Clinical Impact of Adenosine Triphosphate Injection on Arrhythmogenic Superior Vena Cava in the Context of Atrial Fibrillation Ablation

Shinsuke Miyazaki, MD; Hiroshi Taniguchi, MD; Yuki Komatsu, MD; Takashi Uchiyama, MD; Shigeki Kusa, MD; Hiroaki Nakamura, MD; Hitoshi Hachiya, MD; Kenzo Hirao, MD; Yoshito Iesaka, MD

Background—Superior vena cava (SVC) is an infrequent yet an important source of atrial fibrillation. The clinical impact of ATP injection on arrhythmogenic SVC has not been evaluated.

Methods and Results—A total of 43 patients (59±11 years; men, 32) who underwent ATP test for arrhythmogenic SVC after the electric isolation at either initial procedure or repeat procedure were included. Pulmonary vein antrum isolation was performed at index procedure in all patients. SVC was isolated after identifying the arrhythmogenicity at index and repeat atrial fibrillation ablation procedure in 34 (79.1%) and 9 (20.9%) patients, respectively. Atrial fibrillation originated from the SVC spontaneously and under isoproterenol infusion in 30 (75.0%) patients, and immediately after ATP injection in 10 (25.0%) patients. Tachycardia persistently confined to SVC was recorded after electric isolation in 13 (30.2%) patients. SVC reconnection was provoked by ATP test in 7 of 36 (19.4%) patients at acute phase. Among 36 patients with reconnection at baseline, SVC reconnection was provoked by ATP test at median 4.0 (2.25–7.5) months after SVC isolation, reconnection was observed in 12 of 15 (80.0%) patients at repeat procedure. Among 12 patients with reconnection at baseline, SVC reconnection was provoked by ATP test after reisolation in 1 (8.3%) patient. Among 3 patients without SVC reconnection at baseline, reconnection was provoked by ATP test at chronic phase in 1 patient.

Conclusions—Dormant conduction between an arrhythmogenic SVC and the right atrium can be exposed by ATP administration both immediately and late after isolation, potentially facilitating detection and ablation for isolation.

Key Words: adenosine ■ atrial fibrillation ■ catheter ablation ■ superior vena cava

Because it was reported that paroxysmal atrial fibrillation (AF) is most often triggered by the sources inside the pulmonary veins (PVs),1 radiofrequency (RF) catheter ablation of AF is increasingly performed.2,3 Non-PV foci, such as superior vena cava (SVC), have also been established as one of the important sources of AF.4,5 Electric thoracic vein isolation is an established therapy for AF;3,6 however, thoracic vein reconnection, including PV7–9 and SVC,10 is frequently observed in patients with previously isolated veins. Most of these recurrences are associated with very early conduction recovery after RF application. The mechanism has been related to incomplete lesions, which leaves damaged but viable muscle sleeves that can recover,11 and adenosine/ATP test has been reported to be a useful to identify the dormancy after PV isolation at acute12–14 and chronic phases.15 However, the clinical impact of adenosine/ATP injection on SVC reconnection has not been evaluated. The objective of this study is to investigate the clinical impact of ATP injection on arrhythmogenic SVC in the context of AF ablation.

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Methods

Study Population
Among 956 consecutive patients who underwent ablation of paroxysmal or persistent AF in our hospital, arrhythmogenic SVC was identified in 46 (4.8%) patients. Among 46 patients, 43 patients (58.6±10.6 years; men, 32) who underwent ATP test for arrhythmogenic SVC after the isolation at either initial procedure or repeat procedure were further analyzed. All 43 patients underwent PV antrum isolation (PVAI)15–18 at the initial procedure, and additional SVC isolation for arrhythmogenic SVC at either initial or repeat ablation procedures when the arrhythmogenicity was identified. SVC was defined as arrhythmogenic when AF initiated and repetitive premature atrial contractions (PACs)/PAC salvos originated from it during the procedure. The cases wherein only solitary PACs were recorded from SVC were excluded from this study. AF was classified according to the HRS/EHRA/ECAS 2012 Consensus Statement on Catheter and Surgical Ablation of AF.19 All patients gave written informed consent for participation in the study.

