Value of adenosine test to reveal dormant conduction or adenosine-induced atrial fibrillation after pulmonary vein isolation

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Abstract

Background: Recent studies investigating the implications of additional ablation guided by dormant pulmonary vein (PV) conduction testing using adenosine showed conflicting results, and the data about atrial fibrillation (AF) recurrence after trigger site elimination in adenosine-induced AF are still lacking.

Methods: Of 846 patients with paroxysmal AF (PAF) who underwent PV isolation (PVI), adenosine test after PVI was performed in 148 patients.

Results: PVI was successfully achieved in 846 patients. We excluded 58 patients due to loss to the follow-up. A higher rate of AF recurrence was found in the group without adenosine test (136/644, 21%) compared to the group with adenosine test (20/144, 13%, log-rank P = 0.047). In multivariate analysis model for AF freedom during the follow-up period, the only significant clinical predictor of AF freedom was adenosine test (hazard ratio [HR] 1.97; 95% confidence interval [CI]: 1.2–3.23; P = 0.007).

Among 148 patients with adenosine test, 114 (77%) patients showed neither dormant conductions nor AF-induced, 22 (15%) showed positive dormant conductions only, and 12 (8%) revealed adenosine-induced AF (6 of them also showed dormant conduction). After additional ablation in positive dormant conduction group and adenosine-induced AF group, AF recurrence was noted in 4/21 (19%) patients in positive dormant conduction group and 2/11 (18%) patients in adenosine-induced AF group, which was not different from that of patients in negative dormant conduction/ no AF-induced group (14/112, 12%, log-rank P = 0.67).

Conclusions: Adenosine test after PVI to confirm the absence of dormant conduction and triggers initiating AF is beneficial to improve the outcomes after catheter ablation of PAF.

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1. Introduction

Pulmonary vein (PV) isolation (PVI) is the mainstay strategy for atrial fibrillation (AF) ablation. However, recurrence rates of AF following PVI remain an important issue. One of the reasons for AF recurrence is PV reconnection, leading to arrhythmias recurrence [1–3]. Therefore, a significant number of patients may require repeated procedures [2].

Adenosine might identify reconnection of PV by unmasking dormant conduction; in addition, it has a potential to induce AF [4–8]. Recent studies investigating the implications of additional ablation guided by dormant PV conduction showed conflicting results. Some observational studies have suggested that elimination of dormant PV conduction may be associated with better outcomes in patients with paroxysmal AF (PAF) [6,9–11]. However, other studies did not show benefits of this technique during long-term follow-up [12–15]. It still remains to be determined whether dormant conduction-guided further ablation of PV leads to improved rates of durable PV and long-term outcomes following catheter ablation of AF.

Moreover, there is still lack of data about AF recurrence after elimination of adenosine-induced AF triggers. Adenosine-induced AF may have different mechanism compared to adenosine-induced dormant conduction.

In this study, we assessed whether adenosine test performed to reveal dormant conduction or triggers is of value in achieving better outcomes after catheter ablation in patients with PAF.
2. Material and methods

2.1. Study population

A total of 846 patients who underwent PAF ablation at Korea University Medical Center were retrospectively enrolled in this study between January 1, 2008 and October 31, 2014. Patients were included if they were > 18 years of age and were undergoing their first ablation procedure for PAF. Of them, 148 patients received adenosine test with 12–18 mg IV after PVI. We tested dormant conductions and/or trigger site of adenosine-induced AF, performed additional ablation to eliminate dormant conductions and trigger site of adenosine-induced AF, and assessed the recurrence rate of AF after 3 months of blanking period. Patients with a follow-up period less than 6 months were excluded.

2.2. Electrophysiology study and ablation procedures

The electrophysiology study was performed under intravenous sedation. Bipolar recordings were filtered at 30–500 Hz. Electroanatomic mapping was performed using either Ensite NavX (St. Jude Medical, ST Paul, MN, USA) or CARTO (Biosense Webster Inc., Diamond Bar, CA, USA) mapping systems.

