Improving the procedural safety and efficacy of radiofrequency catheter ablation for atrial fibrillation

Studies with special focus on non-paroxysmal atrial fibrillation

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2 Abstract

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, and it is responsible for increased mortality and a reduced quality of life. Its prevalence is rapidly increasing. Catheter ablation has emerged during the past decade as a promising treatment option for paroxysmal and non-paroxysmal AF patients. We investigated various aspects of catheter ablation for AF, particularly in non-paroxysmal AF, with the aim of improving the safety and efficacy of such procedures.

Aims and methods

The patients enrolled in these studies were burdened by symptomatic, drug-refractory AF. Non-paroxysmal AF was the clinical arrhythmia in the majority of the individuals. All patients underwent an electrophysiological study and subsequently an ablation procedure that included pulmonary vein isolation and in selected cases, complex fractionated electrogram (CFE) ablation. The first study aimed to assess long-term outcomes in a population of exclusively non-paroxysmal AF patients who were followed up regularly for an average of 40 months. In the second study we investigated the effects of flecainide on the distribution and extension of CFE areas. For this purpose, two separate CFE maps (before and after flecainide administration) were created and compared. In the third study we assessed the correlation between catheter-tissue contact force and impedance fall. Qualified ablation points were selected and the corresponding contact force and impedance fall data were retrieved and analyzed.
Results and conclusions

An approach consisting of pulmonary vein isolation and CFE ablation appears to provide favorable long-term outcomes in a high proportion of patients. Multiple procedures are often required to attain positive results. Although post-ablation atrial tachycardia frequently occurs, it may represent a step towards long-term success. Longer AF duration and female gender appear to predict a higher likelihood of procedural failure.

Intraprocedural administration of flecainide in non-paroxysmal AF patients reduces the extension of CFE areas but preserves their original localization. The employment of a CFE-mean cut-off of 80 ms may facilitate the identification of stable CFE areas. The CFE areas that thus disappear may be functional and therefore may be an inappropriate target for ablation.

Increasing degrees of catheter-to-tissue contact force lead to a larger impedance fall suggesting improved lesion formation. Under stable catheter conditions, a contact force greater than 5 g seems to create adequate lesions. However, a contact force beyond 20 g is associated with late impedance rise, and may be a warning of an increased risk of complications.
3 List of publications


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4 Abbreviations

AAD: antiarrhythmic drug
AF: atrial fibrillation
AFCL: atrial fibrillation cycle length
AT: atrial tachycardia
AV: atrioventricular
CF: contact force
CFE: complex fractionated electrogram
CS: coronary sinus
ECG: electrocardiogram
GP: ganglionated plexi
IF: impedance fall
LA: left atrium
LAA: left atrial appendage
LAD: left atrial diameter
LVEF: left ventricular ejection fraction
MR: magnetic resonance
MV: mitral valve
PV: pulmonary vein
PVI: pulmonary vein isolation
RA: right atrium
ROC: receiver operating characteristic
SR: sinus rhythm
5 Introduction

“Fibrillation, like flutter, may also on occasion be terminated in the auricle by cold or pressure very locally applied”
Sir Thomas Lewis, 1925

5.1 DEFINITION AND HISTORY

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by rapid and chaotic activation of the atria. As early as in the 17th century, Harvey observed ante-mortem chaotic motion in the atria (presumably representing AF) during open-chest examination of dogs. A century later de Sénac correlated palpitations and irregular cardiac pulsation, two common AF symptoms, with the presence of abnormalities in the mitral valve (MV). In the early 20th century, with the development of the electrocardiogram (ECG), AF began to be paid more attention. An irregular ventricular response, the absence of P waves and presence of fibrillatory atrial activity are well established ECG criteria for the diagnosis of AF.

5.2 EPIDEMIOLOGY

AF is the sustained cardiac arrhythmia that is most commonly encountered in clinical practice. In the western world, its prevalence is estimated at between 1% and 2% of the adult population, but it is significantly higher among individuals over 70 years of age. The annual incidence of AF was estimated by the Framingham Study to be 3.1/1000 in males and 1.9/1000 in females aged 55 to 64 years. When considering individuals of between 85 to 94 years of age, these figures increase to 38/1000 and 31/1000. Males are affected by more symptomatic forms of AF which also tend to appear earlier in life than in females. Data from the Rotterdam study estimated the
lifetime risk of developing AF at about 25% in individuals aged 40 or more\textsuperscript{9}. Given the growing number of elderly people in the western society, the prevalence of AF is likely to increase in the near future\textsuperscript{10}. Epidemiological projections estimate a rise in the number of AF patients of up to 12 million in the United States and 13 million in Europe by 2030\textsuperscript{11, 12}.

The presence of idiopathic AF (lone AF) in an otherwise healthy subject accounts for around 10% of all AF patients\textsuperscript{13, 14}. In the majority of the cases, AF is secondary to cardiac or non-cardiac conditions. Important cardiac conditions for the development of AF are valvular heart disease, ischemic heart disease, cardiac surgery, hypertension, myocarditis, and dilative and hypertrophic cardiomyopathy\textsuperscript{8}. Important non-cardiac conditions for the development of AF are chronic obstructive pulmonary disease, hyperthyroidism, sleep apnea syndrome, acute infections, pulmonary embolism, binge drinking, obesity and diabetes\textsuperscript{15-18}.

5.3 PATHOPHYSIOLOGY

Despite over a century of research, the precise mechanisms that start and perpetuate AF are incompletely understood. Like other cardiac arrhythmias, AF requires a trigger for its initiation and a substrate for its maintenance.

In pioneering work performed during the 1950s, Moe et al. suggested that AF was maintained by multiple independent wavelets propagating randomly in a tissue with highly dispersed refractoriness\textsuperscript{19}. This “multiple wavelet theory” postulated that a critical myocardial mass would be required for AF to be sustained indefinitely.

Moe’s observations were confirmed almost 20 years later by the work of Allessie et al., which demonstrated simultaneous propagation of multiple independent wavelets in an acetylcholine dog model of AF\textsuperscript{20}. The validity of this theory also found support in the positive outcomes of the Cox maze surgical procedure in which atrial lesions are created with the aim of compartmentalizing the left atrium (LA)\textsuperscript{21}. The multiple wavelet theory is currently the most highly credited among clinical electrophysiologists.
At the beginning of the last century, Sir Thomas Lewis observed that the central excitation wave of AF showed a strong predilection for moving around a stable channel\textsuperscript{22}. His statements, although criticized by his contemporaries, are nowadays being reconsidered. There is increasing evidence that, at least in some cases, AF propagates through stable circuits, also called rotors, as they rotate around an unexcited core\textsuperscript{23-27}.

5.3.1 Triggers

In the 1990s, the availability of more sophisticated recording systems contributed to the search for the triggers of AF. Haïssaguerre first reported a series of three patients in whom AF episodes were triggered by an ectopic atrial focus\textsuperscript{28}. The subsequent milestone work demonstrated that episodes of AF are consistently initiated by focal activity, mostly (94\%) originating from the pulmonary veins (PVs). Ablation targeting these foci resulted in the disappearance of AF in 62\% of the patients during the follow-up\textsuperscript{29}. Apart from the PVs, additional sources of focal activity may be found in the LA body (particularly in the ligament of Marshall and MV annulus), the right atrium (RA) body (particularly in the crista terminalis, fossa ovalis and Eustachian ridge), superior and inferior caval veins and the coronary sinus (CS)\textsuperscript{29-35}. Histological studies showed that the nature of increased PVs automaticity depends on the anatomy of the LA\textsuperscript{36, 37}. Myocardial muscular sleeves extend deeply into the wall of the PVs, particularly in the left PVs\textsuperscript{36, 37}. The intersection of myocardial and connective tissue from the PV wall determines anisotropic conduction, which creates the perfect substrate to enhance focal activity\textsuperscript{36, 38}. These findings received remarkable resonance in the field of invasive electrophysiology and virtually launched the era of AF ablation.

