



# Necessity of Repeat Ablations to Eliminate Atrial Fibrillation

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## Abstract

Atrial fibrillation (AF) is the most common human arrhythmia and leads to increased morbidity and mortality. Because of demographic changes, the prevalence of AF will increase in the next decades, requiring better primary prevention strategies and better treatment options. In 1998, Haissaguerre et al. described triggering foci in the pulmonary veins (PV) as the prevailing pathophysiological initiator of paroxysmal AF. Since then, multiple studies have been conducted using the technique of pulmonary vein isolation (PVI) to eliminate AF. In short term follow-up, success rates of 60-75% in patients with paroxysmal AF are reached, with significantly worse results in persistent AF of approximately 50%. Due to arrhythmia recurrence, multiple procedures are often necessary, especially in patients with persistent AF, to achieve these results. It is supposed that the cause of arrhythmia recurrence is pulmonary vein reconnection in patients with paroxysmal AF, and insufficient substrate modification or new substrate development in patients with persistent AF. Future techniques like contact force control might improve lesion formation leading to improved PVI and substrate modification.

## Introduction

Atrial fibrillation (AF) is the most common human arrhythmia with an overall incidence of 1-2% in the general population, increasing with age.<sup>1,2</sup> AF leads to a higher risk of thromboembolic events including stroke<sup>3</sup> and increased mortality.<sup>4</sup> Because of demographic changes, the prevalence of AF will increase in the next decades, requiring improved primary prevention strategies and better treatment options.<sup>5</sup>

### Rate versus rhythm control:

The two prevailing therapy strategies for AF, rhythm and rate control, were compared in large scale randomized studies. Using different anti-

arrhythmic medications to achieve rhythm control these trials<sup>6-9</sup> could not show an advantage of rhythm control in comparison to rate control strategies regarding mortality. However, stable sinus rhythm could only be achieved in 23-60% of patients of the rhythm control group, and antiarrhythmics led to increased hospitalization and higher proarrhythmic event rates in patients on rhythm control.<sup>9,8</sup>

Thus, it was concluded that antiarrhythmic drugs were not the appropriate method to reach rhythm control.

Moreover, especially in paroxysmal AF, rate control frequently does not eliminate symptoms of AF, which considerably impair quality of life of the patients suffering from this arrhythmia.

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## Catheter ablation in atrial fibrillation

Research to find another therapeutic approach for rhythm control continues. Since Haissaguerre et al.<sup>10</sup> described triggering foci in the pulmonary veins (PV) as a prevailing cause for the development of AF, electrical isolation of the pulmonary veins (PVI) has become the cornerstone ablation strategy in patients with paroxysmal AF when antiarrhythmic medication has failed.<sup>11,12</sup>

In patients with persistent AF, not only the initiating trigger for AF is important, but also the AF maintaining substrate, i.e. parts of the atrial myocardium, which support by their modified electrophysiological properties the continuation of AF. Consequently, PVI alone has shown only low to moderate success rates.<sup>13,14</sup> Currently, most studies use PVI combined with various additional ablation techniques for substrate modification, such as, ablation lines deployed in the left atrium.

### Results of PVI in paroxysmal AF

After the establishment of complete isolation of all reachable PVs as the accepted endpoint in paroxysmal AF ablation, a multitude of studies were published dealing with this approach. Reported success rates of PVI were high in these publications with approximately 75-85% of patients completely free of arrhythmia. In the last years, with increased patient monitoring using sequential Holter-ECGs, transtelephonic monitoring or implanted monitoring systems, success rates dropped to a more realistic 60-75%.<sup>15-18</sup> However, in most published studies results are presented as combined efficacy after 1 or multiple ablation procedures.

In a prospective assessment by Winkle et al.<sup>19</sup> single procedure success was 60.9% after a follow-up time of 4 years. Patients who needed repeat ablation had a higher success rate after the second procedure and the overall success was 83.6% after 1.3 procedures.

Combination of PVI with other ablation approaches such as linear ablation or limited AF substrate ablation, remained restricted to a few studies, mostly because of limited or no advantage over PVI alone.<sup>13,20,21</sup>

## Ablation techniques and results in persistent AF

As outlined above, sole elimination of initiating trigger by PVI resulted in low success rates in persistent AF. First results with long left atrial linear lesions to dissect the atria in smaller, not proarrhythmic compartments, also showed non-satisfying results.<sup>22</sup>

By the introduction of refined 3D mapping systems and highly improved visualization tools to display the patient's individual anatomy as well as to continuously monitor all intracardially placed catheters, the results of linear ablation in persistent AF could be substantially improved.<sup>23-25</sup>

In 2004, Nademanee et al.<sup>26</sup> have shown that areas of complex fractionated atrial electrograms (CFAE) correlate with areas of slow conduction and pivot points of reentrant wavelets, i.e. CFAE correspond to atrial substrate maintaining AF. In 121 patients with persistent and paroxysmal AF, biatrial CFAE ablation was performed with no attempt to isolate the PV. After 1 year, stable sinus rhythm was present in 91% of patients after 1.15 ablation procedures.

