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EPS and Arrhythmia

The Electrical Characteristics and Clinical Significance of the Effect of Adenosine on Dissociated Activity after Circumferential Venous Isolation in Patients with Atrial Fibrillation

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Background: Dissociated activity can occur after circumferential thoracic vein isolation for treating atrial fibrillation (AF). However, its clinical significance and response to adenosine remain unclear.

Methods: Fifty-three patients (10 women, 11 with non-paroxysmal AF, with mean age 54.4 ± 11.2 years) with slow dissociated activity after thoracic vein isolation for AF ablation were analyzed. Adenosine (12 mg) was injected intravenously into 30 patients, and the responses of the dissociated activities were recorded.

Results: The clinical characteristics and the rate of recurrence did not differ between patients with and without dissociated activity. Dissociated activity was most frequently observed at the right superior pulmonary vein (PV) (61%), left superior PV (26%), right inferior PV (5%), left inferior PV (4%), and non-PV sites (4%). The locations of dissociated activities were associated with the AF trigger sites (p = 0.004). Adenosine injection decreased the cycle length of dissociated activity in 13 patients (group 1) and increased it in 17 patients (group 2). Dissociated activity disappeared in 7 patients (41%) (group 2) after adenosine injection. During the mean 33 ± 17 months of follow-up, group 2 patients had a lower AF recurrence rate (24%) than group 1 patients (62%) (p = 0.035).

Conclusions: The locations of dissociated activity were closely associated with the AF trigger sites. The responses to adenosine may predict AF recurrence in patients with dissociated activity.

Key Words: Ablation • Atrial fibrillation • Dissociated activity

INTRODUCTION

Catheter ablation is considered to be a customary treatment for atrial fibrillation (AF). Pulmonary vein (PV) isolation, with the endpoint of disconnecting the electrical activity between the venous site and the atrium, is the key to effective catheter ablation of AF.[1,2] The ectopic focus inside the superior vena cava (SVC) could also contribute to both the initiation and maintenance of AF.[3] The dissociation of spontaneous PV or non-PV electrical activity from the atrial electrical activity, called "dissociated activity," can occur after circumferential PV isolation (CPVI) or SVC isolation.[4] The incidence, characteristics, and clinical significance of dissociated activity

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vary with different patient populations. In a previous report, most of the studied patients demonstrated dissociated activity in at least one PV after PV isolation.[5] However, another report showed that dissociated PV electrical activities occurred in only about 12% of patients, without a significant difference in the clinical success rate.[6] A recent study demonstrated that isolated PV electrical activities might identify a subgroup of patients with a low recurrence rate of AF after CPVI.[7] The mechanism of dissociated activity either from PV or from a non-PV site, however, is still not clear. The purpose of this study was to investigate the clinical and electrophysiological characteristics of dissociated activity in patients with AF, as well as its response to adenosine.

METHODS

Patient population

Five hundred and seventy consecutive AF patients (age, 54 ± 11 years; paroxysmal/non-paroxysmal, 431/139 patients) with symptomatic and drug-refractory AF, who received catheter ablation between 2006 and 2010, were retrospectively included in this study. Of them, 53 (9.3%) patients showed slow dissociated activity after CPVI or SVC isolation for AF and were enrolled for further investigation.

Electroanatomic mapping and signal analysis

Each patient underwent electrophysiological examination and catheter ablation in the fasting, nonsedative state after they provided a written informed consent. The procedural details are referred to in Chang et al.[8] All antiarrhythmic drugs, except amiodarone, were discontinued for at least 5 half-lives before the electrophysiological examination and the ablation. A 7-French deflectable decapolar catheter with a 2-mm interelectrode distance and 5-mm space between each electrode pair (Atrial Fibrillation Division, St. Jude Medical Inc., Minnetonka, MN, USA) was inserted into the coronary sinus (CS) through the right internal jugular vein. A 3D geometry of the atrium was constructed, and mapping was performed with a 4-mm closed-loop irrigated-tip catheter (Chilli II; Boston Scientific, Natick, MA, USA) or a 4-mm open-loop irrigated-tip catheter (Therapy Cool Path Duo, St Jude Medical). The steerable catheter was inserted into the left atrium (LA) alongside the transseptal sheath within the same puncture site and then dragged around the endocardial surface of the LA by using the NavX contact mapping system. The bipolar electrograms were filtered between 32 and 300 Hz and recorded digitally. The PV ostia were identified by fluoroscopy and marked on the 3D map of the LA. The presence of dissociated activity is defined as the continuous appearance of venous focal electrical potentials dissociated from the atrial rhythm. The trigger of AF is defined as an ectopic beat which is from any thoracic vein, and can induce a burst of rapid, repetitive atrial beats or initiation of AF.[13]

