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Clinical Implication of Adenosine Test at Repeat Atrial Fibrillation Ablation Procedure

The Importance of Detecting Dormant Thoracic Vein Conduction

Shinsuke Miyazaki, MD; Atsushi Kobori, MD; Yuki Komatsu, MD; Taishi Kuwahara, MD; Takashi Uchiyama, MD; Shigeki Kusa, MD; Hiroshi Taniguchi, MD; Hitoshi Hachiya, MD; Kenzo Hirao, MD; Mitsuaki Isobe, MD; Atsushi Takahashi, MD; Yoshito Iesaka, MD

Background—Pulmonary vein reconnection after electrical isolation is commonly observed in the context of atrial fibrillation ablation and is associated with recurrent atrial tachyarrhythmias. Adenosine test was performed to identify acute dormant conduction immediately after pulmonary vein isolation at index procedure. However, the utility of adenosine test at repeat procedure has not been reported.

Methods and Results—We report 5 paroxysmal atrial fibrillation cases without any structural heart disease in which dormant thoracic vein conduction was associated with recurrent atrial tachyarrhythmias. All patients had undergone circumferential ipsilateral pulmonary vein isolation at the index procedure. Superior vena cava isolation was performed if superior vena cava-triggered atrial fibrillation was identified. At the index procedure, adenosine test did not provoke venous reconnection. At the repeat procedure, adenosine provoked clinical arrhythmia in 4 out of 5 cases after transient reconnection between culprit thoracic vein and atrium despite absence of reconnection at the start of the procedure. After the elimination of the dormant conduction gaps, all patients were free from recurrent arrhythmia.

Conclusions—Adenosine provokes dormant thoracic vein conduction associated with the late recurrence of atrial tachyarrhythmias after previous thoracic vein isolation. Thus, adenosine provocation test can specifically help identify and target the cause of recurrent atrial arrhythmia. (*Circ Arrhythm Electrophysiol.* 2012;5:1117-1123.)

Key Words: adenosine ■ atrial fibrillation ■ catheter ablation ■ dormant conduction ■ pulmonary vein isolation

Catheter ablation of atrial fibrillation (AF) is increasingly performed because it was reported that paroxysmal AF is most often triggered by the sources inside the thoracic veins such as pulmonary veins (PVs) and superior vena cava (SVC).¹⁻³ Electrical PV isolation is the cornerstone of AF ablation, and it is well-known that the majority of recurrent atrial tachyarrhythmias result from the reconnection of PVs in patients with paroxysmal AF.^{4,5} Because adenosine can reveal dormant PV conduction immediately after isolation, adenosine test has been recognized as a useful technique to predict acute PV reconnection at the index AF ablation procedure.⁶⁻¹⁰ However, the utility of adenosine test at repeat ablation procedure undertaken for recurrent atrial tachyarrhythmias has not been reported. We present a series of cases of recurrent atrial tachyarrhythmias in which the successful elimination of adenosine-provoked transient thoracic vein reconnection led to freedom from recurrent arrhythmia.

Clinical Perspective on p 1123

Methods

All patients underwent circumferential PV antrum isolation (PVAI)¹¹⁻¹⁵ for drug-refractory symptomatic paroxysmal AF at the index procedure.

Catheter Ablation at Index Procedure

All antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. All patients were effectively anticoagulated for >1 month before the procedure. Transesophageal echocardiography was performed to exclude atrial thrombi. The surface ECG and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (LabSystem PRO; Bard Electrophysiology). The bipolar electrograms were filtered from 30 to 500 Hz. A 7-F 14-pole 2-site-mapping catheter (Irvine Biomedical) was inserted through the right jugular vein and positioned in the coronary sinus for pacing, recording, and internal AF cardioversion. The electrophysiological study was performed under mild sedation obtained with either dexmedetomidine or pentazocine and hydroxyzine pamoate.

The ablation strategy has been described previously.¹³⁻¹⁵ In brief, after a trans-septal puncture, 2 long sheaths (SL0; AF Division, St Jude Medical) were introduced into both superior PVs. Pulmonary venography during ventricular pacing and contrast esophagography

