Noninvasive Diagnosis of Dual AV Nodal Physiology in Patients With AV Nodal Reentrant Tachycardia by Adenosine Triphosphate Test

Yasuo Okumura,1 MD, Ichiro Watanabe,1 MD, Naohiro Oshikawa,1 MD, Riko Masaki,1 MD, Kimie Okubo,1 MD, Kenichi Hashimoto,1 MD, Tatsuya Kofune,1 MD, Takeshi Yamada,1 MD, Rie Wakita,1 MD, Yasuhiro Takagi,1 MD, Satoshi Saito,1 MD, Yukio Ozawa,1 MD, and Katsuo Kanmatsuse,1 MD

SUMMARY

Atrioventricular nodal reentrant tachycardia (AVNRT) is a relatively common paroxysmal supraventricular tachycardia. This study investigated whether adenosine-5’-triphosphate (ATP) injection during sinus rhythm might be useful in the noninvasive diagnosis of dual AV nodal pathways.

The study group consisted of 9 patients with slow/fast AVNRT and 11 control patients without antegrade dual AV nodal physiology (DAVNP). ATP (2.5 to 30 mg, in 2.5-mg increments) was injected during sinus rhythm until signs of DAVNP (≥ 50 msec increase or decrease in AH or PR interval in two consecutive beats) or ≥ second-degree AV block was observed. DAVNP was diagnosed by ATP test in all 9 patients with slow/fast AVNRT. DAVNP was observed by ATP test in 3 of the 11 control patients. Thus, the test had a sensitivity of 100% and specificity of 73%.

ATP test given during sinus rhythm is useful for identifying patients with dual AV nodal pathways who are prone to AVNRT. (Jpn Heart J 2003; 44: 655-666)

Key words: Dual atrioventricular nodal pathways, Adenosine-5’-triphosphate test, Supraventricular tachycardia

Atrioventricular nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT) are relatively common supraventricular tachycardias1) that can be cured with radiofrequency ablation. However, AVNRT and AVRT are both paroxysmal arrhythmias that may repeatedly elude clinical diagnosis. Patients with such arrhythmias often experience multiple episodes of rapid palpitations before a correct diagnosis is made. Adenosine-5’-triphosphate (ATP) is a highly effective drug for the termination of paroxysmal supraventricu-
lar tachycardia (PSVT). Less is known, however, about the effects of ATP injection during sinus rhythm in patients with PSVT. Because the refractory period of the antegrade fast pathway of the AV node is usually longer than that of the antegrade slow pathway, we speculated that ATP would affect these two pathways differently during sinus rhythm. We evaluated the effects of ATP injection during sinus rhythm in patients with typical AVNRT and compared them with those observed in a control group of patients without antegrade dual AV nodal physiology.

**METHODS**

**Patient population:** The study population consisted of 20 consecutive patients referred to the Department of Cardiology, Nihon University Hospital, for electrophysiological study (EPS) and radiofrequency ablation treatment for PSVT or paroxysmal atrial fibrillation. There were 7 men and 13 women ranging in age from 25-70 years with a mean of 46 years. None of the patients had a history of asthma, a known contraindication to ATP administration, or was treated with drugs known to interfere with ATP metabolism (eg, aminophylline, dipyridamole, benzodiazepines). All antiarrhythmic drugs were withdrawn five half lives before the study. Informed written consent was obtained from all patients and their families before inclusion in this study.

**Electrophysiological study:** Two 6F quadripolar electrode catheters and one hexapolar electrode catheter (Cordis-Webster, Diamond Bar, CA, USA) were introduced percutaneously through the right and left femoral veins and positioned in the right ventricular apex, high right atrium, and His bundle area, respectively. A 7F decapolar electrode catheter (Daig/St Jude Medical, Minnetonka, MN, USA) was introduced into the coronary sinus through the right internal jugular vein. Baseline EPS included the following protocols: 1) delivery of 1 to 3 extrastimuli during pacing from the right atrial appendage at two basic cycle lengths (750 and 600 msec or 600 and 450 msec) until the atrial refractory period was reached; 2) incremental high right atrium pacing until second-degree AV nodal conduction block occurred; 3) incremental rapid ventricular apical pacing up to the ventriculoatrial block cycle length; and 4) delivery of ≥ 2 ventricular extrastimuli during ventricular pacing at two basic cycle lengths (750 and 600 msec or 600 and 450 msec). If sustained tachycardia was not induced by use of these protocols, isoproterenol was administered in incremental doses until the basic sinus rhythm increased by ≥ 25%, and the stimulation protocol was repeated.

