modest degrees of success in restoring normal SR but most patients do require 'multiple' ablation treatments.

Thoracoscopically assisted surgical ablation offers patients an alternative choice of therapy to catheter ablation. Small keyhole incisions are used to access the heart instead of opening up the chest cavity as in traditional open-heart surgery. This procedure has been developing in the last few years with small studies showing good results but to date there has been no study comparing these two types of treatment in patients with long-standing persistent AF. Therefore we do not know which one is better and this has prompted us to conduct this study to try and help answer this question.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form to show you have agreed to take part. You may choose not to participate in this study or you may leave the study at any time without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?
We will first check that you meet the entry criteria and are willing to participate in all parts of the study. If you are, you will sign a consent form following which we will arrange a convenient date for you to undergo 'baseline' assessments including tests of heart rhythm and function (listed below). These tests are important, as they will allow us to see how you are before and after the treatments. The tests will include the following: -

- **History & clinical examination** – similar to when you attend for an outpatient clinic.
- **AF Symptom score** - a short questionnaire about your symptoms that takes 1 minute to complete.
- **Blood tests** - blood will be taken for routine tests (blood count/kidney/liver/thyroid). Some samples will be stored for tests looking at specific proteins relevant to heart function.
- **ECG -** to check you are in AF.
- **Echocardiogram** - you are likely to have had this heart ultrasound scan at some point. It looks at the heart muscle and valve function and takes 20-25 minutes.
- **Cardiac MRI scan –** a sophisticated scan that looks at your heart in great detail and takes about 60 minutes.
- **Ambulatory ECG** (wearable heart monitor) - you will wear the monitor at home so we can check your heart rhythm and rate during routine activities. The recorder should be removed if you have a bath or shower; you will be shown how to put it back on. We will arrange its return with you.

After these tests your case will be discussed by rhythm specialists and cardiac surgeons and a collective clinical decision will be made as to which procedure you will be allocated to: **thoracoscopically assisted surgical ablation** or **catheter ablation.** Your consent will clearly outline that you are happy to allow this clinical decision to be made by the panel of experts. You will then be followed up over a period of 12 months after which your participation in the study will end.
If I participate - what will happen if I am assigned to surgical ablation?

What is thoracoscopically assisted surgical ablation?
The procedure is a minimally invasive surgical technique performed under general anaesthetic. It does not involve 'open heart' surgery; instead small keyhole incisions are made on both sides of the chest. This provides access to the areas responsible for causing AF, which is the left upper chamber of the heart (left atrium). A number of 'heat lesions' (referred to as ablation) will be created on the outer surface of the left atrium by applying an instrument called a radiofrequency clamp. These ablation areas will develop into scars to isolate the areas responsible for the initiation of the rhythm abnormality allowing the heart to maintain normal SR. During thoracoscopic surgical ablation of AF, only a selected part of the upper heart chambers are treated, so the main pumping chambers are unaffected.

The thoracoscopically assisted surgical ablation procedure
You will be admitted to a hospital ward the afternoon before or morning of your procedure, where medical staff (including an anaesthetist) will assess you. A drip-tube (cannula) will be inserted in your

arm for routine blood tests and for administering medications. You should not eat or drink (except sips of water to take tablets) for **6 hours** before your procedure.

The operation itself will be performed whilst you are asleep under general anaesthesia in the operating theatre and will last 2-4 hours. No blood thinning medication will be used during the procedure and in fact, if you are on warfarin this will have been stopped 5 days before the procedure.

Once you are under anaesthetic, a special camera will be inserted in the gullet to visualise the heart during the procedure and exclude any clots. Two small incisions (5mm) will be made on the side of the chest wall to allow access to the heart. One of these incisions will be subsequently enlarged (5cm) and used to facilitate the introduction of instruments. The right side of the heart will be operated on first. A camera and specialised instruments will be used to facilitate performance of the operation with radiofrequency, a special energy source, used to create heat lesions on the surface of the heart to eliminate the abnormal areas of electrical activity. These heat lesions subsequently turn into scar tissue, which stops the irregular heart rhythm from being propagated in the upper chamber of the heart. The procedure will then be repeated on the left side, with similar incisions on the left side of the chest. If you remain in AF despite ablation, you may undergo an electrical shock (DC cardioversion) to restore SR.
In addition, the atrial appendage, a small outpouching of the upper chamber of the heart, may be excised (removed) depending on the surgeon's assessment of feasibility and safety. The benefit of this is that it may further reduce the risk of stroke caused by AF. If it is excised, a biopsy (small sample of this tissue) may be kept and stored (for a maximum of 5 years) for additional/future research at the Royal Brompton & Harefield NHS Foundation Trust site.

At the end of the operation a small plastic tube will be positioned in the chest cavity to allow drainage of blood (generally removed after 24-48 hrs) and the incisions will be closed. You will then be observed on the Intensive Care Unit (ICU) for 12-24 hours and transferred to a ward thereafter. You will be started on appropriate painkillers in addition to your normal preoperative medication including warfarin (warfarin will generally be started the day after the procedure). You should expect to be in hospital for 3-5 days.
The benefits of the procedure can take 3 months to become fully manifest and the heart may go back into an irregular rhythm in the early (3 months) post-operative period. This does not signify failure of the procedure and an electric shock may be required to convert the heart back into a normal SR.