5.3.2 Substrate

There is solid evidence that, with the perpetuation of AF, the atria undergo electrical and structural remodeling\textsuperscript{39-45}. Electrical remodeling occurs within a few minutes of
the onset of AF and leads to a shortening of the refractory period and a reduction in conduction velocity\textsuperscript{39, 42-45}. The changes that account for structural remodeling take place over a longer period of time and include hypertrophy of the myocytes, an increase in interstitial fibrosis, changes in the expression of ionic channels and reversal to a fetal gene program\textsuperscript{45}. The ultimate result of this process is almost invariably the dilation of the LA\textsuperscript{45}. According to Moe’s theory, AF termination is dependent on the statistical probability of all wavelets extinguishing simultaneously. This implies that in a larger LA more wavelets coexist, thus increasing the likelihood that AF will persist for longer periods.

The classic aphorism “AF begets AF” has been widely used to describe the clinical evolution of this arrhythmia\textsuperscript{40}.

5.3.3 Contributing factors

Tentative observations have suggested that autonomic nervous system activity may be implicated in the AF process\textsuperscript{46-51}. It has been demonstrated that the onset and perpetuation of AF are preceded by variations in autonomic tone\textsuperscript{46}. Specifically, it appears that a parasympathetic response increases vulnerability to AF and may elicit PV firing\textsuperscript{50, 51}. These assertions are further supported by the promising results of catheter ablation aimed at the ganglionated plexi (GP)\textsuperscript{47-49}.

High circulating levels of inflammation markers, such as C-reactive protein and myeloperoxidase, are frequently found in AF patients, suggesting that there may be a correlation between AF and inflammation\textsuperscript{16, 45, 52-55}. This association is also supported by the high incidence (up to 50\%) of AF in patients undergoing cardiac surgery\textsuperscript{52, 54, 56, 57}. However, currently available data do not clarify whether inflammation is the cause or the consequence of AF.

Finally, single and multiple gene mutations have been reported in families with a high burden of AF. Some of these genes codify for ion channel proteins (e.g. KCNx family) whilst others are implicated in intercellular connection (e.g. Connexin40)\textsuperscript{58, 59}. Knowledge about AF genetics is growing rapidly. This new information will enhance
our understanding of AF mechanisms and may enable a genotype-based medicine to be developed.

5.4 CLINICAL IMPLICATIONS

Common symptoms such as palpitations, fatigue, shortness of breath and dizziness are often correlated with the onset of AF. On the other hand, sustained AF episodes may lead to progressive deterioration of atrial and ventricular function that may culminate in overt congestive heart failure.

Episodes of AF occur in >50% of patients with concomitant dysfunction of the sinus node (sick sinus syndrome) which suggests a causal relationship. Sick sinus syndrome is currently the most common indication (>50%) for permanent pacemaker implantation.

Because of reduced blood flow in the LA and left atrial appendage (LAA), AF poses a serious risk of systemic embolization, particularly to the brain. Patients at high risk (assessed by their CHADS$_2$ or CHA$_2$DS$_2$VASC score) are therefore required to undergo systemic anticoagulation as a preventive measure against cerebrovascular accidents. Although stroke is the most feared complication of AF and results from major cerebral embolization events, some studies have suggested that microembolization over time could be related to various degrees of dementia.

Finally, data from the Framingham Study have showed that the presence of AF alone is associated with a 1.5 to 1.9-fold increase in risk of mortality.

5.5 CLASSIFICATION

AF is classified according to the duration of the episodes: “paroxysmal” indicates recurrent AF episodes terminating spontaneously within seven days; “persistent” indicates AF lasting beyond seven days or requiring electrical or pharmacological cardioversion to be stopped; “longstanding persistent” indicates persistent AF lasting over one year. The term “non-paroxysmal”, although not included in the current guidelines, is commonly used to identify persistent and longstanding persistent AF.
Finally, the expression “permanent AF” identifies those patients in whom AF is accepted and restoration of the sinus rhythm (SR) will no longer be attempted.

5.6 THERAPEUTIC OPTIONS

5.6.1 Direct current cardioversion

Direct current cardioversion is often employed in the management of AF patients. Although the acute success of this intervention is excellent, recurrences of AF are very common (71%-84% at one year).

Direct current cardioversion alone is of limited importance in the long-term management of AF patients. However it may be an important tool when used in combination with medical therapy or with catheter ablation.

5.6.2 Antiarrhythmic medications

Antiarrhythmic drug (AAD) treatment has for several decades been the main treatment option for AF patients. All AADs currently available are flawed by their variable efficacy and by some degree of pro-arrhythmogenic effects.

AAD treatment can be employed in two different strategies: either aiming at controlling the ventricular rate (rate-control strategy), or at restoring and maintaining SR (rhythm-control strategy). In the AFFIRM study, over 4000 AF patients were randomized to either a rhythm-control or rate-control strategy and were followed for a median of 3.5 years. The rhythm-control group suffered higher mortality (although not statistically significant, p=0.08), more hospitalizations and more adverse events than the rate-control group. However, a sub-analysis of the AFFIRM study suggested that in elderly patients the risk of drug adverse events may outweigh the benefit of a rhythm-control strategy. Moreover, they showed that the higher mortality in the rhythm-control group was mainly due to non-cardiovascular deaths. The RACE study showed that rhythm-control therapy was associated with improvement of
the left ventricular function and a reduction in the left atrial diameter (LAD)\textsuperscript{74}. Similarly, the SAFE-T study concluded that sustained SR was associated with an improved quality of life and exercise performance\textsuperscript{75}.

### 5.6.3 Surgery

As cardiac surgery improved, more and more interest was focused on developing a surgical treatment for cardiac arrhythmias. After extensive testing on dog models in the mid-1980s, Cox managed to establish a surgical approach (Cox maze procedure) that could be employed in humans and that gave excellent results in both paroxysmal and non-paroxysmal AF\textsuperscript{21}.

Despite refinements in the technique, the Cox maze procedure remains highly invasive. Nowadays only AF patients who have to undergo cardiac surgery for other reasons (bypass graft, valve replacement, etc.) are considered as candidates for this operation\textsuperscript{69}.

In the last decade, off-pump techniques such as surgical AF ablation and the totally endoscopic AF ablation have been developed. Pulmonary vein isolation (PVI) and LAA obliteration can be additionally performed in these procedures. However, the indications for and clinical importance of these new approaches are still unclear\textsuperscript{69}.

### 5.6.4 Catheter ablation

In an attempt to offer a less invasive alternative to the Cox maze procedure, catheter ablation for AF was developed and promptly emerged as an additional therapeutic option. Following several randomized trials, it is now recognized that catheter ablation is superior to AADs in improving AF symptoms and quality of life\textsuperscript{76-78}. Furthermore, a number of retrospective studies were able to show that AF-free patients following successful ablation are at similar risk of stroke and mortality as patients without AF\textsuperscript{79-81}. However, a definite answer to whether catheter ablation improves stroke and mortality risk is still awaited and will probably follow the
completion of specifically designed multicenter, randomized trials such as the CABANA and EAST trials\textsuperscript{82, 83}.

