Adenosine-Provoked Atrial Fibrillation Originating From Non–Pulmonary Vein Foci
The Clinical Significance and Outcome After Catheter Ablation

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CME Objective: The existence and location of non-pulmonary vein foci revealed by adenosine testing has a prognostic value in the clinical outcome after pulmonary vein isolation for paroxysmal atrial fibrillation.

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ABSTRACT

OBJECTIVES The goal of this study was to systematically investigate the incidence and clinical significance of non-pulmonary vein (PV) foci revealed by adenosine/adenosine triphosphate (ATP) testing during atrial fibrillation (AF) ablation.

BACKGROUND ATP is reported to provoke AF.

METHODS A total of 464 patients with consecutive paroxysmal AF undergoing ATP testing after PV antrum isolation were included.

RESULTS AF originating from non-PV foci was provoked in 26 (5.6%) total patients during first (n = 20) or repeat (n = 8) ablation procedures. Dormant PV conduction was also revealed by ATP testing in 6 patients. Non-PV foci were located in the superior vena cava (SVC) (i.e., the SVC group) and atria (i.e., the atria group) in 10 and 18 (9 each in the right and left atria) patients, respectively. In the multivariable analysis, being female was the sole independent predictor of ATP-provoked AF originating from non-PV foci (hazard ratio [HR]: 2.52 [95% confidence interval (CI): 1.069 to 5.929]; p = 0.034). After additional ablation targeting non-PV foci, freedom from recurrent AF after the last procedure was similar between the SVC group and patients without ATP-provoked AF but was significantly lower in the atria group than in others (p = 0.0008). Atria group membership (HR: 3.725 [95% CI: 1.692 to 8.199]; p = 0.001) and being female (HR: 1.538 [95% CI: 1.189 to 1.989]; p = 0.001) were significant independent predictors associated with recurrence after the last procedure in the multivariable Cox regression model.

CONCLUSIONS ATP provoked AF originating from non-PV foci under isoproterenol in 5.6% of patients undergoing paroxysmal AF ablation. ATP testing might be useful for identifying and eliminating AF originating from the SVC. The atria group was associated with a poor outcome after the last procedure despite efforts to eliminate non-PV foci. (J Am Coll Cardiol EP 2015;1:127–35) © 2015 by the American College of Cardiology Foundation.

METHODS

STUDY POPULATION. The study consisted of 464 consecutive patients who underwent ATP testing after a PVAI during the initial ablation procedure for paroxysmal AF at our hospital. AF was classified according to the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Association 2012 Consensus Statement on Catheter and Surgical Ablation of AF (3). All patients provided written informed consent.

MAPPING AND ABLATION PROTOCOL. Antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. Any atrial thrombi were excluded by using transesophageal echocardiography. The surface electrocardiogram and bipolar intracardiac electrograms were continuously monitored.
and the data stored on a computer-based digital recording system (LabSystem PRO, Bard Electrophysiology, Lowell, Massachusetts). The bipolar electrograms were filtered from 30 to 500 Hz. A 7-F, 20-pole, 3-site mapping catheter (BeeAT, Japan Life- line Co., Ltd., Tokyo, Japan) was inserted through the right jugular vein for pacing, recording, and internal cardioversion. The 4 proximal electrodes, 8 middle electrodes, and 8 distal electrodes were positioned in the superior vena cava (SVC), high right atrium (RA), and coronary sinus, respectively, throughout the procedure. The procedure was performed under minimal sedation with pentazocine and hydroxyzine pamoate.

