

Predictors of Atrial Fibrillation Recurrence After Catheter Ablation

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Abstract

Atrial fibrillation (AF) catheter ablation is a well-known treatment option for patients with drug refractory AF. The increasing number of electrophysiology laboratories able to perform this procedure will create an economic impact in the coming years, which each cardiac electrophysiologist will have to face with. Identification of predictors of recurrence of AF after catheter ablation is therefore of primary importance to reduce health costs and improve long-term results of this intervention. The aim of this review is to give a brief overview on published literature on the topic and henceforth to increase the awareness of cardiac electrophysiologists on the importance of selecting of the right candidates for this intervention.

Introduction

Since its introduction into clinical practice in the late nineties,¹ catheter ablation of atrial fibrillation (AF) has become a well-established therapeutic option for the treatment of patients with symptomatic drug refractory AF. Nevertheless, the great interest of cardiac electrophysiologists in this new treatment option is facing a crisis after the publication of medium and long term efficacy data.^{2,3} Indeed, a recent meta-analysis⁴ which included 63 studies on the topic, evidenced a single-procedure success rate of ablation with no antiarrhythmic drug therapy after 12 months follow-up of 57%, significantly more than the sole antiarrhythmic therapy, which resulted in a 52% freedom from arrhythmias at one year. After adding multiple procedures, success rate was 71% in absence of antiarrhythmic drugs and 77% with antiarrhythmic drugs.

According to the Heart Rhythm Society's consensus document,⁵ catheter ablation's success should be defined as freedom from symptomatic or asymptomatic AF, atrial tachycardia, or atrial flutter lasting ≥ 30 seconds after AF ablation. One year success is defined as freedom from arrhythmic events without antiarrhythmic drugs documented from the end of the blanking period (usually lasting three months after ablation) to 12 months of follow-up. Long-term success is considered as freedom from arrhythmic events from the end of the blanking period to at least 36 months follow-up following the ablation procedure off of antiarrhythmic drugs. AF

ablation guidelines also included the definition of clinical or partial success as reduction ($\geq 75\%$) of AF burden assessed with a device, able to record ECG tracings or intracardiac electrograms in the presence or absence of antiarrhythmic drugs.

Certainly, success rate is affected by patient characteristics because AF includes different subtypes and occurs in different clinical subsets. The identification of the predictors of maintenance of sinus rhythm after catheter ablation is high desirable since it would certainly help all the community of cardiac electrophysiologists in reducing unnecessary procedures, in limiting complications and in reducing health care costs. The main scope of this manuscript is to give a brief overview of these predictors on the basis of what has been already published in the literature.

Types and Mechanisms of AF Recurrences

It is now widely recognized that there are different types of recurrence of AF.⁵ Early recurrence (ER) is defined as a recurrence of AF within three months of ablation, whereas recurrence post ablation is defined as an atrial fibrillation relapse more than 3 months following the intervention. Late recurrences (LR) of AF occurs 12 months or more after ablation. Since in a significant proportion of cases, relapse consists of atrial flutter or atrial tachycardia, the occurrence of these arrhythmias should also be considered as a recurrence. This classification has a clinical significance since there are various mechanisms behind different types of recurrences and not all recurrences will lead to later relapses. Recent studies have significantly widened the follow-up duration (over five years), introducing a new subtype of AF relapse, regarded as very late recurrences (VLR).

Early Recurrence

ER after catheter ablation of AF is fairly common: Bertaglia found

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46% of atrial tachy-arrhythmias relapse during the first three months of follow-up.⁶ Moreover the incidence of ER is maximum soon after the procedure, which decreases in the following days.⁷ Although, the prevalence of ER is not negligible, it has been widely recognized that a good proportion of patients experiencing ER are free of significant atrial arrhythmias at prolonged observation. Nevertheless, the occurrence of LR is more frequent in the subgroup with ER.⁸ These data suggest that ER is probably linked to the procedure, even if the mechanisms involved in determining it have not completely been understood. The application of radiofrequency energy provokes a thermal injury followed by a fibrotic response in myocardial tissue.⁹ Furthermore, a transient imbalance between sympathetic and parasympathetic tone has been reported after ablation and may potentially contribute to arrhythmic recurrences in this phase.^{10,11} Several studies have demonstrated a progressive growth of ablation lesions over the procedure: thus the lack of a complete scar across the atrial wall in the first days after the ablation can cause ER, while lesion maturation accounts for persistence of sinus rhythm.^{11,12} Another possible explanation for the uncertain clinical impact of ER is the occurrence of atrial reverse structural and electrical remodeling after ablation: indeed maintenance of sinus rhythm affects positively conduction velocities and effective refractory periods of the atria, which results in less susceptibility to initiation and perpetuation of atrial arrhythmias.¹³