Catheter ablation of AF

In patients with paroxysmal AF, CPVI was performed with continuous radiofrequency (RF) energy while repositioning the catheter tip every 40 seconds at 25 Watts, 40 °C for the Chilli catheter and 25 Watts, and 45 °C for the Coolpath catheter. After circumferential ablation was completed, the ipsilateral superior and inferior PV potentials were carefully recorded using a circular catheter (Spiral SC, Atrial Fibrillation Division, St. Jude Medical, Inc.) during sinus rhythm or CS pacing. Supplementary ablations were applied along the circumferential lines close to the earliest ipsilateral PV spikes. For patients with non-paroxysmal AF, a stepwise AF catheter ablation procedure was performed as referred to in Chang et al.[8]

Step 1 (isolation of PVs): Continuous circumferential lesions were created encircling the right and left PV ostia as mentioned above.

Step 2 [continuous complex fractionated atrial electrograms (CFAE) site ablation]: If AF did not stop after step 1, an additional CFAE ablation was performed sequentially according to the results of the CFAE maps after the circumferential PV isolation. The CFAE ablation was confined to the continuous CFAEs (primarily those with a fractionation interval of < 50 ms) in the LA, right atrium, SVC, or CS. The endpoint of the continuous CFAE ablation was prolonging the cycle length (CL), eliminating the CFAEs (FI > 120 ms), or abolishing the local fractionated potentials (bipolar voltage < 0.05 mV).

Step 3 (non-PV ectopy ablation): If the AF still did not stop after steps 1 and 2, sinus rhythm was restored

by electric cardioversion. If non-PV ectopies initiating AF were identified after cardioversion, isolation of the arrhythmogenic SVC or CS ostium was guided by the circular catheter recordings from the SVC-atrial junction and CS-atrial junction, respectively. In patients with other non-PV AF ectopic beats, catheter ablation was performed in the area with the earliest electrical activity. The total activation time was defined as the time interval from the earliest to the latest activation point in the atrium. Voltage of the left atrium and right atrium are measured at sinus rhythm by NavX contact mapping system. The bipolar mapping points were collected and analyzed by use of the offline software.

Adenosine test

In 30 patients with dissociated activity, we administered the intravenous bolus of adenosine 12 mg and measured the CL of the dissociated activities before and after adenosine infusion for 8 consecutive beats. The mean CL of the 8 beats is defined as the CL of the dissociated activity. If reconnection was noted or the dissociated activity was suppressed after adenosine, then the mean CL was calculated by the previous recorded number. Patients in whom adenosine triggered AF or shortened the CL of the dissociated activity were classified as group 1, and those in whom adenosine suppressed the dissociated activity and prolonged the CL were classified as group 2. In group 1, PV isolation was performed repeatedly to ensure that no AF occurred after the procedure. The CL was not calculated for patients whose dissociated activity either lead to AF or disappeared. All patients were confirmed with isolation between thoracic veins and atria at the end of the procedure.

Post-ablation follow-up

Patients underwent a follow-up (2 weeks after the catheter ablation, then every 1-3 months thereafter) at our cardiology clinic or with the referring physicians. Antiarrhythmic drugs were prescribed for 8 weeks to prevent any recurrence of AF (within a blank period, defined as < 3 months after the ablation). When the patients experienced symptoms suggestive of a tachycardia after the ablation, a 24-h Holter monitoring or a cardiac event recording was performed to define the cause of the clinical symptoms. Regular 24-h Holter monitoring or cardiac event recording was performed every 3 months. If more than one episode of recurrent symptomatic AF was documented after the blank period, the patients were encouraged to receive a second ablation procedure, or antiarrhythmic drugs were prescribed to control the recurrent AF. AF recurrence is defined as an episode lasting more than1 minute and confirmed by an electrocardiogram 3 months after the ablation.