The ablation was performed according to a strategy described previously (12,13). In brief, after a transseptal puncture, pulmonary venography during ventricular pacing and contrast esophagography were performed. Heparinized saline was infused to maintain the activated clotting time at 250 to 350 s. Ipsilateral PVs were circumferentially and extensively ablated by using a double-Lasso technique (Lasso, Biosense Webster, Inc., Diamond Bar, California) guided by a 3-dimensional mapping system (CARTO 3, Biosense Webster, Inc.). The endpoint was achievement of bidirectional conduction block between the left atrial appendage or septum close to the trans-septal hole depending on the coronary sinus—superior vena cava (SVC) = superior vena cava

AF = atrial fibrillation
ATP = adenosine triphosphate
CI = confidence interval
GP = ganglionic plexus
HR = hazard ratio
LA = left atrium
PV = pulmonary vein
PVAI = pulmonary vein antrum isolation
RA = right atrium
RF = radiofrequency
SVC = superior vena cava

**Follow-up.** The patients underwent continuous, in-hospital electrocardiogram monitoring for 2 to 4 days after the procedure. The first outpatient clinic visit was 3 weeks’ post-procedure. Subsequent follow-up procedures at the outset, the PVs were checked with a circumferential catheter, and any reconnected PVs were reisolated. ATP tests were undertaken with the same protocol as during the index procedure even in cases without any PV reconnections at baseline (14). When an arrhythmogenic SVC was identified during the procedure (Figure 1), an electrical isolation was performed. The ablation endpoint was elimination of all SVC potentials recorded on the mapping catheter (15). The cavotricuspid isthmus was also ablated to create bidirectional conduction block if common atrial flutter was identified.

**FIGURE 1** Adenosine Triphosphate Provoked Atrial Fibrillation Originating From Superior Vena Cava

Two circular mapping catheters were placed in the ipsilateral left pulmonary veins. After the completion of the pulmonary vein antrum isolation, an adenosine/adenosine triphosphate test was performed during sequential atrial (coronary sinus [CS]) and ventricular (right ventricular apex [RVA]) pacing. Atrial fibrillation was initiated from the superior vena cava (SVC) (red arrow) after atrioventricular block. LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein.

The cavity of the isthmus was also ablated to create bidirectional conduction block if common atrial flutter was identified.

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visits consisted of clinical interviews, electrocardiograms, and 24-h Holter monitoring every 3 months at our cardiology clinic. No antiarrhythmic drugs were prescribed after the procedure. Patients with palpitations were encouraged to use patient-activated event recorders for 30 consecutive days. For the detection of any asymptomatic events, an external loop recorder was used (SpiderFlash, Sorin Group, Clamart, France), which enabled the automatic detection of any atrial tachyarrhythmias for 14 consecutive days (16). Recurrence was defined according to the patient’s symptoms and/or if an arrhythmia lasting >30 s was documented.

**Statistical analysis.** Continuous data are expressed as the mean ± SD for normally distributed variables or as the median (25th to 75th percentiles) for nonnormally distributed variables, and they were compared by using a Student t test or Mann-Whitney U test, respectively. Categorical variables were compared by using the chi-square test. All parameters with a significance of <0.2 in the univariable analysis were entered into a multiple logistic regression analysis. The multivariable Cox method was used to determine the predictors of recurrent arrhythmias. Variables whose univariable analyses had p values <0.05 were included in the multivariable Cox regression model. A Kaplan-Meier analysis was used to determine the percentage of patients free from recurrence. The difference in the arrhythmia-free survival was evaluated by using the log-rank test. The proportional hazards assumption was investigated graphically, with a test based on Schoenfeld residuals.

The following variables were evaluated in association with being arrhythmia-free after the procedure: age, sex, body mass index, presence of structural heart disease, hypertension, left atrial diameter, left ventricular ejection fraction, CHADS2 score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus [1 point for presence of each], and stroke/transient ischemic attack [2 points]), CHA2DS2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category score), pro-B-type natriuretic peptide level, high-sensitivity C-reactive protein level, estimated glomerular filtration rate, and ATP-provoked AF. A probability value of p < 0.05 indicated statistical significance.