5.6.5 Atrioventricular (AV) node ablation

Symptomatic AF patients who are refractory to AADs and who do not qualify for AF ablation (because of exclusion criteria, poor prognosis or patient’s preference) can be referred to pacemaker implantation (preferably biventricular pacing devices) and subsequently to AV node ablation. In this brief procedure, the physiological AV conduction is permanently interrupted by means of catheter ablation\textsuperscript{84, 85}. In this way, AF will continue in the atria, but the ventricular response will be regulated by the pacemaker. Previous studies demonstrated that this strategy can improve symptoms and increase left ventricular ejection fraction (LVEF) in selected patients\textsuperscript{86, 87}.

5.7 CATHETER ABLATION TECHNIQUES

Catheter ablation is a percutaneous procedure in which catheters are advanced to the heart from a mini-invasive vascular access. The procedure is performed under fluoroscopic guidance and, more recently, assisted by a three-dimensional navigation system. Catheter ablation for AF can be performed using various energy sources (such as cryoenergy, ultrasound and laser) but radiofrequency is by far the most frequently used worldwide. Application of radiofrequency energy induces irreversible thermal damage in the myocardium thus preventing impulse formation and/or conduction in the targeted area.

5.7.1 Trigger-based ablation

Successful ablation aimed at focal sources of AF was first reported in 1994 by Haïssaguerre\textsuperscript{28}. Following the definition of the important role of electrical activity arising from the PVs, focal ablation at these foci was initially attempted\textsuperscript{29}. Modest outcomes and high incidence of PV stenosis following focal ablation led to the development of PVI procedures\textsuperscript{88, 89}. This strategy was first performed with a
segmental approach, targeting the earliest site of activation (breakthrough) at the PV ostium\textsuperscript{90, 91}. Later, Pappone introduced the circumferential approach, in which PVI was achieved by deploying circumferentially contiguous lesions at a distance \( \geq 5 \text{ mm} \) from the PV ostia (Figure 1)\textsuperscript{92}. This purely anatomical approach provided satisfactory results with shorter procedures and an improved safety profile.

PVI has now become the cornerstone of AF ablation. There is unanimous agreement that PVI represents the minimum endpoint for ablation of both paroxysmal and non-paroxysmal AF\textsuperscript{69}. Moreover, restored PV conduction can be demonstrated in the vast majority of patients admitted for a repeated ablation procedure\textsuperscript{93-95}. Electrical reconnection of the PVs is believed to be the principal responsible mechanism for recurrences of AF. Finally, patients in whom extra-PV ectopies have been demonstrated can benefit by additional ablation targeting these foci\textsuperscript{31, 33, 34}.

Figure 1 – Posteroanterior view of the left atrium (reconstructed by the Carto3\textsuperscript{TM} system), showing displacement of ablation lesions (red dots) for circumferential pulmonary vein (PV) isolation. LAA: left atrial appendage, LSPV: left superior PV, LIPV: left inferior PV, RIPV: right inferior PV, RSPV: right superior PV.
5.7.2 Substrate-based ablation

Although stand-alone PVI has provided satisfactory clinical results in paroxysmal AF, its application appears to be insufficient in non-paroxysmal AF. With the exception of a minority of centers, there is agreement that in these patients there is a need to additionally target the substrate that is perpetuating the arrhythmia.\textsuperscript{34,69}

Current strategies to modify AF substrate include linear ablation, complex fractionated electrogram (CFE) ablation, GP ablation and rotor ablation.

The first report of curative catheter ablation for non-paroxysmal AF was presented by Swartz et al. in 1994, and consisted of a set of linear lesions in the LA.\textsuperscript{96} In the same year, a similar approach with linear ablation targeting the RA was described by Haïssaguerre.\textsuperscript{97}

Although successful, linear ablation was initially restrained by the limited technology available and by a high rate of complications. Nowadays, several centers perform a roof line (connecting the left superior PV with the right superior PV) and a mitral isthmus line (from the inferior aspect of the left inferior PV to the MV annulus) as an adjunctive strategy to PVI (Figure 2).\textsuperscript{98}

In the late 1990s, the presence of fractionated electrograms (later denominated CFEs) was first associated with areas of slow conduction and pivot points and believed to represent crucial regions for AF maintenance.\textsuperscript{99} In an immunohistological study, CFE areas were found to represent enhanced tissue fibrosis with a reduced expression of gap junction proteins.\textsuperscript{100}

Involvement of CFE areas in AF maintenance is further supported by the clinical results following ablation aiming at these regions. Nademanee et al. established a new ablation approach by solely targeting CFE areas in paroxysmal and non-paroxysmal patients. AF termination was achieved in 95% of the patients and SR maintenance in 91% at one year follow-up.\textsuperscript{101} However, these results could not be reproduced by other centers.

In spite of the questionable worth of stand-alone CFE ablation, adjunctive CFE
ablation to PVI is used by several centers in the treatment of non-paroxysmal AF (Figure 3)\textsuperscript{98}.

A combination of linear and CFE ablation is performed in the “stepwise approach”\textsuperscript{102, 103}. In this technique, ablation is aimed at sequential targets: PVI, superior vena cava and CS isolation, ablation at sites of complex electrical activity and finally roof and mitral lines. Previous reports have shown remarkable acute and long-term success following these extensive procedures\textsuperscript{102, 104, 105}. Moreover, their authors were able to show that the order of the targets was irrelevant to the clinical outcomes, suggesting similar importance of all these mechanisms to the maintenance of AF\textsuperscript{103}.

\textbf{Figure 2} – Anteroposterior view of the left atrium (reconstructed by the EnSite NavX\textsuperscript{TM} system), showing displacement of ablation lesions for roof line (green dots between RSPV and LSPV) and mitral isthmus line (green dots between LIPV and the MV annulus). MV: mitral valve, other abbreviations as in Figure 1.
The epicardial localization of GPs makes them amenable to ablation. It is widely accepted that autonomic innervation is involved in the pathophysiology of AF. However, clinical outcomes from GP ablation, either alone or in combination with PVI, are not consistent and more research is needed to assess the importance of these targets in AF ablation\textsuperscript{47-49}.

Recent developments in mapping tools have led to the reconsideration of the localized source hypothesis whereby organized rotors may drive and maintain human AF. Narayan et al. employed custom software to map AF rotors and reported impressive outcomes following PVI and rotor ablation\textsuperscript{26}. The results of ongoing multicenter trials may well produce more evidence in support of rotor mapping and ablation.

**Figure 3** – Right anterior oblique view of the left atrium (reconstructed by the EnSite NavX\textsuperscript{TM} system), showing a complex fractionated electrogram map and displacement of ablation lesions (green dots) corresponding with areas of high fractionation (white and red color). Abbreviations as in Figures 1 and 2.
5.7.3 Procedural endpoints

One of the factors contributing to the widespread use of PVI is its straightforward endpoint. Electrical conduction block from the LA to the PV is used by most centers to document PVI, and is considered a sufficient endpoint for paroxysmal AF ablation\textsuperscript{106}. A small proportion of operators may employ additional pacing maneuvers to increase the specificity of PVI assessment\textsuperscript{107,108}.

Conversely, catheter ablation in non-paroxysmal AF is currently restrained by undefined endpoints. AF termination, non-inducibility, conduction block over linear lesions, CFE abatement and the disappearance of vagal responses have all been utilized in clinical practice. While some of these endpoints are technically difficult to assess, others are flawed by a high degree of subjectivity and their clinical importance has yet to be confirmed\textsuperscript{109}.

