Catheter ablation for non-paroxysmal atrial fibrillation. A review

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Atrial fibrillation (AF), the most common cardiac arrhythmia is associated with increased morbidity and mortality. The higher mortality is due to the risk of heart failure and cardioembolic events. This in-depth review focuses on the strategies and efficacy of catheter ablation for non-paroxysmal atrial fibrillation. The main medical databases were searched for contemporary studies on catheter ablation for non-paroxysmal AF. Catheter ablation is currently proven to be the most effective treatment for AF and consists of pulmonary vein isolation as the cornerstone plus additional ablations. In terms of SR maintenance, it is less effective in non-paroxysmal AF than in paroxysmal patients. but the clinical benefit in non-paroxysmal patients is substantially higher. Since pulmonary vein isolation is ineffective, a variety of techniques have been developed, e.g. linear ablations, ablation of complex atrial fractionated electrograms, etc. Another paradox consists in the technique of catheter ablation. Despite promising results in early observation studies, further randomized studies have not confirmed the initial enthusiasm. Recently, a new approach, pulsed-field ablation, appears promising This is an in-depth summary of current technologies and techniques for the ablation of non-paroxysmal AF. We discuss the benefits, risks and implications in the treatment of patients with non-paroxysmal AF.

Key words: atrial fibrillation, catheter ablation, radiofrequency ablation, pulmonary vein isolation

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INTRODUCTION – EPIDEMIOLOGY OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common cardiac arrhythmia in adults[1]. The risk of developing AF increases progressively with age, from a prevalence of 0.1% in individuals under 55 years of age to 9.0% in individuals 80 years and older[2]. In adults, the current prevalence of AF is 2–4% (ref.[3]). In the United States (US) alone, at least 3–6 million people have AF (ref.[4]), and the numbers are projected to reach 6–16 million by 2050 (ref.[5]). In Europe, AF in 2010 was ≈ 9 million in those older than 55 and is expected to reach 14 million by 2060 (ref.[6]). AF is associated with increased mortality and morbidity that primarily occur as a result of arrhythmia complications. According to the epidemiological Framingham Heart Study, AF was associated with a 1.5- to 1.9-fold mortality risk. The decreased survival seen with AF is present in men and women and occurs across a wide range of ages[7]. Higher mortality is linked to associated heart failure and cardioembolism[8]. From a clinical point of view, AF can be described as paroxysmal (PAF) and non-paroxysmal (NPAF); the latter is divided into persistent (PeAF) or long-standing persistent (LSPeAF) atrial fibrillation). Permanent atrial fibrillation presents as an AF form in which no further therapeutic attempts at SR restoration and maintenance are considered[9,10]. During the time course, initially, short and silent AF micro-paroxysms commonly progress to PAF and subsequently to NPAF forms. In a recent meta-analysis, non-paroxysmal AF was associated with a highly significant increase in thromboembolism and death compared with PAF (ref.[11]). PAF develops into the NPAF form with an overall incidence of 5.5% per year; aging, an enlarged left atrium, myocardial infarction, and valvular diseases were independent risk factors for early transition to sustained forms of AF (ref.[12]).

Since 1998 when the Bordeaux group introduced the first use of catheter ablations (CA) for AF, several different methods of CA have been developed. This article will review current technologies and techniques for catheter ablation of AF, show the benefits, and discuss new approaches and strategies for CA in non-paroxysmal AF patients.

DIFFERENCES IN THE PATHOPHYSIOLOGY OF NON-PAROXYSMAL AF

Most AF triggers originate from the pulmonary veins (PVs). Therefore, pulmonary vein isolation is the cornerstone for AF treatment and is usually highly effective in treating paroxysmal AF. However, not all triggers are in the PVs, and the presence of non-pulmonary triggers is higher in non-paroxysmal AF. Non-PV triggers were identified in up to 44% of the patients with LSPeAF, and their presence is a strong predictor of AF recurrence after a CA procedure[13].

Successful conversion and SR maintenance decreases with AF duration. The pathophysiological triangle for AF includes the triggers of arrhythmia initiation, the structural substrate that enables the maintenance of the arrhyth-

mia, and modulators that, through multiple mechanisms, promote the propensity toward AF (ref.[14]). Structural changes of the atria, mainly progressive atrial fibrosis, play an important role in AF maintenance in patients with non-paroxysmal AF and are referred to as fibrotic atrial cardiomyopathy[14,15]. Fibrotic atrial cardiomyopathy is a progressive disease. Atrial fibrosis interferes directly with impulse propagation by forming barriers to electrical conduction, creating a tissue substrate conducive to macro- or micro-reentry. Furthermore, direct electrical fibrocyte-cardiomyocyte interactions can cause changes in cardiomyocyte electrophysiology, and perivascular fibrosis impairs the oxygenation of cardiomyocytes. Since non-pulmonary triggers and structural atrial changes are often present in non-paroxysmal AF patients, the lower efficacy of pulmonary vein isolation (PVI) is not surprising (Fig. 1). Several approaches targeting substrate modification and non-pulmonary triggers, in addition to PVI, have been developed to improve freedom from non-paroxysmal AF (ref.[16]). However, none of them have been shown to improve patient outcomes significantly.

INDICATIONS FOR CATHETER ABLATION AND CURRENT LEVEL OF EVIDENCE

Restoring and maintaining a normal SR is a crucial element in the management of AF patients. Several small (~200 pts.) trials have compared the effect of anti-arrhythmic drugs (AADs) with catheter ablation on SR maintenance, and in all these trials, CA for AF was consistently superior to pharmacological treatment. According to a meta-analysis of studies comparing CA with AADs, the single-procedure success rate of CA off of AADs therapy was 57% (95% CI, 50–64%), multiple procedure success rate off of AADs was 71% (95% CI, 65–77%), and the multiple procedure success rate on AADs was 77% (95% CI, 73–81%) (ref.[17]). On the other hand, except for patients with heart failure, there was no evidence that catheter ablation is associated with an improved prognosis, i.e., a reduction in stroke, heart failure, or mortality. In the CABANA trial, the largest RCT comparing catheter ablation with pharmacological treatment in the general AF population, there was no significant difference in the primary composite endpoint of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest in 2,204 patients during the 5-year follow-up in an intention-to-treat analysis (8.0% vs. 9.2%, respectively; hazard ratio, 0.86 [95% CI, 0.65–1.15]; P=0.30) (ref.[18]). However, although a clinical benefit was not demonstrated, CA was clearly superior relative to AF recurrences (HR 0.52, [95% CI, 0.45–0.60]; P<0.001) and the quality of life[19]. The CABANA trial agrees with a previous meta-analysis of 12 RCTs comparing CA and AADs on the quality of life in 1,707 patients, which demonstrated the superiority of CA over AADs (ref.[20]).

