Impact of Pulmonary Vein Isolation on Fractionated Atrial Potentials and Ganglionated Plexi in Patients With Persistent Atrial Fibrillation

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Summary

Some patients with persistent atrial fibrillation (AF) acquire long-term freedom from AF by pulmonary vein (PV) isolation alone. The aim of the present study was to evaluate the characteristics of their atrial substrate.

We studied 20 patients with persistent AF to examine the distribution of fractionated atrial potentials (FAP) with vagal reflexes elicited by high frequency stimulation (HFS) with the use of the CARTO system before and after the PV isolation.

Both the %FAP area defined as a proportion of the FAP area to the total left atrial area (34.3 ± 10.3 to 21.5 ± 10.2%; P < 0.0001) and number of GP sites with vagal reflexes (4.0 [3.0, 5.0] to 2.0 [1.0, 2.8]; P < 0.0001) were markedly decreased after the PV isolation. Seven (35%) patients had AF recurrences, and they had a greater %FAP area after the PV isolation than those without (32.8 [22.1, 37.3] versus 13.8 [10.9, 19.9]; P = 0.0049). A %FAP area after the PV isolation of > 20% was significantly associated with an AF recurrence (odds ratio 20.0, 95% confidence interval 2.26-470.34; P = 0.018). No significant difference was found between the patients with and without AF recurrence in the reduction rate of anatomic sites of GPs with a vagal reflex induced by the HFS.

A more marked reduction in the FAP area by the PV isolation was significantly associated with a better outcome in patients with persistent AF. (Int Heart J 2014; 55: 494-498)

Key words: Ablation, Atrial substrate, Complex fractionated atrial electrocardiograms, High frequency stimulation

Pulmonary vein (PV) isolation is the cornerstone of catheter ablation in patients with paroxysmal atrial fibrillation (AF), and thus has been suggested as a potential first-line treatment in selected patients with paroxysmal AF.1 However, the long-term outcome of PV isolation alone for persistent AF is still far from acceptable when compared with that of paroxysmal AF.2 Accordingly, some ablation strategies such as linear ablation, ablation targeting complex fractionated atrial electrocardiograms (CFAE)3 or ganglionated plexi (GPs),4 have been developed as adjunctive ablation strategies to the PV isolation. On the other hand, it is also true that in some patients with persistent AF, PV isolation alone enables them to restore sinus rhythm over an extended period of time even without any additional ablation strategies.5 Unfortunately, as it now stands, there is no way to discriminate in advance between the patients with persistent AF who will be cured by the PV isolation alone and those who will not.

CFAE provide variable information with regard to a substrate favoring AF6 and GPs play important roles in the development and maintenance of AF, and further, they are closely related.7 The CFAE area8,9 and number of GPs10 both are known to be reduced after PV isolation in patients with persistent AF, and therefore this ablation strategy is presumed to be more than just a trigger elimination. In the present study, we attempted to determine what patients with persistent AF could gain a benefit from PV isolation alone by means of analyzing the alterations in the CFAEs and GPs before and after the PV isolation.

Methods

Patients: This study was conducted at the Cardiovascular Center of Nagoya Daini Red Cross Hospital from February 2011 to January 2012. Consecutive patients with symptomatic persistent AF were eligible for inclusion if they were scheduled to undergo ablation for the first time. Persistent AF was defined as continuous AF that was sustained beyond 7 days. Patients were excluded from the study if they had longstanding persistent AF defined as continuous AF with a duration of greater than 1 year.10 A patient with AF was not ablated if they were 75 years or older or had a left atrial diameter of 55 mm or

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greater. All antiarrhythmic drugs (AADs) were discontinued for 5 half-lives before the ablation procedure. Adequate oral anticoagulation therapy with warfarin (an international normalized ratio of 2.0–3.0) or dabigatran at a dose of 110 mg or 150 mg twice daily was administered no less than 1 month before the procedure, and they were withdrawn the day before the ablation without any heparin bridging. All patients underwent transthoracic and transesophageal echocardiography prior to the procedure to rule out the formation of any LA thrombi. Written informed consent was obtained from all patients, and the study protocol was approved by the hospital research committee.

**Procedures:** The mapping and ablation procedures were undertaken during AF under conscious sedation. The activated clotting time was kept at a level of 350-400 seconds by the administration of heparin throughout the procedure. Two decapolar circumferential catheters (Lasso; Biosense Webster, Diamond Bar, CA) and a 3.5-mm-tip open irrigated ablation catheter (EZ steer, Biosense Webster) were introduced into the left atrium (LA) by transseptal catheterization. The subsequent procedural steps are described as follows.