Radiofrequency ablation was performed using an open irrigated-tip catheter guided by a circular mapping catheter. Ablation lesions were delivered at power settings between 25 W and 30 W for 20–40 s using a power-controlled mode. Circumferential-antral ablation was performed around the left and right PVs. Power settings were generally kept at 25 W when ablating in the posterior left atrium (LA) near the esophagus and lesion duration was limited to 20 s. After completion of the circumferential-antral ablation lesion set, a circular mapping catheter was placed sequentially into each of the ipsilateral PVs to assess for electrical isolation. Ablation of the carinal region was performed at the physician’s discretion as needed to achieve complete PVI. The endpoint of ablation was complete PVI as defined by entrance and exit block.

2.3. Adenosine injection test protocol

Adenosine was infused following electrical isolation of each PV. Adenosine test was started from 12 mg. The end-point of protocol was inducible atrioventricular block, sinus arrest, or sinus bradycardia. If a 12-mg dose failed to induce atrioventricular block, sinus arrest, or sinus bradycardia, the operator repeated the adenosine injection in the same pulmonary vein with increased adenosine doses titrated up to 18 mg. In our study, none of patients failed to show atrioventricular block or sinus arrest or sinus bradycardia with 18 mg of adenosine. Isoproterenol was not used during adenosine test.

The local site of the earliest dormant conduction was evaluated with a circular mapping catheter placed in the PVs, while the trigger site of AF was evaluated with multi-electrode catheters positioned in the LA, right atrium, coronary sinus, and superior vena cava. We performed additional ablation in cases of dormant conduction or trigger site of adenosine-induced AF. Repeated testing with adenosine was performed and if dormant conduction or AF induction was still present, repeated ablation and adenosine testing were performed until dormant conduction or adenosine-induced AF was no longer present. At the end of procedure, all PV’s were re-interrogated, and isoproterenol infusion at a rate of 10–20 µL/min was used to detect any residual non-PV trigger. Additional ablation was performed if any trigger was found during isoproterenol infusion.

2.4. Follow-up schedule

All patients’ ECG and Holter data during follow-up at 3 months, 6 months, and 12 months or whenever patients visited were collected. Additional long-term (> 1 month) event recording was performed if symptoms were reported. Recurrence of AF was defined as documented any atrial tachycardia (AT) or AF lasting > 30 s on Holter or one-month event recorder ECG and recorded after a three-month blanking period. Anticoagulants and antiarrhythmic...
3. Results

PVI was successfully achieved in all 846 patients (698 patients without adenosine test and 148 patients with adenosine test). We excluded 58 of 846 patients due to loss to the follow-up (54 patients in the group without adenosine test, two patients in negative dormant conduction/no AF-induced group, one patient in positive dormant conduction group, one patient in adenosine-induced AF group) (Fig. 1).

3.1. Comparison between the group with adenosine test and the group without adenosine test

After exclusion of patients due to loss to follow-up, 644 patients were finally in the group without adenosine test and 144 patients in the group with adenosine test. Baseline clinical characteristics of each group are shown in Table 1.

No significant differences with respect to age, sex, body mass index (BMI), AF duration, left ventricular ejection fraction (LVEF), diabetes, history of myocardial infarction (MI)/percutaneous coronary intervention (PCI)/structural heart disease (SHD) (including left ventricular hypertrophy, hypertrophic cardiomyopathy, atrial septal defect/patent foramen ovale, valve insufficiency more than mild degree) were detected between the groups. The LA size and prevalence of hypertension were significantly higher in the group without adenosine test (P < 0.05). Non-PV foci were only observed in the group without adenosine test (10 patients). The non-PV foci sites were septum (three patients) and superior cava vein (seven patients). We succeed to eliminate non-PV foci in all patients. Only one of them had AF recurrence during the follow-up period.

Over a mean follow-up period of 10.85 ± 2.5 months AF recurrence was noted in 136 of 644 patients (21%) from the group without adenosine test. Over a mean follow-up period of 11.31 ± 2.5 months AF recurrence was noted in 20 of 144 patients (13%) from the group with adenosine test. The mean follow-up period in the group without adenosine test was significantly shorter than that in the group with adenosine test ($P=0.03$). In spite of a shorter follow-up period, a significantly higher rate of AF recurrence was detected in the group without adenosine test compared to the group with adenosine test (21% vs. 13%, $P=0.047$; Fig. 2).