**Results**

**Prevalence and clinical characteristics.** A successful PVAI was achieved in all 464 study patients, and dormant PV conduction was revealed by ATP testing in 164 (35.3%) during the initial procedure. Among the 464 first and 115 second ablation procedures, AF originating from non-PV foci was provoked repeatedly by ATP injections in 20 (4.3%) and 8 (6.9%) patients, respectively. AF was provoked during both the first and second procedures in 2 patients. Therefore, in total, ATP-provoked AF originating from non-PV foci was observed in 26 (5.6%) patients. AF was initiated from non-PV foci spontaneously, during an isoproterenol infusion, and after electrical cardioversion in 7, 3, and 2 other patients, respectively. The clinical characteristics of the patients with and without ATP-provoked AF are shown in Table 1.

In the univariable analysis, a younger age, female sex, and higher glomerular filtration rate showed a trend toward being associated with ATP-provoked AF originating from non-PV foci. In the multivariable analysis, female sex (hazard ratio [HR]: 2.52 [95% confidence interval (CI): 1.069 to 5.929]; p = 0.034) was the sole independent pre-procedural predictor of ATP-provoked AF originating from non-PV foci.

**Response to the ATP injection during the initial procedure.** Among the 20 patients in whom AF originating from non-PV foci was provoked by ATP injections during the initial procedure, AF terminated spontaneously at a median of 180 s (40 to 595 s) after initiation in 9 (45.0%) patients; it persisted and required electrical cardioversion to be terminated in the remaining 11 (55.0%) patients. Immediate recurrent AF after cardioversion was observed in 4 (20.0%) patients and was initiated from the SVC in all patients. AF was provoked before, during, and following the occurrence of AV block after ATP injections in 3 (15.0%), 16 (80.0%), and 1 (5.0%) patients, respectively. An AF trigger was identified in the SVC, RA, and LA in 9 (45.0%), 5 (25.0%), and 6 (30.0%) patients, respectively (Figure 2). In patients with AF originating from the SVC, an electrical SVC isolation was successfully achieved in all patients. In 11 (55.0%) patients with AF originating from the atria, focal ablation targeting the non-PV foci was added, and a subsequent repeat ATP test did not provoke any AF except in 1 patient. A transient PV reconnection was observed according to an ATP test in 6 (30.0%) patients at the right-sided, left-sided, and bilateral ipsilateral PVs in 1, 3, and 2 patients, respectively. These transient PV reconnections did not lead to the initiation of AF.

After the initial ablation procedure, 55.3% of the patients were free from any recurrent arrhythmias without any antiarrhythmic drugs at 1 year. There was
no significant difference in the freedom from recurrent arrhythmias after the initial procedure between the patients with and without ATP-provoked AF (p = 0.61) (Figure 3).

RESPONSE TO THE ATP INJECTION DURING THE REPEAT PROCEDURE. Among 115 patients undergoing a second procedure, PV reconnections were observed in 98 (85.2%) patients. Among 8 patients in whom AF was provoked by an ATP injection during the repeat procedure, AF terminated spontaneously at a median of 75 s (30 to 300 s) after the initiation in 4 (50.0%) patients; it persisted and required electrical cardioversion to terminate it in the remaining 4 (50.0%) patients. Immediate recurrent AF after cardioversion was observed in 3 (37.5%) patients, and AF initiated from the SVC, RA, and LA in 1 each. AF was provoked during AV block after an ATP injection in all patients. An AF trigger was identified in the SVC, RA, and LA in 1 (12.5%), 4 (50.0%), and 3 (37.5%) patients, respectively (Figure 2). In the patient with AF originating from the SVC, an electrical SVC isolation was successfully achieved. In 7 patients with AF originating from the atria, focal ablation targeting the non-PV foci eliminated the ATP-provoked AF in 5 (62.5%) but not in 3 (37.5%) patients. No PV reconnections were provoked in any of the patients with the ATP test.

After the second procedure, 50% of the patients were free from recurrent arrhythmias without any antiarrhythmic drugs at 1 year. Among the 4 patients with recurrent arrhythmias, the ATP-provoked AF was eliminated in 2 but not in the remaining 2 patients.