5.7.4 Indications for atrial fibrillation ablation

Catheter ablation is a therapeutic option that is currently considered only for symptomatic AF patients who are refractory or intolerant to at least one Class I or Class III AAD\textsuperscript{69}. The latest HRS/EHRA/ECAS expert consensus statement suggests the following indications:

- **Paroxysmal AF**: catheter ablation is recommended, class I, level of evidence A
- **Persistent AF**: catheter ablation is reasonable, class IIa, level of evidence B
- **Longstanding persistent AF**: catheter ablation may be considered, class IIb, level of evidence B

It is recognized that in certain cases, catheter ablation may also be regarded as first-line therapy for AF. Finally, it is emphasized that such indications only apply if AF ablation is performed in experienced centers by appropriately trained electrophysiologists\textsuperscript{69}.
5.7.5 **Clinical outcomes**

The field of AF ablation has undergone a huge expansion in the past decade. In order to improve outcomes, new ablation techniques and technology have been developed. For several reasons, outcomes of AF ablation as retrieved from the literature have been inconsistent. As suggested by a recent meta-analysis, heterogeneity in outcomes may have its origin in differences between patient populations, ablation techniques, definitions of procedural success and follow-up monitoring modalities.

It is acknowledged that the outcomes of paroxysmal and non-paroxysmal AF should be considered separately, as they reflect two different stages of the disease. In five randomized clinical trials in which PVI was compared to AAD treatment for paroxysmal AF, success rates of ablation ranged between 66% and 89% whereas AAD outcomes lay between 16% and 42%.

Recently, two independent studies (RAAFT-2 and MANTRA-PAF) compared in a randomized fashion AADs to catheter ablation as first-line therapy in patients with paroxysmal AF. The RAAFT-2 study concluded that patients undergoing catheter ablation experienced a lower rate of recurrences of AF than those administered AADs. The MANTRA-PAF study, on the other hand, found no significant difference in the cumulative AF burden after a two-year follow-up.

Outcomes of non-paroxysmal AF are more controversial as there is no consensus on what should be the endpoint after successful PVI. Moreover, several ablation strategies are employed and the results are usually inconsistent between different centers. Stand-alone PVI is believed to be insufficient in these patients and clinical success is poor (20%). Adjunctive roof and mitral linear ablation produces improved outcomes in patients with non-paroxysmal AF. Arya et al. reported a 12-months success rate of 75% while Willems et al. had a 69% success rate after a mean follow-up of 16 months. Adjunctive CFE ablation after PVI has also been shown to be beneficial with outcomes ranging from 56% to 94% in several single and multi-center trials. Ultimately, a step-wise approach seems to confer...
the best outcomes, with the proportion of AF-free patients lying between 79% and 95\%\(^{104, 121}\).

Data from a worldwide survey on the efficacy of AF ablation reported a medium-term success rate of around 75% in paroxysmal AF and 64% in non-paroxysmal AF patients off all AADs\(^{122}\).

5.7.6 Shortcomings

Recurrences of arrhythmias

Recurrences of arrhythmias following AF ablation are frequent. The most common arrhythmia to relapse is AF. A large-scale study revealed AF recurrence rates of 31.5% in paroxysmal and 41.0% in non-paroxysmal AF patients\(^{123}\). Similar findings were demonstrated by other studies\(^{110, 124, 125}\). AF recurrences are most frequent in the mid-term (<1 year) but can also occur >3 years after the index procedure\(^{124, 126}\). Patients who experience multiple AF recurrences are often considered for a repeat ablation procedure.

Recurrences of atrial tachycardia (AT) on the other hand, mostly occur during the first months following ablation and particularly in non-paroxysmal AF patients\(^{119, 127, 128}\). Occurrences of AT are believed to be mediated by catheter ablation itself and can significantly complicate the management of these patients\(^{129}\). These arrhythmias respond poorly to AAD and they usually lead to higher ventricular rates and more severe symptoms. A repeat dedicated ablation session is the most effective treatment for post-ablation AT.

Complications

Catheter ablation for AF may lead to a wide range of complications, some of which may be life-threatening. A worldwide survey incorporating over 16,000 patients and 20,000 procedures reported an overall complication rate of 4.5%, with death occurring in 0.15% of the patients. The most common complications were cardiac perforation leading to cardiac tamponade (1.31%), neurological events (stroke or transient ischemic attack, 0.94%) and access-site vascular complications (1.47%)\(^{122}\). It
must be noted that this survey had a potential bias. Complication rates in the “real world” might be higher. Other known complications of AF ablation include PV stenosis, phrenic nerve damage and atrio-esophageal fistula, the latter being very rare but almost invariably fatal\textsuperscript{130}.

Finally, concerns have been raised for the remaining atrial functionality in those non-paroxysmal AF patients who have undergone extensive ablation\textsuperscript{131}. Preliminary results from an analysis of 40 patients after step-wise ablation suggest that in spite of significant scarring, left atrial functionality recovered in those who maintained SR\textsuperscript{105}.

**Cost-effectiveness**

Despite the increasing enthusiasm for AF ablation, it must be reminded that the techniques are still under development and that these procedures may also increase the economic burden on healthcare systems.

Compared to AAD treatment, AF ablation has a high initial cost. Canadian data estimated a total cost per AF ablation procedure of 9,590 C$. Another report suggested that AF ablation was cost-neutral compared to AAD, four years after the procedure\textsuperscript{132, 133}. Similarly in the UK, AF ablation was found potentially cost-effective if the benefits in terms of quality of life were maintained for five years\textsuperscript{134}. Although these studies seem to favor AF ablation, it must be noted that they rely on the assumption that outcomes at 12 months are maintained until five years from the initial procedure. Moreover, these studies do not take into account that a significant proportion of patients continue AAD treatment after having undergone AF ablation thus leading to additional cost and risk of AAD side-effects\textsuperscript{135}. A recent review concluded that the scientific evidence currently available (particularly in regard to hard endpoints) is insufficient to permit conclusions about the cost-effectiveness of AF ablation to be drawn\textsuperscript{135}. 
5.8 CURRENT CHALLENGES AND CONTROVERSIES OF AF ABLATION

Challenging and unresolved aspects of AF ablation include patient selection, incomplete understanding of the mechanisms involved in AF and quality assurance of ablation lesions.

Clinical outcomes of AF ablation can be very different from patient to patient. It is reasonable to suppose that improved patient selection would ameliorate ablation outcomes and avoid the risk of complications in individuals with a poor prognosis. The definition of pre-procedural parameters that can predict long-term outcomes is therefore an open issue in AF ablation.

So far parameters such as age, gender, AF type, body mass index, LAD, LVEF, AF cycle length (AFCL), AF history, presence of diabetes, hypertension or other cardiac disease have been examined with widely variant results\textsuperscript{121, 123, 124, 136-139}. Even echocardiographic measurement of LAD, a parameter which may depict the degree of remodeling of the LA, has not shown consistency between studies\textsuperscript{140-142}. Moreover, these parameters may be related and act as reciprocal confounders. For this reason it could be worthwhile to define statistical models that allow such complex interactions to be taken into account.

Although there is unanimous agreement on the importance of electrical activity arising from the PVs in triggering AF, the mechanisms that sustain the arrhythmia are poorly understood. This aspect is particularly relevant in non-paroxysmal AF patients in whom a trigger-based ablation (with stand-alone PVI) does not appear to be sufficient to guarantee satisfactory results\textsuperscript{109, 116}. New insights into the pathophysiology of AF may allow the development of a mechanistic (rather than empirical) ablation strategy for non-paroxysmal AF patients. Such a strategy may enable us to obtain positive long-term outcomes with the minimum extent of collateral myocardial damage. A definition of precise procedural endpoints is also required to improve reproducibility between different centers.
Electrical reconnection of the PVs is often observed in AF patients who are accepted for a second ablation procedure. A repeat PVI usually improves long-term results. Catheter ablation is mostly performed under fluoroscopic guidance. Although three-dimensional navigation systems are extremely useful to the electrophysiologist, catheter stability and contact with the atrial wall are highly dependent on the experience and the tactile skills of the operator.