**Step 1** Electroanatomical mapping was undertaken with the use of a CARTO 3 mapping system (Biosense Webster). The bipolar electrograms filtered from 30 to 500 Hz were obtained from the entire area of the LA endocardial surface except for the LA appendage, and were analyzed using CFAE software on CARTO-RMT (Biosense Webster). Nademanee, et al initially introduced an algorithm for CFAE using the CARTO system, and researchers have modified it and developed new ones. In the present study, we used the algorithm reported by Nakagawa, et al to create CFAE maps. The bipolar potentials were considered as fractionated atrial potentials (FAP) if they had (1) an amplitude of 0.03-0.2 mV and (2) an inter-potential interval of 15-80 ms. The number of intervals between the FAP segments during a 2.5-second recording was determined and displayed in an interval confidence level (ICL) map in a color-code manner (Supplemental Figure 1). The FAP area was defined as the area of the LA in which more than 40 FAP segments were identified during a 2.5-second recording. The proportion of the FAP area to the total area of the LA endocardial surface was manually calculated. The location of the FAP areas in the LA were visually analyzed, and it was determined whether any FAP areas were identified in the following 5 GP anatomic sites known to be accessible from the LA endocardium: superior left GP (SLGP), anterior right GP (ARGP), inferior left GP (ILGP), inferior right GP (IRGP), and Marshall tract GP (MTGP).

**Step 2** High frequency stimulation (HFS) was then delivered to the 5 presumed GP sites with a frequency of 20 Hz, amplitude of 20 V, and pulse duration of 10 ms for 5 seconds per each site (BC-1100; Fukuda Denshi, Tokyo). The sites in the LA were identified as locations of GPs if they had a vagal reflex defined as a prolongation of >50% of the R-R interval under invasive arterial monitoring, elicited by the HFS (Supplemental Figure 1).

**Step 3** Circumferential ablation lines were created around the left- and right-sided ipsilateral PVS using an irrigated catheter in accordance with the double Lasso technique. Radiofrequency energy was delivered with a maximum power of 35 W for 20 seconds at each site. The temperature was limited to 43°C. The endpoint of the PV isolation was either the elimination or the dissociation of the PV potentials recorded from the circular catheters placed within the PVs and exit block from the PVS. The locations of the GPs and FAP areas were not marked on the electroanatomic maps at the time of the PV isolation so that the operators could create ablation lines without knowledge of those locations, and they were delineated on the map only after the PV isolation had been completed.

**Steps 4 and 5** The FAP mapping and GP mapping were then repeated again as in the same manner before the PV isolation to test whether the distribution of the FAP areas changed and a vagal reflex was still induced at the anatomic sites of the GPs after the PV isolation.

**Step 6** Transthoracic cardioversion was applied to restore sinus rhythm. Finally, the cavitricuspid isthmus was ablated with an endpoint of bidirectional conduction block.

**Follow-up:** The oral anticoagulants were restarted after confirming hemostasis of the access sites. Previously ineffective AADs were resumed the day after the ablation. The patients were discharged from the hospital 2 days after the ablation and were scheduled to be followed up at the outpatient clinic at 2 weeks, and 3, 6, 9, and finally 12 months after the procedure. Twelve-lead electrocardiograms were obtained at all clinical visits, and 24-hour Holter monitoring was performed at 3-month intervals during the follow-up period. An episode of AF or atrial flutter detected by a 12-lead electrocardiogram or Holter monitoring that occurred after the 3 month blanking period was considered a recurrence of AF if it had a duration of 30 seconds or more. When AF recurved, sinus rhythm was restored by using transthoracic cardioversion or the intravenous administration of AADs. Discontinuation of the oral AADs was encouraged in patients who remained free of AF for 3 consecutive months; however, the AADs were continued when they were reluctant to discontinue.

**Endpoints:** The endpoints of the present study were (1) the pre and post %FAP area defined as the proportion of the FAP area to the total area of the LA endocardial surface before and after the PV isolation, respectively, and the distribution of the FAP area in the GP anatomic sites before and after the procedure, (2) the number and location of GP anatomic sites with a vagal reflex elicited by the HFS before and after the PV isolation, and (3) a recurrence of AF arising more than 3 months after the ablation.