CLINICAL OUTCOME IN PATIENTS WITH ATP-PROVOKED AF ORIGINATING FROM NON-PV FOCI. In all 26 patients, the reproducibility of ATP-provoked AF was confirmed, and a mean of 4.0 ± 3.2 APT tests per procedure were performed. No multiple non-PV foci were observed in any patients. Freedom from recurrent AF after the last procedure was significantly lower in the 26 patients with ATP-provoked AF.

### Table 1: Clinical Characteristics of Patients With and Without ATP-Provoked AF

<table>
<thead>
<tr>
<th></th>
<th>ATP-AF (+) (n = 26 [5.6%])</th>
<th>ATP-AF (-) (n = 438 [94.4%])</th>
<th>Univariable p Value</th>
<th>Multivariable p Value</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>58.7 ± 12.8</td>
<td>62.6 ± 10.8</td>
<td>0.083</td>
<td>0.136</td>
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<tr>
<td>Female</td>
<td>11 (42.3)</td>
<td>121 (27.6)</td>
<td>0.107</td>
<td>0.034</td>
<td>2.52</td>
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<td>SHD</td>
<td>1 (3.9)</td>
<td>50 (11.4)</td>
<td>0.231</td>
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<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (57.7)</td>
<td>251 (57.3)</td>
<td>0.969</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.0 ± 3.8</td>
<td>24.3 ± 3.7</td>
<td>0.692</td>
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<td>CHADS₂ score</td>
<td>0.73 ± 0.96</td>
<td>0.79 ± 0.93</td>
<td>0.745</td>
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<tr>
<td>CHA₂DS₂-VASc score</td>
<td>1.54 ± 1.58</td>
<td>1.58 ± 1.38</td>
<td>0.889</td>
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<td></td>
</tr>
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<td>LA diameter, mm</td>
<td>39.9 ± 5.5</td>
<td>40.3 ± 5.8</td>
<td>0.724</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>65.5 ± 9.0</td>
<td>66.5 ± 7.0</td>
<td>0.476</td>
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<tr>
<td>proBNP, pg/ml</td>
<td>270 ± 356</td>
<td>332 ± 1,033</td>
<td>0.801</td>
<td></td>
<td></td>
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<tr>
<td>hs-CRP, mg/dL</td>
<td>0.17 ± 0.28</td>
<td>0.24 ± 0.81</td>
<td>0.662</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated GFR, ml/min</td>
<td>77.3 ± 17.8</td>
<td>71.1 ± 19.4</td>
<td>0.114</td>
<td>0.393</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

AF = atrial fibrillation; ATP = adenosine triphosphate; CHADS₂ score = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus (1 point for presence of each), and stroke/transient ischemic attack (2 points); CHA₂DS₂-VASc score = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; hs-CRP = high-sensitivity C-reactive protein; LA = left atrium; LV = left ventricular; proBNP = pro-B-type natriuretic peptide; SHD = structural heart disease.

FIGURE 2 Distribution of the Origins of ATP-Provoked AF

Non-pulmonary vein foci were identified along the crista terminalis (CT), septum, and close to the distal CS. AF = atrial fibrillation; ATP = adenosine triphosphate test; IVC = inferior vena cava; PW = posterior wall; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein; other abbreviations as in Figure 1.
originating from non-PV foci during either the initial or second procedure compared with those without ($p = 0.002$) (Figure 4A). However, when the patients with ATP-provoked AF were divided into 2 groups, including patients with AF originating from the SVC (i.e., the SVC group) and those with AF originating from the atria (i.e., the atria group), the freedom from recurrent AF after the last procedure was significantly lower in the atria group but similar in the SVC group compared with patients without ATP-provoked AF ($p = 0.0008$) (Figure 4B).