Although this has never been formally demonstrated, it is believed that intermittent or poor contact during the first few seconds of ablation may result in the development of local myocardial edema that can hamper lesion transmurality. Under such circumstances, the tissue is only partially damaged and the healing of the edema (a process that can take from hours to days) may restore electrical conduction (leading for instance to PV reconnection).

Proposed strategies to tackle this issue include pacing maneuvers, prolonged observation time, administration of steroids, isoproterenol or adenosine and improved catheter stability and contact. The latter aspect is believed to be crucial. No matter what the ablation target is, good quality lesions are fundamental to obtaining the best results from catheter ablation. Previous experimental work has shown that higher contact force (CF) leads to larger and deeper lesions.

In the past, parameters such as catheter tip temperature, electrogram voltage reduction and impedance fall (IF) have been used as surrogates for catheter-tissue contact to monitor lesion development. Although useful, these parameters are flawed by various limitations which make their interpretation rather poor and unspecific.

Recently, CF sensing ablation catheters, which allow accurate, quantitative measurement of the CF applied to the cardiac tissue, have been developed. Data from initial experience suggest that this technology is of great value, although further investigations are still needed to define and validate a safe and effective range of CF for clinical application.
6 Aims

The aims of these studies were to investigate clinical results and technical aspects of AF ablation.

1. To analyze long-term follow-up results and predictors of arrhythmia recurrence in a population of non-paroxysmal AF patients treated exclusively with a combined PVI + CFE ablation strategy.

2. To determine the effects of intravenous flecainide on the distribution and extension of CFE areas in patients undergoing catheter ablation for non-paroxysmal AF.

3. To evaluate the relationship between catheter-to-tissue CF and IF during catheter ablation for AF.
7 Methods

Patient Material

These three studies included a total of 124 symptomatic AF patients that had previously attempted at least one AAD without success. Paper I and II involved only non-paroxysmal AF patients, while paper III involved mostly paroxysmal AF patients (94.3%) undergoing a first ablation procedure.

The average age of the patients was 59±8 years. Females were in a minority (18/124, 14.5%). Hypertension was common (51/124, 41.1%), but there was a low incidence of structural cardiac disease (17/124, 13.7%). The echocardiographic data indicated a tendency to LA enlargement although the LVEF was preserved (>45%) in all the patients. Beta-blocker was by far the most common class of AAD attempted.

All patients underwent systemic anticoagulation with warfarin. An international normalized ratio value within the therapeutic range (>2.0) for at least four weeks was required before AF ablation. Detailed information about patient demographics is provided in each paper.

Patients were referred to our institution from all over Norway. The study population was enrolled from the operation schedule. The studies were approved by the Regional Ethics Committee of Western Norway and were performed in accordance with the Declaration of Helsinki.

Electrophysiological study and ablation set-up

All the procedures included in the studies were performed at Haukeland University Hospital between 2007 and 2013. Conscious sedation with diazepam and morphine was used in all the patients and the procedures. Patients were admitted at the hospital one day prior to procedure, and warfarin was stopped two days before the procedure. Low molecular weight heparin was administered if necessary.

Vascular access was obtained by puncturing the right and left femoral veins. Left atrial catheterization was performed via a transseptal puncture or via a patent foramen
ovale, where available. A 20-pole mapping catheter (Livewire™, St Jude Medical) was positioned in the RA with the distal poles in the CS. A 10-pole circular catheter (Lasso™, Biosense Webster or Optima™, St. Jude Medical) was inserted through a long sheath in the LA and was used to confirm PV isolation. Finally, an open-irrigated ablation catheter (specific models are reported in each individual paper) was advanced in the LA through the same transseptal puncture as for the long-sheath and was used for mapping and ablation.

A three-dimensional electroanatomical system (Carto3™, Biosense Webster or EnSite NavX™, St. Jude Medical) was employed in all the procedures for catheter navigation and for mapping purposes. An advanced recording system (Lab System Pro™, Bard Electrophysiology) was used to visualize and record intracardiac electrograms.

Radiofrequency ablation was always delivered in a temperature-controlled mode at an irrigation flow-rate of 15-20 ml/min and a temperature cut-off of 50°C. Energy was generally delivered for 60 s at each location and the power was titrated to a maximum of 35W for PVI or 40W for cavotricuspid isthmus ablation. In paper III, power was limited to 30W.

Ablation targets

PVI was performed by ablating circumferentially, in a point-by-point pattern at the PV antra (1-2 cm proximally to the ostium). Entrance block (confirmed by the 10-pole circular catheter) was used as endpoint for PVI. Differential pacing from the LAA was used to confirm PVI in the left PVs. Patients in AF at the end of the procedure received a direct current cardioversion before sheath removal in order to document PVI in SR.

CFE ablation was performed in non-paroxysmal AF patients targeting areas of highly fragmented potentials (CFE-mean<80 ms). Prior to ablation, a CFE map was created by the electroanatomical mapping system by sampling continuous recording from the distal electrode of the ablation catheter. In paper II, a second CFE map was collected before ablation but after administration of intravenous flecainide.
CFE mapping and ablation were performed in the LA in all patients. Additional mapping and ablation were delivered in the CS and RA in selected patients at the operator’s discretion. The endpoint of CFE ablation was the disappearance of fractionated electrograms.

Linear ablation was performed exclusively to treat ATs. Activation mapping and entrainment pacing were employed to locate the critical isthmus. Endpoints of linear ablation were AT termination and, if possible, demonstration of conduction block across the line.

A cavotricuspid isthmus line was performed in patients with a clinically documented history of typical atrial flutter. Bidirectional conduction block was the endpoint of cavotricuspid isthmus ablation.

**Follow-up**

Patients were monitored for 24 hours and usually discharged the day after the procedure under warfarin. Anticoagulation and AAD were continued for at least three months regardless of procedural outcome. All patients were followed up on an ambulatory basis at three, six and 12 months with clinical examination, ECG and echocardiography. Depending on arrhythmia recurrence and symptoms, medications were either discontinued or modified. After the first year, follow-up was performed in selected patients depending on the clinical situation.

We defined “success” when patients remained completely arrhythmia-free after a blanking period of three months; “clinical improvement” when previously persistent AF patients had only occasional short episodes of self-terminating arrhythmia but great improvement of symptoms; “failure” when patients experienced recurrences of persistent arrhythmia.

Paper I included repeated ablation procedures that were scheduled in 36 unsuccessful patients at least six months after the index procedure. In paper II clinical outcomes were evaluated only by considering the index procedure.
Data collection

Data in paper I were retrieved from the procedural reports and from the patients’ medical journal.

Data in paper II were retrieved from the three-dimensional navigation system (EnSite NavX). Every CFE mapping point was annotated on a pre-formatted form with the corresponding CFE-mean value, average electrogram amplitude and anatomical location. CFE and scar areas were measured by the system and expressed in cm$^2$.

Data in paper III were retrieved from the three-dimensional navigation system (Carto3). Qualified lesion points were selected according to specific enrolling criteria. CF and impedance data were registered automatically by the system. Anatomical location of points and force-direction angle were annotated on a pre-formatted form by a remote operator.

