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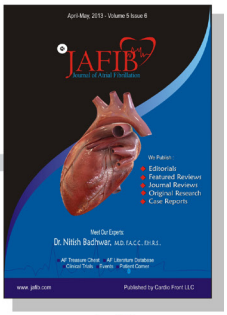

Prerequisites for Exploring Predictors of Chronic Atrial Fibrillation Recurrence After Ablation

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Abstract

The ablation treatment for the atrial fibrillation extends to the persistent atrial fibrillation now. However, the cure rate of persistent atrial fibrillation by Radiofrequency Ablation is lower than paroxysmal atrial fibrillation and we really want to know is the information that what kind of persistent atrial fibrillation ablation therapy is effective for. Therefore, it is wished the predictors of recurrence after the ablation for the persistent atrial fibrillation is confirmed, but does not yet confirm. The cause that is not confirmed seems to be present in many factors including the gene which the atrial fibrillation occurs in and persist, the change of pathology into remodeling according to progression of atrial fibrillation and strategy of the ablation corresponding to them. Left atrium diameter, Duration of atrial fibrillation and Cardiac Function that are involved deeply in atrial muscle and electric remodeling, and Ablation strategy corresponding to them are considered based on the conventional report. It can be stated now, however, that persistent atrial fibrillation patients with some degree (although this "some degree" has not been clearly defined) of enlarged left atrium diameter, prolonged atrial fibrillation duration, or decreased cardiac function may also revert to sinus rhythm with Radiofrequency Ablation, more efficient treatment may be developed in the future and reversion to sinus rhythm may increase the benefit to patients. In summary, RF ablation for persistent AF is currently required with further study of the predictors of recurrence after the ablation for the persistent atrial fibrillation.

Introduction

Basis for Exploring Predictors of Atrial Fibrillation Recurrence after Ablation

When exploring predictors of the recurrence of atrial fibrillation (AF) after ablation for persistent AF, the natural history of AF needs to be understood as the basis of exploration. Most cases of AF occur in the paroxysmal form, which may progress to persistent AF during its course. There are several predictors of the onset of AF.[1] In addition, there are predictors of the progression from paroxysmal to persistent AF, i.e., the HATCH score, [2] although this score has not been completely established and is currently being studied in various researches. Nonetheless, it is very likely that there are predictors of progression.[3] Therefore, it is necessary to recognize these underlying predictors (of the onset of paroxysmal AF and of the progression from paroxysmal to persistent AF) when exploring predictors of AF recurrence after ablation for persistent AF (see Table 1).

The predictors of AF onset include all risk factors considered in the $CHADS_2$ score, which is a predictor of stroke onset, and many risk factors for arteriosclerosis and/or ischemic heart diseases. As such, the predictors of AF onset largely overlap the

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aggravating factors of the cardiovascular system. Even in cases where AF can be temporarily controlled with ablation, AF is likely to recur if the factors/diseases mentioned above are not treated. Whether treatment is provided for these factors/diseases after ablation may largely affect the recurrence of AF; however, many of these factors cannot be completely eliminated by treatment. It is therefore necessary to recognize that the predictors of AF onset remain as predictors of AF recurrence after ablation.

"Upstream therapy" with angiotensin receptor blockers (ARBs) is a pharmacological treatment option for AF (as opposed to ablation), which has markedly lost its value as a treatment for AF.[4,5] The root cause of this loss may be its inability to prevent and/or control all the above factors of AF onset.

The difference between medication and ablation is that ablation can directly treat the mechanism of AF onset and is able to radically treat the disease in some cases. Accordingly, the optimal ablation strategy may vary depending on the status of AF to be treated.

In summary, whether the environmental factors (general condition) of the patient treated have improved by ablation constitute the basis of the discussion regarding predictors of AF recurrence after ablation. Only on this basis should the status of patient/AF at the time of ablation and/or the ablation strategies used be evaluated as potential predictors.

Mechanism of Onset of Atrial Fibrillation and Ablation Strategy

It has been demonstrated that the development of premature atrial contractions (PAC) originating in the pulmonary veins (PVs) and PV tachycardia are closely involved in the onset of paroxysmal AF (PAF) as a trigger.[6] Spiral wave reentry within the atrium has been also demonstrated to be responsible for PAF onset.[7] Atrial remodeling as a structural abnormality of atrial muscle is closely involved in this reentry.

Upon PAF onset, atrial electrical remodeling induces calcium (Ca) overload as phase 1 due to rapid atrial excitement, which leads to shortening of the refractory period.[8] Because the sole symptom is shortening of the refractory period at this point, only the acceleration of left atrial (LA) conduction occurs and structural abnormality of the left atrium that causes spiral wave reentry does not necessarily occur; therefore, it is theoretically considered that PV isolation that inhibits the triggers can sufficiently control AF at this stage of the disease.