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were performed to obtain the relative locations of the PV ostia via the esophagus; 100 IU/kg body weight of heparin was administered after the trans-septal puncture, and heparinized saline was additionally infused to maintain the activated clotting time at 250 to 350 seconds. Two decapolar circular mapping catheters (6-mm interelectrode spacing of 20 mm diameter or 4.5-mm interelectrode spacing of 15 mm diameter; Lasso; Biosense Webster) were placed in the superior and inferior PVs, and the left and right ipsilateral PVs were circumferentially ablated guided by a 3-dimensional mapping system (CARTO; Biosense Webster). Posteriorly, ablation was performed anatomically in the left atrium (LA), \approx 1 to 3 cm from the PV ostia. Anteriorly, ablation was performed on edge of the left PVs guided by early PV potentials. The electrophysiological endpoint was the achievement of bidirectional conduction block between LA and PVs, and the anatomic endpoint was the creation of complete continuous circumferential lesion around the ipsilateral veins.^{15,16} In cases 1, 2, and 5, radiofrequency (RF) current was delivered point-by-point with 3.5-mm externally irrigated-tip quadripolar ablation catheter (Thermocool; Biosense-Webster) with power up to 35 W, target temperature \leq 38°C, and irrigation rate of 30 mL/min. The power was limited to 20 W on the posterior wall, close to the esophagus. In cases 3 and 4, RF current delivery was applied with an 8-mm tip ablation catheter (Japan Lifeline) in the temperature-controlled mode, with a target temperature of 55°C and maximum power of 35 W on the LA posterior wall and 40 W at the anterior aspect of the PVs. After completing the PVAI, 2 circular mapping catheters were placed in the ipsilateral PVs and a 30- or 40-mg bolus of ATP was injected to unmask dormant PV conduction. Any gap responsible for dormant conduction was eliminated by additional RF application.⁷⁻⁹ At the repeat procedure, the dormant conduction was evaluated in the same way.

SVC isolation was added if the SVC triggering AF was identified during the procedure. The circular mapping catheter was placed at the level of the lower border of the pulmonary artery above the SVC-right atrial junction guided by SVC angiography. RF energy was delivered point-by-point using 4-mm nonirrigated-tip catheter in a temperature-controlled mode with maximum temperature set at 50°C and maximum power at 35 W. Before RF delivery, high-output pacing (10 mA) was performed at every site; if diaphragmatic stimulation was observed, then ablation was avoided locally to prevent phrenic nerve injury. The endpoint of ablation was to eliminate all SVC potentials on the mapping catheter.

Follow-up

Patients underwent continuous in-hospital ECG monitoring for 3 days after the procedure. The first outpatient clinic visit was 3 weeks after the ablation procedure. Subsequent follow-up visits consisted of clinical interview, ECG, and 24-hour Holter monitoring every 3 months at our cardiology clinic. No antiarrhythmic

drugs were prescribed after the procedure. Patients with palpitations were encouraged to use an event recorder. Recurrence was defined according to the patient's symptoms, and if arrhythmia lasting $>$ 30 seconds was documented. A repeat procedure was strongly recommended for the patients with documented recurrent atrial tachyarrhythmia.

Results

Among 72 and 105 patients who underwent repeat ablation procedure for recurrent atrial arrhythmias after catheter ablation for paroxysmal AF at Tsuchiura Kyodo Hospital and Yokosuka Kyosai Hospital, adenosine test was performed in 42 and 7 patients, respectively. Three cases (case 1, 2, and 5) were identified in the former center, and 2 cases (case 3 and 4) were identified in the latter. Summary of the patient data is shown in the Table.

Case 1

A 74-year-old man with a paroxysmal AF and a history of cerebral infarction was admitted for catheter ablation. The LA size was 37 mm and left ventricular function was normal on the echocardiogram. The starting rhythm at the index procedure was AF. After electrical cardioversion, immediate repetitive AF recurrence was identified from the left superior PV (LSPV), the culprit vein. After achievement of circumferential PVAI during AF, sinus rhythm was restored by electrical cardioversion. No AF recurrence was observed thereafter. Adenosine test did not provoke any dormant LA-PV conduction. Two weeks later, symptomatic AF recurrence was documented, and a second procedure was performed 7 weeks after the index procedure.

The patient was in sinus rhythm at the start of the second procedure. PV reconnection was not observed. Adenosine test provoked transient reconnection of LSPV just before the atrioventricular block (Figure 1A), followed by initiation of AF from reconnected LSPV lasting 60 seconds (Figure 1B). After the elimination of this dormant conduction gap, adenosine test was repeated. No dormant conduction was observed. No adverse events were observed and the patient has been free

Table. Summary of the Patient Data

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, y	74	59	61	63	65
Sex	M	M	M	F	M
AF type	PAF	PAF	PAF	PAF	PAF
Structural heart disease	No	No	No	No	No
Culprit thoracic vein	LSPV	Right PVs	RSPV	SVC	Left PVs, non-PV
Dormant conduction exposed at index procedure	No	No	No	No	No
Type of recurrence	PAF	PAF	AT	PAF	PAF
Number of repeat sessions	2	3	2	2	2
Duration from the index procedure, mo	2	1	2	2	3
AF/AT induction after reconnection exposed by adenosine	Yes	No	Yes	Yes	Yes
Follow-up period, mo	12	6	36	24	6

AF indicates atrial fibrillation; AT, atrial tachycardia; F, female; LSPV, left superior pulmonary vein; M, male; PAF, paroxysmal AF; PV, pulmonary vein; RSPV, right superior pulmonary vein; and SVC, superior vena cava.