You will then be followed up formally at regular intervals undergoing the same assessments and investigations as the other (catheter ablation) group of patients. At these visits, your medication will be carefully reviewed and adjusted as necessary to ensure that you are on optimal treatment.

If I participate - what will happen if I am assigned to catheter ablation?

What is catheter ablation?
Catheter ablation was introduced in the late 1980s and can be used to treat many heart rhythm problems. This minimally invasive procedure has been adapted and developed in the last 10 years to treat more complex rhythms such as AF. It is performed under general anaesthetic by passing a long wire (*catheter*) to the heart, through a small puncture in the leg. Radiofrequency energy is passed down this catheter to create 'heat lesions' (ablation) on the inner surface of the heart (mainly left atrium) to eliminate the abnormal electrical impulses. Subsequently, those areas will scar and isolate the areas responsible for the initiation of the rhythm abnormality allowing the heart to maintain normal SR. Each treated area is very small (3-4mm) so the technique can be applied in an accurate point-by-point fashion. During catheter ablation of AF, only a selected part of the upper heart chambers are treated, so the main pumping chambers are unaffected.

The catheter ablation procedure
You will be admitted to a hospital ward the afternoon before or morning of your procedure, where medical staff will assess you, including an anaesthetist. A drip-tube (cannula) will be inserted in your arm for routine blood tests and for administering medications. You should not eat or drink (except sips of water to take tablets) for **6 hours** before your procedure.

The procedure itself will be performed whilst you are asleep under general anaesthesia in the operating theatre and will last 3-5 hours. Unlike, thoracoscopic surgical ablation, warfarin does not need to be stopped for the procedure and in fact additional blood thinning medication (heparin) will be used during the procedure to minimise clot formation on the equipment used (this is not required for thoracoscopic surgical ablation).

Once you are under anaesthetic, a special camera will be inserted in the gullet to visualise the heart during the procedure and exclude any clots then, via a small puncture in your groin area small plastic tubes will be placed in the veins and possibly the artery. Thin plastic-coated wires called *catheters* will be inserted through the tubes and steered to the heart. The ablation will then be performed using radiofrequency, a special energy source, used to create 'heat lesions' on the inner surface of the heart to eliminate the abnormal areas of electrical activity. These 'heat lesions' subsequently turn into scar tissue, which stops the irregular heart rhythm from being propagated in the upper chamber of the heart. If you remain in AF despite ablation, you will undergo an electrical shock (DC cardioversion) to restore SR.

At the end of the procedure, blood thinning will be stopped and the tubes removed from your groin. Some patients may be looked after in intensive care or 'recovery' for a few hours before returning to the ward. You will need to lie flat for 1-2 hours after the procedure to reduce the chance of groin bleeding. You will continue with your normal preoperative medication and typically, you will be discharged the day after the procedure unless you require other medical care.

The benefits of the procedure can take 3 months to become fully manifest and the heart may go back into an irregular rhythm in the early (3 months) post-ablation period. This does not signify failure of the procedure and an electric shock may be required to convert the heart back into a normal SR.

You will then be followed up formally at regular intervals undergoing the same assessments and investigations as the other (surgical ablation) group of patients. At these visits, your medication will be carefully reviewed and adjusted as necessary to ensure that you are on optimal treatment.

What happens if I get a recurrence of AF after 3 months?
Recurrence of AF *after 3 months* suggests the first procedure was not completely effective – we would then offer a second ablation procedure, as per standard practice. All cases at this stage will be performed by catheter ablation regardless of your initial procedure (it is technically difficult to perform a second thoracoscopic surgical procedure). A recurrence generally indicates that you need some 'top up' ablation, which is best provided by catheter ablation. For those who have had an initial catheter ablation we know that a significant proportion of patients do need more than one ablation procedure to achieve long-term remission from AF.

If after 2 procedures, further procedures are clinically required, they will be conducted outside of the study protocol as the study wishes to evaluate outcomes having had a maximum of 2 procedures. In any case, it is difficult to fit in more than 2 procedures within the study timeframe.

What follow-up will I receive after my ablation procedure?
We would like to find out about the effect of each type of treatment with regard to your symptoms, heart rhythm and heart function. Hence we will arrange a follow-up timetable with you (as below) for

repeat tests after your ablation treatment. The same follow-up schedule applies to patients having either type of ablation treatment.

The tests include all the same things you would have had at the start of the study such as ECGs, blood tests, a small wearable ECG heart monitor, a symptom questionnaire and cardiac MRI scans. You will not have all of these tests at each visit but a selection from them and this is detailed below in the follow-up schedule (boxes below). At each follow-up visit, all the tests are performed that same day and you will be carefully assessed and your medical treatments reviewed and adjusted as necessary.

