Radiofrequency ablation of atrial fibrillation

Clinical results and studies of mechanisms

Eivind Solheim

Dissertation for the degree philosophiae doctor (PhD)
at the University of Bergen

2011

Dissertation date: 30.09.2011

Scientific environment

Jian Chen, MD, PhD

Associate professor

Institute of Medicine, University of Bergen and

Department of Heart Disease, Haukeland University Hospital, Bergen, Norway

and

Ole-Jørgen Ohm

Professor Emeritus

Institute of Medicine, University of Bergen, Bergen, Norway

Contents

1 Acknowledgements

This thesis is based on studies carried out at the Institute of Medicine, University of Bergen and the Department of Heart Disease, Haukeland University Hospital, between 2005 and 2011. The work was funded by the Norwegian Foundation for Health and Rehabilitation and was also supported by Western Norway Regional Health Authority. A Trond Mohn endowment and the Research Council of Norway provided the remote magnetic navigation system.

First of all, I wish to thank my main supervisor, Associate Professor Jian Chen, who introduced me to the field of cardiac electrophysiology and to clinical research, and has guided me through this process with energy and enthusiasm. I am most grateful to his ability to see through complex problems and to always ask the right questions.

My second supervisor, Professor Emeritus Ole-Jørgen Ohm, recruited me to this project, and has made substantial contributions throughout the entire process. With his enthusiasm for research and strategic thinking he has encouraged my project from the initial idea to the finished manuscript, and ensured that progress has been made, in spite of all my other non-scientific projects.

I am thankful to Per Ivar Hoff, the leader of the tachyarrhythmia unit, for encouraging my clinical training in ablation and electrophysiology, and for constructive criticism in the preparation and writing of the manuscripts.

My co-worker and good friend, Morten Kristian Off, has also contributed significantly to this thesis. His technical and theoretical skills have been of great importance for both the clinical work and the research involved. With good humour and his easy manner, he has made work-days more enjoyable in the laboratory, the office and at lunchtime in the cafeteria.

I am also most grateful to Peter Schuster and my good other colleagues at the arrhythmia unit, and to all the nurses I have worked with in the electrophysiology laboratory: Mærlyn Flatabø, Asbjørg Holme, Berit Refsdal, Mawahib Al-Azawy, Ivar Hansen, Merete Nøstbakken, Bjørg Anita Dalseid, Eva Torsvik and Kjersti Larsen. Thank you for your important assistance and for the good social environment in the lab!

Danuta Lund has helped me keep tabs on the project's financial aspects and accounting, and I greatly appreciate her positive approach to all my questions.

Professor Jan Erik Nordrehaug, head of the Department of Heart Disease, has created space for clinical research in the department, and provided excellent working conditions.

I also wish to thank Hugh Allen for his help in dealing with linguistic problems in both the individual papers and in this thesis.

This thesis would not have been possible without the cooperation of the patients, and I am grateful for their participation.

Finally, I wish to thank my family, my most beloved wife Jorid and our first-born son Sigurd, for their loving support.

2 Abstract

Introduction

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia. AF requires a trigger that initiates the arrhythmia, and the presence of a predisposing substrate that perpetuates it. Approximately 90% of paroxysmal AF episodes are initiated by triggers within the pulmonary veins (PVs), and the elimination of these foci, together with modification of the substrate, is the basis of most radiofrequency ablation (RFA) techniques.

The aim of these studies was to illuminate various aspects of atrial fibrillation mechanisms, mapping and ablation methods, and clinical results.

Methods

The patients in these studies had either symptomatic paroxysmal, persistent or long-standing persistent AF, and had failed to respond to at least one anti-arrhythmic drug. Patients underwent electrophysiological study and RFA in a fasting, sedated state. Vascular access was obtained, and after transseptal puncture, an irrigated-tip ablation catheter was used for mapping and ablation of the left atrium (LA) and for additional lines or focal ablation. In the course of this study, the techniques employed to achieve PV isolation evolved, and details of the isolation techniques involved at each stage are described in each paper.

In the first study, complex fractionated atrial electrograms (CFAE) during AF were mapped in both atria. In the second, we specifically monitored the atrio-PV conduction delay (the shortest interval from local atrial electrogram to the PV potential) in each PV before and during ablation. In the third study, patients underwent either a conventional ablation procedure or a magnetic guided procedure with or without an irrigated catheter. Two cardiac

biomarkers, troponin T (TnT) and cardiac creatine kinase (CKMB) were used to compare the myocardial injury created by the different catheters. In the next study, atrial volume calculations based on cardiac computed tomography were performed, and the cardiac biomarker N-terminal pro-brain natriuretic peptide (NT-pro-BNP) was measured, before ablation and at long-term follow-up. The final clinical follow-up study employed a quality-of-life questionnaire.

Results and conclusions

CFAEs are preferentially distributed in specific areas in both atria. Persistent AF patients had more CFAEs than those with paroxysmal AF, and CFAEs were more widespread in both atria. Temporal signal stability also appeared to be higher in persistent AF.

Atrio-PV conduction delay was more frequently observed in the left common PV and both of the superior PVs during PV isolation. Veins with focal activity displayed a higher incidence of conduction delay.

The procedure and total ablation times were longer, and time-corrected release of TnT was higher, when the remote magnetic system was used in AF ablation. There was a statistically significant positive correlation between total ablation time and post-ablation levels of TnT and CKMB in all groups.

LA volume and NT-pro-BNP levels fell only after successful AF ablation, and NT-pro-BNP correlated with LA volume both at baseline and follow-up. The arrhythmia burden also correlated with both NT-pro-BNP and LA volume. A decrease in NT-pro-BNP after RFA may be a marker of ablation success.

AF may recur late, but most AF recurrences occurred within six months of the RFA procedure.

3 List of publications

1. Solheim E, Off MK, Hoff PI, Schuster P, Ohm O-J, Chen J. Characteristics and distribution of complex fractionated atrial electrograms in patients with paroxysmal and persistent atrial fibrillation. J Interv Card Electrophysiol 2010;28:87-93.

2. Off MK, Solheim E, Hoff PI, Schuster P, Ohm O-J, Chen J. Atrio-pulmonary vein conduction delay during pulmonary vein isolation for atrial fibrillation is related to vein anatomy, age and focal activity. Pace 2009;32:S207-10.

3. Solheim E, Off MK, Hoff PI, De Bortoli A, Schuster P, Ohm O-J, Chen J. Remote magnetic versus manual catheters: evaluation of ablation effect in atrial fibrillation by myocardial marker levels. J Interv Card Electrophysiol 2011, DOI 10.1007/s10840-011-9567-z (*in press*).

4. Solheim E, Off MK, Hoff PI, De Bortoli A, Schuster P, Ohm O-J, Chen J. N-terminal pro-B-type natriuretic peptide level at long-term follow-up after atrial fibrillation ablation: A marker of reverse atrial remodeling and successful ablation. *Accepted for publication September 2011, J Interv Card Electrophysiol.*

5. Solheim E, Hoff PI, Off MK, Ohm O-J, Chen J. Significance of late recurrence of atrial fibrillation during long-term follow-up after pulmonary vein isolation. Pace 2007;30:S108-11.

4 Abbrevations

AF = Atrial Fibrillation

LA = Left Atrium

PV = Pulmonary Vein

RFA = Radiofrequency Ablation

ECG = Electrocardiogram

CFAE = Complex Fractionated Atrial Electrogram

CT = Computed Tomography

NT-Pro-BNP = N-terminal-Pro-Brain Natriuretic Peptide

TnT = Troponin T

CKMB = Creatine Kinase’s cardiac isoform MB

5 Introduction

5.1 Background

5.1.1 History

The first descriptions of one of the clinical signs of atrial fibrillation (AF), chaotic irregularity of the pulse, date back several hundred years. As early as in the seventeenth century Harley described “fibrillation of the auricles” in animals (1). In the early twentieth century Einthoven’s string galvanometer made it possible to record the electrical activity of the heart, and the clinical and physiological attributes of AF were described. Lewis was the first to conclude that AF was the atrial rhythm underlying the irregularity of the pulse (2). At first, he postulated that activity from one or more heterogeneous centres accounted for both premature beats, regular tachycardia and finally, AF (3). Later he produced the circus movement hypothesis (4), which in the course of time was developed in complexity, encompassing the possibility of a mother rotor giving rise to several independent rotors.

Various theories of the mechanisms of atrial fibrillation evolved further, and in the late nineteen-fifties Moe proposed the “multiple wavelet hypothesis” (5). His work on experimental models led him to postulate that AF was self-sustaining and depended on fractionation of wave fronts around areas of refractory tissue. About thirty years ago, Allessie presented electrophysiological evidence for the importance of atrial conduction blocks for the perpetuation of AF (6). During further work his group demonstrated re-entry and rotor mechanisms (7), not far from what had been suggested more than fifty years previously by Lewis. Evidence shows that sustained AF requires continuously depolarizing wave fronts, favoured by the remodelling of the atria, with shortening of the refractory period and formation of areas of slow conduction.

Haissaguerre's key article, which demonstrated the importance of the pulmonary veins (PVs) for the initiation of paroxysmal AF (8), started the era of ablation treatment of AF in the late 1990s. However, the mechanisms of AF have not been fully elucidated.

5.1.2 Epidemiology

AF is the most common form of sustained cardiac arrhythmia, affecting approximately 1-2 percent of the general population (9). In the western world this proportion seems likely to increase during the coming decades, mainly due to the aging of the populations. The prevalence of the arrhythmia increases with age, occurring in up to 5 percent of people aged 75 or over. The number of AF patients may be underestimated due to unrecognized, asymptomatic AF, which may be missed in epidemiological studies (10).

AF increases the risk of stroke (11) and is also recognized as an independent predictor of morbidity and mortality (12, 13), with a two-fold increase in death rate. Stroke and related complications are the main causes of the increased morbidity and mortality in AF patients, but impaired left ventricular function by tachycardiomyopathy, loss of atrial contractile function and increased left ventricular end-diastolic filling pressure also contribute to AF-related morbidity (14).

5.1.3 Associated conditions

According to the guidelines (15), AF can be described as a first diagnosed episode and later as recurrent AF. The arrhythmia is then further defined as paroxysmal, persistent, longstanding-persistent or permanent (accepted) AF. AF is associated with a vast number of cardiovascular conditions, and on the basis of pathophysiology, secondary AF is distinguished from lone AF. Hypertension, heart failure, valvular dysfunction, cardiomyopathy, cardiac ischaemia, thyroid disorder, diabetes mellitus, obesity and sleep

apnoea are among the recognised risk factors, and lone AF is very much a diagnosis of exclusion, reported in approximately 10% of the total AF population (16).

5.2 Pathophysiology

5.2.1 Left atrial size

Increased LA size is a risk factor for the development of AF, but AF in itself may also cause dilatation of the LA through the atrial remodelling process. Enlargement of the LA is often asymmetrical and may occur in the medial-lateral, as well as the superior-inferior axes. The standard assessment of LA size is based on echocardiographic measurement of the anteroposterior dimension in the parasternal long-axis view. Although this measurement has been used extensively in clinical and research work, it is now recognised as an inaccurate representation of LA size (17, 18). The relationship between LA size and cardiovascular disease burden in general has been shown to be stronger for the volume than for the diameter of the LA (18, 19).

5.2.2 PVs and triggers of AF

AF requires a trigger that initiates the arrhythmia, and the presence of a predisposing substrate that perpetuates it. Haissaguerre et al. demonstrated that approximately 90% of paroxysmal AF episodes were initiated by triggers within the PVs (8) and this discovery was the basis of most ablation techniques now in use (20, 21). The myocardial sleeves around the PVs and their junctions with the LA were early mentioned as a possible site of pathological importance (22), and conduction tissue with pacemaker activity has been demonstrated within the myocardial sleeves (23). The muscular tissue around the PV-LA junctions also has a very complex structure and local re-entry circuits in this area may also act as an important substrate for AF. Complex electrograms around the PV ostia have been recorded in clinical

studies (24, 25), supporting the importance of this area also for the perpetuation of AF. Targeting the area outside the PV ostia may therefore be important in AF ablation (26, 27).

Previous studies have reported significant degree of variability in the anatomy of the PVs (28-30). Four distinct PV ostia are present in up to 60% of patients, but a common left trunk or an additional (middle) right-sided vein are frequent anatomical variants. Although the PVs account for the majority of triggers, other areas such as the superior caval vein, the vein of Marshall, the coronary sinus, the posterior LA and the LA auricle have also been shown to be important for AF initiation (8, 31-33).