**Definitions:** Dual AV nodal physiology (DAVNP) was defined as a ≥ 50 msec increment in the A2H2 interval following a 10-msec decrement of the A1-A2 interval with a single atrial extrastimulus (A1). Absence of DAVNP was defined as the failure to demonstrate DAVNP until AV nodal refractoriness was reached.
**ATP test:** The effects of ATP on AV nodal conduction were evaluated during sinus rhythm. ATP (Adephos-Kowa Pharmaceutical Co., Japan) was injected through a right antecubital vein as a rapid bolus, followed by a 20-mL flush of saline, during continuous simultaneous 12-lead surface ECG and intracardiac electrogram recording. The initial dose of ATP was 2.5 mg. Repeated small doses (in 2.5-mg increments) were given at 1 to 2 minute intervals (after return of the sinus rate to the control value) to avoid the adverse effects of ATP until one of the following prospectively defined end points was observed: signs of DAVNP following ATP injection (see below) or second- or third-degree AV block. Once one of the study end points (signs of DAVNP or AV block) was achieved for a particular dose of ATP, the reproducibility of the test was assessed using an identical dose of ATP. If the second dose of ATP failed to achieve the same end point, a third dose of ATP was tested, and the definitive result taken for analysis was the one observed in 2 of the 3 ATP tests. The ATP test was performed after completion of the baseline diagnostic study. Whenever isoproterenol administration was used during the baseline study, the ATP test was performed after discontinuation of isoproterenol and return of the sinus rate to baseline. All patients with a sudden $\geq 50$-msec increment of their AH interval after ATP administration were correctly identified (by the presence of a similar increment in PR interval) by the investigators who looked only at surface leads. All instances of ATP-induced AV nodal echo beats were correctly identified from surface 12-lead ECGs with our prospectively defined criteria (a $> 70\%$ increment in P-P interval or appearance of retrograde P waves at the end of the QRS complex after a sinus beat conducted with a long RR interval).

**Definitions used in the ATP test:** Signs of DAVNP following ATP injection were considered to be present when at least one of the following events occurred after ATP injection: $\geq 50$-msec increase or decrease in AH or PR interval in two consecutive sinus beats, an AV nodal echo beat was observed, or AVNRT developed. Diagnosis of AVNRT and AV nodal echo beats was based on intracardiac recordings.

**Statistical analysis:** Data are expressed as the mean $\pm$ SD. Statistical comparison of data was performed using the t-test for unpaired samples or the Chi-square test as appropriate. A value of $P < 0.05$ was considered statistically significant.

**RESULTS**

No patient was found to have evidence of organic heart disease, nor was any patient excluded from this study due to severe side effects or intolerance to ATP. Nine patients were found to have inducible, sustained, typical (slow/fast) AVNRT (S/F AVNRT), 2 patients had inducible sustained atypical (fast/slow) AVNRT (F/
S AVNRT), 5 patients had concealed Wolff-Parkinson White (cWPW) syndrome, 2 patients had manifest WPW (mWPW) syndrome after successful radiofrequency ablation of an accessory pathway, 1 patient had focal atrial fibrillation, and 1 patient had inducible atrial tachycardia (AT). Electrophysiological demonstration of DAVNP (E-DAVNP) was observed in 8 (89%) of the 9 patients with S/F AVNRT. In 1 patient without signs of DAVNP after a single atrial extrastimulus, S/F AVNRT was induced by two atrial extrastimuli. E-DAVNP was not observed in 8 patients without S/F AVNRT. Three of the 11 patients (27%) without S/F AVNRT (cWPW syndrome, AT, and focal fibrillation) had E-DAVNP (Table I).