Mapping and Ablation Protocol
All antiarrhythmic drugs were discontinued for ≥5 half-lives before the procedure. All patients were effectively anticoagulated for ≥1 month before the procedure. Transesophageal echocardiography was

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From the Cardiology Division, Cardiovascular Center, Tsuchiura Kyodo Hospital, Tsuchiura, Ibaraki, Japan (S.M., H.T., Y.K., T.U., S.K., H.N., H.H., Y.I.); and Heart Rhythm Center, Tokyo Medical and Dental University, Tokyo, Japan (K.H.).
Editor for this article was Kenneth A. Ellenbogen, MD.
Correspondence to Shinsuke Miyazaki, MD, Cardiology Division, Cardiovascular Center, Tsuchiura Kyodo Hospital, 11-7 Manabeshin-machi, Tsuchiura, Ibaraki 300-0053, Japan. E-mail mshinsuke@k3.dion.ne.jp
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performed to exclude atrial thrombi. An enhanced cardiac computer tomography was performed for the evaluation of relevant cardiac anatomy before the procedure in all patients. The surface ECG and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (LabSystem PRO, Bard Electrophysiology, Lowell, MA). The bipolar electrograms were filtered from 30 to 500 Hz. A 7-F 14-pole 2-site mapping catheter (Irvine Biomedical Inc, Irvin, CA) was inserted through the right jugular vein and positioned in the coronary sinus for pacing and internal AF cardioversion. It enabled continuous monitoring of coronary sinus and SVC-right atrium (RA) junction by distal and proximal 7-pole electrodes, respectively, during the whole procedure. The electrophysiological study was performed under mild sedation obtained with pentazocine and hydroxyzine pamoate.

**Ablation Procedure**

The ablation was performed according to the strategy described previously. In brief, after a transseptal puncture, 2 long sheaths (SL0, AF Division, St. Jude Medical, Minneapolis, MN) were introduced into both superior PVs. Pulmonary venography during ventricular pacing or immediately after ATP injection, and contrast esophagography were performed to obtain the relative locations of the PV ostia vis-a-vis esophagus. A 100-IU/kg body weight of heparin was administered after the transseptal puncture, and heparinized saline was also infused to maintain the activated clotting time at 250 to 350 seconds. Two circular mapping catheters (Lasso, Biosense Webster, Diamond Bar, CA) were placed in the superior and inferior PVs, and the left- and right-sided ipsilateral PVs were circumferentially and extensively ablated guided by 3-dimensional (3D) mapping system (CARTO3, Biosense Webster). Posteriorly, ablation was performed anatomically in the left atrium (LA), ≈1 to 3 cm from the PV ostia. Anteriorly, ablation was performed on edge of the left PVs guided by earliest PV potential. The electrophysiological end point was the achievement of bidirectional conduction block between LA and PVs and the anatomic end point was the creation of complete circumferential lesion around the ipsilateral veins. RF current was delivered point-by-point with 3.5 mm externally irrigated-tip quadripolar ablation catheter (Thermocool, Biosense Webser) with power up to 35 W, target temperature ≤38°C and irrigation rate of 30 mL/min. The power was limited to 20 W on the posterior wall close to the esophagus.

After completing the PVAI, a 30-mg bolus of ATP was injected to unmask dormant PV conduction with administration of isoproterenol, and any gap responsible for dormant conduction was eliminated by additional RF application(s) until any dormant conduction was not observed. A repeat procedure was strongly recommended for the patients with documented recurrent atrial tachyarrhythmia.

**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 3-month blanking period. Patients with palpitations were encouraged to use an event recorder. Recurrence was defined according to the patient’s symptoms, and if arrhythmia lasted >30 seconds, it was documented. A repeat procedure was strongly recommended for the patients with documented recurrent atrial tachyarrhythmia.

**Statistical Analysis**

Continuous data are expressed as mean±SD for normally distributed variables and were compared using Student t test. Categorical variables were compared using the χ² test. A P value of <0.05 indicated statistical significance. Single variable logistic regression analysis was used to determine the association between preprocedural factors and arrhythmogenic SVC. The following patient variables were evaluated in association with arrhythmogenic SVC: age, sex, presence of structural heart disease, hypertension, AF type, LA diameter, and left ventricular ejection fraction.

**Results**

**Clinical Characteristics**

The clinical characteristics of patients with and without arrhythmogenic SVC are shown in Table 1. On univariate
analysis, hypertension (hazard ratio=0.40; 95% confidence interval, 0.18–0.80; \(P=0.015\)) and persistent AF (hazard ratio=0.38; 95% confidence interval, 0.13–0.89; \(P=0.045\)) were significantly less frequent in patients with arrhythmogenic SVC than those without (Table 1).

The clinical characteristics of patients in whom ATP test was undertaken are shown in Table 2. The preprocedural cardiac computer tomography showed normal anatomy of PVs except left common PV in 3 (7.0%) patients and 3 right PVs in 3 (7.0%) patients. One (2.3%) patient had coronary artery disease. Successful PVAI was achieved in all patients at the index procedure. In total, 20 (46.5%) and 5 (11.6%) patients underwent second and third procedure for recurrent atrial tachyarrhythmias.