Statistics

Continuous variables were presented as mean ± standard deviation or as median and interquartile range when data did not follow a normal distribution. The Kolmogorov-Smirnov test was used to confirm normal distribution of the data. Categorical variables were presented as percentages and compared by the chi-squared test. For comparison between continuous variables we used paired and unpaired t-tests, Wilcoxon signed-rank test and Mann-Whitney U test as appropriate. In paper III we used the Kruskal-Wallis test and the Friedman test as non-parametric alternatives for the analysis of variance. Associations between continuous variables were presented as rank correlations (Spearman's rho). Univariate and multivariate logistic regressions were used for predictor analysis. Optimal cut-offs for specific continuous predictors were determined by minimizing the distance from the optimal test in a receiver operating characteristic (ROC) curve. Statistical analysis was performed with SPSS Statistics for Windows, Version 19.0 (IBM Corp. 2010). All tests were two-tailed. A p-value $<0.05$ was considered to be statistically significant.
8 Results

Paper I

We studied 66 non-paroxysmal AF patients (mean age 58±9 years, 86% male) who underwent exclusively PVI + CFE ablation and were followed up for a mean of 40±14 months.

After the first ablation procedure, 21 (31.8%) patients were arrhythmia-free, 20 (30.3%) displayed clinical improvement and 25 (37.9%) suffered recurrences of persistent atrial arrhythmias. After multiple procedures (112 in total, mean 1.7±0.7 per patient), 38 (57.6%) patients were arrhythmia-free, 15 (22.7%) displayed clinical improvement and 13 (19.7%) suffered recurrences of persistent atrial arrhythmias. A total of five major complications were recorded (4.5%). Twenty-five patients (37.9%) developed AT following PVI + CFE ablation. In 12 cases a repeat ablation session was required to treat the AT.

Thirty-six patients (54.5%) underwent multiple procedures. In all the repeat procedures, manifest electrical reconnection of one or more PVs was observed and additional PVI was therefore performed. All 12 of those who started the repeat procedure in SR and all 8 of those who started in AT displayed a procedural benefit, compared to 9 out of 16 of those who started the repeat procedure in persistent AF (p<0.05).

Multivariate analysis revealed that female gender and duration of uninterrupted AF were independent predictors of long-term procedural failure (p=0.01 and 0.004 respectively, OR 12.31 and 1.49 respectively). ROC analysis estimated an uninterrupted AF duration of 3.5 years as the optimal cut-off point for predicting procedural failure (sensitivity 85%, specificity 74%).
Paper II

We enrolled 23 non-paroxysmal AF patients (mean age 59±7 years, 91% male) to study the effect of intravenous flecainide on the distribution and extension of CFE areas.

Before flecainide administration, a CFE-mean value cut-off <120 ms resulted in CFE areas covering an average of 52.6±26.6% of the total LA surface. A lower CFE-mean cut-off resulted in a significantly smaller proportion of the CFE area.

Following flecainide administration, the duration of the QRS complex was slightly but significantly prolonged (104±15 vs. 111±18 ms, p<0.001). The CFE-mean value increased in all patients, from an average of 111.5±55.3 ms to 132.3±65.0 ms (p<0.001). An analogous increase was found by separately analyzing each segment. AFCL in the LAA was similarly affected (155.1±20.8 vs. 195.0±27.1 ms, p<0.001). Overall, average atrial electrogram amplitude decreased significantly after flecainide administration (0.30±0.31 vs. 0.25±0.20 mV, p<0.001) as well as the electrogram amplitude measured in the LAA (0.96±0.68 vs. 0.64±0.34 mV, p<0.01). The area detected as scar by the system increased (1.6±4.2 to 4.2±6.6 cm², p<0.01) in all patients following flecainide administration. Prolongation of CFE-mean values and abatement of electrogram amplitude led to a decrease in the extension of CFE areas. We observed a reduction of CFE area in all regions and in all the patients (average 32.9%) after flecainide administration. We observed a large degree of spatial preservation of CFE areas following flecainide administration, with an average of 80.9% of preserved CFE areas.

A lower CFE-mean value was found in the portions of CFE areas that were preserved than in those that disappeared (73.8±17.4 vs. 89.4±17.1 ms; p<0.001). ROC analysis estimated a CFE-mean value of 78 ms as the best cut-off point for predicting the disappearance of CFE areas following flecainide administration (71% sensitivity, 66% specificity). A higher electrogram amplitude was found in the preserved CFE portions compared to those that disappeared (0.37±0.28 vs. 0.28±0.20 mV; p<0.001).

After a mean follow-up of 22.1±5.0 months, 65.2% of patients maintained stable SR.
Paper III

We studied 35 AF patients (mean age 61±9 years, 80% male) to explore the relationship between catheter-to-tissue CF and IF during ablation.

Average CF recorded was 9.0 g (IQR 9.0, total range 1-48 g). Higher CF and maximum IF were recorded in the right superior PV than in the left inferior (p<0.001) and left superior PV (p<0.05).

Data points were allocated to five groups according to CF value. Group I included points with CF ranging from 1 to 5 g (n=107), Group II from 6 to 10 g (n=131), Group III from 11 to 15 g (n=76), Group IV from 16 to 20 g (n=36) and Group V for lesions exceeding 20 g (n=44). All the groups showed an acute IF in the first 10 s of ablation, followed by a plateau phase in Group I and by a progressive fall in the other groups. Maximum IF appeared at 50 s of ablation in Groups II, III and IV, and at 40 s in Group V. Group V showed a statistically significant rise in impedance during the last 20 s of ablation, from a median IF of 20.0 Ω to 15.0 Ω (p<0.01).

Comparisons between the groups showed that levels of IF were statistically different (p<0.001) at each time point between all groups, except between Groups III and IV. Similar results were found for maximum IF. A linear correlation was demonstrated between maximum IF and CF (Spearman’s rho=0.54; p<0.01).

Finally, we evaluated the impact of force-direction angle on CF and maximum IF. The median CF of the points with 0-30° (4.0 g) was significantly lower than those with 30-60° (11.0 g, p<0.001) and 60-135° (10.0 g, p<0.001). Similar results were also found for maximum IF (10.0 Ω, 15.0 Ω and 16.0 Ω) in lesions with force-direction angles of 0-30°, 30-60° and 60-135° respectively (p<0.001).
9 General discussion

The field of AF ablation has expanded significantly in recent years. Regarded as an experimental approach less than two decades ago, this treatment has now become a routine procedure\textsuperscript{69}. Although it was initially developed for paroxysmal AF patients, catheter ablation is also increasingly used in the treatment of non-paroxysmal AF. In this subgroup of patients however, evidence is still scarce and controversial\textsuperscript{115, 116, 153}.

A multicenter randomized trial recently compared ablation and AAD in persistent AF\textsuperscript{154}. At the end of the one-year follow-up, 70.4% of the patients in the ablation group were arrhythmia-free, compared to 43.7% in the AAD group. A similar single-center non-randomized investigation reported an arrhythmia-free proportion of 76% in patients who underwent ablation versus 46% in those who were managed with AAD\textsuperscript{155}. Patients receiving AAD were additionally more likely to undergo electrical cardioversion and to develop side-effects from their medications\textsuperscript{155}.

In spite of these encouraging findings, which favor the potential advantage of catheter ablation, the definition of clinical outcomes in non-paroxysmal AF has been more challenging than in paroxysmal AF\textsuperscript{116}. Heterogeneity in patient selection, procedural strategy, technological equipment and follow-up may represent plausible causes of this lack of consistency\textsuperscript{115, 153}.