3-Month Follow-Up
ECG & Ambulatory ECG monitor
AF Symptom Score
Blood tests
Cardiac MRI

6-Month Follow-Up
ECG & Ambulatory ECG monitor
AF Symptom Score

9-Month Follow-Up
ECG & Ambulatory ECG monitor
AF Symptom Score
Blood tests
Cardiac MRI & Echocardiogram

12-Month Follow-Up
ECG & Ambulatory ECG monitor
AF Symptom Score
Blood tests

After this time, the study will be completed, and you will be referred back to your original specialist doctor. We will then analyse all the results from the patients who have participated in the study. Once the data analysis is complete, we aim to publish the results in scientific journals and present them at scientific meetings. All participants will be notified of the outcomes, via your GP or in person. If you continue to require specialist heart-rhythm care, you will be offered further follow up in an appropriate cardiology clinic at Royal Brompton or Harefield Hospital.

Are there any financial incentives for participation?
There are no financial incentives for participation.

What will I have to do?
Involvement in this study should not impose any restrictions to your current lifestyle. There are no specific dietary restrictions. After a procedure it is generally advised that you should not drive for 3-5 days afterwards. Otherwise you can drive, drink, take part in sport or indeed do anything that is within the purview of the advice given by your doctor considering your atrial fibrillation. You will be required to continue taking the medications that have been prescribed earlier unless instructed otherwise.

What are the alternatives for diagnosis or treatment?
You do not have to participate in this study to receive treatment for your condition. The other form of treatment is using various tablets, which you are already likely to be on.

What are the possible disadvantages and risks of taking part?
Your safety is of utmost importance to us. We appreciate that all medical treatments involve some degree of risk, but this is offset against their potential benefits. Neither arm of the study involves experimental treatments in that both thoracoscopic surgical ablation and catheter ablation therapies

are recognised treatments for patients with AF. Royal Brompton and Harefield NHS Foundation Trust is one of the largest UK centres for catheter ablation for AF. Although thoracoscopically assisted surgical ablation is a relatively new procedure, our surgeons have extensive experience in thoracoscopic surgery and surgical ablation and they will be combining these two skills to provide the thoracoscopic ablation procedure. Hence, highly experienced health care professionals will oversee your care.

All procedures involving the heart carry a small risk of a significant complication. However, this should be balanced against both the long-term risk of stroke/major bleeding (if remaining in AF and on warfarin) – approximately 1% per year, the benefits of being back in normal sinus rhythm, and the possibility of side effects and adverse reactions on rhythm-control medication.

There are small risks associated with general anaesthesia and use of the ultrasound camera that is placed in the gullet. During the procedure small amounts of intravenous contrast (dye) may be used during catheter ablation which carries a very small risk of an allergic reaction requiring treatment (0.01%) patients with an increased risk to approximately 0.05% in asthmatics or patients with food and drug allergies, and in patients with prior reaction to contrast. A special type of contrast (low osmolar) is used in all cases to minimise these risks. The risk of death is exceedingly low, between 0.001 – 0.0001%.

The catheter ablation procedure itself is associated with the following possible complications, of which you should be aware:

- Stroke or other major blood clots 0.5-1% risk.
- Cardiac tamponade in 1-2% of cases, this is blood leak around the heart during or after the procedure which may require a small plastic tube to be inserted to drain the fluid. Rarely, in about 1 in 500 cases (0.2%), the leakage has to be operated on by open chest surgery.
- Narrowing of a blood vessel (pulmonary vein stenosis) that carries blood from the lungs back to the heart. Rare with modern ablation techniques with a risk of 0.5%.
- Bruising and other problems relating to blood vessel damage may occur but usually resolve spontaneously or with minor treatment with only 1-2% risk of significant complications
- The nerve responsible for the movement of one side of the breathing muscle (diaphragm) can rarely be damaged by ablation in 0.3% of cases and is generally reversible over time.
- Inadvertent ablation of the specialised conducting tissues of the heart can require insertion of a permanent pacemaker but the risk is very low at approximately 0.25%.
- Life-threatening complications are rare: according to a worldwide survey, the risk of death associated with catheter ablation of AF is 0.1%.

Can you tell me more about the exposure to ionising radiation?
You will be exposed to some radiation if you have catheter ablation procedures in the same way as you would if you were not taking part in this study. We are all exposed to natural background radiation every day of our lives, and each X-ray or nuclear medicine examination adds a small additional dose on top of this. A catheter ablation is equivalent to 1 to 4 years of natural background radiation, depending on how long the procedure lasts. Such radiation exposure may slightly increase the risk of developing cancer many years or decades later. To quantify this, we have worked out the maximum exposure you could receive under this study protocol - *three* ablation procedures (likely only to be two), each with the maximal permitted X-ray dose (*i.e. the majority of patients will receive a much lower dose, thus the following risk is an overestimate on both counts)*. At this level of exposure, about 1 in 700 people may acquire a cancer during their whole lifetime. We all have about a 1 in 3 to 1 in 4 chance of getting cancer during our lives, so the actual increase in risk is small (e.g. 33.3% increased to 33.5%). Skin injury such as redness similar to sunburn may rarely occur, but should not occur using modern X-ray equipment and methods. Total radiation dose at ablation will be minimised

by use of pulsed X-ray and special mapping systems.