An increased age, higher CHA$_2$DS$_2$-VASc score, being female, and ATP-provoked AF originating from non-PV foci were correlated with a recurrence after the last procedure as identified by the univariable analysis, and being female (HR: 1.538 [95% CI: 1.189 to 1.989]; $p = 0.001$) and ATP-provoked AF originating from non-PV foci (HR: 3.328 [95% CI: 1.632 to 6.783]; $p = 0.001$) were the significant factors in the multivariable Cox regression model (Table 2). Further analysis revealed that the atria group was significantly associated with a recurrence after the last procedure (HR: 3.725 [95% CI: 1.692 to 8.199]; $p = 0.001$), but the SVC group was not ($p = 0.247$). Similarly, when analyzing the 115 patients undergoing repeat procedures, being female (HR: 2.595 [95% CI: 1.095 to 6.147]; $p = 0.030$) and ATP-provoked AF originating from non-PV foci (HR: 3.324 [95% CI: 1.284 to 8.603]; $p = 0.013$) were the significant factors associated with recurrence after the last procedure in the multivariable Cox regression model.

**DISCUSSION**

**MAJOR FINDINGS.** First, the ATP test under an isoproterenol infusion provoked AF originating from non-PV foci in 5.6% of patients undergoing paroxysmal AF ablation. Second, being female was the sole independent predictor of ATP-provoked AF originating from non-PV foci. Third, the SVC was the important source (38.2%) of non-PV foci, revealed by results of the ATP test, which can aid in the identification of an arrhythmogenic SVC during the procedure. Fourth, ATP-provoked AF originating from the atria was the independent predictor associated with a recurrence of arrhythmia after the last procedure.

**ADENOSINE/ATP TEST IN THE CONTEXT OF AF ABLATION.** The adenosine/ATP test has been used for the identification of the dormancy during the initial procedure after electrical isolation (8-10). A prospective study is ongoing to investigate the clinical implications of targeting dormant PVs by additional ablation (17). Datino et al. (18) showed that adenosine acutely restores the PV–LA conduction by hyperpolarizing the PV cells and thereby enhancing the Na$^+$ current availability. A similar dormancy was also reported in PVs during the chronic phase after
the isolation (14), at the cavotricuspid isthmus, after achievement of linear conduction block (19), at the SVC after isolation (20), presumably with a similar mechanism.

The ATP test is also useful for provoking AF during the procedure. Isoproterenol is widely used to identify AF triggers, and it usually provokes catecholamine-dependent arrhythmias. In the present study, additional ATP injections were used to identify non-PV foci. Recently, Tao et al. (21) reported that the ATP test facilitated the identification of arrhythmogenic PVs in patients with paroxysmal AF undergoing ablation. They showed that the majority of ATP-induced AF originated from the PVs. In contrast, ATP tests were undertaken after the PVAI in our large consecutive series, and the prevalence of ATP-provoked AF originating from non-PV foci was 5.6% with isoproterenol infusions.

The identification of an arrhythmogenic SVC is generally challenging despite electrical isolation being an established effective therapy (22). In our series, the SVC was the important source of non-PV foci revealed by ATP, and the ATP test aided in the identification of the arrhythmogenicity. A better clinical outcome can be expected in cases with an arrhythmogenic SVC because the complete elimination of the trigger is relatively easy by electrical isolation. In fact, the clinical outcome after the last procedure was similar in the SVC group and in those without ATP-provoked AF. Conversely, the clinical outcome was significantly poorer in the atria group. This finding might be explained by the difficulty in identifying the precise foci from a single earliest beat by using conventional mapping techniques and the low reproducibility of AF induction by the ATP test. Among the 8 patients in whom AF was provoked by the ATP test during the second procedure, 6 patients did not have any ATP-provoked AF during the initial procedure, presumably due to the variable autonomic tone during the time course and the impact of the PVAI on the autonomic tone. Recently, Zhang et al.