Statistical analysis

Parametric data were reported as the mean ± SD and analyzed with an unpaired *t*-test, except that the differences before and after adenosine administration were analyzed by a paired *t*-test. The chi-square test with Yates' correction was used for categorical data. The cumulative risk of AF recurrence within each group was estimated using the Kaplan-Meier method. A value of $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed using SPSS software, version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical and electrophysiological characteristics of dissociated activity

Table 1 shows a comparison of the clinical variables between patients with and those without dissociated activity. There is no significant difference between these 2 patient groups in baseline clinical and electrophysiological characteristics, including the rate of recurrence. Dissociated activity was most frequently observed at the right superior PV (RSPV) (n = 35, 61%), followed by left superior PV (LSPV) (n = 15, 26%), right inferior PV (RIPV) (n = 3, 5%), left inferior PV (LIPV) (n = 2, 4%), and non-PV sites (n = 2, 4%) (Figure 1). Seven of the fifty-three patients (13%) had dissociated activities in more than one location. Five of them had dissociated activities over RSPV and LSPV, one had dissociated activities over LSPV and LIPV, and the other had dissociated activities over all 4 PVs. If the trigger site located in PV with dissociated activities, we defined the trigger of AF and the dissociated activities as related. The location of dissociated activity was significantly related to the trigger sites of AF ($p = 0.04$) (Figure 2). A discordant location of the dissociated activity and the triggering vein was found in 9 patients. Of them, 4 patients showed dissociated ac-

tivity from the RSPV but the trigger site was from the LSPV; in 2 patients with dissociated activity from the RSPV and 2 patients from the LSPV, the trigger site could not be definitively identified. In 1 patient with dissociated activity from the ligament of Marshall (LOM), the trigger site was from the RSPV.

Table 1. Clinical and electrophysiological characteristics of patients with or without dissociated activity

	Without dissociated activity n = 517	With dissociated activity n = 53	p value
Age, years	53.8 ± 11.2	54.4 ± 11.2	0.704
Men, n (%)	381 (73.6)	44 (82.2)	0.186
PAF, n (%)	390 (75.4)	41 (77.8)	0.823
LA, mm	39.6 ± 6.2	38.6 ± 7.2	0.321
LVEF (%)	58.8 ± 8.0	57.6 ± 8.9	0.337
CAD, n (%)	125 (24.1)	15 (28.6)	0.774
Hypertension, n (%)	239 (46.2)	19 (35.5)	0.169
Diabetes, n (%)	59 (11.5)	9 (17.8)	0.211
Hyperlipidemia, n (%)	135 (26.2)	12 (22.2)	0.562
Recurrence, n (%)	239 (46.2)	19 (35.8)	0.950
TAT of LA, ms	125.6 ± 98.5	116.9 ± 47.3	0.572
Voltage of LA, mV	1.9 ± 0.8	1.8 ± 0.8	0.772
TAT of RA, ms	125.1 ± 84.2	110.1 ± 30.1	0.590
Voltage of RA, mV	1.9 ± 0.7	1.9 ± 0.6	0.919

CAD, coronary artery disease; LA, left atrium; LVEF, left ventricle ejection fraction; PAF, paroxysmal atrial fibrillation; RA, right atrium; TAT, total activation time.

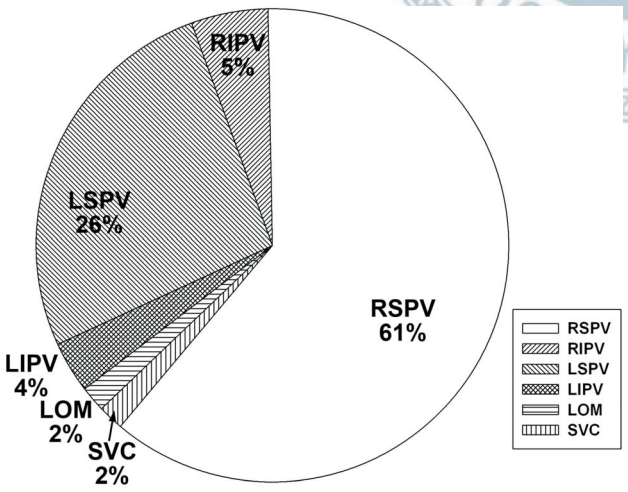

Figure 1. *Distribution of dissociated activities after thoracic vein isolation. LIPV, left inferior PV; LOM, ligament of Marshall; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior pulmonary vein (PV); SVC, superior vena cava.*

Response to adenosine

Among patients with dissociated activity, the clinical characteristics of those in groups 1 and 2 are shown in Table 2. There was no significant difference between the 2 patient groups, except that group 1 patients had a higher rate of recurrence than group 2 patients (62% vs. 24%, p = 0.035) at the mean follow-up of 31 ± 17 months. The survival curve shows that group 2 patients had a better outcome than group 1 patients (Figure 3).