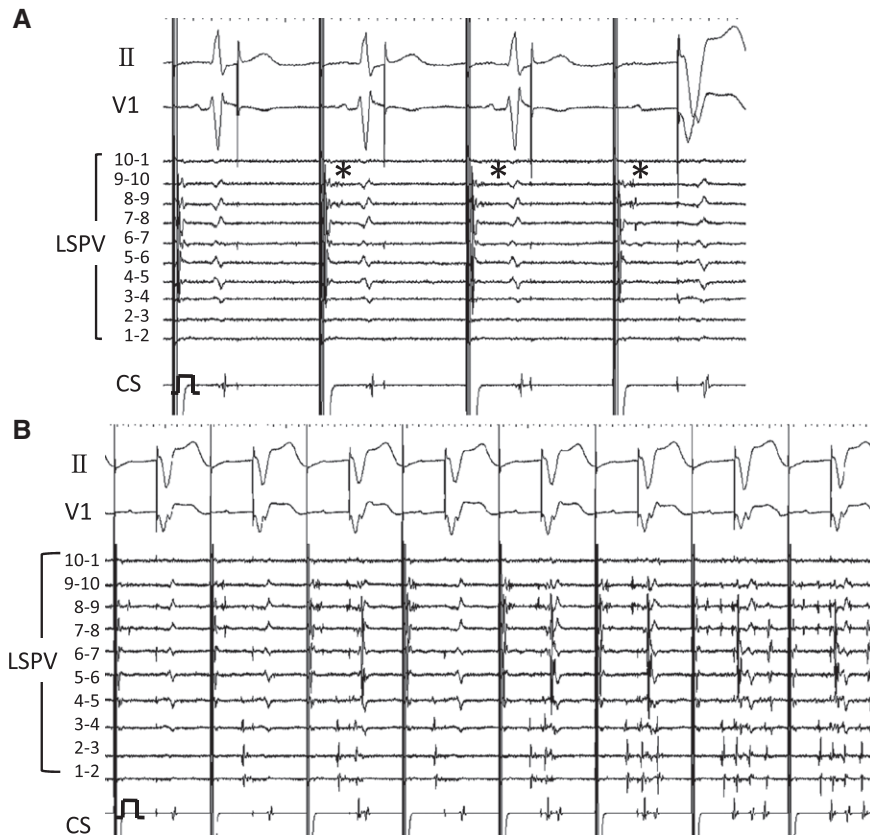


Figure 1. **A**, In the absence of pulmonary vein (PV) reconnection at the start of the second procedure, transient reconnection (*) between the left atrium (LA) and left superior PV (LSPV) was revealed by adenosine test during sequential pacing from the coronary sinus (CS) and right ventricular apex. After transient reconnection between the LA and LSPV (**A**), atrial fibrillation initiated from the left superior PV (**B**).

from any atrial arrhythmia while not using antiarrhythmic drugs for 12 months after the second (last) procedure.

Case 2

A 59-year-old man with a paroxysmal AF was admitted for catheter ablation. The LA size was 38 mm and left ventricular function was normal on the echocardiogram. Paroxysmal AF was observed most of the day on 24-hour Holter monitoring before the first procedure (AF burden >90%). The starting rhythm was sinus and all PVs were circumferentially isolated. Dissociated PV activity was recorded in LSPV and right PVs. Dormant PV conduction was not provoked by adenosine test. Two weeks after the index procedure, AF recurrence was documented and incessant AF similar to that documented before the index procedure (AF burden >90%) was recorded again on the 24-hour Holter monitoring. Second procedure was performed 1 month after the index procedure.

Short-lasting occurrences of AF happened repetitively at the start of the second procedure. Dissociated PV activity with a cycle length of 2000 ms was recorded in the right PVs. LSPV was reconnected and responsible for the paroxysms of AF triggered by an ectopy, which otherwise occurred in a concealed bigeminal fashion (Figure 2A). The conduction gap between LSPV and LA was closed by 1 RF application at the roof of LSPV. Dissociated activity was recorded in the LSPV. Premature atrial contraction or atrial tachyarrhythmias were not observed after the reconnection of LSPV without and with isoproterenol. Adenosine provoked transient reconnection (for 2 beats only) between right PVs and LA (Figure 2B), which was not treated by RF application. One day later, paroxysmal

AF recurred with frequent, short-coupled, premature atrial contractions. The AF burden was <10%. Three days after the second procedure, we performed the third procedure for recurrent paroxysmal AF.

The patient was in sinus rhythm without any premature atrial contraction at the start of the third procedure. No PV reconnection was recognized without and with isoproterenol infusion. Dissociated activity was observed in LSPV and right PVs. Adenosine again provoked LA–right PV reconnection transiently. The gap causing this dormant conduction was successfully eliminated by RF application. No adverse events were observed and the patient has been free from any atrial arrhythmia without antiarrhythmic drugs for 6 months thereafter.

