

# Nonpharmacological Therapies for Atrial Fibrillation

Guest Editors: Miguel A. Arias, Adrian Baranchuk,  
Máximo Rivero-Ayerza, and Atul Verma





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## Editorial

# Nonpharmacological Therapies for Atrial Fibrillation

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Whilst atrial fibrillation (AF) is the commonest sustained arrhythmia worldwide, it is also the arrhythmia of the elderly with a lifetime AF risk >20% in the over 80s [1]. We are thus on the brink of an AF pandemic, not only due to our ever-aging population but also as a consequence of our population becoming increasingly obese and diabetic. In the US alone, it is expected that the current AF prevalence of ~5 million will at least double by the middle of the century [1]. This represents a huge drain on healthcare resources, not only from the direct management of the arrhythmia but from the management of the associated increased rates of stroke, heart failure, and dementia.

In the last decade, the care of AF has been revolutionised [2] so that now we can realistically hope to cure some of our AF patients through nonpharmacological therapies such as catheter ablation or surgery. This issue examines the current state of such therapies, points to their strengths, and their weaknesses. One area where improvement is required is the management of AF in the elderly; as eloquently reviewed by L. M. Haegeli and F. Duru, the elderly are often difficult to treat medically because of their multiple comorbidities and are often denied formal anticoagulation from which they stand to gain the most benefit. The elderly more often succumb to the proarrhythmic effects of rhythm management drugs and yet they are poorly represented in all the major trials of catheter ablation.

Catheter ablation is fast becoming the first line care for paroxysmal AF. One exciting new way to administer this therapy is through cryoablation. J. Ruskin et al. reviews how

this therapy is similarly as effective as radiofrequency ablation but with less pain and possibly with less acute thrombogenicity. However, it is not as useful in persistent AF, but what does work reliably in these patients is a contentious issue as discussed in the article by K. P. Letsas et al. Here the authors show that persistent AF cannot be treated by PAVI (pulmonary antral vein isolation) alone but what is the plus other remains contentious, especially as so many of the extra manoeuvres increasing the risk of organised atrial tachycardias as per S. Castrejón et al. Such tachycardias are often more troublesome than the original AF, and the financial cost, as well as the emotional trauma, has to be considered when one is weighing up the costs of management by medication in comparison to management by nonpharmacological care as nicely discussed by Y. Khaykin and Y. Shamiss. Another potential cost saving step would be the performance of catheter ablation without interruption of anticoagulation as promoted by P. Santangeli et al.

In the last decade, the incorporation of alternative adjuncts to the traditional “cut and sew” has made the surgical management of AF quicker and less technically demanding. In this issue, we have three excellent reviews on the advancements of surgical management. M. Castella et al. examine the highly successful Cox-Maze III procedure and how it has been developed with new adjuncts, whilst N. Hiari concentrates more on the pathophysiology of AF and how, like catheter ablation, the new adjuncts in surgery are struggling with how best to treat persistent AF. L. Harling et al. discussed each of the adjuncts in turn before remonstrating

how one of the major drawbacks in establishing their clinical usefulness is the lack of homogeneity of (i) techniques used and (ii) types of AF treated in the various trials. One area of variation is the ligation of the left atrial appendage to reduce the risk of thromboembolism. The ability to do this procedure as an routine percutaneously procedure is coming ever closer with advances in left atrial appendage occlusion devices as reviewed by T. Contractor and A. Khasnis.

The paper by K. Mischke et al. reports on their basic science research into rate control of AF by cooling. This phenomenon is attractive in the management of new onset AF in septic patients with low blood pressure as these patients are often resistant to cardioversion and all traditional agents are negatively inotropic. Perhaps in the future, we will be looking at active cooling as already instituted for post arrest patients.

We hope you enjoy this issue that succinctly explores the depth and breadth of currently available nonpharmacological therapies for AF. Such therapies, which offer the potential to cure, will doubtless become more and more essential as we attempt to cope with the Tsunami of AF that is approaching. And so looking to the future, it is going to be both exciting and challenging for interventional electrophysiologists of the catheter and the blade.

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## Review Article

# Organized Atrial Tachycardias after Atrial Fibrillation Ablation

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The efficacy of catheter-based ablation techniques to treat atrial fibrillation is limited not only by recurrences of this arrhythmia but also, and not less importantly, by new-onset organized atrial tachycardias. The incidence of such tachycardias depends on the type and duration of the baseline atrial fibrillation and specially on the ablation technique which was used during the index procedure. It has been repeatedly reported that the more extensive the left atrial surface ablated, the higher the incidence of organized atrial tachycardias. The exact origin of the pathologic substrate of these tachycardias is not fully understood and may result from the interaction between preexistent regions with abnormal electrical properties and the new ones resultant from radiofrequency delivery. From a clinical point of view these atrial tachycardias tend to remit after a variable time but in some cases are responsible for significant symptoms. A precise knowledge of the most frequent types of these arrhythmias, of their mechanisms and components is necessary for a thorough electrophysiologic characterization if a new ablation procedure is required.

## 1. Introduction

Organized atrial tachycardias (AT) are a common problem after atrial fibrillation (AF) ablation (post-AF ablation AT—PAFAT). Since the first isolated case reports [1–5], several mechanisms [6] and different times of onset following the index procedure have been reported. A new ablation procedure often solves this arrhythmic problem [5, 7–14]. Nevertheless, this rhythm disorder merits a special attention for different reasons: (1) it has a high incidence and is often very symptomatic, (2) the complexity of the atrial arrhythmogenic substrate, which may be responsible for the frequent concurrence of several types of AT mechanisms in the same patient, (3) the variety of mapping and ablation approaches which have been reported and (4) the fact that PAFATs mechanisms may be linked to the mechanisms responsible for AF maintenance.

This paper reviews the incidence, clinical presentation, mechanisms, electrophysiological characterization and ablation of PAFAT. Finally, a brief review of organized ATs presenting during the AF ablation procedure is also provided.

## 2. Incidence

The real incidence of PAFAT cannot be easily extracted from published series because most of them either focused just on left [15–17] or macroreentrant (MR) AT [18, 19], or did not report the incidence of cavotricuspid isthmus-dependent (CTI) atrial flutter, which is responsible for 7–10% [20–22] of all PAFATs. This latter figure is even higher in patients with previous cardiac surgery [23]. In addition, the reported incidence of PAFAT is probably underestimated in most of these series because only symptomatic patients were referred for a new ablation procedure [21, 24]. All these reasons explain in part that the reported incidence of sustained PAFAT varies widely. However, differences in PAFAT incidence mainly depend on the following two factors: the predominant type of AF before the index procedure and the approach [8, 12, 13] used for AF ablation.

The incidence of PAFAT ranges between 4.7 and 31% and is usually higher after circumferential pulmonary veins (PV) ablation using wide-area circular lesions around ipsilateral PVs (*circumferential pulmonary vein ablation—CPVA*) [25]

or when additional ablation lines are incorporated in the procedure than with other ablation approaches [15–18, 20, 21, 24, 26, 27]. This group of patients whose AF was treated with CPVA is by far the one in which PAFATs have been most extensively studied. However, several variants of the original CPVA technique have been reported in recent years. Abatement of PV electrograms within the encircled area was the main endpoint of the original series and PV electrical isolation (PVI) has been required only in the most recent ones [26–28]. Despite this evolution [29], the PAFAT incidence apparently has remained apparently unchanged. The number and location of additional ablation lines had been also heterogeneous among the different reported series but it seems that additional lines may have a greater impact on PAFAT incidence than on AF recurrences. Pappone et al. [25] and Anousheh et al. [27] found that by adding roof, posterior, or mitral isthmus ablation lines the development of new-onset macroreentrant AT was reduced in comparison to CPVA alone, as far as conduction block across these lines was achieved.

The incidence of AT is much lower after less extensive AF ablation approaches such as segmental ostial PVI [1, 30, 31] or circumferential antral PVI [32], especially when no additional ablation lines are used or only the electrically active PVs are targeted [23, 24, 33–39]. The incidence of AT with these latter approaches ranges between 2% and 7.7%. The only discrepant incidence value with this approach is the 29% found by Ouyang et al. [38] but that one could have been related to the modification of the standard PV isolation technique which these investigators used. The lower incidence of PAFAT found following segmental ostial PVI could be partially related to the smaller proportion of patients enrolled with persistent/chronic AF enrolled in these studies, as opposed to the studies in which CPVA was employed. Patients with long-standing persistent/chronic AF have both more electrical and anatomical atrial remodeling [40, 41] and low-voltage and scar areas [34] than patients with paroxysmal AF. These scar areas have been associated with MR circuits and may configure the substrate for organized AT [13, 34, 35]. This hypothesis was congruent with a ninefold higher AT incidence in patients with persistent forms of AF reported by Porter et al. (2.4% versus 20%) [42]. Actually, this is not the case because the proportion of patients with persistent/chronic AF in the studies in which CPVA plus lines was used reached 17%–36.5% [15–18, 20, 21, 24, 26, 27], a percentage similar to that reported in the series in which segmental or circumferential antral PV isolation was performed (8%–43%) [23, 24, 33–39]. As a consequence, factors directly linked to the ablation technique in itself seem to determine the PAFAT incidence, although the scarce studies that have compared both techniques have yielded conflictive results [43, 44].

Finally, there are some other strategies globally characterized by an extensive atrial ablation which aims at terminating AF, rendering it noninducible or at least transforming it into an organized AT amenable to mapping: complex fractionated atrial electrograms (CFAEs) ablation [45], alone or as an adjunct to PVI isolation, and stepwise approaches comprising sequential addition of conventional techniques

[46]. The incidence of PAFAT in patients initially treated with CFAE ablation alone or combined with PVI [45, 47–53] is 7.6%–24%, but Nademanee et al. published a remarkable study with 674 patients in which a low incidence of right atrial flutter (2.4%) and no cases left AT [52] were reported. Most of the patients included in these series suffered persistent, permanent, or chronic AF (33%–100%). On the other hand, a number of papers have reported the incidence of AT after stepwise AF ablation or addressed specifically AT appearing after these approaches [46, 53–59]; the incidence of PAFAT in this context oscillates between 23%–44%. Stepwise techniques are resorted to for long-lasting persistent forms of AF almost exclusively (23%–100% of patients in these series).

### 3. Clinical Aspects

From a clinical point of view, PAFATs are characterized by: early onset after the index procedure, multiplicity of arrhythmia types in the same patient (not always recognizable on the surface ECG), frequent and important symptoms refractory to management with rate-controlling drugs, limited amenability with antiarrhythmic drugs, high recurrence rate after cardioversion, and to sum up, very frequent requirement of at least one subsequent ablation procedure to cure them.

*3.1. AT Time of Onset after AF Ablation.* Chang et al. [28] demonstrated that multiple ATs can be induced in 16.3% of patients immediately after circumferential PVI isolation, and this proportion rises (38%) when a more extensive ablation is used [19]. In other cases, an organized AT of a “totally” different nature such as typical CTI-dependent flutter appears during AF ablation [60]. These findings suggest that the substrate capable of maintaining organized ATs is already present at this stage. It may explain why the onset of AT occurs relatively early in the follow-up after AF ablation, with an average time of onset between 2, 7–13 weeks [15–19, 55]. Ouyang et al. [38] and Themistoklakis et al. [35] reported that more than 80% of the ATs they studied had appeared during the first 2 and 4 weeks after the AF ablation procedure, respectively.

*3.2. Clinical Course.* Chugh et al. [18] proposed to reserve a new ablation for patients in whom the AT eventually persists symptomatic after a prudential observation period, because according to their reported experience, up to a third of patients presented complete resolutions of their ATs (spontaneously or after electrical cardioversion) and an additional 4.7% achieved good clinical control under pharmacologic treatment alone. This cautious proceed is further guaranteed because in other studies, with different AF ablation techniques, 45–64% of patients remained free of AT recurrences after a few months had elapsed [15, 17, 19, 45].

Although PAFATs are most commonly persistent (78% [59]–92% [56]) instead of paroxysmal, they tend to cause important symptoms (even syncope in 28% of patients

studied by Pappone et al. [17]). Commonly, PAFAT are more problematic for patients than the original AF, specially because organized atrial arrhythmias are usually associated to faster ventricular response thus requiring electrical cardioversion more frequently [15, 19, 20]. In addition, these PAFATs respond poorly to antiarrhythmic drugs (only 4.7% [22]–18% [20] of patients on antiarrhythmics are oligosymptomatic enough as to reject a new ablation procedure), and in some cases interruption of antiarrhythmics could be beneficial to avoid recurrences [33].

**3.3. Multiple Different Arrhythmias in the Same Patient.** This is one of the most prominent features of PAFAT. Haïssaguerre et al. [56] and Deisenhofer et al. [15] described 70–81% of their patients to have more than one arrhythmia mechanism during the electrophysiologic study. Other authors [15, 19, 57, 58, 61] have reported that the average number of different AT mechanisms per patient varies between  $1.8 \pm 1.2$  and  $3.4 \pm 2.4$  and that, in subsequent recurrences, the clinical AT is different to the original one in 79% of cases [21].

**3.4. Predictive Factors of AT Occurrence.** Several circumstances have been postulated to contribute to a more elevated risk of PAFAT: extensive ablation [21, 24, 26], incompletely ablated areas [15, 27, 62], PV reconnection [34, 38], early debut of atrial arrhythmias post AF ablation [18, 21, 35, 63], and previous long-lasting AF [17, 35]. Extensive ablation may increase the incidence of AT both directly, creating conduction barriers that eventually would define and stabilize a reentry circuit spatially separated from the ablated area [21, 64], and indirectly, enhancing the probability of conduction gaps [17], sometimes with complex tridimensional structure [65].

## 4. Types of PAFAT

### 4.1. Macroreentrant Circuits after AF Ablation (Figure 1)

**4.1.1. Frequency and Types.** Macroreentrant (MR) ATs are considered the most frequent arrhythmias after AF ablation, comprising 57%–91% of the total. Nevertheless, some relevant studies have made clear that it may not always be so. Haïssaguerre et al. [56] and Deisenhofer et al. [15] reported that the so-called small-loop or localized reentry could be as frequent a mechanism as MR. Shah et al. [37], Ouyang et al. [38] and Gerstenfeld et al. [33] published data according to which focal or small-loop reentry was the most frequent mechanism (77%, 88%, and 100%, resp.). These striking differences could reflect not only, in the first instance, a renewed interest in a more detailed characterization of the frequently neglected “focal” atrial tachycardias [66–68], but also the possibility that more limited ablation strategies such as those used in these studies (PV segmental or circumferential isolation alone [33, 37, 38]) are not so liable to cause MR tachycardias. Perimitral atrial flutter is the most common type of MR circuit arising after AF ablation (39%–61%), closely followed by roof-related or peri-PV tachycardias (9%–61%), typical right atrial flutter

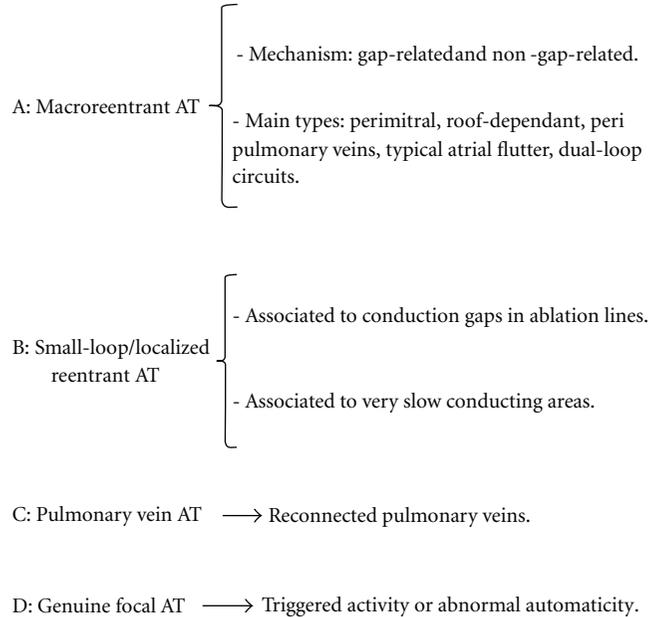


FIGURE 1

(15%, although in some case series this was the most frequent arrhythmia [45, 52]), and other circuits involving the coronary sinus (5%–7%), the interatrial septum (10%–18%), or the anterior atrial wall [64] (3%) [15–21, 33, 37–39, 45, 52, 54, 56, 57, 62, 69]. It is noteworthy that complex dual-loop circuits are not rare (22%–55%) [16, 21].

**4.1.2. Identification and Mapping of MR Circuits.** This mechanism is suspected when the activation sequence map yields results congruent with a sequentially continuous electrical activity accounting for at least 80%–90% of the tachycardia cycle length (CL). Activation sequence maps are usually obtained with tridimensional (3D) electroanatomic mapping systems in which every local activation time is represented as a color of a continuous spectrum, thus creating a visual representation of the sequence of activation. If the diameter of the circuit is  $\geq 3$  cm, the earliest activated area is close to the latest one (the typical “early meets late” or “head meets tail” aspect), and if the range of local activation times encompasses most of the CL, macroreentry is probable. The boundaries delimiting the circuit (such as sites harboring double potentials separated  $\geq 50$  ms, low-voltage areas characterized by voltages  $\leq 0.05$ –1 mV, anatomical obstacles) are commonly included in the activation map representation in order to depict the course of the activation front with more anatomical accuracy. This method of creating an activation sequence map was the most frequently used in the studies previously cited. In spite of its widespread acceptance, activation maps can be sometimes misleading [56, 70] and lead to equivocal results. Typically, when the entire MR circuit is not accessible or some parts of the activation sequence cannot be registered with certainty [36, 71], the activation map of a MR circuit can be misinterpreted as an apparent centrifugal activation of the atria with a presumptive, but false, focal origin [36]. The limitations

of the activation mapping are posed by a nonsystematic collection of points during which critical areas of the circuit [72] may be missed, the intrinsic difficulty of assigning an objectively exact activation time to a multicomponent or low-voltage fractionated electrogram, and the presence of multiple areas of slow conduction or conduction block resulting in an abnormally prolonged time to complete LA activation [73] in such a way that some atrial areas are activated very late. Some modifications of the conventional point-by-point construction of activation maps have been attempted in order to simplify the approach and gain accuracy. For example, the use of multielectrode catheters [72] or the elegant refinement of this technique reported by De Ponti et al. [74].

In addition, the documentation of a sequential atrial activation through the entire AT cycle length is insufficient to establish the existence of an atrial MR arrhythmia: the only unequivocal proof is the demonstration of fusion during entrainment or, what is even more compelling, return cycles after entrainment matching the tachycardia CL from at least two distant sites. In this respect, entrainment mapping with fusion affords the ultimate evidence of a reentrant mechanism irrespective of the “focal” appearance of the activation map [33, 36, 39, 71]. A detailed analysis of entrainment maps has not been carried out in most studies: in some cases entrainment techniques have been used [16, 19, 20, 28, 34, 75] only exceptionally, and in other cases entrainment has been used in a limited way just to confirm that certain sites of interest (particularly putative isthmuses candidate for ablation) belong to the circuit [17, 21, 22, 58, 62, 72]. On the other hand, entrainment mapping has been used by some investigators in a more comprehensive manner to determine the true spatial location of the circuit [15, 36, 57, 64]. Some authors have manifested a certain reluctance against an exhaustive use of entrainment mapping [76] not only because of its limitations (it is not always possible to demonstrate fusion, specially when reentrant circuits are small [37]) but also because there exist a potential risk of terminating the AT into sinus rhythm, a different AT or AF.

#### 4.2. Focal Mechanisms (Figure 1)

**4.2.1. Definition and Types.** The identification of a focal AT [6] is based on two criteria: (a) centrifugal spread of the activation front in all directions from the site of earliest atrial activation [75], (b) range of activation duration less than the AT CL [16, 17], or in other words, sequential electrical activity accounting for less than 80%–90% of the CL [21, 22]. However, it is sometimes very difficult to discriminate between reentrant and focal mechanisms [36, 56], specially in a previously ablated atria. Due to this difficulty, a number of subordinate criteria have been proposed to suspect a focal origin [6, 33, 53, 57, 68]: (a) CL variations >10%, (b) discrete P-waves with clear isoelectric intervals between them, (c) inconsistent return cycles after entrainment pacing from several locations, (d) identical P wave and atrial activation sequence during pacing at the focus site and

during the clinical AT, and (e) QS wave on the monopolar lead located on the origin of the AT. It must be noted that a focal origin of the electrical activation does not necessarily involve a “genuine” focal mechanism, such as enhanced automaticity or triggered activity. In this regard, it might be useful to remember that any confusion of terminology must be avoided: the term “focal AT” refers primarily to a pattern of concentric activation from a focus/source [6], the mechanism of which could indistinctly consist on (micro) reentry, abnormal automaticity, or triggered activity. In consequence, the use of the term “focal” as a synonym for *automatic or triggered mechanism* is confuse [6].

A particular subgroup of focal ATs [77] are characterized by (a) adenosine insensitivity (they present neither termination nor transient suppression), (b) low-amplitude potentials at the focus site, (c) long-duration electrograms (spanning a great portion of the cycle length) at the origin site, and (d) a response to overdrive pacing consistent with entrainment. All these features, considered together, strongly advocate reentry as the underlying mechanism. Sanders et al. [68] studied 27 tachycardias with a catheter specially designed for high-density mapping, establishing a localized reentry mechanism in 8 of them. The most relevant finding of this approach was the indisputable demonstration of sequential electrical activity during  $95.2 \pm 4.5\%$  of the CL, together with prolonged fractionated electrograms at the sites of origin. Takahashi et al. [55] achieved similar results using conventional activation and entrainment mapping, but they also measured the size of the circuit (always <2 cm), the width of the isthmus (variable between <5 and 10 mm) and confirmed the spatial relationship of these small-loop reentry circuits to previously ablated areas. The close relationship between low-voltage zones (LVZs) or scar areas and the site of origin of the focal AT was reassured by Higa et al. [67] using noncontact mapping. Surrounding LVZs can sometimes configure a preferential exit channel from the AT focus [78]. These microreentry or small-loop reentry circuits fairly explain why Mohamed et al. [79] demonstrated that the closer to the AT focus the entrainment site is located, the shorter is the return cycle minus CL difference, a type of response that suggest a reentrant circuit when can be obtained consistently [80]. Finally, such sites harboring localized reentrant circuits have been directly proved or strongly proposed to be involved in the maintenance of AF [81, 82].

Deisenhofer et al. [15] have differentiated two types of small-loop reentry circuits (<3 cm) on the basis of a very reasonable argumentation: (a) small-loop reentry circuits related to gaps on previous ablation lines and (b) small-loop reentry circuits related to areas with markedly slow conduction, generally located in close proximity to previously ablated areas but not related to conduction gaps. Schematic small-loop reentry circuits resultant from the modification of a previous arrhythmogenic substrate by radiofrequency lesions were hypothesized by Merino in 2006 [73].

The other two focal mechanisms (automaticity and triggered activity) have not been so well defined in patients presenting PAFAT and would remain an exclusion diagnosis

when MR or localized reentrant circuits could not be confirmed. Their typical responses to adenosine and overdrive pacing along with their typical clinical presentation as repetitive burst of tachycardia can serve as clues to suspect the diagnosis [77, 83].

**4.2.2. Frequency and Preferential Locations.** In general, focal ATs constitute a minority group. For example, Deisenhofer et al. [15] did not report any focal ATs in their series, but it must be noted that 31% of the PAFATs they studied were too unstable for complete characterization. Gerstenfeld et al. [33], on the other hand, initially attributed a focal mechanism to all PAFATs they found after segmentary PVI. This assumption was somewhat doubtful because all these tachycardias manifested a fused intracardiac activation sequence during entrainment. On the basis of entrainment maneuvers the same authors published a second report [39] in which only one of five PAFATs had a presumable pure focal mechanism and the other four cases were small-loop reentries. These results underscore the capital importance of the differentiation between a *focal activation pattern* and a true *focal mechanism*. The first one habitually results from small-loop reentries or conduction barriers which can mask a MR mechanism [34, 73].

Rostock et al. [57], Chae et al. [21], and Mesas et al. [16] published a prevalence of focal AT which varies between 12–28% of the total PAFATs. The immense majority of these focal PAFATs were found near the PV antra in close relationship to previously ablated areas (41–100%) [16, 21, 57]. Apart from this preferential location, PAFATs with a confirmed or putative focal mechanism have been described as being scattered in many other places such as the coronary sinus (23%), interatrial septum (11–12%), LA roof and LA inferior wall [21, 57].

## 5. Electrophysiologic Characterization of PAFAT

A precise knowledge of the arrhythmogenic substrate as well as a great familiarity with the electrophysiologic properties of AT circuits is essential to identify and ablate their critical components.

**5.1. Conduction Gaps.** Conduction gaps are simply narrow parcels of surviving cardiac tissue still capable of effective electrical conduction which connect two zones otherwise separated by an interposed area of nonconducting tissue. This area of conduction block generally consists on scar tissue caused by radiofrequency or other modalities of energy delivered for ablation. Therefore, a gap is always a portion of cardiac muscle which has been either reversibly damaged by the ablation catheter, independently of the nature and intensity of the lesion (inflammation, edema, alteration of membrane properties [84]) or not damaged at all. Obviously, gaps can be already present immediately after the AF ablation procedure. These residual gaps are typical in atrial regions which are hardly accessible to radiofrequency energy for whatever reason: catheter instability, edema formation, tissue

thickness that prevents the transmural of the lesions, or tricky anatomical areas such as the ridge between the left upper pulmonary vein and the left atrial appendage [17, 85, 86]. More frequently, however, conduction gaps appear later as true “reconnections” [87] of the previously ablated areas.

**5.1.1. Relationship between Gaps and PAFAT.** Despite multiple targeted radiofrequency applications during an AF ablation procedure, multiple or single gaps can persist in a significant number of patients (5–19%) [17, 88, 89]. These incomplete lines have been proved to be a strong promoting factor of AT [17, 27, 43]. The extreme examples of this cause-effect relationship are exemplified by some published cases of (a) acute organization of AF into a MR AT gaps located in ablation lines which have been deployed just a few minutes before [75] and (b) gap-dependent MR ATs which can be induced shortly after apparently complete PV circumferential isolation [60]. The reason most frequently adduced to explain the presence of conduction gaps is immediate or delayed conduction recovery. Certainly, this is the only acceptable hypothesis when PV isolation and bidirectional conduction block across other additional lines was reliably confirmed [16–18, 62, 89] previously.

In turn, gap-related macroreentry is the most habitual type of MR PAFAT (65%–96%) [16, 21, 28, 58, 62, 89] and multiple gaps are habitually required [36, 71, 73]. In addition, a relevant proportion of focal or small-loop reentrant ATs have also been found spatially related to single (100% of focal AT reported by Mesas et al. [16] and Luik et al. [60]) or double gaps (35% of small-loop reentry reported by Deisenhofer et al. [15]). Pure PV tachycardias [73] after AF ablation as those published by Ouyang et al. [38] deserve a particular comment because they are a direct consequence of PV reconnections through gaps.

**5.1.2. Identification of Gaps.** Conduction gaps are viable tissue surrounded by permanent lesions; in consequence, they are located in incompletely ablated areas which can be revealed by magnetic resonance image techniques due to the presence of preserved atrial muscle bundles. It has been demonstrated that up to a maximum of 20% of the surface of the tissue where radiofrequency has been applied (areas usually marked by lesion dots on the 3D navigation systems) may correspond to viable tissue (not affected by gadolinium late-enhancement) [90]. To date, however, the efficacy of this approach to detect very small bundles of viable atrial myocytes has not been validated. An indirect way to suspect the presence of conduction gaps in ablation lines is the simultaneous achievement of AT interruption and bidirectional block across the line using a single or a few focal radiofrequency applications [38]. A detailed activation map can offer a more direct proof of the participation of gaps in a MR circuit when the activation front traverses perpendicularly the place where a prior ablation line was created [21, 60]. The exact position of ablation lines relative to the AT circuit can be checked by side-by-side comparison of the AT activation map and the tridimensional reconstruction of the LA obtained during the initial AF ablation procedure, or with

techniques of image integration implemented in modern 3D navigation systems, which allow for a more exact delineation of the spatial relationship between incomplete ablation lines and the circuit of the AT [91]. The most direct evidence which identifies a conduction gap is the presence of a single potential flanked by double potentials. The single potential (frequently fractionated) corresponds to the viable muscle and the double potentials to the ablation line lying at both sides of the gap [16].

**5.1.3. Conduction Properties of Gaps.** Noncontact mapping technology has provided greatly detailed images of the activation wavefront propagation across an ablation line through a gap: the activation front narrows upon reaching the gap and widens again at the other side of the line [92]. However, electrical conduction through discontinuous ablation lesions is a complex phenomenon influenced by the width of the gap, its geometry, and possibly the time elapsed since the lesions were created. In this sense, certain experimental models suggest that there is a minimum width necessary for gaps to conduct (habitually 3 mm [93]). Besides, the gap size can modulate the conduction velocity of the wavefront crossing it, in such a way that the narrower the gap, the slower the conduction velocity [93]. As a result, small gaps are usually characterized by long-duration and very fractionated potentials small gaps usually showing [93–95]. The overall delay is not exceedingly great in comparison to normal tissue [94] and has been deemed to lack clinical relevance, insofar as small gaps are still capable of relatively fast conduction [38]. The solid results of Melby et al. [95] reaffirm both ideas: only very small gaps tend to manifest features of slow conduction (as a matter of fact, fragmented electrograms are a prominent distinctive mark of conduction gaps in the clinical setting [16, 38, 58]), and the overall conduction velocity impairment is small, allowing for effective conduction of very rapid paced rhythms and even AF.

On the other hand, conduction properties of gaps depend not only on their width but also on their geometrical configuration: angled or “L-” shaped gaps are much less likely to conduct than bifurcated (“Y-” shaped) or straight gaps [65]. In general, sodium-channel blockers are effective in preventing gap-related electrical conduction in experimental models [65].

**5.1.4. Frequent Locations of Gaps.** Rostock et al. [87] reported the distribution of sites of conduction recovery in roof lines and mitral isthmus lines: 66% of gaps in the mitral isthmus line were localized in the upper portion, close to the left inferior pulmonary vein and the left atrial appendage; 54% of gaps in the roof line were found in close relation to the right superior pulmonary vein ostium. Both preferential sites are the result of anatomical structures that condition a worse stability of the catheter and areas of greater wall thickness more difficult to ablate with transmural lesions. Similarly, Mesas et al. [16] found also a preferential location of gaps near the septum and the superior segment of the lateral left atrium, in both cases around the PV antra. Chang et al. [60]

reported that the preferential location was another difficult place: the left atrial appendage ridge. However, Ouyang et al. [38] did not find any preferential distribution for 32 conduction gaps in circumferential lines around the PV ostia, in spite of the fact that gaps were approximately twice as frequent around the left PV.