The LA size was greater and the prevalence of hypertension was significantly higher in the group without adenosine test.

### Table 1
Baseline characteristics of groups with and without adenosine test.

|                      | Without adenosine test (n=644) | With adenosine test (n=144) | P value |
|----------------------|--------------------------------|----------------------------|---------|
| Age (years)          | 56.08 ± 10.9                   | 55.76 ± 10.9               | 0.751   |
| Male sex (%)         | 480 (74)                       | 118 (81)                   | 0.0067  |
| BMI                  | 24.63 ± 3.1                    | 24.54 ± 3.4                | 0.773   |
| AF duration (months) | 53.64 ± 74.8                   | 51.64 ± 55.3               | 0.767   |
| LA size (mm)         | 39.44 ± 5.5                    | 38.38 ± 5.8                | 0.042   |
| LVEF (%)             | 56.33 ± 4.3                    | 56.39 ± 3.8                | 0.877   |
| Hypertension (%)     | 265 (41)                       | 40 (27)                    | 0.003   |
| Diabetes mellitus (%)| 48.7 (7)                       | 8 (5)                      | 0.479   |
| Previous PCI / MI (%)| 21.3 (3)                      | 3 (2)                      | 0.598   |
| SHD (%)              | 82 (12)                        | 18 (12)                    | 1.000   |

BMI=body mass index, AF=atrial fibrillation, LA=left atrium, LVEF=left ventricular ejection fraction, PCI=percutaneous coronary intervention, MI=myocardial infarction, SHD=structural heart disease

### Table 2
Predictors of AF freedom during follow-up following pulmonary vein isolation.

|                      | Hazard ratio | 95% CI | P value |
|----------------------|--------------|--------|---------|
| Age                  | 0.98         | 0.96–1 | 0.197   |
| Male sex             | 1.21         | 0.76–1.93 | 0.418   |
| BMI                  | 0.94         | 0.89–1 | 0.082   |
| AF duration          | 1.00         | 0.99–1 | 0.352   |
| LA size              | 1.03         | 1–1.07 | 0.051   |
| LVEF                 | 0.97         | 0.93–1.01 | 0.203   |
| Hypertension         | 1.11         | 0.74–1.67 | 0.608   |
| Diabetes             | 1.29         | 0.67–2.46 | 0.440   |
| Previous PCI/MI      | 0.32         | 0.04–2.33 | 0.262   |
| SHD                  | 1.28         | 0.8–2.04 | 0.294   |
| Adenosine test       | 1.97         | 1.2–3.23 | 0.007   |

AF=atrial fibrillation, CI=confidence interval, BMI=body mass index, LA=left atrium, LVEF=left ventricular ejection fraction, PCI=percutaneous coronary intervention, MI=myocardial infarction, SHD=structural heart disease

2.5. Statistical analysis

Continuous variables were expressed as means ± standard deviations. For comparison of two groups of normally distributed continuous variables, Student’s t test was performed. For comparison of > 2 groups of normally distributed continuous variables, one-way analysis of variance was performed. If significant differences were found, a post-hoc analysis using the Scheffe’s test was performed. For pairwise comparisons of categorical variables, the Chi-square test was used.

Survival plots were generated using Kaplan-Meier survival analysis. Comparisons between survival curves were performed using the log-rank test. Predictors of AF recurrence were analyzed with multivariate Cox regression model. All statistical tests were two-sided and P values < 0.05 were considered statistically significant. All statistical calculations were performed using SPSS version 17.0 (IBM Corp., Armonk, NY, USA).
Table 3
Baseline characteristics of patients who received adenosine test.