Therefore, according to the European Society of Cardiology (ESC) guidelines, catheter ablation of AF should be recommended to symptomatic AF patients when anti-arrhythmic medication has failed as a class I level recommendation or in symptomatic AF patients as first-line therapy as a class IIa recommendation to ameliorate symptoms and, as such, to improve the quality of life[21]. Since the publication of these guidelines, two additional trials were published comparing CA to AAD treatment of AF patients without previous AAD treatment. Wazni et al. compared CA using cryoablation with AADs in 203 AAD naive (new diagnosed) AF patients. At the 12-month follow-up, CA patients were in sinus rhythm (SR) significantly more often than AAD patients (74.6% vs. 45.0%, P<0.001) (ref.[22]). Andrade et al. randomized 303 patients with symptomatic, but untreated, AF to CA (cryoablation) or AADs. At 12 months, AF recurrence was present in 42.9% of CA patients vs. 67.8% of ADD patients (HR 0.48, 95% CI, 0.35–0.66, P<0.001) (ref.[23]). In both studies, the presence of adverse events was the same in both arms. Since both studies demonstrated the superiority and safety of CA over AADs in symptomatic AF patients without previous anti-arrhythmic treatment, it can be expected that it will be reflected in the new

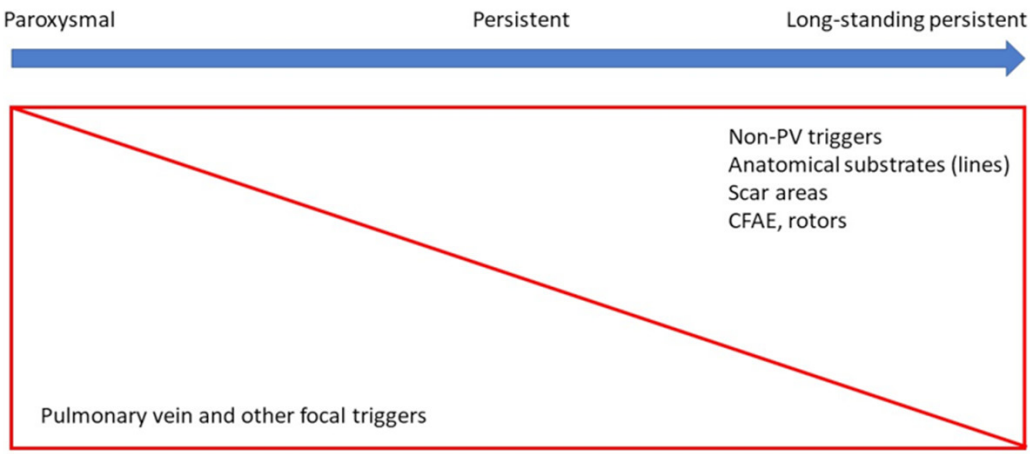

Fig. 1. Mechanism of triggering and maintanance of atrial fibrillation during progression from paroxysmal to non-paroxysmal forms.

Table 1. Clinical studies on CA in AF in HF patients.

	Indication	Primary endpoint	No of patients	SR maintenance	LV EF change	Results of primary endpoint
AATAC	Persistent AF, dual-chamber implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator, NYHA II to III, and LVEF < 40%	Recurrence of AF	203	70% vs. 34% (*P*<0.001)	8.3% vs. 5.0% (*P*=0.02)	95% (CI, 28%–47%) (*P*<0.001).
CAMTAF	Persistent AF, symptomatic HF, and LV ejection fraction < 50%	Difference in LV ejection fraction on TTE at 6 months	390	–	40% vs. 31% (*P*=0.015)	14.2% (CI, −26.2%–−2.2%) (*P*=0.030)
CAMERA-MRI	Persistent AF, left ventricular ejection fraction [LVEF] ≤ 45%	Change in LVEF on repeat CMR at 6 months	301	–	18.3% vs. 4.4 % (*P*<0.0001)	Mean difference in EF improvement: +14.0%, 95% CI, 8.5%–19.5%
CASTLE-AF	HF, AF (paroxysmal or persistent)	All-cause death, hospitalization for worsening HF	398	63.1% vs. 21.7% (*P*<0.001)	8.0% vs. 0.2% (*P*=0.005)	HR 0.62 (95% CI, 0.43–0.87), *P*=0.007

guidelines. However, neither study was designed to demonstrate the clinical benefit of CA in terms of reduction of two major clinical complications.

A different situation exists for AF patients with heart failure (HF). AF and HF frequently coexist and together confer a poor prognosis. HF can be a consequence of AF, especially in patients with AF and a fast ventricular rate, i.e., tachycardia-induced (or AF-induced) cardiomyopathy[24]. On the other hand, AF is present in more than half of those with another HF etiology (e.g., coronary artery disease, valve disease, and dilated cardiomyopathy). According to some reports, AF develops even in more than one-third of individuals with HF (ref.[25,26]). Many studies have shown that CA is linked to favorable clinical results in patients with HF (ref.[17,28]); a summary of randomized studies on CA in HF patients is shown in Table 1. In the AATAC trial, CA was not only superior to amiodarone for SR maintenance in patients with HF and non-paroxysmal AF, it was also associated with a reduction in unplanned hospitalization and mortality[29]. Over the 2-year follow-up, the unplanned hospitalization rate was 31% in CA patients compared to 57% in amiodarone patients (*P*<0.001). Similarly, compared to amiodarone patients, significantly lower mortality was observed in CA patients (8% vs. 18%, *P*=0.037). In the smaller CAMTAF trial, CA was effective in restoring SR in selected patients with persistent AF and HF; it also improved LV function, functional capacity, and HF symptoms compared with the medical treatment (rate control) group[30]. The CAMERA-MRI trial enrolled patients with decreased left ventricular (LV) ejections fraction (EF) (≤ 45%) and persistent AF. All patients underwent cardiac magnetic resonance (CMR) at baseline to assess the degree of left ventricular fibrosis and the LV EF. Patients were randomized to either CA or medical treatment. At six months, LV EF improved by 18 ± 13% in the CA group compared to 4.4 ± 13% in the medical group (*P*<0.0001). The EF improved or normalized (LV EF ≥ 50%) in 58% vs. 9% in the medical group (*P*=0.0002), and CA patients exhibited less ventricular fibrosis on the six-month CMR. Thus, SR restoration and maintenance with CA significantly improved LV function[31]. The CASTLE-AF study demonstrated an improved prognosis with CA in HF patients with AF. This study randomized 398 patients with HF and AF to CA using radiofrequency energy or medical treatment; in the latter group, efforts to maintain SR were recommended. Patients were NYHA class II-IV, had an LVEF ≤ 35%, and all had implanted ICDs. The primary endpoint was a composite of death from any cause or hospitalization for worsening heart failure. After a median follow-up of 37.8 months, the primary composite end point occurred in significantly fewer patients in the ablation group (28.5%) than in the medical-therapy group (44.6%), resulting in an HR of 0.62 (95% CI, 0.43–0.87), *P*=0.007. CA was superior for both components of the primary endpoint, significantly fewer patients in the CA group died (13.4% 25.0%, *P*=0.01) or were hospitalized for worsening heart failure (20.7% vs. 35.9%, *P*=0.004) (ref.[32]). There was also a significant improvement in the LVEF in the CA group vs. the medical group (8.0% vs. 0.2%, *P*=005). Similarly, a recent CASTLE-HTx study[33] showed an important role of catheter ablation in patients with symptomatic atrial fibrillation and end-stage heart failure. A total of 97 patients were assigned to the ablation group and 97 to the medical-therapy group. Catheter ablation was performed in 81 of 97 patients (84%) in the ablation group and in 16 of 97 patients (16%) in the medical-therapy group. After a median follow-up of 18.0 months, a primary end-point event had occurred in 8 patients (8%) in the ablation group and in 29 patients (30%) in the medical-therapy group (hazard ratio, 0.24; 95% CI, 0.11 to 0.52; *P*<0.001). Death from any cause occurred in 6 patients