5.2.3 Substrate and modulating factors

For AF to become sustained, the presence of an atrial substrate of sufficient mass is necessary for the maintenance of re-entrant circuits. Under the influence of both sympathetic and parasympathetic stimulation, the conduction properties of the atrial myocytes may change. This results in a shortening of the duration of atrial refractoriness and a decrease in conduction velocity, both of which facilitate the perpetuation of AF. The arrhythmia usually occurs in patients with structural heart disease, and enlargement of the atria is often present, although it is difficult to determine whether it is the cause or the consequence of AF (14, 15). The prevalence of AF increases markedly with age. A review of histopathological studies (34) pointed out that histological alterations in the course of the normal ageing process may lead in turn to alterations in atrial conduction properties and thus promote the development of atrial arrhythmias. Atrial fibrosis facilitates AF by reducing conduction velocity and possibly creating areas of conduction block. The atrial activation pattern during AF is complex and can be difficult to interpret (35-37). Animal studies have further investigated these mechanisms and may improve our understanding of these complex activation patterns (6, 38, 39).

In the course of the past few years genetic defects, which mainly affect ionic currents, have been identified as causes of AF (40-45). Elucidation of the molecular mechanisms that cause familial AF might also improve our understanding of the more common acquired forms of the disease. Lone AF may be caused by mutations in different genes controlling cardiac excitability (42-45). A common feature of such genetic changes in ion channels is that they result in a shortening of the atrial refractory period and thus create a substrate for AF development. Somatic (missense) mutations in the connexin 40 encoding gene are also described as a non-familiar genetic disorder that leads to an increased propensity for AF (46-47).

The role of the autonomic nervous system in atrial fibrillation have been thoroughly studied (48-51) and results indicate that the occurrence of paroxysmal AF is highly dependent on variations in autonomic tone (52-55). There is evidence for the presence of increased atrial sympathetic innervation in humans with persistent AF, further suggesting that autonomic remodelling is a part of the atrial substrate for the maintenance of AF (56). There appears to be a primary increase in sympathetic tone, with a shift towards vagal predominance, before the onset of AF. In AF ablation, vagal denervation has been shown to potentially increase the success rate (50, 56) and high-density mapping and ablation of ganglionated plexi has also been proposed as an alternate approach for curing AF (57).

Inflammation may also be a contributing factor in AF. Augmented levels of inflammation biomarkers have been reported in AF patients (58-59), and the positive effect of anti-inflammatory agents on the prevention and modulation of AF supports this hypothesis. The notion that inflammation is a pathophysiological determinant in postoperative AF is also supported by studies (60) and further strengthens the concept of inflammation as an important factor in AF.

Electro-anatomical remodelling of the atrial tissue leads to changes in atrial conduction velocities, shortening and dispersions of refractory periods and atrial dilatation (61). The increase in atrial size correlates with the degree of atrial fibrosis (62) and may be used as a measure of the atrial remodelling process. An arrhythmogenic substrate appears to be necessary for the perpetuation of long-lasting AF episodes, and atrial remodelling facilitates the self-perpetuation of AF (63, 64).

5.3 Catheter ablation

5.3.1 Principles of radiofrequency ablation (RFA)

RFA induces local thermal necrosis in the heart (65). Ablation is performed in a temperature-controlled mode and the energy output and the temperatures reached are the main determinants of the ablation effect. Stable catheter-tissue contact is crucial for a predictable ablation effect and a stronger contact force might create deeper ablation lesions (66, 67). Irrigation of the RFA catheter tip has also been shown to be capable of enlarging the size and improving the transmurality of an ablation lesion (68). The ablation lesions may be extended for up to 180 seconds in a single energy delivery (69, 70), although most centres use 60 seconds as a standard application.

5.3.2 Approaches to AF ablation

The two main strategies for AF ablation are trigger-based and substrate-based ablation. Trigger-based ablation of the PVs is regarded as the cornerstone of AF ablation and the most frequently used methods include pulmonary vein (PV) isolation (8), PV antrum isolation (71) and circumferential ablation around the PVs (18, 56, 72). Adding mitral isthmus line, left atrial roofline ablation or both procedures is associated with an improved clinical outcome in

persistent and long-standing persistent AF (73, 74). Right atrial ablation may also improve efficacy in some patients (75).

In substrate-based ablation, areas assumed to be responsible for the perpetuation of AF are localized and ablated. These areas may be identified either by mapping the atria during sinus rhythm (76) or by searching for complex fractionated atrial electrograms (CFAE) during AF (77-80). A combination of the two strategies has also been proposed (81-84). Recent clinical data also suggest a potential role for ganglionated plexi ablation (57). Sites of positive vagal response to high-frequency stimulation are ablated and energy is applied until the response is eliminated.

5.3.3 Endpoints of ablation

The goal of AF ablation is the elimination of triggers and modification of substrate using the least amount of ablation energy necessary. As described above, various ablation strategies, either solely or in combination, have been adopted. Procedural endpoints include electrical PV isolation with confirmed absence or dissociation of PV potentials recorded from a circular mapping catheter (8, 85, 86), reduction of local amplitude inside the encircled area (72), termination of AF during ablation (87) and non-inducibility of AF after ablation (88).

5.4 Patient management

5.4.1 Follow-up after AF ablation

Reported follow-up times after AF ablation differ, but for the last few years at least 12 months has been established as the standard protocol. There is still a need for longer-term (>24 months) follow-up of results after ablation. The main outcome reported after AF ablation procedures is AF burden, both symptomatic and asymptomatic. The ultimate success criterion is freedom from all atrial arrhythmias. It has been well documented that an absence

of symptoms does not represent the true success rate (89, 90), and more than 30% of AF patients have been reported to be asymptomatic (91). Perception of AF episodes might also change after ablation (92) because of altered heart rate or autonomic influence by ablation-induced denervation of the heart. The accuracy of estimating the arrhythmia burden after AF ablation therefore depends upon the duration of the ECG recording (92-95). The best estimate of post-ablation arrhythmia burden and success rate demands a continuous rhythm recording (95-96) but five to seven days of Holter monitoring have been shown to enhance the sensitivity of AF detection (93-97). Transtelephonic ECG recordings have also been used in follow-up after AF ablation (94), but the true correlation of these to AF burden is difficult to determine and night episodes of AF, for example will not be recorded. About 30-50% of patients with recurrence of AF during the first three months after an ablation have no further arrhythmias (98) and therefore the first one to three months after the procedure are often reported as a blanking period.

Echocardiographic examination may reveal improvements in left ventricular function in patients with heart failure after ablation (99). Reverse remodelling with a reduction in the size of the LA has also been reported (100), and different techniques, including echocardiography, computed tomography (CT) and magnetic resonance imaging can be used for LA measurements. Recently, magnetic resonance imaging has also been used to show atrial debulking and tissue changes after AF ablation (101).

5.4.2 Efficacy and complications of AF ablation

It is difficult to compare the real efficacy of AF ablation procedures because of the many different ablation approaches employed, different definitions of success and not least, different methods of follow-up. Although reported success rates have ranged from about 40% to as high as 95%, both review articles and the worldwide surveys report that the mean

success rate is about 75% (101-105). Results are better for paroxysmal than persistent and long-standing persistent AF, and the success rates achieved would seem to have increased during the past few years. AF ablation is now regarded as being effective in restoring sinus rhythm for both paroxysmal and persistent AF, and it improves the quality of life of symptomatic patients. In the latest European guidelines, ablation of symptomatic drug-refractory paroxysmal AF is categorised as a class IIa recommendation, with level of evidence A (15).

Major complications occur in about 4.5% of patients (17, 103,104), typically with lower rates at leading centres. Reported complications consist mostly of stroke/transient ischaemic attack, cardiac tamponade or vascular complications such as femoral pseudoaneurism or arterio-venous fistula. PV stenosis used to be reported in about 1% of cases but has become rarer since most operators now target ablation at some distance from the ostia. Atrio-oesophageal fistula is a serious and often fatal complication, but is very rare (104). The survival of patients undergoing catheter ablation for AF is similar to that of patients treated with anti-arrhythmic drugs, and there are no differences between these groups in rates of stroke or transient ischaemic attack (106). Only one non-randomised study has reported lower mortality and morbidity in patients treated with AF ablation than in patients on anti-arrhythmic drugs (107), but these data need to be reproduced in larger, preferably randomised studies, with a longer follow-up time.

6 Aims of the study

The aim of these studies was to elucidate aspects of atrial fibrillation mechanisms, mapping and ablation methods, and clinical results. Our specific objectives were:

1. To investigate the different characteristics and distribution of complex fractionated atrial electrograms in patients with both paroxysmal and persistent AF.
2. To elucidate the atrio-pulmonary vein conduction delay observed during pulmonary vein isolation.
3. To compare the impacts of standard irrigated catheters with both irrigated and non-irrigated magnetic guided catheters, by measuring marker levels of myocardial injury in atrial fibrillation ablation.
4. To determine the relationship between arrhythmia burden, left atrial volume and natriuretic peptide hormone level at baseline and after long-term follow-up of atrial fibrillation ablation.
5. To describe the time course and incidence of the recurrence of late atrial arrhythmia after pulmonary vein isolation in paroxysmal and persistent atrial fibrillation.

7 Methods

7.1 Study population

All the patients in these studies had either symptomatic paroxysmal, persistent or long-standing persistent AF and had failed at least one anti-arrhythmic drug (≥2 drugs in study 2 and 5). The patients were recruited from all parts of Norway and were referred to Haukeland University Hospital for AF ablation from their local hospitals or cardiologists. Studies 2 and 5 included consecutive patients from the early years (2001-2005) of AF ablation in our hospital; the other studies included non-consecutive patients. Patients with both lone fibrillation and underlying cardiovascular disorders (including hypertension, coronary artery disease, valvular disease and cardiomyopathies) were included in these studies. Details of patient characteristics are presented in each paper. In most of the patients, antiarrhythmic drugs were not discontinued before the procedure, and most patients kept taking their antiarrhythmic drugs during a blanking period (i.e. 1-3 months after ablation). All patients were anticoagulated for ≥6 weeks prior to the procedure. Oral anticoagulation was discontinued in most patients two days before RFA in order to reach an international normalised ratio <2.3. All patients provided informed consent. The study was performed in accordance with the Declaration of Helsinki, and was approved by the local ethics committee (Regional Ethics Committee of Western Norway).

7.2 Electrophysiological study and radiofrequency ablation

7.2.1 Electrophysiological study

Patients underwent electrophysiological study and RFA in a fasting, sedated state. Vascular access was obtained under local anesthaesia through the right and left femoral veins. In all

patients, a 7F 20-pole steerable mapping catheter (Livewire, St. Jude Medical Inc, St. Paul, MN) was positioned in the coronary sinus, looped around the tricuspid annulus. After transseptal puncture or left-sided access through a patent oval foramen, a 10-pole circular mapping catheter (Lasso™, Biosense Webster, Diamond Bar, CA, USA or Optima™, St. Jude Medical Inc), was introduced into the LA through an 8F or 8.5F transseptal introducer. All patients were heparinized after transseptal puncture in order to maintain an activated clotting time of between 200 and 300 seconds.

Selective angiography of all PVs was performed before and after ablation. A focus was defined on the basis of documented single or multiple ectopic events, with or without initiation of AF, and could be observed spontaneously or during provocative manoeuvres (isoproterenol infusion or programmed atrial pacing).

Most patients had four PVs, but a single PV ostium on the left side (left common PV) was present in several patients, as was a third PV on the right side (right middle PV), which was isolated separately. We employed circular mapping catheters with diameters of 15, 20 or 25 mm, based on the PV angiography. PV potentials were defined as in a previous study (108) and recorded in bipolar mode (Lab System Pro, Bard Electrophysiology, Lowell, MA, USA).

7.2.2 Ablation set-up

A 3.5 mm tip irrigated ablation catheter was used for mapping and ablation in the LA and for additional lines or focal ablation (a regular 4-mm tip catheter was used for the early cases and for one subgroup in study 3). Catheter types are specified in each study. We used a Stockert-Cordis radiofrequency generator (Freiburg, Germany) and energy was applied in temperature-controlled mode. The application time of RFA was 40-60 seconds at each site and energy was delivered with a cut-off temperature of 50˚ C (irrigated catheters). The maximum output and irrigation rates were 30-35W/15-20mL/min for PV isolation,

25W/15mL/min in the coronary sinus and 30-40W/20mL/min for linear or CFAE ablation (maximum 35W in LA, 40W in right atrium).