Other centers were not able to achieve such high success rates with CFAE ablation only. In a study by Estner et al.<sup>27</sup>, patients with persistent AF were treated with CFAE alone or CFAE + PVI. After a single procedure, 9% of patients who underwent CFAE-only-ablation were in sinus rhythm, compared to 41% of patients who underwent CFAE + PVI. Furthermore, a multi-center analysis<sup>28</sup> has reported a success rate of 16.3% after a single procedure using CFAE ablation without PVI. On the other hand, a recently published meta analysis showed that adding CFAE ablation to PVI improved the ablation success significantly in patients with persistent AF (62% PVI + CFAE, 47% PVI alone).<sup>13</sup>

In a recently published prospective randomized study by Estner et al., PVI-lines as well as PVI+CFAE showed moderate (36% and 37%), but very comparable single procedure results, which improved substantially by adding re-do procedures.<sup>29</sup>

In 2005, Haissaguerre et al.<sup>30</sup> published a new comprehensive ablation approach in persistent AF, the so-called stepwise approach. It includes a stepwise performance of PVI, biatrial CFAE ablation and finally linear lesions in both atria to achieve an elimination of AF triggers and AF substrate. Ablation endpoint is to reach sinus rhythm during the procedure. The published success rates are high, but include always at least a mean of 1.5-1.8 ablation procedures (most commonly 1-3 procedures) with 50-80% of patients with more than 1 procedure<sup>30,31,29,32</sup> In follow-up, patients who reached the ablation endpoint of AF termination by ablation had the best outcome.

The discussion concerning the "best" ablation strategy in persistent AF (PVI+CFAE, PVI+lines, or stepwise approach) is still ongoing, but the preliminary conclusion can be drawn, that repeat ablations will remain necessary in a large proportion of patients.

### Single procedure and long-term success of AF ablation: new findings

In the last year, long term studies overlooking a follow-up of up to 10 years have been published showing late relapse (>1 year in sinus rhythm) after initial successful ablation and need of repeat ablation procedures to achieve good success rates.

It is still a matter of debate why repeat ablation procedures in patients with AF are necessary, as a single procedure suffices in most other arrhythmias (e.g., AV-nodal reentrant tachycardia or typical flutter treatment with success rates of >90%).

In particular, it is not clear whether repeat ablation is necessary due to the complexity of the arrhythmia itself (and our incomplete understanding of it) or because of shortcomings of the used ablation approaches and techniques.

### Success after single ablation in paroxysmal atrial fibrillation

In the past 3-4 years, several studies<sup>33-35,20,36-43</sup> have reported single ablation procedure success rates in patients with paroxysmal AF (see Table 1). All studies included PVI as an ablation technique, with 69 to 1404 patients treated. Success rates after a single procedure with a blanking period of 6

weeks to 3 months and off antiarrhythmic medication varied from 29-73%. Since the big variation in success rate seems to be closely linked to the quality and quantity of rhythm monitoring after ablation, it can be assumed that the real success rates are probably at approximately 50-60% after one year of follow-up. If follow-up was longer than one year<sup>44,45,33</sup> a yearly decrease of ca. 2.5-4.0% in the percentage of arrhythmia-free patients was observed. For example, Ouyang et al. [34] have shown a time dependence of recurrence with stable sinus rhythm after a single procedure after 1 year of 62%, with a low but steady relapse rate of 2.5-4% thereafter to a final success rate after 5 years of follow-up of 46.6%.

### Success after single ablation in persistent atrial fibrillation

Similar to paroxysmal AF, recent studies<sup>40,46,47,31,27,29,32</sup> have shown success rates after a single ablation procedure of 11-61% (see Table 2), i.e. a lower rate compared to patients with paroxysmal AF. Most of these investigations refer to results off antiarrhythmic medication, and have included substrate modification approaches like CFAE ablation or additional atrial lines in addition to PVI.

### Success after multiple ablations in paroxysmal and persistent atrial fibrillation

In comparison to the success rates after a single ablation procedure in patients with paroxysmal or persistent AF, rates after multiple procedures are significantly higher. As shown in Tables 1 and 2, 59-92% of patients with paroxysmal AF mainly off antiarrhythmic medication and 57-83% of patients with persistent AF show stable sinus rhythm. In patients with paroxysmal AF, 1.1 to 2 procedures per patient were necessary to achieve these results. In patients with persistent AF, 1.3 to 2.3 procedures per patient were required (see tables 1 and 2). The success rates and number of procedures vary between the cited studies due to different ablation approaches (in particular, in patients with persistent AF), different follow-up strategies, and use of antiarrhythmic medication.