**ATP test:** In the 20 patients who completed the ATP test, the ATP dose required to reach 1 of the end points was 13.9 ± 6.0 mg (range 5 to 30 mg). The effects of ATP typically began about 10 seconds after bolus administration, were maximal within the next 5 to 10 seconds, and were always short-lasting (< 1 minute). A sudden and transient increment or decrement in PR interval (≥ 50 msec) was found in 10 (91%) of the 11 patients with E-DAVNP after an ATP injection of 12.0 ± 5.5 mg (range 5 to 22.5 mg) (n = 10)(Figure 1, Table I). One patient with

Table I. Patient Characteristics, Electrophysiological Diagnosis, and Determination of Dual AV Nodal Physiology by Electrophysiological Study and ATP Test

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>PSVT type</th>
<th>E-DAVNP</th>
<th>ATP Test</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>DAVNP</td>
<td>Dose (mg)</td>
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<tr>
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<td>F</td>
<td>62</td>
<td>AVNRT</td>
<td>+</td>
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<td>2</td>
<td>F</td>
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<td>AVNRT</td>
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<td>+</td>
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<tr>
<td>3</td>
<td>M</td>
<td>42</td>
<td>AVNRT</td>
<td>+</td>
<td>+</td>
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<td>4</td>
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<td>67</td>
<td>AVNRT, AFL</td>
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<td>+</td>
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<td>26</td>
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<td>fast/slow AVNRT, AFL</td>
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<td>F</td>
<td>36</td>
<td>AVNRT, SNRT, AFL</td>
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<td>M</td>
<td>27</td>
<td>cWPW synd</td>
<td>+</td>
<td>+</td>
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<td>62</td>
<td>focal fibrillation</td>
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<tr>
<td>20</td>
<td>F</td>
<td>65</td>
<td>AT</td>
<td>+</td>
<td>-</td>
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</table>

AVNRT = atrioventricular nodal reentrant tachycardia; AFL = atrial flutter; SNRT: sinus node reentrant tachycardia; cWPW synd = concealed Walf-Parkinson White Syndrome, mWPW synd = manifest WPW syndrome; AT = atrial tachycardia; PSVT = paroxysmal supraventricular tachycardia; E-DAVNP = electrophysiological dual AV nodal physiology; DAVNP = dual AV nodal physiology; WBB = Wenckebach block; M = male; F = female.
E-DAVNP did not show a jump in PR interval after ATP injection. A ≥ second-degree AV block was observed in 7 (78%) of the 9 patients without E-DAVNP after an ATP injection of 17.1 ± 7.0 mg (range 10 to 30 mg) (n = 7) (P = 0.16 vs DAVNP). Two patients without DAVNP showed a jump in PR interval after 12.5- and 10-mg ATP injections. The maximal AH increment between 2 consecutive beats was significantly greater in those patients with a PR jump (157.6 ± 73.8 msec, range 62 to 323 msec) than in those without a PR jump (45.3 ± 41.7 msec, range 0 to 41 msec) (P = 0.0009). A sudden and transient increment or decrement in PR and AH interval (≥ 50 msec) after ATP injection during sinus rhythm was observed in all 9 patients with S/F AVNRT. Both sudden increments and decrements in PR and AH intervals were observed in 3 patients (33%) with S/F AVNRT. AV nodal echo beats were observed after ATP injection in 4 patients (44%) with S/F AVNRT. Interestingly, injection of ATP provoked reproducible episodes of sustained AVNRT in 1 patient with S/F AVNRT in whom AVNRT could be induced only by two atrial extrastimuli (Case 6) (Figure 2 A, B). Eight
Figure 2 A. Sustained AVNRT was reproducibly induced by a bolus injection of 12.5 mg of ATP. PR interval was prolonged by 173, 256, and 335 (AH interval: 90, 160 and 240) msec then AV conduction through slow pathway was maintained for 15 beats (upper and middle row) which was followed by slow / fast AVNRT (lower row).