## 5.2. Critical Isthmus

**5.2.1. Anatomic Description.** An isthmus can be defined as the narrowest part of the circuit. This definition involves two elements which need a precise characterization. Firstly, the course of the activation front defined as entirely as possible by the middle of activation mapping, entrainment mapping, noncontact mapping or analogous techniques; secondly, the presence of conduction barriers delimiting the anatomic channel through which the activation front traverses. These boundaries can be normal anatomic structures, scar areas, areas of conduction block (double potentials) [96], or previously ablated areas. Jaïs et al. [97] published an interesting study in which they identified critical isthmuses on the basis of an exclusively anatomic concept: an *isthmus* is configured by two lateral barriers and a corridor of normally excitable atrial tissue between them. These authors also demonstrated that a line of ablation transecting these isthmi is an adequate therapy for most macroreentrant AT. Obviously, this approach can be resorted to if the ATs is not stable enough as to resist a detailed entrainment mapping [98] and the participation of the isthmus in the circuit can be demonstrated at least with activation mapping. However, Ouyang et al. [99] showed with conclusive data that isthmi are usually narrow and the typical electrograms registered within them are of very low voltage amplitude (generally <0.5 mV) and multicomponent or fragmented. As a result, isochronal and activation maps are specially limited to characterize them, because it is often really difficult to assign a reliable local activation time to such low-voltage and fragmented electrograms. Furthermore, purely anatomic isthmi are not always the feeblest part of the circuit. For example, the so-called *mitral isthmus* can be specially difficult to block bidirectionally [27], and this difficulty has led some authors to propose an alternative approach: the “anterior (or superior) line”. This line, traced from the mitral annulus to either superior PV, blocks the entire anterior aspect of the left atrium [100, 101].

**5.2.2. The Critical Isthmus from a Functional Point of View.** De Ponti et al. [74] introduced a simple and elegant refinement of the conventional colour-coded activation map as a tool to help localize the zone of “diastolic” activation of the circuit. This strategy consists in a specific parameters setting of the 3D navigation system such that the location of the transition “purple-red” or “purple-white” (the traditional point where “head meets tail”) limit identifies the position of the diastolic isthmus, which, in comparison to the systolic isthmus, is more frequently characterized by low-amplitude potentials and slow conduction [74] and corresponds almost always to the most vulnerable part of the circuit.

Entrainment mapping, in turn, is the most consistent method to determine whether a given point in the atrium belongs to the circuit or not [102, 103]. Isthmi can be defined with mere entrainment criteria [104] as those areas presenting concealed entrainment (defined as identical P-wave morphology and intra-atrial activation sequence during pacing and during AT), first postpacing interval equal to AT CL and a delay between the stimulus artifact and the elicited activation front of at least 40 msec. It seems clear, therefore, that activation mapping and entrainment mapping are complementary strategies [105] to localize the circuit and its course, boundaries, isthmi, slow-conduction areas, and, specially, sites where ablation has more chances to be effective, as Bogun et al. [104] studied in an excellent work only limited by the low number of cases included. Being it so, the true critical isthmus is not only a narrow corridor anatomically defined, but, above all, a site where the tachycardia is interrupted and rendered noninducible with the minimal number of radiofrequency applications. These sites hold some ancillary features which contribute to their identification: long activation times, split or fragmented electrograms, diastolic potentials and matching stimulus P-wave and electrogram P-wave intervals [104].

In the particular setting of PAFAT, isthmi can be constituted merely by gaps or by the interaction between ablated areas, preexisting scar areas and anatomic structures. Both an exclusive anatomical approach [15, 16, 18, 21, 22], and a more functional [17, 37, 61] characterization have been used to detect isthmi under those circumstances.

### 5.3. Low-Voltage Areas and Slow-Conduction Zones

**5.3.1. Preexisting and Iatrogenic Scar Zones and Areas of Slow Conduction.** Whereas patchy fibrosis and increased concentration of type I collagen have been observed in patients with lone paroxysmal AF [106], significant scar areas (characterized by very low voltage,  $\leq 0.1$  mV) have not been described in this group of patients [107]. Some authors have postulated the origin of abnormal atrial zones (LVZs, slow-conduction and scar areas) to be either totally iatrogenic or the result of the interaction between incomplete radiofrequency lesions and specific anatomic structures (ligament of Marshall, autonomic ganglia) [58, 108]. However, there are important cumulative data supporting the existence of these abnormal areas independently of radiofrequency lesions. Taclas et al. [90] noticed that late gadolinium enhancement was sometimes detectable in locations where radiofrequency had not been applied. Moreno-Reviriego et al. [109] demonstrated the presence of a dense scar (characterized by absence of capture at maximal paced impulse output) or low-voltage area in 10 of 16 patients with persistent/long lasting FA. Verma et al. [110] detected scar areas in 6% of AF patients and demonstrated the role of these areas as independent predictors of AF recurrences. Lo et al. [41] investigated the progressive decrease in the mean LA voltage and increase in the extension of low-voltage zones (subtracted the contribution of ablated areas) in patients with AF recurrences after PVI. Lin et al. [111] evaluated the

role of areas characterized by functional conduction block and low voltage in delimiting slow-conduction isthmi as a common mechanism for right atrial flutter and fibrillation. Cummings et al. [34] appreciated that preexisting scar areas may act as an additional substrate for PAFAT because PV reisolation alone was less efficacious to prevent recurrences in patients with scar areas than in those without them. Jais et al. [64] found that some flutter circuits were constituted by areas of slow conduction distant from PV ostia and not targeted by prior ablation. Yoshida et al. [62] concluded that radiofrequency lesions cannot be directly linked to at least 30% of AT that appear late after AF ablation because these tachycardias were not adjacent to ablation sites. In addition, as previously discussed, there is still a lack of demonstrative evidence that slow conduction could be attributed to RF lesions. For example, in spite of the complex conduction properties manifested by partially ablated areas, slow conduction was ruled out by Chorro et al. [112] as the mechanism of the prolonged conduction time measured near radiofrequency lesions because it could be always explained by the conduction detour of the wavefront around the lesion. Besides, it remains without explanation why RF is specially (or exclusively) prone to beget slow conduction and iatrogenic arrhythmias in the LA and not in other substrates such as ventricular scars or RA flutters [73].

**5.3.2. Scars, Low-Voltage Zones, Slow-Conduction Areas, and Atrial Tachycardias.** Independently of their origin, these abnormal areas may play a role in PAFAT for several reasons. First of all, LVZs are an integral part of the critical isthmus of most ATs. Secondly, LVZs and scars can simply make up the lateral boundaries delimiting a MR circuit, as is the case when a perimitral flutter is induced immediately after circumferential PVI [60] or after linear ablation at the roof, perhaps because the circuit is confined within these barriers and stabilized preventing short circuiting [21]. This constraining effect of natural and iatrogenic lateral barriers is most probably necessary for the maintenance of circuits unrelated to ablated zones [64]. There exist a more intricate cause-effect relation between areas of slow conduction and small-loop or localized reentrant AT, because when reentrant circuits are small in size, the phenomenon of slow electrical conduction acquires its most crucial relevance. Typically, small-loop reentrant circuits appear near previous ablation lesions and in places to which a special relevance for AF maintenance is commonly assigned, such as the PV antra [16, 21, 37] or the LAA opening [15, 46, 113]. The critical component of these circuits is a narrow isthmus showing typical low-amplitude fractionated electrograms which span a great part of the CL, indicating slow conduction [37]. In the most extreme examples [15] fractionated potentials lasting up to 140 ms and occupying 60% of the TCL or even the entirety of the CL can be registered [68, 81]. Deisenhoffer et al. [15] revealed something as important as frequently neglected: very slow-conduction areas are not located across ablation lines, on the contrary, they are simply adjacent to them. Consequently, it is reasonable to hypothesize that, if these slow-conduction areas existed

before radiofrequency applications, they could have served as substrate for small and very rapidly rotating circuits implicated in the maintenance of AF. Posteriorly, RF lines could have modified the electrical properties of the circuit, for example, increasing its size and CL. The final result would be the creation of the mechanism of organized ATs as a consequence of the interaction between a previous abnormal substrate responsible for AF maintenance and radiofrequency lesions [73].

**5.4. PV Reconnection and PV-Related Triggering Foci.** PV-related foci of ectopic activity implicated in AF initiation and maintenance seem to play a relevant role in triggering organized PAFAT, although the participation of extra PV triggers should not be underestimated.

As noted before, PVI is the only element of all the AF ablation techniques clearly associated with a reduced incidence of PAFAT. After AF ablation, the persistence of PVI is also fundamental for sinus rhythm maintenance. The most relevant piece of evidence was provided by the great proportion of patients in whom PV reconnection was demonstrated during the PAFAT study and ablation. Ouyang et al. [38] and Chun et al. [114] addressed the problem of PV reconnection in both case series of PAFAT after catheter-guided PVI and surgical Maze, respectively. Their results were incontrovertible: 80% of patients with AT recurrences after catheter ablation and 88% of patients with AT after Maze procedure presented PV reconnection. Similarly, according to a recent study by Sy et al. [115], in the group of patients requiring a second ablation procedure after PVI (48.3% presented recurrences in form of organized PAFAT), 82% of the PV were reconnected. Other authors [33, 34, 36, 39] have also indirectly proved the cause-effect relation between the presence of venoatrial reconnections and PAFAT. In addition, the contribution of ectopic activity arising from the PV to the initiation of organized AT is also proved by the capital importance of PV reconnection to reduce AT recurrences. For example, Cummings et al. [34] evaluated the effect of PV reconnection alone to treat LA flutters following a previous PVI procedure and obtained interesting results: 61% of patients remained free of arrhythmia recurrences off antiarrhythmics and an additional 21% on antiarrhythmics. The importance of abolishing the contribution of PV-related triggers was reported by Wazni et al. [116] as well. Patients with coexistent AF and typical right atrial flutter were included in this study and underwent PVI isolation without concomitant bidirectional cavotricuspid isthmus blockade, which was curative in most of them. Therefore, in the light of all these data PV reconnection remains the milestone of the pathologic process which ultimately leads to PAFAT occurrence, to such an extent that a certain dependence of organized AT on PV triggering foci has to be assumed. The question is whether this relationship is direct or indirect, or in other words, whether PV ectopics are able to initiate organized AT with or without an intermediate period of AF [116, 117]. Both possibilities are likely but it must be noted that, in a simulation study, Gong et al. [118] demonstrated that the atria are more vulnerable to premature beats arising

from the PVs than from other locations and that the vulnerable window for atrial flutter/AF induction (the range of different pacing CL and extrastimuli coupling intervals) is markedly smaller for right atrial foci in comparison to PV foci.

Two reasonable consequences can be drawn from the close relationship between PV reconnection and PAFAT. Firstly, PV reconnection should be considered the first procedural step when a PAFAT ablation is undertaken [14]. Secondly, all measures aiming at reducing the risk of PV reconnection have to be implemented. For example, it is commonly reckoned today that a mere anatomic atrial ablation guided by electroanatomic mapping systems is unreliable in achieving a complete PVI [24, 119]. Consequently, PVI should be assessed routinely by a circular-mapping-guided catheter approach, taking into account that critical areas such as the carina between ipsilateral veins have to be targeted for ablation almost always [120]. Finally, many laboratories have adopted the use of general anesthesia for AF ablation procedures in view of the lower probability of PV reconnection reported by Di Biase et al. [121] or have started to employ magnetic robotic navigation [122, 123]. This new technology has been suggested to improve the catheter stability or to simplify the PVI technique.

## 6. Results of Ablation

In the previous paragraphs we have enumerated the great number of strategies which have been published to localize and characterize the mechanism of PAFAT. All of them should be considered complementary approaches, and their use should be conditioned to the operator experience and to the particular requirements and peculiarities of each AT in an individualized manner. Basically, our experience and the published results of other authors invite to consider that activation mapping should always be complemented with entrainment manoeuvres and that the tridimensional image support afforded by electroanatomic navigation systems is in general advisable to optimize the results of ablation. The algorithm proposed by Knecht et al. [14] and developed by Jaïs et al. [61] deserves the utmost attention because it provides accurate rules to elucidate the most frequent PAFAT mechanisms laying emphasis on simple and precise criteria: PVI reconnection is performed first and then focal, macro-reentrant, and small-loop reentrant mechanisms are systematically sought after in this order.

In spite of the heterogeneity of techniques habitually resorted and the differences in the degree of mechanistic characterization of these arrhythmias, several authors have published convincing results (see Table 1) showing the success rate of PAFAT invasive treatment. The clinical PAFAT can be ablated almost always (70–100% of individual AT). Patel et al. [72] and Deisenhoffer et al. [15] reported a somewhat lower percentage of success (61% and 38%, resp.) which may be explained because most of their patients presented several different ATs. However, recurrences of new organized ATs are not rare (up to 21%–44%). Long-term sinus rhythm maintenance has not been conveniently

TABLE 1

Author and year	Number of patients	Number of ATs studied	ATs amenable to mapping	AT change during entrainment	AT change during RF	AT successfully ablated	Followup: persistence in SR	Followup: AT recurrence	Redo procedures for AT recurrence
Paponne et al. 2004 [17]	39	39	39/39 (100%)	Not reported	Not reported	39/39 (100%)	39/39 (100%)	6/39 (15%) early after ablation	0%
Kobza et al. 2004 [20]	10	20	19/20 (95%)	Not reported	Not reported	16/19 (84%)	Not reported	1/10 (10%)	Not reported
Mesas et al. 2004 [16]	13	14	12/14 (86%)	Not reported	1/14 (7%)	13/14 (93%)	11/13 (85%)	1/13 (8%)	1/13 (8%)
Gerstenfeld et al. 2004 [33]	10	10	9/10 (90%)	1/10 (10%)	0%	9/10 (90%)	9/10 (90%)	0%	0%
Chugh et al. 2005 [18]	28	>28 (30 reported)	28/30 (93%)	1/30 (3%): original AT could not be reinduced	Not reported	Success in 22/28 patients (79%)	18/22 (82%)	3/22 (14%)	3/22 (14%) patients after a successful procedure
Ouyang et al. 2005 [38]	21	17	15/17 (88%)	Not reported	Not reported	14/15 (93%)	21/21 (100%)	0%	0%
Cummings et al. 2005 [34]	23	Only PV reiso-lation	PV reiso-lation only	Not reported	Not reported	100% reiso-lation success	82% of patients	9% of patients	9% of patients
Jais et al. 2006 [64]	14	14	Only a specific type of AT	Not reported	Not reported	14/14 (100%)	11/14 (79%)	3/14 (21%)	2/14 (14%)
Daoud et al. 2006 [19]	9	17	13/17 (76%)	Not reported	Not reported	16/17 (94%)	100% of patients with successful procedure	0%	0%
Chae et al. 2007 [21]	78	155	155/155 (100%)	Not reported	Not reported	134/155 (86%)	60/78 (77%)	18/66 (27%) acute success	14/66 (21%)
Patel et al. 2008 [72]	17	41	33/41 (80%)	7/33 (21%): original AT could not be reinduced	Not reported	25/41 (61%)	13/17(76%)	4/17 (24%)	2/17 (12%)
Satomi et al. 2008 [36]	8	8	Only a specific type of AT	Not reported	Not reported	8/8 (100%)	7/8 (88%)	0%	0%
Takahashi et al. 2008 [55]	9	Multiple (>15) AT	All except one	Not reported	4/9 (44%), all localized reentries	All except 3	8/9 (89%)	1/9 (11%)	None

TABLE 1: Continued.

Author and year	Number of patients	Number of ATs studied	ATs amenable to mapping	AT change during entrainment	AT change during RF	AT successfully ablated	Followup: persistence in SR	Followup: AT recurrence	Redo procedures for AT recurrence
Lim et al. 2008 [89]	18	≥23	20 (at least 3 were not stable enough to be mapped)	Not reported	Not reported	20/20 (100%)	Not clearly reported, 79% including AF patients	Not reported	Not reported
Deisenhoffer et al. 2009 [15]	16	55	38/55 (69%)	Not reported	Not reported	23/55 (42%)	6/16 (38%)	7/16 (44%)	5/16 (31%)
Chang et al. 2009 [28]	26	48	48/48 (100%)	Not reported	5/48 (10%)	48/48 (100%)	20-21/26 (79%)	1/26 (19%)	1/26 (19%)
Rostock et al. 2010 [57]	61	133	132/133 (99%)	5/132 (3,8%)	45/61 initial AT (74%)	124/133 (93%)	50/61 (82%)	7/61 (11,5%)	5/61 (8%)

explored by the studies summarized in Table 1 because the time of follow-up after the PAFAT treatment was not long enough in most cases.

## 7. Organized AT during AF Ablation

AF termination is considered by some authors a desirable but not always attainable objective of AF ablation. The *distillation* [14] of AF into organized AT has been judged a reasonable way to modify the substrate responsible for AF maintenance. However, the extensive ablation this objective usually demands, together with the controversial results which have apparently disproved its efficacy in terms of effective prevention of AF recurrences [124], has precluded a more widespread acceptance of this opinion. At all events, organization of AF into AT during ablation is an interesting phenomenon, worthy of mention because it has given rise to new hypothesis about AF maintenance mechanisms. Some of these organized ATs are not spontaneous. For example, Chang et al. [28] induced organized AT in 16.3% of patients immediately after circumferential PVI, most of them (76%) were gap-related AT and macro-reentrant circuits around the mitral annulus or ipsilateral PVs were the most frequent. In fact, this inducibility guided strategy may be helpful to uncover gaps and latent AT circuits which could eventually acquire clinical relevance afterwards [18]. On the other hand, spontaneous ATs have much more interest from a mechanistic point of view because they could indicate the location of areas relevant for AF maintenance. Scharf et al. studied six cases of spontaneous conversion of AF into focal AT during left atrial ablation. All these ATs had a focal origin adjacent to ablated areas but unrelated to conduction gaps, and what is even more important, three of them had also an exact spatial correspondence with areas that seemed to anchor the fastest frequencies during AF (characterized by a CL during AF 30–40 ms shorter than the mean CL in adjacent zones). These focal sources of organized AT were correctly interpreted as slowed versions of very rapidly firing zones, the mechanism which had been probably modified by the ablation procedure. Only one of them manifested the typical behavior of an automatic focus but the mechanism was not investigated in great detail in the rest. A further and not less exciting insight into the hypothesis that AF and organized AT could be two sides of the same coin was provided by the study of Yoshida et al. [62] In this study the AF ablation strategy consisted in antral PVI and targeting of complex fractionated electrograms until AF converted to sinus rhythm or organized AT. There was a spectral component in the AF periodogram that matched the frequency of the resulting AT in 52% of patients who presented acute transformation of AF into AT. This proportion was higher (79%) when the AF periodogram was evaluated just before conversion to AT. This correspondence between the frequency of the resulting AT and one of the components of the AF periodogram suggests that the AT circuit is already present during AF in some way or another, but hidden behind the fibrillatory process and surpassed by the higher-frequency components of the AF spectrum of frequencies. As for the mechanism

of these resulting ATs, 94% were macro- or micro-reentry circuits, 70% of them located distant from the ablated areas. How crucial is the contribution of these lower-frequency drivers to the global fibrillatory phenomenon? It is evident that the lower-frequency components alone cannot result in fibrillatory activity once the higher-frequency components have been abolished. Nevertheless, it is not known whether the fibrillatory process requires not only the high-frequency drivers to be manifest but also the lower-frequency reentrant circuits to remain stable or what would happen if these subordinate components could be localized and ablated independently in the first instance.

Organization of AF into AT during extensive CAFEs ablation occurs in 36% of cases of paroxysmal AF and in 50% of persistent AF [125]. Different mechanisms of AT in this context were described in pioneer works [46] and have been recently revisited by Nam et al. [53], who have reported the following results: 30% perimitral MR, 30% cavotricuspid isthmus-dependent flutter, 18% roof-dependent MR, 18% focal and 6% of unknown mechanism. These circuits are well-known, amenable to mapping, and commonly ablated in daily clinical practice, from whence comes the opinion that AF organization might be as good an outcome as termination [61].

## 8. Conclusions

The incidence of PAFAT is clinically relevant but depends on the ablation technique initially used to treat AF and on the existence of appropriate anatomic substrates, which sometimes exist before the ablation procedure. Both the mechanisms and elements constitutive of PAFAT circuits are well-known and have been repeatedly and consistently described. This fact, along with the high probability of success when these AT are targeted for ablation, and the low efficacy of antiarrhythmic drugs, implies that an invasive approach should be attempted if these AT became incessant, bad tolerated or do not disappear after a prudential observation period. However, it must be noted that the frequent coexistence of multiple mechanisms and several different types of PAFAT in the same patient determine the special complexity of these procedures, in which PV re-isolation is the pivotal element when reconnection has occurred.

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## Review Article

# Management of Patients with Atrial Fibrillation: Specific Considerations for the Old Age

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Atrial fibrillation (AF) is the commonest of all sustained arrhythmias, and most of the patients seeking medical therapy are in the elderly age group. The management of these patients is particularly difficult due to associated comorbidities. Hypertension, congestive heart failure, left ventricular hypertrophy, and coronary artery disease are often present in the elderly patient population, and therefore, antiarrhythmic drugs often fail due to side effects, proarrhythmia, or poor rhythm control. Recently, radiofrequency catheter ablation has been widely performed as an efficient therapy for recurrent, drug-refractory AF. Nevertheless, patients at old age were underrepresented in prior AF ablation trials, and the current guidelines for catheter ablation of AF recommend a noninvasive approach in the elderly patient group due to the lack of clinical data supporting ablation therapy. However, study results of our group and others are suggesting that catheter ablation is a safe and effective treatment for patients over the age of 65 years with symptomatic, drug-refractory AF, and therefore, patients should not be precluded from catheter ablation only on the basis of age. This paper discusses the pharmacological (rhythm control, rate control, and anticoagulation) and catheter management of AF in the elderly population.

## 1. Introduction

Atrial fibrillation (AF) is the commonest of all sustained arrhythmias, and its prevalence has been increasing. AF confers an important mortality and morbidity outcome from thromboembolism, stroke, heart failure, and significant impairment of quality of life [1, 2]. The prevalence of AF is more prominent with advanced age. About 8 to 10% of people aged over 80 years are suffering from AF [3]. The median age of an AF patient is 75 years, and 70% of the AF patients are 65 to 85 years of age [4, 5]. Within the next twenty to thirty years, the number of patients suffering from AF is expected to double or triple due to an increased AF incidence and aging of the populations in developed western countries (Figure 1) [5, 6].

In former days, the management of AF focused on preventing thromboembolism and controlling heart rate or rhythm. The risk of stroke is increased 5-fold by AF. AF is responsible for around 10–20% of all strokes. In patients age groups 80 to 89 years, this proportion is even

more accentuated and around 25% [7]. Strokes related to AF result often in higher mortality and morbidity rates. The use of oral anticoagulation therapy is an important intervention in preventing AF-related ischemic events. But older people have both higher risk for stroke if not taking oral anticoagulants and higher risk for bleeding with the use of oral anticoagulants [8]. Therefore, the recommendation for anticoagulation is a challenging task for the clinician treating patients with AF in the old age. Disease management is also particularly challenged by comorbidities including hypertension, congestive heart failure, left ventricular hypertrophy, coronary artery disease, and diabetes mellitus which are frequently present in this patient age group. These comorbidities also confer an increased risk for thromboembolic complications or drug-related side effects [9]. Moreover, other endpoints such as left ventricular and atrial function, quality of life, social functioning, silent cerebral embolism and dementia are novel targets of comprehensive AF disease management [10].

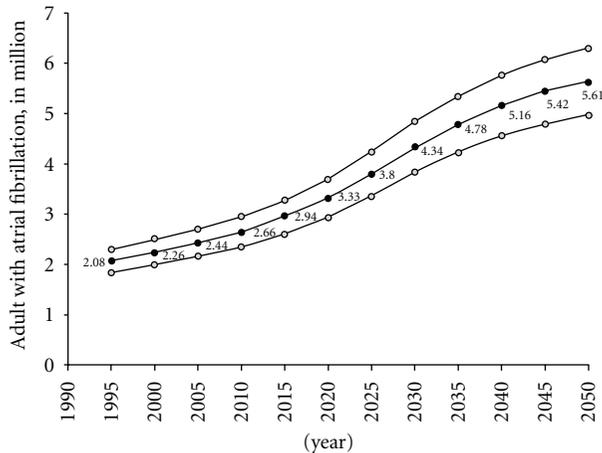


FIGURE 1: Projected number of adults with AF in the United States between 1995 and 2050 from the ATRIA study (the AnTicoagulation and Risk Factors in Atrial Fibrillation Study) [5].

Ablation therapy has emerged as an efficient intervention for recurrent, drug-refractory AF [11–14]. Current ablation techniques have improved, and the complication rates have decreased resulting in increasing number of referrals of patients of old age for catheter ablation of AF [15–18]. Nevertheless, a minority of elderly patients were included in prior AF ablation trials. Friable cardiac structures, which may be at risk for catheter perforation, long procedure times, and the associated comorbidities, are frequently considered to confer an increase of overall peri- and postprocedural risk. For that reason and in the absence of clinical data, the recommendation in the guidelines for catheter ablation of AF advises a conservative approach in patient populations of old age [19]. Nevertheless, with advanced life expectancy, the elderly population group is a rapidly expanding portion of our community making AF an even more important public health concern. Catheter ablation could become a pivotal treatment strategy in the elderly patient population after failure of antiarrhythmic drugs.

## 2. Stroke Prevention in the Elderly

Oral vitamin K antagonists efficiently reduce the risk of cerebrovascular embolism in elderly AF patients as clearly shown in several randomized trials [20, 21]. Patients with AF aged over 75 years have a thromboembolic complication risk of over 4% per year, mandating therapy with oral vitamin K antagonists unless there is a significant risk for major bleeding present. Among each components of the widespread CHADS<sub>2</sub> (cardiac failure, hypertension, age, diabetes, and stroke (doubled)) risk score, age  $\geq$  75 years confers an impaired prognosis for stroke and mortality over hypertension, heart failure, or diabetes [22]. Therefore, the CHADS<sub>2</sub> score was extended recently to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score by considering additional risk factors such as vascular disease (i.e., prior myocardial infarction), age between 65 and 74 years, and female sex (Table 1) [23]. The risk for stroke can be reduced by oral vitamin K antagonists by about 70% and

consecutively the mortality by 33% [24]. But, these agents have a small therapeutic window with an associated hemorrhagic risk complicating anticoagulation management. In general, the anticoagulation intensity should be optimized by keeping the international normalized ratio (INR) between 2.0 and 3.0 [25]. Several studies have shown that low fixed-dose use of an oral vitamin K antagonist or targeting lower INRs (<2.0) in older patient groups increase the risk for stroke without protecting against intracerebral bleeding [25–27]. In cases where oral vitamin K antagonists are contraindicated, antiplatelet therapy with aspirin provides some prevention from cerebrovascular embolism, but much less efficiently than oral vitamin K antagonists [28]. Aspirin reduces the risk for stroke by about 20%. Interestingly, the beneficial effect of antiplatelet therapy on ischemic stroke appears to diminish with increasing age and is no longer present after the age of 77 years [29, 30]. Warfarin was found to be superior to combined therapy with clopidogrel plus aspirin with similar rates of bleeding complications in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study [31]. A novel generation of oral anticoagulants is emerging and being approved for AF such as dabigatran, an oral direct thrombin inhibitor. In a large randomized trial (Randomized Evaluation of Long-Term Anticoagulation Therapy; RE-LY), dabigatran has shown to be superior to warfarin in terms of similar reduction of stroke rates, but lower rates for major bleeding [32]. Apixaban, a novel factor Xa inhibitor, was superior to aspirin for reduction in stroke without increase of major bleeding in 5599 patients (mean age of 70 years), who are unsuitable for vitamin K antagonist therapy, as reported in the AVERROES trial [33]. Elderly patients are less likely than younger patients to receive appropriate anticoagulation and are more likely to have subtherapeutic INR levels. In general practice, fewer than half of eligible patients take warfarin [34, 35]. High fall risk, history of bleeding, nonadherence, and dementia are the major factors

Risk factors	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age $\geq$ 75 years	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74 years	1
Sex category (i.e., female sex)	1
Maximum score	9

TIA: transient ischemic attack; TE: thromboembolic event.

preventing physicians to prescribe oral anticoagulants [36–38]. Therefore, in elderly patients ineligible for vitamin K antagonist therapy, oral direct thrombin or factor Xa inhibitor, dabigatran, or apixaban, respectively, should be considered as an effective and safe option.

### 3. Pharmacological Management in the Elderly

Several randomized trials comparing rhythm control versus rate control in AF patients showed no evidence that the clinical outcome of hospitalization, stroke, and mortality is improved by restoration and maintenance of sinus rhythm despite the clear relationship between AF and cardiovascular events [39–44]. Moreover, rhythm control by pharmacological interventions has been associated with higher mortality in the elderly [40]. However, subgroup analyses and the recent published outcome data of the ATHENA trial signalize that safely maintained sinus rhythm by novel antiarrhythmic drugs may prevent AF-related complications [45, 46]. This placebo-controlled, double-blinded conducted study assessed the efficacy of dronedarone for the prevention of cardiovascular hospitalisation or death from any cause in patients with AF and atrial flutter. Nevertheless, apart from the effect of dronedarone on the composite endpoint driven by cardiovascular hospitalizations in the ATHENA trial, there are no controlled data available that show a benefit of rhythm control therapy beyond improved quality of life. The major studies on rhythm versus rate control were the rate control versus electrical cardioversion (RACE) trial [39], the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) trial [40], and the atrial fibrillation congestive heart failure (AF-CHF) trial [43]. There was also a series of smaller studies performed, including the pharmacological intervention in atrial fibrillation (PIAF) [44], strategies of treatment of atrial fibrillation (STAF) [41], and how to treat chronic atrial fibrillation (HOT CAFÉ) [42]. These studies have shown that primary rate control is not inferior to rhythm control. Therefore, first-line therapy in the elderly patient population with symptomatic AF is usually a primary rate control approach. Betablockers, nondihydropyridine calcium channel blockers, and digoxin are widely used to control the ventricular rate response in AF [35]. Digoxin can be added if impaired left ventricular systolic function is present, but caution should be raised because of potential drug toxicity, especially in elderly patients with frequent impaired renal function and polypharmacy. Previous guidelines recommended targeting a resting heart rate of less than 80 beats per minute. But a recent randomized trial showed no clinical benefit of a strict rate control versus a lenient rate control targeting resting heart rates of about 115 beats per minute in terms of clinical cardiovascular events [47]. Antiarrhythmic drugs with the aim to maintain sinus rhythm may be considered, if patients remain symptomatic despite optimal rate control, but the increased risk for proarrhythmia, drug interactions, and age-related comorbidities in the elderly population should be carefully taken into account. Class Ic antiarrhythmic drugs, flecainide, and propafenone have shown to increase mortality in patients with coronary artery disease [48]. Sotalol

TABLE 2: Major complication rates in a worldwide survey of catheter ablation for AF in 16,309 patients from Cappato et al. [56].

Type of complication	Rate, %
Death	0.15
Tamponade	1.31
Pneumothorax	0.09
Hemothorax	0.02
Sepsis	0.01
Phrenic nerve palsy	0.17
Femoral pseudoaneurysm	0.93
Arteriovenous fistulae	0.545
Valve damage/requiring surgery	0.07
Atrio-esophageal fistulae	0.04
Stroke	0.23
Transient ischemic attack	0.71
PV stenoses requiring intervention	0.29
Total	<b>4.54</b>

PV: pulmonary vein.

