Role of intracardiac defibrillation during the procedure as a predictor of atrial fibrillation recurrence after catheter ablation

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Abstract

Introduction: Intracardiac defibrillation (IDF) is performed to restore sinus rhythm (SR) during radiofrequency catheter ablation (RFCA) of atrial fibrillation (AF). This study aimed to examine the change in the IDF threshold before and after RFCA during the procedure, and furthermore, to evaluate whether the IDF threshold after RFCA was associated with the AF substrate and recurrence of AF. Method: This study enrolled 141 consecutive patients with drug-refractory persistent AF (age 62.5±10.3 years, 84.4% male). Before the RFCA, we initially performed IDF with an output of 1 J. When the defibrillation failed to restore SR, the output was gradually increased up to 30 J. After RFCA, we attempted pacing-induced AF to provoke other focuses of AF. When AF was induced, we again performed IDF to terminate the AF with outputs of 1 to 30 J. The change in the IDF threshold to restore SR before and after RFCA was assessed. Results: The IDF threshold for restoring SR significantly decreased after RFCA (from 11.5±8.6 J to 4.0±3.8 J, $p < 0.001$). During the follow-up (24.3±12.2 months), SR was maintained in 107 patients (75.9%). A multivariate analysis using a Cox proportional hazards model revealed that an IDF threshold of $>$ 5 J after the RFCA was significantly associated with recurrence of AF (HR, 3.99; 95% CI 1.93-8.22; p=0.0001). Conclusion: RFCA decreased the IDF threshold for restoring SR in patients with persistent AF. IDF outputs of $>$ 5 J after RFCA could be a predictor of AF recurrence independent of the AF substrate.

Introduction

Radiofrequency catheter ablation (RFCA) has been shown to be more efficacious than drug therapy in restoring sinus rhythm (SR) in patients with atrial fibrillation (AF). Compared to the other ablation strategies, pulmonary vein isolation (PVI) is a more basic strategy.[1] Furthermore, a trigger ablation is one of the strategies for AF ablation, which is effective for eliminating AF.[2] Isoproterenol (ISP) is often used to induce AF triggers.[3] In addition, defibrillation of induced AF is performed to identify the site of the trigger of spontaneously occurring AF. In those procedures, intracardiac defibrillation (IDF) is often performed to restore SR during RFCA of AF.[4]

There have been many studies about cardioversion of AF, such as regarding the relationship between the defibrillation threshold and maintaining SR in patients without RFCA.[5-11] On the other hand, many other studies have pointed out the relationship between AF recurrence after RFCA and the substrate, such as the left atrium (LA) size and low voltage zones (LVZs). However, a few studies have shown the relationship between the IDF threshold and recurrence of AF after RFCA. Furthermore, there have been no studies to assess the relationship between the IDF and LA substrate. This study aimed to examine the change in the IDF threshold before and after RFCA for eliminating persistent AF during the procedure. Additionally, we

evaluated whether the IDF threshold after RFCA was associated with the recurrence of AF and the AF substrate after the ablation procedure in patients with persistent AF.

Methods

Study population and study design

This study enrolled 141 consecutive patients with drug-refractory persistent AF (age 62.5 ± 10.3 years, 84.4% male), who underwent RFCA between January 2013 and December 2015, in our institute. Persistent AF was defined as AF that was sustained beyond 7 days (including long-standing persistent AF) according to the guidelines.[12] The study patients were followed up for at least 1 year after the AF ablation.

If AF was terminated before the RFCA, we artificially induced AF by high rate burst pacing with a high dose ISP infusion (starting at 5 μg and increasing it up to 10 μg and 20 μg/minute), and we initially performed IDF to identify the earliest site of the trigger premature atrial contraction (PAC) with spontaneously occurring AF. Defibrillation was performed with an output of 1 J. If the defibrillation failed to restore SR with the low output, the output was gradually increased up to 30 J (1, 3, 5, 10, 15, 20, and 30 J). After the RFCA, we attempted pacing-induced AF again to provoke other focuses of AF. When AF was induced artificially, we performed IDF again to terminate the AF with outputs of 1 to 30 J after we waited for two minutes. A change of IDF threshold to restore SR before and after RFCA was assessed. Furthermore, we investigated the relationship between the IDF threshold and recurrence of AF after RFCA.

