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

Running title: Miyazaki et al.; ATP injection for arrhythmogenic SVC

Shinsuke Miyazaki, MD1; Hiroshi Taniguchi, MD1; Yuki Komatsu, MD1; Takashi Uchiyama, MD1; Shigeki Kusa, MD1; Hiroaki Nakamura, MD1; Hitoshi Hachiya, MD1; Kenzo Hirao, MD2; Yoshito Iesaka, MD1

1Cardiovascular Center, Tsuchiura Kyodo Hospital, Tsuchiura, Ibaraki; 2Heart Rhythm Center, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence:
Shinsuke Miyazaki, MD.
Cardiology Division, Cardiovascular Center
Tsuchiura Kyodo Hospital
11-7 Manabeshin-machi, Tsuchiura
Ibaraki 300-0053, Japan
Tel: +81 29 823 3111
Fax: +81 29 826 2411
E-mail: mshinsuke@k3.dion.ne.jp

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Abstract

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

**Methods and Results** - 43 patients (59 ± 11 years; 32 males) who underwent ATP test for arrhythmogenic SVC after the electrical isolation at either initial procedure or repeat procedure were included. PV antrum isolation was performed at index procedure in all. SVC was isolated following identifying the arrhythmogenicity at index and repeat AF ablation procedure in 34 (79.1%) and 9 (20.9%) patients, respectively. AF originated from the SVC spontaneously and/or 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 following electrical isolation in 13 (30.2%) patients. SVC reconnection was provoked by ATP test in 7/36 (19.4%) patients at acute phase. At median 4.0 [2.25-7.5] months after SVC isolation, reconnection was observed in 12/15 (80.0%) patients at repeat procedure. Among 12 patients with reconnection at baseline, SVC reconnection was provoked by ATP test following re-isolation 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**: superior vena cava; adenosine-5'-triphosphate; dormant conduction; catheter ablation; atrial fibrillation
Introduction
Since it was reported that paroxysmal atrial fibrillation (AF) is most often triggered by the sources inside the pulmonary veins (PVs), radiofrequency (RF) catheter ablation of AF is increasingly performed. Non-PV foci, such as superior vena cava (SVC) have also been established as one of the important sources of AF. Electrical thoracic vein isolation is an established therapy for AF, however, thoracic vein reconnection, including PV and SVC, 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 that leaves damaged but viable muscle sleeves that can recover, and adenosine/adenosine triphosphate (ATP) test has been reported to be a useful to identify the dormancy after PV isolation at acute and chronic phases. However, the clinical impact of adenosine/ATP injection on SVC reconnection has not been evaluated. The objectives of this study are to investigate the clinical impact of ATP injection on arrhythmogenic SVC in the context of AF ablation.

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; 32 males) who underwent ATP test for arrhythmogenic SVC following the isolation at either initial procedure or repeat procedure were further analyzed. All 43 patients underwent PV antrum isolation (PVAI) 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/or repetitive 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. All patients gave written informed consent for participation in the study.

Mapping and Ablation Protocol

All antiarrhythmic drugs were discontinued for at least five half-lives prior to the procedure. All patients were effectively anticoagulated for >1 month before the procedure. Transesophageal echocardiography was performed to exclude atrial thrombi. An enhanced cardiac computer tomography (CT) was performed for the evaluation of relevant cardiac anatomy before the procedure in all patients. The surface electrocardiogram (ECG) and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (LabSystem PRO, Bard Electrophysiology, Lowell, MA, USA). The bipolar electrograms were filtered from 30 to 500 Hz. A 7-F 14 pole two site mapping catheter (Irvine Biomedical Inc., Irvin, CA, USA) was inserted through the right jugular vein and positioned in the coronary sinus (CS) for pacing and internal AF cardioversion. It enabled continuous monitoring of CS and SVC-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, two long sheaths (SL0, AF Division, St. Jude Medical, Minneapolis, MN, USA) 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 following the transseptal puncture, and heparinized saline was additionally infused to maintain the activated clotting time at 250–350 s. Two circular mapping catheters (Lasso, Biosense Webster, Diamond Bar, CA, USA) were placed in the superior and inferior PVs, and the left- and right-sided ipsilateral PVs were circumferentially and extensively ablated guided by 3-D mapping system (CARTO3, Biosense Webster). Posteriorly, ablation was performed anatomically in the left atrium (LA), ~1-3 cm from the PV ostia. Anteriorly, ablation was performed on edge of the left PVs guided by earliest PV potential. 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. RF current was delivered point-by-point with 3.5 mm externally irrigated-tip quadripolar ablation catheter (Thermocool, Biosense-Webster, Diamond Bar, CA) with power up to 35W, target temperature ≤ 38°C and irrigation rate of 30 mL/min. The power was limited to 20W 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 exposed by repeat ATP test.