7.2.3 Ablation approach

In the course of this study, techniques to achieve PV isolation evolved, and details of PV isolation are described in each paper. In the early patients (studies 2 and 5) ablation was systematically performed at the earliest exit point of atrio-PV conduction, until the disappearance of the PV potentials. Energy was delivered at the PV ostia, without any attempt to obtain a wider PV circumferential ablation. In the later patients, an electrophysiological approach was still used, but the lesions were created at the antra of the PVs and circular lesions were ablated around each PV (Figure 1). If circles around the superior and inferior ipsi-lateral veins did not overlap, additional ablation to connect these lesion-sets was performed.

Additional left-sided ablation was performed in a relatively large number of patients as described in the individual papers. Ablation approaches included mitral isthmus line (from the mitral annulus to the left inferior PV), roofline (connecting the two superior PVs), two lines connecting the two contra-lateral superior and inferior veins, ablation on CFAEs or a combination. Patients with clinically documented common atrial flutter received an additional right-sided ablation at the cavo-tricuspid isthmus area and bi-directional isthmus block was confirmed.

7.2.4 Specific mapping and ablation protocols

In study 1, CFAE mapping during AF (Complex fractionated electrogram (CFE) mapping tool, St Jude Medical, St Paul, MN, USA) was performed in all patients. Three-dimensional

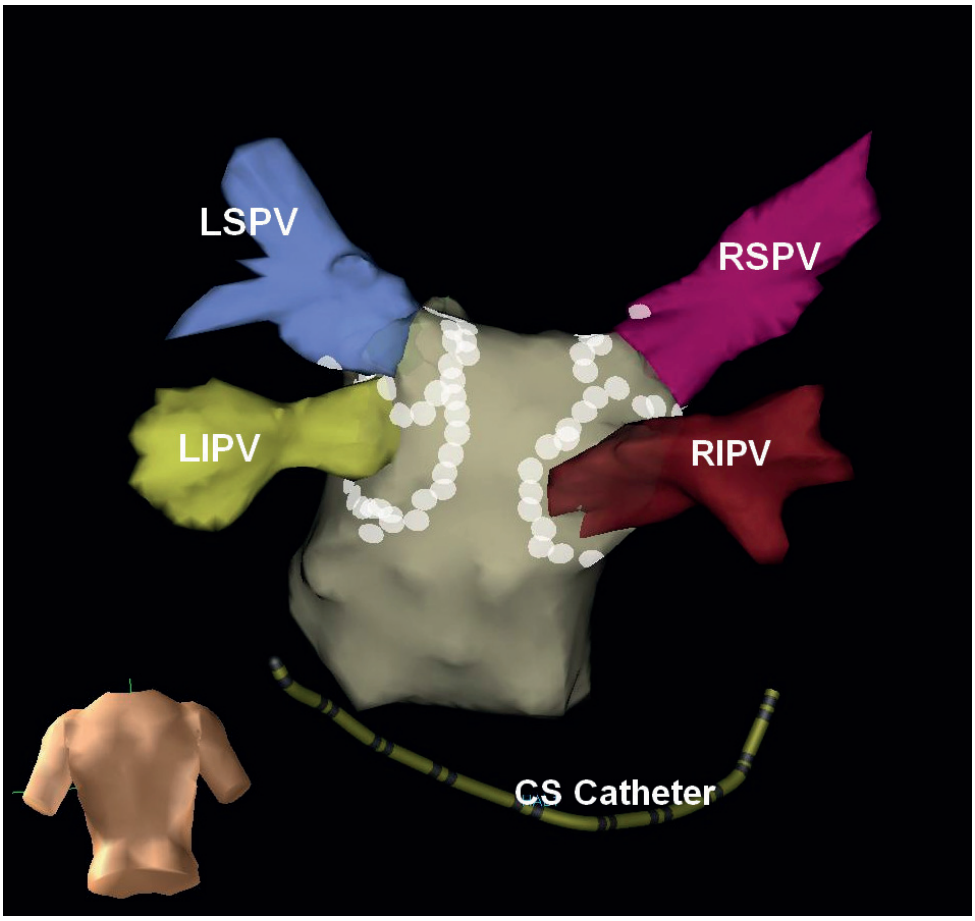

Figure 1. Left atrium, three-dimensional reconstruction, posterior-anterior view. Ablation lesions (white dots) are created circumferential at the antra of each pulmonary vein (PV). A ten bi-pole catheter are placed in the coronary sinus (CS). LSPV - left superior PV, LIPV – left inferior PV, RSPV right superior PV, RIPV right inferior PV.

---

reconstructions were made and global CFAE maps were generated in the left and right atria and the coronary sinus (Figure 2). Electrograms were sampled for eight seconds at all sites. All signals were recorded from a 3.5 mm irrigated ablation catheter and digitally filtered with

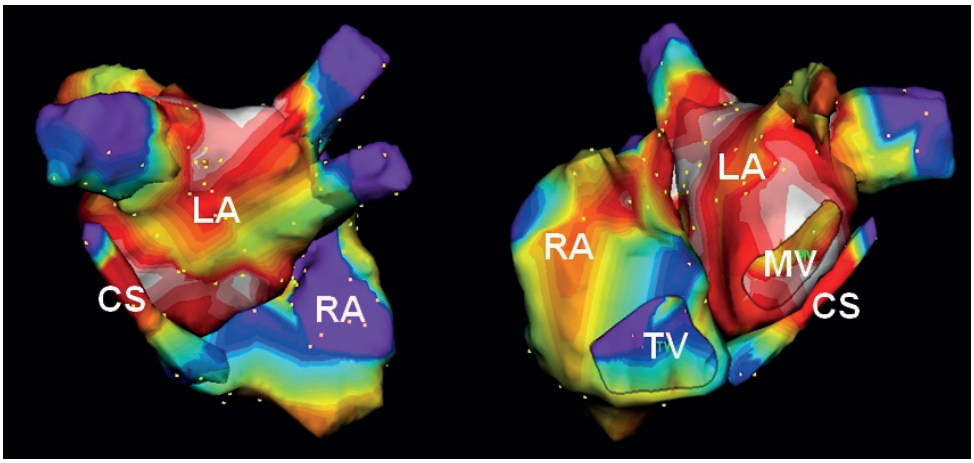

Figure 2. CFAE map of left atrium (LA), right atrium (RA) and the coronary sinus (CS). Left panel: posterior-anterior view, right panel: left-anterior-oblique view. Areas with the shortest CFE mean in white, the longest CFE mean in purple. TV - Tricuspid valve, MV - Mitral valve.

---

a band-pass filter of 32 to 100 Hz. An additional noise filter was switched on if necessary. At each site the automated NavX algorithm calculated the "CFE mean", which is the average time interval (in ms) between consecutive deflections during each sampling period. A stable catheter position and good tissue contact were confirmed during CFAE mapping. The CFAE was defined as a fractionated electrogram that comprised more than two deflections of a prolonged activation complex over an eight-second recording period, with either perturbation of the baseline ("continuous CFAE") or a relatively clear baseline between electrograms with a very short cycle length ≤ 120 ms ("fragmented CFAE"). Electrograms representing a combination of these two characteristics were defined as "mixed CFAEs" .

In study 2, the atrio-PV conduction delay was measured as the shortest interval from local atrial electrogram to the PV potential on all bipolar electrodes, and was monitored in each PV before and during ablation. Conduction delay was defined as the maximum atrio-PV

time interval >20 ms before PV potential disappearance during PV isolation. Figure 3 shows examples of PV potential disappearance and conduction delay during PV isolation. The patients who underwent a repeat PVI were studied separately.

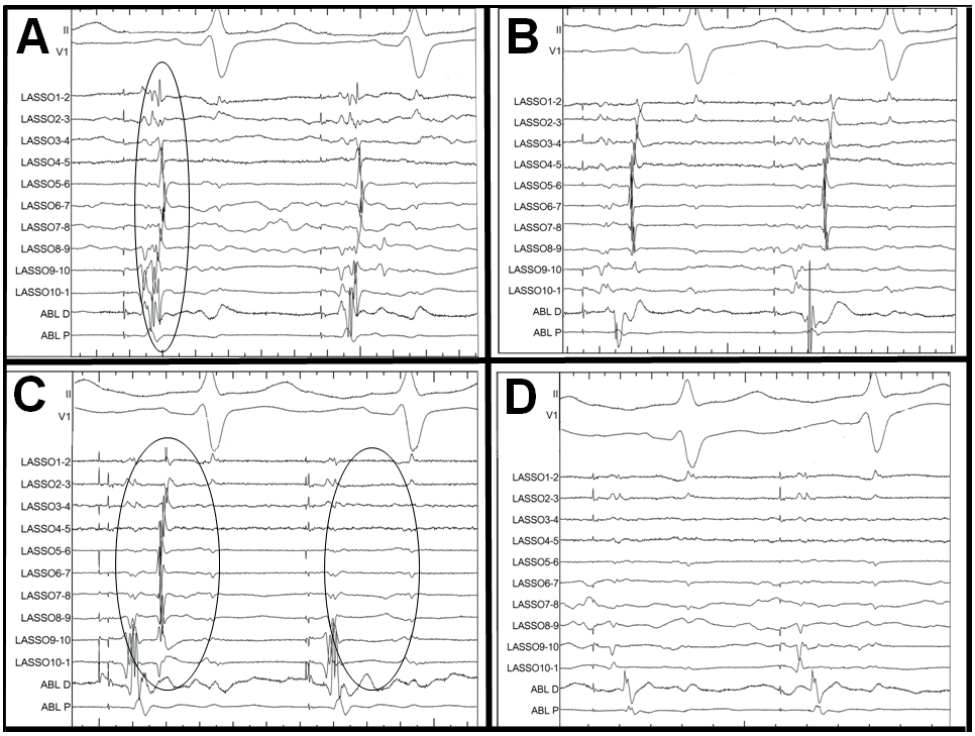

Figure 3. Pulmonary vein (PV) potentials recorded from a circular 10-pole catheter (Lasso 1-10). Panel A shows sharp potentials (encircled) shortly after the atrial signals. In panel B, recorded during isolation of the PV, the vein potentials are delayed compared to the atrial signals. Panel C shows the disappearance of PV potential during ablation. panel D, recorded after ablation, shows complete PV isolation. ABL D and P – Recordings from the distal and proximal pole of the ablation catheter, respectively.

In study 3, patients underwent either a conventional ablation procedure, as described above, or a magnetic guided procedure with or without an irrigated catheter. In the patients who

underwent magnetic guided ablation, the RFA catheter was introduced into the LA through a second transseptal guiding introducer, and LA mapping was performed by Carto™ RMT (Biosense Webster). The three-dimensional mapping system was used in conjunction with the Niobe® II system (Stereotaxis, St. Louis, MO, USA). The RFA lesion sets consisted of a continuous circumferential line around the two ipsilateral PVs, with additional ablation between the two PVs. Energy was applied only when good electrode-tissue contact was indicated by the system monitor. In the irrigated catheter group, a Navistar® RMT ThermoCool® (Biosense Webster) ablation catheter was employed. Application time, output and temperature cut-offs and irrigation rate were the same as for conventional irrigated catheters. In the magnetic non-irrigated catheter group a Navistar Celsius RMT™ (Biosense Webster) ablation catheter was used. For some patients in this group the circular mapping catheter was not employed and PV isolation was confirmed by RFA catheter only (109). Energy was applied with a cut-off temperature of 55˚ C and a maximum output of 40W, and application time was 20 seconds at each site. Charring of the catheter tip raises its impedance and, if this was recognized, the catheter was extracted and the tip checked during the procedure.

In study 4, a three-dimensional mapping system (Ensite NavX™ (St. Jude Medical Inc.) or Carto™XP (Biosense Webster)) was employed in all patients to guide mapping and ablation. Patients underwent ablation additional to PV isolation, depending on the type and duration of AF in each patient.

7.3 Biomarkers

Three different biomarkers, all of which are in standard clinical use, were employed in this work. In studies 3 and 4, venous blood samples from an antecubital vein were obtained from all patients before the procedure commenced. Post-procedure samples in study 3 were collected 24 hours after the start of the procedure. In study 4, blood samples were drawn at

the long-term follow-up visit. Troponin T (TnT), Creatin Kinase's cardiac isoform MB (CKMB) and N-terminal-Pro-Brain Natriuretic Peptide (NT-pro-BNP) were determined using an electrochemiluminescence immunoassay on a Modular E system (Roche Diagnostics, Mannheim, Germany). The analytical detection limits were 0.01µg/L (TnT), 0.1µg/L (CKMB) and 1 pmol/L (NT-pro-BNP), respectively. The TnT cut-off value for diagnosis of myocardial infarction according to ACC/AHA guidelines is 0.03µg/L (110).