Late Recurrences (LR)

Several studies have shown that recurrences after more than 6-12 months from the index procedure are the result of the "reconnection" of the pulmonary veins: the recovery of the electrical conduction between pulmonary veins and left atrium¹⁴ favors the AF relapse. Another type of recurrence is represented by atrial flutter, at the basis of this arrhythmia is an incomplete linear lesion drawn during the ablation procedure.¹⁵ To avoid this circumstance it is essential to achieve complete block across ablation lines. Moreover non-pulmonary veins foci, which are localized outside from the circumferential ablation lines, could also contribute to the initiation of AF.¹⁶

Very Late Recurrences (VLR)

Relapses of AF long after the ablation are the result of the deterioration of the atrial tissue: progression of atrial fibrosis, enlargement of left atrium and the adverse electrical and molecular remodeling of myocardial tissue are involved in this type of recurrences.¹⁷ Thus very late recurrence accounts for the final stage of the atrial electrical disease, even though further investigation on the topic is warranted.

Predictors of Recurrence

To date, several predictors of recurrence have been identified in various studies. Among all the published manuscripts, the systematic review by Balk et al.¹⁸ on predictors of AF recurrence after radiofrequency catheter ablation surely represents one of the most significant original contributions in this field. The Authors have made a huge effort to synthesize all the data reported in 2,169 different citations, focusing their attention on the most significant pre-procedural patient characteristics such as AF type, AF duration, left ventricular ejection fraction, left atrial diameter, gender, age, presence of structural heart disease and presence of hypertension. Their meta-analysis showed that none of these clinical parameters is

able to predict arrhythmia recurrences at a high level of evidence. The only clinical parameter which demonstrated a potential link to AF recurrence was AF type, particularly non-paroxysmal AF, even if only at the univariable analysis and not at multivariable level. This lack of real predictors of AF recurrence is surely related more to the quality and the limitations of the existing literature than to a true absence of association. The studies on AF ablation are extremely heterogeneous with respect to patient characteristics, procedural features and follow-up modalities and this renders any attempt of synthesis very challenging. Furthermore patients undergoing AF ablation have a limited range of variation in the majority of the clinical variables: it's rare that they are younger than 40 years old or older than 70 years old, females represent a minority and left atrial diameters and/or left ventricular ejection fractions are usually aligned on a narrow range of values. Finally, some of these clinical variables are related and this implies that they are not statistically independent and that the simple Cox or logistic regression are too simplified models to account for the complex relationships among factors.

Taking all this in mind, let's give anyway a brief overview of which clinical, procedural and post-procedural predictors have been identified by the most significant single studies for each type of AF recurrence after catheter ablation.

Early Recurrence

Bertaglia et al.¹⁹ observed that the presence of structural heart disease and the lack of successful isolation of all targeted pulmonary veins (PV) are predictors of early atrial tachyarrhythmias recurrence. Other studies²⁰ have indicated hypertension, left atrial enlargement, permanent AF, and lack of superior vena cava isolation as predictors of early relapse of AF after ablation. Otherwise, the termination of AF during the ablation procedure, when compared to failure to terminate the arrhythmia with the necessity of an electrical cardioversion, predicts early and late success.²¹ A longer cycle length of AF is also associated with termination of AF and with overall success as well.²² These data suggest that the presence of structural heart disease or of significant risks factors for heart disease which lead to a higher degree of adverse left atrial remodeling and enlargement might be involved in the complex mechanisms which lead to early recurrence. A different meaning should be assigned to very early recurrence, which occurs within 48 hours from the ablation procedure. Chang et al.²³ found 19% of very early AF recurrences: longer procedural time and lower LA voltage were independent predictors of very early AF recurrences. Koyama²⁴ reported also that an increase in body temperature and C-reactive protein associated with signs of pericarditis in patients with very early recurrence, hypothesizing an inflammatory mechanism as a potential causative factor.