|                      | Negative dormant/No AF-induced (n=112) | Positive dormant conduction (n=21) | Adenosine-induced AF (n=11) | P value |
|----------------------|----------------------------------------|----------------------------------|---------------------------|---------|
| Age (years)          | 55.6±11.2                              | 57.7±9.2                         | 53.1±10.4                 | 0.66    |
| Male sex (%)         | 96 (85)                                | 14 (66)                          | 8 (72)                    | 0.08    |
| BMI                  | 24.4±3.4                               | 25±3.8                           | 24.7±2.8                  | 0.26    |
| AF duration (months) | 53.1±60.4                              | 46.8±29.2                        | 45.8±38.1                 | 0.18    |
| LA size (mm)         | 38.5±5.6                               | 38.9±4.6                         | 36.1±9.3                  | 0.92    |
| LVEF (%)             | 56.4±3.7                               | 56.5±3.2                         | 55.5±6.1                  | 0.27    |
| Hypertension (%)     | 29 (25.9)                              | 8 (38.1)                         | 3 (27.3)                  | 0.51    |
| Diabetes (%)         | 7 (6.3)                                | 1 (4.8)                          | –                         | 0.67    |
| Previous PCI / MI (%)| 7 (6.3)                                | 2 (9.5)                          | –                         | 0.03    |
| SHD (%)              | 12 (10.7)                              | 6 (28.6)                         | –                         | 0.03    |

AF—atrial fibrillation, BMI—body mass index, LA—left atrium, LVEF—left ventricular ejection fraction, PCI—percutaneous coronary intervention, MI—myocardial infarction, SHD—structural heart disease

AF—atrial fibrillation, LSPV—left superior pulmonary vein, RSPV—right superior pulmonary vein, VOM—vein of Marshall, CT—crista terminalis, SVC—superior vena cava, RAA—right atrial appendage

Table 4
Trigger site of adenosine-induced AF.

|                      | Dormant conduction |
|----------------------|-------------------|
| Adenosine-induced AF trigger site | LSPV |
| Patient 1            | LSPV              |
| Patient 2            | RSPV, right atrial septuma |
| Patient 3            | LSPV              |
| Patient 4            | RSPV              |
| Patient 5            | VOM, inside CSb   |
| Patient 6            | VOM               |
| Patient 7            | VOM               |
| Patient 8            | LSPV              |
| Patients 9           | Right atrial CT   |
| Patient 10           | RIPV              |
| Patient 11           | LSPV              |
| Patient 12           | Right atrial septum, right atrial CT, RAAneckb |

AF—atrial fibrillation, LSPV—left superior pulmonary vein, RSPV—right superior pulmonary vein, VOM—vein of Marshall, CT—crista terminalis, SVC—superior vena cava, RAA—right atrial appendage

a Patients excluded from analysis due to loss to follow-up.
b Patients that showed more than one trigger site.

AF as a clinical predictor of AF freedom during follow-up period was adenosine test (hazard ratio [HR] 1.97; 95% confidence interval [CI]: 1.20–3.23; P=0.007) (Table 2).

3.2. Comparison among subgroups of patients who underwent adenosine test

From 148 patients in the group with adenosine test, 114 (77%) patients neither showed dormant conduction nor adenosine-induced AF, 22 (15%) patients showed positive dormant conduction only, and 12 (8%) patients showed adenosine-induced AF (6 of 12 patients also showed dormant conduction). Finally, a total of 28 (19%) patients showed dormant conduction in the group with adenosine test.

We excluded 4 patients from the group with adenosine test (two patients with negative dormant conduction/no AF-induced, one with positive dormant conduction, and one with adenosine-induced AF) due to loss to follow-up (Fig. 1). Baseline clinical characteristics of the subgroups with adenosine test are shown in Table 3.

No significant differences with respect to age, sex, BMI, AF duration, LA size, LVEF, and prevalence of hypertension and diabetes were found between the subgroups. The prevalence of a history of previous PCI/MI and SHD were higher in positive dormant conduction group (P=0.03).

4. Discussion

In patients with PAF undergoing initial PVI, the incidence of AF recurrence was lower in the group with adenosine test performed to confirm the absence of dormant conduction and of triggers.
initiating AF, compared to the group without adenosine test. These results have significant implication for patients with PAF undergoing initial PVI.

4.1. Adenosine-induced dormant conduction and AF recurrence

Although catheter ablation is an effective treatment for PAF, the recurrence rate after PVI remains high. One of the most common reasons for AF recurrence in PAF is recovery of electrical conduction between PV and LA.