The expression of genes including c-fos, c-jun, and Kv1.5 due to intracellular Ca overload occurs in phase 2 of action potential. Above all, increased levels of Kv1.5 mRNA and Kv1.5 protein shorten atrial action potential duration. This is a synergistic effect of atrial muscle stretch and rapid stimulation of the atrium. Increased intracellular Ca via the L-type Ca channel and induced calmodulin and calmodulin kinase II are involved in both of

Table 1 Predictors of PAF Onset and Predictors of Progression from PAF to Persistent AF, **Left:** Predictors of PAF Onset (Modified from Reference 1), **Right:** Predictors of Progression from PAF to Persistent AF (Modified from Reference 2)

				AF/AT Reccurence			
Sl.no	**EF(%)**	**LAD(mm)**	**Strategy**	**Single(%)**	**Multi(%)**	**Mean Change in EF**	**Predictors**
1	36	47	PV1 plus	27	4	0.04 ± 0.16	EF, PV Size
2	35	50	PV1 plus	75	22	0.21 ± 0.13	
3	33	48	PV1 plus	45	12	0.14 ±0.02	
4	42	44	PVI		13	0.14 ±0.09	
5	39	-	CFAE	50		0.08 ±0.08	
6	27	49	PV1 plus		21	0.07 ±0.10	Duration and LA>50mm,not EF
7	41	43	PVL plus	50	21	0.08 ±0.11	LA Size,not EF or Duration

these actions.[9] Shortening of the action potential duration and the refractory period vary in degree from one site to another in the atrium, leading to increased variability of the atrial refractory period. At this stage of the disease, the structure prone to cause reentry is formed. Therefore, it is considered that, at this stage, AF cannot be controlled only by PV isolation for trigger prevention and that linear ablation for LA conduction blocking is required to maintain/control AF.

Subsequently, the expression levels of ion channels, including sodium channel, calcium channel, and transient outward potassium channel, decrease in phase[3,10–12] resulting in so-called atrial remodeling. It is presumed that, at this stage of disease, the quantitative decrease in ion channels reduces the effectiveness of AF prevention of channel blockers targeting ion channels and results in progression to persistent AF. The shallow resting membrane potential of the left atrium at this stage of disease makes abnormal stimulation (i.e., trigger for AF) prone to occur from various sites of the atrium, including those suggesting the involvement of the autonomic nerve (e.g., complex fractionated atrial electrograms [CFAE]) in a manner similar to increased automaticity. In addition, the variability of the atrial refractory period becomes highly enhanced and the structure which maintains AF is completely formed at this stage. Therefore, the ablation strategy at this stage of disease should employ circumferential PV isolation rather than focal PV isolation alone. Circumferential PV isolation isolates the sources of abnormal stimulation (trigger) within the left atrium at the same time as PV isolation. Alternatively, other concurrent ablations, such as CFAE ablation, should be used. In addition, electrical isolation by linear ablation in the left atrium may be required to correct the structure maintaining AF.

Recently, many single nucleotide polymorphisms (SNPs) contributing to AF onset have been identified in genetic studies of AF. These SNPs include one SNP with a strong correlation with AF, Pitx2, and several other SNPs that are weakly correlated with AF. It has been reported that Pitx2 affects the myocardial sleeve, which is a trigger of AF onset

Figure 1: Predictors of PAF onset and Predictors of Progression from PAF to Persistent AF, **Left:** Predictors of PAF Onset (Modified from Reference 1), **Right:** Predictors of Progression from PAF to Persistent AF (Modified from Reference 2)