This clinical study was a retrospective analysis of prospectively collected AF ablation data. The study protocol was approved by the Institutional Review Board (IRB) of Toho University Medical Center Omori Hospital (approval number: M20068). This study was a retrospective observational study, carried out by the opt-out method on our hospital website.

Ablation procedure

Anti-arrhythmic drug (AAD) therapy was stopped at least five half-lives before the ablation. Patients on oral anticoagulation stopped their medications on the day of the ablation. Study patients underwent transesophageal echocardiography to ensure no thrombus in the atrium or left atrial appendage 24h before the ablation.

A 7Fr 20-pole 3-site mapping catheter (BeeAT, Japan Lifeline, Tokyo, Japan) was inserted into the coronary sinus (CS) via the right jugular vein. IDF could be performed with the a BeeAT catheter. Further, catheters were introduced percutaneously through the femoral vein, and a transseptal puncture was performed after verifying the absence of a patent foramen ovale to access the LA. After the transseptal access, a bolus of intravenous heparin (5,000 IU) was administered, with an additional bolus to maintain an activated clotting time of more than 350 s.[13] We used propofol and dexmedetomidine during ablation to obtain deep sedation. We used high dose ISP with a continuous administration to investigate the trigger of the AF before the RFCA. If AF was not present, we effectively induced AF artificially by high rate burst pacing during an ISP infusion. After the AF sustained for more than two minutes, IDF was performed to restore SR. After that, we identified the earliest site of the trigger PAC with spontaneously occurring AF. If reproducible, the trigger was identified as an AF foci. We performed a PVI in all patients. When we detected non-PV foci, we added a focal ablation to that site. After the RFCA, we used high dose ISP and high rate burst pacing to artificially induce AF. After the AF was artificially induced, we again performed IDF with 1 to 30 J to restore SR. The endpoint of our ablation was the absence of spontaneous AF occurring after the ISP infusion.

All the patients underwent an enlarged PVI in order to achieve voltage abatement of the electrograms in the encircled areas. Radiofrequency current was delivered with an irrigated-tip ablation catheter (FlexAbility^{TM}; Abbott, Minneapolis, MN or Thermocool, Biosense Webster, Inc., Diamond Bar, CA, USA) through another long sheath under the guidance of a 3-dimensional (3D) cardiac mapping system (EnSite Precision^{TM}, Abbott or CARTO3, Biosense Webster).

IDF

We used the BeeAT catheter and a dedicated defibrillator (Shock AT, Japan Lifeline, Tokyo, Japan). which together constituted the IDF system approved for use in Japan (*Figure 1*). The BeeAT catheter has 20 poles consisting of a distal set of 8 poles, middle set of 8 poles, and proximal set of 4 poles. The distal 8 poles are positioned in the distal CS and middle 8 poles along the lateral wall of the right atrium (RA). The proximal 4 poles are positioned in the superior vena cava (SVC) and record the SVC activity during the procedure. We selected the catheter sizes (S, M, and L) to fit the LA and RA size of the patients. Cardioversion was effective with a current delivery between those distal and middle sets of electrodes, but they were also able to record the local electrograms.

For cardioversion, a biphasic direct current was delivered between the distal set and the middle set of electrodes synchronized to the R wave of the body surface electrocardiogram. If cardioversion was not possible, we changed the lead of the body surface electrocardiogram to detect and synchronize to any R wave. We started the IDF output at 1 J and went up to 3, 5, 10, 15, 20, and 30 J. The maximum energy output was 30 J with this system. We performed IDF under deep sedation with propofol and dexmedetomidine. When the blood pressure was low, we used phenylephrine.