Adenosine administration has been shown to unmask dormant conduction after PVI by transiently restoring cellular excitability and conduction across circumferential ablation lines [16]. Adenosine hyperpolarizes resting membrane of cardiomyocytes and increases dV/dtmax in PV myocardium [12,16]. These findings suggest that intra-procedural use of adenosine might identify PV at increased risk of reconnection. Recent studies investigating the implications of adenosine test and additional ablation for predicting AF recurrence showed conflicting results [10–15,17].

Previous studies by Lin et al. [13] and Ghanbari et al. [12] showed that adenosine administration and additional ablation failed to improve long-term outcomes. Lin et al. [13] assumed that the relatively small number of patients (152) in their study determined have statically significant difference. In addition, they did not have a control group without adenosine test and patients with persistent AF were included in the analysis. The prevalence of adenosine induced dormant conduction was lower in their study (11%) compared to our study (19%). Similar findings were found by Ghanbari et al. [12]. Even though this study showed a higher incidence of dormant conduction compared to our study (37% vs. 19%), the small number of patients (total 128) probably influenced the results. However, a study by Gula et al. [15] showed that the outcomes of patients with dormant conduction were similar to those without dormant conduction even when dormant conduction was not targeted with additional ablation. Again, this study was limited by a small number of patients (72) compared to our study and the AF recurrence rates presented by Gula et al. [15] may have been significantly underestimated given that only symptomatic AF was documented. Miyazaki et al. [14] found worst outcomes for patients with dormant conduction despite additional ablation, but this study was limited by using a short blanking period of 1 month to define AF recurrence. It may have inflated AF recurrence rate.

The UNmasking Dormant Electrical Reconnection by Adenosine-TriPhosphate (UNDER-ATP trial) [18] showed opposite results compared to our study. This study showed no significant reduction in 1-year recurrent atrial tachyarrhythmia rate by ATP guided PVI compared with conventional PVI. The main differences compared to our study were: (1) Adenosine dose that used in UNDER-ATP trial was based on body weight (0.4 mg/kg body weight). In our study, the adenosine dose was based on inducible atrioventricular block / sinus arrest / sinus bradycardia (started from 12 mg up to 18 mg). However, the optimal dose of adenosine to reveal dormant conduction remains unclear. Therefore, the difference of the adenosine dose might affect the amount of dormant conduction that can be revealed. In addition, repeated adenosine test was always performed in the same PV after additional ablation in our study. If dormant conduction or AF induction was still present, repeated ablation and adenosine testing were again performed until dormant conduction or adenosine-induced AF was no longer present (see adenosine injection test protocol). It was not clear whether repeated adenosine test was performed or not in UNDER-ATP trial.

(2) The incidence of dormant conduction after adenosine test in UNDER-ATP trial was higher compared to our study (27% vs. 15%).

The Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination (ADVICE) randomized trial evaluated the impact of elimination of adenosine-provoked reconnections [11]. This was a multicenter study with large number of patients, which showed that patients with dormant conduction group that underwent additional ablation had better outcomes compared to those without dormant conduction and with dormant conduction but without further ablation. The differences ADVICE trial compared to our study are as follow: (1) Different study design; all population in ADVICE trial received adenosine test. If dormant conductions were observed, they randomised to no additional ablation or further ablation. Therefore, patients with dormant conduction with no further ablation were included in the control group. Our study used patients without adenosine test as a control group. (2) Even though their study mentioned about adenosine-induced AF, they did not characterize such cases and the strategy to eliminate it.

However, our findings support findings of ADVICE trial, and the total number of patients enrolled in our study is comparable to that of ADVICE trial. In ADVICE trial, the group with dormant conduction with further ablation had better outcomes compared to the group with dormant conduction but no further additional ablation, and even better compared to the group without dormant conduction. In our study, the group with positive dormant conduction with further ablation had similar outcomes to the group with negative dormant conduction.

Our study demonstrated that there was significant difference in AF recurrence between the group with adenosine test and the group without it. Since the group without adenosine test is supposed to include similar ratio of patients (15%) with possible dormant conduction or induced AF (8%), AF recurrence rate probably can be prevented by durable PVI or elimination of non-PV triggers.