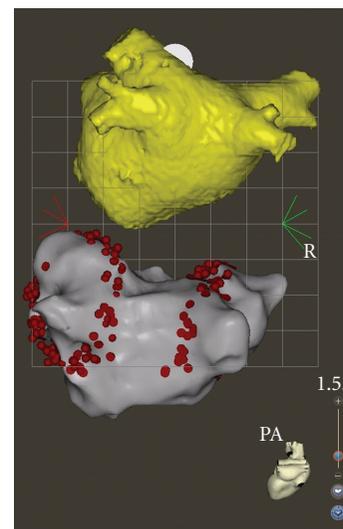


FIGURE 2: Three-dimensional reconstruction (yellow) of the computed tomography imaging and three-dimensional electro-anatomical map (grey) of the left atrium in posteroanterior projection with circumferential ablation (red points) around ipsilateral pulmonary veins using CARTO system (Biosense Webster Inc., Diamond Bar, Calif, USA).

and dofetilide should not be used in patients with renal impairment. Amiodarone is the most effective drug and safe in heart failure patients, but regular follow-up of thyroid, hepatic, and pulmonary function is mandatory because of frequent extracardiac drug toxicity. Therefore, amiodarone should be reserved for use if other antiarrhythmic drugs have failed or are contraindicated.

### 4. Catheter Ablation of AF in the Elderly

An effective alternative option for drug-refractory AF with a rapid ventricular rate response is the transvenous catheter

TABLE 3: Catheter ablation of AF in the elderly.

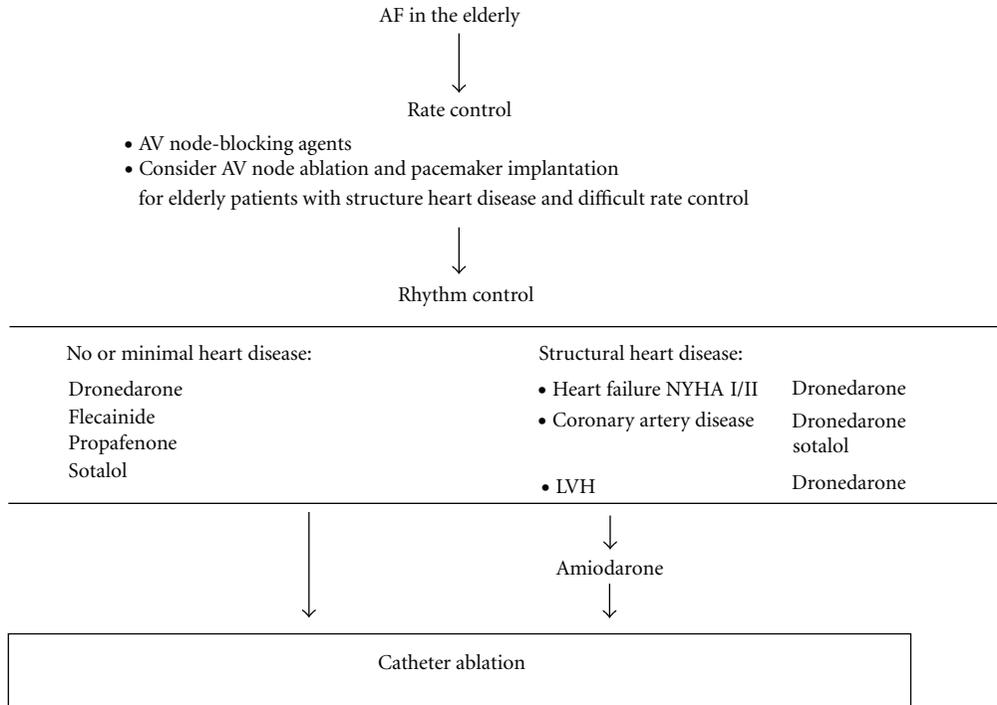
	Haegeli et al. [57]	Bunch et al. [58]	Tan et al. [59]	Zado et al. [60]
Inclusion age (years)	≥65	≥80	≥80 70–79 60–69	65–74 ≥75
Mean age (years)	69 ± 3.5	82 ± 2	84 ± 5 75 ± 4 66 ± 4	68 ± 3 77 ± 2
Number of patients	45	35	49 151 177	185 32
Number of procedures	53	35	53 174 209	228 34
Paroxysmal AF (%)	87	46	55 53 51	62 53
Ablation strategy	PVI ± linear lesions	PVI ± linear Lesions	PVI	PVI
Mean F/U (months)	6	12	18	27
Periprocedural complication rate (%)				
(i) Pericardial tamponade	1.9	2.8	0.2	0.4
(ii) Deep venous thrombosis	0	2.8	0.9	0
(iii) CVA/TIA	0	0	0.7	0.8
(iv) Retroperitoneal bleeding	0	0	0.7	0.4
(v) Pseudoaneurysm/AV fistula	0.30	0	0.5	2.7
Freedom of AF	74%	78%	70% 72% 74%	84% 86%

PVI: pulmonary vein isolation; CVA: cerebral vascular accident; TIA: transient ischemic attack.

ablation of the atrioventricular node and the placement of a permanent pacemaker. The procedure is associated with minimal mortality and morbidity, but this approach does not eliminate AF and the need for anticoagulation [49]. Pathophysiological knowledge that focal sources of ectopic beats arising from the pulmonary veins often initiate AF has led to the development of catheter ablation for AF in the last decade [11]. The majority of ablation strategies currently used involves circumferential ablation around the ostia of the ipsilateral pulmonary veins with the endpoint of electrical isolation of the pulmonary veins from the left atrium [50–52]. Success rates approach 70% to 90% in experienced centers [53]. However, most of the published data are obtained in younger patients aged below 65 years and without heart disease and comorbidities. Catheter ablation for chronic AF is less successful than for paroxysmal AF and is associated with higher complication rates in older patients having structural heart disease [14, 54, 55]. Procedure-related complication rates were reported in a large

worldwide multicenter survey and are listed on Table 2 [17]. In a retrospective analysis of 641 consecutive ablation procedures, the rate for major complications was 5%, and the age greater than 70 years was identified as a significant predictor with an odds ratio of 3.7 [18].

In a recently published study, we reported the clinical outcome of 45 consecutive patients over the age of 65 years who underwent a percutaneous catheter ablation procedure for symptomatic paroxysmal and persistent AF [57]. Among them, none had a significant structural heart disease. All patients underwent wide-area circumferential pulmonary vein isolation for paroxysmal AF with additional linear lesions for persistent AF. The ablation was performed point by point by radiofrequency energy and guided by a three-dimensional electroanatomical mapping system (Figure 2) [61]. The endpoint of the procedure in both paroxysmal and persistent AF patients was electrical isolation of all pulmonary veins, which was assessed using a circular spiral catheter. Our results suggested that catheter ablation of AF



AV, atrioventricular; NYHA, New York heart association class; LVH, left ventricular hypertrophy

FIGURE 3: Decision tree for the therapy of AF in the elderly integrating pharmacological treatment and catheter ablation, modified from the guidelines for the management of AF proposed by the European Society of Cardiology [63].

in elderly patients can be performed with success rates comparable to those in younger patients without an increase in complication rate. Successful maintenance of a stable sinus rhythm could be achieved in nearly 80% of this patient cohort with a mean age of 69 years (Table 3). Zado et al. found similar success and complication rates in patients over 65 years of age [60]. Patients over the age of 80 years in the paper of Tan et al. were less likely to undergo a repeat procedure than younger patients. However, the success and complication rates were not significantly different in the age group over 80 years than in those 60–69 years (70% versus 74% for success rate) [59]. Similarly, the study reported by Bunch et al. found no increased risk of periprocedural complications in patients aged 80 years and older [58]. Available published outcome data for catheter ablation in the elderly population were derived from observational cohort analysis with a follow-up period of up to two years with procedural success defined as freedom from symptomatic AF. A long-term follow-up study reported that the success rate in 100 patients was 63% at 5 years after a median of two procedures per patient [62]. Prospective, randomized trials comparing an invasive versus a conservative pharmacological approach are required to address the remaining questions on best management of AF in the elderly population. A decision tree integrating different choices of rate and rhythm control and pharmacological therapy versus catheter ablation of AF in this selected elderly patient population is proposed in Figure 3 based on the current guidelines of the European Society of Cardiology [63].

### 5. Conclusion

Elderly patients differ considerably from patients in the younger age group as they have a higher incidence of AF associated with a higher thromboembolic risk due to advanced age and frequent multiple comorbidities. In addition, the adverse side effects of antiarrhythmic drugs, such as proarrhythmia, are more commonly observed in the elderly patient population. Nonrandomized studies in patients aged 65 years and more with symptomatic drug-refractory AF have shown that catheter ablation can be performed with comparable safety and efficiency as with younger patients. Therefore, ablation therapy may be considered as an appropriate therapeutic option also for the older group of patients if antiarrhythmic drug treatment fails. Patients should not be precluded from undergoing AF catheter ablation exclusively on the basis of age.

### Conflict of Interests

The authors declare that there is no conflict of interests.

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## Review Article

# Surgical Treatment of Atrial Fibrillation: A Review

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Atrial fibrillation is the most commonly sustained arrhythmia in man. While it affects millions of patients worldwide, its incidence will markedly increase with an aging population. Primary goals of AF therapy are to (1) reduce embolic complications, particularly stroke, (2) alleviate symptoms, and (3) prevent long-term heart remodelling. These have been proven to be a challenge as there are major limitations in our knowledge of the pathological and electrophysiological mechanisms underlying AF. Although advances continue to be made in the medical management of this condition, pharmacotherapy is often unsuccessful. Because of the high recurrence rate of AF despite antiarrhythmic drug therapy for maintenance of sinus rhythm and the adverse effects of these drugs, there has been growing interest in nonpharmacological strategies. Surgery for treatment of AF has been around for some time. The Cox-Maze procedure is the gold standard for the surgical treatment of atrial fibrillation and has more than 90% success in eliminating atrial fibrillation. Although the cut and sew maze is very effective, it has been superseded by newer operations that rely on alternate energy sources to create lines of conduction block. In addition, the evolution of improved ablation technology and instrumentation has facilitated the development of minimally invasive approaches. In this paper, the rationale for surgical ablation for atrial fibrillation and the different surgical techniques that were developed will be explored. In addition, it will detail the new approaches to surgical ablation of atrial fibrillation that employ alternate energy sources.

## 1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. The overall prevalence of AF in the population ranges between 1 and 2%. The relationship between AF and age is strong. The prevalence doubles with each decade of age, reaching almost 9% at the age of 80–89 years [1, 2]. This can be an underestimate of the real number as it overlooks the undetected asymptomatic AF cases and paroxysmal AF.

Although atrial fibrillation can be considered an innocuous arrhythmia, it is associated with serious morbidity and mortality [3]. First, it increases the risk of thromboembolism and stroke, as a result of blood stasis in the left atrium. It has been estimated that AF results in three- to five-fold increase in stroke risk [4]. Second, the irregularly irregular heart beat leads to symptoms palpitations, shortness of breath, anxiety, and reduced exercise tolerance in the patient. Third, atrial fibrillation leads to a number of cardiac and hemodynamic

changes including a reduced myocardial systolic function and tachycardia-induced cardiomyopathy [5, 6].

In addition to the clinical morbidity and mortality of AF, it imposes a huge burden on the economy. Stewart and colleagues looked at the cost that AF imposes on health and social services in the UK in 1995 [7]. AF accounted for 0.62% of the UK National Health Service (NHS) expenditure, which is equivalent to £244 million. Hospitalization and drug prescriptions accounted for 50% and 20% of this expenditure respectively. The expenditure is expected to rise as the incidence of AF continues to rise due to the increase of the number of people over the age of 80 years. Thus, AF is an extremely expensive public health problem.

Given the great impact of atrial fibrillation on health resources and patients' welfare, several pharmacological and surgical therapies have been developed over the years. The purpose of this review is to review the rationale for surgical ablation of atrial fibrillation and describe the different

approaches and procedures used in the ablation of atrial fibrillation in cardiac surgery patients.

## 2. Rationale for Surgical Ablation

AF is present in up to 50% of patients undergoing mitral valve surgery and in 1% to 6% of patients presenting for coronary artery bypass grafting (CABG) or aortic valve surgery [8–11]. Atrial fibrillation is strongly associated with mitral valve dysfunction, hence most studies focus on patients who have mitral valve dysfunction. In those patients, atrial fibrillation is a marker of advanced cardiovascular disease and is associated with a more severe left ventricular dysfunction and a greater left atrial enlargement [11–13].

AF onset can be considered a relative indication for mitral valve surgery in those who have mitral valve dysfunction [9]. However, mitral valve surgery alone does not revert AF back into sinus rhythm [14, 15]. In most instances mitral valve surgery alone does not cure AF. When the duration of AF preoperatively is longer than six months, the risk of remaining in AF is 70–80%. In contrast, when the duration of preoperative AF is less than three months, particularly if it is paroxysmal, there is an 80% cure rate after mitral valve surgery [12, 14, 16]. Therefore, ablation should be added to the mitral valve procedure in any patient with AF greater than six months duration or in any patient with AF that is not paroxysmal.

## 3. Pathophysiology of Atrial Fibrillation

There is general agreement that AF requires a trigger for its initiation and a substrate for its maintenance. Triggers include atrial ectopic foci, changes in atrial wall tension, and alteration in autonomic tone [17–19]. The substrate is an atrial abnormality, frequently inflammation or fibrosis, and it causes electrical dysfunction that favours development of AF.

These substrates and triggers have been localized anatomically to the pulmonary veins and the left atrium [20]. The mechanism underlying the pulmonary vein ectopy is still under investigation. After triggers propagate into the atrial myocardium, fibrillation is maintained by continuation of these trigger beats with breakdown of conduction or by intra-atrial reentrant processes.

Our understanding of AF initiation and maintenance stems from previous experimentally founded theories that address the genesis of AF. One theory considers AF to be a manifestation of one or more reentry circuits (multiple-wavelet theory) or reentrant rotors involving the atrial surface [21]. The second theory postulates AF to be the result of fibrillatory conduction throughout the atria originating from a rapid discharge from one or several foci (focal theory) [22]. Both mechanisms are relevant to the clinical spectrum of AF.

The clinical classification of AF is helpful in management. Chronic AF can be classified into three subtypes: paroxysmal, persistent, and permanent [23]. Paroxysmal AF is defined as episodes that start and stop by themselves, generally lasting less than 24 hours but sometimes lasting up to 7 days.

Persistent AF is defined as episodes lasting more than 7 days or that require termination, either pharmacologically or electrically. Permanent AF is defined as longstanding continuous episodes, where repeated attempts to terminate have either failed or not tried.

Cardiac remodelling (electrical, contractile, and structural) is another important part of the pathophysiology of AF. It plays a role in determining whether AF is persistent or permanent. There has been an explosion of research into atrial remodelling during AF and the converse process of “reverse remodeling” [24, 25].

## 4. Surgical Treatment Options

The development of new surgical approaches to AF has been predicated upon two factors: understanding that the pulmonary veins and left atrium are critical to the initiation and maintenance of AF and development of ablation tools that use alternate energy sources to facilitate rapid and safe creation of lines of conduction block under direct vision.

Surgical therapy ranges from simple procedures such as removal or plication of the left atrial appendage to reduce the risk of thromboembolic complications [26–28] to a variety of procedures aimed at preventing the recurrence of AF.

### 4.1. Historical Background before the Cox Maze

**4.1.1. Left Atrial Isolation.** In 1980, Williams and colleagues developed the left atrial isolation procedure by using animal models [29]. This procedure isolated the left atrium electrically from the remainder of the heart without disrupting normal conduction. This was successful in isolating AF to the left atrium and restoring the remainder of the heart to sinus rhythm.

The left atrial isolation has been applied clinically by Graffigna and associates [30] to a hundred patients with chronic AF and mitral valve disease. They showed that sinus rhythm has been restored in 72% of those patients, with a mean follow up of 14.6 months. However, the obvious shortcoming of this approach is continued fibrillation of the left atrium and its uncertain impact on the risk of thromboembolism.

**4.2. The Corridor Procedure.** In 1985, Guiraudon and coworkers [31] introduced the corridor procedure for AF, creating an isolated strip of muscle which links the sinoatrial and AV nodes (Figure 1), thus driving ventricle rate via the AV node-His bundle complex. This approach failed to achieve sinus rhythm in a significant number of cases. In addition, atrial areas outside the narrow right atrial corridor continued to fibrillate with persistent loss of atrial transport function and persistent risk of thromboembolism.

**4.3. The Cox Maze.** All the above-mentioned procedures fall short of the ideal, which is the cure of the arrhythmia and resolution of its principle adverse consequences (thromboembolism). The Cox-Maze III operation or the Maze procedure is the gold standard for surgical treatment of AF. In fact,

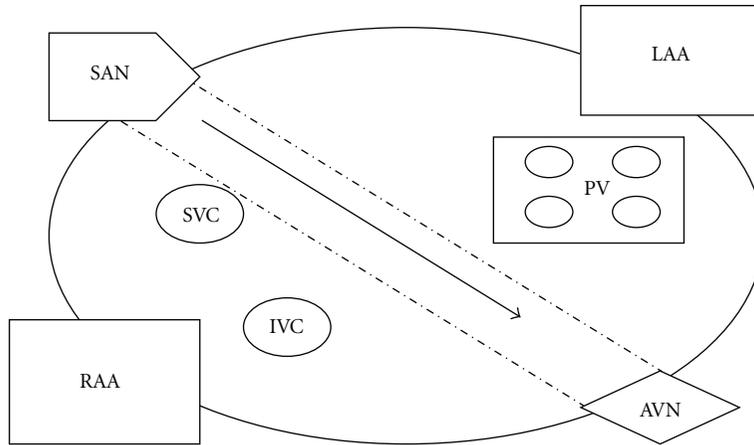


FIGURE 1: The Corridor Procedure designed by Guiraudon in 1985. Arrow show the direction of flow of electrical current. (SN: SA node, PV: pulmonary veins, AVN: atrioventricular node, SVC: superior vena cava, IVC: inferior vena cava, LAA: left atrial appendage, and RAA: right atrial appendage).

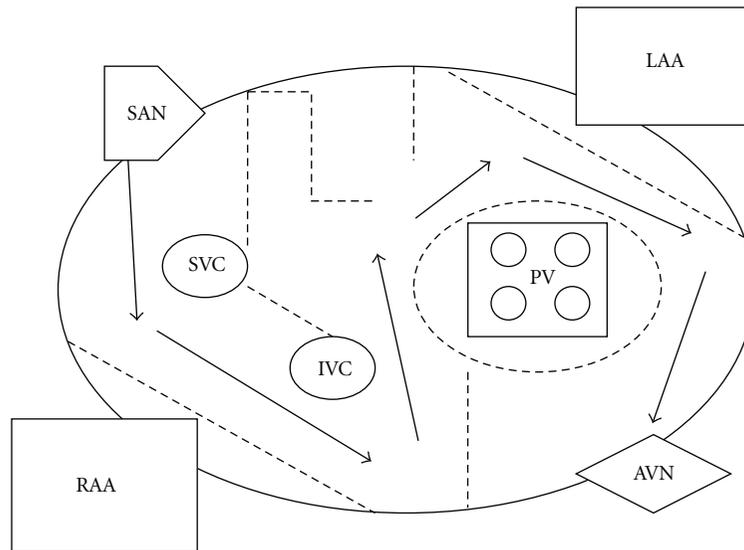


FIGURE 2: The Cox-Maze III lesion pattern described by James Cox in 1991 with cut and sew technique. Arrows show the direction of electrical current flow from the SA node to the atrioventricular node. (SN: SA node, PV: pulmonary veins, AVN: atrioventricular node, SVC: superior vena cava, IVC: inferior vena cava, LAA: left atrial appendage, and RAA: right atrial appendage).

it is the most effective curative therapy for AF yet devised [32–34].

In 1991, Jimmy Cox described the Maze procedure for the surgical cardioversion of AF. Cox et al. designed the procedure based on experimental and clinical evidence concerning the pathophysiology of AF. To improve results and simplify the operation, they modified the procedure twice, culminating in the Cox-Maze III. In the Maze procedure, incisions are made strategically to interrupt the multiple macroreentrant circuits and direct the sinus impulse from the sinoatrial node to the atrioventricular node along a specified route (Figure 2). The Maze procedure includes encircling and isolating the pulmonary veins and excising the left and right atrial appendages. Although the Maze procedure may be performed with minimal invasiveness

through a small chest wall incision, the operation requires cardiopulmonary bypass and cardiac arrest. In experienced hands, the Maze procedure requires 45 to 60 minutes of cardiopulmonary bypass and cardiac arrest. The operation may be performed alone or in conjunction with other cardiac surgical procedures, such as mitral valve surgery or coronary bypass grafting.

Cox et al. [35] have reported the largest series of patients undergoing the Maze III procedure. Among 118 patients, operative mortality was 2%. AF was cured in 93% of patients at 8.5 years of followup, and only 2% of patients required long-term postoperative antiarrhythmic medication.

The postoperative success was unaffected by presence of mitral valve disease, left atrial size, and type of AF (paroxysmal, persistent, or permanent). However, the atrial

fibrillatory wave and left atrial diameter were independent predictors of sinus rhythm restoration after the maze procedure in patients with chronic atrial fibrillation and organic heart disease [36].

Temporary postoperative AF and atrial arrhythmias were common, occurring in 38% of patients. This problem was attributed to a shortened atrial refractory period; most importantly, postoperative AF was temporary and did not diminish long-term results. Fifteen percent (15%) of patients required new pacemakers postoperatively. This was a result of the underlying sinus node dysfunction rather than the Maze procedure itself. In spite of multiple right and left atrial incisions, the right atrial transport function was demonstrated in 98% of patients, and the left atrial transport function was demonstrated in 93% of patients. Furthermore, the Maze procedure virtually eliminated the risk of stroke or other thromboembolism [37]. Other medical centres reproduced these excellent results that confirm the safety of the Maze procedure and its efficacy at restoring sinus rhythm leading to the virtual elimination of late strokes. In spite of these excellent results, the Maze procedure has been relatively underused, and even in patients requiring cardiac surgery for other reasons. The perceived surgical complexity and magnitude of the operation can account for these trends.

**4.4. New Approaches for Surgical AF Ablation.** In an attempt to decrease the ischemic time and the on-pump time, the Cox-Maze III has evolved to a procedure that uses the latest ablation technology instead of the traditional “cut and sew” method to achieve the designated areas of conduction block. The main techniques use thermal energy to create the desired electrical barriers. These include microwave, bipolar radiofrequency, laser, and cryotherapy. The new techniques appear to be less time consuming and less technically demanding.

Microwave energy has been used to create transmural lesions on the arrested heart, but transmural is inconsistently achieved. In a prospective randomized trial, Schuetz and colleagues [38] used a combination of microwave ablation and atrial size reduction to restore sinus rhythm in 80% of patients presenting with permanent atrial fibrillation. In another study, microwave and unipolar radiofrequency produced equivalent results (80% freedom from AF at 1 year) when used to create the Cox-Maze III lesion set [39].

The most extensive experience has been with dry unipolar radiofrequency devices. Analysing 16 studies that employed this method for ablation, Khargi and colleagues [40] found that AF has been eliminated in an average of 78% of patients with permanent AF. The success rate ranged from 42 to 92%.

Stulak et al. [41] analysed data from 56 patients who underwent the bipolar radiofrequency (RF) ablation lesions to both atria using the Cox-Maze III incision map. Results from this study showed that the use of RF ablation was associated with significantly less freedom from AF both at hospital discharge and after 15 months of followup. They were 5 times more likely to be in AF on followup. However, the use of RF while performing concomitant surgery may

simplify the procedure, but with a lower chance of treating AF.

**4.5. Minimally Invasive Procedures.** The surgical treatment of atrial fibrillation has evolved further with time and has become technically simpler and faster with the advent of new ablative technologies. Complete endoscopic ablation with microwave energy has been performed with good success and few complications. Pruitt and colleagues [42] studied fifty patients with atrial fibrillation (33 paroxysmal and 17 permanent) who underwent thoracoscopic or robotic-assisted off-pump epicardial microwave ablation. Those investigations reported no perioperative death, a mean length of stay of 4 days, and a 79.5% (35 of 44 patients) success rate overall, with much better cure rates in paroxysmal disease (93.5%) than in permanent disease (69.2%). In 5 patients (10.0%) microwave ablation and subsequent electrophysiology intervention failed and a Cox-Maze III operation was performed to achieve cure or sinus rhythm.

In another study, Beyer and colleagues [43] performed a multicenter study of 100 patients with atrial fibrillation (39 paroxysmal, 29 persistent, and 32 permanent) who underwent bilateral minithoracoscopic, video-assisted, pulmonary vein ablations using bipolar radiofrequency, ganglionic mapping and ablation, and LAA resection. The mean operative time was 253 minutes, and the mean length of stay was 6.5 days. Results showed that there was an 86% overall success rate (93% paroxysmal, 96% persistent, and 71% permanent), 62% discontinuation of antiarrhythmic drugs, and 65% discontinuation of anticoagulation. However, there was a 13% rate of complication (pacemaker implantation, phrenic nerve injury, postoperative hemothorax, and transient ischemic attack) over a mean follow-up time of 13.6 months.

There are many promising innovations using minimal-access procedures for standalone and concomitant AF. It is prudent to say that within a few years, surgeons will be performing a number of surgical ablations with minimal complexity and maximum effectiveness, using port-accessed, video-assisted, and robot-assisted surgical techniques and specialized navigation instruments.

## 5. Conclusion

There are three epidemics of cardiovascular disease in the 21st century: atrial fibrillation, congestive heart failure, and the metabolic syndrome. AF is common in patients presenting for cardiac surgery. If it is left untreated, it increases morbidity and mortality. Therefore, one should consider surgery for AF in those patients.

One of the most significant obstacles facing the widespread adoption of surgical approaches is the lack of large controlled studies and trials that evaluate the different techniques and methods for surgical ablation of AF. In addition, further understanding of the fundamental electrophysiological mechanism of AF will aid in finding new approaches and a cure for this arrhythmia. AF must be targeted quickly because the longer the patient is in AF, the harder it becomes for him/her to revert back to sinus rhythm, “AF begets AF.”

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## Review Article

# Cryoballoon Catheter Ablation in Atrial Fibrillation

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Pulmonary vein isolation with catheter ablation is an effective treatment in patients with symptomatic atrial fibrillation refractory or intolerant to antiarrhythmic medications. The cryoballoon catheter was recently approved for this procedure. In this paper, the basics of cryothermal energy ablation are reviewed including its ability of creating homogenous lesion formation, minimal destruction to surrounding vasculature, preserved tissue integrity, and lower risk of thrombus formation. Also summarized here are the publications describing the clinical experience with the cryoballoon catheter ablation in both paroxysmal and persistent atrial fibrillation, its safety and efficacy, and discussions on the technical aspect of the cryoballoon ablation procedure.

## 1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age [1]. Pulmonary vein (PV) isolation with catheter ablation is one of the primary treatments for symptomatic AF refractory or intolerant to antiarrhythmic medications [1]. In some cases, it may be even appropriate to perform AF ablation as first-line therapy, particularly in selected symptomatic patients with heart failure and/or reduced left ventricular ejection fraction [2]. The main goal in catheter ablation is complete electrical isolation of the PVs, and therefore the success of the procedure and the reduction of procedure-related complications require careful identification of the PV ostia and application of ablation to the PV antra.

Currently radiofrequency (RF) energy is the most commonly used energy source for ablation. Many studies demonstrated the efficacy of RF energy for the treatment of AF. However, this form of energy is associated with various complications including thromboembolic events, PV stenosis, and atrio-esophageal fistula [3]. Thus, new energy sources have been investigated for the treatment of AF. These include cryothermal energy, ultrasound, and laser [4]. Recent clinical and preclinical studies demonstrated that the cryothermal energy application using a balloon catheter for PV isolation is an effective treatment for AF [5, 6].

The purpose of this paper is to review the current literature for better understanding of the utility of cryoablation

for the treatment of patients with AF. The literature was searched in PubMed from 1950 to February 2011 with the keywords “atrial fibrillation,” “cryosurgery,” and “catheter ablation” published in English. A total of 100 references were found. All full-text articles and their references were reviewed and included in this paper if they were relevant to our presentation.

## 2. Effects of Cryothermal Energy at the Cellular Level

Cryothermal energy causes progressive necrosis in the absence of significant alteration of tissue structure at thaw. The effect of ablation on the cellular ultrastructure has been evaluated in studies using a cryoprobe cooled to  $-60^{\circ}\text{C}$  with expanding nitrous oxide [7]. Ice crystals were observed to form inside the cells during ablation, with a resulting cell damage that is osmotic rather than mechanical [7]. Micro-circulatory changes have also been described leading to tissue necrosis. Acute changes in subcellular organelle structure and mitochondrial destruction occur in 1 minute at  $-70^{\circ}\text{C}$ . The mitochondria appear enlarged, with decreased matrix density and disrupted cristae. Striking depletion of glycogen stores takes place within 1 hour of thaw. Subsequent changes up to 10 hours after thaw are most notable for progressive mitochondrial damage. Then, the hemorrhagic and inflammatory phase starts and results in fibrosis. The cryothermal

energy lesion formation can be divided in three sequential stages which are the freeze/thaw phase, the hemorrhagic-inflammatory phase, and the replacement fibrosis phase. The resulting lesions are minimally thrombogenic, have sharp well-demarcated margins, and exhibit minimal tissue disruption and preserved basic underlying tissue architecture [8, 9]. Thus the histopathologic changes of cryoablation are likely to be associated with low arrhythmogenic potential.

### 3. Clinical Application of Cryoablation

Cryothermal energy has been used in treatment of cardiac arrhythmias for the past 3 decades, especially in supraventricular arrhythmias. Cryoablation was performed as early as 1977 to the atrioventricular (AV) conduction system [10]. Harrison et al. studied cryoablation using a hand-held nitrous oxide-cooled cryogenic probe in 20 dogs and subsequently in three patients with drug-resistant, life-threatening supraventricular tachycardias [10]. In the same year accessory pathway elimination by cryoablation was demonstrated by Gallagher et al. [11]. Since then, numerous experimental and clinical studies have evaluated the efficacy and safety of cryoablation [4, 5, 9, 12–14].

A multicenter clinical trial in patients with AV nodal reentry tachycardia (103 patients), AV reentrant tachycardia (51 patients), and AF (12 patients) demonstrated that cryoablation is a safe and effective strategy for the treatment of supraventricular arrhythmias [12]. Catheter-based cryoablation was found to be a safe alternative to RF ablation for slow pathway modification, accessory pathway termination, and AV junction ablation. Acute procedural success was achieved in 83% of the overall group, and long-term success after 6 months was 91%. Cryomapping (cooling the catheter tip to  $-30^{\circ}\text{C}$ ) successfully identified ablation targets in the majority of the patients, and the electrophysiologic effects of cryomapping were reversible within minutes in 94% of the attempts.

Also, a prospective, randomized trial in patients with recurrent narrow QRS-complex tachycardia suggestive of AV nodal reentry tachycardia compared cryoablation with RF ablation and showed a procedural success rate of 91% in the RF group and 93% in the cryoablation group [13]. The median number of cryothermal applications was significantly lower than the number of RF applications. Both fluoroscopy and procedural times were comparable. No cryoenergy-related complications were observed, and no permanent AV conduction block occurred. Long-term clinical success was comparable in both groups.

Currently cryoablation is used to treat various forms of ventricular and supraventricular arrhythmias including AV nodal reentry tachycardia, AV reentrant tachycardia, atrial flutter, and focal atrial tachycardia [12–18]. Compared to RF ablation, cryoablation has been associated with lack of pain during energy delivery, homogenous lesion formation, less destruction to surrounding vasculature, preserved tissue integrity, and lower risk of thrombus formation [5–9, 12–14]. Lesion reversibility is another advantage of cryoablation over RF energy and is useful for ablation of accessory

pathways in proximity to the conduction system [12–15]. Moreover, cryoablation can be applied within venous structures, like the coronary sinus and the middle cardiac vein with less risk of thrombosis compared to RF ablation [14, 19]. It has been shown that cryoablation in the coronary sinus within 2 mm of the left circumflex artery produces myocardial lesions similar to RF ablation with lower risk of coronary artery stenosis [19].

