Effects of Adenosine Triphosphate on Ventriculoatrial Conduction

Usefulness and Problems in Assessment of Catheter Ablation of Accessory Pathways

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The effects of adenosine triphosphate (ATP) on ventriculoatrial (VA) conduction were examined before and after accessory pathway (AP) ablation, with emphasis on assessment of the complication of dual atrioventricular (AV) node pathway. By evaluating the differences in the response to ATP of APs and other pathways, we assessed the usefulness and problems of this method. Of 59 patients who underwent AP ablation, 31 showed pre-excitation and 28 had concealed APs. A dual AV node pathway was found in 9 patients (15.3%) before ablation. After ablation, a dual AV node pathway was newly found in 9 patients. Thus, the total number of patients with a dual AV node pathway was 18 (30.5%). VA conduction over APs was not blocked in 26 of 29 patients, but the remaining 3 APs were blocked transiently by ATP. ATP caused VA block over the AV node in 15 of 16 patients and a dual AV node pathway in all 11 patients. In contrast, VA conduction over the retrograde fast pathway was blocked in 9 of 14 patients with AV node re-entrant tachycardia. ATP has little effect on APs, so observation of the response to ATP provides a more reliable and useful means of evaluating successful ablation. With this method, however, it is important to consider the possibility of the presence of ATP-sensitive APs and ATP-resistant retrograde fast pathways. The influence of ablation-induced injury has not been fully clarified. It is therefore essential to take into account various data, including the comparison between data obtained before and after ablation.

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Key Words: Accessory pathway; Catheter ablation; Adenosine triphosphate; Dual atrioventricular node pathway; Ventriculoatrial conduction

Catheter ablation of accessory pathways (APs) using radiofrequency current has recently been reported to have a high degree of efficacy and safety. Its role as a radical treatment for Wolff-Parkinson-White syndrome has been established. Whether the AP has been successfully ablated can be assessed by the disappearance of pre-excitation in anterograde conduction. However, this is not always easy to assess in retrograde conduction. Some investigators have reported the presence of APs characterized by decremental conduction properties and have described changes in the characteristics of conduction over the APs due to ablation. Thus, questions remain regarding confirmation of complete discontinuation of retrograde conduction over APs. Retrograde conduction over the fast pathway has been reported to show good conductivity in cases of atrioventricular (AV) node re-entrant tachycardia. These phenomena give rise to problems when determining whether ventriculoatrial (VA) conduction is mediated by the AP or the AV node. Thus, the presence of a dual AV node pathway can greatly affect evaluation of the

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outcome of ablation in patients with Wolff-Parkinson-White syndrome.

Adenosine triphosphate (ATP) is often used to treat paroxysmal supraventricular tachycardia. The electrophysiologic effects of ATP administered intravenously have been thought to be due to the breakdown product adenosine. These agents have been reported to act selectively on the AV node. This feature of ATP has also been used to clarify the mechanism of tachycardia. As ATP has a short half-life and little effect on hemodynamics, it can be administered repeatedly.

The present study was undertaken to assess the effect of ATP on APs, and compare its effect on the AV node with its effects on the dual AV node pathway, with a view to analyzing the utility and problems of ATP application for evaluation of the outcome of AP ablation.

Methods

Before and after catheter ablation of APs, electrophysiologic studies were carried out to assess the dual AV node pathway and to identify the route of VA conduction. By the use of these tests, the effects of ATP on each pathway of VA conduction were assessed.

Patient Characteristics

The subjects taking part in this study were 59 consecutive patients with Wolff-Parkinson-White syndrome who underwent AP ablation. The patients consisted of 38 men and 21 women with a mean age of 44 ± 17 years (range 16–76 years). Wolff-Parkinson-White syndrome was manifest in 31 patients and concealed in 28 patients. Fifty-seven patients had no evidence of structural heart disease, 1 had hypertrophic heart disease, and 1 had hypertensive heart disease.