Figure 2 B. Magnified surface ECG of Figure 2A. Arrows represent P wave of the surface ECG.
patients developed ≥ second-degree AV block after ATP injection of 16.9 ± 6.5 mg (range 10 to 30 mg) (Figure 3). Signs of DAVNP after ATP injection of 12.5 ± 6.6 mg (range 7.5 to 20 mg) were observed in 3 patients without S/F AVNRT. Two of these 3 patients had E-DAVNP (Cases 12 and 19), and another patient whose AH interval increased by 145 msec after administration of ATP did not show E-DAVNP after a single atrial extrastimulus (Case 9). Of note, none of the patients in this study developed atrial fibrillation after ATP administration.

**Correlation of the ATP test with the electrophysiologic evaluation:** E-DA VNP was observed in 11 (55%) of the 20 patients. In 10 (91%) of these 11 patients, DAVNP was also confirmed by the ATP test. Of the remaining 9 patients who had no E-DAVNP, 2 patients (22%) had signs of DAVNP by the ATP test ($P = 0.0045$). In 9 (75%) of the 12 patients with signs of DAVNP by the ATP test, S/F

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**Case 14. 40 y.o./F** cWPW synd (Wenckebach block)

![Waveform](image)

**Figure 3.** Effect of ATP on AV conduction during sinus rhythm in a patient with concealed WPW syndrome. Progressive prolongation of the PR and AH with PR and AH increment < 50 msec was observed, which was followed by AV block after injection of 20 mg of ATP. Arrows indicate P wave of the surface ECG.
AVNRT was induced during the EPS. In 8 patients with a negative ATP test, S/F AVNRT could not be induced during the EPS (Table II). Thus, the results of the ATP test predicted the induction of sustained S/F AVNRT with a positive predictive value of 75%, a negative predictive value of 100%, a sensitivity of 100%, and a specificity of 73% (Table III).

DISCUSSION

Main findings  Since spontaneous ECG manifestations attributable to dual AV nodal conduction are uncommon, we developed a noninvasive diagnostic test
that uses ATP administration to identify patients with dual AV nodal pathways who are prone to AVNRT. ATP administration during sinus rhythm revealed signs suggestive of DAVNP in all (100%) patients with inducible sustained S/F AVNRT but in only 27% of patients without S/F AVNRT. These results suggest that this ATP test may be a useful bedside test for identifying patients prone to AVNRT.

Diagnostic value of ATP test: Curtis, et al have shown that adenosine is more effective on the antegrade fast pathway than on the slow pathway.5) Due to this differential responsiveness of adenosine to fast and slow pathways, Tebbenjohanns, et al investigated the injection of adenosine during sinus rhythm and found that it was useful in the diagnosis of dual AV nodal pathways.6) Belhassen, et al administered ATP during sinus rhythm for the noninvasive diagnosis of DAVNP in patients with AVNRT.7,8) Since the electrophysiological effects of ATP in humans are in great part due to adenosine, the final product of the degradation of ATP, and because the molecular weight of ATP is about twice that of adenosine, one may expect that results similar to those reported in Belhassen's paper will be observed with doses of adenosine that are about half the dose of ATP.9) Adenosine is not clinically available in Japan so we also used ATP to predict which patients with DAVNP are prone to PSVT.

We prospectively defined a 50-msec increment or decrement in the AH and PR intervals between 2 consecutive beats after ATP injection as suggestive of DAVNP. Selection of this 50-msec value as a cutoff point may seem rather arbitrary. This cut off point is, however, similar to that used during routine electrophysiological testing.11) In fact, the magnitude of the jump in AH and PR intervals observed in patients with AVNRT after ATP injection was far more impressive in all of the patients with S/F AVNRT (mean AH increment of 157.6 ± 73.8 msec). Moreover, AV nodal echo beats occurred in 44% of patients showing a ≥ 50-msec increase, and even sustained episodes of S/F AVNRT were triggered in 1 patient after ATP injection (Case 6). This strongly suggests that the sudden increment in AH interval that followed ATP injection during sinus rhythm indeed represented ATP-induced blockade of the fast AV nodal pathway with subsequent conduction over the slow AV nodal pathway rather than merely decremental AV nodal conduction.