Are there any benefits to me if I participate in the study?

The reason we are performing the study is to establish which form of treatment is better in restoring normal SR in patients with long-standing persistent AF. It will help provide valuable information for the management of this condition but at present we do not know which of the two treatment groups will benefit more. In addition, it is possible that participants may benefit from being in the clinical trial simply because of undergoing more detailed tests and slightly more frequent visits to see doctors than usual (depending on your previous circumstances). This might provide the opportunity for us or your doctor to look after any heart problems more closely and to pick-up any other health related problems sooner than in routine clinical care.

What happens when the research study stops?

At the end of the research, your care will continue as usual.

Are there any reasons why I should not participate in the study?

You should not take part in this study if you are pregnant or if you are planning to become pregnant. You will not be able to participate in any other clinical trial for the entire period you are participating in this trial.

What if relevant new information becomes available?

Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If this happens, we will tell you about it and discuss with you whether you want to continue in the study. If you decide not to carry on we will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form. Also, on receiving new information we might consider it to be in your best interests to withdraw you from the study. We will explain the reasons and arrange for your care to continue.

What if I do not want to carry on with the study?

If you do not want to take part in this study, you will receive standard care as determined by your doctor. Your participation in this study is voluntary and you may withdraw from the study at any time without prejudice to your future medical care. Should you decide to withdraw from the study for any reason, you are asked to contact Dr Shouvik Haldar immediately via the Royal Brompton Hospital switchboard, research office number 0207 352 8742 or email shouvikhaldar@nhs.net. Should your participation in the study be terminated, regardless of the reason, you will not suffer any penalties or loss of benefits to which you are otherwise entitled.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers (Dr Shouvik Haldar via the Royal Brompton Hospital switchboard or 020 7352 8742 or shouvikhaldar@nhs.net) who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure via Royal Brompton and Harefield Patient Advice and Liaison Service (PALS).

What if something goes wrong?

In the event that something does go wrong and you are harmed during the study due to someone's negligence then you may have grounds for legal action for compensation against the Royal Brompton and Harefield NHS Foundation Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you. NHS indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.

Will my taking part in the study be kept confidential?
If you do decide to participate you will be assigned a participant code, which will be used as a patient identifier. This will mean that all information that is collected about you during the course of the research will be kept strictly confidential and be anonymised. Any information about you that leaves the hospital will also have your all of your personal details removed so that you cannot be recognised from it. We will request your consent before informing your GP about your participation in the study.

Will my General Practitioner / Family doctor (GP) be informed of my involvement?
Provided you consent to this, your GP will be informed that you are participating in the study and kept informed of your medical progress. We may exchange information regarding your general medical health with your GP.

What will happen to the results of the research study?
Your medical records will be made available for review by the study investigators and regulatory authorities (who periodically check that the studies are being carried out correctly). The information in these records will be kept confidential but on rare occasions the law may require disclosure to third parties. At the end of the project all the research results are gathered together and analysed. The researchers have a professional responsibility to publish their findings, however your identity will not be revealed. Most research is published in the medical press – if you are interested in knowing the overall results of the study, ask the researchers about this. You are entitled to see any results or information about you under the Freedom of Information Act.

Who is organising and funding the research?
*Royal Brompton and Harefield Hospital NHS Foundation Trust i*s sponsoring the research but there is no external funding for this research to be carried out. The doctors conducting the research are not being paid for including you in the study.

Who has reviewed the study?
All research in the NHS is looked at by an Independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by Oxfordshire REC A Research Ethics Committee. In addition approval has been gained from *Royal Brompton and Harefield Hospital NHS Foundation Trust* Research & Development Offices.

Contact for Further Information
If you would like any further information about the study, either now or at time during the course of the study, please ask a member of the Research Team at:

Dr Shouvik Haldar, Research Fellow in Cardiac Electrophysiology
Email: shouvikhaldar@nhs.net, or telephone the research office number 0207 352 8121 Extn 8742.

Alexandra Wise, BHF Arrhythmia Nurse Specialist - Ask for bleep 1146 via Brompton switchboard
Email a.wise@rbht.nhs.uk

For urgent matters outside of normal working hours, you may contact:
On-call cardiology registrar, via Brompton switchboard

Thank you for taking the time to consider this study. If you do choose to participate, you will be given

a copy of this information sheet to keep and also a copy of the consent form that you will be asked to sign.