**Arrhythmogenicity of Thoracic Veins**

The arrhythmogenicity of SVC was identified at the index procedure in 34 (79.1%) patients and at the repeat procedure in 9 (20.9%) patients (7 at the second procedure and 2 at the third procedure) during follow-up of mean 18.3±20.7 months (Figure 3). Therefore, SVC isolation was performed in 34 patients at the index, 7 patients at the second, and 2 patients at the third ablation procedure. No complications were observed except transient right phrenic nerve palsy in 1 (2.3%) patient during the procedure, which recovered within a month. AF initiation from SVC was observed in 40 (93.0%) patients, and repetitive PACs/PAC salvos originating from the SVC were observed in the rest of patients. Among 40 patients, AF originated spontaneously and under isoproterenol infusion from the SVC during the procedure in 30 (75.0%) patients; however, AF initiated immediately after ATP injection in 10 (25.0%) patients. A persistent tachycardia confined to the SVC was recorded after its electric isolation in 13 (30.2%) patients.

An AF trigger was identified in the left veins in 14 of 43 (32.6%) patients (superior 8, inferior 4, common 2) and in the right veins in 10 of 43 (23.3%) patients (superior 8, inferior 2). Twenty-two (51.2%) patients had arrhythmogenic SVC alone.

**ATP Test for Arrhythmogenic SVC**

ATP test was undertaken after the SVC isolation in 36 (83.7%) and 15 (34.9%) patients at acute phase (in the same session as SVC isolation) and at chronic phase (in the different session from SVC isolation), respectively.

SVC reconnection via 1 conduction gap was provoked by ATP test in 7 (19.4%) patients at acute phase (transiently in 5 [13.9%] and persistently in 2 [5.6%] patients). All conduction gaps were successfully closed by additional RF applications. In 1 patient, transient regular SVC tachycardia was provoked without SVC reconnection (Figure 4). In 2 patients, ATP test provoked transient SVC reconnection which resulted in SVC fibrillation.

At the index procedure, ATP test was undertaken in 31 of 34 patients who underwent SVC isolation. Dormant SVC,
left ipsilateral and right ipsilateral PVs were provoked in 6 (19.4%), 6 (19.4%), and 4 (12.4%) patients, respectively ($P=0.73$).

At median 4.0 (2.25–7.5) months after SVC isolation, SVC reconnection was revaluated in 15 (34.9%) patients. Thoracic vein reconnection was observed in ≥1 vein in all patients. SVC and PV reconnection was observed in 12 (80.0%; Figure 5) and 10 (66.7%) patients, respectively. SVC was successfully reisolated in all 12 patients with SVC reconnection at baseline. Among the 12 patients, SVC reconnection via 1 conduction gap was provoked by ATP test after its reisolation in 1 (8.3%) patient. Among 3 (20%) patients without SVC reconnection at baseline, SVC reconnection was provoked by ATP test at chronic phase in 1 patient. In the patient, ATP-exposed SVC reconnection resulted in AF. In another patient, ATP provoked transient SVC fibrillation without any SVC reconnection (Figure 6). In this case, ATP injection had resulted in the initiation of AF from SVC at the index procedure 5 years before the second procedure.

Among 12 patients who were subjected to SVC reisolation at repeat procedure, 1 (8.3%) underwent third ablation procedure 24 months after the second procedure. SVC and PV reconnection was again observed and the conduction gap was closed by RF applications.

Thirty-nine (90.7%) of 43 patients were free from any atrial tachyarrhythmias without antiarrhythmic drugs (mean, 12.7±9.7 months) after the last ablation procedure (mean, 1.58 procedures; total, 68 ablation procedures).

### Discussion

#### Major Findings

To our knowledge, this is the first study to investigate the impact of ATP injection on arrhythmogenic SVC in the context of AF ablation. Following are its important findings. First, ATP test provokes SVC reconnection after electric isolation much like PVs. Second, ATP test provokes SVC to trigger AF in 25% of patients with arrhythmogenic SVC, which can aid in identification of arrhythmogenic SVC during the procedure. Third, the arrhythmogenicity of SVC is not rarely observed during the repeat procedure for recurrent atrial tachyarrhythmias. Fourth, the SVC dormant conduction could be exposed not only at the acute phase but also at the chronic phase.