Case 3

A 61-year-old man with normal LA diameter and left ventricular ejection fraction underwent circumferential PVAI for paroxysmal AF. After successful PVAI, adenosine test under isoproterenol infusion provoked no reconnection or arrhythmia. Four weeks later, atrial tachycardia (AT) lasting several hours occurred 2 to 3 times per week. He underwent the second procedure 2 months after the index procedure.

The starting rhythm at the second procedure was sinus. All 4PVs were isolated, and dissociated PV potentials were observed in the right superior PV (online-only Data Supplement Figure IA). Isoproterenol infusion did not provoke any arrhythmia. AT could not be induced by programmed stimulation. Adenosine test reproducibly provoked transient LA–right superior PV reconnection (online-only Data Supplement Figure IB). Rapid right superior PV firing

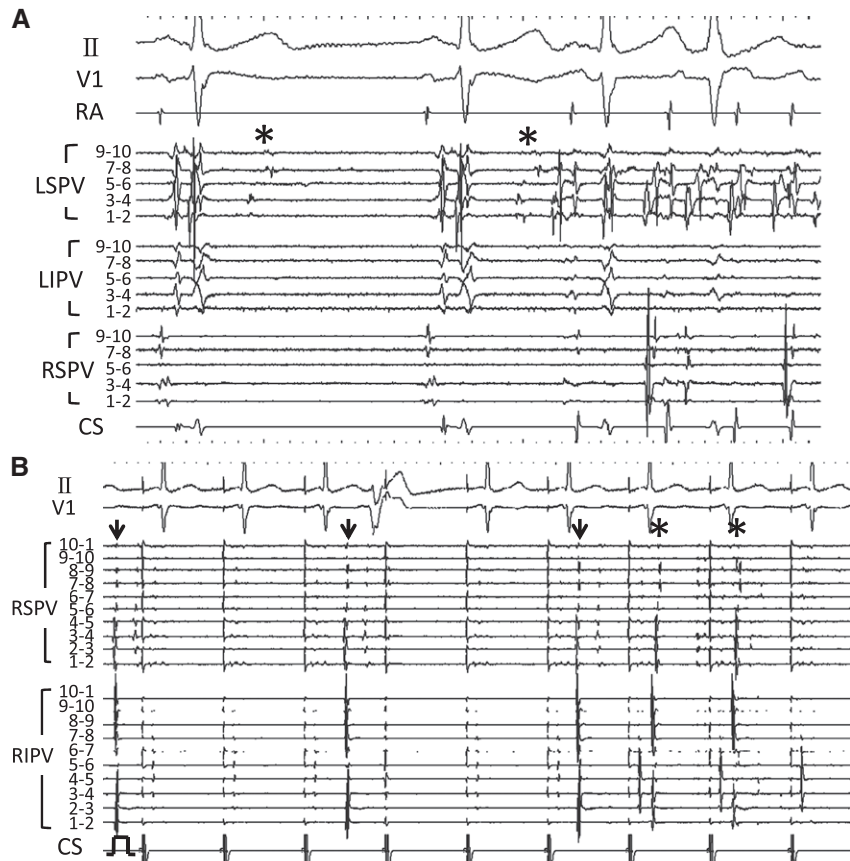


Figure 2. **A**, Three circular mapping catheters placed in the left superior, left inferior, and right superior pulmonary veins (PVs) show atrial fibrillation initiation from the left superior PV by concealed bigeminal PV ectopy (*) at the second procedure. **B**, Two circular mapping catheters placed in the right superior and inferior PVs at the second procedure record dissociated PV activity, with a cycle length of 2000 ms (arrows) proving both entrance and exit block between the ipsilateral right PVs and the left atrium (LA). Adenosine provoked transient reconnection (*) between the LA and ipsilateral right PVs via a gap around the right inferior PV during atrial pacing from the coronary sinus. LIPV indicates left inferior pulmonary vein; RA, right atrium; RSPV, right superior pulmonary vein.

occurred spontaneously during the reconnection, which caused AT with the same P-wave morphology as the clinical AT (Figure 3). We eliminated the right superior PV–LA reconnection with a single RF application. After follow-up of 36 months, the patient has been free from atrial arrhythmias without antiarrhythmic drugs.

Case 4

A 63-year-old woman with paroxysmal AF, no structural heart disease, and normal echocardiographic parameters was referred for AF ablation. During the index procedure, AF initiation from the SVC was observed after circumferential PVAI. Electrical SVC isolation was performed. Adenosine did not provoke any thoracic venous reconnection. One month later, symptomatic AF recurred and she underwent the second procedure after 2 months.