(6%) in the ablation group and in 19 patients (20%) in the medical-therapy group (hazard ratio, 0.29; 95% CI, 0.12 to 0.72). In patients with atrial fibrillation and end-stage heart failure, the combination of catheter ablation and guideline-directed medical therapy was associated with a lower likelihood of a composite of death from any cause, implantation of a left ventricular assist device, or urgent heart transplantation than medical therapy alone.

The clinical benefit of CA in HF patients was also present in a subgroup of CABANA patients with a history of HF and decreased LVEF at randomization. In the intention-to-treat analysis, the ablation arm had a 36% relative reduction in the primary composite end point (hazard ratio, 0.64 [95% CI, 0.41–0.99]) and a 43% relative reduction in all-cause mortality (hazard ratio, 0.57 [95% CI, 0.33–0.96]) compared with drug therapy alone over a median follow-up of 48.5 months[34]. Except for the aforementioned randomized studies, several non-randomized observational studies on CA for AF in HF patients have been published. According to a meta-analysis of 26 randomized and observational studies with 1,838 patients, the efficacy of maintaining SR was 60% (54–67%), with a significant improvement in LVEF by 13%. Time from the first detection of AF was the most important predictor of success[35]. To sum up, CA for HF is clearly superior to medical treatment and is associated with improved prognosis and LVEF improvement. The success rate of CA of AF in HF patients is lower than non-HF patients for several reasons, such as a greater frequency of non-paroxysmal AF forms or a higher degree of LA dilation; nonetheless, the clinical benefit of CA appears to be higher. In most studies on CA of AF, SR maintenance is often assessed as the absence of an AF recurrence lasting more than 30 sec. However, in HF patients, even a transition of a sustained arrhythmia to the paroxysmal form is of great importance to HF progress and patient prognosis.

THE EFFECT OF CATHETER ABLATION ON QUALITY OF LIFE IN NON-PAROXYSMAL AF

Several studies have documented the positive effects of catheter ablation for AF on QoL. QoL in studies on CA of AF was assessed using specific QoL questionnaires. The most often used questionnaires were the SF-36 (Short Form Health Survey), EQ-5D (EuroQoL 5-Dimension), AFEQT (Atrial Fibrillation Effect on QualiTy of Life), Mayo AF Specific Symptoms Inventory, and the University of Toronto Atrial Fibrillation Severity Scale (AFSS), but other similar questionnaires are available. SF-36 has 36 questions covering eight domains of health (i.e., physical function, limitations due to health problems, emotional problems, etc.). The EQ-5D contains five questions with a 5-component scale, including mobility, self-care, usual activities, pain, and anxiety/depression. The SF-36 and EQ-5D are often used in other areas of medicine and have been extensively validated but have low specificity for AD-related QoL changes. In contrast, the AFEQT consists of 20 questions and evaluates health-related quality of life across three domains, i.e., symptoms, daily activities, and treatment concerns, which are more specific for AF. In a comparison of CA to AADs, CA was superior to medical treatment in all components. Interestingly, a trend toward a decrease in several SF-36 individual components and summary scores was observed as follow-up times increased in both CA and AAD-treated patients. In studies assessing symptom frequency and severity in greater detail, CA led to larger improvements compared to AADs. The effect of CA on QoL can differ for paroxysmal and non-paroxysmal AF patients. Bulková et al. compared changes in QoL after CA of paroxysmal and non-paroxysmal AF. They documented a significant increase in the QoL of both groups during the long-term (all $P<0.00001$), but improvement was significantly greater in non-paroxysmal patients compared to paroxysmal patients[36]. The positive effect of CA in non-paroxysmal patients was seen not only in patients with complete AF freedom but also in patients with good arrhythmia control, where very infrequent AF paroxysms were achieved without the use of anti-arrhythmic drugs. Similar findings were published by Osmancik et al. In their report on the effect of hybrid ablation in non-paroxysmal AF patients, QoL improved significantly in patients with complete SR maintenance and patients with only AF paroxysms but remained unchanged in patients with recurrences of sustained arrhythmias[37]. Improvement in QoL was also described in "asymptomatic" persistent AF patients after CA. AF is often termed "asymptomatic" when it is incidentally discovered during a routine clinical examination. In such patients, AF-related symptoms could be less expressed and cannot be revealed during routine clinical examinations. If assessed in more detail, such as using validated questionnaires, AF-related symptoms could be found (or compared). Therefore, several reports have documented improvements in QoL, as assessed using a standardized questionnaire, after CA of asymptomatic persistent AF patients[38,39]. Even though current ESC guidelines remain restrictive with their recommendations on CA for non-paroxysmal AF, these patients seem to benefit more from the procedure than paroxysmal patients. The greater improvement might be explained by a more profoundly reduced QoL prior to the procedure.

STRATEGIES FOR CATHETER ABLATION OF ATRIAL FIBRILLATION

As noted earlier, PVI only is rarely sufficient for treatment of non-paroxysmal AF. In the next paragraphs, techniques of CA that were tested for CA of non-paroxysmal AF will be discussed.