In patients with dissociated activity, patients with adenosine injection had a recurrence rate of 40% (12 in 30 patients), and those without adenosine injection had a recurrence rate of 30% (7 in 23 patients). There was no significant difference in the recurrence between patients with and

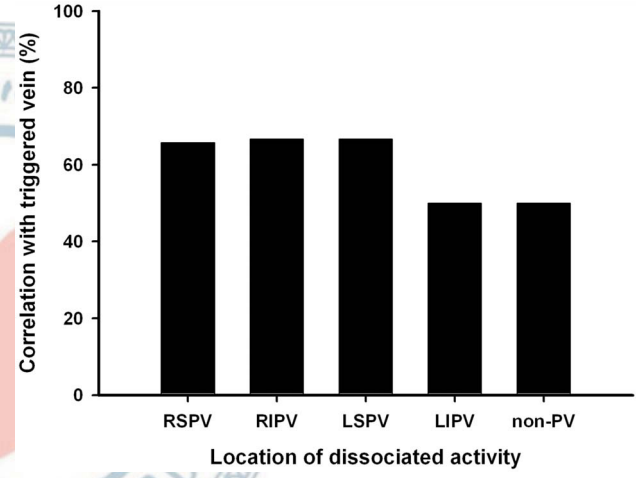

Figure 2. *Correlation of dissociated activity and the trigger foci of atrial fibrillation (AF). Abbreviations are as in Figure 1.*

Table 2. Clinical characteristics of patients with dissociated activity

	Group 1 (n = 13)	Group 2 (n = 17)	p value
Age, years	52.5 ± 9.0	53.9 ± 10.7	0.685
Male, n (%)	3 (23)	4 (24)	0.977
PAF, n (%)	9 (69)	16 (94)	0.070
LA, mm	38.3 ± 8.9	37.0 ± 6.5	0.701
LVEF, %	54.1 ± 6.4	61.8 ± 7.6	0.014
CAD, n (%)	3 (25)	3 (19)	0.690
Hypertension, n (%)	2 (17)	6 (38)	0.227
Diabetes, n (%)	1 (8)	2 (13)	0.724
Hyperlipidemia, n (%)	5 (38)	3 (17)	0.227
Recurrence, n (%)	8 (62)	4 (24)	0.035

RF, radiofrequency; other abbreviations are as in Table 1.

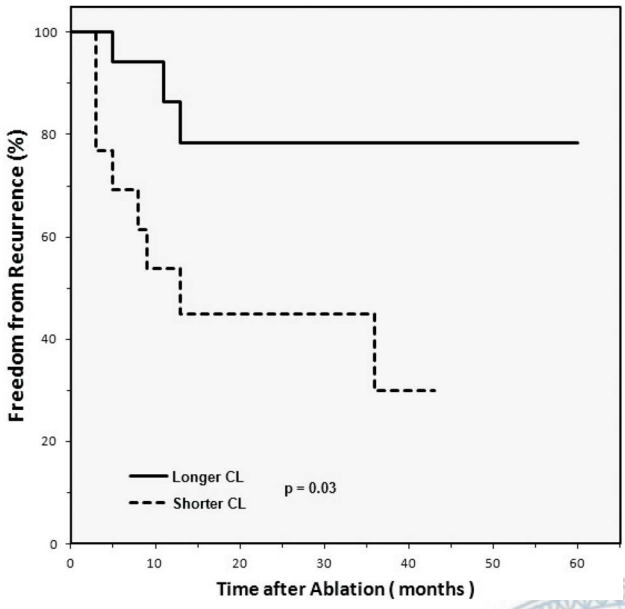

Figure 3. *Rate of freedom from AF in groups 1 and 2 patients. Abbreviations are as in Figure 1.*

without adenosine injection (40% vs. 30%, p = 0.47).