SVC Isolation

If the arrhythmogenicity of SVC was suspected during the procedure, we placed 2 or 3 circular mapping catheters in SVC and PV(s) to identify the arrhythmogenic vein (Fig. 1). At the index procedure, we administered ATP at least 2 times and isoproterenol infusion after PVAI in all
cases. If AF persisted during the procedure, we tried to identify the AF trigger following internal cardioversion. At the repeat procedure, we undertook the same protocol as during the index procedure. Then, we tried to induce AF by programmed stimulation. If the induced AF persisted, we tried to identify the AF trigger following internal cardioversion.

When the arrhythmogenicity of SVC was identified during the procedure, SVC isolation was performed during pacing from high right atrium (RA). Guided by SVC angiography, the circular mapping catheter was placed at the level of the lower border of the pulmonary artery above the SVC-RA junction. During sinus rhythm, the SVC potentials were fused with the local RA signals necessitating ablation during high RA pacing. RF energy was delivered point-by-point for 30 seconds each using a 4 mm tip non-irrigated catheter in a temperature-controlled mode with maximum temperature set at 50°C and maximum power at 35W. Before RF delivery, high output pacing (10 mA) was performed at every site and if diaphragmatic stimulation was observed, ablation was avoided locally to prevent phrenic nerve injury. The endpoint of ablation was to eliminate all SVC potentials on the mapping catheter.

A 30 mg bolus of ATP was injected to unmask dormant SVC conduction (Fig. 2), and any gap responsible for dormant conduction was eliminated by additional RF application(s).

Follow-Up

Patients underwent continuous, in-hospital ECG monitoring for 3 days following 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 h 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/or if arrhythmia lasting longer than 30 seconds was
documented. A repeat procedure was strongly recommended for the patients with documented recurrent atrial tachyarrhythmia.

**Statistical Analysis**

Continuous data are expressed as mean ± standard deviation for normally distributed variables, and were compared using Student’s t-test. Categorical variables were compared using the chi-square test. A probability value of p<0.05 indicated statistical significance. Single variable logistic regression analysis was used to determine the association between pre-procedural 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 pre-procedural cardiac CT 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 (Fig. 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/or 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 following its electrical isolation in 13 (30.2 %) patients.

An AF-trigger was identified in the left veins in 14/43 (32.6 %) patients (superior 8, inferior 4, common 2) and in the right veins in 10/43 (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 one 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 (Fig. 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 at least one vein in all patients. SVC and PV reconnection was observed in 12 (80.0 %) (Fig. 5) and 10 (66.7 %) patients, respectively. SVC was successfully re-isolated in all 12 patients with SVC reconnection at baseline. Among the 12 patients, SVC reconnection via one conduction gap was provoked by ATP test following its re-isolation 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 (Fig. 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 re-isolation 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 following electrical isolation as like PVs. Second, ATP test provokes SVC to trigger AF in 25% of patients with arrhythmogenic SVC, which can aid 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. Histological findings show that atrial myocardial sleeves extend into SVC for up to average 13.7 ± 13.9 mm. Arruda et al. reported 12% incidence of SVC triggers in a cohort of 190 AF patients by administrating isoproterenol during the procedure. Higuchi et al. 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. Electrical SVC isolation is an established therapy for arrhythmogenic SVCS. While empiric SVC isolation in addition to PVAI improves the outcome of AF ablation in patients with paroxysmal AF is under debate, 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.\textsuperscript{7} 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.\textsuperscript{10} 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.\textsuperscript{22} 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.

\textit{Adenosine/ATP Test}

Although adenosine/ATP test has been used for identification of dormant PV conduction at the index procedure after electrical isolation,\textsuperscript{12-14} the clinical implications of targeting dormant PVs by additional ablation have not been proven and remain to be tested in a prospective, randomized manner.\textsuperscript{27} Datino and their group elegantly showed that adenosine acutely restores PV-LA conduction by hyperpolarizing PV cells and thereby enhancing \(Na^+\) current availability.\textsuperscript{11} The difference between dormant and non-dormant veins lies primarily in the degree of RF-induced depolarization. Non-dormant 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 paper has reported that similar dormancy was also observed at the cavo-tricuspid isthmus after achievement of linear conduction block.\textsuperscript{28} 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 utility 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 cathecolamine-dependent atrial tachyarrhythmias. Adenosine is a purine nucleoside closely related to adenosine-5’-triphosphate important in multiple biochemical processes.29 Both exert a transient negative chronotropic and dromotropic response on the sino-atrial and atrio-ventricular 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 utility of ATP test on arrhythmogenic SVCs. 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 SVCs have arrhythmogenic PVs, as well and the PV reconnection might impact the clinical outcome.