LINEAR ABLATIONS IN TREATMENT OF NON-PAROXYSMAL AF

Linear ablation has been utilized to create electrical barriers that prevent atrial macro-reentrant arrhythmias. A left atrial linear ablation consists of two standard lines, one along the roof line connecting the cranial aspects of

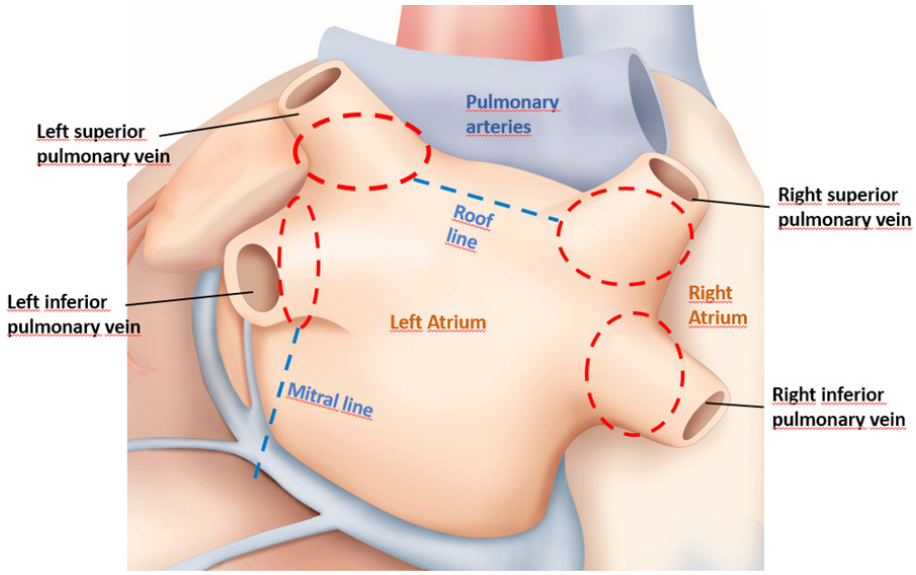

Fig. 2. Linear ablation in patients with non-paroxysmal atrial fibrillation.

the upper PVs and a second line (the mitral isthmus line) connecting the lateral mitral annulus and the left inferior PV. The latter requires an ablation within the coronary sinus (CS) and can be replaced by an anteroseptal line connecting the RSPV with the anterior mitral annulus. The last linear ablation connects the tricuspid annulus with the inferior cava vein to prevent CTI-dependent atrial flutter (Fig. 2). The creation of incomplete lesion lines is pro-arrhythmic. Achieving complete lesion lines and a persistent conduction block across the lines is challenging in the left atrium but is critical to eliminating the arrhythmia[40]. The importance of linear ablation was studied in several observational and four randomized studies. The feasibility of roof ablations was initially studied by Hocini et al.[41]. Ninety patients with paroxysmal AF were divided into two cohorts, (1) an empiric LA roofline linear ablation plus PVI and (2) PVI alone. At the 15 ± 4-month follow-up, significantly more patients in the roofline group were arrhythmia-free compared to those with PVI alone (87% vs. 69%, P=0.04). Similarly, Jaïs et al. evaluated PVI and a cavotricuspid isthmus (CTI) linear ablation in 100 patients with AF; they also examined its efficacy compared to 100 patients undergoing the same procedure plus a linear mitral isthmus (MI) ablation in a prospective, non-randomized study. This study further demonstrated the efficacy of an additional mitral isthmus ablation. At the 1-year follow-up, SR maintenance was present in 87% of patients with and 69% of patients without MI ablation (P<0.001) (ref.[42]). So far, four randomized studies with 1,042 patients have evaluated the importance of linear lesions. In three studies, the linear lesions included both roof and mitral lines, while in one study, only the mitral line was performed. An acute block across the MI (31–76%) and roof line (44–93%) was achieved with variable consistency[43]. Fasini et al. demonstrated, in a randomized study including 187 patients, that the addition of the mitral line compared to PVI alone was more successful in maintaining sinus rhythm at the 1-year follow-up (71% vs. 53%, P<0.01), especially in patients with persistent AF (ref.[44]). Similarly, Willems et al. randomized 62 persistent AF patients to PVI or PVI plus left atrial lines (roof and mitral line). After a 14-month follow-up, AF freedom was present in only 20% of PVI patients compared to 69% of patients with additional ablations (i.e., roof and mitral line) (P<0.001) (ref.[45]). Gaita et al. randomized 204 AF patients (both paroxysmal and non-paroxysmal) to PVI vs. PVI plus left atrial lesions. In a subgroup of non-paroxysmal AF patients after a single procedure, AF freedom was present in 27% and 19% at 1 and 3 years, resp. in the PVI group vs. 45% and 41%, resp. in the PVI + left atrial lesions group. After a second procedure, the 3-year success rate was 39% with PVI and 75% with PVI plus left atrial lesions[46]. Unfortunately, the results of these three aforementioned randomized studies were not confirmed in the STAR-AF II trial. This trial compared PVI (67 pts) vs. PVI plus complex fractionated atrial electrograms (CFAE) ablation (263 pts.) vs. PVI plus additional liner ablations (roof, mitral isthmus, 259 pts.) in 589 patients with non-paroxysmal AF. In the PVI + lines group, complete conduction block across both lines was documented in 74% of patients during the procedure. After 18 months, recurrence of AF after one ablation procedure had occurred in 41% of patients assigned to PVI and 54% of patients assigned to PVI + linear ablations (P=0.15) (ref.[47]). Repeat ablation was performed in 21% of patients in the PVI group and 33% of patients in the PVI + lines group, but rates of AF freedom after two ablation procedures were also not significantly different among groups (72% PVI vs. 58% PVI + lines patients, P=0.18). The procedure time was significantly shorter for pulmonary-vein isolation alone than for the other two approaches (P<0.001). According to the meta-analysis of all randomized trials comparing PVI to the PVI + linear lesions approach, there was no difference in the risk of AF recurrence with adjunctive linear ablation compared to PVI alone (RR 0.64; 95% CI, 0.37, 1.09; P Ľ 0.10).

COMPLEX FRACTIONATED ATRIAL ELECTROGRAMS (CFAE)