7.4 Imaging

In study 4, all patients underwent cardiac computed tomography (CT) imaging on the day before the ablation procedure and at the final follow-up visit. Imaging was performed using a 64-slide scanner (Aquillion 64, Toshiba, Japan) either with or, in patients with AF during imaging, without ECG-gated techniques. Data were acquired during one breath-holding, after a bolus injection of contrast (Iomeron 400mg I/mL). For ECG-gated images, we used 0.5 mm and for non-gated images 1.0 mm slide thicknesses.

LA three-dimensional reconstructions and volume computations were performed using the Ensite NavX™ Verismo system (St. Jude Medical Inc.). An automated algorithm calculates the LA volume on the basis of the three-dimensional coordinates. Before chamber volume was calculated, the pulmonary veins were excluded at the ostia. The LA auricle could not be reconstructed in all the patients, and was therefore also excluded (111).

7.5 Follow-up

7.5.1 Post-procedural patient management

All patients were monitored for at least 24 hours after the procedure, and were discharged under oral anticoagulation. For most patients, antiarrhythmic drugs were continued for at least three months. Antiarrhythmic drug therapy was discontinued after successful

elimination of AF, and oral anticoagulation was also discontinued unless other risk factors were present.

7.5.2 Clinical outcome and definitions

In studies 3, 4 and 5, we collected data on clinical outcome. The patients were followed on an ambulatory basis, either in our out-patient clinic or by their own local hospitals and referring cardiologists. All patients underwent clinical examination and at least one Holter registration at three and six months after the procedure. Additional clinical examination, including ECG recordings, was performed if indicated by symptoms. Recurrence was strictly defined as ≥1 episode of AF after a blanking period of three months in study 3 and one month in study 4 and 5. In study 3, patients were followed for one year after the relevant ablation procedure and patients who underwent a repeat procedure during the follow-up period were regarded as failures. Ablation success definitions in studies 4 and 5 were based on the result at the end of follow-up, and patients may have undergone additional ablation procedures.

7.5.3 Additional follow-up

In study 4, all patients were examined at our clinic at the end of follow-up with a further seven days of cardiac rhythm monitoring using a specially developed event recorder for AF detection (AF Alarm, Medtronic, MN). Self-reported AF burden was graded according to a modified arrhythmia frequency and severity scale (112), with 1-10 points for each frequency and duration of AF episodes (range 2-20). AF burden was reported in all patients at baseline and in patients with recurrence also at follow-up. CT imaging and blood sampling were also performed at the end of follow-up.

In study 5, all the patients completed a quality-of-life questionnaire at the end of the study, including symptoms, medications, satisfaction, and a 0–10 self-evaluation score on

arrhythmia burden. The clinical condition before the procedure was scored as 0 and 10 represented complete freedom from symptoms of arrhythmia. We defined late recurrence as any relapse of AF between 6 and 12 months, and very late recurrence >12 months after the procedure.

7.6 Statistics

Discrete variables are reported as counts or percentages and continuous variables as mean ± standard deviation, or median and range for non-normal distributed data. Continuous variables were assessed for characteristics of distribution by the Kolmogorov-Smirnov test. Comparisons were performed using Student's t-test or one-way analysis of variance (ANOVA) for parametric data and the Mann-Whitney U-test for non-parametric data. Discrete variables were compared by the $\chi 2$ test or Fisher's exact test. In study 2, trend lines were obtained by the method of least squares, using Microsoft Excel software (Microsoft Corp., Redmond, WA, USA). Correlations were calculated by means of linear regression analysis and Spearman's rank correlation tests. In study 3, Levene's test was employed to test the variances between groups. A receiver operator characteristic curve and best cut-off were calculated and plotted in study 4 using R version 2.12.0 (The R Foundation for Statistical Computing, Vienna, Austria). SPSS software package versions 13.0-17.0 (SPPS Inc., IL, USA) were used for all other statistical analyses. Values of $p < 0.05$ were considered to be statistically significant.

8 Results

8.1 Paper I - Complex fractionated atrial electrograms

In this study we investigated the different characteristics and distribution of complex fractionated atrial electrograms in both atria in patients with paroxysmal and persistent AF. Twenty AF patients (10 persistent) scheduled for ablation were included in this observational study.

The NavX™ system was used to map both the left and right atria and the coronary sinus in all patients. An automated algorithm calculated the average time interval between consecutive deflections (CFE-mean). All recordings were visually inspected off-line and interpreted as either continuous, fragmented, mixed CFAE or non-CFAE, and their locations were determined. Electrograms with intermittent CFAE characteristics during the eight seconds recording interval were regarded as non-CFAEs.

Persistent AF patients had more CFAEs than those with paroxysmal AF (52% vs. 44% of total registrations, $p<0.05$), and CFAEs were more widespread in both atria in persistent AF. There were also more continuous CFAEs (70% vs. 59% of total CFAEs, $p<0.05$), and fewer mixed and intermittent CFAEs (22% vs. 30% and 16% vs. 21% of total CFAEs, respectively, $p<0.05$) in persistent AF, indicating higher temporal signal stability. Fragmented CFAEs had more high-voltage signals than other groups. Employing the automated algorithm for CFAE mapping, a CFE-mean cut-off value of ≤80ms provides sensitivities and specificities of 87.4% and 81.2% respectively. CFAEs seemed to be most common in preferential areas and displayed different patterns in the two atria.

8.2 Paper II - Pulmonary vein potentials

We investigated the delay in atrio-pulmonary vein conduction during segmental PV isolation in various PVs in 385 AF patients (mean age: 54 ± 11 years; 74 women). PV potentials were registered using a circular ten-pole catheter placed at the PV ostia. The time delay from local atrial potential to PV potential was measured in each vein. Conduction delay was defined as the longest interval >20 ms before elimination of PV potentials observed during PV isolation.

In patients who underwent their first PV isolation procedure, conduction delay was more frequently observed in the left common and right and left superior PVs (84.2%, 67.9%, and 66.2%, respectively) and less frequently in the left and right inferior and right middle PVs (54.3%, 40.0%, and 30.8%, respectively). Veins with conduction delay required more ablation applications (12.4 vs 9.9) and a larger fraction of ablated segment (72.3% vs 63.7%). Conduction delay was observed in 75.2% (109/145) of the PVs in which focal activity was detected. Older patients had a higher incidence of PVs with conduction delay than younger patients. No gender differences were identified. The observations of conduction delay in preferential PVs were not valid in patients undergoing repeat procedures.

8.3 Paper III - Catheter impact on myocardial injury

We measured myocardial markers in 114 AF patients in order to compare the effects of irrigated and non-irrigated remote magnetic navigated catheters with a manual irrigated catheter in AF ablation. The patients underwent AF ablation using either a conventional manual irrigated catheter (CIR, n=65) or a magnetic navigated system utilizing either an

irrigated (RMI, n=23) or non-irrigated catheter (RMN, n=26). Levels of TnT and CKMB were measured before and after ablation.

The procedure and total ablation times were longer when the remote magnetic system was used. All groups displayed pronounced increases in markers of myocardial injury after ablation, demonstrating a significant correlation between total ablation time and post-ablation levels of TnT and CKMB (CIR: $r=0.61$ and 0.53, $p<0.001$; RMI: $r=0.74$ and 0.73, $p<0.001$; and RMN: $r=0.51$ and 0.59, $p<0.01$). Time-corrected release of TnT was significantly higher in the CIR group than in the other groups, and remote magnetic catheters may create more discrete and predictable ablation lesions as measured by myocardial enzymes. 59.6% of the patients were free of AF at follow-up (12.2±5.4 months) and there were no differences in success rate between the three groups.

8.4 Paper IV Atrial reverse remodelling

We investigated the relationship between arrhythmia burden, LA volume and NT-pro-BNP at baseline and after long-term follow-up of AF ablation. We studied 38 patients (23 paroxysmal, six women, mean age 56±11) who had been scheduled for AF ablation.

After a mean period of 22±5 months, 28/38 patients (11/15 persistent) were free of AF recurrence. At baseline there were no differences in mean LA volume (125 vs. 130 cm^3, $p=0.7$) or median NT-pro-BNP (33.5 vs. 29.5 pmol/L, $p=0.9$) between patients whose ablation had or had not been successful. At long-term follow-up there was a marked decrease in LA volume (105 vs. 134 cm^3, $p<0.05$) and level of NT-pro-BNP (7 vs. 17.5 pmol/L, $p<0.05$) in the successful ablation patients. In patients with AF recurrence, no statistically significant differences between baseline and follow-up measurements were identified. NT-pro-BNP correlated with LA volume both at baseline ($r=0.71$, $p<0.001$) and at

follow-up ($r=0.57$, $p<0.001$). Arrhythmia burden correlated with both NT-pro-BNP ($r=0.47$, $p<0.01$) and LA volume ($r=0.52$, $p<0.01$). A decrease up of > 25% of the baseline value of NT-pro-BNP at follow-up had a specificity of 0.89 and a sensitivity of 0.6 (receiver operator characteristics, accuracy 0.82) for ablation success.

8.5 Paper V Late recurrence of AF

In this study we examined the rates and time course of AF recurrence after PV isolation at very long-term follow-up. We included 278 consecutive patients with drug-refractory AF (50 women, mean age 53±11 years). PV isolation was based on the disappearance of PV potentials recorded from a circumferential catheter after segmental ostium ablation. Cavo-tricuspid isthmus lines and additional left atrial lines were performed in 124 and 28 patients respectively. Patients were monitored for 26±11 months (range 12–56).

A relatively high AF recurrence rate was observed after segmental PV isolation. A total of 120 (34 women) patients (43%) suffered a recurrence of AF, and the majority of recurrences occurred within six months of the first procedure. Only 14 patients (12%) experienced the first recurrence more than six months after the procedure. There were no differences in incidence or time of occurrence of late recurrences between patients with paroxysmal or persistent AF. A significantly higher recurrence rate was observed in patients with persistent AF.

9 General discussion

9.1 Pathophysiology

9.1.1 Anatomical considerations

AF leads to remodelling of the atria, and measurements of LA size may provide important information. Previous studies have demonstrated that a larger LA predicts worse outcome after AF ablation (113). There is also evidence that LA size is a predictor of the cardiovascular outcome in a population (114). After successful restoration of sinus rhythm atrial volume may decrease due to a reverse remodelling process. In study 4, we measured LA volumes before and long-term after AF ablation. Our results did not identify pre-ablation LA volume as a predictor of ablation success, but we demonstrated a significant reduction in LA volume only in patients whose ablation procedure had been successful.

There are differences in PV configuration and size both between patients and among the different veins in each patient. PV potential conduction delay in the different PVs was investigated in study 2. We found that the left common PV had the highest proportion of, and the longest mean, conduction delay, followed by the right superior, left superior, left inferior, right inferior and right middle PV. The diameter of a left common trunk is always large, and the superior PVs are usually larger than the inferior ones (115). This suggests that the incidence and duration of conduction delay are related to anatomical factors, in particular to the PV diameter.

In study 1, we investigated the anatomical distribution of CFAE in both atria. Other studies have demonstrated a higher density of CFAE around the PVs in paroxysmal than in persistent AF patients (116-117). In our study, the average calculated CFE mean of the PVs was significantly shorter in paroxysmal than in persistent AF, although manual signal

interpretation did not reveal this difference. We defined the borders between the PVs/auricles and the atria as being located at the anatomical ostia. CFAEs located at the antra of the PVs and auricles were therefore counted as part of the LA, which may explain the differences in the observations.

Consistent with previous studies, there were more CFAEs in the LA and CS (118-119). Previous studies have identified the atrial septum, LA roof, posterior LA, mitral annulus, base of the left auricle and the PVs as the most likely sites for CFAEs (77-79). Our study also revealed significantly more CFAEs in the anterior region of LA. Moreover, more CFAEs in the LA roof and more widely spread CFAEs in the right atrium were seen in persistent AF.

9.1.2 Triggers of atrial fibrillation

PVs are the most important structures for the initiation of AF (8). More recent evidence from a simulation study suggests that a mechanism of dynamically induced repolarisation dispersion underlies the induction of AF by atrial ectopic foci (120). The likelihood of re-entry induction varied according to ectopic focus location and timing, with the largest vulnerable window corresponding to the PV region.