CONSENT FORM

Royal Brompton & Harefield NHS
NHS Foundation Trust

A Study to Assess *C*atheter *A*blation Versus Thoracoscopic *S*urgical *A*blation in Persistent *A*trial *Fi*brillation (CASA-AF)

Study Number: Patient Identification Number for this trial:
Name of Researcher: Dr Tom Wong **Please initial box if you agree**

1. I confirm that I have read and understand the information sheet dated 14/03/2011 (version 7) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study, may be looked at by researchers involved in the study, or responsible individuals involved in the study, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to blood samples being taken for analysis, and kept and stored, if required, for future analysis. I understand that no genetic tests will be performed on this blood. ☐

5. I agree to any biopsy samples being taken, to be kept and stored, if required, for additional / future research. ☐

6. I agree for the allocation of my first procedure to be decided by a panel of experts as stated in the patient information sheet ☐

7. I agree to my GP being informed of my participation in the study ☐

I hereby agree to take part in the above research study.

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher	Date	Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes

CASA-AF Patient Study ID number _____

Sex **Male / Female**

Confirm Inclusion/Exclusion Criteria Met _____

STUDY ARM **THORACOSCOPIC ABLATION** **CATHETER ABLATION**

DATE OF ENROLLMENT (baseline investigations) _____

DATE OF INDEX PROCEDURE to mark start of follow up _____

DATE OF 6/52 ECG follow-up _____

DATE OF 3M follow-up _____

DATE OF 6M follow-up _____

DATE OF 9M follow-up _____

DATE OF 12M follow-up _____

Inclusion

1. Age ≥18 years and ≤ 80
2. Symptomatic persistent AF (≥1≤5 years), refractory to at least 1 AAD and/or DCCV
3. Patient is legally competent and willing and able to sign informed consent form
4. Patient is willing and able to adhere to follow up visit protocols for the duration of the study

Exclusion Criteria

1. Left ventricular ejection fraction < 40%
2. Cardiovascular implantable electronic device (contraindicates MRI imaging)
3. Contraindication to anticoagulation
4. Thrombus in the LA despite anticoagulation
5. CVA within the previous 6 months
6. Previous thoracic & cardiac surgery (including interventions for AF such as Cox-maze procedure)
7. Prior LA catheter ablation with the intention to treat AF
8. Prior AV nodal ablation
9. Patients actively participating in another research study will be not be permitted to enrol. Patients who have been involved with other research studies will be able to participate after a minimum period of 3 months after completion of prior study follow up.
10. Co-morbid condition that in opinion of investigator confers undue risk of GA or thoracoscopic surgery.

CASA-AF Patient Study ID number _____

BASELINE ASSESSMENT

PAST MEDICAL HISTORY

(free text)

Coronary artery disease **Y/N** Myocardial infarction **Y/N**
Percutaneous coronary intervention **Y/N**
CABG **Y/N**
Valve operation **none, MV repair, MVR, AVR, other_____**
Implantable Device NOT in-situ ☐

COPD/asthma **Y/N** Smoking **Current / ex- (>3months) / never**
Diabetes **Insulin / tablet /diet / N**
Thyroid **Hyper / Hypo/ N**
Hypertension **Y/N** Renal disease **Y/N**
CVA **Y/N** TIA **Y/N**

Comments/Other (free text) _____

ARRHYTHMIA CHARACTERISTICS

First known AF **_____**

Duration of AF _____ (should be long-standing persistent >1 < 5 years)

Past DC cardioversion? N/ Y - number: **1,2,3, >3**
Previous SVT **Y/N** Previous typical flutter **Y/N**
Prior AV node ablation **Y/N** Prior other (non-AF) ablation **Y/N**

SYMPTOMS
Palpitation **Y/N**
Syncope **Y/N**
Angina **Y/N**
Breathlessness **Y/N**
Orthopnoea (no. pillows) **(n=____)**
PND **Y/N**
Ankle swelling **Y/N**
Fatigue **Y/N**
Comments _____

MEDICATION Allergy **Y/N** _____ Warfarin dose (mg) _____

Baseline		**3/12**	**6/12**	**9/12**	**12/12**
Drug Name	Dosage (mg)/ day				

Previous/failed AADs: **None** **Amiodarone**
Sotalol **class I**
other

Comments_____

CLINICAL EXAMINATION

DATE_____

Height _____**m** Weight _____**kg**

BP (mmHg) _____ **/**_____

Heart rate: _____**bpm**

JVP: **normal /raised / markedly raised (>10cm)**

Murmur **none** **systolic diastolic _____**

3rd HS **Y/N** 4th HS **Y/N**

Chest **normal**

crepitations **wheeze**
reduced breath sounds dull to percussion

P. oedema: **none** **mild** *(ankle)* **moderate** *(knee)* **severe** *(thigh-sacral)*

Comments: _____

INVESTIGATIONS
Date_____
Comments _____

Blood tests. ☐

Hb (g/dl)	Plts (x10^9/L)	WCC (x10^9/L)	INR
Na (mmol/L)	K (mmol/L)	Urea (mmol/L)	Creat (μmol/L)
Bili (μmol/L)	ALP (U/L)	ALT (IU/L)	Albumin (g/L)
CRP (mg/L)	fT4 (pmol/L)	TSH (IU/L)	
BNP (pmol/L)	TGF Beta	ANP	