Long-term follow-up

All patients were followed up for at least 12 months. We saw all patients at every 0.5, 1, 2, 3, 4, and 6 months, and every 6 months thereafter. Anticoagulation drugs were also used for at least 3 months and were continued based on the patients' risk for thrombus embolisms determined using the $CHADS_2$ or CHA_2DS_2-VASc score.[12]Each doctor decided whether or not to use AADs. The 12-lead electrocardiogram (ECG) and clinical assessments were performed at each visit. Further, 24h-Holter monitoring was performed at 0.5, 1, 2, 3, and 6 months after the initial ablation and every 6 months thereafter. The study patients were asked to record all episodes of any symptoms suggestive of arrhythmias such as palpitations, dizziness, or shortness of breath and report that to us as soon as possible. In such cases, an immediate ECG and 24 h Holter monitoring at the nearest clinic during the symptomatic period were suggested. Recurrence was defined as atrial arrhythmia episodes including AF, atrial flutter, and other atrial tachycardias lasting more than 30s after the first 3-month blanking period.

Statistical analysis

All continuous data were expressed as means ± standard deviation, medians (quartile: 25-75%), or numbers (expressed as percentage, %). The comparison between groups was analyzed using univariate (unpaired Student's t -test and Fisher's exact test) and multivariate analyses with a Cox hazard model. A p -value of < 0.05 was considered statistically significant. Recurrence curves were plotted using the Kaplan-Meier method. All statistical analyses were performed with R commander, which is a graphical user interface for R (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Baseline characteristics and AF recurrence after RFCA

The mean age was 62.5 ± 10.3 years, 119 (84.4%) were male, and the body mass index (BMI) was 24.6 ± 3.3 kg/m^2. The mean $CHADS_2$ and CHA_2DS_2-VASc scores were 1.3 ± 1.1 and 2.1 ± 1.5, respectively. The mean left atrial diameter (LAD) was 43.2 ± 6.3 mm, and the left ventricular ejection fraction (LVEF) was 64.6 ± 10.5%. Those baseline characteristics are listed in *Table 1* .

The mean follow-up period after the procedure was 24.3 ± 12.2 months. One hundred seven patients (75.9%) were in SR and 34 (24.1%) developed an AF recurrence. As shown in *Table 1* , the AF recurrence group had a longer duration of AF, higher use rate of AADs after the RFCA, and higher IDF threshold after the RFCA as compared to that in the no-recurrence group ($p < 0.05$). However, there were no significant differences in the age, sex distribution, BMI, $CHADS_2$ score, Creatinine, brain natriuretic peptide (BNP), LAD, LVEF, non-PV foci, and IDF threshold before the RFCA between the two groups.

RFCA and IDF

AF was induced artificially in all patients after the RFCA to provocate AF triggers. The IDF threshold to restore SR was significantly decreased after the RFCA (from 11.5 ± 8.6 J to 4.0 ± 3.8 J, $p < 0.001$). There was no difference in the IDF threshold between the recurrence and no-recurrence groups before the RFCA (*Table 1*), however, the threshold in the no-recurrence group was significantly lower than that in the recurrence group after the RFCA as shown in*Figure 2* . A cut-off point analysis showed that as IDF threshold after the RFCA of > 5 J was the optimal point that discriminated those with AF recurrence from the rest of the participants as shown in *Figure 3* (sensitivity 68.0% and specificity 65.2%). We divided the patients into two groups according to IDF outputs of [?] 5 J or > 5 J. Of all the patients, the number of patients whose IDF output that restored SR was [?] 5 J was 117. *Table 2*shows that the IDF threshold before the RFCA, LAD, and BNP in the patients with an output of [?] 5 J were significantly lower than those in the patients with an output of > 5 J. On the other hand, there were no significant differences in the LVEF, duration of AF, and non-PV foci between the two groups. The presence of an LVZ in the LA significantly differed between the two groups (17 patients, 14.5% vs. 8 patients, 33.3%, $p = 0.039$).

The recurrence rate of AF was significantly higher in the patients with an output of > 5 J than in those with an output of [?] 5 J (22 patients, 18.8% vs. 12 patients, 50%, $p = 0.003$). Further, the Kaplan-Meier model showed that an IDF threshold after RFCA of > 5 J was associated with a recurrence of AF ($p< 0.001$) as shown in *Figure 4* .