9.1 Patient selection: a key to improving clinical outcomes of non-paroxysmal AF ablation

It is recognized that non-paroxysmal AF represents a highly heterogeneous group of patients in terms of symptoms and cardiac comorbidities. Patient selection in non-paroxysmal AF is therefore an important variable in the assessment of clinical outcomes of catheter ablation\textsuperscript{35}. In the above-mentioned work by Mont et al., the inclusion of relatively young and healthy AF patients may have contributed substantially to the final outcomes\textsuperscript{154}.
Several parameters have been previously investigated as potential predictors of long-term outcomes but the results are inconsistent\textsuperscript{117, 121, 123, 136, 138, 139, 156-158}. In paper I, we showed that the duration of uninterrupted AF was a strong predictor of AF recurrence. While clinical outcomes were satisfactory with an AF duration $\leq 4$ years, poor results were obtained in patients with an AF duration $>4$ years. Although the duration of uninterrupted AF has previously been reported as a potential predictor, some authors have suggested an AF duration $<2$ years as a prudent indication for AF ablation\textsuperscript{137, 139, 156, 158}. Larger studies are needed to clarify this discrepancy and to define an ideal AF duration cut-off as inclusion criteria for non-paroxysmal AF ablation.

Because of the propensity of AF to self-perpetuation, AF duration and left atrial size might be closely correlated. In paper I we did not find any association between LAD and long-term outcomes. Contrasting findings suggest that echocardiographic measurement of LAD does not represent an accurate estimate of real LA size\textsuperscript{140, 142, 159}. Some authors have suggested that other measurements such as LA sphericity or LA volume obtained from magnetic resonance (MR) scans may be more reliable indicators of AF remodeling\textsuperscript{140, 144, 159}.

MR has also recently been employed to quantify fibrosis in the LA\textsuperscript{35, 160}. Preliminary reports have shown that a lower amount of fibrosis yields to better long-term outcomes after catheter ablation\textsuperscript{35, 160}. This new information suggests that atrial remodeling not only contributes to the perpetuation of AF but may also limit the efficacy of curative AF ablation. Most interestingly, it has been demonstrated that the remodeling process can be stopped and reversed by the presence of SR, and that measures that aim to restore SR before ablation may have positive effects on the long-term outcomes\textsuperscript{142, 161-164}.

In paper I we also observed that females had significantly poorer prognoses than males. This finding has been previously shown, although inconsistently, and the reasons are unclear\textsuperscript{138, 165}. The prevalence of extra-PV foci seems to be higher in females. Extra-PV foci mapping and ablation can be challenging and are not routinely performed\textsuperscript{32, 163, 164, 166}. A number of authors have additionally observed that female
AF patients are managed less aggressively than their male counterparts in terms of AADs and direct current cardioversions. When finally offered catheter ablation, female patients are subject to a delayed referral to this procedure possibly with more advanced stages of atrial remodeling\textsuperscript{157, 166}. Finally, in paper II we reported that female patients manifested by far the lowest proportion of CFE area in the LA (<5%). This observation may support the hypothesis that the AF substrate could be different in females and males. If this is the case, future AF ablation techniques could be specifically tailored to female patients.

9.2 Procedural strategy: PVI+CFE ablation is a plausible approach for non-paroxysmal AF

An additional factor complicating the comparison of clinical trials for non-paroxysmal AF is the variety of ablation strategies employed. Most authors agree that stand-alone PVI is not sufficient in non-paroxysmal AF\textsuperscript{69}. Linear and CFE ablation are currently widely employed as adjunctive strategies although it is not yet clear which provides the best results. The results from the multicenter, randomized, STAR-AF II trial may throw light on this issue\textsuperscript{120}.

In paper I we showed that a procedural strategy consisting exclusively of PVI plus adjunctive CFE ablation led to satisfactory long-term results in a mixed population with persistent and long-standing persistent AF. After multiple procedures and an average follow-up of over three years, 80.3% of the patients enjoyed clinical benefits from the treatment including 57.6% that remained arrhythmia-free.

Ablation of CFE areas is an accepted strategy, albeit controversial, for the treatment of non-paroxysmal AF. The conflicting results described in the literature could originate from a lack of consensus regarding the definition of CFE, mapping technique or ablation endpoint\textsuperscript{167-169}.

In localizing CFE areas for instance, dedicated CFE mapping tools are employed by some centers while others only use “visual inspection”. Moreover, there is no
agreement regarding what should be the endpoint of CFE ablation; AF termination, CFE disappearance and CFE organization have all been adopted. These incongruences affect not only clinical results but also the safety profile and duration of these procedures. As shown in paper II, CFE areas are widespread and, according to the criteria used, may cover >50% of the LA surface. In order to abolish all these areas, extensive ablation must be performed, with potentially increased procedural time and risk of complications.

Arguments in support of CFE ablation include the high degree of stability of CFE areas, frequent occurrence of AFCL prolongation or AF termination during targeting of these areas and plausible mechanistic association with the AF substrate.

The temporal and spatial stability of CFE areas is crucial to prove any involvement of these regions with the substrate maintaining AF. A complete lack of stability on the other hand, would suggest that CFEs originate from passive atrial activation and that their role in AF is only functional. In paper II we demonstrated a high degree of spatial and temporal stability of CFE areas. Over 80% of CFE areas registered 40 minutes after flecainide administration were localized within the spatial limits of previously mapped CFE areas. Although conflicting data concerning CFE stability have been published, the semi-automated measurements performed in our study may strengthen our results as well as the consistency of our findings among patients.

Several authors reported that changes in AF (prolongation of AFCL or termination into AT or SR) occur frequently during CFE ablation. Such acute changes may suggest that ablation targeting these areas does in fact affect the substrate maintaining AF. In paper I we reported an acute termination of AF into SR in 36.6% of the procedures during CFE ablation, either directly from AF or via AT. However, it should be remembered that the mechanism by which CFE ablation contributes to changes in AF is still unclear.

Finally, CFEs were originally linked to areas of fibrosis that may have represented pivot points of rotors perpetuating AF. The wide distribution of CFEs in patients with persistent and long-standing persistent AF could be a consequence of an
increased amount of fibrosis due to AF remodeling. Some reports have also shown that CFE areas are characterized by lower electrogram amplitude than non-CFE areas. However, discordant results concerning the relationship between CFE and fibrosis are reported in the literature. Recently, Jadidi et al. investigated the correlation between fibrosis and CFEs using delayed enhancement MR and found that 41% of continuous CFE areas were found in regions of “patchy fibrosis” and 11% in regions of dense fibrosis, while the majority (48%) were found in areas of healthy tissue. These interesting results add to previously published data and prove that at least some CFEs are functional and represent unspecific targets for ablation.

It has been suggested that, if CFE ablation is pursued, it would be of importance to distinguish between culprit and functional CFEs. In paper II we showed that intravenous flecainide can be administered in order to partially eliminate functional CFE, estimated to be more than 30% and to highlight culprit CFE. A CFE-mean cut-off of 80 ms may facilitate the identification of stable CFE areas. Long-term outcomes of ablation targeting exclusively CFE areas after flecainide and with a CFE-mean <80 ms were comparable to previous studies, thus supporting that disappeared areas are functional.

The implementation of these two measures in clinical practice could greatly reduce the amount of atrial myocardium targeted for CFE ablation with potentially great benefit for procedural safety. It has in fact been suggested that extensive ablation in the LA may bring a higher risk of complications and increase the incidence of post-ablation ATs.

9.3 Technological advances: contact force monitoring

The main limitation of radiofrequency catheter ablation today is the unpredictable formation and endurance of its lesions. Although it has not been formally demonstrated, there is agreement that poor lesion quality leads to a transient effect and may eventually result in arrhythmia recurrences.
Experimental studies have shown that sub-optimal CF is associated with inadequate lesion formation\textsuperscript{148, 149}. Following the availability of CF-sensing catheters, a great deal of research has been focusing on this topic\textsuperscript{94, 95, 150-152, 183-186}.

Previous studies have shown how CF varies significantly in different locations in the LA. Lower degrees of CF are achieved in the left PVs and particularly in the left superior PV\textsuperscript{94, 184}. These observations may explain the difficulty of isolating the left superior PV and the frequent occurrence of its electrical reconnection.