Electrophysiologic Study

Informed written consent was obtained from all patients before the study. All antiarrhythmic agents were discontinued at least 24 h before the study. Each patient underwent electrophysiologic study in the fasting state under mild sedation. Three 6F quadrripolar electrode catheters (Mansfield/Webster, USA) were inserted percutaneously with an interelectrode distance of 5 mm into the right femoral vein and advanced under fluoroscopic guidance to the high right atrium, His bundle position and right ventricular apex. A 6F catheter with 3 groups of 4 circumferential electrodes arranged in an orthogonal configuration (Jackman catheter; Mansfield/Webster) was positioned from the left subclavian vein into the coronary sinus. Electrocardiographic leads I, aVF, and V1 as well as intracardiac electrograms from multiple sites were simultaneously displayed and recorded with the EP Lab system (Quinton Electrophysiology, Canada). Electrophysiologic study was performed to determine the conduction properties and location of the AP and its involvement in tachycardia. The study protocol included the following: (1) atrial extrastimulation during sinus rhythm and during atrial pacing cycle length at 600 and 400 msec; (2) incremental atrial pacing up to a cycle length of 220 msec or until a second-degree AV block was obtained; (3) ventricular extrastimulation during ventricular pacing cycle length at 600 and 400 msec; (4) incremental ventricular pacing up to a cycle length of 220 msec or until a second-degree VA block was obtained. The pacing stimuli were 2 msec in duration, and were provided by a digital programmable stimulator.

Ablation Protocol

Catheter ablation was performed immediately after the initial electrophysiologic study. A 7F quadripolar steerable electrode catheter (Mansfield-Webster/ Webster/EP Technologies, USA) with a 4-mm distal electrode (interelectrode distance between the 2 distal electrodes of 2 mm) was inserted percutaneously into the right femoral artery in patients with left-sided AP and into the right femoral vein or left subclavian vein in patients with right-sided AP, and was positioned above or below the mitral or tricuspid valve. The target ablation site was identified based on the following electrogram criteria: (1) the shortest local AV intervals in sinus rhythm and local ventricular electrogram preceding onset of the delta wave of the surface electrocardiographic in patients with pre-excitation; (2) the shortest local VA intervals during AV re-entrant tachycardia or ventricular pacing in patients with concealed APs; (3) stable and continuous electrical activity between the atrial and ventricular electrograms; (4) AP potential. Radiofrequency current was delivered at 10–30 W between the distal electrode of the ablation catheter and a large-diameter skin patch electrode. A 13.56-MHz radiofrequency generator (Novafame, Internova, Japan) was used in patients 1–8, and the other patients received current of frequency 520 kHz (HAT-2005, Dr. Ospyka, Germany) or 500 kHz (CAT 500, Central Industry, Japan). Energy was applied during sinus rhythm in patients with pre-excitation and during AV re-entrant tachycardia or ventricular pacing in patients with concealed APs. Application of energy was maintained.
for 30–60 sec but was terminated immediately in the event of an increase in impedance or displacement of the catheter electrode. The electrophysiologic study was repeated 20 min after the final application of radiofrequency current and 7 days after the procedure to verify the absence of AP conduction and to exclude the presence of another AP or other arrhythmias.

**Assessing the Presence of a Dual AV Node Pathway**

The complication of a dual AV node pathway and the accompanying AV node echo or AV node re-entrant tachycardia induction were examined before and after AP ablation. The presence of a dual AV node pathway was defined as sudden prolongation of the AH interval or the VA interval of at least 50 msec or a 10–20 msec shortening of the coupling interval induced by atrial and ventricular premature stimulation.

**Determination of the Pathway of VA Conduction**

VA conduction was judged to involve the AP in the following cases: (1) cases in which the retrograde atrial excitation sequence was eccentric; (2) cases in which the VA conduction time remained constant during continuous ventricular pacing or premature ventricular stimulation; and (3) cases showing pre-excitation of the atria by a ventricular extrastimulus delivered when the His bundle was refractory during tachycardia. VA conduction was judged to involve the AV node in the following cases: (1) cases in which the VA conduction time showed decremenatal properties following continuous ventricular pacing or premature ventricular stimulation; and (2) cases in which the earliest retrograde atrial excitation occurred in the His bundle electrogram.