The absence of endothelial disruption with cryoablation results in less thrombogenicity and may offer an opportunity for improved safety during ablations in the left side of the heart [5–9]. This may be important when large areas of the endocardium are ablated such as in AF ablation procedures. All these characteristics of cryoenergy, in addition to the ability to use it with a balloon, make it an attractive source of energy for PV isolation.

### 4. Balloon-Based Ablation Catheter

Point-to-point ablation using a focal catheter for PV isolation is associated with technical difficulties and requires experienced operators with high level of skills. Pulmonary vein isolation using a focal cryocatheter has been studied and was found to be associated with long procedure times [20]. The cryoballoon catheter was designed with the aim of facilitating PV isolation [4–6, 21].

### 5. Cryoballoon for Pulmonary Vein Isolation

*5.1. Ablation Technique.* Currently only one balloon design is available for clinical use (Medtronic Inc, Minnesota, Minn). This system includes an over-the-wire balloon catheter which is cooled using nitrous oxide ( $\text{N}_2\text{O}$ ) [4–6, 22–27]. The balloon shaft size is 10.5 F and has a deflection mechanism. It is introduced into the left atrium using a 14 Fr steerable sheath. The shaft has a central lumen that can accommodate a wire for support and also used for contrast and saline injection.

The wire is used to engage the vein first. The balloon is inflated outside the vein and advanced over the wire to occlude the vein (Figure 1). Obtaining a complete occlusion is crucial for successful isolation. An incomplete occlusion will lead to flow around the balloon and prevents the temperature from reaching low enough levels necessary for adequate ablation. A complete occlusion is typically confirmed by injecting contrast in the lumen at the balloon tip. Once occlusion is confirmed, the contrast is flushed using saline and freezing is started. If successful, a dip in the temperature curve is observed indicating a better occlusion. Lesions are usually 240–300 sec long and PV isolation is usually achieved with one lesion in most patients [22–24]. Most operators apply one additional lesion after isolation.

Currently, two sizes of the cryoballoon catheter are available, 28 mm and 23 mm diameter. It is advisable to use a 28 mm balloon regardless of the size of the vein in order to reduce the risk of complications such as PV stenosis and phrenic nerve injury. A quadripolar catheter is usually positioned in the superior vena cava for continuous

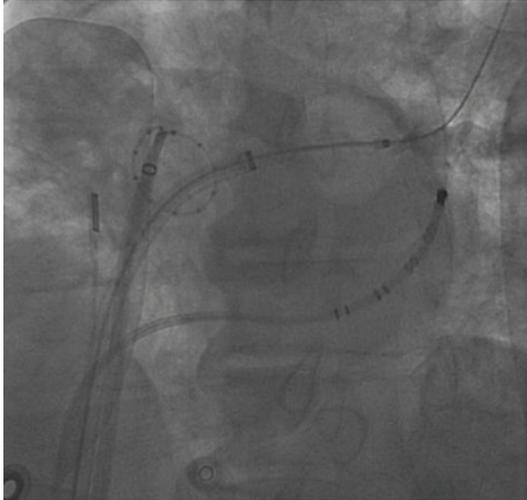


FIGURE 1: Cryoballoon catheter placement for pulmonary vein isolation with fluoroscopic A. Fluoroscopic appearance (30° left anterior oblique view) of the cryoballoon inflated in a left superior pulmonary vein. The guidewire was advanced in a pulmonary vein branch, and the occlusion is confirmed by the absence of flow during contrast injection in the vein. The circular mapping catheter is placed at the ostium of the right superior pulmonary vein. A multipolar catheter in the coronary sinus and an intracardiac echocardiography catheter in the mid-right atrium are visible.

phrenic nerve stimulation during cryoablation of right PVs. Intracardiac echocardiogram and color Doppler can be used to confirm occlusion and the site of gaps if present (Figure 2). Recently, the use of transesophageal echocardiography with color Doppler was described allowing real-time visualization of the cryoballoon during ablation [28].

After ablation, PV isolation is assessed using a circular mapping catheter inserted in the left atrium via a separate transeptal puncture [22, 25, 29]. A small caliber circular mapping that can be advanced in the central lumen instead of the wire can also be used to confirm isolation.

In some patients technical challenges can be encountered leading to the inability to obtain a complete occlusion. Two maneuvers can be helpful if complete occlusion cannot be achieved by advancing the balloon. The first involves trying to engage a different branch with the wire. This can provide a better alignment of the catheter shaft with the axis of the PV. The second maneuver is the “pull-down” technique [24]. This can be useful when a gap is present at the inferior border of the vein and cannot be closed despite advancing the balloon. With this technique, freezing is started despite the presence of the gap. At about 60–90 sec into the freeze, the balloon and the sheath are both pulled down gently in order to close the gap at the inferior portion of the vein. This should be done very carefully because of the risk of severe vascular damage if excessive force is applied. If occlusion and isolation cannot be obtained despite these maneuvers, a standard point-by-point ablation catheter can be used for completion.

The sites of PV reconnection have been analyzed in some studies [24, 29–31]. The inferior border of the veins as well

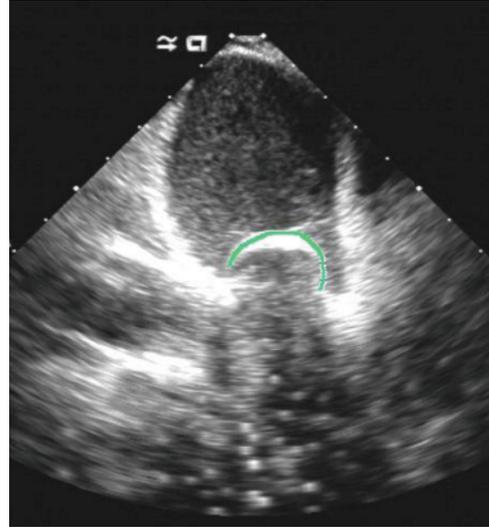


FIGURE 2: An intracardiac echocardiographic image demonstrates total occlusion of left superior pulmonary vein by cryoballoon catheter.

as the ridge between the left atrial appendage and the left PV was found to be the sites where most reconnections occurred. This is likely to be the result of sharp catheter angulation with loss of central cryoballoon alignment with the axis of the PVs.

*5.2. Clinical Results: Efficacy of the Procedure.* To date over 10,000 PV procedures have been performed worldwide. There have been many publications describing the clinical experience with the cryoballoon in both paroxysmal and persistent AF [22–41].

An early report by Van Belle and colleagues described 57 consecutive patients with paroxysmal AF who underwent cryoballoon ablation [22]. Eighty-four percent of the targeted PVs were successfully isolated using the cryoballoon and the rest required a standard cryocatheter to achieve isolation. A daily monitoring of rhythm demonstrated a significant reduction in AF burden. Klein et al. reported the result of cryoballoon ablation in 21 patients with symptomatic paroxysmal AF in 2008 [26]. A total of 95% of PVs were isolated, and 86% of the patients remained free of AF after 6 months based on periodic holter monitoring. Subsequently, Neumann et al. evaluated the efficacy of cryoballoon ablation in 293 patients with paroxysmal and 53 patients with persistent AF [23]. Ninety-seven percent of the PVs were isolated with either cryoballoon alone or in combination with a standard cryocatheter. Maintenance of sinus rhythm was reported in 74% and 42% of the patients with paroxysmal and persistent AF, respectively. In a recent study by Ahmed et al. [24], the permanence of PV isolation after cryoballoon ablation was tested in 12 patients with paroxysmal AF. Eighty-eight percent of PVs remained isolated at 8–12 weeks after the initial procedure.

The most comprehensive result regarding the efficacy and safety of the cryoballoon catheter ablation for the

treatment of AF was obtained from the STOP-AF trial [32, 33]. This trial randomized patients with paroxysmal drug-refractory AF in a 2:1 fashion to either PV isolation with cryoballoon ablation or antiarrhythmic drug therapy. Balloon-only isolation of PVs was achieved in 90.8%, and the overall procedural success ( $\geq 3$  PVs isolated) was achieved in 98.2% of the patients. Nineteen percent of the patients needed a repeat cryoablation procedure within the 90-day blanking period. The success rate at 12-month followup was 69.9%.

The use of cryoballoon for PV isolation in patients with persistent AF has been associated with high rates of arrhythmia recurrence [23, 34, 35]. This is not surprising knowing that the left atrial substrate and not only the PVs play a role in AF maintenance in this subgroup of patients. A study from our group investigated the combined use of cryoballoon PV isolation and conventional RF ablation of areas of complex fractionated electrograms in 22 patients with persistent AF [27]. After a single procedure, 86% of patients were AF-free at 6-month followup.

In this study the followup was performed in most patients using implantable loop monitors allowing automatic detection of asymptomatic AF. In addition to AF-free survival, AF burden reduction was also analyzed in some studies. Van Belle et al. studied 144 patients with symptomatic AF refractory to antiarrhythmic drugs who underwent cryoballoon PV isolation [36]. Followup was performed using daily transtelephonic ECG monitoring, 24 h Holter-ECG, and an arrhythmia-focused questionnaire to document AF. After ablation, AF burden was reduced from 26% to 9%.

**5.3. Complications of Cryoballoon Catheter Ablation.** Phrenic nerve palsies (PNP), PV stenosis, and other complications have been reported with cryoballoon PV isolation [22–41]. In the STOP AF study, PNP was reported in 29 out of 259 procedures (11.2%) [32, 33]. Of these, only four (13.8%) patients had persistent PNP at 12 months. PNP can occur with isolation of the right superior and less commonly the right inferior PV.

Another important procedural complication with the cryoballoon is PV stenosis. Although earlier studies showed no significant incidence of PV stenosis following cryoballoon ablation, STOP-AF trial demonstrated 3.1% risk of PV stenosis in its study population [32, 33]. This complication is likely associated with ablation of the tubular portion of the vein. As a result, it is believed that the use of the 28 mm balloon can reduce this complication because this larger balloon is less likely to be positioned inside the vein during ablation [25]. For the same reason, it is believed that the use of the larger balloon will carry a lower risk of PNP.

There are no reports of atrioesophageal fistula associated with the use of the cryoballoon. The effect of cryoballoon PV isolation on the esophagus has been studied [37]. Luminal esophageal temperature was significantly decreased ( $>1$  degrees C) in 62 of 67 (93%) patients, and reversible esophageal injuries were seen in 17% of patients. However, no atrial-esophageal fistula was documented and the follow-up endoscopy confirmed healing of all ulcers.

Other procedure-related complications with the use of the cryoballoon are similar to RF ablations including stroke, pericardial effusion or tamponade, femoral vein access complications, and cerebral embolism [22–41].

**5.4. Comparison with Conventional Radiofrequency Catheter Ablation.** Both conventional focal RF ablation and cryoablation are used for PV isolation and both are shown to be effective [1–3, 22–44]. Recent studies compared clinical outcome of cryoballoon ablation for PV isolation with RF ablation in regards to the safety and the efficacy of the procedure [30, 35, 42].

Linhardt et al. demonstrated in a case-control study of 40 patients with paroxysmal atrial fibrillation that cryoballoon ablation has similar success rate to RF ablation in addition to similar procedure and fluoroscopy times [42]. Kojodjojo et al. studied the efficacy of a strategy using a large cryoballoon to perform antral PV isolation in 124 patients with paroxysmal and persistent AF [35] and compared it with RF ablation. At one-year followup, 77% of paroxysmal and 48% of persistent AF patients remained free from AF after a single procedure. In the RF group 72% of the patients with paroxysmal remained free of AF. The procedural and fluoroscopic times with cryoablation were shorter than RF ablation. A recent study from Kühne et al. confirmed the shorter procedure duration with cryoablation compared to RF ( $166 \pm 32$  versus  $197 \pm 52$  minutes) [30]. In this study, a total of 55 patients with paroxysmal AF were studied: 25 patients underwent PVI using a 28-mm cryoballoon and 25 patients using an open-irrigation RF catheter. The number of procedures was not different in the 2 groups ( $1.2 \pm 0.4$  in cryoablation versus  $1.3 \pm 0.6$  in RF ablation) with a success rate at one-year followup of 88% in the cryoballoon group and 92% in the RF group. Another study, the Freeze AF trial, is being planned to compare cryoballoon catheter ablation with open-irrigation RF ablation in a randomized clinical study including 244 patients with paroxysmal AF [43].

## 6. Conclusions

Cryoballoon catheter ablation is a safe and effective technique for PV isolation to treat paroxysmal AF. Overall success rate in persistent AF is lower. Potential procedural complications related to cryoballoon ablation include PNP and PV stenosis as well as rare neurological complications.

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## Review Article

# Strategies in the Surgical Management of Atrial Fibrillation

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Atrial fibrillation (AF) is associated with substantial morbidity, mortality, and economic burden and confers a lifetime risk of up to 25%. Current medical management involves thromboembolism prevention, rate, and rhythm control. An increased understanding of AF pathophysiology has led to enhanced pharmacological and medical therapies; however this is often limited by toxicity, variable symptom control, and inability to modulate the atrial substrate. Surgical AF ablation has been available since the original description of the Cox Maze procedure, either as a standalone or concomitant intervention. Advances in novel energy delivery systems have allowed the development of less technically demanding procedures potentially eliminating the need for median sternotomy and cardiopulmonary bypass. Variations in the definition, duration, and reporting of AF have produced methodological limitations impacting on the validity of interstudy comparisons. Standardization of these parameters may, in future, allow us to further evaluate clinical endpoints and establish the efficacy of these techniques.

## 1. Introduction

Atrial fibrillation (AF) is associated with significant morbidity and mortality in both medical and surgical patients. Results from the Framingham Heart study found AF to be associated with an overall lifetime risk of 1 in 4 adults aged 40–95 years or 1 in 6 of those without previous myocardial infarction or congestive cardiac failure [1]. Coronary artery bypass grafting alone has been associated with an incidence of AF reaching 30% in multicentre observational studies [2, 3] and may be significantly higher following valvular surgery [4]. More importantly, postoperative AF has been found to triple the risk of death from cardiac causes and quadruple the risk of stroke and other disabling embolic events [2].

The original “corridor” procedure for the treatment of AF was described by Guiraudon in 1985, but for a number of reasons was soon superseded by the “Maze” procedure as described by Cox et al. in 1991 [5, 6]. His work outlined a series of “cut and sew” lesions which aimed to direct electrical impulses in one direction through the atrium, disrupting the macro reentrant circuits which allow the

development and propagation of AF. This procedure, whilst effective, was not without its complications, and the resultant inability to mount a tachycardic response to exercise and left atrial dysfunction led to two further adaptations of this procedure culminating in the Cox Maze III lesion set [5]. These modifications resulted in an improvement in the rates of postoperative sinus rhythm and long-term sinus node function, leading to fewer pacemaker implantations after surgery. Furthermore, improved long-term atrial transport function, low rates of arrhythmia recurrence, and a low incidence of thromboembolic complications could support the application of the maze procedure in patients where nonsurgical therapy has failed.

However, the maze procedure has been limited to a few specialist centres due to its technical difficulty and a lack of widespread experience. Its requirement for median sternotomy and cardiopulmonary bypass (CPB) also fuelled the search for an alternative, less invasive technique. Surgical ablative devices and modifications to the lesion set now allow, in some cases, for a minimally invasive, off-pump, beating heart approach. However, it is important to note that at the present time these techniques may not attain a similar

level of long-term freedom from AF as the classical Maze III procedure [7].

This review describes the evolution of AF surgery, from “cut and sew” to ablative techniques, using novel energy delivery systems. We discuss its role both as a standalone and concomitant procedure and highlight the current indications and outcomes for the most common techniques described in the literature.

## 2. Corridor Procedure

Originally proposed by Guiraudon in 1985, the corridor procedure isolated the atria, allowing only a single conduction pathway between the sinoatrial (SA) and atrioventricular (AV) node, thereby re-establishing a regular ventricular rhythm [8]. The procedure achieved good rates of freedom from AF, however isolation of the atria from the SA node allowed the remaining atria to continue to fibrillate and did not restore atrial transport function. The thromboembolic risk of AF therefore remained and, as such, the procedure has since been superseded by the “cut and sew” Maze.

## 3. The “Cut and Sew” Maze

Cox et al. described the original maze procedure in 1991 [6, 9]. Between September 1987 and 1994, a total of 123 patients were included in his trial. The first 32 patients underwent the Cox-Maze I procedure, however, at late followup several limitations were revealed. The first of these was the inability to generate an appropriate sinus tachycardia in response to exercise. This was felt to be a consequence of placing the surgical incision at the junction of the superior vena cava (SVC) with the right atrium (RA) too anteriorly. This incision was removed in Maze II procedure; however, several other modifications necessary to maintain the efficacy of Maze I resulted in significantly more technical difficulty with this procedure. The left-sided exposure with Maze II was very limited and required division of the SVC. Furthermore, it became necessary to patch the SVC with autologous pericardium to prevent stenosis. Additionally, Maze II resulted in a similar degree of left atrial (LA) dysfunction as Maze I. Division of Bachmann’s bundle during both procedures markedly slowed inter-atrial conduction, in turn causing synchronous contraction of the left atrium and ventricle, eliminating the LA “kick”. Further modification to the lesion set therefore culminated in Maze III procedure, which both eliminated the need for an SVC patch and improved left-sided exposure [5].

The “cut and sew” Maze III procedure has been associated with good long-term results, in Cox’s original study 93% of patients remained free from AF or flutter recurrence at 8.5-year followup and all recurrences were successfully cardioverted with one antiarrhythmic drug [10]. Similarly encouraging results have been published by other groups (Table 1).

Despite its efficacy at terminating AF, several aspects of the Maze III procedure have limited its uptake to a few specialist centres. Primarily this reflects the technical difficulty

of the procedure and the requirement for median sternotomy and cardiopulmonary bypass. Many surgeons feel that such an approach is too invasive for the sole treatment of cardiac arrhythmia, limiting it to patients undergoing concomitant coronary or valve surgery. In addition, even with the Maze III procedure, the early and late effects on atrial mechanical function have raised concern [11]. However, as yet the long-term effects of reduced atrial contraction on potential thromboembolic complications have not been studied in depth and remain a focus for further research.

## 4. Surgical Ablation and the Cox Maze IV

The introduction of novel energy delivery systems (Table 4) allowed for the development of Maze IV procedure as described by Damiano and Gaynor in 2004 [12]. This provided the potential advantages of a reduction in postoperative morbidity, without reducing efficacy or completeness of the lesion set. During Maze IV procedure, whilst both left and right arteriotomies are performed surgically, radiofrequency ablation reproduces many of the surgical incisions of Maze III procedure with additional cryoablation added to complete the lesion set to the mitral annulus (Figures 1(a) and 1(b)). In their original study, Gaynor and colleagues reported a 93.1% freedom from AF at 6 months but admitted that followup at the time of publication was insufficient to allow comparison to Maze III lesion set [13]. Since this time various permutations on Maze IV lesion set have been implemented, these are summarised in Table 3.

## 5. Radiofrequency Ablation

In the attempt to achieve a less invasive technique capable of producing results comparable to the cut and sew Maze III, procedure the use of radiofrequency (RF) ablation has grown rapidly in popularity. RF techniques are capable of producing a continuous and transmural lesion set in conjunction with a reduction in both operating time and technical difficulty [14]. Whilst RF ablation is safe, it should be carefully applied, avoiding direct contact with the pulmonary veins (PV), to prevent PV stenosis. The risk of intercavity thrombus formation and the potential for collateral oesophageal or circumflex injury should also be considered and bipolar devices used where possible [14].

Along with the advent of this innovation came multiple changes to the lesion set creating difficulties in evaluating its results against those of the “cut and sew” Maze III (Table 2). In their multicentre study closely replicating Maze III lesion set, Raman et al. achieved excellent results with concomitant RF ablation reporting 84% freedom from AF at 3 months, 90% at 6 months, and 100% at 12 and 18 months [15]. Notably however, only 15 of the 110 patients had reached 12-month followup at the time of publication and following the procedure all patients were kept on a regimen 200 mg amiodarone for 6 months unless contraindicated.

Pulmonary Vein Isolation (PVI) alone has been performed by a number of groups and has produced good results in paroxysmal AF; however the results in longstanding

TABLE 1: Freedom from AF at final follow up after “cut and sew” maze procedure.

Study	Type of procedure	Number of patients	Duration of followup (years) (Mean $\pm$ SD)	Freedom from AF at final followup (%)
Cox et al., 1996 [10]	Lone maze	178	8.5	93
Lönnnerholm et al., 2008 [11]	Lone maze	52	4.7 $\pm$ 1.0	86.5
Prasad et al., 2003 [75]	Lone maze	98	5.4 $\pm$ 3.0	79.6 (no AAD*)
	Concomitant	86	5.4 $\pm$ 2.7	95.9 (with AAD) 73.4 (no AAD) 97.5 (with AAD)
Ad et al., 2009 [59]	Lone Maze	33	9.8 $\pm$ 7.7	91.0
	Lone and Concomitant maze	76	9.8 $\pm$ 7.7	84.0
Stulak et al., 2007 [7]	Concomitant	56	0.7 (2.75–7)**	92.0
Gaynor et al., 2005 [13]	Concomitant	253***	6.1 (0.5–15.5)**	92.2

\*AAD: Anti Arrhythmic Drugs, \*\*median (range), \*\*\*includes 33 Maze I, 16 Maze II, 197 Maze III, and 30 Maze IV.

TABLE 2: Summary of results obtained by radiofrequency ablation.

Study	N	Lesion set	Type of AF and aetiology	Concomitant or lone surgery	Mean followup $\pm$ SD (months)	Freedom from AF at mean followup (%)	Overall mortality at last f/u (%)
Srivastava et al., 2008 [16]	160	Overall					
	40	Biatrial	Persistent >3 months Rheumatic	Concomitant	40	62.5	10
	40	LA only				57.5	7.5
	40	PVI				67.5	10
	40	None				20.0	5
Wang et al., 2009 [17]	299	Overall				85.0	2.3
	149	LA+ cavotricuspid	Permanent	Concomitant	28 $\pm$ 5	85.2	1.3
	150	Biatrial				84.1	4.7
Chiappini et al., 2004 [18]	40	CM III	Chronic	Concomitant	16.5 $\pm$ 2.5	88.5 at last f/u	7.5
Beukema et al., 2008 [19]	285	Modified Maze (biatrial)	Permanent	Concomitant	43.6 $\pm$ 25.4	57.1 at last f/u	27.4%
Topkara et al., 2006 [20]	168	Endocardial 82.9% epicardial 17.1%. Variable lesion set	Paroxysmal Persistent Lone	Concomitant and Lone	Last f/u 24 months	75.3	Not specified for RF only

AF have been suboptimal with significantly higher recurrence rates reported [31–34]. Several small studies report freedom from AF after RF PVI ranging from 87% at 6 months [31] and 71% at 3.3-year mean followup [35]. When combined with left atrial appendage (LAA) excision, ligament of Marshall (LoM) or ganglionic plexus ablation, PVI has yielded rates of freedom from AF ranging from 87–87.5% at 6 months [31, 32] and 65% at 1-year follow up [36].

As with all ablative techniques, these interstudy variations in success rate must be considered cautiously whilst taking into account the criteria for diagnosis and reporting of AF. The move from telephone questionnaire and one-off ECGs to long-term monitoring after the publication of the heart rhythm society (HRS) consensus guidelines may have influenced reporting of AF recurrence rates. Incompletely transmural lesions may also explain the higher recurrence

rates seen with RF over the “cut and sew” technique. Innovations such as cooled tip and bipolar electrodes have allowed for greater efficiency with RF ablation; however, confirmation of transmuralty remains a problem. Factors related to the electrode (duration of application, contact with tissue), the myocardial tissue (tissue convection and conductance), and the surrounding environment (convective cooling due to blood flow) all play an important role [14]. As such, it is difficult to produce uniform settings for each instrument and the need for feedback to confirm transmuralty remains important. Whilst some of these groups report the use of impedance measurements or entry and exit stimulation as confirmatory mechanisms [36, 37] others lack any form of feedback [31, 35, 38]. It is also possible that even in the presence of complete transmuralty early postoperative reinnervation of the myocardium may

TABLE 3: Summary of results from alternative ablative technique.

Study	Modality	n	Lesion set	Approach	Lone or concomitant	Type of AF and aetiology	Mean f/u $\pm$ SD (months)	Freedom from AF	Mortality at last f/u
Vicol et al., 2008 [21]	Microwave	41	Left atrial (endocardial)	Median sternotomy	Concomitant	Permanent	5.37 $\pm$ 0.91	39.3% at 5 years	17%
Pruitt et al., 2007 [22]	Microwave	100	PVI + LAA line	Thoracoscopic	Lone	Paroxysmal (64%) Persistent (11%) Permanent (25%)	23.1	42% at last followup	3%
Topkara et al., 2006 [20]	Microwave	85	PV lesion 98.8%	Median sternotomy	Concomitant 99% Lone 1%	Persistent	16.8 $\pm$ 12	66.7% at 12 months	3.5% 30 day mortality
			Mitral annulus lesion 68.2%	Minimally invasive 21.2%					
Radiofrequency	120	LA ablation 32.9%	Median sternotomy	Concomitant 99% Lone 1%	Persistent	9.6 $\pm$ 7.2	71.4% at 12 months	3.4% 30 day mortality	
		Flutter lesion 15.3%	Median sternotomy						
		PV lesion 94.2%	Minimally invasive 5.0%						
		Mitral annulus lesion 64.2%	Minimally invasive 5.0%						
Knaut et al., 2006 [23]	Microwave	59	PVI + mitral annulus (Allessie's lesion set, endocardial)	Median sternotomy	Concomitant	Permanent	—	52% at 1 year	11.5% at 1 year
			PV box lesion + LAA line (endocardial)	Minimally invasive	74% at 1 year				
Molloy 2005 [24]	Microwave	29	Left Atrial + Ligament of Marshall (epicardial)	Median sternotomy	Concomitant	Permanent 86% Paroxysmal 14%	315 days	82% at mean followup	3.6%
Hurlé et al., 2004 [25]	Microwave	9	Biatrial (endocardial)	Median sternotomy	Concomitant	Permanent	5.2 $\pm$ 3.3	62.5% at mean followup	11%
Wisser et al., 2004 [26]	Radiofrequency	29	Biatrial (endocardial)	Median sternotomy	Concomitant	Permanent	24.2 $\pm$ 1.3	* 81% at 12 months	8.7%
Mitnovetski et al., 2009 [27]	High frequency ultrasound	10	Epicardial	Median sternotomy	Concomitant	Permanent 71% Paroxysmal 29%	9 (3–13)	75% at mean followup 78% at mean followup	7.1%

TABLE 3: Continued.

Study	Modality	n	Lesion set	Approach	Lone or concomitant	Type of AF and aetiology	Mean f/u ± SD (months)	Freedom from AF	Mortality at last f/u
Topkara et al., 2006 [20]	Microwave	143	PV lesion 96.8% Mitral Annulus 48.7% LAA 33.0%	Median sternotomy	Concomitant 96.8% Lone	Persistent 75.8% Paroxysmal	Recorded data at 3, 6, 12, and 24 months follow up	75.3%	4.9% postoperative
	Radiofrequency	169	Flutter lesion 17.7% PV box lesion only 41.9%	Median sternotomy	Concomitant 96.8% Lone	Persistent 75.8% Paroxysmal	Recorded data at 3, 6, 12, and 24 months follow up	73.8%	4.9% postoperative
	Laser	27	(82.9% endocardial; 17.9% epicardial)					71.4%	
Baek et al., 2006 [28]	Cryoablation	93	Cox Maze III	Median sternotomy	Concomitant	Chronic	26.6 ± 15.2	84%	3.2%
		77	Kosakai-Maze					86% at last follow up	1.3%
Gillinov et al., 2006 [29]	Cryoablation	31	PVI alone						
		80	PVI + connecting lesions	Median sternotomy	Concomitant	Paroxysmal	Median 13.5	Prevalence of AF of flutter 9% at 1 year f/u	8.5% at 6 months
		41	Cox Maze III						
Chen et al., 2001 [30]	Cryoablation and Radiofrequency	13	Maze II, III					73% at 3 months	15.4%
		48	Maze IV	Median Sternotomy	Concomitant	Chronic	3 Months	81% at 3 months	2.1%
		58	No Maze (Control)					11% at 3 months	6.9%

\* Sinus Rhythm: Microwave—59.0% at 12 months; 60.0% at 24 months; Radiofrequency—57.1% at 12 months.

TABLE 4: Comparison of ablative modalities.

	Transmurality	Endocardial	Epicardial	Advantages	Potential complications	Use outside research and clinical trials	Accuracy (width/depth ratio)
Radiofrequency	Variable improved with bipolar devices	Yes	Yes	Able to produce fast and effective lesion set	Risk of inter-cavity thrombus formation, char formation, collateral damage to circumflex artery and oesophagus and PV stricture	Yes	Moderate
Cryoablation	Good	Yes	Yes	Preserves cellular architecture and capable of producing mitral and tricuspid isthmus lesions. Minimal collateral damage, able to produce well-demarcated lesion, adheres to myocardium to produce good contact with tissue, low risk of bleeding or perforation	Potential risk of coronary artery damage	Yes	Moderate
Microwave	Variable	Yes	Yes	Lower risk of thromboembolism, minimal char formation, and minimal collateral damage	Potential for circumflex artery damage	Yes	Good
High Frequency Ultrasound	Excellent	No	Yes	Advantage of fast, transmural epicardial lesions with theoretical potential to visualize wall thickness and perform tailor made lesion	Risk of collateral damage and perforation	No	Poor
Laser	Excellent	Yes	Yes	Able to produce fast, deep, and uniform lesions	Risk of crater formation and perforation	No	Poor

precipitate AF recurrence. In 2006, Kangavari and colleagues highlighted an upregulation of nerve growth factor (NGF) following RF ablation [39], potentially resulting in nerve sprouting and AF recurrence. Further work is now required to identify whether this phenomenon translates into a clinically significant effect.

## 6. Cryoablation

Cryoablative devices use argon and helium delivered under high pressure to producing cooling of  $-55$  to  $-60^{\circ}\text{C}$ . This initially results in cellular disruption which is followed by inflammation and fibrosis to produce a homogeneous, full thickness disruption to cellularity without causing stromal damage [14].

The results with cryoablation have been variable from 60% at 3.6-year followup [40] to 82.3% at 3.8-year followup [41]. With their more extensive lesion set, Funatsu et al. report a freedom from AF of 84.1% and 80.2% at 3- and 5 years, respectively [42]. These results can be seen to

be comparable to RF ablation, however outcomes of large directly comparative studies are still awaited [43].

Several advantages have been described with the use of cryoablation over other ablative techniques. The first of these is a visual confirmation of transmuralty provided by frosting along the ablation line. Secondly, by maintaining the integrity of vascularity and preserving collagen, less damage to the surrounding tissues has been reported [14]. Cryoablation also causes significantly less endocardial thrombus volume potentially reflecting the preservation of the endothelial cell layer. Additionally, cryoablation has practical benefits, technically enabling the surgeon to create an isthmus lesion from the pulmonary veins to the mitral annulus and allows an electrical isolation of the atrium that cannot easily be achieved with RF or microwave ablation.