Several investigations have also sought to validate the utility of this technology in assessing lesion development; IF has often been selected as the parameter of comparison for this purpose\textsuperscript{93, 184-187}. In paper III we demonstrated a significant association between catheter tip-to-tissue CF and IF. Although other authors have confirmed our results, the correlation coefficient (Spearman’s rho=0.54) found in paper III between CF and IF was higher than had been observed in similar studies\textsuperscript{184, 187}. The reasons for this difference may be found in the rigorous selection of qualified points in our study based on a strict assessment of catheter stability. In this light, the results of paper III acquire additional significance, and suggest that CF plays an even more important role when employed together with improved catheter stability. This supposition is confirmed by the positive effects of adopting a steerable sheath (a tool that potentially improves catheter stability) to support the ablation catheter during AF ablation\textsuperscript{117, 188}.

Recently, findings from preliminary studies on CF technology have been used to develop annotation algorithms that may improve real-time assessment of lesion quality. A recent study investigated the clinical benefits of an algorithm that validates only ablation points characterized by an IF >5\% and by a catheter movement <2 mm. When applied to AF ablation, these parameters led to a significant reduction in acute PV reconnection and a higher (although not statistically significant) proportion of arrhythmia-free patients\textsuperscript{93}.

Impedance monitoring has also previously been used in the prevention of acute complications. Under stable catheter conditions, a sudden rise in impedance during
ablation may be observed ahead of steam pops or thrombus formation, and indicates that energy delivery should cease\textsuperscript{189}. The results of paper III show that a high CF (>20 g) may lead to a late impedance rise occurring after 40 s of ablation; this underlines the fact that procedural safety may benefit from the constant monitoring of CF and IF. Controlling CF or alternatively, reducing ablation duration when a high CF is obtained, may curtail the incidence of complications.

9.4 Follow-up considerations: definition of clinical endpoints and impact of arrhythmia recurrences after ablation

The latest expert consensus document draws attention to the importance of standardized follow-up routines for the evaluation of clinical trials involving AF patients. Total freedom from atrial arrhythmia in the absence of AAD is the most objective definition of success and should be the preferred endpoint for all AF ablation trials\textsuperscript{69}. In a clinical setting, however, this may be difficult to achieve in non-paroxysmal AF patients.

Recently, Tondo et al. have shown that 46% of patients after ablation experienced AF recurrences that were completely asymptomatic\textsuperscript{190}. Other reports have underlined how quality of life improves significantly with the reduction of AF burden, even when AF recurs\textsuperscript{191, 192}. Finally, AADs can reduce significantly AF recurrences after catheter ablation\textsuperscript{118, 193, 194}. How should these outcomes be considered in a clinical setting?

The current guidelines state that referral to catheter ablation is mainly dependent on the presence of symptomatic AF\textsuperscript{59}. This thus acknowledges that the disappearance or improvement of AF symptoms should be regarded as satisfactory outcomes\textsuperscript{69, 190, 191}.

In paper I, besides the 57.6% of patients who remained arrhythmia-free after the procedure, a further 22.7% had significant improvement of their symptoms. Most of these patients remained in stable SR for a long time and later experienced episodes of self-terminating paroxysmal AF.
An additional issue concerns the intensity of the follow-up after ablation. Martinek et al. showed that the proportion of arrhythmia-free patients fell with the implementation of more sensitive tools for arrhythmia detection\textsuperscript{195}.

Patients included in paper I were followed up for an average of over three years with Holter recordings, ECG and clinical examination. A stricter follow-up was employed in the first year from the ablation, with visits at three, six and 12 months. The intensity of further follow-up depended on the clinical situation.

Previous studies have shown that recurrences of arrhythmia following AF ablation are most common in the first 12 months but may occur up to three years following ablation\textsuperscript{123-125}. Recurrences of AF after ablation also seem to appear more often in non-paroxysmal AF patients\textsuperscript{110, 124, 125}. The results of paper I confirm these findings: while recurrences occurred during the first 12 months in 42 patients (63.6%), only three (4.5%) suffered late recurrences (>12 months) up to 40 months from the initial procedure. Although rare, the development of very late recurrences raises a dilemma on the safety of discontinuing anticoagulation in those patients at high cerebrovascular risk.

With regard to late arrhythmia recurrences, it is also of interest to consider AT and AF separately. Previous work has suggested that when AF is the clinical arrhythmia that recurs in the follow-up, PV reconnection may be the main mechanism involved\textsuperscript{93-95, 146}. In paper I, all the patients who underwent a repeat procedure had signs of reconnection of at least one PV. This is consistent with other observations\textsuperscript{125, 196}.

Recurrences of AT are relatively more frequent among non-paroxysmal AF patients\textsuperscript{119, 127, 128}. It has been reported that the incidence of AT is linked to the extension of ablation performed in the LA\textsuperscript{129, 181}. It is not clear which ablation strategy produces the highest risk of developing AT\textsuperscript{119, 167}. When linear ablation is chosen as the procedural strategy, post-ablation ATs are often characterized by a macro-reentry caused by recovered conduction over the lines\textsuperscript{129}. When CFE areas are targeted, post-ablation ATs can be characterized by either a macro- or a micro-reentry caused by areas of extremely slow conduction\textsuperscript{197, 198}. 
Post-ablation ATs may complicate the management of non-paroxysmal AF patients, but at the same time, they could also be regarded as a favorable prognostic factor. Although this often requires an extra procedure, mapping and ablation of AT is feasible. Patients who have undergone a repeat ablation session because of AT have a better long-term prognosis than those with a repeat ablation because of recurrences of AF\textsuperscript{127,199}. Results from paper I show that all the patients (100\%) who underwent a repeat ablation procedure because of AT had clinical improvement at follow-up compared with only 56\% of those whose repeat ablation was due to persistent AF. It thus appears reasonable to suggest that AT should not be regarded as a complication but as an encouraging step towards stable SR. Future research should be addressed to the improvement of mapping techniques in order to facilitate ablation treatment of these arrhythmias.

\textit{Study limitations}

Our results come from three single-center, non-randomized studies in which no control group was employed. The number of patients involved, especially females, was relatively small. However, this is consistent with previous literature and reflects the actual proportion of female patients referred for catheter ablation.

Paper I was a retrospective study and, because of the follow-up protocol, we realize that some asymptomatic recurrences of arrhythmia may have been underestimated.

In paper II, the study material was retrieved only from the LA. Conclusions therefore cannot be extrapolated to the PVs, RA and CS.

In paper III, there were significant differences between the number of points in the different CF groups. Obtaining stable catheter contact is more challenging when high CF is applied and these differences probably express this difficulty.
10 Conclusions

1. After long-term follow-up, a strategy of combined PVI + CFE ablation seems to provide a reasonable rate of arrhythmia-freedom and clinical improvement in non-paroxysmal AF patients. Patients with uninterrupted AF duration ≤ 4 years appear to benefit most from this ablation strategy. Female gender and longer duration of uninterrupted AF are predictors of long-term failure.

2. Flecainide reduces the extension of CFE areas in non-paroxysmal AF patients by slowing atrial conduction velocity and diminishing complexity and amplitude of atrial electrograms. CFE areas appear to be spatially and temporally stable after flecainide administration. These findings may influence approaches to CFE ablation and reduce ablation time and procedural duration.

3. IF correlates significantly with catheter tip-tissue CF level during 60 s of ablation. CF exceeding 5 g produces greater IF, which probably indicates adequate lesion formation. CF greater than 20 g may lead to late tissue overheating.
11 References


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