At the start of the second ablation, all 4 PVs and SVC were isolated and no dormant PV conduction was revealed by adenosine test. However, a transient right atrial–SVC reconnection was reproducibly provoked by adenosine. Rapid SVC firing occurred spontaneously during the reconnection (online-only Data Supplement Figure IIA). We eliminated the right atrial–SVC reconnection successfully. After a follow-up of 24 months, the patient has been free from atrial arrhythmias without antiarrhythmic drugs.

Case 5

A 65-year-old man with paroxysmal AF and hypertension was referred for AF ablation. The LA size was 37 mm and left

ventricular function was normal on the echocardiogram. At the index procedure, circumferential PVAI and focal ablation targeting premature atrial contractions from the LA septum were undertaken. Adenosine test did not reveal dormant PV conduction. One month later, symptomatic AF recurrence was documented on antiarrhythmic drug, necessitating a second procedure 3 months after the index procedure.

At the second procedure, all 4 PVs were found to be isolated. Adenosine provoked transient LA–left inferior PV reconnection (online-only Data Supplement Figure IIB), followed by rapid left inferior PV firing (online-only Data Supplement Figure III). The dormant conduction gap was eliminated by 1 RF application. After 6 months, the patient has been free from atrial arrhythmia with the same antiarrhythmic drug, which was continued after the index procedure.

Discussion

The most important finding of this study is that dormant thoracic vein conduction leading to late recurrent atrial tachyarrhythmia after AF ablation can be revealed by adenosine test at the repeat ablation procedure. The elimination of dormant thoracic vein conduction gap alone at the repeat procedure leads to complete freedom from recurrent atrial tachyarrhythmia. It is critical to identify the mechanism of recurrent atrial tachyarrhythmias at the repeat procedure. In our series of cases, there were no residual reconnections between the atrium and the culprit thoracic veins at the start of the repeat procedure, but they were transiently provoked by adenosine injection. Thus, the provocative test provided the mechanism

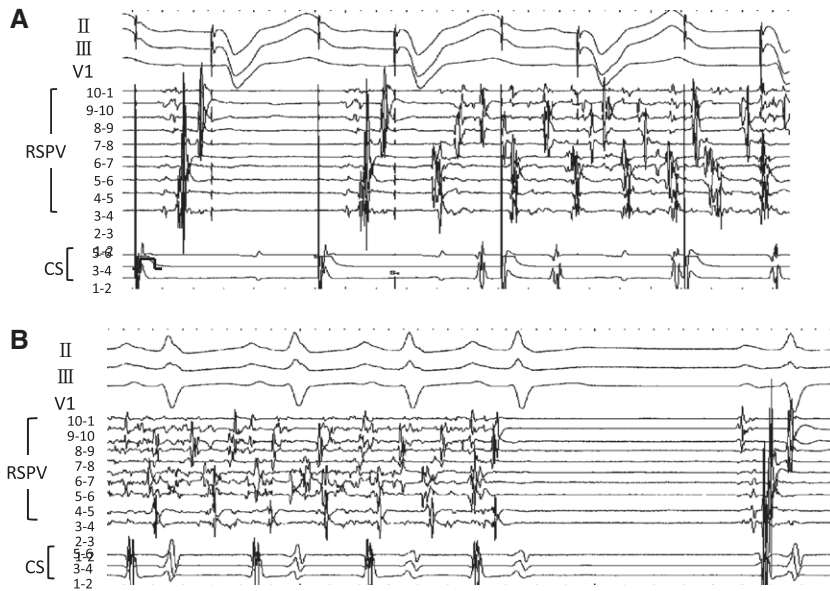


Figure 3. After adenosine provoked transient reconnection between the right superior pulmonary vein (PV) and left atrium, rapid PV firing was induced during sequential pacing from the coronary sinus and right ventricular apex (A). PV firing resulted in an atrial tachycardia, which terminated with cessation of PV firing (B).

of the arrhythmia and identified specific targets of ablation, which led to successful and sustained elimination of recurrent arrhythmias.

PV Reconnection and Recurrent Atrial Tachyarrhythmias

It is well-known that PV reconnections often are associated with paroxysmal AF recurrences, and achieving durable PV isolation is difficult using current technology.^{4,5} Cheema et al¹⁷ showed recurrence of PV conduction in >90% of patients 1 hour after initial electrical isolation. Cappato et al⁴ demonstrated that late conduction recurrence across acutely disconnecting RF lesions delivered at the ostia of the multiple PVs is a common finding in patients undergoing catheter ablation of AF. Recently, Kowalski demonstrated that PVs showing electrical reconnection after catheter-based antral ablation frequently reveal anatomic gaps or nontransmural lesions at the sites of catheter ablation, and that return of PV conduction after catheter-based isolation procedures is assumed to be attributable to failure to create permanent contiguous transmural lesions in at least part of the ablation line by histological study.¹⁸

Adenosine Test at the Index Ablation Procedure

Adenosine test has been used to identify dormant conduction after electrical PV isolation at the index procedure.⁶⁻¹⁰ Datino et al¹⁹ elegantly showed that conduction recovery was related to adenosine-induced hyperpolarization of the PVs via an increase in the inward rectifier potassium current I_{Kado} in a canine preparation. Hyperpolarization facilitated the closure of the inactivated sodium channels, making them available for activation, and resulted in resumed conduction in tissue where reversible thermal heating had occurred. They concluded that adenosine might be useful to identify lesions with thermally mediated reversible membrane depolarization likely to recover over a time frame of minutes.