ECG ☐

QRS rate (bpm) _____
Rhythm at evaluation: **sinus, AF, AT, other _____**
QRSd (ms) _____
Axis (degrees) _____
LBBB/RBBB **no, LBBB, RBBB, other _____**

CARDIAC MRI ☐

ECHOCARDIOGRAM ☐

AF SYMPTOM SCORE ☐ Score _____

CHADSVASC ☐ Score _____

SF 36 QUESTIONNAIRE ☐ Score _____

Blanking Period 6/52 ECG

ECG ☐

QRS rate (bpm) _____

Rhythm at evaluation: **sinus, AF, AT, other _____**

If Atrial Arrhythmia at 6/52 book date for DCCV within 4/52 _____

Follow-up 3 Months

Any major adverse event: **Y/N**
If y _____

Any unplanned hospital admission? Y/N _____

Significant clinical event? Y/N _____

3 month CLINICAL EXAMINATION

DATE_____

Height _____**m** Weight _____**kg**

BP (mmHg) **_____/_____**

Heart rate: _____**bpm**

JVP: **normal raised** **markedly raised (>10cm)**

Murmur **none** **systolic diastolic _____**

3rd HS **Y/N** 4th HS **Y/N**

Chest **normal**
crepitations **wheeze**
reduced breath sounds dull to percussion

P. oedema: **none** **mild** *(ankle)* **moderate** *(knee)* **severe** *(thigh-sacral)*

Comments: _____

3 month INVESTIGATIONS

Date_____
Comments (free text)_____

Blood tests ☐

BNP (pmol/L) _____

TGF beta _____

ANP _____

ECG ☐

QRS rate (bpm) _____

Rhythm at evaluation: **sinus, AF, AT, other _____**

CARDIAC MRI ☐

AF SYMPTOM SCORE ☐ Score _____

CHADSVASC ☐ Score _____

SF 36 QUESTIONNAIRE ☐ Score _____

AMBULATORY ECG MONITORING ☐

If Atrial Arrhythmia at 3/12 – Book date for re-do procedure_____

Follow-up 6 MONTHS

Any major adverse event: **Y/N**
If y _____

Any unplanned hospital admission? Y/N _____

Significant clinical event? Y/N _____

6 month CLINICAL EXAMINATION

DATE_____

Height _____**m** Weight _____**kg**

BP (mmHg) **_____/_____**

Heart rate: _____**bpm**

JVP: **normal raised** **markedly raised (>10cm)**

Murmur **none** **systolic diastolic _____**

3rd HS **Y/N** 4th HS **Y/N**

Chest **normal**
crepitations **wheeze**
reduced breath sounds dull to percussion

P. oedema: **none** **mild** *(ankle)* **moderate** *(knee)* **severe** *(thigh-sacral)*

Comments: _____

6 month INVESTIGATIONS

Date_____
Comments (free text)_____

Blood tests ☐

BNP (pmol/L) _____

TGF beta _____

ANP _____

ECG ☐

QRS rate (bpm) _____

Rhythm at evaluation: **sinus, AF, AT, other _____**

ECHOCARDIOGRAM ☐

AF SYMPTOM SCORE ☐ Score _____

CHADSVASC ☐ Score _____

SF 36 QUESTIONNAIRE ☐ Score _____

AMBULATORY ECG MONITORING ☐

Follow-Up 9 MONTHS

Major adverse event: **Y/N**

Any unplanned hospital admission? Y/N _____

Significant clinical event? Y/N _____

9 month CLINICAL EXAMINATION

DATE_____

Height _____**m** Weight _____**kg**

BP (mmHg) _____**/**_____

Heart rate: _____**bpm**

JVP: **normal raised** **markedly raised (>10cm)**

Murmur **none** **systolic diastolic** _____

3rd HS **Y/N** 4th HS **Y/N**

Chest **normal**
crepitations **wheeze**
reduced breath sounds dull to percussion

P. oedema: **none** **mild** *(ankle)* **moderate** *(knee)* **severe** *(thigh-sacral)*

Comments: _____

9 MONTH INVESTIGATIONS

Date_____
Comments (free text)_____

ECG ☐

QRS rate (bpm) _____

Rhythm at evaluation: **sinus, AF, AT, other _____**

CARDIAC MRI ☐

AF SYMPTOM SCORE ☐ Score _____

CHADSVASC ☐ Score _____

SF 36 QUESTIONNAIRE ☐ Score _____

AMBULATORY ECG MONITORING ☐

Final visit 12 MONTHS

Major adverse event: **Y/N**

Any unplanned hospital admission? Y/N _____

Significant clinical event? Y/N _____

12 month CLINICAL EXAMINATION

DATE_____

Height _____**m** Weight _____**kg**

BP (mmHg) _____**/**_____

Heart rate: _____**bpm**

JVP: **normal raised** **markedly raised (>10cm)**

Murmur **none** **systolic diastolic** _____

3rd HS **Y/N** 4th HS **Y/N**

Chest **normal**
crepitations **wheeze**
reduced breath sounds dull to percussion