Late Recurrences

Recurrence of AF 6 months after the ablation is the expression of pulmonary veins reconnection or incomplete transmural injury of the radiofrequency energy.²⁵ One study²⁶ underlined that overweight/obesity, metabolic syndrome and ER are independent predictors of AF relapse. Interestingly, the relationship between early and late recurrence has been put under observation in several studies. A prolonged procedure time and inducibility of AF or AT immediately after ablation has been found to independently predict late recurrence in patients with early recurrences of atrial tachycardia.²⁷

Koyama²⁴ found a lower rate of late recurrence among patients that experienced a very early recurrence after ablation, whereas

patients that had a relapse after the first 48 hours, had a higher rate of recurrence after 6 months. Similar results were obtained by Themistoclakis²⁰ et al.: very early relapse was associated to a better final outcome when compared to recurrence within one month. This data has been confirmed by a recent meta-analysis²⁸ that demonstrated recurrence within the first 30 days as the strongest predictor of future relapse.

ECG features have also been analyzed and related with AF recurrences. Low amplitude F waves in lead aVF and V1, for example, have demonstrated to be associated with late AF recurrence after ablation.²⁹ Right atrium enlargement, more than 2 procedural attempts, AF duration and left atrial enlargement (> 43 mm) have also been included in the variegated and heterogeneous list of atrial arrhythmia recurrence after ablation.^{30,31} As stated above, AF type may predict the outcome of the ablation, since nonparoxysmal AF is associated to 60% higher risk of relapse when compared to paroxysmal AF.¹⁸ These data suggest that the failure to maintain sinus rhythm after more than 6 months from the procedure is strongly associated to an ineffective ablation procedure, since in the majority of cases it is possible to demonstrate pulmonary veins reconnection or development of atrial tachycardia around incomplete ablation lines. Furthermore, when PV reconnection is not present, the relapse is the consequence of the adverse electrical and anatomical remodeling associated with AF: repeated ablation attempts, low amplitude ECG waves and atrial enlargement are strictly linked to myocardial fibrosis and lack of viable myocardial tissue. Thereby, since AF type is a hallmark of the underlying substrate, indication to catheter ablation in patients with non-paroxysmal AF should be well balanced by cardiac electrophysiologists since these patients have undoubtedly a worse outcome.

Predictors of Very Late Recurrence

Very late recurrence has not been deeply evaluated in scientific studies. Just few scientists have performed long term follow up after ablation. Recurrence occurring more than 12 months from the procedure, is not excessively frequent and has been related to hypertension and left atrial enlargement.³² Mainigi found that the only predictors of very late recurrence were weight > 200 lbs and the presence of non-PV triggers in case of a repeated ablation,³³ whereas other studies have underlined the role of right atrial foci.¹⁶ In one of the studies with the longest follow-up, Weerasooriya et al.³⁴ found that valvular heart disease and non-ischemic cardiomyopathy were predictors of very late recurrence. On the basis of these data, very late recurrence can be considered a new type of AF, not depending on earlier triggers (e.g. PV foci), but originating from other areas of atrium with a more advanced degree of adverse remodeling.

Conclusions:

Identification of predictors of recurrence of AF after catheter ablation is a challenging task due to the extreme heterogeneity of the data published in the literature. More research on the topic is warranted, together with a combined effort to standardize AF catheter ablation procedures and strict adherence to the international guidelines available nowadays on this type of intervention.

References:

1. Haissaguerre M, Marcus FI, Fischer B, Clementy J. Radiofrequency catheter ablation in unusual mechanisms of atrial fibrillation: report on three cases. *J Cardiovasc Electrophysiol.* 1994; 5: 743–751.