CFAE were first described in 2004 by Nademanee et al.[48]. They are defined as continuous atrial activity, complex fractionated potentials, or low voltage electrograms with a short cycle length of less than 120 milliseconds over a 10-second period[49] (Fig. 3). The first report on the CFAE-based approach to AF ablation showed excellent efficacy. In 121 enrolled patients, the ablation consisted of CFAE identification, and ablations were performed from the CFAE location to the closest anatomical barrier. Standard PVI was not performed, but most CFAE-targeted ablations originated in or close to the PVs. This approach resulted in AF termination in 95% of patients during the procedure, 76% achieved AF freedom one year after the first procedure, and 91% after a second procedure[48]. While the first results were promising, further investigators could not confirm this success. Oral et al. performed CFAE-based ablations in the left atrium and the CS. Out of 100 patients, AF terminated in only 12% to SR during the procedure. At 14 months of follow-up, AF-freedom was present in only 33% of patients after a single procedure[50]. In 2009, the same team randomized 100 patients with non-paroxysmal AF after PVI to either an additional CFAE ablation or cardioversion. At the 10-month follow-up, 36% of the cardioversion vs. 34% of the CFAE group (P=0.84) were in SR (ref.[51]). Kim et al. investigated the combination strategy of combining PVI and linear lesions followed by CFAE ablation in patients with LSPAF. The prospective randomized study revealed that additional CFAE ablation resulted in a numerically (but statistically insignificant) higher AF recurrence compared to PVI + linear lesions (32.1% vs. 18.5%, P=0.166) (ref.[52]). In the RASTA study, three different ablation strategies were compared in 156 patients with persistent AF, (1) PVI, (2) PVI plus empirical ablation on common non-PVI trigger sites (mitral annulus, fossa ovalis, etc.), and (3) PVI plus additional CFAE ablations. Freedom from atrial arrhythmias (while off anti-arrhythmic drugs at one year after a single ablation procedure) was worse in the third arm (29%) compared to the first arm (49%) and the second arm (58%) P=0.004 (ref.[53]). The largest study on this topic was the randomized Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR-AF) trial that compared three different AF ablation approaches, CFAE vs. PVI vs. PVI+CFAE in 100 patients with persistent or high-burden paroxysmal AF. In contrast to previous studies that used a visual approach, the STAR AF study used automated software to improve the objectivity of CFAE. The approach consisting of PVI + CFAE had the highest efficacy compared with PVI or CFAE alone. After one procedure, PVI + CFAE had significantly higher freedom from AF (74%) compared to PVI (48%) and CFE (29%), P=0.004. After two procedures, PVI + CFAE still had the highest success (88%) compared to PVI (68%) and CFE (38%) (P=0.001) (ref.[54]). In 2015, Providência et al. performed a meta-analysis of 13 studies involving 1,415 patients. They found that PVI + CFAE had no superiority over standard PVI procedures in patients with paroxysmal or persistent AF. They also found that PVI+CFAE ablation vs. PVI alone did not improve the overall rate of freedom from AF or reduce the number of episodes of atrial tachycardia in patients with persistent AF (OR, 1.01; 95% CI, 0.63–1.64; P=0.96) or long-standing persistent AF (OR, 0.84; 95% CI, 0.24–2.96; P=0.79) (ref.[55]). Similar findings were reported in another meta-analysis of 10 studies on CFAE vs. linear ablations. Compared to PVI, the addition of a CFAE ablation offered no significant improvement in arrhythmia-free survival (RR 0.86; 95% CI, 0.64–1.16) (ref.[43]). Several technical issues in the CFAE-based ablation approach significantly limit the use

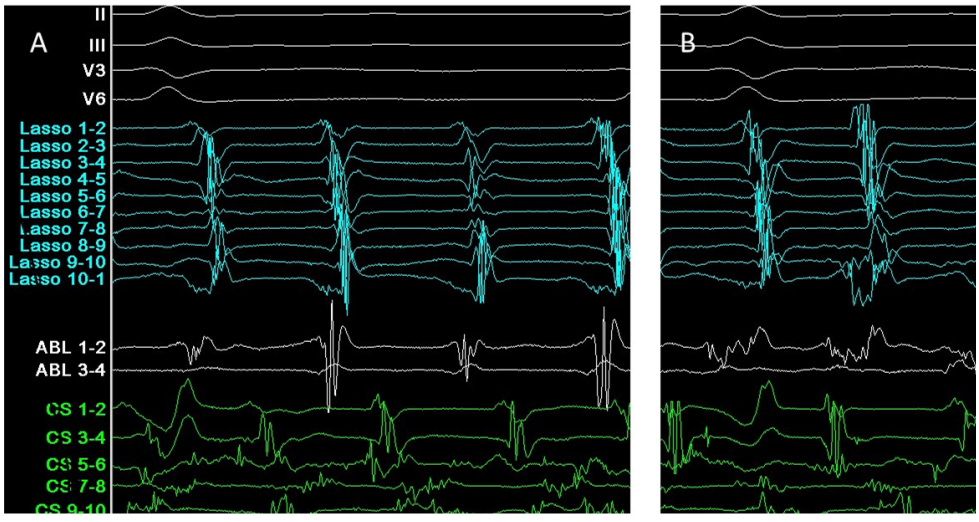

Fig. 3. An example of complex fractionated left atrial electrogram. Lasso catheter (upper part, blue) is in the left atrial appendage, 10-polar catheter (green) in the coronary sinus. Signal on ablation catheter is of high-amplitude and low-frequency when positioned on the anterior part of the base of the LAA (left part, A), and of small amplitude and high frequency when positioned on the posterior aspect of the LAA (right part, B).

of this technique. The first is the detection and location of CFAE within the atria. The visual approach, which was used originally, was very subject-dependent. An automated algorithm helped overcome these limitations; however, the question regarding the temporal stability of CFAE remains. While the location of fibrotic areas remain stable, CFAE sites are more likely to be found in areas of healthy atrial tissue. Furthermore, the optimal procedure (ablation) endpoint is not known. While the endpoint of PVI is objective and reproducible between centers and studies, endpoints for CFAE ablations (and other substrate-based ablation strategies) are much more subjective.

STEPWISE APPROACH IN TREATMENT OF NON-PAROXYSMAL AF

A stepwise approach means a gradual stepwise and pre-planned ablation of structures involved in the initiation and maintenance of non-paroxysmal AF. The ablation procedure involves PVI, ablation of areas of fragmented atrial electrograms (defragmentation of the left atrium), and ablation in the coronary sinus and right atrium. Roof and mitral lines are often part of the stepwise approach. The endpoint is either SR restoration or the transition of AF into regular AT, which can be mapped and ablated in the next step. It has been shown that mapping and ablation in both atria are necessary in the stepwise approach for ablation of non-paroxysmal AF. Furthermore, the resulting rhythm is often an intermediate rhythm representing the transition to regular AT, which can be subsequently mapped and ablated to yield SR. An essential part of the stepwise approach is the non-inducibility of AF or AT at the end of the procedure, which, when done, doubles the success rate for AF freedom[56]. The stepwise approach was initially described and investigated by the Bordeaux group. They showed that ablation could change the disorganized rhythm of AF into an organized rhythm associated with consistent atrial activation sequences maintained predominantly by localized sources which could then be further mapped and ablated[57]. Termination of present atrial fibrillation (CAF) can be achieved by catheter ablation using a stepwise approach. In another study by Sebag et al. with 159 persistent AF patients, the stepwise approach resulted in a success rate of 64% at the mid-term follow-up[58]. The importance of mapping and ablation in both atria was also shown in other studies. For instance, in the study by Rostock et al., 88 non-paroxysmal AF patients were investigated with a procedural endpoint of the termination of AF. AF termination was achieved in 77% of patients: 55% during CA in the left atrium and 26% during ablation in the right atrium. In the remaining 19% of patients, AF was terminated during CS ablation. After a mean follow-up of 20 months, 81% of patients were in sinus rhythm[59]. Fiala and others described the modes and sites of SR restoration. Fiala et al. compared 100 patients with long-lasting PeAF to 35 patients with short-lasting PeAF and 59 patients with sustained episodes of paroxysmal AF, all underwent a stepwise ablation approach with an endpoint of SR restoration. SR was restored in 38%, 83%, and 97% of patients with long-lasting Pe, short-lasting persistent, and paroxysmal AF, resp. (P<0.001). PVI ablations leading to SR termination were more common in paroxysmal patients (97% paroxysmal vs. 8% of long-lasting Pe patients). In non-paroxysmal patients, SR was restored much more often via conversion into LA tachycardia in long-standing PeAF (79%) patients, compared to short-lasting (52%) or paroxysmal (4%) patients, in whom direct conversion to SR was more often used. SR restoration by ablation was associated with better clinical outcomes in these patients[60]. Although the stepwise approach has been documented as effective for non-paroxysmal patients, it is very time-consuming, and the approaches differ between centers. Moreover, randomized trials that compared strategies similar to the stepwise approach (i.e., RASTA and STAR-AF II) did not show that additional ablation beyond PVI resulted in higher AF freedom during follow-up.