### Cause of arrhythmia recurrence

Most of the studies cited above have shown

Table 1

Studies with single and multiple procedure success in patients with mainly paroxysmal AF. All studies show that after multiple procedures the success rates improve significantly. Off AAD = off antiarrhythmic drugs. CPVI: circumferential PVI, SPVI: segmental PVI, APVI: antral PVI, SVC: superior vena cava., CPVA: circumferential pulmonary vein ablation, CTI: cavotricuspid isthmus Only studies with declaration of single and multiple procedures success and declaration of procedures were included.

Study	N	Single procedure success	Multiple procedure success	Number of procedures	Paroxysmal/persistent AF
Gerstenfeld et al. 200639	97	58%	79%	1.4	PVI of arrhythmogenic vein, off AAD
Dixit et al. 200838	103	59%/61%	90%/94%	1.2	74% paroxysmal, off AAD, endpoint: AF control, all PVI versus PVI of arrhythmogenic vein
Van Belle et al. 200835	141	49%	59%	1.2	Cryoballoon, off AAD
Fiala et al. 200859	110	56%/57%	80%/80%	1.4	SPVI vs. APVI, off AAD
Deisenhofer et al. 200921	98	75%/76%	74%/83%	1.3/1.4	PVI v. PVI + CFAE
Bhargava et al. 200936	1404	73%	88%	1.2	728 Paroxysmal, 676 persistent, off AAD APVI + SVC
Di Biase et al. 200920	103	89%/23%/91%	86%/92%	1.1	APVI vs CFAE vs APVI + CFAE, 15% AAD
Ouyang et al. 201034	161	47%	79%	1.5	CPVI, off AAD
Sawhney et al. 201043	66	58%/51%	85%/85%	1.3/1.4	SPVI versus CPVI+roof line, mitral isthmusline, off AAD
Verma et al. 201042	101	74%/48%/29%	88%/68%/38%	2	PVI+CFAE, PVI, CFAE, 96% without AAD
Fichtner et al. 201141	356	35%	59%	1.5	SPVI, off AAD
Miyazaki et al. 201151	574	65%	84%	1.4	Paroxymal and persistent AF, off AAD, in paroxysmal CPVI + tricuspid isthmus, in persistent AF additional left atrial lines
Pappone et al. 201160	99	73%	91%	1.3	CPVA + left atrial lines, CTI
Weerasooriya et al. 201133	100	40%/37%/29% after 1, 2, 5 years	87%/81%/63% after 1,2, 5 years	2	63%/37% parox/pers Parox: PVI + CTI Pers PVI+ CTI+left atrial lines
Winkle et al. 201119	843	60.9%/42.9%/35.2	83.6%/62.2%/57.3	1.3	Parox, /pers.,/ longlasting pers. after 4 years

a requirement for repeat ablation procedures to achieve good success rates. This leads to the question of the cause of arrhythmia recurrence.

### Paroxysmal atrial fibrillation: the problem is PV reconnection

In 2003, Cappato et al. [48] have shown that 4.6

months after initially successful PVI, 83% of formerly isolated PVs showed reconnection; this figure drops only slightly to 73% in patients undergoing a third ablation procedure. The percentage of patients with reconnected PVs during repeat PVI ranges from 73-95%.<sup>37,44,35,46,49,50</sup>

Even in patients with late relapse after an arrhyth-

Table 1

Studies with single and multiple procedure success in patients with mainly persistent AF. All studies show that after multiple procedures the success rates improve significantly. Off AAD = off antiarrhythmic drugs, PVI: pulmonary vein isolation, CPVI, circumferential PVI, APVI.: antral PVI, CFAE: complex fractionated atrial electrocardiograms. . Only studies with declaration of single and multiple procedures success and declaration of procedures were included.

Study	N	Single procedure success	Multiple procedure success	Number of procedures	Ablation approach
Oral et al. 2007 47	100	33%	57%	1.44	CFAE ablation, off AAD
Elayi et al. 2008 40	144	11%/40%/61%	28%/83%/94%	2	Permanent AF, success rates with AAD Comparing CPVI, APVI, CFAE + PVI
Estner et al. 2008 27	141	77	9/41%	1.3	CFAE vs. CFAE + PVI, off AAD
Rostock et al. 2008 32	88	38%	81%	1.8	stepwise
Oral et al. 2009 46	119	36%/34%	68%/60%	1.3	APVI versus APVI + CFAE, off AAD
Estner et al. 2011 29	116	37%/39%	54%/56%	1.25/1.28	CPVI+lines, vs SPVI+CFAE
Rostock et al. 2011 31	395	27%	79%	2.3	Stepwise approach with PVI, CFAE and if needed lines, 15% AAD

mia free interval of >1 year PV reconnection seems to be the main problem.<sup>45,44,51</sup>