A multivariate analysis using Cox proportional hazards models (models 1 and 2) after adjusting for the patient background, LAD, duration of AF, and use rate of AADs after the RFCA, revealed that an IDF threshold of > 5 J after the RFCA (HR, 3.99; 95% CI 1.93 - 8.22;$p = 0.0001$) was significantly associated with recurrence of AF (*Table 3*).

Discussion

Main Findings

The main findings were as follows. First, the IDF threshold to restore SR in patients with persistent AF was significantly decreased after the RFCA. Second, the IDF threshold in the no-recurrence group was significantly lower than that in the AF recurrence group, however, before the RFCA, there was no difference in the IDF threshold between the recurrence and no-recurrence groups. Third, the outputs of the IDF (threshold > 5 J) after RFCA were an independent predictor of a recurrence of AF.

IDF and AF

Some reports have assessed the efficacy and safety of transvenous internal atrial cardioversion performed in patients with persistent AF.[14, 15] The IDF is an effective procedure for restoring SR in patients with AF.[6] Further, there are few complications with IDF. Boriani G etc. reported myocardial injury following repeated internal atrial defibrillations.[16]Although, minor elevations in the troponin I level were detected, it suggested minor asymptomatic myocardial injury. There was no relationship between an elevated troponin I level and the number of shocks or amount of energy delivered. Therefore, the BeeAT catheter and dedicated defibrillator could be used multiple times for IDF, and because of that they are useful for checking triggers. The maximum energy output of this system was 30 J. Although the mean number of IDFs was 9.1 ± 7.5 times (max 28 times) per RFCA procedure, there were no complications associated with the IDF in our study. All patients were restored to sinus rhythm by the IDF with an output of less than 30 J.

The electrode position for the outcome of the IDF was very important. Thus, low-energy biphasic shocks positioned between the RA and CS were effective for cardioverting AF. The distal 8 poles of the BeeAT catheter were positioned in the distal CS and the middle 8 poles along the lateral wall of the RA. We selected the different catheter sizes (S, M, and L) to fit the LA and RA size of the patients. Therefore, an appropriate IDF could be performed in this study. Furthermore, the IDF was less affected by the LA size than by an external defibrillation catheter that fit the LA size.[6]

IDF and AF substrate

The factors for the persistence of AF are regarded as trigger factors and arrhythmogenic substrate factors, which play a role as an AF perpetuator.[17, 18] The triggers generally initiate AF and the substrate plays a critical role in AF persistence. Therefore, as the AF duration prolongs, LA remodeling proceeds, and the AF substrates increase. Thus, the success rate of AF cardioversion is inversely correlated to the LA size, because the fibrosis accompanying atrial dilatation increases the AF substrate.[19] There are many reports about predictors associated with recurrence of AF after electrical cardioversion, such as the LA size, age, and BNP.[20-22] However, there are few reports on cardioversion after AF ablation.

In the present study, RFCA significantly decreased the IDF threshold for restoring SR (Figure 1). The conditions for IDF were the same before and after the RFCA; we induced AF artificially with high rate burst pacing and ISP. After the AF sustained for more than two minutes, IDF was performed to detect any AF triggers. Although the main strategy for RFCA in our institute is an AF trigger ablation, an extensive encircling PVI or posterior wall isolation might decrease the AF substrate. That suggests that RFCA could eliminate or decrease both AF triggers and the substrate, and further, it could decrease the cardioversion threshold. Thus, the difference in the cardioversion threshold before and after RFCA may reflect the elimination of the AF substrate and triggers. There were some cases with LA enlargement but without a low voltage area in our study. In those cases, the IDF threshold could reflect the AF substrate, which could not be assessed by electrophysiology. Additionally, our study revealed that the lower output IDF ([?] 5 J) group after the RFCA was associated with a lower recurrence of AF. In fact, in patients with an output $>$ 5 J, the LAD was larger, and there was a greater presence of an LVZ in the LA. Thus, the LA remodeling proceeded in those patients. An IDF threshold of $>$ 5 J was a strong predictor of AF recurrence in a multivariate analysis after adjusting for the patient background, LAD, LVZ, duration of AF, and administration of AADs after the RFCA. Furthermore, the presence of an LVZ disappeared in the multivariate analysis model 1. Additionally, the ablation strategies (such as an SVC isolation, posterior wall isolation, and focal ablation) did not have any significant value for detecting AF recurrence or the IDF threshold (*Tables 1 and 2*). The IDF method was useful for assessing whether RFCA could decrease the AF substrate during the RFCA procedure.