## 7. Microwave Ablation

Microwave ablation produces a well-demarcated area of thermal injury and is not only capable of producing transmural

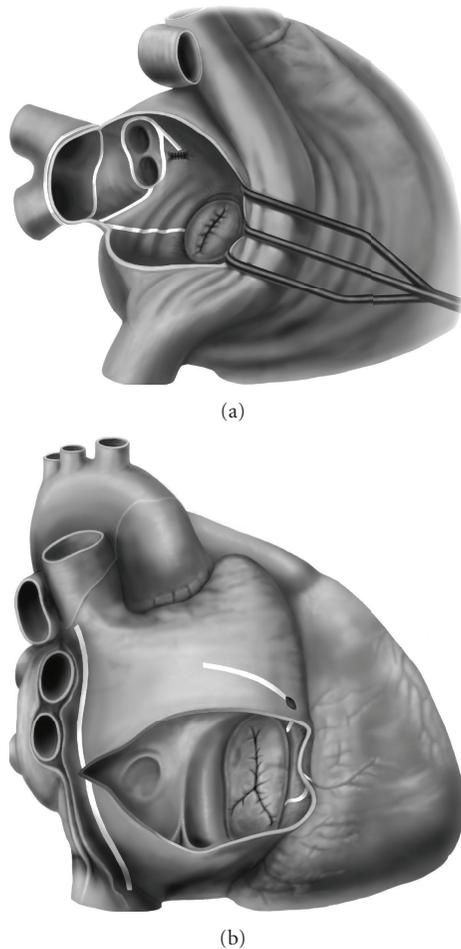


FIGURE 1: (a) Left atrial Maze III lesion set. (b) Right atrial Maze III lesion set.

lesions when applied to the epicardial surface but may be more easily applicable to minimally invasive techniques. However, the overall results for this new technology have been less encouraging (Table 3). Whether this is a reflection of the technology or the quality of lesion set is uncertain. Current data reflects a combination of LA and biatrial procedures, each with slightly different patterns of ablation and in different types of AF. In a trial of 41 patients, Vicoli and colleagues performed a series of LA endocardial ablations in patients with chronic secondary AF (>1 year) undergoing concomitant cardiac surgery via median sternotomy [21]. Whilst the 1-year freedom from AF was 80%, by a mean follow up of 5.37 years only 39% had long-term freedom from AF. Similarly, thoracoscopic studies have reported relatively high incidences of AF recurrence. Both Puritt [22] and Koistinen [44] combined a population of lone paroxysmal, persistent and permanent AF in their studies. Puritt reported freedom from AF to be 42% at long-term followup (mean 23.1 months) whereas Koistinen reported 59% at 1 year. A lack of homogeneity is clearly exemplified here in both patient selection and treatment strategies. Puritt's group performed PVI alone, ligating the left atrial

appendage (LAA) only when it was found to be enlarged, whereas Koistinen performed PVI with an LAA extension, ligating the LAA in 85% and including a right atrial and intercaval line in 25%. However, their published results reflect the group as a whole, and it is therefore impossible to identify the precise cause of such high rates of AF recurrence.

It is indeed possible that part of this explanation may arise from inadequacies in the technology itself. "Heat sink" secondary to poor contact with atrial tissue and the absence of a feedback mechanism may have resulted in inadequate transmural and incomplete disruption of reentrant circuits. Alternatively, these results may reflect a drawback in their study design. It is recognised that structural remodelling seen in longstanding AF makes PVI alone suboptimal and necessitates a more extensive lesion set of the kind described in the Maze III procedure. Furthermore, by limiting ablation lines to the LA, the potential for development of RA flutter or macro-reentrant circuits is not excluded, potentially explaining a degree of this recurrence. This data should therefore be interpreted with caution, calling for a more homogeneous approach to study design before definitive conclusions can be drawn.

## 8. High-Frequency Ultrasound Ablation

High-Frequency Ultrasound (HIFU) creates localised hyperthermic lesions and is capable of producing transmural lesions when applied epicardially. It is a relatively new ablative modality and as such current guidelines from the National Institute for Health and Clinical Excellence (NICE) only approve it for use in specially organised audit or research [45]. Current results are however encouraging, reporting a freedom from AF of 85% at 6 months [46, 47] and 86.2% at 18 months [48]. However, evidence of oesophageal and mediastinal injury has been documented following HIFU catheter ablation, with one group reporting a case of fatal atriioesophageal fistula reported at 31 days following this technique [49]. Whilst no such problems have been identified with concomitant HIFU ablation during other cardiac surgery a potential for collateral damage is recognised in the literature [45].

Despite these concerns, the theoretical possibility of combining the imaging benefits of ultrasound with ablative techniques could potentially produce an effective device which not only allows the surgeon to quantify atrial wall thickness and deliver a tailor made ablation, but also confirms transmural [14].

## 9. Laser Ablation

Laser ablation uses high-energy optical beams to create a narrow, well-demarcated, and nonarrhythmogenic thermal lesion [14]. Animal studies have demonstrated that laser ablation is able to produce rapid and histologically transmural lesions capable of electrophysiologically isolating the atrium [20]. Whilst there is a lack of large multicentre human trials in this modality, smaller studies have reported positive results. Hamman and coworkers examined 28 patients with

variable types of AF. They performed a limited left-sided lesion set in patients with paroxysmal AF but extended this to include right-sided lesions in those with persistent or permanent AF. At a mean followup of 18 months, 76% were free from all tachyarrhythmias. At present, no device-related complications have been reported in the above studies however, some potential concerns have been raised with this technology. Poor visibility of the scar necessitates careful monitoring of the path and extent of the lesion, and it should be remembered the excess heat produces the potential for crater formation, perforation, and tissue loss [14].

## 10. Thoracoscopic Maze Procedures

The invasive nature of median sternotomy combined with endocardial ablation, atriotomy, and cardiopulmonary bypass has historically limited the standalone surgical treatment of AF. Over the past decade, the development of flexible, epicardial ablative devices has allowed for the evolution of minimally invasive procedures, thereby offering a surgical strategy in symptomatic patients failing catheter ablation. By reducing surgical trauma, totally thoracoscopic approaches offer the advantage of improved postoperative recovery and a reduction in hospital stay. More recently, the application of robotic techniques may offer both improved surgical dexterity and increased visualization [50, 51].

However, early thoracoscopic techniques have been subject to a number of limitations. The use of a range of ablative modalities, as well as the variability and limited nature of the lesion set, has led to difficulties in interpretation of the overall results. Whilst freedom from AF reaching 91% has been obtained at 3 and 6 months [52, 53], long-term followup has been less encouraging [22, 36, 54]. Presently, thoracoscopic modalities are also largely limited to PVI in patients with paroxysmal AF. Furthermore, whilst less invasive than median sternotomy, the majority of these procedures still require minithoracotomy, carrying with it its own postoperative morbidity [32]. Finally, thoracoscopic and robotic techniques are associated with higher operative cost and a steep learning curve for the surgeon [55]; consequentially prolonging operative time and limiting their application to centres with sufficient resource.

The role of thoracoscopic and robotic procedures in the surgical management of AF therefore remains an exciting area of development. At present whilst it should be considered in the treatment of pAF, further larger studies are required to quantify its long-term outcomes.

## 11. Lesion Sets

Consideration of the pathophysiology of the underlying arrhythmia is vital when deciding upon an appropriate treatment plan [56]. The onset and type of AF (primary/lone AF versus secondary AF), right and left atrial dimensions are of paramount importance in determining a surgical strategy. For example, it is well recognised that patients with persistent AF have poorer results with PVI in comparison to those with paroxysmal AF. In 1998, Haïssaguerre et al. mapped

the majority of triggering foci in paroxysmal AF to the pulmonary vein ostia [57] and demonstrated the potential for RF ablation of these foci to treat AF. In permanent or persistent AF however, the self-perpetuating nature of the arrhythmia and presence of macro-reentrant circuits eliminates the requirement for these triggers to repeatedly initiate the arrhythmia [56]. As such, the physical size of these circuits in comparison to the triggering foci seen in paroxysmal AF often necessitates the need for intervention beyond PVI alone.

Atrial size has also recurrently been implicated as an independent risk factor for the recurrence of AF following surgical ablation [58–60]. In patients with a normal RA, the prolonged refractory period only allows for the development of a single macro-reentrant circuit. However, patients with RA enlargement have the potential for the development of multiple macro-reentrant circuits and as such biatrial intervention should be considered [56]. Conversely, in secondary AF without concomitant RA enlargement, macro reentrant drivers are mainly confined to the LA and consequently isolated LA procedures may be sufficient. However, it should be noted that standalone LA procedures do not eliminate the potential to generate RA flutter. An additional cavotricuspid “flutter lesion” may therefore be required in LA only lesion sets [56].

## 12. Permanent AF

Permanent AF is associated with changes in the atrial substrate including a reduction in the ERP, shortened action potential and wavelength. Furthermore, myocardial fibrotic changes slow conduction velocity and perpetuate the arrhythmia. As such, permanent AF presents further challenges in maintaining long-term freedom from the arrhythmia following surgical intervention. Isolated PVI is not recommended in the treatment of primary persistent AF due to high rates of AF recurrence [61]. Higher failure rates have also been seen in the treatment of primary chronic AF with standalone left atrial procedures. Following their standalone LA radiofrequency lesion set, Speziale et al. describe a recurrence rate of 18.5% in persistent lone AF compared to 5.3% in paroxysmal AF at 6-month followup ( $P < .001$ ) [31]. Similarly, Cui et al. report a 67.7% freedom from AF at 12 months in long-standing persistent “lone” AF compared to 80% in paroxysmal “lone” AF following minimally invasive RF ablation [62]. Haïssaguerre and Cox et al. provide a potential explanation to this recurring problem based on a change in the right atrial substrate. Mapping atrial electrograms in the majority of patients reveals prolonged right atrial AF cycle lengths, reflecting a driving mechanism from the LA. However, approximately 20% of patients with persistent AF exhibit shorter cycle lengths indicating a right atrial driver [63]. It follows that shorter AF cycle lengths may allow for more than one macro reentrant circuit to be set up and as such neither standalone LA procedures nor the addition of a right atrial cavotricuspid lesion will prevent AF recurrence [56, 63]. In such patients, a complete biatrial Maze III procedure may be the only way to ensure long-term freedom from AF.

### 13. Atrial Size Reduction

The concept of an atrial critical mass above which the propagation and maintenance of AF is favoured was originally proposed by Garrey in 1914 [64]. More recent work has quantifiably demonstrated this hypothesis, with both increased left atrial area [58, 65] and reduced effective refractory period (ERP) favouring sustained AF [65]. By reducing the area in which the macro reentrant circuits that propagate AF can be set up, atrial reduction surgery may therefore potentially sustain freedom from AF. In their study of 80 patients with enlarged left atrium (ELA) undergoing concomitant atrial reduction at the time of the CryoMaze III procedure, Marui and colleagues demonstrate a significant improvement in long-term freedom from AF at both 12 and 24 months [66]. Scherer et al. also show improved freedom from AF in patients undergoing concomitant LA reduction (61.1 versus 70% at 36 months), although this did not reach statistical significance [67]. The overall results of atrial reduction surgery found within the literature are outlined in Table 5. A wide range in freedom from AF is seen here (58–100% at last followup), reflecting the variability in the duration of preoperative AF, atrial reduction techniques used and the concomitant procedures performed. Whilst a role for atrial reduction procedures is therefore apparent in patients with ELA, further evidence is required to define clear clinical guidelines.

### 14. Success Rate Monitoring

With the advent of a multitude of new technologies it has become more important than ever to produce a drive towards a homogeneous definition of the criteria constituting AF recurrence or surgical failure. A number of studies report results based on telephone questionnaires and single ECG strips with a lack of long-term monitoring, others report surgical success based upon postoperative thromboembolic events without defining recurrence at all. This has been the focus for a number of criticisms surrounding a potential over-representation of success rates with the Cox Maze III “cut and sew” procedure [36]. Since the publication of the Heart Rhythm Society expert consensus guidelines [73] there is now a move to report any period of AF or flutter recorded for greater than 30 seconds on Holter monitoring as a recurrence of AF. However, the use of long-term monitoring devices is not without its associated shortcomings. Patient compliance may be poor, and in those systems requiring self-triggering, asymptomatic paroxysms may not be adequately captured. Some long-term systems solely determining AF on the basis of R-R variability may not register paroxysms that do not produce such a variation. Conversely, some long-term systems may register irregular premature atrial beats as AF, resulting in premature atrial beats caused by nonisolated triggers outside the PV cuff being recorded as AF recurrence [59]. When assessing the current data and planning further work, one should therefore keep this under consideration. The question has also been raised that if episodes of unsustained AF are asymptomatic and last between 30 seconds and 5 mins, are these of clinical significance? The answer

to this certainly involves a number of factors and in part will depend on the frequency of these episodes and the risk of thromboembolic complications although relevant information appears to be sparse and inconclusive. Indeed, quality of life (QoL) scores have been shown to improve significantly following surgery for AF, with health-related QoL scores equivalent to an age-matched general population at long-term followup (mean 4.6 years) [74]. We therefore believe that whilst clinical significance should be considered when discussing AF recurrence rates, we must be cautious to comply with uniform reporting criteria to allow meaningful interstudy comparisons to be made.

### 15. Anticoagulation

The duration of anticoagulation following AF surgery either by ablative or “cut and sew” techniques remains variable within the literature. Surgical ligation of the left atrial appendage and lower AF recurrence rates have resulted in low rates of thromboembolic complications following surgical intervention [75, 76] and whilst concomitant valve surgery may necessitate the need for permanent anticoagulation, varying strategies have been implemented in standalone procedures. In their 1999 study of the “cut and sew” maze procedure reporting a 0.4% stroke rate at 11-year followup, Cox and colleagues did not advocate anticoagulation without a prior history of thromboembolism. Whilst these results are encouraging, a consensus for short-term anticoagulation can be found throughout the literature. As such, in 2008 Henry and Ad produced guidelines on the management of anticoagulation following the Maze procedure. These recommendations advise all patients to be commenced on warfarin for 3 months postoperatively unless otherwise contraindicated. Before the discontinuation of anticoagulation, confirmation of sinus rhythm should take place by means of long term holter monitoring. At this point, any patients found to be in AF should continue anticoagulation until this has been resolved [24].

### 16. Summary

Surgical treatment for AF has been available for two decades since the original description of the Cox-Maze procedure. Technical advances, including novel energy delivery systems for the creation of atrial lesion sets, and a better understanding of the pathogenesis of AF have also validated surgical ablation as an efficacious concomitant procedure and, occasionally, as a standalone treatment. These advances have paved the way for the development of less invasive approaches, some of which eliminate the need for median sternotomy and CPB.

However, comparative studies of patients undergoing surgical ablation versus either established antiarrhythmic therapy or between different lesion sets and varying energy sources have endured certain methodological limitations. AF definition (and duration) has remained variable in numerous studies, when it is well established that AF burden can significantly influence outcomes. Secondly, the most

TABLE 5: Freedom from AF following atrial size reduction.

Reference	Group	Procedure**	n	Duration of Pre op AF (months)	Atrial diameter (mm)	Followup (months)	Freedom from AF
Wang et al., [68]	ELA	Modified full RF Cox Maze III + batrial reduction	83	45 ± 87	Pre op 64 ± 12 Post op 49 ± 8	19 ± 16 (Last f/u)	90% at last f/u
	GLA	procedure with reef imbricate technique	39	56 ± 67	86 ± 17	51 ± 11	58% at last f/u
Scherer et al., [67]	Study	LA reduction procedure + RF Maze III	20	>12	60 ± 15	36 (Last f/u)	70.0%
	Control	RF Maze III only	20	>12	69 ± 19	55 ± 6	61.1%
Badhwar et al., [69]		RF Maze III + LA reduction	70	49.3 ± 58	67 ± 12	43 ± 6	92.6% at 0-6/12 93.8% at 7-12/12 92% at 1 year
	Study	Cryoablation modified LA maze III + volume reduction	44	169.2 ± 64.8	67.1 ± 7.8	47.6 ± 6.3	90% at 12/12 87% at 24/12 100% at 36/12
Marui et al., [66]	Control	Cryoablation modified LA maze III only	36	114 ± 61.2	64.5 ± 6.7	62.1 ± 7.9	69% at 12/12 67% at 24/12 64% at 36/12
		LA reduction	27	>12	60.2 ± 9.8	44.5 ± 7.0	12 (Last f/u) 63% at 1 year*
Sankar and Farnsworth, [72]		LA reduction	23	46.8 ± 34.8	81 ± 14.7	48 ± 7.7	100% at last f/u
		MV replacement + CABG + LA reduction	1	228	69	41	Pt remained in SR at last f/u

\* 19% of patients described as "free from AF at 1 year" suffered from intermittent, symptomatic pAF during the 1-year followup period.

\*\*All patients underwent concomitant MV ± TV ± AV procedures ± CABG at the time of procedure outlined.

common endpoint, freedom from AF after surgery, must be evaluated in view of the use (or not) of antiarrhythmic medications and the duration of followup. Finally, what is often considered as procedural success or “cure” for symptomatic persistent AF may occasionally represent its transformation to silent paroxysmal AF that has not been adequately captured. Many of these issues are highlighted in the systematic review by Khargi and colleagues, who demonstrate that whilst sinus rhythm conversion rates in patients undergoing the conventional Cox-Maze III versus alternative energy sources are equivalent, there is significant heterogeneity between studies [77].

Despite this, there is a consensus towards the usefulness of surgical AF ablation especially in patients with structural heart disease. The report of the Heart Rhythm Society (HRS) Task Force indicates that AF ablation must be offered to all patients undergoing other cardiac surgery, as long as the risk of this concomitant procedure remains low, there is a reasonable chance of success, and the surgeon has appropriate experience in antiarrhythmia surgery. With respect to standalone surgical ablation, the HRS Task Force suggests that it may be considered for symptomatic patients willing to undergo surgery, who are either not candidates for catheter-ablation or in whom catheter ablation has failed [20]. However, since these recommendations were published in 2007 there have been no robust multicentre randomised clinical trials to overcome some of the reported limitations or to evaluate tangible endpoints such as functional capacity and long-term mortality.

Despite encouraging long-term success rates with open interventions, the invasiveness of median sternotomy in the standalone treatment of AF continues to remain an important consideration. Conversely, whilst percutaneous catheter based techniques offer a minimally invasive approach, the long-term freedom from AF may be variable. As such, there has been growing interest in establishing a minimally invasive approach, either thoroscopically or by minithoracotomy which may potentially offer a “middle ground”, combining the success rates of conventional open surgery with reduced procedural trauma. However, at the present time the application of these techniques is limited to a few specialist centres, and long-term outcome data is awaited before recommendations can be made.

In conclusion, this review highlights the widespread acceptance of both “cut and sew” and ablative techniques in the restoration of sinus rhythm, via both open and minimally invasive approaches. Equally we raise the need for well-conducted studies to establish a comparative efficacy in the different types of AF and more accurately evaluate clinical endpoints. The advances in minimally invasive technologies and robotics render the future of surgical AF management an encouraging prospect.

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## Review Article

# Atrial Fibrillation Ablation without Interruption of Anticoagulation

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Atrial fibrillation (AF) can be cured by pulmonary vein antrum isolation (PVAI) in a substantial proportion of patients. The high efficacy of PVAI is partially undermined by a small but concrete periprocedural risk of complications, such as thromboembolic events and bleeding. A correct management of anticoagulation is essential to prevent such complications. Performing PVAI without interruption of oral anticoagulation has been demonstrated feasible by our group in previous studies. Recently, we reported that continuation of therapeutic warfarin during radiofrequency catheter ablation consistently reduces the risk of periprocedural stroke/transient ischemic attack without increasing the risk of hemorrhagic events. Of note, interrupting warfarin anticoagulation may actually increase the risk of stroke even when bridged with heparin. The latter strategy is also associated with an increased risk of minor bleeding. With regard to major bleeding, we found no significant difference between patients with a therapeutic INR and those who were bridged with heparin. Therefore, continuation of therapeutic warfarin during ablation of AF appears to be the best anticoagulation strategy. In this paper we summarize our experience with AF ablation without interruption of anticoagulation.

## 1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in Western countries, with an estimated 30 million patients affected by 2050 across United States and Europe alone [1]. Atrial fibrillation has a significant impact on morbidity mainly related to symptoms, heart failure, and thromboembolic events and is the most frequent arrhythmic cause of hospital admission in the USA [1–3]. In addition, AF is associated with excess mortality independently of thromboembolic complications [4]. To date, the most effective treatment for AF is radiofrequency catheter ablation, and pulmonary vein antrum isolation (PVAI) is the mainstay of such an approach [5]. The major drawback of catheter

ablation of AF consists in its potential risk of periprocedural complications [6], with thromboembolic and hemorrhagic complications being among the most common and insidious ones [7, 8]. Despite the introduction of novel ablation technologies, such as open irrigation catheters, and the widespread use of systemic anticoagulation with heparin, the risk of periprocedural thromboembolism remains not negligible, reaching up to 2.8% in large series [6, 9]. With these premises, the development of novel strategies able to further decrease the risk of periprocedural thromboembolism without increasing the risk of bleeding is crucial.

Oral anticoagulant therapy with warfarin is the current standard of care for the treatment of AF, with a strikingly favorable balance between thromboembolic protection and

bleeding complications when adequate monitoring of international normalized ratio (INR) is achieved [10]. For years, discontinuation of warfarin before ablation associated with the periprocedural use of unfractionated and low molecular weight heparin and bridging with warfarin after ablation has been the most widespread anticoagulation protocol in patients undergoing catheter ablation of AF [5, 11]. We firstly described the feasibility of AF ablation without interruption of oral anticoagulation [12] and recently reported that this approach is able to potentially abolish thromboembolic complications without increasing the risk of bleeding [13]. Accordingly, AF ablation without interruption of anticoagulation is nowadays the standard protocol in our center. In this paper, we summarize our approach to anticoagulation in patients undergoing AF ablation.

## 2. Preprocedural Management

Patients eligible for catheter ablation of AF are started on warfarin as outpatients, at least 2 months before the scheduled procedure. All patients receive weekly INR monitoring during the 4 to 6 weeks preceding the procedure, with a target INR of 2 to 3. Preprocedural transesophageal echocardiography (TEE) is performed only in patients showing subtherapeutic INR values in the month prior to the procedure. Patients who demonstrate INR values consistently above 2 in the month before the procedure are directly sent to ablation. We routinely do not discontinue therapeutic warfarin before the procedure.

## 3. Periprocedural Management

Ablation procedure is performed under general anesthesia. Four venous accesses are obtained: two right and one left femoral venous accesses, and one right internal jugular vein access. Femoral venous accesses are usually obtained with the Seldinger technique or with ultrasound guidance in difficult cases. The right internal jugular vein is accessed with ultrasound guidance or under fluoroscopic guidance with a wire or a deflectable catheter advanced into this vein via the right femoral vein sheath. A double transeptal puncture is performed with the assistance of intracardiac echocardiography (ICE) [13, 14]. Before transeptal punctures, all patients receive a bolus of unfractionated heparin (10,000 Units), followed by a noncontinuous infusion to maintain an activated coagulation time (ACT) > 300 seconds. We found important the addition of unfractionated heparin to periprocedural therapeutic warfarin, since soft thrombus can still be observed on the transeptal sheath or left atrial catheters in patients with periprocedural therapeutic INR.

Radiofrequency energy is delivered with an open irrigated ablation catheter with a maximum temperature of 42°C, power up to 45 W, and flow rate of 30 cm<sup>3</sup>/min. Intracardiac echocardiography is continuously used to monitor the electrode surface during ablation, to assist with catheter positioning and identify coagulum formation, and to monitor for complications including pericardial effusion. An esophageal temperature probe is always inserted to assist

with power titration during posterior wall ablation. At the end of the left atrial ablation, we partially reverse heparin anticoagulation with up to 40 mg of protamine guided by the ACT and remove the sheaths when the ACT is less than 250 seconds.

With this approach there is no increased incidence of major bleeding complications compared with bridging therapy [13]. The majority of the major bleedings are related to cardiac tamponade, which can be effectively managed with emergent pericardiocentesis, together with heparin interruption and reversal with protamine, and warfarin reversal with fresh-frozen plasma or prothrombin complex concentrate [13]. All patients requiring pericardiocentesis are discharged on anti-inflammatory agents for two weeks. If continued significant drainage or reaccumulation of the pericardial effusion occurs despite these measures, emergent open surgical exploration is considered. Notably, there is also no difference in rates of emergent surgical exploration between patients with periprocedural therapeutic INR and those who discontinue warfarin, although patients on therapeutic anticoagulation are more likely to have a larger amount of blood removed from their pericardium for stabilization and require more blood transfusion units [13].

## 4. Postprocedural Management

All patients receive a single dose of aspirin (325 mg) before leaving the electrophysiology laboratory and continue their warfarin dosage regimens to maintain a target INR of 2 to 3.

The beneficial effect of periprocedural therapeutic INR possibly extends also to the postprocedural period. After ablation the thromboembolic risk may be further increased by the procedure-related endothelial damage, which may activate the coagulation cascade and increase the risk of thromboembolism [15].

Therefore, warfarin discontinuation may be associated with an increased thromboembolic risk also in the postprocedural period, since reaching a therapeutic INR after the procedure may take several days, and the risk of left atrial thrombosis during AF is strikingly time dependent.

All patients are strictly monitored for outcome and complications during overnight hospital stay, and on the following day prior to discharge using symptom assessment, serial neurological examinations, and puncture site checks. All patients are instructed to call in case of any symptom development and to send weekly transtelephonic electrocardiogram transmissions for the first 5 months after ablation. Progress of recovery and symptoms are assessed as well by a dedicated nurse. In case of symptoms or suspected complications patients are asked to seek medical attention at either a local emergency department or our emergency department or to follow up with their local physician. All documentations from these visits are collected by our AF center. Moreover, all patients present for followup 3 to 4 months after ablation with the electrophysiologist who performed the procedure.

With regard to the out-of-hospital long-term anticoagulation management, patients are referred to dedicated

anticoagulation clinics with the aim of maintaining a stable therapeutic INR level. We follow a standard, uniform, and validated protocol of long-term postprocedural anticoagulation management [16]. Briefly, oral anticoagulation is discontinued, regardless of the CHADS<sub>2</sub> score, if patients do not experience any recurrence of atrial tachyarrhythmias, severe pulmonary vein stenosis (pulmonary vein narrowing >70%), and severe left atrial mechanical dysfunction, as assessed by transthoracic echocardiography.

Patients with a CHADS<sub>2</sub> score  $\geq 1$  experiencing early recurrence of AF are maintained on warfarin for at least 6 months. In these patients, warfarin is discontinued if there is no AF recurrence in the last 3 months without antiarrhythmic drugs, and aspirin 81 to 325 mg is started. In case of new AF recurrence after warfarin discontinuation in patients with a CHADS<sub>2</sub> score  $\geq 1$ , oral anticoagulation is restarted.

## 5. Discussion

Our approach to periprocedural anticoagulation has been extensively validated in previous work [12, 13, 17]. In particular, we found that a conventional anticoagulation approach, which included warfarin discontinuation with peri- and postprocedural bridging with unfractionated and low-molecular-weight heparin actually increases the risk of bleeding and thromboembolic complications, as compared to no periprocedural interruption of oral anticoagulation [12, 13, 17].

Our most recent report provides strong evidence that performing AF ablation under therapeutic INR is a safe and effective approach to virtually abolish the risk of thromboembolic complications [13]. We reported a multicenter prospective comparison of three anticoagulation protocols in 9 centers performing the same ablation procedure. A total of 6,454 patients were included in the study, of whom 2,488 underwent ablation with an 8-mm ablation catheter and preprocedural warfarin discontinuation (Group 1), 1,348 underwent ablation with an open irrigated catheter and preprocedural warfarin discontinuation (Group 2), and 2,618 underwent ablation with an open irrigated catheter without preprocedural warfarin discontinuation (Group 3). Overall, periprocedural thromboembolic complications occurred in 39 (0.6%) patients, with a rate of 1.1% in Group 1, and of 0.9% in Group 2. Notably, no patient of Group 3 experienced periprocedural thromboembolism (Figure 1). These data support also the appropriateness of our approach to TEE based on the intensity of anticoagulation in the month preceding the procedure, especially considering that 1,178 (45%) Group 3 patients had persistent AF, and 498 (19%) long-standing persistent AF.

At multivariable analysis, which adjusted for age, gender, coronary artery disease, type of AF, heart failure, diabetes, hypertension, and prior stroke, the anticoagulation strategy of ablation with a therapeutic INR was a strong independent predictor of lower periprocedural thromboembolic events (odds ratio 0.54, 95% confidence interval 0.32 to 0.89,  $P = .017$ ). With regard to bleedings, the pooled

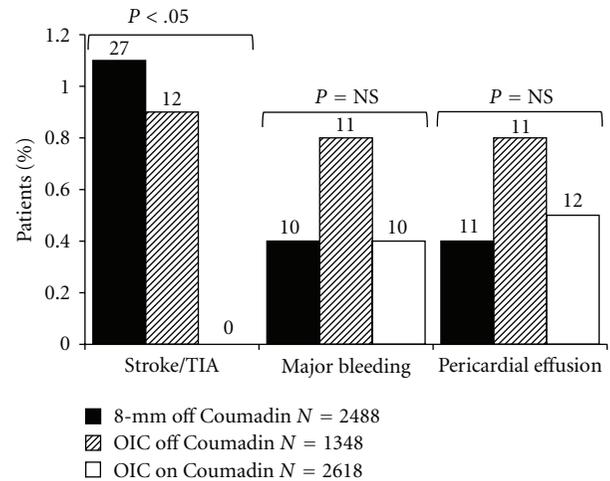


FIGURE 1: Complications of radiofrequency catheter ablation of atrial fibrillation in 6,454 patients referred to our institution between 2002 and 2009. TIA = transient ischemic attack; 8-mm = 8-mm nonirrigated ablation catheter; OIC = open irrigated ablation catheter; off/on Coumadin = periprocedural discontinuation/maintenance of therapeutic oral anticoagulant therapy with warfarin (Coumadin).  $P$  from multiple comparison between OIC on Coumadin and 8-mm and OIC off Coumadin: data from Di Biase et al. [13].

rate of major bleeding complications (i.e., bleeding requiring interventions including transfusions, hemothorax, retroperitoneal bleeding) and pericardial effusion in patients who discontinued warfarin before the ablation procedure (Groups 1 and 2) was 1.1%, whereas in Group 3 was 0.8% (Figure 1). If also minor bleedings were included, patients who discontinued warfarin before ablation procedure had a pooled rate of bleeding complications of 20.7%, while patients who were maintained on warfarin had a rate of 4.8%.

Translating such percentages into treatment effects, the net clinical benefit associated with AF ablation without interruption of oral anticoagulation is overwhelming (Figure 2), with an estimated 170 thromboembolic or hemorrhagic complications avoided every 1,000 patients ablated.

In the most recent survey on AF catheter ablation, Cappato et al. reported thromboembolic and hemorrhagic complication rates in 16,039 patients undergoing AF ablation between 2003 and 2006 in 521 centers distributed worldwide [18]. All these patients had oral anticoagulant discontinuation before the ablation procedure. Accordingly, thromboembolic and bleeding complication rates in this large survey were fairly consistent with that reported in Group 1 and 2 patients of our study [13, 18]. Based on our findings it is estimable that, if periprocedural oral anticoagulation was not discontinued in all patients included in the survey, more than 2,700 thromboembolic or hemorrhagic complications would have been avoided worldwide from 2003 to 2006. Therefore, there are cogent data supporting the benefit of AF ablation without discontinuation of oral anticoagulation.