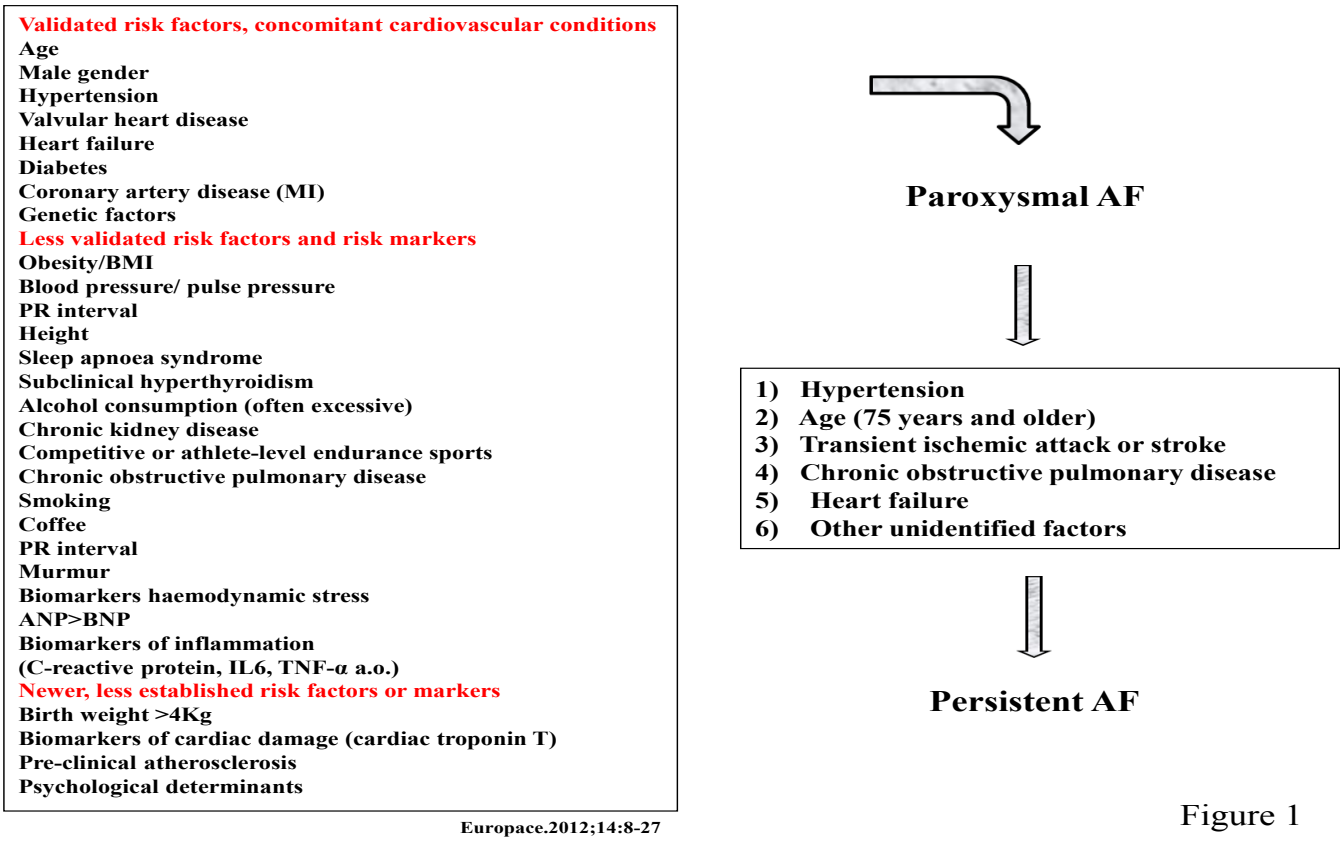


Figure 1

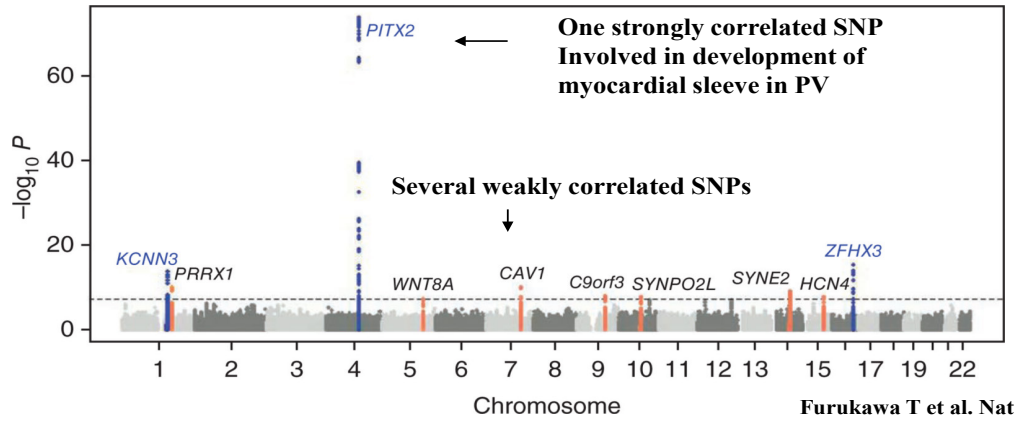
(i.e., PAC originating in PV), while other weakly correlated SNPs affect the AF-maintaining mechanism such as remodeling (see Figure 2).[13]

When persistent AF reaches phase 3 where genetic factors are also involved, radical cure of the disease is likely to be impossible even with all available ablation techniques (stepwise approach). This assumption is a limitation of ablation for persistent AF and is supported by all previous reports on ablation for persistent AF, in which the success rate of the procedure never achieved 100%.

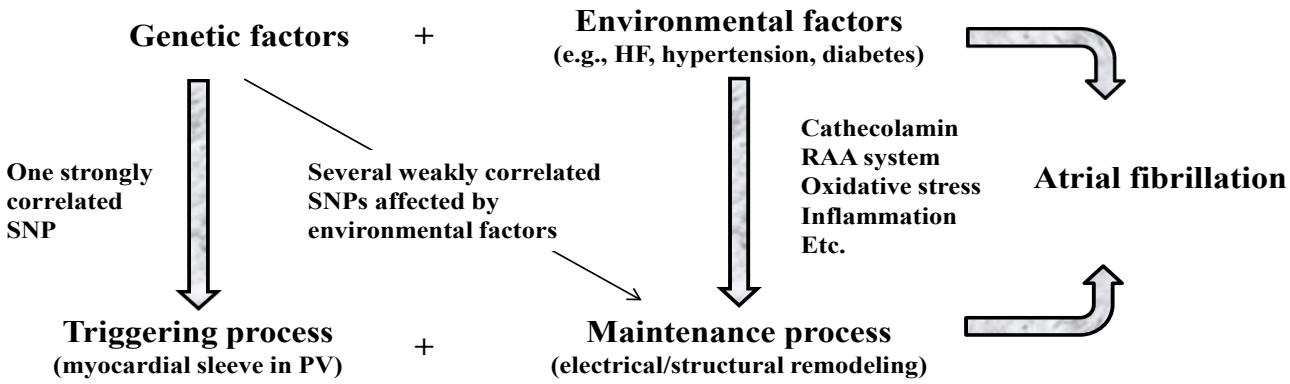
Evolution of Ablation Strategies

In 1998, Haïssaguerre et al.[14] noted frequent action potentials in the PVs and reported that these potentials trigger the onset of PAF. Since then, electrical isolation of PV (PV isolation) has been performed as a radiofrequency (RF) ablation technique for PAF with the hope of preventing the conduction of pulmonary vein activation in the left atrium where it may serve as a trigger of PAF. The initial PV isolation was a focal or segmental isolation technique which isolates each of four PVs using the potentials traveling from the PVs to the left atrium as a guide. In 2001, Pappone et al.[15] reported circumferential PV isolation, which simultaneously isolates all four PVs (left superior, left inferior, right superior, right inferior). This approach had been made feasible by the use of a 3D-mapping system enabling anatomical RF ablation as well as confirmation of whether electrical isolation has been successfully completed. It was reported that this new approach provided more favorable results than focal isolation.[16] Although RF ablation had previously been indicated for PAF only, it has also been performed in patients with persistent AF since 2003. As for RF ablation for persistent AF, linear RF ablation in the left atrium was considered necessary to block conduction within the left atrium in order to prevent LA reentry. Linear RF