AF recurrence and other factors

AADs after RFCA were a strong confounding factor for an AF recurrence. In our study, the LA size in the patients with an output of $>$ 5 J was larger than that in those with an output of [?] 5 J. However, the IDF threshold remained as an independent predictor of an AF recurrence. These findings suggested that a greater AF substrate remained in the patients with an output $>$ 5 J after the RFCA. On the other hand, there was no significant difference in the presence of non-PV foci between the patients with an output of [?] 5 J and those with an output $>$ 5 J. In addition, the LA size was not associated with AF recurrence, however, the LA size was larger in the patients with an output of $>$ 5 J. Those findings suggested that not only eliminating AF triggers but also approaching the LA substrate were important, because those patients with an output of $>$ 5 J had a higher rate of AF recurrence and greater AF substrate. Recent studies have demonstrated that the efficacy of substrate ablation is questionable.[23, 24] In our study, AADs after the RFCA could not prevent AF recurrence especially in patients with an output of $>$ 5 J. Therefore, further studies are need to study those patients with an output of $>$ 5 J.

Limitations

This study had some potential limitations. First, it was a retrospective and observational study at a single institute. We did not have many patients with persistent AF, which might have caused a statistical bias. Second, we did not perform a substrate ablation such as a line, complex fractionated atrial electrogram (CFAE), rotor, and LVZ ablation. However, recent studies have revealed that only the efficacy of the PVI has been proven.[25-28] In this study, there was no significant difference in the non-PV foci between the two groups. Third, we also considered the effects of the confounding predictors for AF recurrence. However, the IDF threshold was a useful predictor for AF recurrence because the IDF remained after a multivariate

analysis after adjusting for the patient factors.

Conclusion

RFCA decreased the IDF threshold for restoring SR in patients with persistent AF. Outputs of the IDF of > 5 J after RFCA could be a predictor of a recurrence of persistent AF independent of an AF substrate. IDF is useful for assessing whether RFCA could decrease the AF substrate during the procedure.

Conflict of Interest

This research received no grants from any funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that there is no conflict of interest.

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Tables and Figure Legends

Table 1: Patient characteristics of those with and without atrial fibrillation recurrence

Table 2: Patient characteristics between intracardiac defibrillation output groups of [?] 5 J and >5 J

Table 3: Clinical factors for atrial fibrillation recurrence determined by univariate and multivariate analyses

Figure 1 : (A) A 7Fr 20-pole 3-site mapping catheter (BeeAT, Japan Lifeline, Tokyo, Japan) and (B) dedicated defibrillator (Shock AT, Japan Lifeline, Tokyo, Japan)

Figure 2: The change in the intracardiac defibrillation threshold before and after RFCA

There was no difference in the IDF threshold between the no-recurrence group and recurrence group before the RFCA, however, the threshold in the no-recurrence group was significantly lower than that in the recurrence group after the RFCA. The red colored line and words show the recurrence group, and the black colored lines and words show the no recurrence group. RFCA = radiofrequency catheter ablation, IDF = Intracardiac defibrillation

Figure 3: The ROC curve for recurrence and intracardiac defibrillation threshold after RFCA

Cut-off point analysis show that an intracardiac defibrillation threshold after the RFCA of > 5J was the optimal point that discriminated those with AF recurrence from the rest of the participants (sensitivity 68.0% and specificity 65.2%).

Figure 4 : Kaplan-Meier curve for the recurrence of atrial fibrillation

Kaplan-Meier survival analysis for long-term sinus rhythm maintenance after RFCA.

Patients with an intracardiac defibrillation threshold after the RFCA of > 5J had a higher risk of recurrence than those with an intracardiac defibrillation threshold after the RFCA of [?] 5J.

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fig11.docx available at https://authorea.com/users/354749/articles/478215-role-of-intracardiac-defibrillation-during-the-procedure-as-a-predictor-of-atrial-fibrillation-recurrence-after-catheter-ablation

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