#### Arrhythmogenic SVC

The SVC has been described as one of the most common sources of non-PV triggers.\textsuperscript{4,5} Histological findings show that atrial myocardial sleeves extend into SVC for up to average 13.7±13.9 mm.\textsuperscript{23,24} Arruda et al.\textsuperscript{25} reported 12% incidence of SVC triggers in a cohort of 190 AF patients by administrating isoproterenol during the procedure. Higuchi et al.\textsuperscript{26} demonstrated long myocardial sleeves measuring >30 mm and large SVC potentials with amplitude >1.0 mV in patients wherein AF was triggered from the SVC. Electric SVC isolation is an established therapy for arrhythmogenic SVCs.\textsuperscript{5} Although empirical SVC isolation in addition to PVAI improves the outcome of AF ablation in patients with paroxysmal AF is under debate.\textsuperscript{25} SVC isolation is essential in patients with arrhythmogenic SVC.
Thoracic Vein Reconnection

It is well known that recurrences after AF ablation are very often associated with PV reconnections. The most convincing evidence for the crucial role of successful PV-LA disconnection in curing AF comes from reports that describe a dramatic difference in the PV reconnection rate between patients cured of AF and those with recurrences. Repeat procedures to ensure PV isolation significantly improve long-term outcomes in patients who have recurrent AF. However, it is well recognized that achieving durable PV isolation is difficult using current technology.

SVC reconnection after SVC isolation is also frequently observed at repeat ablation procedure. In our series, reconnection of SVC was associated with the recurrent atrial tachyarrhythmias in 80% of the patients. Delivering higher RF energy for durable SVC isolation has a potential risk of phrenic nerve injury. The use of provocative measures, such as ATP, might be useful by increasing the detection of acute SVC reconnection. Our study showed that SVC dormancy can be exposed by ATP-infusion test at both index and repeat procedure.

Adenosine/ATP Test

Although adenosine/ATP test has been used for identification of dormant PV conduction at the index procedure after electric isolation, the clinical implications of targeting dormant PVs by additional ablation have not been proven and remain to be tested in a prospective, randomized manner. Datino et al elegantly showed that adenosine acutely restores PV-LA conduction by hyperpolarizing PV cells and thereby enhancing Na+ current availability. The difference between dormant and nondormant veins lies primarily in the degree of RF-induced depolarization. Nondormant PVs are depolarized more severely than dormant veins, so that even with adenosine-induced hyperpolarization, their resting membrane potentials remain at values higher than the threshold for restoring excitability. Recent article has reported that similar dormancy was also observed at the cavo-tricuspid isthmus after achievement of linear conduction block. Considering the similarities between SVC and PV, the mechanism of dormant SVC reconnection in this study may be similar to that of dormant PV conduction.

Another use of ATP test in the context of AF ablation is to provoke atrial tachyarrhythmias during the procedure. Isoproterenol is widely used to identify AF triggers in the vast majority of laboratories; however, it usually provokes catecholamine-dependent atrial tachyarrhythmias. Adenosine is a purine nucleoside closely related to adenosine-5′-triphosphate important in multiple biochemical processes. Both exert a transient negative chronotropic and dromotropic response on the sinoatrial and atrioventricular nodes. In our series, AF-triggering SVC was provoked by ATP injection in 25% of the patients, which was the clue to identify the arrhythmogenicity. As this study has shown, the arrhythmogenicity was
identified at repeat procedure in 20.9% of the patients, which suggested that it is not always easy to identify the arrhythmogenic SVC at index AF ablation procedure.

Study Limitations
First, this study cannot prove the clinical use of ATP test on arrhythmogenic SVC. A randomized prospective trial is necessary to answer this question. However, such a study seems to be difficult because the majority of the patients with arrhythmogenic SVC have arrhythmogenic PVs, as well and the PV reconnection might impact the clinical outcome.

Conclusions
Dormant SVC conduction is exposed by ATP test at acute and chronic phase after electric isolation of the arrhythmogenic SVC. ATP can provoke SVC to trigger AF, thereby helping identification of arrhythmogenic SVC during the procedure. In the context of AF ablation, ATP test can potentially improve strategic outcomes.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Superior vena cava (SVC) has been established as one of the important sources of atrial fibrillation, and the electric isolation is the standard ablation strategy for the arrhythmogenic SVC. Adenosine/ATP test has been reported to be a useful to identify the dormancy after pulmonary vein isolation at acute and chronic phases. However, the clinical impact of ATP on arrhythmogenic SVC has not been evaluated. The present study has demonstrated that (1) dormant conduction between an arrhythmogenic SVC and the right atrium could be exposed by ATP administration both immediately and late after isolation; (2) ATP provoked SVC to trigger atrial fibrillation in 25% of patients with arrhythmogenic SVC, which could aid in identification of arrhythmogenic SVC during the procedure; and (3) the arrhythmogenicity of SVC was not rarely observed during the repeat procedure for recurrent atrial tachyarrhythmias. Thereby, in the context of atrial fibrillation ablation, ATP test potentially improves strategic outcomes.
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