Figure 2: AF-related genes and AF (Modified from Reference 14), **Upper panel:** Many single nucleotide polymorphisms (SNPs) contributing to AF onset have been identified including one SNP with a strong correlation with AF (Pitx2) and several SNPs with a weak correlation, **Lower panel:** Relationships between genetic factors related to AF, triggering factors of AF onset, environmental factors, and AF maintenance process (atrial remodeling)

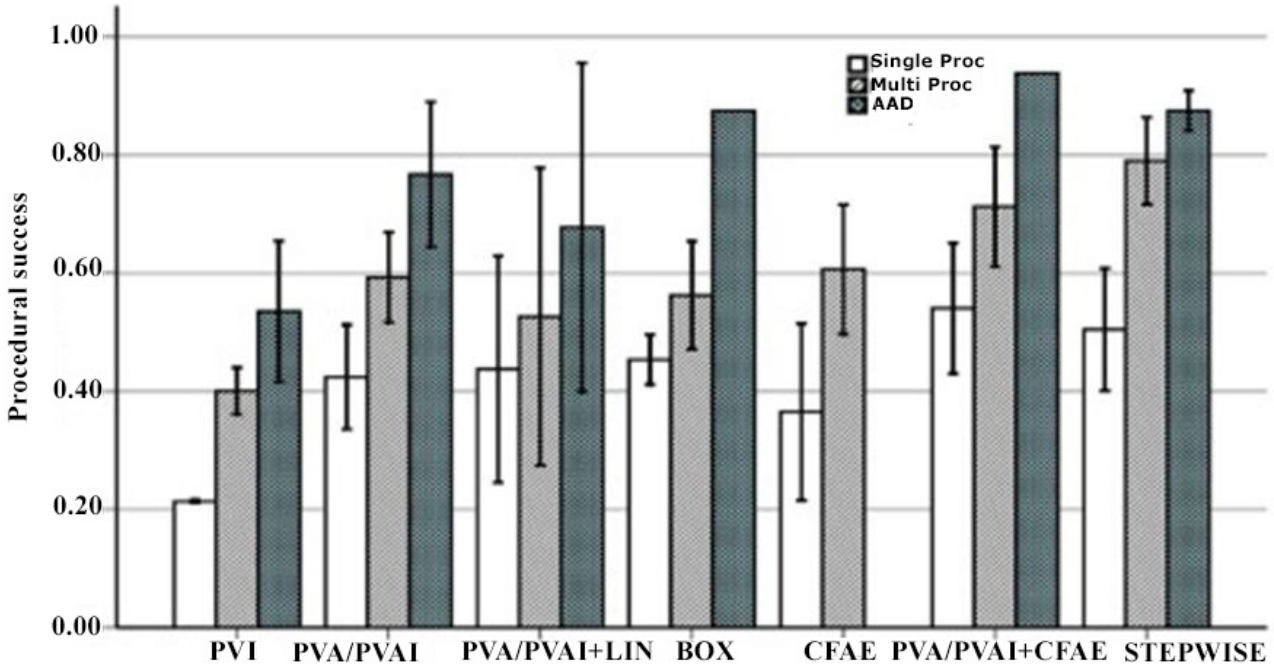


Furukawa T et al. Nat Genet. 2012;44:670-5.



ablation of the following sites was therefore performed in addition to PV isolation[17–19]: the roof of the left atrium (from the superior wall of the orifice of the left superior PV to the superior wall of the orifice of the right superior PV), the region between the mitral annulus and the inferior wall of the orifice of the left inferior PV (mitral isthmus), the region between the mitral annulus and the inferior wall of the orifice of the right inferior PV, and the anterior and posterior mitral annulus. Around the same time, Nademanee et al.[20] reported, based on LA mapping during AF, that CFAE in the left atrium is a good indicator of RF ablation. Pappone et al. found, during circumferential PV isolation, a site where RF ablation had induced a decrease in blood pressure and caused atrioventricular block. They focused on the lower AF recurrence rate in these cases, judged that this site is the vagal nerve on the basis of its autonomic mechanism, analyzed the autonomic mechanism, and reported that, if the vagal nerve is blocked and isolated by RF ablation, the AF recurrence rate is lowered .[21] Later, Lemery et al. defined a site at which high-frequency, high-power stimulation provided during AF prolongs the R-R interval by ≥50%, increases blood pressure by ≥20 mmHg, and causes distress in anesthetized patients as ganglionated plexuses (GP), and reported that RF ablation of this site lowers the AF recurrence rate.[22] In light of the mechanism of AF onset, ablation strategies have shifted toward targeting AFs occurring in atrial muscles with more progressed remodeling, in other words, persistent AF. However, a recent study[23] reported that segmental ablation alone rather than with additional linear ablation reduces complications originating from the left atrium (e.g., tachycardia) in the case of initial ablation for PAF patients with less progressed remodeling. Another report [24] indicated that not all CFAEs may be responsible for AF maintenance. Although CFAE is considered responsible for AF maintenance through autonomic innervation, it is

Figure 3: **Upper panel:** Clinical success of various ablation techniques for persistent/long-standing persistent atrial fibrillation, **Lower panel:** Success rate of ablation for persistent AF and predictors in patients with low cardiac function