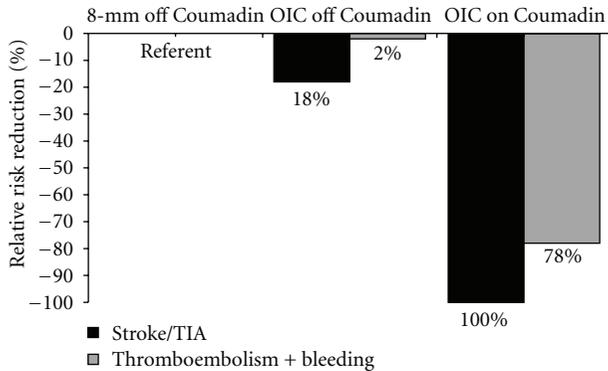


FIGURE 2: Benefits of atrial fibrillation ablation without interruption of oral anticoagulation. TIA = transient ischemic attack; 8-mm off Coumadin (referent group) = 8-mm nonirrigated ablation catheter with periprocedural discontinuation of therapeutic oral anticoagulant therapy with warfarin (Coumadin); OIC off Coumadin = open irrigated ablation catheter with periprocedural discontinuation of therapeutic oral anticoagulant therapy with Coumadin; OIC on Coumadin = open irrigated ablation catheter with periprocedural maintenance of therapeutic oral anticoagulant therapy with Coumadin: data from Di Biase et al. [13].

Since the acute reversal of the anticoagulant effect of warfarin is possible only through infusion of fresh coagulation factors, we routinely type- and cross-match all patients, so that packed red blood cells and fresh frozen plasma are readily available for infusion in case of hemorrhagic complications. If the preprocedural INR is above 3.5, we partially reverse the anticoagulant effect with one to two units of fresh frozen plasma.

Of interest, the strategy of ablation under therapeutic INR could also be more cost-effective compared to bridging therapy with enoxaparin, which is expensive and may be inconvenient for many patients.

## 6. Conclusions

Radiofrequency catheter ablation of AF without discontinuation of oral anticoagulation significantly reduces the risk of thromboembolic and minor bleeding complications. Maintenance of periprocedural therapeutic INR should be considered the anticoagulation strategy of choice among patients submitted to catheter ablation of AF.

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## Research Article

# Rate Control in Atrial Fibrillation by Cooling: Effect of Temperature on Dromotropy in Perfused Rabbit Hearts

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**Background.** Cooling has emerged as a therapeutic option in critically ill patients (especially after cardiac resuscitation) and might also have a negative dromotropic effect in atrial fibrillation. We sought to determine the impact of cooling on electrophysiologic properties of Langendorff-perfused rabbit hearts. **Methods and Results.** In 20 isolated Langendorff-perfused rabbit hearts, the temperature of the tissue bath was changed between 17 and 42°C. With decreasing temperature, significant increases of the spontaneous sinus cycle length, decreases of the mean ventricular heart rate during atrial fibrillation, and relevant increases of atrial and ventricular refractory periods were observed (ANOVA  $P < .01$ ). **Conclusions.** Cardiac hypothermia leads to a significant drop of mean ventricular heart rate during atrial fibrillation. Negative chronotropy and dromotropy induced by moderate cardiac hypothermia might be a feasible therapeutic approach in patients with hemodynamically relevant tachyarrhythmias in a CCU/ICU setting.

## 1. Introduction

Therapeutic hypothermia has been used in survivors of cardiopulmonary resuscitation, patients with brain trauma and with acute myocardial infarction [1–3]. Mild systemic hypothermia might theoretically be used for rate control in critically ill patients with supraventricular tachycardias instead of or on top of drug therapy.

Many drugs with negative dromotropic effects also decrease left ventricular inotropy and are thus contraindicated in patients with significant heart failure and supraventricular tachycardias. In this animal study, we sought to investigate the effect of negative chronotropy and especially dromotropy in Langendorff-perfused rabbit hearts.

## 2. Materials and Methods

Animal care and euthanasia were performed according to the guidelines of the American Society of Physiology with institutional approval and permission of the competent authorities (Bezirksregierung Köln). Female New Zealand

white rabbits aged 3–6 months were euthanized and the beating hearts removed. After cardioplegia, Langendorff-perfusion was performed in 20 isolated hearts. The tyrode used for perfusion consisted of 130 mM NaCl, 5.6 mM KCl, 24.2 mM NaHCO<sub>3</sub>, 2.2 mM CaCl<sub>2</sub>, 0.6 mM MgCl<sub>2</sub>, 1.2 mM NaH<sub>2</sub>PO<sub>4</sub>, and 12.2 mM glucose and was equilibrated with 95% O<sub>2</sub> and 5% CO<sub>2</sub>.

Bipolar electrodes were positioned on the surface of right and left atrium and right ventricle. The temperature of tyrode and tissue bath was changed in 5-degree steps between 17 and 42°C (constant temperature Bath T1000, P.M. Tamson, Netherlands) (Figure 1).

The pacing threshold was determined at each temperature level. We measured the atrial and ventricular refractory period (AERP and VERP) by extrastimulus testing. The antegrade and retrograde Wenckebach periods (AWB and RWB) were determined by decremental pacing. Stimulations were performed at twice the pacing threshold. Atrial fibrillation was induced by continuous high-frequency burst stimulation with 100 ms. If atrial fibrillation could not be induced, it was simulated by continuous stimulation with



FIGURE 1: Langendorff-perfused rabbit heart.

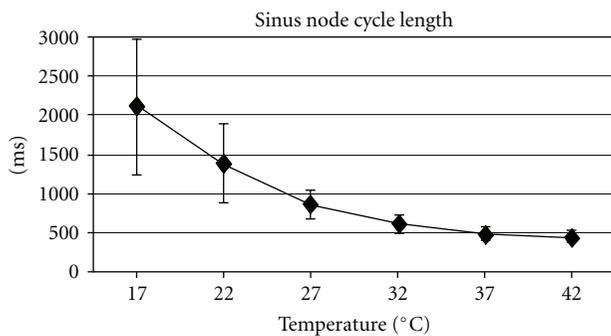


FIGURE 2: Spontaneous sinus cycle length depending on temperature.  $P < .05$  for any temperature level.

100 ms. During atrial fibrillation, the mean ventricular heart rate was determined by averaging all cycle lengths during intervals of 30 sec.

**2.1. Statistical Analysis.** Results are presented as mean  $\pm$  1 standard deviation. Two-sided student's  $t$ -test was used to compare spontaneous cycle length, refractory periods, AWB, RWB, and mean ventricular rate during atrial fibrillation.  $P$  values  $< .05$  were considered significant.

### 3. Results and Discussion

**3.1. Results.** With decreasing temperature, significant increases of the spontaneous sinus cycle length, the mean ventricular heart rate during atrial fibrillation, and relevant increases of AERP, VERP, AWB, and RWB were observed (ANOVA  $P < .01$ ).

At moderate hypothermia of 32°C, a 25–40% decrease of cardiac chronotropy and dromotropy could be obtained (Figures 2 and 3).

The effects of temperature on atrial and ventricular refractory periods as well as AWB and RWB are shown in Figure 4.

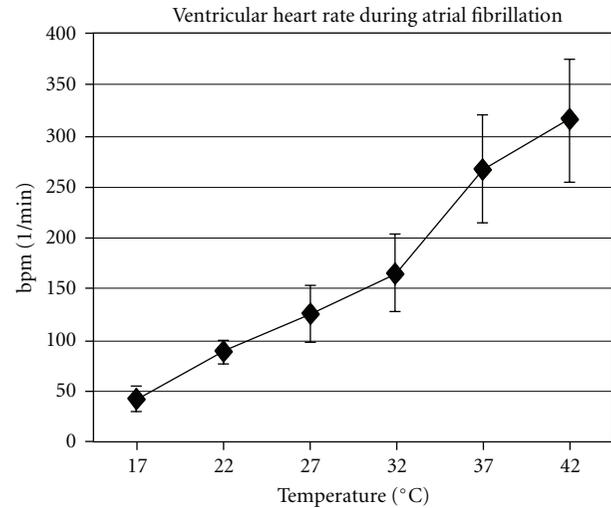


FIGURE 3: Average ventricular heart rate during atrial fibrillation (high-frequency atrial stimulation). A gradual cardiac hypothermia causes a gradual negative dromotropic effect.  $P < .05$  for any temperature level. bpm: beats per minute.

An increased ventricular vulnerability was noted at a temperature level of 42°C; induction of ventricular fibrillation occurred in 13 hearts, whereas ventricular fibrillation was observed in 2 hearts at other temperature levels.

**3.2. Discussion.** The activity of biological tissue depends on its temperature. The rate of biological processes usually decreases by half to two-thirds with a decrease in temperature of 10°C [4].

Supraventricular tachycardias often complicate acute heart failure or sepsis in critically ill patients. The deleterious effect of tachycardia on cardiac output cannot be well addressed by pharmacological approaches as many drugs which exert significant negative dromotropic effects also decrease left ventricular inotropy and may decrease systemic vascular resistance.

Cardiac hypothermia has been used as a therapeutic option in patients after cardiac arrest and in patients with brain injury [1–3, 5, 6].

In our animal study, we have demonstrated a decline in ventricular heart rate of about 8% per degree C of cooling. A mild hypothermia of 32°C resulted in a significant decrease in ventricular heart rate from 267/min to 166/min (38%) during atrial fibrillation in this animal model. The spontaneous cycle length increased from 485 to 615 ms (27%) during mild hypothermia of 32°C. In addition, atrial and ventricular refractory periods increased significantly with a decrease in temperature. Appleton et al. studied cardiac electrophysiology properties in mice and used mild hypothermia (33–34°C) as well as hyperthermia [7]. The results of this in vivo mice study are congruent to our results with regard to refractory periods. Ventricular rate during atrial fibrillation, however, was not tested in the study by Appleton et al.

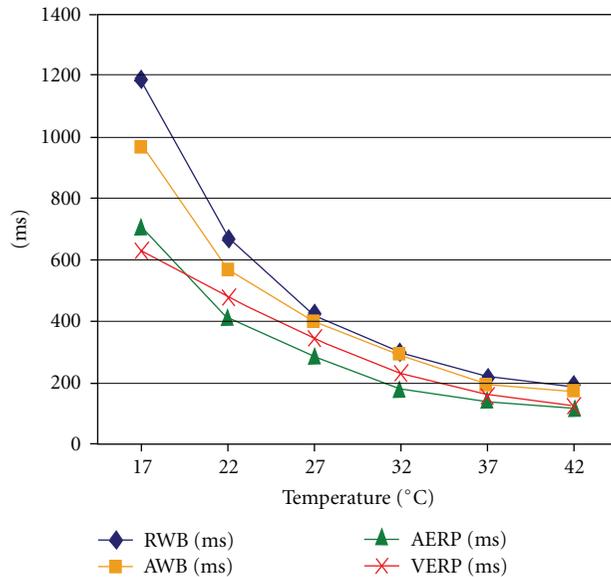


FIGURE 4: Antegrade and retrograde Wenckebach point (AWB/RWB) and atrial/ventricular refractory periods (AERP/VERP) with regard to temperature. Hypothermia causes negative dromotropy and an increase in effective refractory periods.  $P < .05$  for any temperature level.

A high percentage of patients treated by mild hypothermia after resuscitation due to cardiac arrest suffer from acute myocardial infarction. Those patients are prone to develop arrhythmias including atrial fibrillation. The incidence of atrial fibrillation after cardiac arrest is around 15%, and atrial fibrillation is associated with a higher mortality rate [8, 9]. Hypothermia might reduce the ventricular rate during atrial fibrillation. Although we can only speculate on the effect of cooling in patients, extrapolation of our animal data would suggest a reduction in ventricular heart rate of about 30% during mild hypothermia, for instance, from 150/min to 105/min. In the majority of patients, a ventricular heart rate  $<110$ /min during atrial fibrillation has been shown to be sufficient for rate control [10]. In addition, cooling might be a therapeutic approach of last resort in critically ill patients with sustained supraventricular tachycardias which cannot be controlled by cardioversion and pharmacotherapy. There is initial experience with a right atrial cooling system used for cardiothoracic surgery [11]. Hypothetically, selective AV nodal cooling could slow down the ventricular rate in critically ill patients with refractory atrial fibrillation without the need for systemic hypothermia. However, this would require technical solutions in order to deliver cooling to a distinct cardiac area.

#### 4. Limitations

The results we obtained were from an isolated heart model, and no in vivo data are available. Data on repolarization, left ventricular refractory periods or inotropy were not gathered.

Differences between human and rabbit electrophysiology may limit the applicability of the results of the study. Al-

though the rabbit cardiac action potential is of shorter duration than the human action potential, its shape is very similar. In addition, the kinetic properties of human and rabbit cardiac slow delayed rectifier potassium current (IKs) are comparable [12]. Even though the numerically reconstructed human If is considerably smaller than the typical rabbit If, Verkerk and Wilders describe a striking similarity between human and rabbit If with regard to the net membrane current [13].

#### 5. Conclusions

Cardiac hypothermia induces a relevant decrease in ventricular heart rate during atrial fibrillation. Thus, moderate cardiac hypothermia might be used as a new therapeutic tool in critically ill patients nonresponding to electrical cardioversion or pharmacotherapy.

#### Conflict of Interest

The authors declared that there is no conflict of interests.

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## Review Article

# Left Atrial Appendage Closure in Atrial Fibrillation: A World without Anticoagulation?

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Atrial Fibrillation (AF) is a common arrhythmia with an incidence that is as high as 10% in the elderly population. Given the large proportion of strokes caused by AF as well as the associated morbidity and mortality, reducing stroke burden is the most important part of AF management. While warfarin significantly reduces the risk of AF-related stroke, perceived bleeding risks and compliance limit its widespread use in the high-risk AF population. The left atrial appendage is believed to be the “culprit” for thrombogenesis in nonvalvular AF and is a new therapeutic target for stroke prevention. The purpose of this review is to explore the evolving field of percutaneous LAA occlusion. After briefly highlighting the risk of stroke with AF, problems with warfarin, and the role of the LAA in clot formation, this article discusses the feasibility and efficacy of various devices which have been developed for percutaneous LAA occlusion.

## 1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. It has an estimated prevalence of 1% in the adult population translating into greater than two million cases in the United States [1]. The projected number of individuals with AF in the United States of America is expected to be approximately 10 million by 2050 [2]. With better methods of diagnosing AF, especially paroxysmal AF, as well as increasing physician awareness, the actual burden may be higher than expected. AF is fraught with the serious complication of thromboembolism. Although anticoagulation is effective, patients and physicians both seek alternative means to avert the risk of stroke from thromboembolism due to the need for monitoring and bleeding complications as well as the potential for drug interactions. Left atrial appendage (LAA) closure devices have become an attractive option for this purpose. In this review, we will summarize the available literature and evidence for use of percutaneous left atrial appendage closure as an alternative to chronic anticoagulation.

## 2. Stroke Risk in Atrial Fibrillation

AF increases the risk of stroke by 4 to 5 folds in nonrheumatic patients [3] and 17 folds in the setting of rheumatic mitral stenosis [4]. It is responsible for 10% of all ischemic strokes and half of all cardioembolic strokes [5]. The impact of AF as a risk factor for stroke increases with age. While the annual incidence of stroke due to atrial fibrillation is 1.5% in patients aged 50–59 years, almost a quarter of the strokes in patients aged 80 to 89 years are secondary to AF [3]. Perceived adverse effects related to anticoagulation also increase with age, which may result in a paradoxical underuse in a population at highest risk for stroke [6].

Paroxysmal AF (PAF), which accounts for 25% of AF, has the same risk of stroke as permanent/persistent AF [7]. In a recent study, up to 23% patients with stroke/TIA of unknown etiology (cryptogenic stroke) were found to have PAF on subsequent monitoring [8]. Given that cryptogenic stroke accounts for 36% of all strokes [9], the stroke burden attributed to PAF has been hitherto significantly underestimated. With better methods of diagnosing PAF in patients

with cryptogenic stroke, such as transtelephonic EKG monitoring [10] and mobile cardiac outpatient telemetry [8], the number of patients potentially requiring anticoagulation is expected to increase in the future.

Apart from a sheer increase in numbers, AF-related strokes also tend to be more severe when compared to other causes of thromboembolism, likely due to the larger size of thrombi [11, 12]. Consequently, there is a significant impact on the quality of life as well as longevity with an estimated 28-day mortality of 20% post-AF-related stroke [13]. Thus, reducing the stroke burden is a *sine qua non* of AF management.

### 3. Underuse of Anticoagulation in AF

Warfarin dramatically decreases the risk of stroke in patients with valvular as well as nonvalvular AF. In a meta-analysis of randomized controlled trials, warfarin resulted in a 64% relative risk reduction for stroke when compared to placebo [14]. Another meta-analysis revealed that warfarin is almost three times more effective than antiplatelet agents in preventing strokes (relative risk reduction 64% for warfarin versus 20% for antiplatelet agents) [15].

However, several studies have reported underuse of warfarin in eligible patients with AF. In a large cross-sectional study, 45% patients with moderate to high-risk AF did not receive warfarin [16]. Similarly, a recent cohort study of Medicare beneficiaries with atrial fibrillation revealed that only two thirds of ideal anticoagulation candidates were prescribed warfarin, with significant differences in use, monitoring, and effectiveness of warfarin among different ethnic groups [17]. Given the high incidence of atrial fibrillation and associated risk factors for stroke, a small percentage of underuse could translate into a huge hurdle to stroke prevention in the population.

Table 1 outlines important reasons for warfarin underutilization. Fear of major bleeding, especially hemorrhagic strokes and gastrointestinal bleeding, is a major reason for this underuse [18, 19]. This fear is not without reason; a meta-analysis revealed that the risk of intracranial hemorrhage is doubled with warfarin when compared with aspirin [15]. Anticoagulants ranked first in 2003 and 2004 in the number of deaths from drugs causing “adverse effects in therapeutic use” [20]. The perceived risk is greater in elderly patients with AF [21], and “fall risk” is estimated in rather ambiguous ways in this population. Inconvenience of INR monitoring for rural populations, drug, and dietary interactions as well as compliance are other limiting factors [22]. For unclear reasons, warfarin is also underused in females compared to males [23].

Novel anticoagulants, such as the thrombin inhibitors (dabigatran) and the factor Xa inhibitors (rivaroxaban) have a wider therapeutic window. There is minimal dietary and drug interference with these agents and INR monitoring is not required. While these may decrease many of the concerns associated with warfarin, they do not address issues related to bleeding and compliance [24]. A case in point is that of dabigatran, which is superior to warfarin in preventing

TABLE 1: Causes of warfarin underutilization.

(1) Risk of bleeding (perceived or real)
(a) Intracranial hemorrhage
(b) Gastrointestinal bleeding
(c) Other major bleeds (retroperitoneal, hematuria, etc.)
(2) Perceived Fall Risk (and associated bleeding risk)
(3) Difficulty with INR monitoring
(a) Geographical barriers
(b) Lack of insurance/primary care physician
(4) Non-compliance
(5) Patient preference
(6) Physician unawareness (such as need in paroxysmal AF*)
(7) Pharmacokinetic interference
(a) Drug interaction
(b) Dietary interference
(8) Ethnic and gender disparities

\* AF: atrial fibrillation.

strokes but has a similar risk of major bleeding at the currently approved dose [25]. Similarly, there was no difference in major bleeding event rates between rivaroxaban and warfarin groups in the recent ROCKET-AF trial [26]. Also, cost-effectiveness and efficacy of these novel agents in real world setting remain to be seen.

### 4. Left Atrial Appendage: The Culprit?

The left atrial appendage is an embryological remnant that functions during conditions of volume overload as a reservoir and mediator of adaptive responses to decrease circulating blood volume [27]. Compared to the right atrial appendage, the LAA is anatomically prone to stasis by virtue of having a long, tubular structure as well as a narrow junction with the atrium [28]. Multiple studies have found a predilection for thrombus to form within the LAA in patients with mitral valve disease (irrespective of underlying rhythm) and nonvalvular AF.

The hematological and endocardial substrate for thrombogenesis in the LAA is yet to be elucidated, but the structural basis has been defined. All known variables associated with thrombus formation, including LAA size and flow pattern, are altered due to AF-associated LAA dysfunction [27]. Post-mortem LAA cast analysis from patients with AF revealed that its size was much larger in patients with AF [29]. A specific type of LAA flow pattern in patients with AF (Type III indicating no identifiable flow waves with AF) was associated with a higher incidence of LAA thrombus [30]. These represent the macroscopic basis of LAA thrombus formation in the setting of AF.

In contrast to patients with valvular AF, it is hypothesized that the LAA may be the major source for emboli in nonvalvular AF. This is based on an analysis of 23 studies utilizing echocardiographic, operative, and postmortem evaluations of the left atrium and LAA in patients with AF (Table 2). The percentage of thrombi found in the LAA was significantly higher in patients with nonvalvular AF than in valvular

TABLE 2: Left atrial appendage as a source of thrombi in nonatrial fibrillation.

- 
- (i) Hypothesis is based on a landmark study by Blackshear and Odell [31]
  - (ii) Findings from studies in settings of operation, autopsy, or transesophageal echocardiography were combined
  - (iii) 23 studies including close to 5,000 subjects with rheumatic or nonrheumatic AF\* were reviewed
  - (iv) Thrombi presented in the appendage but extending into the atrium was classified as a LAA\*\* thrombus
  - (v) While 57% of atrial thrombi in rheumatic AF occurred in the appendage, 91% of left atrial thrombi were located in the atrial appendage in nonrheumatic AF ( $P < .0001$ )
  - (vi) Many have pointed out that merely finding a thrombus in the LAA does not prove that it is the source of cardio-emboli in AF-related ischemic stroke [32]
  - (vii) This study set the stage to investigate the benefit of LAA occlusion in reducing nonrheumatic AF-related stroke burden
- 

\* AF: atrial fibrillation; \*\* LAA: left atrial appendage.

AF (91% versus 57%;  $P < .001$ ) [31]. This data, however, does not confirm that the LAA is the “source” of emboli in AF-related ischemic stroke, and many have questioned this theory [32]. Nevertheless, many surgical as well as non-invasive methods to occlude the LAA have been assessed to reduce stroke burden and confirm this hypothesis.

## 5. Methods of LAA Occlusion

**5.1. Surgical.** Several studies have assessed the feasibility, safety, and efficacy of surgical LAA occlusion [33, 34]. Given its invasive nature, surgical LAA occlusion is only performed in patients requiring other cardiac surgery such as mitral valve surgery and maze procedures. The addition of this simple, quick procedure to the aforementioned surgeries can reduce stroke burden in many patients with established AF or at high risk for AF. However, its efficacy for occluding the LAA and preventing thromboembolic events has been questioned, with a study demonstrating that surgical LAA occlusion is frequently incomplete [35]. Continuous advancements in open surgical LAA occlusion technique are being made with better methods for intra-operative confirmation of success (TEE), and outcomes are expected to improve in the future.

**5.2. Nonsurgical.** There are several percutaneous devices, which have been used for LAA occlusion. Of these, only the WATCHMAN device is FDA approved. Table 3 summarizes studies, which have analyzed the feasibility and efficacy of different devices.

## 6. The Amplatzer Septal Occluder (AGA Medical Corp., Golden Valley, Minn)

The Amplatzer septal occluder, which was originally used for patent foramen ovale or atrial septal defect closure, was tested for LAA closure in a preliminary analysis of 16

patients across four centers [36]. There was a single event of asymptomatic device embolization due to inappropriate size; no other complications or thromboembolic episodes were reported in a short followup period of four months. However, no further trials were conducted with this system, which paved the way for the LAA-specific devices. The Amplatzer Cardiac Plug is another device by the same manufacturer which is currently being compared with warfarin in the Amplatzer Cardiac Plug trial.

## 7. The PLAATO System (eV3, Plymouth, Minn)

The PLAATO implant consists of a self-expanding nitinol cage coated with a special expanded polytetrafluoroethylene (ePTFE) membrane to occlude blood flow into the orifice while allowing tissue incorporation. The ePTFE membrane ensures benign healing [42], resulting in endothelialization of the implant in 2 to 3 months. A custom 14Fr transseptal sheath is used to deliver the implant into the LAA, and small anchors along the struts of the implant hold it in position.

After initial animal studies confirmed safe LAA occlusion with this system [43], a feasibility study was conducted in Europe in 15 patients with chronic, nonrheumatic AF and contraindications to warfarin therapy [37]. All patients were at high risk for thromboembolism based on CHADS2 criteria [44] or spontaneous echo contrast in the LAA on TEE. The device was successfully implanted in all patients with an average implant time of 90 minutes. Periprocedural hemopericardium delayed successful implantation in one patient by a month, and the device needed to be exchanged due to inappropriate size in 4 patients. A one month followup showed stable implant position, and there were no reported late complications or embolic events. An addendum to this study reported successful implantation in 16 additional patients (with another case of hemopericardium).

Subsequently, the larger PLAATO multicenter study reported results from multiple sites in North America and Europe with a followup period of up to 17 months [38]. Patients with nonrheumatic AF of at least three months duration with contraindications to warfarin and high risk for thromboembolic events were included. The latter was based on CHADS2 criteria, presence of coronary artery disease, or echographic criteria (moderate to dense spontaneous echocardiographic contrast or blood flow velocity  $<20$  cm/s within the LAA), thus expanding inclusion criteria from the previous feasibility study. Percutaneous LAA occlusion was successful in 108 of 111 patients, with an average procedure time of 68 minutes. There were two reported major adverse events in a single patient within the first month. A total of 5 patients (4.5%) experienced hemopericardium during the entire followup; four of these five had no long-term sequelae. Based on a mean CHADS2 score of 2.5, the estimated stroke risk in the population was 6.5%. This was reduced to almost a third (2.2%/year) with the PLAATO system for strokes alone; TIA was not included.

The largest feasibility study for the PLAATO system was conducted in North-America and utilized a prospective, nonrandomized study design enrolling 64 patients across

TABLE 3: Studies evaluating percutaneous left atrial appendage closure devices.

No.	Study	Study design	Year	Device	Comparison	Subjects (n)	Population	Followup (mean)	Results	Adverse events
(1)	Meier et al. [36]	Prospective	2003	Amplatzer Septal Occluder	None	16	AF-continuous/paroxysmal; c/i to coumadin	4 months	0% stroke/TIA	Device embolization (1)
(2)	Sievert et al. [37]	Prospective	2002	PLAATO	None	15	Chronic, nonrheumatic AF; c/i to coumadin	1 month	0% stroke/TIA	Hemopericardium (1), device exchange (4)
(3)	Ostermayer et al. [38]	Prospective	2005	PLAATO	None	111	Chronic nonrheumatic AF patients at risk for stroke; c/i to coumadin	10 months	Stroke/TIA 2.2% (versus estimated 6.3%)	Implant failure (3), Hemopericardium (5)
(4)	Block et al. [39]	Prospective	2009	PLAATO	None	64	C/P AF; CHADS <sub>2</sub> ≥ 2; c/i to coumadin	5 years	Stroke 3.8% (versus estimated 6.6%)	Cardiac tamponade (1), (%)
(5)	Sick et al. [40]	Prospective	2007	WATCHMAN	None	75	C/P AF; CHADS <sub>2</sub> ≥ 1; eligible for coumadin	2 years	0% stroke/TIA	Implant failure (2), device failure, embolization, or pericardial effusion (6), TIAs (2)
(6)	PROTECT AF [45]	Randomized Controlled Trial	2009	WATCHMAN	Warfarin	707	C/P AF; CHADS <sub>2</sub> ≥ 1; eligible for coumadin	18 months	>99% probability of noninferiority for stroke/TIA prevention	Adverse events higher among controls

AF: atrial fibrillation, c/i: contraindication, C/P: Chronic/Paroxysmal, PLAATO: percutaneous left atrial appendage transcatheter occlusion, and PROTECT AF: WATCHMAN left atrial appendage system for embolic protection in patients with atrial fibrillation.

10 centers [39]. The inclusion criteria for this study were broader than the previous, smaller feasibility studies. Due to the similar risk for thromboembolic events, patients with either permanent or paroxysmal AF were selected for inclusion. Risk for developing thromboembolic events was defined by a CHADS2 score  $\geq 2$  or the presence of any of the multiple high-risk echocardiographic findings. More than 98% of the patients met the primary end point of no major adverse events (i.e., stroke, cardiac, or neurological death, MI or requirement of surgery related to the PLAATO procedure). In the five-year followup, there was only one adverse event (cardiac tamponade) attributed to the procedure, indicating an improved safety profile with time and experience (the learning curve effect). There were no other procedure-related adverse events, device failures, or malfunctions throughout the study period. The estimated yearly combined rate of stroke/TIA was 6.6%, calculated from the mean CHADS2 score of 2.6 in the study population. This was reduced to a rate of a 3.8%/year with the PLAATO system. Despite the encouraging results, there were no subsequent studies comparing the device to warfarin therapy.

## 8. WATCHMAN Device (Atritech Inc., Plymouth, Minn)

Similar to the PLAATO implant, the WATCHMAN LAA closure device consists of a self-expanding nitinol frame [41]. It also has fixation barbs; however, the permeable polyester fabric only covers the surface exposed to the left atrium. It is available in five different sizes ranging from a diameter of 21 to 33 mm. The implant is preloaded within a catheter and requires an access sheath for delivery into the LAA.

A preliminary feasibility study tested this device in 75 patients across multiple centers in Europe and North America. Subjects with chronic or paroxysmal nonvalvular AF eligible for warfarin therapy and a CHADS2 score  $\geq 1$  were included [40], thus having broader inclusion criteria than feasibility studies for PLAATO. After implantation, patients were discharged on warfarin which was discontinued at 45 days if LAA remained successfully sealed by echocardiographic criteria. The initial 16 patients received the first generation device. The device was subsequently redesigned and implantation of a second-generation device was attempted in 59 patients. Adverse effects were much lesser with second- than first-generation device, including core wire failure (0/59 versus 2/16), device embolization (0/59 versus 2/16), and internal bleeding (0/59 versus 1/16). Though minor pericardial effusions were more common with the second-generation device (3/59 versus 0/16 with first generation), there was one case of pericardial effusion requiring treatment in each group. Based on the CHADS2 score, the expected annual stroke risk of 1.9% was reduced to 0% with this device over a followup period of two years.

The PROTECT AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) is the first study that directly compared a LAA occlusion device head-to-head with warfarin therapy [45]. It was primarily designed to assess noninferiority of

the WATCHMAN device against warfarin. This prospective randomized control trial used inclusion criteria similar to the initial feasibility study, choosing patients with paroxysmal, persistent or permanent nonvalvular atrial fibrillation, and a CHADS2 score of  $\geq 1$ . A computer-generated sequence randomized selected patients ( $n = 707$ ) to the device ( $n = 463$ ) and warfarin therapy ( $n = 244$ ) in a 2:1 ratio. Those randomized to intervention subsequently discontinued warfarin after transesophageal echocardiographic (TEE) demonstration of complete LAA closure or a residual jet  $< 5$  mm in width. Following this, dual antiplatelet therapy (aspirin and clopidogrel) was prescribed until the end of a 6-month followup period. This was in contrast to the PLAATO recipients, who only received dual antiplatelet therapy for four to six weeks without any warfarin therapy. The device was successfully implanted in 88% of those assigned to the intervention group, of which 92% could stop taking warfarin at 6 months. The primary efficacy event rate for occurrence of stroke (ischemic or hemorrhagic), cardiovascular or unexplained death, or systemic embolism was 3/100 patient-years in the intervention group and 4.9/100 patient-years in the control group (rate ratio [RR] 0.62, 95% CI 0.35–1.25) with a greater than 99% probability of noninferiority. Though the primary safety event rate for occurrence of hemorrhage or procedure related complications was greater in the intervention group of the “intention to treat” population (7.5 versus 4.4 per 100 patient-years; RR 1.69 (95% CI 1.01–3.19)), the rate was higher in the control group amongst those successfully treated with device or warfarin (1.5 versus 4.4 per 100 patient-years; RR 0.35 (95% CI 0.15–0.80)).