In study 2 we investigated PV potential conduction delay in veins with focal trigger activity. Larger PVs may be associated with larger muscle fascicles connecting the PVs to the atrium than small PVs. A previous study concluded that patients with focal AF had larger PVs than controls (121). In our study PVs with focal activity displayed more conduction delay than PVs without such activity. PVs associated with conduction delay needed more extensive ablation. One possible explanation is that these veins may have larger myocardial fascicles, which are responsible for the focal activity. This may facilitate conduction between foci inside the PVs and the atrial tissue, leading to the onset of atrial fibrillation. A higher

incidence of conduction delays in older than in younger patients was demonstrated. One reason for this may be that older patients have developed more fibrotic tissue around the PVs, which could disturb atrio-PV conduction or create areas of slower conduction. It has been shown by others that PV and LA diameters increase with age (122), and in our study, larger veins also had a higher incidence of conduction delay.

Several studies have identified recovered PV-LA conduction as an important factor also for recurrent AF after PV isolation (123-125). In study 5, we performed repeated catheter ablation in 54 patients, all of whom showed recovered PV conduction. However, only limited data regarding the extent of PV reconnection in patients after successful ablation are available , and the clinical utility of this finding needs further investigation.

9.1.3 Substrate for the maintenance of atrial fibrillation

Although the mechanisms involved are still not fully understood, there is evidence to connect CFAE to areas with a known pathophysiological substrate for the perpetuation of AF. Increased fibrosis has been demonstrated in CFAE sites compared with non-CFAE sites (126). In study 1, we found more CFAEs in patients with persistent AF than in paroxysmal AF patients. Persistent AF patients also displayed a lower proportion of high-amplitude signals. Electrograms in CFAE areas are of lower voltage than those in non-CFAE areas (127), suggesting that CFAE may be related to atrial remodelling and the extent of fibrous tissue. An association between CFAEs and ganglionated plexi has also been shown in an animal model, which suggests that mechanisms of the autonomic nervous system may also play a role in formation of CFAEs (128, 129).

Konings et al. (35) classified the atrial electrograms recorded during AF into four different categories; single deflections, short doubles, long doubles and fragmented signals, and demonstrated that these signals indicated different conduction patterns. In study 1, we

classified two main types of fractionated atrial electrograms - fragmented and continuous CFAEs. The fragmented CFAEs might correspond to single deflections as described by Konings et al, indicating local conduction delay, and may be related to atrial microfibrosis. The continuous CFAEs, with an incessant perturbation of baseline, may account for the areas of slow conduction or pivot points of activation. In our study, patients with persistent AF displayed more continuous CFAEs than those with paroxysmal AF, a finding consistent with a previous study (130).

Our study also revealed significantly more widely spread CFAE in the right atrium in persistent AF patients than in patients with paroxysmal AF, which suggests that AF may be a two-chamber disease in persistent AF patients. One study showed that sinus rhythm was restored by right atrial ablation in about 15% of patients with persistent AF (131). However, another study suggested that right atrial CFAEs were only “bystanders” of no clinical significance (78). The significance of right-sided CFAEs and the role of the right atrium for perpetuation of AF needs further investigation. In paroxysmal AF lower temporal signal stability, as demonstrated with more mixed and intermittent CFAEs, is suggestive of a lesser degree of atrial remodelling and thus less AF substrate. This has also been demonstrated by others (132).

9.2 Catheter ablation

9.2.1 Pulmonary vein isolation

In the course of the past decade, AF ablation has evolved from being an experimental procedure to one of the most common ablations performed in the electrophysiology laboratory (8). PV isolation has formed the basis of ablation therapy in all our studies. Except for a few initial patients in studies 2 and 5, all PVs were isolated in all our patients. Electrical isolation has been confirmed with a circular mapping catheter in the PV ostium in

all patients, except for a subgroup in study 3. New methods of PV isolation have been developed in the course of this work. In the earlier patients (studies 2 and 5), a segmental approach, as initially described by Haïssaguerre (8), was adopted, with ablation applications closer to the ostium. In studies 3 and 4, energy was applied circumferentially around each PV antrum. In re-isolations of PVs, fewer ablation applications were needed, as we have shown in study 2.

In study 3, we performed AF ablation procedures using three different catheters in a non-randomized study. There were no statistically significant differences in outcome using the different ablation catheters. Nor were there any differences in marker levels in patients whose ablation were or were not successful. Longer procedure and ablation application times were shown when a circular mapping catheter was employed to confirm PV isolation (non-irrigated magnetic navigated group), which may indicate a more thorough ablation procedure. A better clinical outcome when PV isolation is confirmed has been demonstrated by other studies (133, 134).

9.2.2 Different ablation approaches

In the initial patients described in study 5, there were very high recurrence rates among patients with persistent and long-standing persistent AF. Other clinical studies have also demonstrated poor results after trigger-based ablation alone in patients with persistent AF (18), and extensive ablation is required to obtain stable sinus rhythm (135). Multiple procedures and additional ablation strategies are often required to restore stable sinus rhythm. Different approaches have been shown to improve the outcomes. Adding left atrial lines has been shown to be effective in improving clinical outcome in persistent and long-standing persistent AF (73, 74). Right atrial ablation may also provide incremental improvements in some patients (75). Several studies have also shown an improved outcome when fractionated electrograms are targeted in addition to PV isolation (136, 137). The

strategy of CFAE ablation is based on the hypothesis that the areas with CFAE are essential for the perpetuation of AF (77). The differences in success within and between techniques suggest that the optimal ablation technique for the treatment of persistent and especially long-standing persistent AF is unclear. Nevertheless, long-standing persistent AF can also be effectively treated by a combination of extensive index catheter ablation and repeat procedures (138). In study 3, there were no differences in clinical outcome using different catheter types. The proportion of tailored ablation in addition to PV isolation was similar in all groups, which suggests that the choice of procedural strategy is more important than the type of catheter used to reach the ablation endpoints.

9.2.3 Catheters and technology

Catheters and mapping technology have evolved in the course of the past decade. Irrigated ablation catheters and three-dimensional mapping systems have become standard equipment. Other aspects of ablation technology have also been shown to be feasible, and a wide range of specialised catheters designed for PV isolation have been developed. A circular multi-electrode ablation catheter, a high-density basket catheter and a cryoballoon catheter are available on the market, and studies using laser technology (laser balloon) have also been performed. These catheters are placed at the LA-PV antrum and provide clinical outcomes similar to those of standard point-by-point PV isolation (139-140).

In study 3 we employed a remote magnetic navigation system and compared the ablation effect, as indicated by myocardial marker release, to manual irrigated catheters. Considerably lower time-corrected TnT level was associated with the magnetic navigated system, whether irrigated or non-irrigated catheters were employed. This suggests that myocardial injury, as indicated by enzyme release, was lower with the magnetic system than when the manual ablation technique was employed. One possible explanation for this is that lesions created by the magnetic navigated catheters may be more sharply defined, because of

the positional stability of the system, than those made with manual catheters. The manual catheters may be less stable and may slide over the endocardium, resulting in larger, but shallower and thus less effective, ablation lesions. This lack of stability may also create more undesirable myocardial damage. Magnetic navigated catheters may therefore cause less myocardial damage and still be effective. It has been suggested that similar mechanisms are involved in cryoablation, when the ablation catheter freezes to the endocardium (141-142).

With the magnetic navigated system, catheter-tissue contact status can be monitored, but no guidance of catheter-tissue contact was available with manual catheter ablation. Others have demonstrated that a substantially stronger contact force might create deeper ablation lesions (66, 143).

In the early years of AF ablation, navigation in the LA was performed using fluoroscopy and electrogram interpretation alone (8, 108). Later, the use of three-dimensional navigation systems have been adopted in most AF ablation procedures. These systems incorporate various tools, such as image integration and automated signal interpretation. In studies 1, 3 and 4, we utilised navigation systems for guidance of mapping and ablation.

9.3 Patient management

9.3.1 Follow-up after ablation

Patients in this study were followed up on an out-patient basis. Anti-arrhythmic drugs were discontinued after three to six months if they were free of AF. Oral anti-coagulants were discontinued after six months if no risk factors were identified.

In study 4, we investigated the relationship of NT-pro-BNP and LA volume to ablation success. In accordance with the results of previous studies (144, 145), baseline NT-pro-BNP values decreased significantly in patients after successful restoration of sinus rhythm. Patients with recurrence of AF had no significant reduction in NT-pro-BNP after ablation. Even though we included patients with low AF burden and baseline NT-pro-BNP within the normal range, the decrease of NT-pro-BNP in patients after successful ablation was statistically significant and correlated with the reduction in LA volume. NT-pro-BNP before ablation was not a valid predictor of ablation outcome, but measurement of NT-pro-BNP at baseline and follow-up may add value to the clinical evaluation of ablation success. In accordance with a previous study (146), we found that LA volume was more robust than LA anterioposterior diameter as a marker of successful ablation. Other studies have shown that the measurement of NT-pro-BNP and LA size add incremental predictive value before AF ablation (113, 144, 147). In our study, baseline values of NT-pro-BNP and LA size did not differ in patients whose ablation had or had not been successful. Augmented LA dimensions have been observed in patients with recurrent AF (148), but we could not reproduce this finding. However, some of our patients whose ablation was unsuccessful did experience a marked decrease in AF burden, which may have influenced the degree of LA dilatation.

9.3.2 Efficacy and complications

We provided long-term follow-up data in studies 3, 4 and 5, and reported success rates

comparable to other published data. In studies 3 and 5, the definition of success was based on clinical examinations, self-reported symptoms, ECG recordings and 24-hour Holter monitoring. After ablation, asymptomatic AF may be present, and 24-hour Holter monitoring may therefore not provide a true measure of success (92). The patients in study 4 therefore underwent an additional long-term event recording session at the end of follow-up. Previous studies have documented high recurrence rates in persistent AF following PV isolation alone (18), consistent with our findings in study 5. At the time of follow-up in this study, 12% of all recurrences had occurred later than six months after RFA. We found no differences in the time of recurrence between paroxysmal and persistent AF patients. It has been suggested that there may be a larger proportion of right-sided trigger mechanisms in patients with very late recurrences of AF (123), but the timelines and mechanisms of late AF recurrences have not yet been fully elucidated.

Thromboembolisation from the LA auricle is one of the most important causes of AF-related stroke events and impaired function, and dilatation of the auricle has been associated with thrombus formation. Reverse remodelling of the LA auricle after successful AF ablation (149) could theoretically indicate a decrease in thromboembolic risk after ablation. We excluded the LA auricle from the volume calculations and therefore cannot provide data on this topic.

One patient in study 5 had a major PV stenosis that required intervention. In study 4, we identified one patient with an asymptomatic PV narrowing, but for the other studies we cannot provide data, and patients were not investigated if there were no symptoms suggestive of PV injury. Some patients were observed for pericardial effusion after ablation without need for intervention, but none developed cardiac tamponade. No other procedure-related complications, such as atrio-eosophageal fistula, transient ischaemic attack or major bleeding, were observed.

9.4 Study limitations

All the studies were non-randomized and from the experience of a single centre, which limits the significance of outcome comparisons between groups. Studies 1 and 2 were observational studies without clinical data on ablation outcome. The numbers of patients in study 1, 3 and 4 were relatively small. In accordance with other studies, there were significantly more male than female patients. Specific gender differences were not further explored. Some patients underwent individually tailored ablation in addition to PV isolation, which also may limit the interpretation of the clinical results between groups.

9.5 Future perspectives

Although much progress has been made in both techniques and equipment for AF ablation during the past few years, new methods will continue to evolve. Traditional RFA may be challenged by the further development of other energy sources such laser or cryoenergy, and new navigation and catheter-handling methods are in constant progress. There will be a need for randomized multi-centre studies that focus on the development and quality assurance of both methods and technology. A growing population of AF patients may necessitate better guidelines for both the selection of patients beneficial for ablation, especially long-standing persistent AF, and ablation approaches. More standardised patient follow-up methods would have enabled better comparisons of clinical data and outcomes to be made. Only limited data on very-long term success rates are as yet available, and there is a need for larger studies on stroke risk and long-term mortality and morbidity after AF ablation.

10 Conclusions

1. Complex fractionated atrial electrograms tend to occur in certain areas and in different patterns in both atria. The left atrium and coronary sinus are more fractionated than the right atrium. Patients with persistent atrial fibrillation tend to have more fractionated electrograms and more continuous fractionated electrograms, and they display higher temporal signal stability than patients with paroxysmal AF.