Legend: **Upper panel:** Rates are shown for single-procedure, drug-free success (white), multiple-procedure success (diagonal cross hatch), and antiarrhythmic drug (AAD)–assisted success (dark double hatch). Error bars represent ±1 SD; bars are absent when estimate is based on one study. BOX = posterior wall isolation; CFAE = complex fractionated electrogram ablation; LIN = conventional linear ablation; PVA = pulmonary vein antrum ablation; PVAI = pulmonary vein antrum isolation; PVI = pulmonary vein isolation; STEPWISE = stepwise ablation technique.(Reference 27), **Lower panel:** single: success rate with a single procedure, Multi: success rate with multiple procedures CFAE = ablation of complex fractionated atrial electrograms; PVI = pulmonary vein isolation; PVI plus = pulmonary vein isolation and substrate modification (CFAE and/or linear ablation); Modified from Reference 31

also recorded in patients with no history of AF in whom AF was induced by electrical stimulation. As described above, no methodology of RF ablation for AF has yet been established, and ablation strategies may differ by institutions. Nonetheless, as RF ablation for AF is widely performed today, the differences in expertise and methodology between institutions appear to be reducing.

Investigation on Predictors of AF Recurrence

It is difficult to generally define the predictors of AF recurrence due to differences in the situation at the onset of AF, status of AF, and/or ablation strategy. Furthermore, not all reports on ablation for AF have evaluated the predictors of AF recurrence. Therefore, potential predictors of AF recurrence have to be figured out based on the situation at the onset of AF, status of AF, and success rate of each ablation strategy provided in previous reports. Because individual reports include different patient demographics, stages of AF, or ablation strategies, pooling these data may compromise the association between individual aspects of AF and the corresponding ablation strategies.

In fact, multivariable analyses conducted in a previous review article[25] showed that "nonparoxysmal AF may be a clinically useful proxy for a combination of confounded variables, none of which alone is an independent predictor of AF recurrence." This may be true to some extent. Accordingly, separate evaluations of each potential predictor are required. What is the difference between paroxysmal and persistent AF in the context of determining the predictors of AF recurrence after ablation? Both the predictors of AF onset and the predictors of progression to persistent AF as mentioned above underlie this consideration. Most persistent AF episodes are the consequence of progression from PAF. The pathological difference between these two forms of AF is progression of atrial remodeling. Progression of remodeling may differ by patient due to the complex involvement of environmental and genetic factors. It is widely accepted that the potential indicators of remodeling include the duration of AF, LA diameter, and cardiac function.

Strategy

A review on ablation for persistent AF (of 32 reports published from 1999 to 2009)[26] evaluated the success rate of ablation procedures, mainly by strategies (upper panel of Figure 3). The results of this review can be summarized as follows:

1) The success rate was higher with multi-procedures than with a single procedure, where the difference was especially marked in the case of PV isolation (PVI). When electrical isolation of both the PV and left atrium is performed, temporary conduction block of the heart muscle adjacent to the ablation site may occur, followed by the resumption of conduction over time (so-called myocardial stun). This may be considered the achievement of complete electrical isolation. Due to this phenomenon, AF recurrence is an unpreventable event when a single procedure is employed. The difference between single and multiple procedures was also large with CFAE ablation. CFAE ablation is a topic currently drawing wide attention; however, many aspects of CFAE remain unclear, for example, CFAE itself may be changed by pharmacological denervation, CFAE can also be recorded when AF is intentionally induced in patients with no clinical AF, and whether all CFAEs can be ablated. Hence, further studies are warranted with regard to CFAE. Based on the above, a single procedure without a scheduled multi-procedure is a potential predictor of AF recurrence.
2) In light of the mechanism of onset, atrial remodeling in phase 3 is already established in persistent AF. Based on the mechanism of onset/maintenance of persistent AF, an ablation strategy employing PVI alone is considered a predictor of AF recurrence.
3) Comparison PV antrum ablation (PVA)/PV antrum isolation (PVAI) alone and PVA/PVAI + linear ablation revealed that, despite additional use of linear ablation, the success rate was similar in single procedures and lower with PVA/PVAI + linear ablation in multi-procedures. While some reports have indicated the potential of concurrent linear ablation to cause new onset of arrhythmia, previous reports have stated that it may increase the success rate.[18–20] Further studies are warranted to better understand the impact of concurrent linear ablation. Multi-procedures achieved better results when box ablation, which includes linear ablation, was performed. This suggests that the target site and degree of linear ablation may affect the success rate.

In the review above, maximum LA diameter was

53 mm ± 6 mm, follow-up period was up to 36 months, and no information was provided regarding cardiac function. This review article discussed reports published by 2009 and the article itself was published in 2010. Today, many institutions use CFEA ablation or linear ablation concurrently rather than PVAI alone and the variability among institutions is less prominent than before.

There is a limitation that strategy-related predictors of AF recurrence can only be assumed based on existing reports. Nonetheless, ablation strategies employing PVI alone and single procedures are considered as strategy-related predictors of AF recurrence. No other strategies showed a clear difference; however, further studies are warranted for CFEA ablation and linear ablation. Although experience of the procedures may also affect recurrence, no criteria are available to determine whether a physician is "experienced". Since the development of a 3D-mapping system has enabled confirmation of successful completion of isolation, the differences between physicians are now less than before.