As for the subgroup of the paroxysmal AF patients in group 1 and 2, there was also no significant difference in clinical characteristics, except the recurrence rate. If patients had recurrence, then anti-arrhythmic drugs (AAD) were prescribed (Table 3).

After the injection of 12 mg adenosine, the CL of the dissociated activity of group 1 (13 patients) shortened from 2053 ± 1201 to 1841 ± 1167 ms (p = 0.04). Figure 4 showed an example of the mean value for one of the patients in each group. Figure 5 showed the change of the mean CL of group 1 and group 2 patients. AF triggered by the pulmonary electrical activity after adenosine infusion was found in 1 patient. In this patient, the trigger originated from the LIPV, which was also the location of the dissociated activity. Although further ablation was performed and all residual PV potentials were eliminated with confirmation of bidirectional block, 8 patients from group 1 developed recurrence during follow-up. Three of the 8 patients received ablation for the second time. In one of these 3 patients, the trigger was found to be from the RSPV, which was not the previous site of dissociated activity (LPV); another patient received further ablation and the trigger was shown to be from the RSPV, which was the same site of both the previous trigger and dissociated activity. In the third patient, the trigger was noted to be from the RSPV and LPV, although the previous procedure showed dissociated activity from LPV. There seemed no rules of the first and second ablation. In group 2, dissociated activity disappeared after adenosine infusion in 8 of 17 patients (47%). In the remaining 9 patients, CL was prolonged from 1998 ± 605 to 2814 ± 1110 ms (p = 0.02). Only 4 of the 17 patients (24%) developed recurrence during follow-up. One of the 4 patients had recurrent PV potential in the LIPV after adenosine injection, which was different from the origin of the dissociated activity (RIPV). Two of the 4 patients received a second procedure. One patient with recurrence had an atrial tachycardia from the previous location of the dissociated activity and the trigger site. Another patient had a recurrence of AF from the RSPV, which was also the site of the dissociated activity in the first procedure.

Acute electrical reconnection of the PV after adenosine injection was found in 8 (62%) and 2 (12%) patients in group 1 and 2 respectively. CFAE mapping was performed on 6 patients (3 in each group). In group 1, 2 of the 3 patients were noted with the same area for CFAE and dissociated activities. In group 2, only 1 patient was with the same place.

DISCUSSION

Incidence and distribution

Willems et al.[4] reported that slow dissociated activi-

Table 3. Clinical characteristics of patients with dissociated activity of paroxysmal atrial fibrillation in group 1 and group 2

	PAF of group 1 (n = 9)	PAF of group 2 (n = 16)	p value
Age, years	51.6 ± 9.0	52.7 ± 10.7	0.789
Male, n (%)	7 (78)	12 (75)	0.876
LA, mm	36.6 ± 5.7	36.0 ± 6.0	0.823
LVEF, %	56.9 ± 5.0	61.0 ± 7.4	0.153
CAD, n (%)	1 (11)	4 (25)	0.405
Hypertension, n (%)	2 (22)	6 (38)	0.432
Diabetes, n (%)	2 (22)	2 (13)	0.524
Hyperlipidemia, n (%)	1 (11)	6 (38)	0.158
Recurrence, n (%) (Use AAD)	6 (67)	4 (25)	0.041

AAD, antiarrhythmic drug; PAF, paroxysmal atrial fibrillation; RF, radiofrequency; other abbreviations are as in Table 1.