Correlation with EPS results: The increment in AH interval seen when following the EPS tended to be greater than that seen during the ATP test (195.3 ± 66.1 msec vs 158.7 ± 77.2 msec, P = 0.055). As ATP was injected for noninvasive diagnosis during sinus rhythm, the ATP-related changes occurring in the sinus rate might have influenced the results. In fact, adenosine injection during constant atrial pacing in patients with AVNRT has been found to result in a greater increment in AH interval.5) Nevertheless, we found good correlation of the incre-
ment (or decrement) in AH interval between that obtained during the pacing protocol and that obtained during the ATP test ($P = 0.013$, $R = 0.71$) (Figure 4). More interestingly, a ≥ 100-msec increment in AH interval after ATP injection was observed in all 9 patients with S/F AVNRT. However, the increment in AH interval was smaller (95 and 62 msec) in the 2 patients who had E-DA VNP without S/F AVNRT ($P = 0.018$ vs S/F AVNRT). Injection of ATP during sinus rhythm revealed signs of DAVNP in all (100%) patients with inducible sustained S/F AVNRT. However, the ability of a positive ATP test to predict S/F AVNRT was 75%. Tebbenjohanns, Belhassen, et al and also administered incremental doses of ATP or adenosine during sinus rhythm in patients with AVNRT and in control groups with other types of SVT. In both of their studies, the sensitivity of the ATP or adenosine test was almost 75%, and the specificity was over 90%. The sensitivity of the ATP test in our study was even higher (100%), but the specificity was lower (73%). In contrast to these previous studies, the present study included a relatively small number of patients, we injected ATP in 2.5-mg increments, and we included patients with other forms of SVT with DAVNP and also F/S AVNRT. More interestingly, in 1 patient without E-DA VNP by one atrial extrastimulus, S/

![Figure 4](image-url)  
Figure 4. Correlation between the increment in AH interval by one atrial extrastimulation and that by ATP.
F AVNRT was induced following the AH increment only by ATP injection (Case 6). Furthermore, DAVNP was observed by ATP injection in a patient with F/S AVNRT in whom E-DAVNP could not be shown by a single atrial extrastimulus. These findings support the theory that the apparently “smooth” AV node refractory curve consists of two distinct components representing both fast and slow AV nodal pathways, even when the typical discontinuity is absent. 10)

**Limitations:** ATP injection was not performed during constant atrial pacing, which would have avoided the ATP-related changes in sinus rate and could have enabled better quantification of the changes in AV conduction. Instead, we preferred to inject ATP during sinus rhythm to make the test more readily applicable for clinical bedside use.

DAVNP was observed using the ATP test in patients without S/F AVNRT. Thus, the existence of DAVNP itself was not consistent with S/F AVNRT. However, the increment in PR interval > 100 msec is suggestive of S/F AVNRT based on our data.

**Clinical implications:** PSVT can easily be treated by radiofrequency catheter ablation. However, arrhythmias of this type are not often recorded because they are short-lasting. Therefore, patients with PSVT often undergo a diagnostic EPS. The results of the present study suggest that ATP may be useful in the non invasive diagnosis of DAVNP in patients prone to AVNRT. In the present study, signs suggestive of DAVNP after injection of ATP were found in all (100%) patients with inducible S/F AVNRT, possibly because of the small increments in ATP doses that were used.

**Conclusions:** Injection of ATP during sinus rhythm may be a useful bedside test for identifying patients with DAVNP who are prone to AVNRT. This test should be considered as a noninvasive adjunct in patients with undocumented palpitations suggestive of PSVT.

**REFERENCES**