P. oedema: **none** **mild** *(ankle)* **moderate** *(knee)* **severe** *(thigh-sacral)*

Comments: _____

12 MONTH INVESTIGATIONS

Date_____
Comments (free text)_____

ECG ☐

QRS rate (bpm) _____

Rhythm at evaluation: **sinus, AF, AT, other _____**

CARDIAC MRI ☐

ECHOCARDIOGRAM ☐

AF SYMPTOM SCORE ☐ Score _____

CHADSVASC ☐ Score **_____**

SF 36 QUESTIONNAIRE ☐ Score _____

AMBULATORY ECG MONITORING ☐

Case report form for CASA-AF RF ablation procedures

Patient Study ID _____ RFA number **1 2** Site **HH / RBH**
Date ____/____/_____ Operator 1 _____ Operator 2 _____
3D mapping system: **NavX Velocity/ CARTO**
Procedure time (min) _____ Ablation time (sec) _____ Saline dose (ml)_____
Heparin dose (IU)_____ Fluoroscopy time (min) _____ Dose Area Product (cGycm2) _____
Baseline rhythm **AF, SR, AT/flutter**

Log all time points on Bard – annotate all geometry and CFE maps

Start time _____ **Femoral access time** _____ **Transeptal x2 access time** _____
RA geo_____ -_____ **RACFE**_____ -_____ **LA geo**_____ -_____ **LA CFE**_____-_____

Time Start---end		Tick if done	Block	Cumulative RF time (sec)	AFCL *after* stage (ms)		CFE map
					LAA	RAA	
	Baseline						
	PVI		Y/N				
	Roof line		Y/N				
	MVI line		Y/N				
	Epicardial CS						
	CFAE						
	Other (redo) _____						
	SVC iso (redo						
	CTI (redo)		Y/N				

End time (sheaths out) _____
Termination of AF **No** **To AT (_____)** **To SR**
DCCV required>SR **No** **Yes – successful** **Yes – unsuccessful (_____)**
Comments (free text)
_____
Procedural complications (up until discharge form hospital)

None / Stroke or TIA / Tamponade / Vascular / other_____
Rhythm at discharge **SR** **AF** **AT** **other** _____
ITU stay if needed (days)_____ Hospital stay (days) __

CASA-AF Thoracoscopic AF Ablation Protocol

CASA-AF Study ID Date

Site

Operator

Type of EP Catheter Used	
Procedure Start Time	

Lesion Set PVI + GP Ablation + Box Lesion (Superior & Inferior Line)

RIGHT SIDE

Baseline PV Testing pre-ablation
Surgical pen

EP Catheter

Right PV Bipolar Clamp Ablations (document no. of seconds for each application)
Total No of Applications

Post PVI Entrance Block (surgical pen on PV side of line – absent potentials)

Initial GP Mapping +ve / -ve

Inferior Box Line Ablation (document no. of seconds for each application)

Total No of Applications

GP Ablation (document no. of seconds for each application)
Total No of Applications

Post Ablation GP Mapping +ve / -ve (should have no remaining vagal effect)

Superior Box (Roof) Line Ablation (document no. of seconds for each application) (line done from LSPV towards RSPV)
Total No of Applications

LEFT SIDE

Baseline PV Testing pre-ablation
Surgical pen

EP Catheter

Left PV Bipolar Clamp Ablations

Total No of Applications

Post PVI Entrance Block
Surgical pen - PV side of line
EP Catheter

DCCV to SR (No. of times and Joules used)

Box Lesion Entrance Block - Surgical Pen / EP Catheter within Box – Quiet?

Box Lesion Exit Block
Pace within box to show outside of box (PV antrum) is not capturing

Left PV Exit Block
Pace PV side of PVI line to show body of atrium (via surface ECG) not capturing

SWITCH BACK to RIGHT SIDE FOR TESTING

Right PV Exit Block
Pace PV side of PVI line to show body of atrium (via surface ECG) not capturing

Re-test Right PV Entrance Block with EP Catheter

Complications

Notes	
Finish Time	
Total Time	

EHRA Score

Classification of AF-related symptoms (EHRA score)	
EHRA class	**Explanation**
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued

AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

The SF-36v2™ Health Survey

Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by filling in the bubble that best represents your response.

EXAMPLE

This is for your review. Do not answer this question. The questionnaire begins with the section ***Your Health in General*** below.

For each question you will be asked to fill in a bubble in each line:

1. **How strongly do you agree or disagree with each of the following statements?**

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
a) I enjoy listening to music.	○	●	○	○	○
b) I enjoy reading magazines.	●	○	○	○	○

Please begin answering the questions now.

Your Health in General

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

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

GH

2. **Compared to one year ago, how would you rate your health in general now?**

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

H

Please turn the page and continue.