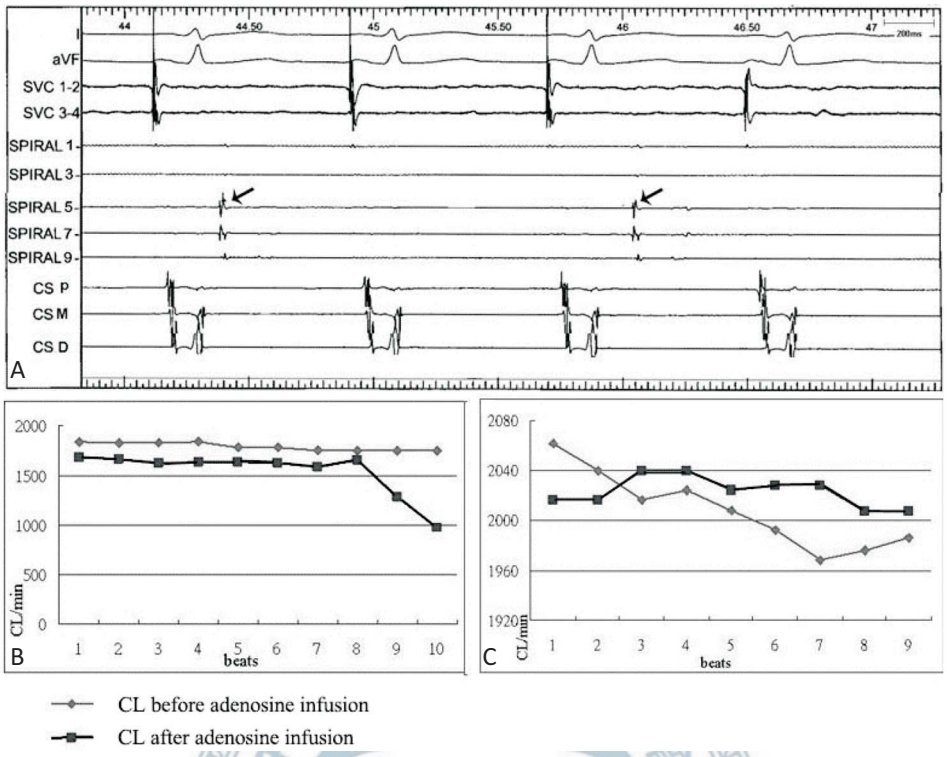

Figure 4. *Tracing of dissociated activities. (A) Dissociated PV activities recorded from the spiral catheter. The solid arrows indicate the dissociated activity recorded by the spiral catheter in the right superior pulmonary vein. (B) Group 1: the cycle length (CL) of the dissociated activity became shorter after adenosine injection (from 1786 ± 41 to 1534 ± 228 ms). (C) Group 2: the CL of the dissociated activity became longer after adenosine injection (from 2008 ± 31 to 2023 ± 12 ms). Narrow line indicates the CL before adenosine infusion; bold line indicates the CL after adenosine infusion. CSD, coronary sinus distal; CSM, coronary sinus middle; CSP, coronary sinus proximal; SVC, superior vena cava. Other abbreviations are as in Figure 1.*

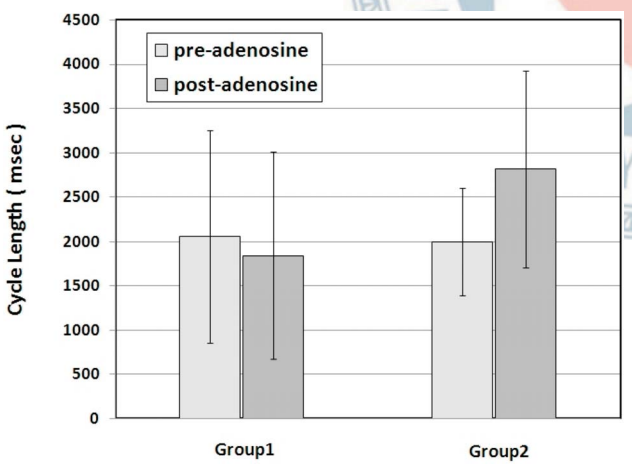

Figure 5. *The change of the mean CL of group 1 and group 2 patients before and after adenosine infusion.*

ties are detectable within 9% of disconnected PVs, which was similar to our result. Other studies reported incidences of around 23% to 97.2%.[5-7,9] Ouyang et al.[5] reported that regular or irregular automatic activity dissociated from the atrial activity was observed in 97.2% and 20% of patients without and with previous segmental ostial ablation, respectively. These discordant findings could be explained by the differences in the definition of dissociated activities, the study population, and the ablation approach. We didn't calculate the number of patients with short time, irregular dissociated activity. In terms of the location of dissociated activity, the most common site is the RSPV, followed by the LSPV, RIPV, and LIPV. The finding that the right PV is the most common location is compatible with the reports from other investigators,[5-7] except for Lee et al.[10] who reported that the LSPV is a more common site than the RSPV. The exact mechanism of the dissociated activity occurred more frequently in the RSPV is uncertain. Ouyang reported that the high incidence of automatic activity within the PVs might be due to more myocardium with a potential for automatic activity within the isolated area.[5] RSPV is closer to the embryogenic cells from the sinus node, which may be associated with the high incidence of dis-

sociated activity. Furthermore, in 2 patients in our study, the dissociated activity was from a non-PV area: one was from the SVC and the other was from the LOM. Weerasooriya et al.[6] reported a dissociated potential recorded in the SVC after ablation. Hwang et al.[11] reported that the Marshall bundle may serve as the origin of focal AF in some patients. A dissociated potential could occur in the arrhythmogenic thoracic vein.