Previous retrospective studies suggested that the elimination of adenosine-provoked dormant PV conduction leads

to better clinical outcome after an initial AF ablation procedure.⁸⁻¹⁰ However, these studies were retrospective and single-center, and the period during which the AF ablation was performed differed between them. Therefore, rapidly changing procedural techniques and increasing operator experience should have influenced the results of these noncontemporaneous studies. Moreover, it is well-known that PV reconnection spontaneously occurs frequently after isolation;¹⁷ therefore, the utility of adenosine test at the index procedure has not yet been established. In fact, a previous report studied whether the adenosine test and the 30 minutes of waiting similarly revealed the conduction gap responsible for acute conduction recovery. The study showed that the agreement between these methods was only moderate and that the latter was more efficient.²⁰ Actually, even if the adenosine-provoked dormant conduction gap was eliminated at the initial procedure, PV reconnection leading to the recurrence of tachyarrhythmias was frequently observed in the repeat sessions.^{4,5,15} An important multicenter randomized study (ADVANCE) is currently assessing whether the elimination of dormant PV conduction will translate into a lower rate of recurrent AF.²¹

Adenosine Test at the Repeat Ablation Procedure

This study demonstrates that the absence of PV reconnection at the start of the repeat session does not always mean durable PV isolation, and that identifying any dormant conduction by provocation maneuver can be useful to eliminate recurrent atrial tachyarrhythmias. One can speculate that PV could intermittently reconnect with LA in a clinical setting, which could lead to AF/AT recurrence. A previous report showed that a conduction gap could be at a different location during the third procedure when compared with the second procedure in some patients after circumferential PVAI.²² This might be explained by the intermittent PV reconnection/dormant PV conduction. It is quite difficult to evaluate pure contribution of adenosine test at the index procedure because of the possibility of time-dependent spontaneous PV reconnection and the impact of RF-induced reversible tissue edema or

inflammation. Reversible edema or inflammation could take longer to reverse than resting membrane potential, with eventual gaps developing in the RF-induced scar that allow recovery of conduction. Previous studies showed that the majority of patients with recurrent atrial tachyarrhythmias had PV reconnection even after the elimination of any dormant PV conduction at index procedure. This might be partly explained by the RF-induced reversible tissue edema or inflammation. However, the possibility of time-dependent spontaneous reconnection and tissue edema/inflammation can be eliminated later at the repeat procedure. Although the purinergic effect of adenosine might impact on the susceptibility of AF, our data showed that dormant conduction was associated with recurrence. These cases highlight the clinical utility of adenosine test at repeat AF ablation procedure, and also the importance of durable thoracic vein electrical isolation in the context of AF ablation. Adenosine test should be considered, especially when a culprit vein is identified at the index procedure and dissociated activity is observed without any reconnection at the start of the repeat procedure.

Clinical Implications

These observations confirm the importance of dormant thoracic vein conduction as a cause of late recurrence of atrial arrhythmias. When any PV–LA conduction is not observed during a repeat procedure, evaluation of dormancy using adenosine might reveal the etiology of recurrent atrial arrhythmia and might help cure it.

Study Limitation

Because the adenosine test has not been performed systemically at the repeat procedure in consecutive cases, the precise frequency of dormant thoracic vein conduction is not clear.

Conclusions

Adenosine test can reveal dormant thoracic vein conduction associated with late recurrence of atrial tachyarrhythmias after a previous thoracic vein isolation procedure. Adenosine test thereby can elucidate the etiology of recurrent atrial arrhythmia attributable to dormant thoracic vein conduction in patients with paroxysmal AF. Our data suggest that thoracic veins might be underestimated as the triggers of late recurrent paroxysmal AF/AT.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The utility of adenosine test at repeat ablation procedure undertaken for recurrent atrial tachyarrhythmias has not been reported. The results of the present study demonstrate that adenosine test could reveal dormant thoracic vein conduction associated with late recurrence of atrial tachyarrhythmias after previous thoracic vein isolation procedure. Adenosine test thereby can elucidate the etiology of recurrent atrial arrhythmia attributable to dormant thoracic vein conduction in patients with paroxysmal atrial fibrillation. When any pulmonary vein—left atrium conduction is not observed during a repeat procedure, evaluation of dormancy using adenosine might reveal the etiology of recurrent atrial arrhythmia and might help cure it. The present study suggests that thoracic veins might be underestimated as the triggers of late recurrent paroxysmal atrial tachyarrhythmias.