4.2. Adenosine-induced AF and AF recurrence

It has been shown that adenosine can induce AF in humans [19]. The true mechanism is unclear, but previous studies speculated that adenosine-induced AF might have the same mechanism with vagally-mediated AF, since adenosine and acetylcholine’s cellular electrophysiological effects are mediated by an identical signal transduction cascade to induce significant antiadrenergic effects [8,20].

However, there is still lack of data about AF recurrence after elimination of the trigger site in cases of adenosine-induced AF. Thus, clinical significance of this phenomenon is unknown [21].

Previous studies showed an incidence of adenosine-induced AF between 4.3% and 29.6% [7,11,22]. Our study showed that incidence of adenosine-induced AF was 8%. Tao et al. [7] and Zhang et al. [22] showed no differences of patient’s characteristics between patients with adenosine-induced AF compared to patients without adenosine-induced AF, which was relevant to the results of our study. Trigger sites of adenosine-induced AF varied between the two previous studies. In study by Tao et al., the most common trigger site of adenosine-induced AF was LSPV (42%), whereas Zhang et al. [22] reported that the most common trigger site was SVC (69%).

Our data showed that LSPV with positive dormant conduction was the most common trigger site (30%). Interestingly, three of 12 patients showed more than one trigger site. In such cases, we ablated the first trigger site, a second trigger site appeared from a different site. Again, we ablated the second trigger site until AF terminated and AF was no longer initiated. Repeated testing with adenosine was performed and if AF induction were still present, repeated ablation and adenosine testing were again performed until AF was no longer reinitiated. In two of six patients with adenosine induced-AF, trigger site came from non-pulmonary vein, but in four patients dormant conduction and trigger of
Adenosine-induced AF came from the same PV. Zhang et al. [22] also found similar findings: they showed three cases of adenosine-induced AF and LA-PV reconnection, but the onset of the induced AF had no relationship with LA-PV reconnection. We also assumed no relationship between dormant conduction and adenosine-induced AF, because the mechanism of dormant conduction and adenosine-induced AF is different.

Zhang et al. [22] also showed that the success rate of adenosine-induced AF after additional ablation on trigger site was higher than that of group without AF initiated after adenosine. Our study supports the results of the Zhang et al. and provides important insights for clinicians to find the trigger site in cases of adenosine-induced AF, even when patient has more than one trigger site. However, it still remains to be determined whether this strategy improves the outcome in patients with adenosine-induced AF.

Finally, adenosine test is important to exclude presence of dormant conduction or AF reinitiated after PVI. Elimination of dormant conductions and trigger sites of adenosine-induced AF may play an important role in achieving better outcomes, but further large-scaled prospective studies are necessary.

4.3. Study limitations

This study has several limitations. First, this was a retrospective study; therefore, AF recurrence could have been underestimated because we could have also missed some asymptomatic events.

Second, the follow-up duration was relative short. However, AF recurrence was higher in the group without adenosine test compared to the group with adenosine test, despite a shorter mean follow-up period in the group without adenosine test. If the group without adenosine test had longer follow-up compared to the group with adenosine test, AF recurrence might become higher than estimated. In Kaplan Meier survival analysis between the groups with and without adenosine test, the curve appeared to diverge early after three months of blanking period, and became more obvious at one year of follow-up, we could not speculate whether this trend will be consistent or not after one year. The difference may not be found in the long-term follow-up, but longer follow-up would be desirable to confirm it.

Third, the number of patients in positive dormant conduction group and adenosine-induced AF group were relative smaller compared to negative dormant conduction/no AF-induced group. Comparisons among these three groups showed no statistical differences, but we assume that a larger sample of positive dormant conduction and adenosine-induced AF patients is needed to confirm these results.

Finally, we could not systematically collect data for some factors that may influence the results, such as timing of adenosine administration after PVI, physician decision for selecting patients who did get adenosine test and who did not, and variation of catheter contact and improved mapping and ablation technology in recent years that may have influenced durable PV isolation.

5. Conclusions

Adenosine test performed after PVI to confirm negative dormant conduction and no triggers initiating AF is beneficial to improve the outcomes after catheter ablation of PAF.

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Disclosures

All authors declare no conflict of interest related to this study.