2. The left common and superior pulmonary veins have a higher incidence of conduction delay during the first pulmonary vein isolation procedure than the usually smaller inferior veins. Conduction delay is more often observed in older patients and in those pulmonary veins that display focal activity. Veins with conduction delay required more ablation applications and a larger area of ablation around the ostia.

3. Remote magnetic navigated catheters may create more discrete ablation lesions with a more predictable effect as measured by myocardial enzymes. This system may require longer ablation time to reach the procedural endpoints than manual procedures. Remote magnetic non-irrigated catheters do not appear to be inferior to magnetic irrigated catheters in terms of myocardial marker release and clinical outcome.

4. NT-pro-BNP correlates with atrial volume and arrhythmia burden in AF patients. At long-term follow-up there is a marked decrease in left atrial volume and NT-pro-BNP only in patients whose ablation has been successful. A decrease in NT-pro-BNP of >25% from the baseline value may be a useful marker of ablation success.

5. Segmental pulmonary isolation has a relatively high recurrence rate, and there is an increase in the recurrence rate also later than 12 months after the procedure. Nevertheless, the vast majority of AF recurrence occurred earlier than six months

after RFA. No differences in the time course of late recurrence in patients with either paroxysmal or persistent atrial fibrillation were observed.

11 References

1. Flegel KM. From delirium cordis to atrial fibrillation: historical development of a disease concept. Ann Intern Med. 1995;122:867-73.
2. Lewis T. Auricular fibrillation and its relationship to clinical irregularity of the heart. Heart. 1910;1:306-72.
3. Lewis T, Schleiter HG. The relation of regular tachycardias of auricular origin to auricular fibrillation. Heart. 1912;3:173-93.
4. Lewis T, Drury AN, Iliescu CC. A demonstration of circus movement in clinical fibrillation of the auricles. Heart. 1921;8:361-9.
5. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J. 1959;58:59-70.
6. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. The leading circle concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res. 1977;41:9-18.
7. Konings KT, Kirchhof C, Smeets JL, Wellens HJ, Penn OC, Allessie MA. High-density mapping of electrically induced atrial fibrillation in humans. Circulation 1994;89:1665-80.
8. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339:659-66.
9. Kannel WB, Abbot RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: The Framingham study. N Engl J Med 1982;306:1018-22.

10. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrialfibrillation in older adults. Circulation 1997;96:2455–61.

11. Chesebro JH, Fuster V, Halperin JL. Atrial fibrillation-risk marker for stroke. N Engl J Med 1990;323:1556–8.

12. Benjamin EJ, Wolf PA, D'Agostino RB, Silberschatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation 1995;92:835–41.

13. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. Outcome parameters for trials in atrial fibrillation: executive summary. Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). Eur Heart J 2007;28:2803–17.

14. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Levy S, Crijns HJ. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26:2422–34.

15. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA).

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS). Europace 2010;12:1360–1420.

16. Kozlowski D, Budrejko S, Lip GYH, Rysz J, Mikhailidis DP, Raczak G, Banach G. Lone atrial fibrillation: what do we know? Heart 2010;96:498-503.
17. Lester SJ, Ryan EW, Schiller NB, Foster E. Best method in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829-32.
18. Leung DY, Boyd A, Ng AA, Chi C, Thomas L. Echocardiographic evaluation of left atrial size and function: current understanding, pathophysiologic correlates, and prognostic implications. Am Heart J 2008;156:1056-64.
19. Tsang TS, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, Cha SS, Seward JB. Prediction of cardiovascular outcomes with left atrial size: is volume superior to area or diameter? J Am Coll Cardiol 2006;47:1018-23.
20. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Calabrò MP, Mazzone P, Ficarra E, Di Gioia C, Gulletta S, Nardi S, Santinelli V, Benussi S, Alfieri O. Atrial electroanatomic remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. Circulation 2001;104:2539-44.
21. Oral H, Knight BP, Tada H, Ozaydin M, Chugh A, Hassan S, Scharf C, Lai SW, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002;105:1077-81.
22. Nathan H, Eliakim M. The junction between the left atrium and the pulmonary veins: An anatomic study of human hearts. Circulation 1966;34;412-22.
23. Perez-Lugones A, McMahon JT, Ratliff NB, Saliba WI, Schweikert RA, Marrouche NF, Saad EB, Navia JL, McCarthy PM, Tchou P, Gillinov AM,

Natale A. Evidence of specialized conduction cells in human pulmonary veins of patients with atrial fibrillation. J Cardiovasc Electrophysiol 2003;14:803-9.

24. Suenari K, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Huang SY, Tai CT, Nakano Y, Kihara Y, Tsao HM, Wu TJ, Chen SA. Relationship between arrhythmogenic pulmonary veins and the surrounding atrial substrate in patients with paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol. 2011;22:405-410.
25. Chen J, Off MK, Solheim E, Hoff PI, Schuster P, Ohm OJ. Spatial relationships between the pulmonary veins and sites of complex fractionated atrial electrograms during atrial fibrillation. Pacing Clin Electrophysiol 2009;32 Suppl 1:S190-3.
26. Ho SY, Cabrera JA, Tran VH, Farré J, Anderson RH, Sánchez-Quintana D. Architecture of the pulmonary veins: relevance to radiofrequency ablation. Heart 2001;86:265–70.
27. Weiss C, Gocht A, Willems S, Hoffmann M, Risius T, Meinertz T. Impact of the distribution and structure of myocardium in the pulmonary veins for radiofrequency ablation of atrial fibrillation. Pacing Clin Electrophysiol 2002;25:1352-6.
28. Kato R, Lickfett L, Meininger G, Dickfeld T, Wu R, Juang G, Angkeow P, LaCorte J, Bluemke D, Berger R, Halperin HR, Calkins H. Pulmonary vein anatomy in patients undergoing catheter ablation of atrial fibrillation: lessons learned by use of magnetic resonance imaging. Circulation 2003;107:2004-10.
29. Mansour M, Refaat M, Heist EK, Mela T, Cury R, Holmvang G, Ruskin JN. Three-dimensional anatomy of the left atrium by magnetic resonance angiography: implications for catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2006;17:719-23.

30. Mlcochová H, Tintera J, Porod V, Peichl P, Cihák R, Kautzner J. Magnetic resonance angiography of pulmonary veins: implications for catheter ablation of atrial fibrillation. Pacing Clin Electrophysiol. 2005;28:1073-80.

31. Higuchi K, Yamauchi Y, Hirao K, Sasaki T, Hachiya H, Sekiguchi Y, Nitta J, Isobe M. Superior vena cava as initiator of atrial fibrillation: factors related to its arrhythmogenicity. Heart Rhythm 2010;7:1186-91.

32. Valles E, Fan R, Roux JF, Liu CF, Harding JD, Dhruvakumar S, Hutchinson MD, Riley M, Bala R, Garcia FC, Lin D, Dixit S, Callans DJ, Gerstenfeld EP, Marchlinski FE. Localization of atrial fibrillation triggers in patients undergoing pulmonary vein isolation: importance of the carina region. J Am Coll Cardiol 2008;52:1413-20.

33. Di Biase L, Burkhardt JD, Mohanty P, Sanchez J, Mohanty S, Horton R, Gallinghouse GJ, Bailey SM, Zagrodzky JD, Santangeli P, Hao S, Hongo R, Beheiry S, Themistoclakis S, Bonso A, Rossillo A, Corrado A, Raviele A, Al-Ahmad A, Wang P, Cummings JE, Schweikert RA, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Lewis WR, Natale A. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. Circulation 2010;122:109-18.

34. Falk RH. Etiology and complications of atrial fibrillation: Insights from pathology studies. Am J Cardiol 1998;82:10N–17N.

35. Konings KT, Smeets JL, Penn OC, Wellens HJ, Allessie MA: Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. Circulation 1997;95:1231-41.

36. Steven D, Seiler J, Roberts-Thomson KC, Inada K, Stevenson WG. Mapping of atrial tachycardias after catheter ablation for atrial fibrillation: use of bi-atrial activation patterns to facilitate recognition of origin. Heart Rhythm. 2010;7:664-72.

37. Yamazaki M, Vaquero LM, Hou L, Campbell K, Zlochiver S, Klos M, Mironov S, Berenfeld O, Honjo H, Kodama I, Jalife J, Kalifa J. Mechanisms of stretch-induced atrial fibrillation in the presence and the absence of adrenocholinergic stimulation: interplay between rotors and focal discharges. Heart Rhythm. 2009;6:1009-17.

38. Ryu K, Shroff SC, Sahadevan J, Martovitz NL, Khrestian CM, Stambler BS. Mapping of atrial activation during sustained atrial fibrillation in dogs with rapid ventricular pacing induced heart failure: evidence for a role of driver regions. J Cardiovasc Electrophysiol 2005;16:1348-58.

39. Ryu K, Sahadevan J, Khrestian CM, Stambler BS, Waldo AL. Use of fast fourier transform analysis of atrial electrograms for rapid characterization of atrial activation-implications for delineating possible mechanisms of atrial tachyarrhythmias. J Cardiovasc Electrophysiol 2006;17:198-206.

40. Campuzano O, Brugada R. Genetics of familial atrial fibrillation. Europace. 2009;11:1267-71.

41. Darbar D, Herron KJ, Ballew JD, Jahangir A, Gersh BJ, Shen WK, Hammill SC, Packer DL, Olson TM. Familial atrial fibrillation is a genetically heterogeneous disorder. J Am Coll Cardiol 2003;41:2185–92.

42. Arnar DO, Thorvaldsson S, Manolio TA, Thorgeirsson G, Kristjansson K, Hakonarson H, Stefansson K. Familial aggregation of atrial fibrillation in Iceland. Eur Heart J 2006;27:708–12.

43. Chen YH, Xu SJ, Bendahhou S, Wang XL, Wang Y, Xu WY, Jin HW, Sun H, Su XY, Zhuang QN, Yang YQ, Li YB, Liu Y, Xu HJ, Li XF, Ma N, Mou CP, Chen Z, Barhanin J, Huang W. KCNQ1 gain-of-function mutation in familial atrial fibrillation. Science. 2003;299:251-4.

44. Yang Y, Xia M, Jin Q, Bendahhou S, Shi J, Chen Y, Liang B, Lin J, Liu Y, Liu B, Zhou Q, Zhang D, Wang R, Ma N, Su X, Niu K, Pei Y, Xu W, Chen Z, Wan H, Cui J, Barhanin J, Chen Y. Identification of a KCNE2 gain-of-function mutation in patients with familial atrial fibrillation. Am J Hum Genet. 2004;75:899-905.

45. Olson TM, Michels VV, Ballew JD, Reyna SP, Karst ML, Herron KJ, Horton SC, Rodeheffer RJ, Anderson JL. Sodium channel mutations and susceptibility to heart failure and atrial fibrillation. JAMA 2005;293:447-54.

46. Gollob MH, Jones DL, Krahn AD, Danis L, Gong XQ, Shao Q, Liu X, Veinot JP, Tang AS, Stewart AF, Tesson F, Klein GJ, Yee R, Skanes AC, Guiraudon GM, Ebihara L, Bai D. Somatic mutations in the connexin 40 gene (GJA5) in atrial fibrillation. N Engl J Med 2006;354:2677-88.

47. Juang JM, Chern YR, Tsai CT, Chiang FT, Lin JL, Hwang JJ, Hsu KL, Tseng CD, Tseng YZ, Lai LP. The association of human connexin 40 genetic polymorphisms with atrial fibrillation. Int J Cardiol. 2007;116:107–112.

48. Oral H, Morady F. Autonomic innervation, atrial electrogram morphology, and atrial fibrillation. J Am Coll Cardiol 2007;50:1332-4.

49. Liu P, Guo JH, Zhang HC, Wang MX, Li XB, Zhang P, Yi Z, Sun JL. Vagal effects on the occurrence of focal atrial fibrillation originating from the pulmonary veins. Circ J 2009;73:48-54.

50. Yamada T, Yoshida N, Murakami Y, Okada T, Yoshida Y, Muto M, Inden Y, Murohara T. Vagal modification can be a valid predictor of late recurrence of paroxysmal atrial fibrillation independent of the pulmonary vein isolation technique. Circ J 2009;73:1606-11.

51. Scherlag BJ, Yamanashi W, Patel U, Lazzara R, Jackman WM. Autonomically induced conversion of pulmonary vein focal firing into atrial fibrillation. J Am Coll Cardiol 2005;45:1878-86.

52. Amar D, Zhang H, Miodownik S, Kadish AH. Competing autonomic mechanisms precede the onset of postoperative atrial fibrillation. J Am Coll Cardiol 2003;42:1262-8.

53. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation 2002;105:2753-9.

54. Schauerte P, Scherlag BJ, Pitha J Scherlag MA, Reynolds D, Lazzara R, Jackman WM. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation 2000;102:2774-80.

55. Gould PA, Yii M, McLean C Finch S, Marshall T, Lambert GW, Kaye DM. Evidence for increased atrial sympathetic innervation in persistent human atrial fibrillation. Pacing Clin Electrophysiol 2006;29:821-9.

56. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, Mazzone P, Tortoriello V, Landoni G, Zangrillo A, Lang C, Tomita T, Mesas C, Mastella E, Alfieri O. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. Circulation 2004;109:327-34.

57. Lu Z, Scherlag BJ, Lin J, Yu L, Guo JH, Niu G, Jackman WM, Lazzara R, Jiang H, Po SS. Autonomic mechanism for initiation of rapid firing from atria and pulmonary veins: evidence by ablation of ganglionated plexi. Cardiovasc Res 2009;84:245-52.

58. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK.

Inflammation as a risk factor for atrial fibrillation. Circulation. 2003;108:3006-10.

59. Toutouzas K, Synetos A, Drakopoulou M, Stefanadi E, Tousoulis D, Lerakis S, Stefanadis C. The role of inflammation in atrial fibrillation: A myth or a fact? Am J Med Sci 2009;338:494-9.

60. Anselmi A, Possati G, Gaudino M. Postoperative inflammatory reaction and atrial fibrillation: Simple correlation or causation? Ann Thorac Surg 2009;88:326-33.

61. Kojodjojo P, Peters NS, Davies DW Kanagaratnam P. Characterisation of the electroanatomical substrate in human atrial fibrillation: The relationship between changes in atrial volume, refractoriness, wavefront propagation velocities, and AF burden. J Cardiovasc Electrophysiol 2007;18:269-75.

62. Knackstedt C, Gramley F, Schimpf T, Mischke K, Zarse M, Plisiene J, Schmid M, Lorenzen J, Frechen D, Neef P, Hanrath P, Kelm M, Schauerte P. Association of echocardiographic atrial size and atrial fibrosis in a sequential model of congestive heart failure and atrial fibrillation. Cardiovasc Pathol 2008;17:318-24.

63. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995;91:1588-95.

64. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954-68.

65. Thomas SP, Aggarwal G, Boyd AC, Jin Y, Ross DL. A comparison of open irrigated and non-irrigated tip catheter ablation for pulmonary vein isolation. Europace 2004;6:330-5.

66. Eick OJ, Wittkampf FH, Bronneberg T, Schumacher B. The LETR-Principle: a novel method to assess electrode-tissue contact in radiofrequency ablation. J Cardiovasc Electrophysiol 1998;9:1180-5.

67. Zheng X, Walcott GP, Hall JA, Rollins DL, Smith WM, Kay GN, Ideker RE. Electrode impedance: an indicator of electrode-tissue contact and lesion dimensions during linear ablation. J Interv Card Electrophysiol 2000:4:645-54.

68. Gerstenfeld EP, Jacobson J, Bazan V, Lazar S, Tomaszewski JE, Marchlinski FE, Michele J. Comparison of high power, medium power, and irrigated-tip ablation strategies for pulmonary vein isolation in a canine model. J Cardiovasc Electrophysiol 2007;18:849-53.

69. Hartung WM, Burton ME, Deam AG, Walter PF, McTeague K Langberg JJ. Estimation of temperature during radiofrequency catheter ablation using impedance measurements. Pacing Clin Electrophysiol 1995;18:2017-21.

70. McRury ID, Diamond S, Falwell G, Schlichting A, Wilson C. The effect of ablation sequence and duration on lesion shape using rapidly pulsed radiofrequency energy through multiple electrodes. J Interv Card Electrophysiol 2000;4:307-20.

71. Verma A, Marrouche NF, Natale A: Pulmonary vein antrum isolation: Intracardiac echocardiography-guided technique. J Cardiovasc Electrophysiol 2004;15:1335-40.

72. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F, Salvati A, Dicandia C, Calabro MP, Mazzone P, Ficarra E, Di Giola C, Gulletta S, Nardi S, Santinelli V, Benussi S, Alfieri O. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. Circulation 2000;102:2619-28.

73. Pak HN, Oh YS, Lim HE, Kim YH, Hwang C. Comparison of voltage map-guided left atrial anterior wall ablation versus left lateral mitral isthmus ablation in patients with persistent atrial fibrillation. Heart Rhythm 2011;8:199-206.

74. Senga M, Fujii E, Sugiura S, Yamazato S, Sugiura E, Nakamura M, Miyahara M, Ito M. Efficacy of linear block at the left atrial roof in atrial fibrillation. J Cardiol 2010;55:322-7.

75. Takahashi Y, Takahashi A, Kuwahara T, Fujino T, Okubo K, Kusa S, Fujii A, Yagishita A, Miyazaki S, Nozato T, Hikita H, Hirao K, Isobe M. Clinical characteristics of patients with persistent atrial fibrillation successfully treated by left atrial ablation. Circ Arrhythm Electrophysiol 2010;3:465-71.

76. Pachon MJ, Pachon ME, Pachon MJ, Lobo TJ, Pachon MZ, Vargas RN, Pachon DQ, Lopez MF, Jatene AD: A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. Europace 2004; 6:590-601.

77. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T: A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004; 43:2044-53.

78. Oral H, Chugh A, Good E, Wimmer A, Dey S, Gadeela N, Sankaran S, Crawford T, Sarrazin JF, Kuhne M, Chalfoun N, Wells D, Frederic M, Fortino J, Benloucif-Moore S, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F: Radiofrequency catheter ablation of chronic atrial fibrillation guided by complex electrograms. Circulation 2007;115:2606-12.

79. Schmitt C, Estner H, Hecher B, Luik A, Kolb C, Karch M, Ndrepepa G, Zrenner B, Hessling G, Deisenhofer I: Radiofrequency ablation of complex fractionated atrial electrograms (CFAE): Preferential sites of acute termination and

regularization in paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2007;18:1039-46.

80. Nademanee K, Schwab M, Porath J, Abbo A: How to perform electrogram-guided atrial fibrillation ablation. Heart Rhythm 2006;3:981-4.

81. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A: Ablation for longstanding permanent atrial fibrillation: results from a randomized study comparing three different strategies. Heart Rhythm. 2008;5:1658-64.

82. Deisenhofer I, Estner H, Reents T, Fichtner S, Bauer A, Wu J, Kolb C, Zrenner B, Schmitt C, Hessling G: Does electrogram guided substrate ablation add to the success of pulmonary vein isolation in patients with paroxysmal atrial fibrillation? A prospective, randomized study. J Cardiovasc Electrophysiol 2008;20:514-21.

83. Verma A, Mantovan R, Macle L, De Martino G, Chen J, Morillo CA, Novak P, Calzolari V, Guerra PG, Nair G, Torrecilla EG, Khaykin Y. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. Eur Heart J. 2010;31:1344-56.

84. Oral H, Chugh A, Yoshida K, Sarrazin JF, Kuhne M, Crawford T, Chalfoun N, Wells D, Boonyapisit W, Veerareddy S, Billakanty S, Wong WS, Good E, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F: A randomized assessment of the incremental role of ablation of complex fractionated atrial electrograms after antral pulmonary vein isolation for long-lasting persistent atrial fibrillation. J Am Coll Cardiol 2009;53:782-9.

85. Oral H, Knight BP, Tada H, Özaydin M, Chugh M, Hassan S, Scharf C ,Lai SWK, Greenstein R, Pelosi F Jr, Strickberger SA, Morady F. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002;105:1077-81.

86. Ouyang F, Bänsch D, Ernst S, Schaumann A, Hachiya H, Chen M, Chun J, Falk P, Khanedani A, Antz M, Kuck KH. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. Circulation 2004;110:2090-6.

87. O'Neill MD, Wright M, Knecht S, Jaïs P, Hocini M, Takahashi Y, Jönsson A, Sacher F, Matsuo S, Lim KT, Arantes L, Derval N, Lellouche N, Nault I, Bordachar P, Clémenty J, Haïssaguerre M. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. Eur Heart J 2009;30:1105-12.

88. Jaïs P, Hocini M, Sanders P, Hsu LF, Takahashi Y, Rotter M, Rostock T, Sacher F, Clementy J, Haissaguerre M. Long-term evaluation of atrial fibrillation ablation guided by noninducibility. Heart Rhythm 2006;3:140-5.

89. Page RL, Tilsch TW, Connolly SJ, Schnell DJ, Marcello SR, Wilkinson WE, Pritchett EL; Azimilide Supraventricular Arrhythmia Program (ASAP) Investigators. Asymptomatic or "silent" atrial fibrillation: frequency in untreated patients and patients receiving azimilide. Circulation 2003;107:1141-5.

90. Defaye P, Dournaux F, Mouton E. Prevalence of supraventricular arrhythmias from the automated analysis of data stored in the DDD pacemakers of 617 patients: the AIDA study. The AIDA Multicenter Study Group. Automatic Interpretation for Diagnosis Assistance. Pacing Clin Electrophysiol 1998;21:250-5.

91. Savelieva I, Camm AJ. Silent atrial fibrillation--another Pandora's box. Pacing Clin Electrophysiol 2000;23:145-8.

92. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C, Kottkamp H. Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. Circulation 2005;112:307-13.

93. Kottkamp H, Tanner H, Kobza R, Schirdewahn P, Dorszewski A, Gerds-Li JH, Carbucicchio C, Piorkowski C, Hindricks G. Time courses and quantitative analysis of atrial fibrillation episode number and duration after circular plus linear left atrial lesions: trigger elimination or substrate modification: early or delayed cure? J Am Coll Cardiol 2004;44:869-77.

94. Senatore G, Stabile G, Bertaglia E, Donnici G, De Simone A, Zoppo F, Turco P, Pascotto P, Fazzari M. Role of transtelephonic electrocardiographic monitoring in detecting short-term arrhythmia recurrences after radiofrequency ablation in patients with atrial fibrillation. J Am Coll Cardiol 2005;45:873-6.

95. Verma A, Minor S, Kilicaslan F, Patel D, Hao S, Beheiry S, Lakkireddy D, Elayi SC, Cummings J, Martin DO, Burkhardt JD, Schweikert RA, Saliba W, Tchou PJ, Natale A. Incidence of atrial arrhythmias detected by permanent pacemakers (PPM) post-pulmonary vein antrum isolation (PVAI) for atrial fibrillation (AF): correlation with symptomatic recurrence. J Cardiovasc Electrophysiol 2007;18:601-6.

96. Steven D, Rostock T, Lutomsky B, Klemm H, Servatius H, Drewitz I, Friedrichs K, Ventura R, Meinertz T, Willems S. What is the real atrial fibrillation burden after catheter ablation of atrial fibrillation? A prospective rhythm analysis in pacemaker patients with continuous atrial monitoring. Eur Heart J 2008;29:1037-42.

97. Dagres N, Kottkamp H, Piorkowski C, Weis S, Arya A, Sommer P, Bode K, Gerds-Li JH, Kremastinos DT, Hindricks G. Influence of the duration of Holter monitoring on the detection of arrhythmia recurrences after catheter ablation of atrial fibrillation. Implications for patient follow-up. Int J Cardiol. 2010;139:305-6.

98. Li XP, Dong JZ, Liu XP, Long de Y, Yu RH, Tian Y, Tang RB, Zheng B, Hu FL, Shi LS, He H, Ma CS. Predictive value of early recurrence and delayed cure after catheter ablation for patients with chronic atrial fibrillation. Circ J 2008;72:1125-9.

99. Hsu LF, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquié JL, Scavée C, Bordachar P, Clémenty J, Haïssaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med. 2004;351:2373-83.

100. Müller H, Noble S, Keller PF, Sigaud P, Gentil P, Lerch R, Shah D, Burri H. Biatrial anatomical reverse remodelling after radiofrequency catheter ablation for atrial fibrillation: evidence from real-time three-dimensional echocardiography. Europace 2008;10:1073-8.

101. Segerson NM, Daccarett M, Badger TJ, Shabaan A, Akoum N, Fish EN, Rao S, Burgon NS, Adjei-Poku Y, Kholmovski E, Vijayakumar S, DiBella EV, MacLeod RS, Marrouche NF. Magnetic resonance imaging-confirmed ablative debulking of the left atrial posterior wall and septum for treatment of persistent atrial fibrillation: rationale and initial experience. J Cardiovasc Electrophysiol 2010;21:126-32.

102. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Packer D, Skanes A. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 2005;11:1100-5.

103. Fisher JD, Spinelli MA, Mookherjee D, Krumerman AK, Palma EC. Atrial fibrillation ablation: reaching the mainstream. Pacing Clin Electrophysiol 2006;29:523-37.

104. Cappato R, Calkins H, Chen SA, Davies W, Iesaka Y, Kalman J, Kim YH, Klein G, Natale A, Packer D, Skanes A, Ambrogi F, Biganzoli E. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:32-8.

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

106. Dagres N, Varounis C, Flevari P, Piorkowski C, Bode K, Rallidis LS, Tsougos E, Leftheriotis D, Sommer P, Hindricks G, Kremastinos DT. Mortality after catheter ablation for atrial fibrillation compared with antiarrhythmic drug therapy. A meta-analysis of randomized trials. Am Heart J 2009;158:15-20.

107. Pappone C, Rosanio S, Augello G, Gallus G, Vicedomini G, Mazzone P, Gulletta S, Gugliotta F, Pappone A, Santinelli V, Tortoriello V, Sala S, Zangrillo A, Crescenzi G, Benussi. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 2003;42:185-97.

108. Haissaguerre M, Jais P, Shah DC, Garrigue S, Takahashi A, Lavergne T, Hocini M, Peng JT, Roudaut R, Clémenty J. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation 2000;101:1409-1417.

109. Chen X, Pehrson S, Svendsen JH. Remote magnetic navigation for atrial fibrillation. Heart Rhythm 2008;5:S171 (Abstract).

110. Anderson JL, Adams CD, Antman EM et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial

infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, American College of Physicians, Society for Academic Emergency Medicine, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2007;50:652–726.

111. Lester SJ, Ryan EW, Schiller NB, Foster E. Best methods in clinical practice and in research studies to determine left atrial size. Am J Cardiol 1999;84:829-832.

112. Darbar D, Roden DM. Symptomatic burden as an endpoint to evaluate interventions in patients with atrial fibrillation. Heart Rhythm 2005;2:544-9.

113. Abecasis J, Dourado R, Ferreira A, Saraiva C, Cavaco D, Santos KR, Morgado FB, Adragão P, Silva A. Left atrial volume calculated by multi-detector computed tomography may predict successful pulmonary vein isolation in catheter ablation of atrial fibrillation. Europace 2009;11:1289-94.

114. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS. Left atrial size. Physiologic determinants and clinical applications. J Am Coll Cardiol 2006;47:2357-63.

115. Kim YH, Marom EM, Herndon JE, McAdams HP. Pulmonary vein diameter, cross-sectional area, and shape: CT analysis. Radiology 2005; 235:43–49.

116. Wu J, Estner H, Luik A, Ücer E, Reents T, Pflaumer A , Zrenner B, Hessling G, Deisenhofer I. Automatic 3D mapping of complex fractionated atrial electrograms (CFAE) in patients with paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2008;19:897-903.

117. Chen J, Off MK, Solheim E, Hoff PI, Schuster P, Ohm O-J. Spatial relationships between the pulmonary veins and sites of complex fractionated atrial electrograms during atrial fibrillation. Pacing Clin Electrophysiol 2009;32:S190-3.

118. Roux J-F, Gojraty S, Bala R, Liu CF, Hutchinson MD, Dixit S et al: Complex fractionated electrogram distribution and temporal stability in patients undergoing atrial fibrillation ablation. J Cardiovasc Electrophysiol 2008;19:815-20.

119. Park JH, Pak H-N, Kim SK, Jang JK, Choi JI, Lim HE et al: Electrophysiologic characteristics of complex fractionated atrial electrograms in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2009;20:266-72.

120. Gong Y, Xie F, Stein KM, Garfinkel A, Culianu CA, Lerman BB, Christini DJ. Mechanism underlying initiation of paroxysmal atrial flutter/atrial fibrillation by ectopic foci: a simulation study. Circulation 2007;115:2094-102.

121. Lin WS, Prakash VS, Tai CT, Hsieh MH, Tsai CF, Yu WC, Lin YK, et al. Pulmonary vein morphology in patients with paroxysmal atrial fibrillation initiated by ectopic beats originating from the pulmonary veins: Implications for catheter ablation. Circulation 2000;101:1274–1281.

122. Pan NH, Tsao HM, Chang NC, Chen YJ, Chen SA. Aging dilates atrium and pulmonary veins: Implications for the genesis of atrial fibrillation. Chest 2008; 133:190–196.

123. Gerstenfeld EP, Callans DJ, Dixit S, Zado E, Marchlinski FE. Incidence and location of focal atrial fibrillation triggers in patients undergoing repeat pulmonary vein isolation: implications for ablation strategies. J Cardiovasc Electrophysiol. 2003;14:685-90.

124. Cappato R, Negroni S, Pecora D, Bentivegna S, Lupo PP, Carolei A, Esposito C, Furlanello F, De Ambroggi L. Prospective assessment of late conduction recurrence across radiofrequency lesions producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. Circulation 2003;108:1599-604.

125. Lemola K, Hall B, Cheung P, Good E, Han J, Tamirisa K, Chugh A , Bogun F, Pelosi F Jr, Morady F, Oral H. Mechanisms of recurrent atrial fibrillation after pulmonary vein isolation by segmental ostial ablation. Heart Rhythm 2004;1:197-202.

126. Liu X, Shi H-F, Tan H-W, Wang X-H, Li Z, Gu, J-N. Decreased connexin 43 and increased fibrosis in atrial regions susceptible to complex fractionated atrial electrograms. Cardiology 2009;114:22-9.

127. Park JH, Pak H-N, Kim SK, Jang JK, Choi JI, Lim HE , Hwang C, Kim YH. Electrophysiologic characteristics of complex fractionated atrial electrograms in patients with atrial fibrillation. J Cardiovasc Electrophysiol 2009;20:266-72.

128. Lu Z, Scherlag BJ, Lin J, Niu G, Ghias M, Jackman WM , Lazzara R, Jiang H, Po SS. Autonomic mechanism for complex fractionated atrial electrograms: Evidence by fast Fourier transform analysis. J Cardiovasc Electrophysiol 2008;19:835-42.

129. Katrisis D, Giazitzoglou E, Sougiannis D, Voridis E, Po SS. Complex fractionated atrial electrograms at anatomic sites of ganglionated plexi in atrial fibrillation. Europace 2009;11:308-15.

130. Tada H, Yoshida K, Chugh A, Boonyapisit W, Crawford T, Sarrazin J-F, Kuhne M, Chalfoun N, Wells D, Dey S, Veerareddy S, Billakanty S, Wong WS, Kalra D, Kfahagi A, Good E, Jongnarangsin K, Pelosi F Jr, Bogun F, Morady F, Oral H. Prevalence and characteristics of continuous electrical activity in patients

with paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2008;19:606-12.

131. Matsuo S, Lellouche N, Wright M, Bevilacqua M, Knecht S, Nault I , Lim KT, Arantes L, O'Neill MD, Platonov PG, Carlson J, Sacher F, Hocini M, Jaïs P, Haïssaguerre M. Clinical predictors of termination and clinical outcome of catheter ablation for persistent atrial fibrillation. J Am Coll Cardiol 2009;54:788-95.

132. Stiles MK, Brooks AG, Kuklik P, John B, Dimitri H, Lau DH, Wilson L, Dhar S, Roberts-Thomson RL, Mackenzie L, Young GD, Sanders P. High-density mapping of atrial fibrillation in humans: Relationship between high-frequency activation and electrogram fractionation. J Cardiovasc Electrophysiol 2008;19:1245-53.

133. Hocini M, Sanders P, Jaïs P, Hsu LF, Weerasoriya R, Scavée C, Takahashi Y, Rotter M, Raybaud F, Macle L, Clémenty J, Haïssaguerre M. Prevalence of pulmonary vein disconnection after anatomical ablation for atrial fibrillation: consequences of wide atrial encircling of the pulmonary veins. Eur Heart J 2005;26:696-704.

134. Gerstenfeld EP, Callans DJ, Dixit S, Zado E, Marchlinski FE. Incidence and location of focal atrial fibrillation triggers in patients undergoing repeat pulmonary vein isolation: implications for ablation strategies. J Cardiovasc Electrophysiol 2003;14:691-2.

135. Elayi CS, Verma A, Di Biase L, Ching CK, Patel D, Barrett C, Martin D, Rong B, Fahmy TS, Khaykin Y, Hongo R, Hao S, Pelargonio G, Dello Russo A, Casella M, Santarelli P, Potenza D, Fanelli R, Massaro R, Arruda M, Schweikert RA, Natale A. Ablation for longstanding permanent atrial fibrillation: results

from a randomized study comparing three different strategies. Heart Rhythm. 2008;5:1658-64.

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

137. Tilz RR, Chun KR, Schmidt B, Fuernkranz A, Wissner E, Koester I, Baensch D, Boczor S, Koektuerk B, Metzner A, Zerm T, Ernst S, Antz M, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: a lesson from circumferential pulmonary vein isolation. J Cardiovasc Electrophysiol 2010;21:1085-93.

138. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm 2010;7:835-46.

139. Bulava A, Haniš J, Sitek D, Ošmera O, Karpianus D, Snorek M, Rehoušková K, Toušek F, Pešl L. Catheter ablation for paroxysmal atrial fibrillation: a randomized comparison between multielectrode catheter and point-by-point ablation. Pacing Clin Electrophysiol 2010;33:1039-46.

140. Hofmann R, Hönig S, Leisch F, Steinwender C. Pulmonary vein isolation with Mesh Ablator versus cryoballoon catheters: 6-month outcomes. J Interv Card Electrophysiol 2010;29:179-85.

141. Oswald H, Gardiwal A, Lissel C, Tu H, Klein G. Difference in humoral biomarkers for myocardial injury and inflammation in radiofrequency ablation versus cryoablation. Pacing Clin Electrophysiol 2007;30:885-90.

142. Hochcolzer W, Schlitterhardt D, Arentz T, Stockinger J, Weber R, Bürkle G, Kalusche D, Trenk D, Neumann FJ. Platelet activation and myocardial necrosis

in patients undergoing radiofrequency and cryoablation of isthmus-dependent atrial flutter. Europace 2007;9:490-5.

143. Zheng X, Walcott GP, Hall JA, Rollins DL, Smith WM, Kay GN, Ideker RE. Electrode impedance: an indicator of electrode-tissue contact and lesion dimensions during linear ablation. J Interv Card Electrophysiol 2000:4:645-54.

144. Kurosaki K, Tada H, Hashimoto T, Ito S, Miyaji K, Naito S, Oshima S, Taniguchi K. Plasma natriuretic peptide concentrations as a predictor for successful catheter ablation in patients with drug-refractory atrial fibrillation. Circ J 2007;71:313-20.

145. Sacher F, Corcuff JB, Schraub P, Le Bouffos V, Georges A, Jones SO, Lafitte S, Bordachar P, Hocini M, Clémenty J, Haissaguerre M, Bordenave L, Roudaut R, Jaïs P. Chronic atrial fibrillation ablation impact on endocrine and mechanical cardiac functions. Eur Heart J 2008;29:1290-5.

146. Hof I, Arbab-Zadeh A, Scherr D, Chilukuri K, Dalal D, Abraham T, Abraham T, Lima J, Calkins H. Correlation of left atrial diameter by echocardiography and left atrial volume by computed tomography. J Cardiovasc Electrophysiol 2009;20:159-63.

147. Hwang HJ, Son JW, Nam B-H, Joung B, Lee B, Kim JB, Lee MH, Jang Y, Chung N, Shim WH, Cho SY, Kim SS. Incremental predictive value of pre-procedural N-terminal pro-B-type natriuretic peptide for short-term recurrence in atrial fibrillation ablation. Clin Res Cardiol 2009;98:213-8.

148. Lo LW, Lin YJ, Tsao HM, Chang SL, Udyavar AR, Hu YF, Ueng KC, Tsai WC, Tuan TC, Chang CJ, Tang WH, Higa S, Tai CT, Chen SA. The impact of left atrial size on long-term outcome of catheter ablation of chronic atrial fibrillation. J Cardiovasc Electrophysiol 2009;20:1211-6.

149. Chang S-H, Tsao HM, Mu MH, Tai CT, Chang SL, Wongcharoen W, Lin YJ, Lo LW, Hsieh MH, Sheu MH, Chang CY, Hou CJ, Chen SA. Morphological changes of the left atrial appendage after catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2007;18:47-52.