There were several concerns about the trial design, such as using a noninferiority hypothesis to compare two different modalities of treatment, that is, a drug and a device. The risk of hemorrhagic stroke in the warfarin group (1.6 per 100 patient-years) was much higher than that reported in previous trials (0.5 per 100 patient-years in a meta-analysis of 6 randomized clinical trials [46]) and this may have influenced the noninferiority results for primary efficacy. Also, the rate of serious pericardial effusion requiring drainage was fairly high in the device group (4.8% versus 0%). The FDA has recommended longer followup studies with this device, and another trial is being planned by investigators.

## 9. Future Perspective

Percutaneous LAA occlusion devices may represent the “holy grail” in reducing nonvalvular AF-related stroke burden. Researchers have been constantly looking for easier methods for this, and a single procedure with short-term anticoagulation is more feasible than life-long anticoagulation and associated bleeding risks. Oral anticoagulants may become “alternative” agents in nonvalvular AF subjects who are not suitable for device implantation.

However, there are many questions that remain unanswered. Though only the WATCHMAN device is under consideration for FDA approval, results from feasibility studies of PLAATO are encouraging. A trial with the

Amplatzer Cardiac Plug device is also underway. Long-term studies with these devices and head-to-head comparisons may be necessary before deciding the “best” device. Different trials have used varied regimens for periprocedural antiplatelet/anticoagulant therapy and contrasting these protocols is imperative. If postprocedural warfarin therapy is needed, populations at high-risk or ineligible for warfarin therapy may also be unsuitable for device implantation. This will leave a huge proportion of the AF population at high-risk for stroke without any therapeutic modality. Despite the benefit of LAA occlusion, procedure-related adverse events such as pericardial effusion and device embolization remain concerning. Once this procedure gains popularity, longer followup studies in real-world settings will help assess the actual risk of adverse events. The role of this device in the face of newer, safer, and more efficacious oral anticoagulants, such as dabigatran and rivoroxaban, also remains to be seen. A recent indirect comparison of data from the PROTECT-AF and RE-LY trial revealed that the Watchman device would fail to meet noninferiority when compared to dabigatran [47]. Prospective, head-to-head trials are required to address this question.

## 10. Conclusion

While warfarin has significantly reduced stroke risk in patients with AF, it is still underused secondary to perceived risk for hemorrhagic complications and drug interactions. The LAA is considered to play a major role in thrombogenesis in patients with nonvalvular AF and is a new target for stroke prevention. The FDA has withheld the approval of WATCHMAN device, and better designed trials with a longer followup are necessary to evaluate this method in comparison to warfarin and novel oral anticoagulants.

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## Review Article

# Current State of the Surgical Treatment of Atrial Fibrillation

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Surgery of atrial fibrillation (AF) was first described in 1991 by James Cox in what was named the Cox-Maze procedure, and over the years it has been considered the gold-standard treatment, with best results in maintaining sinus rhythm in the long term. Nevertheless, the complexity and aggressivity of the first techniques of cut-and-sew limited the application of this procedure, and few centers were dedicated to AF surgery. In the past years, however, new devices able to ablate atrial tissue with cryotherapy, radiofrequency, or ultrasounds have facilitated this operation. In the mid-term, other energy devices with laser or microwave have been abandoned due to a lack of consistency in getting transmural lesions in a consistent and reproducible manner. Additionally, better knowledge of the physiopathology of AF, with the importance of triggering zones around the pulmonary veins, has started new minimally invasive techniques to approach paroxysmal and persistent AF patients through thoracoscopy.

## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting 1% of the general population and with its prevalence increasing with age [1]. Most important, AF has well-documented consequences as disabling symptoms, elevated stroke risk and major risk of congestive cardiac failure, being an independent predictor of death [2]. In summary, it represents a high cost on the health public systems of most developed countries.

Surgeons were the first ones to treat AF effectively and reverse it to sinus rhythm. James Cox described a series of surgical procedures known as Cox-Maze technique, between 1988 and 1991, that crystallized in the Cox-Maze III. This surgical approach was directed to divide both right and left atria by a series of cuts and sutures to redirect the electrical impulse to close-end paths, to finalize atrial depolarization, and be ready for the next sinus node impulse. This operation also included the exclusion of both atrial appendages and the isolation of the four pulmonary veins and the posterior wall of the left atrium. Although very effective, with over 91% patients maintaining sinus rhythm at 10 years, few surgical groups performed the Cox-Maze procedure due to the aggressiveness of it, with long suture lines and prolonged myocardial ischemic times [3, 4].

In the last decade, three factors have changed the approach of surgeons to AF: first, a better understanding of the electrophysiological basis of AF. In 1998, Haissaguerre described that most patients with paroxysmal AF have electric triggering zones localized within the antrum of the pulmonary veins [5], and that isolation of these areas was able to control AF effectively. However, later studies have demonstrated that pulmonary vein isolation alone was insufficient to control persistent or long-standing persistent AF and that a maze approach is needed to be added in these patients. Also, multiple studies have shown better results when the maze procedure was applied biatrially, compared to when only the left atrium is approached [6].

The second factor has been the development of new surgical tools able to create a similar lesion set of the Cox-Maze procedure faster and less aggressively, but maintaining a consistent, transmural, and linear lesions. Initially, these were clamps or catheters delivering heat or cold, with microwave ultrasounds, radiofrequency, laser, or liquid nitrogen, and argon, respectively. Nowadays, cryotherapy, bipolar radiofrequency, and ultrasounds are the most used energy sources and are recognized as a useful treatment by the 2010 Guidelines of the European Society of Cardiology (ESC) together with the European Association of

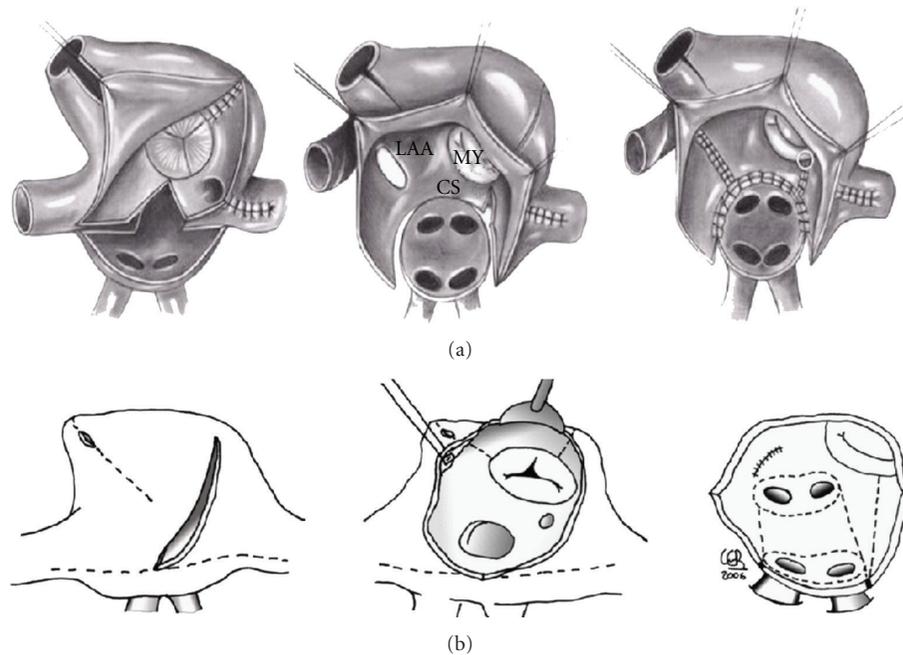


FIGURE 1: (a) Cox-Maze III: Lesion pattern described by James Cox in 1991 with cut and sew technique. (b) Cox-Maze IV: Similar lesion pattern, with alternative energy lesion in dotted lines and trying to minimize incisions in both atria. Only the left appendage is excised.

Cardiothoracic Surgeons (EACTS) and the European Heart Rhythm Association (EHRA) [7, 8].

Finally, there has been increasing scientific evidence concerning cardiac surgeons of the deleterious effects of AF in cardiac patients and the importance of treating this arrhythmia. Recent studies relate preoperative AF with worse survival rates after valvular or coronary surgery [9]. Furthermore, patients with successful maze procedures have shown better long-term survival rates, higher freedom from stroke, and thromboembolic events, improved ventricular ejection fraction and exercise tolerance [7].

All the above factors have expanded the indications for the surgical treatment of concomitant AF to most patients with coronary or valvular surgery. For patient with long-standing persistent AF, the Cox-Maze procedure is still the gold standard treatment with the best results at 10- and 15-year followup.

## 2. Current Surgical Strategies

The initial Cox-Maze III operation (“Cut-and-sew technique”) described by James Cox consists in multiple biatrial lesions that interrupt the multiple reentrant circuits and redirects the sinus impulse to the atrioventricular node. This technique has shown excellent results, with over 90% sinus rhythm restoration over 15 years, although the initial series included a large percentage of patients with paroxysmal AF. When applied to long-standing AF concomitant to valvular disease, this technique has shown a 75–80% success rates. As seen in Figure 1(a), this operation includes several features. First, it isolates all pulmonary veins and the posterior wall of the left atrium. Second, it interferes in all concentric atrial

structures that can facilitate atrial flutter. Those are, in the left side, the mitral annulus and the left appendage, and, in the right side, the entrance of both the superior and inferior venae cavae, the tricuspid annulus and the right appendage. Third, the procedure finishes with the excision of right and left appendages, the later to avoid the main source of atrial thrombi. The most important lines are the one connecting the pulmonary veins with the mitral annulus, to avoid left atrial flutter, and the line to the tricuspid annulus [10].

As main setbacks of this operation, besides the need for long incisions that need to be sewed back prolonging myocardial ischemia and extracorporeal circulation times, between 45 minutes and 1 hour, were the need of pacemaker in 10% of patients, and a certain degree of chronic fluid retention in some patients, attributed to a lack of natriuretic peptide secretion induced by bilateral appendage amputation.

Nowadays, most surgeons apply different energy sources to perform the Cox-Maze procedure, then naming it Cox-Maze IV (Figure 1(b)). Heat-based energy sources include bipolar radiofrequency or ultrasounds. Cryotherapy can be applied using liquid nitrogen or argon. To create effective lesions that block the electrical impulse, the temperature applied to the tissue must reach 60°C or minus 65°C during two minutes to create fibrosis. Instruments have been designed in the form of long clamps to create a consistent transmural lesion line without causing injury to surrounding tissues. Other energy types initially described, as microwave or monopolar radiofrequency, were abandoned due to lack of consistent transmural lesions or by increased risk of collateral injuries. But, besides different instrumentation, the actual lesion pattern remains basically the one described by Cox

in 1991, with few exceptions. First, most surgeons avoid the atrial septal lesion, making this procedure no longer associated with a higher need of pacemaker implantation than what it is associated to whatever concomitant procedure is coupled with. Second, to avoid possible deficit of atrial natriuretic peptide production, only the left appendage is excluded.

The direct vision of the heart and the rapid creation of transmural lesions with these techniques add only 15 to 30 minutes to the surgical time. Surgeons tend to minimize the cut and sew lesions to the ones needed to access the atria, trying to perform the maximum number of lines with cold or heat therapies. Several techniques have been described to avoid coronary artery injuries when approaching the mitral and tricuspid annulus.

When indicating a surgical therapy to AF, factors influencing success rate must be foreseen. These include atrial dilatation, age, years in AF, and type of AF (paroxysmal, persistent, or long-standing persistent). Probably the most important is atrial dilatation, due to chronic AF or by valvular dysfunction [11]. Scientific evidence shows that Cox-Maze procedure is less effective when left atrial postero-anterior diameter reaches 60 mm, and even when effective, atrial electrical stimuli transport usually is impaired. Type of AF is also an important condition for success rates. While pulmonary vein isolation has showed good results in patients with paroxysmal atrial fibrillation, persistent and long-standing persistent patients benefit from the complete biatrial lesion set in order to get sinus rhythm maintenance over 80% at 10 years. Therefore, surgical approach must be tailored in these patients [12].

### 3. Minimally Invasive Techniques for Isolated AF

With the development of new energy sources for atrial fibrillation and a better knowledge of the pathophysiology of AF, different surgical instruments have been created to allow a minimal invasive approach and effectively treat AF without big thoracic incisions. Energy is applied epicardially through direct vision with clamps that allow long transmural lesions. Moreover, epicardial ganglionic plexi around the pulmonary veins can be identified and ablated, and the left appendage excised or clipped to minimize thromboembolic events.

In 2005, Wolf published a series of 27 patients with pulmonary vein ablation with epicardially applied bipolar radiofrequency and left appendage exclusion. This procedure was named Mini-Maze IV (Figures 2 and 3). The sinus rhythm was restored in 91% of patients with previous paroxysmal AF, without mortality and a low morbidity. The procedure was performed through bilateral 5 cm thoracotomy incisions and video-thoracoscopy assistance [13]. Later on, this operation has evolved to a totally thoracoscopic technique, with three 1 cm incisions in each side. Moreover, new connecting lesions from the right to the left superior veins and to the mitral annulus have been described to treat persistent AF patients [14, 15].

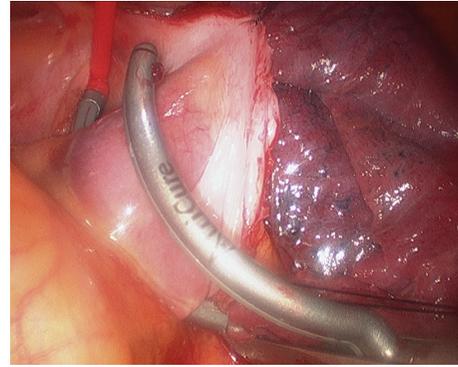


FIGURE 2: Pulmonary vein ablation by bipolar radiofrequency through a thoracoscopic approach. The ablation line can be seen in the left atrium at the antrum of the pulmonary veins.



FIGURE 3: New clip device to close the left atrial appendage through sternotomy or thoracoscopic approaches.

These procedures have shown especially good results in patients with failed previous catheter ablation. In our series of 61 patients of pulmonary vein isolation with bipolar radiofrequency, postoperative sinus rhythm was maintained in 82% paroxysmal, 60% persistent, and 20% long-standing persistent AF patients at 12 months. LA size >45 mm and AF type showed to be preoperative factors that significantly influenced outcome [16]. The recent 2010 Guidelines of the ESC and EACTS recommends, minimally invasive surgical ablation of AF without concomitant cardiac surgery to patients with lone symptomatic AF after failure of catheter ablation [7, 8].

### 4. Conclusions

With better knowledge of the physiopathology of AF and easier access to energy sources that create consistent transmural lesions, surgery of atrial fibrillation has made a great impulse from the early days when Cox first described his Maze procedure. Concomitant surgical AF treatment has shown better survival rate, higher freedom from stroke and thromboembolic events, better ventricular function, and better exercise tolerance. Still, success rates are lower in patients with long history of AF, usually with enlarged atria, long-standing persistent AF pattern, and older age. Probably,

the alteration of the atrial substrate, with more fibrotic tissue and established macro-reentrant circuits may limit maze strategies in these patients.

In addition, minimally invasive approaches have been described in the last five years with very good results for isolated paroxysmal or persistent AF. Nevertheless, prospective randomized trials are necessary to confirm their long-term results, compared to catheter ablation.

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## Review Article

# Cost of AF Ablation: Where Do We Stand?

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Atrial fibrillation (AF) is a common and frequently disabling chronic condition associated with significant patient morbidity and affecting an increasing stratum of our ageing society. Direct costs related to atrial fibrillation are comprised from direct cost of medical therapy, catheter ablation, and related hospitalizations and imaging procedures, with indirect costs related to complications of the primary therapeutic strategy, management of related conditions, as well as disability and loss in quality of life related to AF. Over the last decade, catheter ablation became a promising alternative to rate and rhythm control among symptomatic AF patients. The purpose of this paper is to describe the evidence on the financial implications related to ablation based on published data and authors' experience.

## 1. Implications of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia [1]. It is responsible for most arrhythmia-related hospitalizations and leads to the greatest length of hospital stay associated with any disorder of the cardiac rhythm [2]. While associated with increased mortality in the affected patients, atrial fibrillation is thought to be responsible for the majority of thromboembolic events, many of these preventable [3]. Strokes reported with equal frequency in patients with both paroxysmal and permanent atrial fibrillation have been more devastating and associated with greater disability than embolic events related to other cardiac disorders [4–6]. Patients with AF account for 15% of all strokes and are at a significantly increased risk of death due to stroke and heart failure [7]. Of all patients experiencing a stroke related to AF, 60% will be discharged with a new disability while 20% will die [8]. While the most apparent negative outcome of this arrhythmia, strokes are by far just the tip of the iceberg. Patients with AF are prone to develop rapid poorly controlled heart rate associated with significant disability and development of cardiomyopathy in some patients. These patients along with those who have hypertrophic cardiomyopathy and other less obvious etiology of diastolic dysfunction are at substantial

risk of developing congestive heart failure while in AF [9]. Recent evidence also suggests greater mortality simply related to faster heart rates in some patients [10]. A staggering 70%–80% of AF patients are admitted to hospital at some point in the course of their disease. Finally, AF is a source of disability for many younger members of the workforce who feel out of control when their heart rate suddenly becomes erratic. It may lead to frequent hospital visits [11], inpatient and outpatient monitoring, imaging and cardioversion procedures, and, of course, invasive therapies ranging from cardiac pacing in patients with concomitant dysfunction of the sinus node, to ablation of the AV node in concert with permanent pacing or cardiac resynchronization therapy and to the “curative” ablation of the cardiac tissues thought to trigger and perpetuate AF.

## 2. Sources of Cost in AF

Multiple negative health outcomes in AF patients as well as AF treatment strategies contribute to an ever-growing tap drawn on the healthcare system and the society at large. To make matters worse, AF is a disorder affecting preferentially older members of the society with greater than 10% prevalence in those over the age of eighty [4]. This is a disastrous proposition in an aging society with

exponentially increasing occurrence of this condition and subsequently skyrocketing costs related to the associated morbidity, disability, and treatment. A recent systematic review of the cost of AF care revealed that the overall average annual cost to support the system to manage one AF patient is \$7,226 with a range of estimated costs as high as just over \$10,000 [12]. While these costs are substantial, they represent only about one quarter of the entire health system costs for patients with AF. Two studies estimated the entire system cost for all care for patients with AF to range between \$20,613 to \$40,169. Hospitalizations are the most important determination of total cost (58%) with the cost of a single acute admission in Ontario with AF as a primary diagnosis of \$24,096 [13]. Rhythm and rate control strategies targeting disability related to AF have seen little evolution over the years, and no radically new agents have come to market in decades. Multiple comparisons of these strategies have come in short of finding a winner, and both approaches have had significant clinical limitations [14–16].

### 3. Cost Containment Strategies

A number of studies have looked at the potential cost containment strategies. Of these, the most obvious is greater attention to anticoagulation therapy in patients suffering from AF. The bulk of current cost of AF care is related to thromboembolism, yet currently as few as 10%–20% of the AF patients are treated with appropriate prophylaxis strategies [5]. Those who do take oral anticoagulants spend much of their time taking subtherapeutic doses of the medication placing them at risk of stroke, while others take supertherapeutic doses and run a significant risk of bleeding given a very narrow therapeutic range of warfarin. Multiple new medications targeted to prevent stroke in AF patients are becoming available, but while easier to use, these may have their own risks related to lack of reversibility and may carry a substantial upfront cost [17]. A new antiarrhythmic medication, dronedarone, available to the clinicians in Canada for just over a year had shown promise of lesser risk of toxicity and uniquely was shown to reduce morbidity and mortality in AF patients, but has done so despite being no more effective at controlling the actual rhythm disorder than the other drugs. The impact this strategy will have on the cost of care in AF remains to be determined.

Another such strategy has to do with ablation. First promise for a potential cure for AF came in 1998 when it became apparent that ectopic atrial activity originating in the pulmonary veins may be responsible for initiation of AF and could be targeted with radiofrequency energy [18]. The field of targeting AF triggers had seen substantial progress since this discovery with multiple tools coming to market over the last decade in an effort to improve the safety and efficacy of these procedures. Most of these strategies involved delivering various types of energy just proximal to the insertion of the pulmonary veins into the left atrium using conventional, irrigated tip, and circular- and balloon-shaped catheters. Another strategy that was first described in 2004 and had seen much technological attention has

been that of targeting tissues thought to perpetuate AF or presenting so-called AF substrate [19]. These latter efforts have focused on elimination of the viable atrial myocardium displaying particularly disorganized activity during AF or delivering energy over autonomic nerve ganglia thought to initiate and perpetuate the arrhythmia.

These approaches have shown promise in a multitude of individual center and multicenter randomized trials uniformly showing clinical benefit of ablation over antiarrhythmic drug therapy with respect to sinus rhythm maintenance, quality of life, and arrhythmia, related hospitalizations in at least some populations [20–22].

Unfortunately, in this rapidly evolving field most studies have focused on short-term comparisons between ablation and medical therapy as well as on the assessment of the relative efficacy of ablation strategies and tools. While the literature is unanimous in praising ablation as winner with respect to control of symptomatic arrhythmia over 6–12 months, until recently little has been published about the long-term efficacy of ablation and even less about its effect on mortality and embolism. Initial reports of AF ablation suggested greater than 90% freedom from arrhythmia among treated patients. Now a decade later many are publishing results suggesting much more modest upfront benefits with a difficult to ignore success attrition rate. While long term success rates varied drastically in these publications from 9% very late recurrence rate reported by Shah et al. [23] to 92% recurrence rate reported by Katritsis et al. [24], most investigators agreed that AF ablation does not impart cure of this condition in a significant number of patients. Incidentally, our findings of 42% recurrence following pulmonary vein antrum isolation with 30% likelihood of further arrhythmia in patients thought of as “cured” one year following the procedure represent a medium late recurrence rate compared to these publications, are in line with the recent report by Bertaglia et al. [25], and demonstrate a lower annual recurrence rate following the first year compared to the report by Tzou et al. [26]. Moreover, patients suffering from further AF are subjected to multiple repeat procedures further contributing to the growing cost to healthcare. Our well-characterized cohort of patients for the first time illustrated ever-diminishing return on this investment with 50% success of the second and 25% success of the third ablation.

### 4. Ablation versus Medical Therapy: Cost Perspective

Several projections of cost of care of an AF patient have been published in an attempt to estimate the relative cost of ablation and contrast it to the cost of medical therapy over time. A study directly comparing the costs of ablation and medical therapy in the Canadian healthcare environment has been published [27]. Costs related to medical therapy in the analysis included the cost of anticoagulation, rate and rhythm control medications, noninvasive testing, physician followup visits, and hospital admissions, as well as the cost of complications related to this management strategy. Costs related to catheter ablation were assumed to include

the cost of the ablation tools (electroanatomic mapping or intracardiac echocardiography-guided pulmonary vein ablation), hospital and physician billings, and costs related to periprocedural medical care and complications. Costs related to these various elements were obtained from the Canadian Registry of Atrial Fibrillation (CARAF), government-fee schedules, and published data. Sensitivity analyses looking at a range of initial success rates (50%–75%) and late attrition rates (1%–5%), prevalence of congestive heart failure (20%–60%) as well as discounting varying from 3% to 5% per year were performed. In this study, the cost of catheter ablation strategy ranged from ~US\$14,000 to US\$18,000. It was assumed that patients who required anticoagulation prior to ablation would continue on this therapy following the procedure with an annual average followup cost of US\$1400 to US\$1800 among the ablated patients. The annual cost of medical therapy ranged from US\$3,600 to US\$4300. The latter estimate was supported by the findings from the FRACTAL registry which prospectively collected clinical and cost data for 973 patients with atrial fibrillation [28]. The study projected costs of ongoing medical therapy and catheter ablation to equalize at 3.2 to 8.4 years of followup in this study but did not take into account development of the novel antiarrhythmic and thromboprophylactic strategies not available at the time of the publication.

A number of AF cost estimates have been published internationally. Treatment costs associated with followup of AF patients including hospital admissions, emergency room visits, and testing and followup with cardiologists, internists, and family physicians were analyzed in France [29]. This analysis stratified patients according to therapeutic strategy—rate or rhythm control—as well as according to concomitant congestive heart failure symptoms. The authors estimated the average total 5-year cost of AF at 16,539 Euro. In a study from Bordeaux, 118 patients  $52 \pm 18$  years of age with symptomatic drug refractory paroxysmal AF underwent 1–4 pulmonary vein isolation procedures per patient [30]. All patients previously failed at least 2 antiarrhythmic drugs, with close to 80% having failed amiodarone. During a followup period of  $32 \pm 15$  weeks, 72% of them were free of AF without the use of antiarrhythmic drugs. The cost of care was estimated in 2001 Euro. Procedural costs and costs related to hospitalization were obtained from hospital billing data. The cost of medical therapy was based on review of 20 consecutive patients and accounted for antiarrhythmic drugs used, frequency of symptoms prior to ablation, frequency of visits to the emergency room, doctor's office visits, and hospital admissions. All future costs were estimated using 5% discounting/year. It was assumed that patients were hospitalized for 5 days around the time of ablation. Neither complex mapping systems nor intracardiac echocardiography were used or accounted for. Furthermore, it was assumed that patients were treated with a fixed antiarrhythmic routine for 12 months prior to ablation. The projected annual cost of medical therapy was estimated at 1,590 Euros. The upfront cost of ablation was estimated at 4,715 Euros. Assuming that ablation was successful in 28% of all patients, the cost of ongoing care in the ablated patients was estimated at 445 Euros per year. As a result, the costs of

medical therapy and ablation crossed over between four and five years. Since no complications occurred in the ablated patients in this study, these were not accounted for in the analysis. Furthermore, followup costs were accrued only for patients failing AF ablation with no additional cost assigned to followup of the successfully ablated patients.

In an in-depth look at the cost of AF ablation among Medicare patients followed for a year after ablation, Kim et al. found the cost of successful ablation at US\$16,049  $\pm$  12,536 versus US\$19,997  $\pm$  13,958 for failed ablation. Ablation was successful in 51% of the patients in his cohort, similar to our findings [31].

Four papers attempted to perform a cost-benefit analysis of AF ablation with that of medical therapy. In the first of these studies, a Markov decision analysis model looking at 55- and 65-year-old cohorts of patients at low and moderate risk of stroke was created by the investigators [32]. Complications and costs related to AF, medical therapy, and catheter ablation were accounted for. The model assumed that amiodarone would be used for rhythm control and a combination of digoxin and atenolol—for rate control. Eighty percent efficacy of AF ablation was assumed with 30% redo rate during the first year and 2% per year late success attrition rate. It was further assumed that as many as 38% of the patients on rate control would convert to sinus rhythm with annual AF relapse rate of 5%. Moderate risk of stroke was defined as having one risk factor, including diabetes, hypertension, coronary artery disease, or congestive heart failure. Patients at low risk of stroke were assumed to have no such risk factors. For the purpose of the model, patients at moderate risk of stroke were anticoagulated, whereas those at low risk could be on warfarin or aspirin. The model incorporated annual stroke risk of 2.3% and 1.1% for patients treated with aspirin and 1.3% and 0.7% for those on warfarin at moderate and low risk for stroke, respectively. A relative stroke risk of 1.4% per decade was accounted for. Age-adjusted mortality based on life tables and mortality reductions attributable to aspirin and warfarin were accounted for. All health care costs were calculated in 2004 US dollars using 3% discounting per year. Costs were estimated based on Medicare reimbursement rates, hospital accounting information, published literature, and the Red Book for wholesale drug costs. Catheter ablation appeared to be most cost-effective in younger patients at moderate risk of stroke at \$28,700/QALY gained. It was somewhat less cost-effective in the older moderate risk patients at \$51,800/QALY gained and least cost-effective among the younger patients at low risk of stroke at \$98,900/QALY gained. Unfortunately, since no evidence has been presented to date on the efficacy of ablation for prevention of thromboembolic events, the findings of this study are conditional on such evidence coming to light in the years to come.

Eckard et al. developed a decision-analytic model to estimate costs, health outcomes and incremental cost-effectiveness of RFA compared to AAD treatment for AF for a lifetime time horizon [33]. The authors used a decision tree for the initial year in which the RFA procedure is assumed to take place, and a long-term Markov structure for subsequent years. The authors factored in the potential for a second

ablation within a year of the first procedure in patients still suffering from AF. They assumed 70%–80% ablation success within the first year with 1.4 ablations per patient required to maintain rhythm based on Swedish data. The cost of ablation was estimated at around US\$12,000, including the cost of 3–4 days in hospital, all diagnostic examinations necessary as well as the cost of disposables. Annual cost of AF therapy was estimated at US\$2000. In order to estimate QALY weights for different health states, age-adjusted QALY weights based on a Swedish general population were applied for patients in the controlled AF state and used as reference points. A decrement of 0.1 for uncontrolled AF and 0.25 for stroke was applied to the baseline utility in the controlled AF state. With annual success attrition rates of 5%, 10%, and 15% used in the sensitivity analysis, the relative cost of ablation was estimated up to US\$58000 per QALY without assuming stroke prevention related to the ablation strategy.

A similar analysis in the United Kingdom suggested incremental cost effectiveness of ablation at US\$16,000 per QALY in 2008 dollars. The authors of this paper assumed freedom from AF at 84% at one year with 2%–4%/year rate of success attrition over time resulting in their estimates favouring ablation over the other published economic analyses. Further sensitivity analyses found the estimate to depend significantly both on the relative QOL estimate associated with sinus rhythm and on the prognostic implications of being in rhythm [34].

Finally in a more recent paper, Reynolds and his group published a Markov model cost-effectiveness analysis of ablation versus antiarrhythmic therapy in a simulated cohort of patients with paroxysmal drug refractory AF projected over 5 years. The authors assumed 60% success of the ablation approach with a 25% rate of repeat ablation. Utilities for QOL assessment were derived from real-life data, using the FRACTAL registry for the medically treated patients using SF-12 and patients ablated at the authors' institution as well as those enrolled in the A4 trial for derivation of the scores in this cohort based on the SF-36 questionnaire. In the base scenario, the incremental cost per QALY among ablated patients was US\$47,333 with cost neutrality achieved at ~10 years [35].

This latter finding corresponds to the extreme variation in the model originally presented by Khaykin et al, where assuming actual clinical outcomes and costs incurred in the care of over 600 AF patients since 2004, the costs of ablation and medical therapy would be expected to reach parity at 6–9 years for patients with paroxysmal AF and at 8–15 years for patients with nonparoxysmal AF. Unfortunately, there is little well-reported data on AF followup greater than 5 years postablation, and significant advances in technology and medical therapy are typically seen over such an extended period with significant premium associated with new treatment modalities and little concurrent data on any associated clinical benefit over the standard of care. In this environment, exact relative costs of ablation and medical therapy remain elusive leaving us with reasonably well-grounded assumptions at best.