**Statistical analysis:** Continuous variables were summarized as the mean ± SD or median with interquartile ranges, and categorical variables as proportions. Continuous variables were compared using Wilcoxon’s signed-rank test for paired data and the Mann–Whitney U test for unpaired data. Fisher’s exact test was used to compare the categorical variables. Paired dichotomous data were compared using McNemar’s test. Receiver-operating characteristic curve analysis was used to examine the ability of the post %FAP area to identify the patients with AF recurrence. The optimal cut-off value was calculated by determining the post %FAP area providing the greatest sum of the sensitivity and specificity. Univariate logistic regression analysis was performed to determine the odds ratio for AF recurrence. All Statistical analyses were performed using SPSS software version 11.5 (SPSS, Inc., Chicago, Illinois). A P value of < 0.05 was considered significant.
RESULTS

Patients: We examined 20 patients. The clinical characteristics of the patients recruited are summarized in Table I. There were no patients with diabetes or any structural heart diseases, and none were prescribed amiodarone. Planned procedures were completed and AF was terminated by electrical cardioversion in all patients. The total procedural duration was 172 ± 26 min, and the total radiofrequency energy delivered was 37285 ± 11017 J.

Changes in FAP area and GP sites with vagal reflexes before and after PV isolation: The total number of points taken from the LA during mapping before and after the PV isolation was 74 ± 12/patient and 65 ± 10/patient, respectively. Both the %FAP area (34.3 ± 10.3 to 21.5 ± 10.2%; P < 0.0001, Supplemental Figure 2A) and number of anatomic sites of the GPs with a vagal reflex elicited by the HFS (4.0 [3.0, 5.0] to 2.0 [1.0, 2.8]; P < 0.0001, Supplemental Figure 2B) were significantly decreased after the PV isolation. In the analyses of each of the 5 anatomic sites of the GPs, the FAP areas were likely to disappear at the SLGP, ARGP, IRGP and MTGP sites (Supplemental Figure 3A), and a vagal reflex was no longer likely to be induced by the HFS at the SLGP, ARGP, ILGP and MTGP sites after the PV isolation (Supplemental Figure 3B).

AF recurrence and its associated factors: At the end of the follow-up period, 16 (80%) patients remained on some AADs. During the 18.5 ± 5.2 months of follow-up period, in this setting, 7 (35%) patients had AF recurrences. The patients with and without AF recurrence had a similar pre %FAP area (42.9 [38.7, 47.4], versus 32.6 [22.5, 40.7]%; P = 0.097, Supplemental Figure 4A), while the post %FAP area was significantly greater in the patients with AF recurrences (32.8 [22.1, 37.3] versus 13.8 [10.9, 19.9]%: P = 0.0049, Supplemental Figure 4B). Although it did not reach statistical significance, there was a trend toward a smaller reduction rate of the %FAP area after the PV isolation among the patients with AF recurrences as compared to those without (22.4 [17.4, 33.8] versus 46.0 [23.3, 66.9]%: P = 0.054, Supplemental Figure 4C). No significant difference was found between the patients with and without AF recurrences in the number of anatomic sites of GPs with a vagal reflex induced by the HFS before and after the PV isolation, or in its reduction rate (Supplemental Figure 5). The post %FAP area had the ability to discriminate between the patients with and without AF recurrences (area under the curve 0.86, 95% confidence interval [CI] 0.68-1.00; P = 0.01), and its optimal cut-off value was 22.1% with a sensitivity of 0.86 and specificity of 0.85. Univariate logistic regression analysis revealed that a post %FAP area of > 20% was significantly associated with the incidence of AF recurrence (odds ratio 20.0, 95% CI 2.26-470.34; P = 0.018).

DISCUSSION

Impact of PV isolation on the distribution of FAP areas and GP sites with a vagal reflex: We found that the FAP areas became significantly reduced after the PV isolation. A similar finding was previously reported, and Roux, et al proposed the following potential mechanisms: (1) prevention of PV firing from exiting and colliding with LA wavefronts by creating isolation lines at the PV-LA junctions, (2) autonomic modification by ablating the GPs, (3) interruption of intra-atrial muscle bundles promoting the organization of AF by the isolation of the right PVs, and (4) an increase in the atrial fibrillatory cycle length resulting from the PV isolation.