FOCAL IMPULSE AND ROTOR MODULATION – GUIDED ABLATION

A rotor is a phase singularity, i.e., spiral waves that radiate at high speed into the surrounding tissues. The concept of rotor and rotor ablation was first reported by Jalife and colleagues in the ventricular myocardium and then supported by evidence from mapping in isolated animal myocardial cardiomyocytes[61]. Clinically, a rotor can be observed in repetitive, cyclic activation around a core[62]. The concept of rotors (or localized sources) contrasts the older multiwavelet hypothesis that proposed meandering electrical waves as the cause of AF. The multiwavelet hypothesis cannot explain the consistently observed activation patterns in AF, and why in some patients, AF can be terminated after localized ablation. Recent studies show that AF is sustained by a small number of rotors, acting as focal sources, that are remarkably stable over time. Several attempts have been made to develop a technology capable of localizing AF rotors. Bi-atrial mapping using mathematically manipulated data from an electrode vest on the body surface (EcVue, Cardioinsight, OH, USA) or a noncontact intracardiac array (Ensite, Abbott, USA) has been tried to localize rotors. However, most published clinical studies on rotor ablation use a technique of contact mapping, in the form of panoramic electrophysiology study, before subsequent ablation (RhythmView, Topera Medical, and later Abbott, USA). The technique uses a multipolar basket catheter (which can capture unipolar electrograms) inserted into the right and left atrium. Electrograms are analyzed using algorithms that analyze activation using rate dynamics of atrial action potential duration. Software is used to provide the final graphical display of patient-specific AF sources. The map of located rotors and focal sources further enables the ablation of focal sources and rotors (FIRM) using any available ablation catheter. This technology had initially shown promise in AF ablation; however, later randomized studies did

not confirm the initial positive results. The first study on the technical and clinical success of FIRM-guided ablation, the Conventional Ablation for Atrial Fibrillation with or without Focal Impulse and Rotor Modulation (CONFIRM) study, was published by Narayan et al. in 2012. They prospectively enrolled 98 consecutive patients with persistent or paroxysmal AF; in the latter, AF was induced during the procedure. FIRM mapping was done and patients were non-randomly divided into the FIRM group (FIRM-bided ablation + PVI) and the conventional PVI group. In the FIRM group, the average number of rotors was 2.1, with one-third in the right atrium. The acute study endpoint, i.e., AF termination or cycle length prolongation, was present in 85% in the FIRM-guided group and only 20% of patients in the PVI group[63]. After three years, freedom from AF was present in 77.8% of FIRM patients and 38.5% of PVI patients (P=0.001) (ref.[64]). A high degree of success was also observed in a single-center study published by Spitzer et al. In this study, 58 patients underwent FIRM-guided rotor ablation followed by conventional PVI to treat recurrent non-paroxysmal AF. After 6 and 12 months of follow-up, 73.2% and 76.9% of patients remained free from AF/AT, resp. (ref.[65]). Similarly, FIRM-guided ablation in combination with PVI produced 87% freedom from AF after one year in 170 non-paroxysmal patients in a study published by Miller et al. (ref.[66,67]).

Despite the promising results of non-randomized studies on FIRM ablation, they have not been confirmed by retrospective, prospective non-randomized, and randomized studies. An observational study published by Buch et al. revealed poor long-term outcomes with FIRM-guided ablations in patients with paroxysmal and persistent AF; only 37% of patients were free from AF after 18 months of follow-up[68]. In the randomized FIRMAP study, Tilz et al. compared PVI with FIRM-guided AF ablations (without PVI). In the study, 177 were intended to be randomized, but the study was stopped after 51 patients due to significant differences in patient outcomes. Procedural success was similar between both groups; in PVI, all PVs were isolated, and in FIRM-guided patients, three rotors were found on average, and all were successfully ablated (i.e., no other rotors detected by FIRM mapping after ablation). However, after 12 months of follow-up, AF freedom was present in 31.3% of FIRM-guided patients compared to 80% of patients in the PVI group (P=0.004) (ref.[69]). One can argue that this negative result was caused by the absence of PVI in the FIRM-guided group; however, later studies of FIRM-guided ablation yielded similar results. In the REAFFIRM trial, 375 patients were randomized to FIRM + PVI vs. PVI only. There was no demonstrated benefit for FIRM + PVI; AF freedom was present in 69.3% of FIRM+PVI vs. 67.5% for PVI alone. The largest randomized trial on FIRM-guided ablation, OASIS, was retracted from publication due to deviations in the randomization process. Prospective non-randomized studies showed a very low success rate for FIRM-guided ablations (21%, or 12% resp., at 18 months) (ref.[70,71]). In the meta-analysis of PVI vs. PVI + FIRM in non-paroxysmal patients only, after a mean follow-up of 18 months, FIRM-guided ablation with or without PVI was not associated with an improvement in the AF recurrence rate compared to PVI alone (43.4% vs. 45.9%, RR 1.06; 95% CI, 0.77–1.47). According to current evidence, FIRM-guided ablation, with or without PVI, does not appear to significantly impact the reduction of AF (ref.[72]). Currently, several other techniques for localization of AF rotors are under development, such as the CARTOFINDER mapping module and others[73,74]. However, further studies need to test whether these new techniques will be associated with better clinical outcomes.