## 5. Global Perspective

While there is accumulating data from multiple geographies that ablation is both clinically superior and is economically feasible in certain populations, it may not be available globally. Furthermore, despite the advent of international practice guidelines, the care of AF patients, thresholds for application of therapies with an expensive upfront price tag such as ablation may vary dramatically from country to country and between population strata within any given geography. A good illustration of this principle is an in-depth analysis looking at the direct cost of AF care across several European countries for a prespecified patient (female aged <65 years with first-detected AF and no comorbidities at baseline) where costs varied from about US\$1000 per year to US\$2200 [36]. That said, reassuringly, the estimates of cost and cost effectiveness of ablation have been within close range of each other in Canada, the United States, and Europe using a variety of assumptions taken and sensitivity analysis performed, generally speaking supporting the claim of cost effectiveness of ablation.

## 6. Future Considerations

Several developments may impact our understanding of the cost effectiveness of AF ablation in the next decade. First and foremost, the techniques of AF ablation are constantly evolving and we have seen an unprecedented influx of new AF ablation technologies. While all published studies are based on the success of standard point-by-point AF ablation, and most long-term studies followed patients ablated using a solid tip catheter, the broader adoption of irrigated tip catheters in the last few years and new ablation technologies may change the landscape of AF ablation by substantially improving outcomes and reducing resources and operator training necessary to achieve success. Whether this would translate into improved economics of AF ablation will depend to a large extent on the incremental cost of these technologies in relation to incremental success or reduction in the rate of procedural complications.

New antithrombotic agents such as dabigatran may substantially reduce the cost related to anticoagulation management and may usher in an era of intermittent oral anticoagulation targeted to the time the patients actually spend in AF. This may substantially impact the cost of medical therapy, making it more attractive but would also improve the cost of the ablation strategy in patients who would no longer require preoperative bridging of their anticoagulation and will affect the cost of ongoing therapy in patients following ablation.

Similar considerations may apply to the new antiarrhythmic agents which, like dronedarone, may be less likely to cause long-term complications associated with this group of drugs in the past and therefore would be expected to improve the cost of medical therapy.

Finally, a large multicenter international trial, CABANA, will help us get a better understanding of the relative risks and benefits of ablation and medical therapy using “hard”

outcomes of death and stroke and will allow for a definitive cost-effectiveness analysis of AF ablation.

## 7. Conclusions

Atrial fibrillation clearly remains a significant medical disorder with far reaching social and economic implications. Despite significant advances in our understanding of this condition, we are far from having developed a perfect therapeutic strategy for AF. Several new agents that have entered the market show promise for reduction of morbidity and mortality related to this condition, while government initiatives are coming into place to streamline care and avoid preventable and costly negative health outcomes.

Several studies comparing ablation with medical therapy support the claim of short-term benefits related to the invasive therapy among patients with paroxysmal AF. At the same time, recent evidence suggests greater attrition of success among ablated patients over the long run than used in most of these studies. In this climate, previously published literature supporting long-term economic benefit of ablation has to be critically reassessed, and new models based on real life outcomes data need to be looked at to re-evaluate their findings.

Finally, evolution of ablation technologies, antiarrhythmic and antithrombotic agents, and large clinical trials comparing the impact of ablation and medical therapy on morbidity and mortality may radically change our understanding of the economics of AF ablation in the next few years.

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## Review Article

# Current Ablation Strategies for Persistent and Long-Standing Persistent Atrial Fibrillation

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Atrial fibrillation (AF) is associated with an increased risk of cardiac and overall mortality. Restoration and maintenance of sinus rhythm is of paramount importance if it can be accomplished without the use of antiarrhythmic drugs. Catheter ablation has evolved into a well-established treatment option for patients with symptomatic, drug-refractory AF. Ablation strategies which target the pulmonary veins are the cornerstone of AF ablation procedures, irrespective of the AF type. Ablation strategies in the setting of persistent and long-standing persistent AF are more complex. Many centers follow a stepwise ablation approach including pulmonary vein antral isolation as the initial step, electrogram-based ablation at sites exhibiting complex fractionated atrial electrograms, and linear lesions. Up to now, no single strategy is uniformly effective in patients with persistent and long-standing persistent AF. The present study reviewed the efficacy of the current ablation strategies for persistent and long-standing persistent AF.

## 1. Introduction

Atrial fibrillation (AF) is associated with a 2-fold risk of cardiac and overall mortality [1]. Restoration and maintenance of sinus rhythm is of paramount importance if it can be accomplished without the use of antiarrhythmic drugs [2]. Catheter ablation of AF has been widely accepted as an important therapeutic modality for the treatment of patients with symptomatic AF, refractory or intolerant to at least one class I or III antiarrhythmic medication [3–5]. Previous studies have clearly demonstrated the superiority of catheter ablation over antiarrhythmic drug treatment, even in patients with persistent AF [6–11]. The recently published ESC guidelines state that ablation of persistent symptomatic AF that is refractory to antiarrhythmic therapy should be considered a treatment option (class IIa, level of evidence B) [5]. In addition, catheter ablation of AF may also be considered in patients with symptomatic long-standing persistent AF refractory to antiarrhythmic drugs (class IIb, level of evidence C) [5].

Following the work of Haïssaguerre et al. [12], catheter ablation of paroxysmal AF aiming at electrical pulmonary vein isolation (PVI) results in maintenance of sinus rhythm in 60 to 85% of patients [13, 14]. On the contrary, PVI is considered insufficient to eliminate persistent or long-standing persistent AF (more than one year) leading to significantly lower success rate of this method [3, 4, 15, 16]. Substrate modification is usually required in the setting of persistent and long-standing persistent AF [15, 16]. Although different ablation strategies have been reported in persistent and long-standing persistent AF, the reproducibility of these techniques is considered inconsistent. This paper highlights on the current catheter ablation strategies for persistent and long-standing persistent AF.

## 2. Pathophysiology of Atrial Fibrillation

The pathophysiology of AF is multifactorial, complex, and not well defined. Up to date, two main theories have been reported for the initiation and maintenance of AF. The

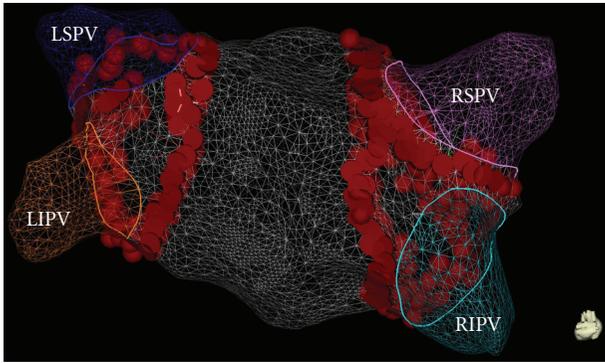


FIGURE 1: Three-dimensional reconstruction of the left atrium using the CARTO 3 map system (Biosense Webster, USA) showing large circumferential ablation lesions around both ipsilateral veins. In this example, additional radiofrequency energy was applied on the interpulmonary isthmus following the large circumferential lesion creating a “figure of eight” model. LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein.

single-focus hypothesis advocates that AF is due to a single automatic focus or a microreentrant circuit [5, 17]. Triggers that originate from the PVs and other thoracic veins appear to be the primary mechanism of AF, particularly in subjects with paroxysmal AF [5, 12, 18]. The multiple re-entrant wavelet hypothesis supports that fractionation of wavefronts propagating through the atria results in self-perpetuating “daughter wavelets” [19, 20]. Multiple re-entrant wavelets are separated by lines of functional conduction block, and AF is perpetuated by slowed conduction, increased atrial mass, and shorter refractory periods [5, 19, 20]. The relationship between these mechanisms is complex, and they often coexist in the same patient, particularly in the setting of persistent AF or long-standing persistent AF [21]. Autonomic factors have also been implicated in the generation of complex fractionated atrial electrograms (CFAEs), an important substrate of AF [3, 4]. Electroanatomic remodeling that develops as AF progresses from paroxysmal to persistent and permanent has been well demonstrated to further facilitate AF (“AF begets AF”) [22]. Atrial dilation, interstitial fibrosis, uncoupling of the myofibrils, loss of myofibrils, deposition of extracellular matrix, loss of gap junctions, resultant anisotropy, conduction slowing and/or block, and shortening of the effective refractory period may facilitate re-entry, which is critical to perpetuation of AF [3]. As a result of progressive electroanatomic remodelling, mechanisms other than PV arrhythmogenicity are strongly involved and perpetuate AF. Therefore, in addition to PVI, left atrial ablation that modifies the substrate is required in the setting of persistent and long-standing persistent AF.

### 3. Ablation Strategies and Success Rates in Persistent AF

3.1. *Pulmonary Vein Antral Isolation.* Ablation strategies which target the PV ostium or the PV antrum aiming at

electrical disconnection of the PVs are the cornerstone of AF ablation procedures. Initial attempts targeted the arrhythmogenic activity within the PVs using a focal approach [12]. Due to the high risk of PV stenosis and the high rate of recurrence, complete electrical isolation of the PVs by segmental ostial ablation quickly replaced the initial approach [23, 24]. Successful electrical isolation is defined by loss of PV potentials (entrance block) and failure to capture left atrium during pacing from the PV (exit block) (Figure 1). Pappone et al. have introduced the circumferential PV ablation (PV antral ablation) without electrical PV disconnection [25]. This technique involves applications of radiofrequency energy 1-2 cm away from the ostia of the PVs until the local electrogram amplitude decreased by  $\geq 80\%$  or to  $< 0.1$  mV. In a randomized trial, Arentz et al. have demonstrated that isolation of a large circumferential area around both ipsilateral PVs with verification of conduction block (pulmonary vein antral isolation (PVAI)) is a more effective treatment of AF than isolation of each individual PV using a segmental approach [26]. The end point of ablation is the absence or dissociation of residual PV potentials in the isolated area as documented with the circular mapping catheter. Figure 2 shows the three-dimensional reconstruction of the left atrium with large circumferential ablation lesions around both ipsilateral veins and additional ablation lines on the interpulmonary isthmus creating a “figure of eight” model.

Segmental PVI or PVAI confirmed by absence or dissociation of PV potentials is the most effective strategy for treatment of most patients with paroxysmal AF [27–29]. Despite achieving a very high rate of electrical PVI, PVI strategies alone have consistently demonstrated a lower success rate in patients with persistent and long-standing persistent AF compared to paroxysmal AF [3, 4, 29–32]. PVI alone in persistent and long-standing persistent AF was associated with a single-procedure, drug-free success rate ranging from 21% to 22% at almost 2 years [33]. On the contrary, PVAI display higher success rates. In a randomized trial, Oral et al. have shown that the success rate of the index procedure after successful PVAI was 36% in patients with long-standing persistent AF [34]. In the same line, Elayi et al. reported a 40% success rate following PVAI in patients with long-standing persistent AF [35]. In a recent study, Tilz et al. have shown that PVAI is sufficient to restore SR in 43.2% of patients with long-standing persistent AF [36]. Cheema et al. have demonstrated that single-procedure success rate is higher in patients who were in AF for  $\leq 1$  year compared with those in AF for  $> 1$  year (50% versus 20%, resp.) [37]. The variations in success rates of these studies may be attributed to the different definitions of long-standing AF as well as at the different end-points for AF ablation. Nevertheless, PVAI with electrical disconnection of the encircled veins within the ablated margins has become the preferable ablation strategy in patients with persistent and long-standing persistent AF. It is of major importance to perform a continuous circumferential line around both ipsilateral PVs, and then to validate for electrical PV disconnection aiming at the earliest residual potential recorded by the circular mapping catheter.

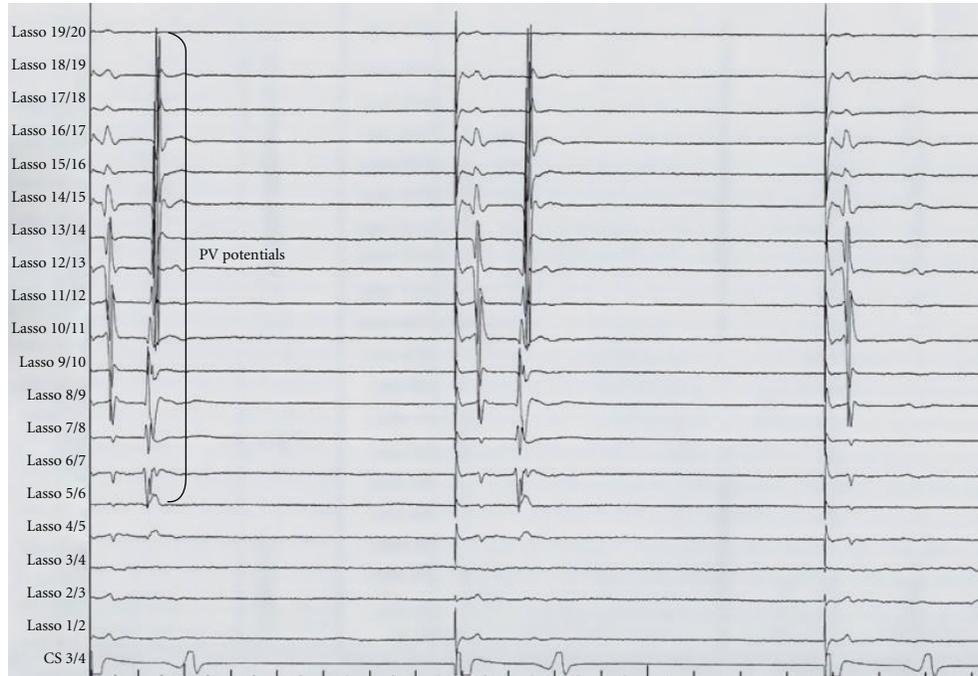


FIGURE 2: Pulmonary vein (PV) potentials recorded from the Lasso catheter bipoles during pacing from the coronary sinus (CS 3/4). In this example, the PV potentials are disappeared in the third-paced beat indicating entrance block.

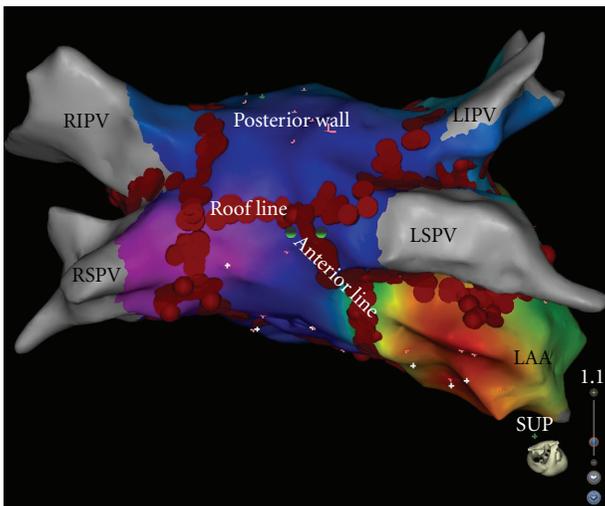


FIGURE 3: Three-dimensional reconstruction of the left atrium using the CARTO 3 map system (Biosense Webster, USA) showing large circumferential ablation lesions around both ipsilateral veins along with roof and anterior lines. LAA: left atrial appendage; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein.

3.2. *Linear Ablation.* Based on the high success rates of surgical MAZE procedures [38], several attempts have been made to reproduce these results by percutaneous catheter-based linear ablations. Linear lesions are intended to modify the arrhythmogenic LA substrate and atrial macro-reentrant circuits involved in maintenance of AF [30, 31, 39,

40]. Addition of linear lesions has been associated with conversion of AF either directly to sinus rhythm or to atrial tachycardia (AT), demonstrating that such lesions significantly modify the substrate for AF [40]. Linear lesions usually include a roof line connecting the left and right superior PVs and a mitral line connecting the mitral annulus to the left inferior PV (Figure 3) [30, 31, 39, 40]. An anterior line connecting the anterior or anterolateral mitral annulus with the left superior PV has been also proven effective for the treatment of perimitral flutter (Figure 3) [41]. Knecht et al. showed that although PVI and electrogram-based ablation without linear lesions are effective for terminating persistent AF in a significant number of patients, macro-reentrant AT requiring LA linear ablation is very likely to occur during the overall follow-up period. In this study, after a followup of more than 2 years, among all the patients ablated for persistent AF, 96% ultimately required a roofline and 86% a mitral line [40]. Linear lesions applied at the mitral isthmus or the roof of the LA increase the AF cycle length by a mean of 20 ms and exert a favourable impact on elimination of AF [39]. In the study of Jaïs et al., 68% of patients required an ablation within the coronary sinus facing the endocardial aspect of the mitral isthmus because of persisting epicardial conduction [39].

LA linear ablation still remains technically challenging. Bidirectional block across the lines has to be confirmed in order to assess completeness of linear lesions [39, 40]. Conduction block of the roof line can be accomplished more frequently compared with the mitral isthmus line. When complete linear block could not be achieved during the index procedure, the incidence of subsequent roof or mitral isthmus-dependent macro-re-entrant AT is higher. In

particular, the incidence of macro-re-entrant ATs in patients with and without conduction block of the roof line at the index procedure was 19% and 50%, respectively [40]. The rates for mitral isthmus line were 26% and 56%, respectively [40].

Willems et al. have investigated the effectiveness of additional substrate modification by left atrial linear lesions as compared with PVI alone in patients with persistent AF in a prospective randomized study [42]. After a mean follow-up time of 487 days, only 20% of patients undergoing stand alone PVI remained in sinus rhythm when compared with 69% following PVI combined with substrate modification. This study clearly shows that PVI alone is insufficient for the treatment of patients with persistent AF. In the same line, Fassini et al. confirmed the additional benefit of mitral isthmus ablation in patients with persistent AF [43]. In a systematic review, PV antral ablation or PVAI along with linear substrate modification was associated with a single-procedure, drug-free clinical success rate ranging from 11% to 74% at approximately 1.5 years [33]. The highly variable success rate is possibly related to different procedural endpoints and/or criteria for linear lesion contiguity.

**3.3. Complex-Fractionated Atrial Electrograms.** CFAEs areas represent potential AF substrate sites and are now considered as important targets for AF catheter ablation [3, 4]. CFAEs indicate sites of slow conduction, wavefront collision, conduction block, or anchor points for reentrant circuits based on the findings of an epicardial unipolar mapping study in humans [44]. CFAEs have also been proposed to indicate sites of ganglionated plexi, as shorter effective refractory period at these sites would allow higher-frequency activation [45]. CFAEs were initially defined by Nademanee et al. as (i) atrial electrograms that are fractionated and composed of two or more deflections averaged over a 10-second recording period and (ii) atrial electrograms with a very short cycle length ( $\leq 120$  ms) with or without multiple potentials when compared with the atrial cycle length recorded from other parts of the atria [46]. Haïssaguerre et al. performed LA ablation at all sites displaying any of the following electrogram features: continuous electrical activity, CFAEs as previously defined, sites with a gradient of activation (significant electrogram offset between the distal and proximal recording bipoles on the map electrode), or regions with a cycle length shorter than the mean left atrial appendage AF cycle length [15]. End points for ablation at sites of CFAEs include complete elimination of CFAEs or slowing and organization of local electrograms [15, 46, 47]. An important limitation of this new approach is that CFAEs are identified by visual inspection, and therefore this process is highly dependent on the operator's judgment. The lack of a consistent, reproducible technique for measuring CFAEs represents a significant challenge in the implementation of the results of studies assessing the impact of CFAEs ablation on procedural outcome. Verma et al. used an automated algorithm (Ensite NavX, St Jude Medical) to define CFAEs sites with cycle lengths  $\leq 120$  ms [48].

Nademanee et al. have initially showed that ablation of CFAEs alone resulted in termination of AF without external

cardioversion in 95% of patients persistent or paroxysmal AF and at one-year followup, 91% of patients were free of arrhythmia and symptoms [46]. On the contrary, Oral et al. reported a modest short-term efficacy of the ablation procedure when targeting only the CFAEs [44]. In particular, only 33% of patients were in sinus rhythm without the use of antiarrhythmic drugs after the index ablation [47]. Similarly, Estner et al. showed that ablation of CFAEs as a stand-alone ablation strategy seems insufficient for the treatment of patients with persistent AF [49]. CFAEs ablation alone has been associated with a single-procedure, drug-free success rates ranging from 24% to 63% at approximately 1 year [33].

A combined approach of PVI or PVAI and CFAEs ablation in persistent AF leads to acute AF termination in 66% and long-term maintenance of sinus rhythm in 74% of cases [50]. The role of ablation of CFAEs following PVAI was investigated in two recent randomized studies. Elayi et al. have shown that CFAE plus PVAI (61%) outperformed PVAI (40%), which was superior to PV antral ablation without electrical isolation (11%) [35]. Oral et al. randomized 119 consecutive patients with long-standing persistent AF to PVAI or PVAI and further CFAEs ablation. These authors found that up to 2 h of additional ablation of CFAEs after PVAI does not appear to improve clinical outcomes in patients with long-standing persistent AF [34]. In the same line, Bencsik et al. have recently demonstrated that CFAEs ablation guided by a dedicated software algorithm and performed after PVAI had no significant impact on the fibrillatory process and displayed a minor role in achieving higher rates of termination and noninducibility in patients with persistent AF [51]. In a systematic review, the single-procedure, drug-free success rates of CFAEs ablation in persistent and long-standing persistent AF as an adjunct to PV antrum ablation, PVAI or PVAI and linear ablation were 50-51%, 36-61%, and 68%, respectively [33]. A recent meta-analysis of six randomized trial has demonstrated that PVI followed by adjunctive CFAEs ablation is associated with increased freedom from AF after a single procedure [52]. However, CFAEs ablation significantly increased mean procedural, mean fluoroscopy, and mean radiofrequency energy application times [52].

**3.4. Nonpulmonary Vein Foci.** Although the PVs are a dominant source of AF, non-PV ectopic activity can trigger AF, and ablation of these ectopic activities can eliminate AF in a specific group of patients. Non-PV triggers are more commonly observed in patients with persistent (8.2%) and long-standing persistent AF (19.1%) in relation to those with paroxysmal AF (2.9%) [53]. Ablation of non-PV foci following PVI can organize persistent AF into focal or macro-re-entrant atrial tachycardias, which can be eliminated, resulting in maintenance of sinus rhythm in the majority of patients [54, 55]. The majority of non-PV foci responsible for initiation of AF are located in the superior vena cava, crista terminalis, coronary sinus, LA free wall, LA appendage, and ligament of Marshall [54, 55].

**3.5. Stepwise Catheter Ablation Approach.** According to the Bordeaux group, [15, 16, 30-32, 56, 57] the stepwise catheter

ablation approach for persistent AF includes (i) PVI as the initial step aiming at elimination of PV electrograms, (ii) electrogram-based ablation aiming at CFAEs and electrograms with activation gradient of at least 70 ms between the distal and proximal recording bipoles of the mapping catheter, (iii) if AF sustains following PVI and electrogram-based ablation, *linear ablation* is carried out including roof and mitral isthmus lines, (iv) finally, the *right atrium (RA) and superior vena cava* are targeted for ablation if implicated as a source perpetuating AF and only after all LA ablation steps. Using this sequential ablation, the Bordeaux group reported termination of chronic AF (including patients with persistent AF) by conversion to either sinus rhythm or atrial tachycardia in 87% of patients during the index procedure and freedom from AF after an 11-month follow-up period in 95% of patients [15, 16]. Interestingly, AF was terminated in only 5% of patients by PVI, in 60% after electrogram-based ablation, and in 84% following linear ablation [15]. AF cycle length has been reported as the strongest independent predictor of procedural AF termination [57]. In a similar study, the single-procedure, drug-free success rate was 55% [58]. Rostock et al. are the only group outside of Bordeaux to report on the stepwise procedure in patients with persistent and long-standing persistent AF. In this series, the stepwise approach was associated with a lower single-procedure, drug-free success rate of 38% at 20 months, which improved to 81% with the integration of repeat procedures [59]. New studies from different centers are required to validate the efficacy of this ablation strategy.

#### 4. End-Points of Catheter Ablation for Persistent and Long-Standing AF

The goal of catheter ablation in persistent AF is trigger elimination and substrate modification. Previous studies have suggested that termination of AF during ablation in patients with persistent and long-standing AF is predictive of long-term maintenance of sinus rhythm [15, 16, 34, 56, 57, 60]. Therefore, restoration of sinus rhythm that occurs directly or more commonly via one or more intermediate ATs may be considered as a procedural end-point. It is of paramount importance to evaluate the presence of electrical PVI as well as the integrity of linear lesions following restoration of sinus rhythm. Even though, CFAEs ablation has become “widespread” in patients with persistent and long-standing AF, important questions regarding procedural end-points still exist. The primary end-points during ablation of AF with this approach are either complete elimination of the areas with CFAEs or conversion of AF to sinus rhythm (either directly or first to an AT) [15, 46, 47, 56, 58]. Although the most robust end-point is AF termination, this generally requires very long procedure times.

As previously stated, restoration of sinus rhythm appears an intuitively ideal end-point. In a prospective study of 153 patients who underwent catheter ablation of persistent AF, a lower incidence of AF recurrence was demonstrated in those patients in whom AF was terminated during the index procedure compared to those without termination (5 versus

39%) [56]. During ablation of persistent and long-standing AF with various strategies, the arrhythmia often organizes into a regular AT and sometimes even terminates into sinus rhythm [15]. In a recent prospective study, Elayi et al. assessed the AF termination mode during catheter ablation in 306 patients with long-lasting persistent AF and whether it predicts long-term sinus rhythm maintenance [60]. During AF ablation, only 6 out of 306 patients converted directly to sinus rhythm and 172 patients organized into AT. AF termination during ablation (conversion to sinus rhythm or AT) predicts the mode of arrhythmia recurrence (AT versus AF), but did not impact on long-term sinus rhythm maintenance after a single or two procedures [60].

In clinical practice, the ideal end-point for AF catheter ablation is freedom from AF without the use of antiarrhythmic medications. There is much controversy regarding the monitoring period as well as the minimum acceptable AF burden. Current definitions of freedom from AF include absence of AF, AF episodes lasting up to 30 s, and absence of symptomatic AF [3, 4]. A “blinking period” of up to 3 months after ablation, during which antiarrhythmic medications may be continued and direct current cardioversion can be performed for early recurrences of arrhythmias, appears to be adequate in order to access the efficacy of an ablation strategy [3, 4].

#### 5. Which Is the Price for an Extensive Ablation Procedure in the Setting of Persistent AF?

Longer procedure time, longer fluoroscopy time, higher complication rates, and high rates of postprocedural ATs are the main consequences of an extensive ablation procedure carried out in the setting of persistent and long-standing persistent AF. In a systematic review of 22 studies (1690 patients with persistent and long-lasting persistent AF), complications have been reported in 4.4% and included pericardial tamponade/effusion (1.4%), vascular complications (0.80%), symptomatic pulmonary vein stenosis (0.71%), cerebrovascular events (0.65%), phrenic nerve injuries (0.3%), and atriopharyngeal fistula (0.06%) [33]. Weber et al. have also reported the development of pulmonary edema following AF ablation, possibly in the setting of a systemic inflammatory response syndrome [61]. Cardiac tamponade is by far the most common fatal complication of AF ablation, occurring in 0.8–6% [3, 4, 62–67]. Death is an uncommon complication of AF ablation, occurring in 0.1–0.15% of subjects [3, 4, 62–67]. Operator’s experience is extremely important regarding safety issues of catheter ablation of AF. Spragg et al. reported that complication rates were higher during the first 100 cases (9.0%) than during the subsequent 541 (4.3%) [67]. Table 1 summarizes the most common complications occurring during catheter ablation of AF.

ATs following the index procedure can occur intraprocedurally or postprocedurally (early or delayed) [68]. Using a stepwise ablation strategy, Haissaguerre et al. demonstrated that persistent AF is usually terminated to an AT (86.5%) (focal or macro-re-entry) and less frequently directly to sinus rhythm (13.5%) [15]. This conversion is preceded by

TABLE 1: Complications during catheter ablation of persistent and long-standing persistent AF.

Type of complication	Symptoms	Incidence
Atrio-oesophageal fistula	Fever, dysphagia	Rare (0.06%)
Vascular complications (Arteriovenous fistula, arterial aneurysm, haematoma)	Pain at puncture site	0.8%
Phrenic nerve injury	Cough, dyspnea, atelectasis, and/or thoracic pain	0.3%
Pulmonary vein stenosis	Cough, hemoptysis, dyspnea, chest pain, and recurrent lung infections	0.71%
Pulmonary edema (18–48 h after the procedure)	Dyspnea, fever, elevated CRP levels	Rare
Cerebrovascular events	Neurological deficit	0.65%
Tambonade/Effusion	Hypotension, dyspnea cardiac arrest	1.4% (0.8–6%)
Death		0.1–0.15%

prolongation of fibrillatory cycle length, with the greatest magnitude occurring during ablation at the anterior LA, coronary sinus, and PV-LA junction [15]. These intraprocedural ATs are more commonly macro-re-entrant circuits involving the mitral or cavotricuspid isthmus or LA roof [68, 69]. Postprocedural (secondary) ATs are often incessant and very poorly tolerated by the patient. Postprocedural ATs are a rapidly growing clinical problem due to the expansion of the ablation strategies in the setting of persistent AF [3, 4]. The incidence of these arrhythmias is higher following circumferential PV ablation than after segmental PVI and is even higher when linear ablation is performed within the LA [68, 69]. ATs have been shown to occur in about 40% of patients who undergo the stepwise ablation approach [15, 69, 70]. These ATs can be focal or macro-re-entrant. More recently, a third intermediate AT category called “localized re-entry” has been reported [69, 70]. Focal ATs are defined by centrifugal activation from a localized region. If there is cycle length variation in left atrial appendage and coronary sinus >15%, focal mechanism is the most likely diagnosis. However, variation <15% does not rule out focal mechanism [70]. A macro-re-entrant mechanism is defined by demonstrating the entire cycle length of activity in a chamber with entrainment at  $\geq 2$  sites displaying a post-pacing interval of <20 msec longer than the tachycardia cycle length [70]. Most macro-re-entrant postprocedural ATs arise from a proarrhythmic effect of incomplete conduction block of linear lesions [68–70]. However, Knecht et al. showed that these macro-re-entrant circuits may also occur in the majority of patients without previously performed linear lesions in the long-term followup [40]. PV recovery should be also considered as a cause of AF recurrence, but may also contribute to either re-entrant or focal ATs [68–70]. Management of secondary ATs includes effective anticoagulation minimizing the risk of thromboembolic events, prevention of tachycardia-induced cardiomyopathy, and control of symptoms. One-third of patients who develop ATs in the first few weeks after AF ablation may not develop recurrent atrial arrhythmias during followup [69]. An initial conservative management strategy including rate control and cardioversion seems reasonable [68, 69]. Symptomatic

patients with ATs that persist beyond 2-3 months should be offered catheter ablation [69].

## 6. Conclusions

In conclusion, catheter ablation of persistent and long-standing persistent AF remains challenging for the electrophysiologists. Up to now, no single strategy is uniformly effective in patients with persistent and long-standing AF. The risk/benefit ratio of an extensive ablation approach has to be carefully evaluated. More lesions prolong not only procedure and fluoroscopy times, but also increase the risk of complications including ATs. For this purpose, the long-term success rates of certain ablation strategies need to be evaluated in randomized trials.

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