We also found that the PV isolation made the vagal reflexes less likely to be induced by HFS particularly at the GP anatomic sites that were close to the isolation lines, which was completely consistent with our recent report in which we presumed that some GPs were unintentionally ablated when they were near ablation lines. Not surprisingly, this finding was closely related to the second causal mechanism mentioned above by which PV isolation reduced the FAP burden. Fractionated electrograms are known to be located around the GP anatomic sites, which is explained by the concept that the fractionated electrograms may reflect focal firing, and the focal firing may in turn largely depend on the GP activity. Therefore, both the FAP area and vagal reflexes were likely to disappear at the sites of GPs that were adjacent to ablation lines after the PV isolation. To state it another way, they tended to remain at GP sites that were far from the PV antrum. Interestingly, however, in individual analyses, we found that in the majority of the presumed GP sites, the presence of an FAP area did not necessarily correspond with the inducibility of a vagal reflex either before or after the PV isolation. In other words, it was not likely that the FAP areas were necessarily identified where vagal reflexes were elicited, and vice versa. It is known that during AF no vagal reflexes are induced with the application of HFS in nearly 20% of the GP anatomic sites, which never means that some GPs are absent in the presumed sites. This may be the main reason for the apparently conflicting finding. Alternatively, the finding may have been somehow related to the fact that we did not deliver radiofrequency energy targeting the GP cell bodies, and therefore they may not have been completely destroyed. Further, it is also important to remember that there was a potential technical issue with respect to identifying the location of the GP.

Significance of the reduction in FAP after PV isolation for achieving freedom from AF: To the best of our knowledge, we have here for the first time showed that a more marked reduction in the FAP areas after PV isolation was significantly associated with a better outcome after ablation in patients with persistent AF. The following are possible explanations.

Some researchers reported that there are 2 types of CFAE, “active” and “passive”. Jadidi, et al stated in their work that the CFAE eliminated by PV isolation may play a “passive” role, and the CFAE remaining even after the PV iso-
lation may reflect pathological changes in the LA such as scar. According to this concept, the more of the latter “active” CFAE that remain after the PV isolation, the more diseased the LA may be. This assumption supports the potential predictive value of the FAP areas remaining after the PV isolation for its outcome.

Assuming that the collision of PV firings with LA wavefronts is one of the major causes of FAP as proposed by Roux, et al.8,10 when the PV firings occurred with a significant frequency, they possibly produce the majority of FAP identified in the entire LA shell. In this situation, complete PV isolation is supposed to bring about not only a marked reduction in the FAP burden but also a favorable outcome by confining the electrical firing to inside the PVs. Namely, the extent of the reduction in the FAP area after the PV isolation may indicate how the maintenance of AF depends on PV foci.

It was reported that CFAE are more likely to be concentrated to the PV antrum in paroxysmal AF than in persistent AF.11,12 Thus, given that PV isolation intensively eliminates the FAP areas around the PVs as shown in the present study or previous ones,8,10 a greater proportion of FAP areas is supposed to be removed by the PV isolation during AF in patients with paroxysmal AF than in those with persistent AF. Accordingly, the patients with persistent AF in whom FAP areas were extensively eliminated after the PV isolation may instead have had an arrhythmogenic substrate close to that characterizing paroxysmal AF. This inference also suggests that there would be a higher curability with PV isolation alone in patients with persistent AF who had smaller FAP areas after the PV isolation.

Clinical implications: Most studies on CFAE or GPs in human hearts were conducted based on the premise of their ablation. Thus, the present study is meaningful in that the direct impact of the PV isolation on the FAP and GPs, and their relationship to the clinical outcome, were analyzed. Therefore, new insight regarding the alteration in the atrial substrate after this crucial ablation procedure was provided for the field of the ablation of atrial fibrillation. Of course, not all patients with persistent AF undergo mapping of FAP and GPs during the ablation procedure. However, our results may provide some clues for identifying patients with persistent AF who will acquire a long-term freedom from AF by PV isolation alone without an ablation targeting CFAE or GPs during their scheduled stepwise ablation procedure.

Limitations: First, the concept of FAP and its algorithm is not widely accepted. Second, the majority of the patients studied were on some AADs at the end of a somewhat shorter follow-up period, and thus the rate of AF recurrence may have been estimated to be comparatively lower. Finally, all the therapeutic interventions we performed during the procedures were only PV isolation with tricuspid isthmus ablation. Nevertheless, the patients had to endure a longer procedural duration due to repeated mapping procedures. For this reason, we failed to recruit a sufficient number of patients, leading to a limited statistical power.

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