Cardiac Function

Limited studies have evaluated predictors of AF recurrence after ablation for persistent AF in patients with low cardiac function. Heart failure is one of the risk factors considered in the HATCH score, and Chen et al.[27] stated that low cardiac function is a predictor of AF recurrence. In contrast, Nadamanee et al.[28] and De Potter T et al.[29] did not find this to be a predictor (see lower panel of Figure 3). The reason for not considering low cardiac function as a predictor of AF recurrence was the assumption that AF patients with low cardiac function show improvement in cardiac function once they reverted to sinus rhythm, which may reduce the load on the atrium, thereby preventing the recurrence of AF.[30] However, it is reported that cardiac function may not necessary improve after reversion to sinus rhythm, depending on the underlying disease which led to low cardiac function (especially in the case of ischemic cardiac diseases). Furthermore, it is suggested that recurrence of AF may not affect cardiac function in some patients, although the reason is unknown.[31] It appears that whether AF depresses cardiac function depends on the underlying disease which led to low cardiac function, although further studies are warranted to confirm this assumption. It is believed that low cardiac function is not a predictor of AF recurrence in persistent AF patients with low cardiac function who have reverted to sinus rhythm and shown improved cardiac function, because these patients no longer have low cardiac function. Meanwhile, low cardiac function may be a predictor of AF recurrence in patients showing no improvement in cardiac function after reversion to sinus rhythm. With regard to cardiac function-related predictors of AF recurrence, new findings would probably be obtained by evaluating "no worsening/change in cardiac function after ablation" as a potential predictor of AF recurrence rather than "low cardiac function."

Left Atrium Diameter

Although LA diameter is not a risk factor considered in the HATCH score, Suzuki et al. [32] reported that the frequency of progression to persistent AF increases by 1.84-fold for each 10-mm enlargement of LA diameter. McCready et al.[33] indicated that LA diameter is a predictor of whether ablation for persistent AF will succeed with a single attempt and specified the criterion for successful ablation as <43 mm. O'Neill et al.[34] reported that both LA diameter and duration of AF are predictors of AF recurrence (mean LA diameter of patients 47 mm ± 9 mm). In contrast, Takahashi et al.[35] (mean LA diameter of patients 44 mm ± 5 mm) and Tilz et al. [36] (mean LA diameter of patients 49 mm ± 6 mm) reported that duration of AF alone is a predictor of AF recurrence and that LA diameter is not. It is doubtful whether a few millimeters of difference in LA diameter impact AF recurrence. Echocardiography is used to determine LA diameter. Because the accuracy of measurement depends on the experience of surgeons, an error of a few millimeters is most likely to be observed no matter how experienced the surgeon. In addition, although LA diameter of <40 mm is currently considered normal, heart size naturally varies according to body size. Left atrial diameter of 40 mm in small and large individuals may not have the same implications. Taking these matters into consideration, it cannot be stated, for example, that LA diameter of ≥45 mm is a predictor and <45 mm is not. Brooks et al.[26] defined, probably based on their experience, the cut-off value for LA diameter as 55 mm; how-

ever, there are few reports on excessively enlarged LA diameters. Heist et al.[37] reported LA diameter as a predictor of successful ablation for persistent AF ($p = 0.002$) although no numerical evaluation was provided (mean LA diameter of patients 45 mm ± 7.7 mm). At this time, the result of Heist et al. appears to be true, and LA diameter may be a potential predictor of AF recurrence. No numerical criteria, however, can be provided at present. A method to accurately indicate the actual progress of LA remodeling has not been established. Left atrial diameter is only a factor representing LA remodeling and is not a definite methodology. Indicators for LA remodeling need to be developed in the future. Whether LA diameter shows a decrease, no change, or an increase after ablation may predict the recurrence of AF to some extent. Note that predictors of ablation failure and predictors of AF recurrence were considered as synonyms based on a report [37] indicating the correlation between the success rate of ablation and the recurrence rate of AF.

Duration of Atrial Fibrillation

Many studies have reported the duration of AF as a predictor of AF recurrence,[28,34,35,36] while some other studies reported that it was not.[29,33] Duration of AF varied among the studies, ranging from one to ten years. It is theoretically considered that the longer the AF duration, the more atrial remodeling progresses; however, the degree of progression varies from patient to patient due to the involvement of genetic factors. The controversy regarding AF duration as a predictor may be partially attributable to the fact that AF duration is not proportional to the degree of progression. Initially after the onset of AF, P-wave peaks are high and the AF cycle is long. As AF progresses to the persistent form, P-wave peaks decrease, AF cycle shortens, and eventually even detection of the P-wave is often difficult. Heist et al.[37] reported the AF cycle as a predictor of AF recurrence ($p < 0.001$) based on the measurement of AF cycle length, although no numerical results were provided and no correlation with AF duration was assessed. Although the duration of AF may be one of the predictors of atrial remodeling, there may be too many confounding factors to consider this as an independent indicator.

Discussion

Our interest is focused on the diagnostic criteria to determine patients with persistent AF in whom ablation can be performed with minimum risk and achieve the most benefit; however, no definitions have been established regarding how many years sinus rhythm should be maintained after ablation to be considered as "no recurrence." Complications of ablation, which are not uncommon, and cost effectiveness[39] should also be considered. Per European guidelines, RF ablation for persistent AF patients with low cardiac function complicated with cardiac failure is not categorized as Class I treatment. The reason for this classification is likely to be the difficulty associated with RF ablation in AF patients with low cardiac function and the high occurrence of complications due to RF ablation. Furthermore, the cost of two ablations for persistent AF is equivalent to 45.3 years of the most expensive drug treatment and 63.9 years of the most inexpensive drug treatment.