Non-PV triggers seem to play a minor role in patients with paroxysmal atrial fibrillation. A study by Wang et al.<sup>49</sup> has shown similar results in patients who underwent PVI compared to patients who underwent PVI and additional isolation of the vena cava superior. In a study by Gavin et al.<sup>52</sup>, additional ablation in the coronary sinus did not lead to a higher rate of sinus rhythm compared to PVI alone. In contrast, patients with AV nodal reentrant tachycardia (AVNRT) and AF have benefited from ablation of AVNRT without PVI, resulting in stable sinus rhythm in 12/13 patients.<sup>53</sup>

It is still not clear if reconnection of PVs is the only cause of arrhythmia recurrence. Until now, only two small studies are available which address this question. Willems et al.<sup>54</sup> have performed robotic PVI in 64 patients with paroxysmal AF. After 3 months, 63% underwent repeat procedure regardless of arrhythmia recurrence. In this investigation, 43% of initially successfully isolated PVs showed reconnection. In patients who had no arrhythmia recurrence compared to patients with arrhythmia recurrence the number of reconnected PVs was significantly lower with 1 versus 2 PVs ( $p = 0.006$ ); fur-

thermore these patients showed a longer left atrial (LA)- PV conduction delay. In patients with still complete isolation of all PVs after 3 months, no symptoms or documentation of arrhythmia recurrence were noted. In a study by Ouyang et al.<sup>55</sup> 7 patients without arrhythmia recurrence underwent a repeat procedure; in these patients all PVs showed isolation compared to patients with arrhythmia recurrence. These results underline the importance of permanent PV isolation.

However, permanent PVI seems difficult to achieve. Yamane et al.<sup>56</sup> have studied 65 patients with paroxysmal AF who underwent PVI by double lasso technique. 30, 60 and 90 minutes after initially successful PVI (293 PVs), 20mg of adenosine and 4-8 $\mu$ g isopreterenol have been applied. If reconnection occurred, repeat PVI was performed and tested again with adenosine and isopreterenol. After 30 minutes, 75 gaps in 53 PVs showed reconnection in 37 patients. After 60 minutes, 64 gaps were still detectable; of these, 54 were new gaps. After 90 minutes, 8 gaps were still inducible. After this extensive PVI and 1 year of follow-up, 92% of patients were in stable sinus rhythm off antiarrhythmic drugs.

In the last year, attempts to render PV isolation more durable were made by measuring the contact force of the ablation catheter tip to the tissue online during ablation. While no reliable data exist on clinical effects of this new technique on follow-up results, the bench-testing and first in-human acute ablation results concerning depth and volume of the ablation lesions are encouraging.<sup>57</sup>

### Persistent atrial fibrillation: the substrate has to be modified sufficiently

Up to now, little is known about the mechanism of arrhythmia recurrence in patients with persistent AF. Since abnormal atrial substrate causes AF persistence, ablation approaches with substrate modification like CFAE-ablation or additional left atrial lines are required for the first ablation.<sup>13</sup> If recurrence is observed, the type of recurrent arrhythmia might indicate the cause of arrhythmia recurrence:

If AF is no longer persistent after one ablation but occurs only paroxysmal, PV reconnection might be the driver for AF recurrence.

If persistent AF reoccurs, the modification of the underlying substrate during the first procedure was probably insufficient. This might be due to incomplete lines or to residual CFAE.

If the type of recurrence is regular atrial tachycardia (AT), it might indicate a profound ablation induced AF substrate modification: after this substrate modification, previously veiled AT, concealed during ongoing AF, become apparent.

In a recent study by Ammar et al.<sup>57</sup>, the arrhythmia recurrence type after the initial ablation predicted the outcome after repeat ablation: with persistent AF, success after repeat ablation was 28%; with AT, success after repeat ablation was significantly higher with 59%; and finally, with paroxysmal AF, 100% success rate after repeat ablation procedure was achieved.

### Conclusion

In patients with paroxysmal and persistent AF good to excellent rates of stable sinus rhythm are

reached using one or multiple catheter ablation procedures. Arrhythmia recurrences leading to repeat ablation procedures seem to be caused mainly by reconnection of formerly isolated pulmonary veins in patients with paroxysmal AF and non-controlled substrate in patients with persistent AF. A third problem might be the development of new triggers or substrate in long-term follow-up.

Promising techniques like contact force measurements to achieve better permanent PV isolation are in development. For persistent AF, termination of AF to sinus rhythm during the first ablation procedure seems to be a first measure to assess sufficient extent of substrate modification.

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