MRI – GUIDED CATHETER ABLATION FOR AF

Atrial fibrosis plays a central role as a substrate in the maintenance and perpetuation of atrial fibrillation. Atrial fibrosis results in alterations in conduction velocity and cellular refractoriness and produces conduction blocks promoting meandering, unstable wavelets and micro-reentrant circuits. Work has been done to explore atrial scar sites as the arrhythmic substrate responsible for the preservation of AF. Delayed enhancement magnetic resonance imaging (deMRI) has been used to assess LA fibrosis prior to ablation and quantify ablation-induced scarring. Several studies have reported the feasibility of delayed-enhancement cardiovascular magnetic resonance imaging (CMR) to quantify fibrosis in the LA; however, the sensitivity of CMR at the atrial level has been questioned. Marrouche's group evaluated the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced MRI. Based on previous observations and according to the degree of fibrosis, patients were staged into four groups: Utah I (≤ 5% LA wall enhancement), Utah II (> 5% to ≤ 20%), Utah III (> 20% to ≤ 35%), or Utah IV (> 35%) (ref.[75]). The importance of MRI-assessed fibrosis was tested in a prospective observational multicenter DECAAF study in 327 patients who underwent MRI before CA for atrial fibrillation. The recurrence of AF at one year was present in 15.3% of patients in stage 1, 32.6% in stage 2, 45.9% in stage 3, and 51.1% in stage 4 (ref.[76]). Although MRI-assessed fibrosis plays an important role in the prognosis and AF recurrences, the ablation approach based on MRI-guided ablation did not show positive results in the randomized multicenter DECAAF II trial[77]. In this study, 843 patients with persistent AF were enrolled and randomized to either PVI only (422 patients) or PVI plus MRI-guided ablation (421 patients). For patients randomized to the PVI plus MRI-guided ablation, the DE-MRI was segmented with a 3D mapping system, and when PVI was achieved, a fibrosis-guided ablation was pursued that consisted in either encircling or covering the fibrotic areas observed on the DE-MRI by ablation. At the one-year follow-up, there was no significant difference in AF recurrence between groups (43.0% in the PVI+MRI-guided vs. 46.1% in the PVI-only group, HR 0.95 (0.77–1.17)). Moreover, adverse events were significantly more common in the PVI + MRI-guided ablation (2.2%) vs. PVI-only (0%), P=0.001.

HYBRID ABLATION

As noted earlier, the success rates of CA in persistent and long-standing persistent AF have been limited despite more tissue being ablated. AF freedom with the surgical Cox-MAZE III and IV procedures was reported in > 90% of patients[78]. Despite the high efficacy, the invasiveness of open-chest, on-pump surgical approach presents significant limitations to the technique. Hybrid ablation should have combined the strengths of and minimized the drawbacks of both the surgical and percutaneous methods. The surgical part is an off-pump, thoracoscopic/epicardial ablation. The procedure is performed under general anesthesia without requiring a sternotomy and cardiopulmonary bypass. Surgical access is via unilateral or bilateral video-assisted thoracoscopy or a subxiphoid/transdiaphragmatic laparoscopy. Ablation lesion sets differ in various publications, but the vast majority include "box lesions" (i.e., posterior wall isolation), which is typically achieved by performing pulmonary vein isolation plus roof and inferior lines; however, a direct ablation of the whole posterior LA wall is also possible. In the majority of publications, the LAA was excluded. Additional ablation lesions can include right-atrial lesions (e.g., superior cava vein isolation, inter-cava lesions), ligament of Marshall resection, or other ablations. Ablations were mainly performed using radiofrequency energy (e.g., a COBRA linear monopolar or bipolar ablation catheter, an AtriCure clamp and rail device, or a nContact device). Based on the surgical approach, devices for thoracoscopic (Atricure, COBRA) and subxiphoid approaches (nContact) can be distinguished. In contrast to thoracoscopic devices intended to create PV isolation and lines, the subxiphoid device ablates the posterior wall completely. Percutaneous procedures follow the surgical ablation to confirm the integrity of surgical lesions, consolidate incompleted surgical lesions, and perform additional substrate-based ablations (such as by adding a cavotricuspid line). Percutaneous ablations were performed either immediately after the surgical part in a hybrid operating theater or as a staged procedure occurring weeks to months after the surgical part. In both scenarios, a hybrid (combined) approach was planned, and the catheter ablation did not represent a "rescue" technique after a failed surgical ablation. Several single-center prospective non-randomized studies have shown the efficacy of the hybrid ablation strategy in non-paroxysmal AF patients. Zembala et al. investigated the safety, feasibility, and effectiveness of the hybrid approach (thoracoscopic ablation followed by catheter ablation) in 70 patients with persistent and LSPAF. Freedom from arrhythmia at 6- and 12 months post-procedure was 78.3% and 84.1%, respectively[79]. Munaretto and Bisleri et al. utilized a sequential staged hybrid approach in 45 patients with LSPAF, with the catheter ablation occurring at least 1-month post-surgical ablation. Freedom from AF was noted in 88.9% (40/45) of patients at 28 months of follow-up[80]. Bulava reported several series of patients treated with the sequential (staged) hybrid method with excellent results[81]. La Meir and Gelsomino showed that hybrid thoracoscopic and transvenous catheter ablation achieves satisfactory results with an AAD-free success rate higher than in either individual procedure. In particular, the bilateral approach with a bipolar device revealed a high success rate independent of AF type[82]. For patients with atrial fibrillation after a failed catheter ablation, a sequential minimally invasive epicardial surgical ablation, followed by an endocardial catheter-based ablation, had higher early success rates than a repeat catheter ablation[83]. Edgerton et al. demonstrated that using a minimally invasive surgical approach to perform a bilateral PV antral isolation and a targeted partial autonomic denervation resulted in 83.7% vs. 56% freedom from AF at six months in patients with paroxysmal AF and persistent/long-standing persistent AF, respectively[84]. According to a study by Osmancik et al., in 59 patients with non-paroxysmal AF who underwent a hybrid approach, i.e., a thoracoscopic ablation followed by a catheter ablation three months later, the probability of arrhythmia-free survival was 54.0% (95% CI, 41.3–66.8) at one year and 43.8% (95% CI, 30.7–57.0) at two years. The main limitation of the hybrid approach is related to the high rate of complications that include early post-procedural death[85]. The most common complication is bleeding from the surgical incision; however, according to published reports, many other complications can occur, including pneumothorax, stroke, phrenic nerve palsy, and renal failure. Besides clinical complications, surgical epicardial ablations seem to have a substantially higher risk of silent cerebral ischemia. In a report by Osmancik et al., new silent ischemic lesions seen on early postoperative magnetic resonance imaging were present in 44.4% (ref.[86]). In a meta-analysis of 22 single-center studies, including data from 925 patients (89% with non-paroxysmal AF), SR maintenance after hybrid ablation was present in 79.4% (95% CI, 72.4–85.7) and 70.7% (95%CI, 62.2–78.7) of patients with and without anti-arrhythmic drugs at 19 months of follow-up, respectively[87]. Although no significant difference in SR maintenance was found between studies using a sequential or staged approach or studies using a fundamental lesion set or box lesions only, a superior result relative to AF freedom was seen if the LAA was excluded 79.5% (95% CI, 71.2–86.8) vs. 55.8% (95% CI, 41.4–69.8), $P<0.001$. The use of the AtriCure Synergy system was found to be superior to the nContact system (82% vs. 68.6% of pts in SR). Atrio-esophageal fistulas only occurred during nContact ablations. The total complication rate across the studies was 6.5% (95% CI, 3.4–10.2), comprising a mortality rate of 0.2%, stroke rate of 0.3%, phrenic nerve injury of 0.3%, and atrio-esophageal fistula (0.4%), the last occurring in Contact monopolar ablations only.