In this article, the most probable potential predictors of AF recurrence, namely, ablation strategy, LA diameter, low cardiac function, and AF duration have been assessed in the context of a discussion on the predictors of AF recurrence after ablation for persistent AF. None of these might be an independent predictor. These potential predictors do not serve as independent predictors even in the case of PAF, except for those caused by factors which can be eliminated with PVI and can be radically cured. In many reports, excessively enlarged LA diameter and persistent AF lasting several decades are excluded from the concept of atrial remodeling. Only in the hope of improving cardiac function through reversion to sinus rhythm, is ablation performed in persistent AF patients with low cardiac function. It can be stated now, however, that 1) persistent AF patients with some degree (although this "some degree" has not been clearly defined) of enlarged LA diameter, prolonged AF duration, or decreased cardiac function may also revert to sinus rhythm with RF ablation; 2) more efficient treatment may be developed in the future; and 3) reversion to sinus rhythm may increase the benefit to patients. In summary, RF ablation for persistent AF is currently required; thus, evaluation of predictors of AF recurrence after RF ablation for persistent AF

has great significance.

Conclusions

Predictors of AF onset and progression to persistent AF are the basis of predictors of AF recurrence after RF ablation for persistent AF.

The difference between paroxysmal and persistent AFs includes the ablation strategy and progression of atrial remodeling. Left atrial diameter, low cardiac function, and AF duration are indicators of remodeling.

As for the ablation strategy, although CFAE ablation and linear ablation remain to be studied, treatment approaches have been established to a certain degree and inter-institutional variations in experience and/or expertise appear to be less than before. Currently available reports show that a high recurrence rate is associated with PVI-alone ablation and single procedures.

Left atrial diameter, low cardiac function, and AF duration are indicators of atrial remodeling that do not serve as independent predictors of AF recurrence; however, they can be used as relative predictors. A combination of these predictors may be established as a predictive index of AF recurrence. Future studies are awaited to establish diagnostic criteria for using ablation for persistent AF.

Disclosures

No disclosures relevant to this article were made by the authors.

References

1. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M, Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R, Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J, Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Stegink W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options--a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. Europace. 2012;14: 8-27.

2. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ, van den Heijkant AC, Allessie MA, Crijns HJ. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. J Am Coll Cardiol. 2010; 55: 725-31.

3. Tang RB, Dong JZ, Long DY, Yu RH, Ning M, Jiang CX, Sang CH, Liu XH, Ma CS. Efficacy of catheter ablation of atrial fibrillation beyond HATCH score. Chin Med J (Engl). 2012; 125: 3425-9.

4. Disertori M, Latini R, Maggioni AP, Delise P, Di Pasquale G, Franzosi MG, Staszewsky L, Tognoni G; GISSI-AF Investigators. Rationale and design of the GISSI-Atrial Fibrillation Trial: a randomized, prospective, multicentre study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of atrial fibrillation recurrence. J Cardiovasc Med. 2006; 7: 29-38.

5. ACTIVE I Investigators, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. Irbesartan in patients with atrial fibrillation. N Engl J Med. 2011; 364: 928-38.

6. Haïssaguerre M., Jaïs P., Shah D. C., Takahashi A., Hocini M., Quiniou G., Garrigue S., Le Mouroux A., Le Métayer P., Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998; 339: 659-666.

7. Ashihara T, Namba T, Ikeda T, Ito M, Nakazawa K, Trayanova N. Mechanisms of myocardial capture and temporal excitable gap during spiral wave reentry in a bidomain model. Circulation. 2004; 109: 920-925.

8. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995; 92: 1954-1968,

9. Daoud EG, Knight BP, Weiss R, Bahu M, Paladino W, Goyal R, Man KC, Strickberger SA, Morady F. Effect of verapamil and procainamide on atrial fibrillation induced electrical remodeling in humans. Circulation. 1997; 96: 1542-1550.

10. Von Wagoner DR, Pond AL, McCarthy PM, Trimmer JS, Nerbonne JM. Outward K+ current densities and Kv1.5 expression are reduced in chronic human atrial fibrillation. Circ. Res. 1997; 80: 772-781.

11. Gaspo R, Bosch RF, Bou-Abboud E, Nattel S. Tachycardia-induced changes in Na+ current in a chronic dog model of atrial fibrillation. Circ Res. 1997; 81: 1045-1052.

12. Goette A, Honeycutt C, Langberg JJ: Electrical remodeling in atrial fibrillation. Time course and mechanisms. Circulation. 1996; 94: 2968-2974.

13. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Müller-Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dörr M, Ozaki K, Roberts JD, Smith JG, Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagoner DR, Magnani JW, Wakili R, Clauss S, Rotter JI, Steinbeck G, Launer LJ, Davies RW, Borkovich M, Harris TB, Lin H, Völker U, Völzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ, Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conen D, Tsunoda T, Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL, Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann HE, Witteman JC, Kao WH, Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McK-

night B, Sjögren M, Newman AB, Liu Y, Gollob MH, Melander O, Tanaka T, Stricker BH, Felix SB, Alonso A, Darbar D, Barnard J, Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kääb S. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet. 2012; 44: 670-5.

14. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998; 339: 659-666.15. Pappone C, Rosanio S, Oreto G, Tocchi M, Gugliotta F, Vicedomini G, Salvati A, Dicandia C, Mazzone P, Santinelli V, Gulletta S, Chierchia S. Circumferential radiofrequency ablation of pulmonary vein ostia: A new anatomic approach for curing atrial fibrillation. Circulation. 2000; 102: 2619-28.

16. Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E, Veerareddy S, Pelosi F Jr, Morady F. Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. Circulation. 2003; 108: 2355-60.