Trigger sites of AF and dissociated activity

AF is frequently triggered from atrial muscular sleeves that extend into the PVs.[12,13] The observations of independent activities in the PVs have raised the possibility that PVs contain pacemaker cells.[14] The PVs contain cardiomyocytes with arrhythmogenic activity due to enhanced automaticity, induction of triggered activity, and genesis of microreentrant circuits.[15] Cheung et al.[16] recently reported that adenosine can suppress the dissociated PV rhythm, but it could also induce new PV ectopies after PV isolation. This finding suggests that the mechanisms of dissociated PV rhythm and of PV triggers that lead to AF may be distinct. In our present study, the location of dissociated activity was closely related to the site of the triggering veins. Adenosine injection caused 2 different responses of the dissociated activity, enhancement and suppression, suggesting both triggered activity and abnormal automaticity could be the possible mechanism of the dissociated activity after PVI. However, Kholová et al.[17] reported that atrial myocardial extensions into the superior and inferior vena cava are present in most humans. Miyazaki et al.[18] demonstrated that the presence of cardiomyocytes with pacemaker activity in SVC and the delayed after depolarization in SVC cardiomyocytes suggest that automaticity or triggered activity may play a role in SVC arrhythmogenesis.[18] In our study, the patient with dissociated activity from the SVC also had the SVC as the trigger site, suggesting the presence of an arrhythmogenic substrate in the SVC. Further studies should be done to investigate the possible mechanism of dissociated activities from non-PV sites.

Recurrence of AF after ablation and change in the CL after adenosine injection

It is well-known that the isolation of PVs and elimination of non-PV triggers can cure AF.[2,12,13] Chen et al.[7] showed that the presence of dissociated activity might identify patients with a lower recurrence rate of AF. In their study, AF recurrence was observed in 18% and 32% of patients with and without dissociated PV, respectively. However, most of the other studies reported that the presence of dissociated PV activity did not predict the outcome of PVI.[6,10,18] An animal study[22] has shown that adenosine could induce hyperpolarization to restore excitability by removing voltage-dependent I_{Na} inactivation, which may explain the reconnection of PVs following ablation. Acute reconnections could still occur on the appearance of dissociated PV activity without the adenosine test, which may explain the similar incidence of recurrence between patients with and without dissociated activity. Furthermore, de Greef et al.[20] reported that the reconnection of the triggering PV is the major cause of recurrence. In the present study, the higher incidence of reconnection of the venous site and the atrium in group 1 may imply the higher recurrence rate after catheter ablation of AF. In our previous study, we reported the different effects of adenosine on atrial tachycardia (AT).[21] Adenosine was not effective in terminating automatic AT but may terminate triggered AT. As for reentrant AT, adenosine had a dose-dependent termination effect. Adenosine can induce AF by the shortening the duration of atrial action potentials. Datino et al.[22] studied the mechanism of adenosine-induced acute reconnection of PVs after RF application, revealing "dormant conduction" and identifying PVs with the risk of reconnection. Adenosine abbreviated the duration of the action potential similarly in the PV and LA but significantly hyperpolarized the resting potential only in the PV. It also induced larger inward rectifier K^+ current in the LA and caused more negative resting potential values in dormant PVs, which were sufficient to restore excitability. In our study, for the patients of group 1, the shorter CL of the dissociated activity after adenosine injection may be consistent with the mechanism of hyperpolarized resting potential. The mechanism of the dissociated activity of group 2 patients is probably from the focal firing in the venous site. This study implies the possibility of a relation between the different mechanisms of dissociated activity and the reconnection of the PV and LA. Therefore, complete PV isolation with a repeat adenosine test in PVs with a shorter CL of dissociated activity might be needed to prevent the recurrence of AF.

CONCLUSIONS

The location of dissociated activity is related to the trigger site of AF. The response to adenosine after ablation may predict the recurrence of AF in patients with dissociated activity.

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