LEFT ATRIAL APPENDAGE ISOLATION

The left atrial appendage is a remnant of the primordial embryonic LA. Over a decade ago, the LAA was recognized as a potential trigger of AF. In 2005, Takahashi et al. reported on a patient with paroxysmal AF, in whom

multiple foci were identified in the LAA and successfully treated by CA and LAA isolation[88]. The arrhythmogenic role of the LAA was not well known until 2010, when the prevalence of triggers firing from the LAA. In a series of 987 patients undergoing a redo-ablation for AF, firing from LAA as the only source of arrhythmia was present in 9.7% of patients, and LAA isolation was associated with only 15% of AF recurrences within 12 months[89]. The BELIEF trial performed by the same group tried to assess the effect of empirical left atrial appendage isolation for the treatment of long-standing PeAF (ref.[90]). In the study, 173 patients were randomized to extensive ablation (PVI + additional LA ablations) with or without LAA isolation. At the 12-month follow-up, 56% in the with LAA isolation group and 28% in the without LAA isolation group were AF-free after a single procedure (P<0.001). After 1.3 procedures, AF freedom at 24 months was reported in 76% of patients in the with LAA isolation group and 56% of patients in the without LAA isolation group (HR 2.24, 95% CI, 1.3–3.8, P=0.003), with no strokes or TIAs in the with LAA isolation group. However, increased thromboembolic risk from the electrically isolated non-contracting LAA was later documented[91]. Fink et al. reported results from 270 patients who underwent LAA isolation as a part of CA for AF (ref.[92]). Stroke or TIA occurred in 9.8% of patients during the follow-up, and LAA thrombus formation was documented in 19.6% of patients. In 150 patients, LAA closure was finally done. In a meta-analysis of 9 studies with 2,336 patients after LAA isolation after PVI, AF freedom was significantly more common in patients with LAA isolation than without (69.3% vs. 46.4%, P<0.001). Although rates of strokes and TIAs were not statistically different between the two groups in the meta-analysis (3% with LAA isolation vs. 1.6% without, RR 1.76, 95% CI, 0.61–6.04), after taking into consideration the low expected event rates in the typically lower-risk patients referred to CA (CHA_2DS_2VASc 2.3 in this report), concerns related to higher stroke risk remain. If LAA isolation is achieved during the ablation procedure, the LAA should be occluded to avoid thrombus formation. Except for percutaneous LAA isolation, which is achieved by standard radiofrequency or cryoablation, electrical isolation of the LAA can be performed using epicardial ligation with a LARIAT device. This device is implanted during the combined endo- and epicardial approach. An external epicardial ligation occludes the LAA and provides electrical isolation of the LAA. This approach was effective in the first observational series[93]; however, it was not confirmed during the subsequent randomized aMAZE trial. In the trial, 404 patients with persistent or long-standing PeAF were randomized to the PVI + LARIAT group and 206 to the PVI-only group. Freedom from AF was present in 64.3% of the PVI + LARIAT group vs. 59.9% of the PVI-only group (P=0.8). Thus, the add-on LAA epicardial closure did not improve the outcomes in terms of SR maintenance.

PVI ONLY OR PVI WITH ADDITIONAL ABLATION?

As noted earlier, PVI as a treatment for paroxysmal atrial fibrillation (AF) is associated with a high success rate; however, outcomes for treating persistent and long-standing persistent AF with PVI alone are substantially lower[94]. In the treatment of non-paroxysmal AF, a paradox exists between the clinical efficacy of CA and the success rate of CA. The clinical benefit of CA for non-paroxysmal AF is higher compared to the clinical benefit of CA for paroxysmal AF. However, the efficacy of CA for non-paroxysmal AF is lower than that in paroxysmal patients, resulting in a significant unmet need in treating non-paroxysmal AF patients. As was shown in previous paragraphs, several different techniques were developed to increase the efficacy of CA for non-paroxysmal AF. Despite positive results in the pilot observational studies, no significant benefits in SR maintenance were confirmed during subsequent randomized studies. To summarize, PVI-only is not associated with satisfied ablation results in non-paroxysmal AF patients, and additive ablation strategies are strongly warranted. However, no up-to-day tested approach was effective with clear significant effect, so it is not possible to advice what should be done in non-paroxysmal AF patient beyond PVI. The current ablation praxis for treating non-paroxysmal AF differs significantly between centers. The current approaches include PVI-only, PVI + linear ablations, or a stepwise approach, depending on the surgeon's skills, preference, and experience.

FURTHER PROGRESS AND NEW METHODS IN CATHETER ABLATION

Many studies focusing on the treatment of non-paroxysmal AF are currently ongoing in recent years concerning new ablation methods to make more durable lesion formations. Contemporary AF ablation is likely limited by two main factors. The first limitation is that the pathophysiological mechanisms that sustain AF are not fully understood or even identified, in contrast to all other arrhythmias in which the perpetuating mechanism is the primary target for ablation. Currently, several new mapping tools are under investigation, such as the multipolar HDGrid catheter for mapping present AF with the NavX Precision system and the OctaRay mapping catheter and the corresponding software. Whether these novel mapping systems, even with use of artificial intelligence, will provide better SR maintenance and improved clinical benefit needs further investigation. And, the second, current tools may not create durable lesions, evidenced by pulmonary vein reconnection and gaps in linear lesions in patients with recurrent AF after ablation. This can be overcome by pulsed-field ablation energy, which appears to have very promising results in efficacy as well as safety. Pulsed-field ablation (PFA) uses high-energy, ultra-short electrical pulses (of microsecond duration)

to selectively and irreversible increase the permeability (electroporation) of cardiomyocyte membranes, which leads to non-thermal cell death[95]. PFA is associated with excellent safety profile reported in clinical studies[96]. In 1-year outcome of 3 studies (IMPULSE, PEFCAT and PEFCAT II), results showed that PVI with a PFA energy catheter in patients with paroxysmal atrial fibrillation results in excellent PVI durability and acceptable safety with a low 1-year rate of atrial arrhythmia recurrence.

PersAFOne study showed safe and durable PVI and LAPW (left atrial posterior wall) ablation in patients with persistent Afib using PFA energy. This extends the potential role of PFA beyond paroxysmal to persistent forms of AF (ref.[97]). However, whether this positive acute „technical" succes will lead to an improved clinical outcome needs a confirmation in randomized studies.

Search strategy and selection criteria

Our research strategy was aimed at evaluating studies on the role of catheter ablation in patients with atrial fibrillation. Scientific articles were searched using the PubMed databases. All searches are up to date.

ABBREVIATIONS

AF, Atrial fibrillation; US, United States; PAF, paroxysmal AF; NPAF, non-paroxysmal AF; PeAF, persistent AF; LSPeAF, long-standing persistent AF; CA, Catheter Ablation; PVI, pulmonary veins isolation; AADs, antiarrhythmic drugs; HF, heart failure; CFAE, Complex fractionated atrial electrograms; PFA, pulsed field ablation.

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