Conclusion
Dormant SVC conduction is exposed by ATP test at acute and chronic phase following electrical 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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Conflict of Interest Disclosures: None.

References:


| Table 1. Clinical characteristics of patients with and without arrhythmogenic SVC |
|---------------------------------|-----------------|-----------------|---|
|                                | SVC-group       | non-SVC group   | P-value  |
| N                               | 46              | 910             |   |
| Age (years)                     | 58.8 ± 10.6     | 60.3 ± 10.5     | 0.38 |
| Men                             | 34 (73.9 %)     | 664 (73.0 %)    | 0.89 |
| Hypertension                    | 9 (19.6 %)      | 345 (37.9 %)    | 0.015|
| Structural heart disease        | 1 (2.2 %)       | 101 (11.1 %)    | 0.056|
| Paroxysmal AF                   | 41 (89.1 %)     | 690 (75.8 %)    | 0.045|
| Left atrial diameter (mm)       | 38.7 ± 5.8      | 39.3 ± 6.0      | 0.57 |
| Left ventricular ejection fraction (%) | 66.5 ± 6.8     | 65.8 ± 6.9      | 0.69 |
Table 2. Clinical characteristics of patients in whom ATP test was undertaken

<table>
<thead>
<tr>
<th>N</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.6 ± 10.6</td>
</tr>
<tr>
<td>Men</td>
<td>32 (74.4 %)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (18.6 %)</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>1 (2.3 %)</td>
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<tr>
<td>Type of AF</td>
<td></td>
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<tr>
<td>Paroxysmal AF</td>
<td>39 (90.7 %)</td>
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<tr>
<td>Persistent AF</td>
<td>4 (9.3 %)</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>38.4 ± 5.7</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>66.9 ± 6.7</td>
</tr>
</tbody>
</table>

Figure Legends:

**Figure 1.** Two circular mapping catheters are placed in SVC and right superior PV for simultaneous mapping to identify AF trigger precisely. AF initiated from right superior PV, then initiated from SVC. SVC: superior vena cava, RA: right atrium, SVC-RA: SVC-RA junction, RSPV: right superior PV, CS: coronary sinus, d: distal, p: proximal.

**Figure 2.** A circular mapping catheter is placed in the SVC. Following electrical SVC isolation, regular dissociated activity is observed in the SVC. ATP test provoked transient AV block (asterisk) during sequential atrial (high right atrium) and ventricular (right ventricular apex) pacing, followed by disappearance of the dissociated activity without any SVC reconnection. HRA: high right atrium, RVA: right ventricular apex.
Figure 3. The summary of the results is shown in the flow chart.

Figure 4. A circular mapping catheter is placed in the SVC. Following electrical SVC isolation at index procedure, ATP test provoked transient regular SVC tachycardia without SVC reconnection at the acute phase.

Figure 5. A circular mapping catheter is placed in SVC. At the second procedure, SVC reconnection was observed at baseline during pacing from the high right atrium (A) and sinus rhythm (B). SVC reconnection was eliminated by a RF application during pacing from the high right atrium (C).

Figure 6. A circular mapping catheter is placed in SVC. SVC reconnection was not observed at baseline of second procedure, however transient confined SVC tachycardia was provoked (asterisk) by ATP injection during sequential atrial (right atrium) and ventricular pacing (right ventricular apex) without any SVC reconnection. It is worth knowing that SVC triggered AF had been identified at the index procedure in this patient.
ATP test for arrhythmogenic SVC: N=43
SVC isolation at 1st procedure: N=34 (79 %)
2nd procedure: N=7 (16 %)
3rd procedure: N=2 (5 %)

Acute phase: N=36 (same session as SVC isolation)

ATP-Reconnection (+) N=7 (19 %)
- Transient N=5
- Persistent N=2

ATP-Reconnection (-) N=29 (81 %)

Chronic phase: N=15 (different session from SVC isolation)

SVC reconnection at baseline: N=12 (80 %)

No reconnection at baseline: N=3 (20 %)

After re-isolation

ATP-Reconnection (+) N=1 (8 %)
ATP-Reconnection (-) N=11 (92 %)
ATP-Reconnection (+) N=1 (33 %)
ATP-Reconnection (-) N=2 (67 %)
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