SUPPLEMENTAL MATERIAL

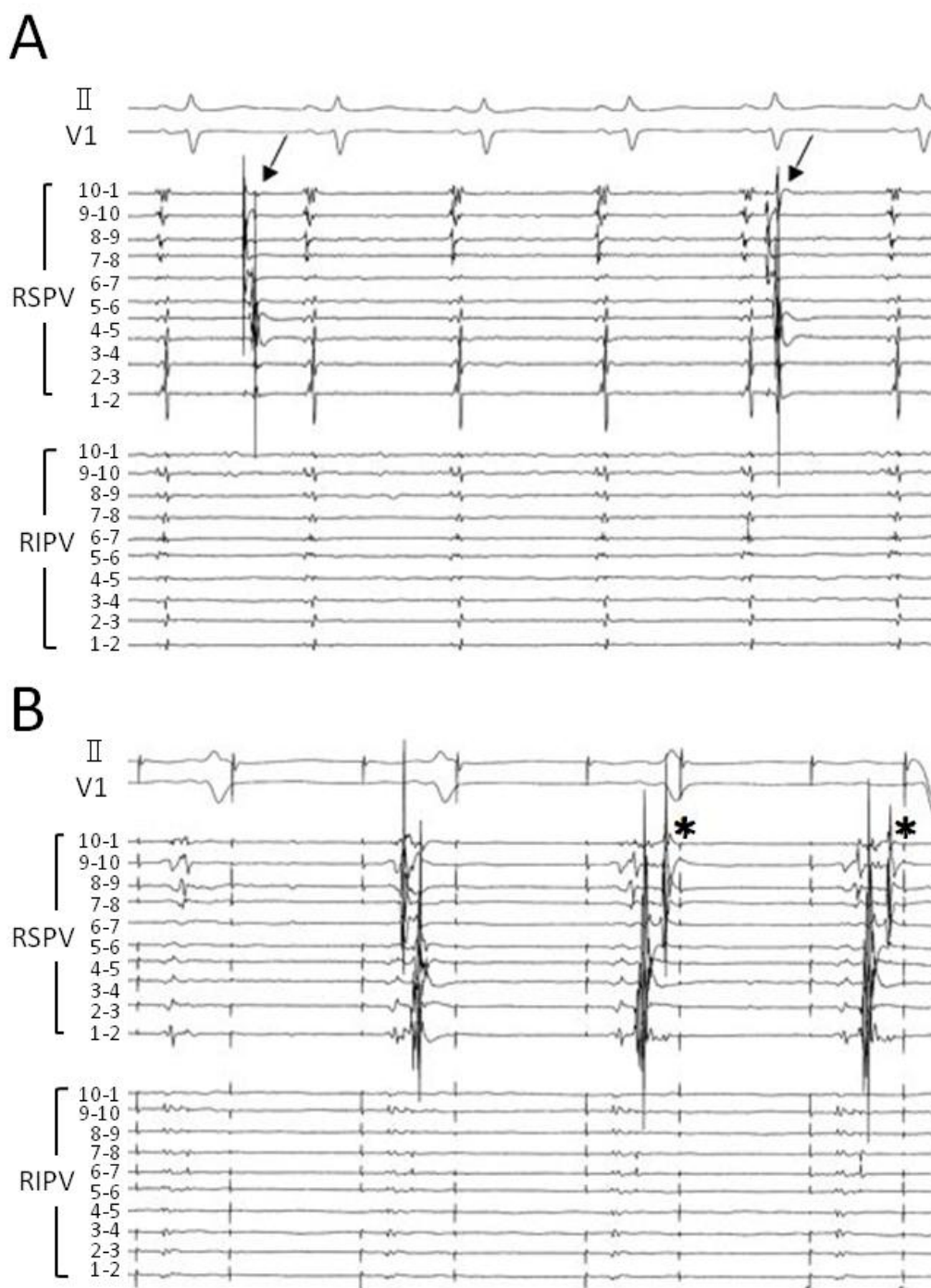
References

Supplemental Figure 1. Two circular mapping catheters are placed in the right ipsilateral PVs at the second procedure. Dissociated PV spikes (arrow) can be seen in the right superior PV (A). Adenosine transiently provoked LA-right superior PV reconnection (asterisk) during sequential pacing from the coronary sinus and right ventricular apex (B).