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

	Yes, limited a lot	Yes, limited a little	No, not limited at all	
a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	O_1	O_2	O_3	PF01
b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	O_1	O_2	O_3	PF02
c) Lifting or carrying groceries	O_1	O_2	O_3	PF03
d) Climbing **several** flights of stairs	O_1	O_2	O_3	PF04
e) Climbing **one** flight of stairs	O_1	O_2	O_3	PF05
f) Bending, kneeling, or stooping	O_1	O_2	O_3	PF06
g) Walking **more than a mile**	O_1	O_2	O_3	PF07
h) Walking **several hundred yards**	O_1	O_2	O_3	PF08
i) Walking **one hundred yards**	O_1	O_2	O_3	PF09
j) Bathing or dressing yourself	O_1	O_2	O_3	PF10

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

	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
a) Cut down on the **amount of time** you spent on work or other activities	O_1	O_2	O_3	O_4	O_5	RP
b) **Accomplished less** than you would like	O_1	O_2	O_3	O_4	O_5	RP
c) Were limited in the **kind** of work or other activities	O_1	O_2	O_3	O_4	O_5	RP
d) Had **difficulty** performing the work or other activities (for example, it took extra effort)	O_1	O_2	O_3	O_4	O_5	RP

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

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

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

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

7. **How much bodily pain have you had during the past 4 weeks?**

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

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

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

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

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

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

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

SF0

11. **How TRUE or FALSE is each of the following statements for you?**

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

GH(
GH(
GH(
GH(

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Tracy Hopkins
To: Haldar Shouvik
Re: tmette@atricure.com has sent you a file via WeTransfer

Hi
Yes of course
Thanks
Tracy

On Mar 26, 2015, at 8:41 AM, "Shouvik Haldar" <shouv76@aol.com> wrote:

> Hi Tracy,
>
> So can I write 'reproduced with permission from Atricure' - these images for inclusion in my MD thesis.
>
> Kindest Regards
>
> Shouvik
>
> > On 25 Mar 2015, at 14:19, Tracy Hopkins <THopkins@atricure.com> wrote:
> >
> > Here we go
> >
> > Begin forwarded message:
> >
> > **Resent-From:** <thopkins@atricure.eu>
> > **From:** WeTransfer <noreply@wetransfer.com>
> > **Date:** March 25, 2015 at 2:08:57 PM GMT
> > **To:** "thopkins@atricure.eu" <thopkins@atricure.eu>
> > **Subject:** **tmette@atricure.com has sent you a file via WeTransfer**
> > **Reply-To:** "tmette@atricure.com" <tmette@atricure.com>

Toorani, Shima
To: Chambers, Richard, Haldar Shouvik Cc: Passey, Mark, Philpott, David
RE: Something like this - I found this on the web

2 April 2015 11:44

TS

Dear Dr Haldar,

Pleasure to meet you virtually.

I would like to confirm that the use of the attached two images for your MD thesis is approved.

Could I please ask, if it is possible, to view the section in your thesis regarding the St Jude products? This is strictly for my information only, so that I have sight of publications regarding our products and not for re-issuing in any way.

If you have any other queries or need any further information, please do not hesitate to contact me.

Kindest regards,
Shima

Shima Toorani (PhD, MEng)
Product Manager
Atrial Fibrillation Division

St. Jude Medical UK Ltd
Capulet House
Stratford Business & Technology Park
Banbury Road
Stratford-upon-Avon
CV37 7GX
Tel 01789 207600
Fax 01789 207601
Mobile +44 (0) 7887 450645
stoorani@sjm.com

From: Chambers, Richard
Sent: 02 April 2015 10:23
To: Toorani, Shima
Cc: Passey, Mark; Philpott, David; Haldar Shouvik
Subject: Fwd: Something like this - I found this on the web

Dear Shima,

I sent the attached image to Dr Haldar & copied the image from SJM Professional. Please can you confirm that I can give permission to Shouvik for using the image in his MD Thesis?

Lagarde, Laurent [CRDBE] 2 April 2015 21:14

To: Shouvik Haldar

RE: Permission to use images for MD thesis

LL

Dear Shouvik,

We allow you to use the images to illustrate your MD thesis.

Wishing good luck and success with the thesis

Best Regards

Laurent Lagarde
EMEA Marketing Manager Catheters
Biosense Webster EMEA
Leonardo Da Vincilaan 15
1831 DIEGEM - BELGIUM
TEL +32 474 922 434
EMAIL llagarde@its.jnj.com
Please visit ThermoCool® SmartTouch™ Catheter website here.

-----Original Message-----
From: GMAIL [mailto:shouv76@gmail.com]
Sent: Thursday, April 02, 2015 9:55 PM
To: Lagarde, Laurent [CRDBE]
Subject: Permission to use images for MD thesis

Dear Laurent,

I know you have already given permission from Biosense Webster to use the images for my MD thesis but if you could reply to this email saying that you do give permission I would be grateful.

I need to print your response out hence the request.

Thank you very much.

Kind regards

Shouvik

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Bibliography

Catheter Ablation of Persistent Atrial Fibrillation: A Practical Guide

Mark O'Neill, George Veenhuyzen, George J Klein

Remedica 2008