2. Sorgente A, Tung P, Wylie J, Josephson ME. Six years follow-up after catheter ablation of atrial fibrillation: a palliation more than a true cure. *Am J of cardiol.* 2012; 109:1179–1186
3. Ouyang F, Tilz R, Chun J, Schmidt B, Wissner E, Zerm T, Neven K, Köktürk B, Konstantinidou M, Metzner A, Fuernkranz A, Kuck KH. Long-term results of catheter ablation in paroxysmal atrial fibrillation: lessons from a 5-year follow-up. *Circulation.* 2010;122:2368–2377
4. Calkins H, Reynolds MR, Spector P, Sondhi M, Xu Y, Martin A, Williams CJ, Sledge I. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systematic literature reviews and meta analyses. *Circ Arrhythm Electrophysiol.* 2009;2:349–361.
5. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. *Heart Rhythm* 2012; 9: 632 – 696
6. Bertaglia E, Stabile G, Senatore G, Zoppo F, Turco P, Amellone C, De Simone A, Fazzari M, Pascotto P. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. *Pacing Clin Electrophysiol.* 2005;28:366–371.
7. Joshi S, Choi AD, Kamath GS, Raiszadeh F, Marrero D, Badheka A, Mittal S, Steinberg JS. Prevalence, predictors, and prognosis of atrial fibrillation early after pulmonary vein isolation: findings from 3 months of continuous automatic ECG loop recordings. *J Cardiovasc Electrophysiol.* 2009;20:1089–94.
8. Andrade JG, Khairy P, Verma A, Guerra PG, Dubuc M, Rivard L, Deyell MW, Mondesert B, Thibault B, Talajic M, Roy D, Macle L. Early recurrence of atrial tachyarrhythmias following radiofrequency catheter ablation of atrial fibrillation. *Pacing Clin Electrophysiol.* 2012;35:106–16
9. Grubman E, Pavri BB, Lyle S, Reynolds C, Denofrio D, Kocovic DZ. Histopathologic effects of radiofrequency catheter ablation in previously infarcted human myocardium. *J Cardiovasc Electrophysiol.* 1999;10:336–342.
10. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, Mazzone P, Tortorello V, Landoni G, Zangrillo A, Lang C, Tomita T, Mesas C, Mastella E, Alfieri O. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. *Circulation.* 2004;109:327 – 334.
11. Hsieh MH, Chiou CW, Wen ZC, Wu CH, Tai CT, Tsai CF, Ding YA, Chang MS, Chen SA. Alterations of heart rate variability after radiofrequency catheter ablation of focal atrial fibrillation originating from pulmonary veins. *Circulation.* 1999;100:2237–2243.
12. Fenelon G, Brugada P. Delayed effects of radiofrequency energy: mechanisms and clinical implications. *Pacing Clin Electrophysiol.* 1996;19:484–489.
13. Li XP, Dong JZ, Liu XP, Long de Y, Yu RH, Tian Y, Tang RB, Zheng B, Hu FL, Shi LS, He H, Ma CS. Predictive value of early recurrence and delayed cure after catheter ablation for patients with chronic atrial fibrillation. *Circ J.* 2008;72:1125–9.
14. Verma A, Kilicaslan F, Pisano E, Marrouche NF, Fanelli R, Brachmann J, Geunther J, Potenza D, Martin DO, Cummings J, Burkhardt JD, Saliba W, Schweikert RA, Natale A. Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein

- conduction. *Circulation* 2005; 112:627–635.
15. Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010; 3:243–248.
 16. Hsieh MH, Tai CT, Lee SH, Lin YK, Tsao HM, Chang SL, Lin YJ, Wongchaoen W, Lee KT, Chen SA. The different mechanisms between late and very late recurrences of atrial fibrillation in patients undergoing a repeated catheter ablation. *J Cardiovasc Electrophysiol* 2006; 17:231–235.
 17. Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial myocardium due to sustained atrial fibrillation in the goat. *Circulation* 1997; 96:3157–3163.
 18. Balk EM, Garlitski AC, Alsheikh-Ali AA, Terasawa T, Chung M, Ip S. Predictors of atrial fibrillation recurrence after radiofrequency catheter ablation: a systematic review. *J Cardiovasc Electrophysiol*. 2010; 21:1208–16.
 19. Bertaglia E, Stabile G, Senatore G, Zoppo F, Turco P, Amellone C, De Simone A, Fazzari M, Pascotto P. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. *Pacing Clin Electrophysiol* 2005; 28:366–371.
 20. Themistoclakis S, Schweikert RA, Saliba WI, Bonso A, Rossillo A, Bader G, Wazni O, Burkhardt DJ, Raviele A, Natale A. Clinical predictors and relationship between early and late atrial tachyarrhythmias after pulmonary vein antrum isolation. *Heart Rhythm* 2008; 5:679–685.
 21. Heist EK, Chalhoub F, Barrett C, Danik S, Ruskin JN, Mansour M. Predictors of atrial fibrillation termination and clinical success of catheter ablation of persistent atrial fibrillation. *Am J Cardiol*. 2012; 10:545–51
 22. Drewitz I, Willems S, Salukhe TV, Steven D, Hoffmann BA, Servatius H, Bock K, Aydin MA, Wegscheider K, Meinertz T, Rostock T. Atrial fibrillation cycle length is a sole independent predictor of a substrate for consecutive arrhythmias in patients with persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;3:351–360.
 23. Chang SL, Tsao HM, Lin YJ, Lo LW, Hu YF, Tuan TC, Suenari K, Tai CT, Li CH, Chao TF, Lin YK, Tsai CF, Wu TJ, Chen SA. Characteristics and significance of very early recurrence of atrial fibrillation after catheter ablation. *J Cardiovasc Electrophysiol*. 2011; 22:1193–8.
 24. Koyama T, Sekiguchi Y, Tada H, Arimoto T, Yamasaki H, Kuroki K, Machino T, Tajiri K, Zhu XD, Kanemoto M, Sugiyasu A, Kuga K, Aonuma K. Comparison of characteristics and significance of immediate versus early versus no recurrence of atrial fibrillation after catheter ablation. *Am J Cardiol* 2009;103:1249–1254.
 25. Deisenhofer I, Estner H, Zrenner B, Schreieck J, Weyerbrock S, Hessling G, Scharf K, Karch MR, Schmitt C. Left atrial tachycardia after circumferential pulmonary vein ablation for atrial fibrillation: incidence, electrophysiological characteristics, and results of radiofrequency ablation. *Europace*. 2006; 8:573–82.
 26. Cai L, Yin Y, Ling Z, Su L, Liu Z, Wu J, Du H, Lan X, Fan J, Chen W, Xu Y, Zhou P, Zhu J, Zrenner B. Predictors of late recurrence of atrial fibrillation after catheter ablation. *Int J Cardiol*. 2013;164: 82–7.
 27. Choi JI, Pak HN, Park JS, Kwak JJ, Nagamoto Y, Lim HE, Park SW, Hwang C, Kim YH. Clinical significance of early recurrences of atrial tachycardia after atrial fibrillation ablation. *J Cardiovasc Electrophysiol*. 2010; 2: 1331–7.
 28. D'Ascenzo F, Corleto A, Biondi-Zoccai G, Anselmino M, Ferraris F, di Biase L, Natale A, Hunter RJ, Schilling RJ, Miyazaki S, Tada H, Aonuma K, Yenn-Jiang L, Tao H, Ma C, Packer D, Hammill S, Gaita F. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol* 2013; 167: 1984–9.
 29. Cheng Z, Deng H, Cheng K, Chen T, Gao P, Yu M, Fang Q. The amplitude of fibrillatory waves on leads aVF and V1 predicting the recurrence of persistent atrial fibrillation patients who underwent catheter ablation. *Ann Noninvasive Electrocardiol*. 2013; 18: 352–8.
 30. Zhao L, Jiang W, Zhou L, Gu J, Wang Y, Liu Y, Zhang X, Wu S, Liu X. Why atrial fibrillation recurs in patients who obtained current ablation endpoints with longstanding persistent atrial fibrillation. *J Interv Card Electrophysiol*. 2013; 37: 283–90.
 31. McCready JW, Smedley T, Lambiase PD, Ahsan SY, Segal OR, Rowland E, Lowe MD, Chow AW. Predictors of recurrence following radiofrequency ablation for persistent atrial fibrillation. *Europace*. 2011; 13: 355–61.
 32. Hsieh MH, Tai CT, Tsai CF, Lin WS, Lin YK, Tsao HM, Huang JL, Ueng KC, Yu WC, Chan P, Ding YA, Chang MS, Chen SA. Clinical outcome of very late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2003; 14: 598–601.
 33. Mainigi SK, Sauer WH, Cooper JM, Dixit S, Gerstenfeld EP, Callans DJ, Russo AM, Verdino RJ, Lin D, Zado ES, Marchlinski FE. Incidence and predictors of very late recurrence of atrial fibrillation after ablation. *J Cardiovasc Electrophysiol*. 2007;18: 69–74.
 34. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, Lellouche N, Knecht S, Wright M, Nault I, Miyazaki S, Scavee C, Clementy J, Haissaguerre M, Jais P. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? *J Am Coll Cardiol* 2011; 57: 160–166.