### TABLE 2 Factors Associated With Recurrent Arrhythmias After the Last Procedure

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariable p Value</th>
<th>Multivariable p Value</th>
</tr>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>0.001</td>
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<tr>
<td>Female</td>
<td>&lt;0.001</td>
<td>1.538</td>
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<tr>
<td>SHD</td>
<td>0.645</td>
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<tr>
<td>Hypertension</td>
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</tr>
<tr>
<td>Body mass index, kg/m²</td>
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<td>CHADS₂ score</td>
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<td>CHA₂DS₂-VASc score</td>
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<td>LA diameter, mm</td>
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<td>LV ejection fraction, %</td>
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<td>proBNP, pg/ml</td>
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<tr>
<td>hs-CRP, mg/dl</td>
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<td>Estimated GFR, ml/min</td>
<td>0.581</td>
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<tr>
<td>ATP-AF</td>
<td>0.004</td>
<td>3.328</td>
</tr>
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<td>ATP-AF from SVC</td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td>ATP-AF from atrium</td>
<td>0.001</td>
<td>3.725</td>
</tr>
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</table>

SVC = superior vena cava; other abbreviations as in Table 1.
MECHANISMS OF ATP-PROVOKED AF. Adenosine is a purine nucleoside closely related to adenosine-5'-triphosphate, which is important in multiple biochemical processes (24). Both exert transient negative chronotropic and dromotropic responses on the sinoatrial and atrioventricular nodes. It is well known that adenosine can induce AF in clinical practice (11), and previous studies have postulated that shortening of atrial action potential duration is the principal mechanism of adenosine-induced AF (25). In addition, adenosine has sympathoexcitatory effects mediated through a baroreflex activation and chemoreceptor stimulation (26).

Another hypothesis is the activation of the autonomic nervous system via the ganglionated plexus (GP). An injection of acetylcholine into the GP at the PV–LA junction has been shown to acutely result in the induction of spontaneous PV ectopy (27). The preferential role of the SVC-aorta GP in modulating the electrophysiological function of the SVC sleeves in canines has also been shown (28). Adenosine and acetylcholine act on identical receptor pathways to induce antiadrenergic effects, and hyperactivity of the SVC-aorta GP induced by direct injection of acetylcholine can lead to rapid firing from the SVC. Thus, adenosine can trigger vagally mediated AF.

The reason why ATP-provoked AF was identified more frequently in female patients is unclear from the present data. Previous large studies showed that the outcome after AF ablation was worse for female patients and speculated that non-PV foci were one of the causes of a higher recurrence rate (29,30). Differences in sex in cardiac autonomic regulation are well known (31). Given that an ATP injection has a strong influence on autonomic tone, it is possible that the impact of ATP on the arrhythmia inducibility has sex differences and that residual non-PV foci after PVAI are revealed more frequently in female patients.

STUDY LIMITATIONS. First, the study used a retrospective and nonrandomized design. Second, although non-PV foci were localized by using a number of multielectrode catheters, identification of precise non-PV foci is challenging because of the lack of a single-beat mapping system. Third, the pure impact of an ATP injection on non-PV foci could not be evaluated because the ATP test was undertaken under an isoproterenol infusion. The utility of the ATP test should be evaluated and compared with other approaches for identifying non-PV foci, such as isoproterenol infusions, in a prospective clinical trial. Fourth, the ATP test was not undertaken before the PVAI, and thus the impact on the PVs was not evaluated.

CONCLUSIONS

An ATP injection under an isoproterenol infusion provoked AF originating from non-PV foci in 5.6% of patients undergoing paroxysmal AF ablation. The SVC was the origin of 38.5% of the non-PV foci revealed by ATP, which aids in identifying an arrhythmogenic SVC. ATP-provoked AF originating from the atri is a significant independent predictor associated with recurrent arrhythmias after the last procedure.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Adenosine injection provoked AF originating from non-PV foci in 5.6% of patients undergoing paroxysmal AF ablation. The SVC was the origin of 38.5% of the non-PV foci revealed by adenosine, which aids in identifying an arrhythmogenic SVC. Moreover, adenosine-provoked AF originating from the atri was a significant independent predictor associated with recurrent arrhythmias after the last procedure.

TRANSLATIONAL OUTLOOK: The utility of the adenosine test should be evaluated and compared with other approaches for identifying non-PV foci, such as isoproterenol infusions, in a prospective clinical trial.
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KEY WORDS adenosine, adenosine triphosphate, atrial fibrillation, catheter ablation, non-pulmonary vein foci