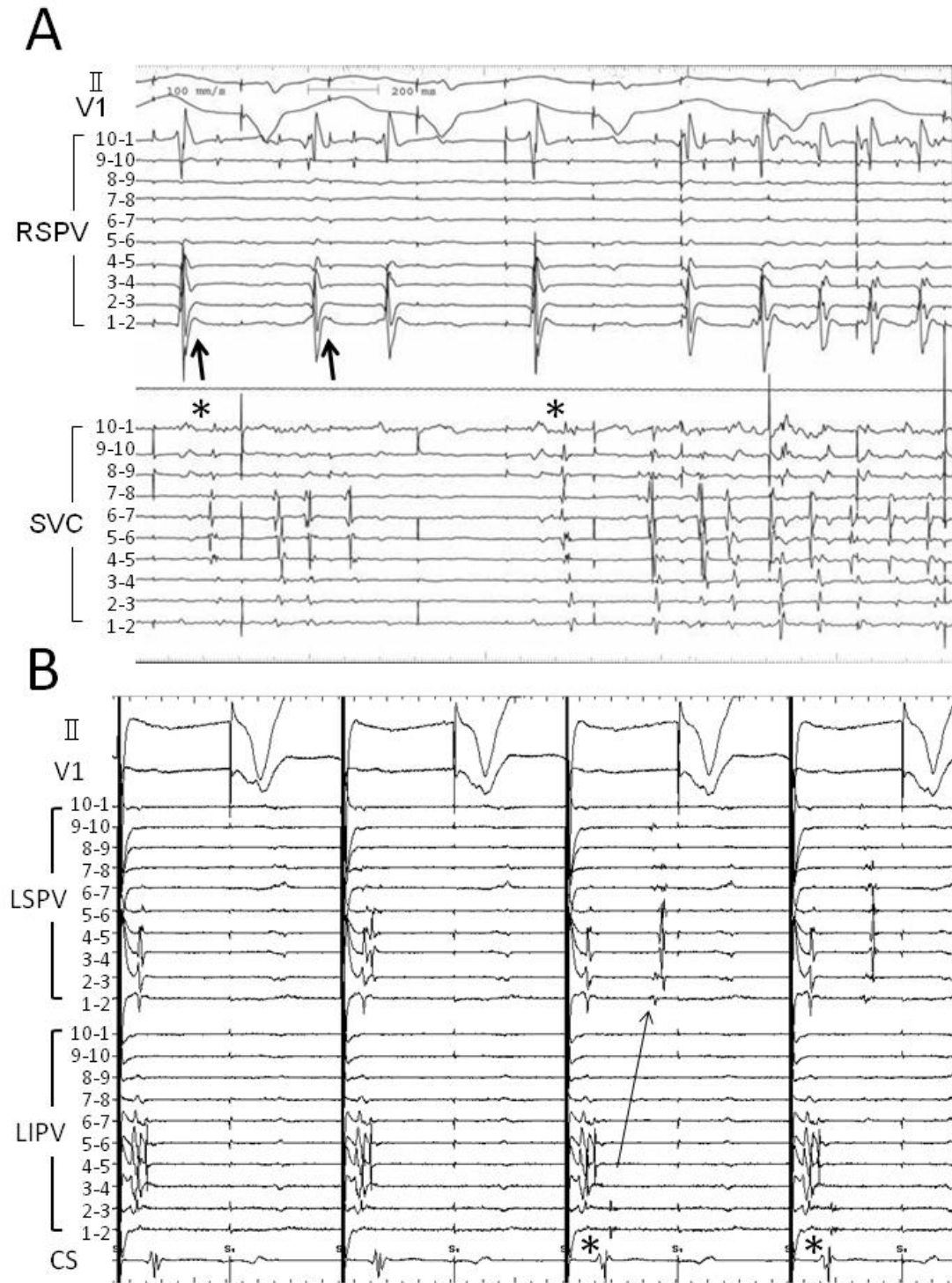
Supplemental Figure 2. A. Two circular mapping catheters placed in the SVC and right superior PV show SVC triggered AF following adenosine-provoked, transient RA-SVC reconnection (asterisk) during sequential pacing from the coronary sinus and right ventricular apex. Note that the far-field SVC potentials are recorded in the right superior PV. Large potentials (arrows) recorded on the circular mapping catheter placed at RSPV ostium are LA potentials. SVC: superior vena cave. B. Two circular mapping catheters placed in the left ipsilateral PVs at the second procedure show transient reconnection (asterisks) between the LA and left ipsilateral PVs via a gap around the left inferior PV provoked by adenosine during sequential pacing from LA appendage and right ventricular apex.

Supplemental Figure 3. Two circular mapping catheters are placed in the left ipsilateral PVs. Following reconnection between LA and left inferior PV, AF initiates from the left PVs during pacing from LA appendage and right ventricular apex (A) and lasts (B).

Supplemental Figure 1.



Supplemental Figure 2.



Supplemental Figure3.