17. Scavée C, Weerasooriya R, Jais P, Hocini M, Haissaguerre M. Linear ablation in the left atrium using a nonfluoroscopic mapping system. J Cardiovasc Electrophysiol. 2003; 14: 554.

18. Sanders P, Jaïs P, Hocini M, Hsu LF, Scavée C, Sacher F, Rotter M, Takahashi Y, Pasquié JL, Shah DC, Garrigue S, Clémenty J, Haïssaguerre M. Electrophysiologic and clinical consequences of linear catheter ablation to transect the anterior left atrium in patients with atrial fibrillation. Heart Rhythm. 2004; 1: 176-84.

19. Jaïs P, Hocini M, Hsu LF, Sanders P, Scavee C, Weerasooriya R, Macle L, Raybaud F, Garrigue S, Shah DC, Le Metayer P, Clémenty J, Haïssaguerre M. Technique and results of linear ablation at the mitral isthmus. Circulation. 2004; 110: 2996-3002.

20. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, Khunnawat C, Ngarmukos T. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004; 43: 2044-53.

21. Pappone C, Santinelli V, Manguso F, Vicedomini G, Gugliotta F, Augello G, Mazzone P, Tortoriello 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: 327-34.

22. Lemery R, Birnie D, Tang AS, Green M, Gollob M.Feasibility study of endocardial mapping of ganglionated plexuses during catheter ablation of atrial fibrillation. Heart Rhythm. 2006; 3: 387-96.

23. 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: 243-8.

24. Atienza F, Calvo D, Almendral J, Zlochiver S, Grzeda KR, Martínez-Alzamora N, González-Torrecilla E, Arenal A, Fernández-Avilés F, Berenfeld O. Mechanisms of fractionated electrograms formation in the posterior left atrium during paroxysmal atrial fibrillation in humans. J Am Coll Cardiol. 2011; 57: 1081-92.

25. 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.

26. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, Hsu LF, Sanders P. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm. 2010; 7: 835-46.

27. Chen MS, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, Rossillo A, Verma A, Cummings J, Erciyes D, Saad E, Bhargava M, Bash D, Schweikert R, Burkhardt D, Williams-Andrews M, Perez-Lugones A, Abdul-Karim A, Saliba W, Natale A. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol. 2004; 43: 1004-9.

28. Nademanee K, Schwab MC, Kosar EM, Karwecki M, Moran MD, Visessook N, Michael AD, Ngarmukos T. Clinical outcomes of catheter substrate ablation for high-risk patients with atrial fibrillation. J Am Coll Cardiol. 2008; 51: 843-9.

29. De Potter T, Berruezo A, Mont L, Matiello M, Tamborero D, Santibañez C, Benito B, Zamorano N, Brugada J. Left ventricular systolic dysfunction by itself does not influence outcome of atrial fibrillation ablation. Europace. 2010; 12: 24-9.

30. Wilton SB, Fundytus A, Ghali WA, Veenhuyzen GD, Quinn FR, Mitchell LB, Hill MD, Faris P, Exner DV. Meta-analysis of the effectiveness and safety of catheter ablation of atrial fibrillation in patients with versus without left ventricular systolic dysfunction. Am J Cardiol. 2010; 106: 1284-91.

31. Dagres N, Varounis C, Gaspar T, Piorkowski C, Eitel C, Iliodromitis EK, Lekakis JP, Flevari P, Simeonidou E, Rallidis LS, Tsougos E, Hindricks G, Sommer P, Anastasiou-Nana M. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. J Card Fail. 2011; 17(11): 964-70.

32. Suzuki T, Yamazaki T, Ogawa S, Nagai R, Yamashita T. J-RHYTHM II Investigators. Echocardiographic predictors of frequency of paroxysmal atrial fibrillation (AF) and its progression to persistent AF in hypertensive patients with paroxysmal AF: results from the Japanese Rhythm Management Trial II for Atrial Fibrillation (J-RHYTHM II Study). Heart Rhythm. 2011; 8: 1831-6.

33. 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.

34. O'Neill MD, Wright M, Knecht S, Jaïs P, Hocini M, Takahashi Y, Jönsson A, Sacher F, Matsuo S, Lim KT, Arantes L, Derval N, Lellouche N, Nault I, Bordachar P, Clémenty J, Haïssaguerre M. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. Eur Heart J. 2009; 30: 1105-12.

35. Takahashi Y, Takahashi A, Kuwahara T, Fujino T, Okubo K, Kusa S, Fujii A, Yagishita A, Miyazaki S, Nozato T, Hikita H, Hirao K, Isobe M. Clinical characteristics of patients with persistent atrial fibrillation successfully treated by left atrial ablation. Circ. Arrhythm Electrophysiol. 2010; 3: 465-71.

36. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, Mathew S, Yoshiga Y, Wissner E, Kuck KH, Ouyang F. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg Sequential Ablation Strategy. J Am Coll Cardiol. 2012; 60: 1921-9.
37. 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; 110: 545-51.
38. Shah RU, Freeman JV, Shilane D, Wang PJ, Go AS, Hlatky MA. Procedural complications, rehospitalizations, and repeat procedures after catheter ablation for atrial fibrillation. J Am Coll Cardiol. 2012; 59: 143-9.
39. Noro M, Kujime S, Ito N, Enomoto Y, Nakamura K, Sakai T, Sakata T, Sugi K. Cost effectiveness of radiofrequency Catheter Ablation vs. Medical Treatment for Atrial Fibrillation in Japan-Cost Performance for Atrial Fibrillation-. J Circulation 2011; 75: 1860-1866.