**Effect of ATP**

ATP was administered as bolus intravenous injections at incremental doses (0.1, 0.2, 0.3, 0.4 mg/kg) after a stable 1-to-1 VA conduction was confirmed during continuous right ventricular pacing before and immediately after ablation. If VA conduction was not blocked by the initial dose (0.1 or 0.2 mg/kg), the dosage was increased until the appearance of VA conduction block, or until a maximum dosage of 20 mg had been delivered, or until symptoms limited further ATP administration. The frequency of ventricular stimulation was 120–150 beats/min and was kept at least 20 beats/min lower than the frequency level that could induce VA block. The effects of ATP on the VA conduction of each pathway were analyzed by measuring changes in VA conduction time. VA conduction time was measured from the onset of ventricular activation to the atrial electrogram of the catheter showing the earliest retrograde atrial excitation during right ventricular pacing.

Patients with Wolff-Parkinson-White syndrome were divided into 3 groups: (1) the AP group (patients in whom VA conduction involved an AP); (2) the AVN group (patients in whom the AV node was normal, ie, a dual AV node pathway was absent, after ablation); and (3) the DP group (patients who had a dual AV node pathway after ablation).

Fourteen patients with common type AV node re-entrant tachycardia served as the control group (the AVNRT group). The data were compared among these 4 groups.

**Statistical Analysis**

Data are expressed as means±SD. Student’s paired t test was used to analyze simple pairs of measurements. For 3 or more conditions, significant trends were identified by 1-way factorial analysis of variance (ANOVA). When the F value obtained by ANOVA was significant (p<0.05), the Fisher PSDL was used to compare pairs of mean values.

**Results**

Sixty-seven APs were found in 59 patients, including 2 APs in each of 8 patients. All patients had stable orthodromic AV re-entrant tachycardia. Of the 67 APs, 30 were located in the left free wall, 12 in the left posteroseptal region, 18 in the right free wall, 6 in the right posteroseptal region and 1 in the right anteroseptal region. It was not possible to discontinue conduction over 4 APs in 3 patients. In 2 patients, each of whom had an AP, AV re-entrant tachycardia was successfully controlled by modifying the conductivity over their APs. In 54 (91.5%) of the 59 patients, the AP was completely ablated. Control of the APs was eventually achieved in 56 (94.9%) patients.

**Complication of Dual AV Node Pathway (Table 1)**

Before ablation, anterograde pre-excitation was present in 31 patients and concealed AP was present in 28 patients. The jump-up phenomenon, which is an indicator of the complication of dual AV node pathway, was seen in 9 patients (15.3%) before ablation, ie, 7 patients with concealed APs and 2 patients with pre-excitation who were diagnosed as having dual AV node pathway before ablation on the grounds that the effective refractory period of the AP was longer than that of the AV node. AV node re-entrant tachycardia was induced in 2 patients with concealed Wolff-Parkinson-White syndrome, and ablation of the slow pathway resulted in disappearance of AV node re-
Table 1 Dual Atrioventricular Node Pathway in Wolff-Parkinson-White Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Pre-Ablation</th>
<th>Post-Ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifest=31</td>
<td>2 (6.5%)</td>
<td>9 (29.0%)</td>
</tr>
<tr>
<td>Anterograde</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Retrograde</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Bidirectional</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Concealed=28</td>
<td>7 (25.0%)</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>Anterograde</td>
<td>6 (AVNRT 1)</td>
<td>5</td>
</tr>
<tr>
<td>Retrograde</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Bidirectional</td>
<td>1 (AVNRT 1)</td>
<td>2</td>
</tr>
<tr>
<td>Total:59 patients</td>
<td>9 (15.3%)</td>
<td>18 (30.5%)</td>
</tr>
</tbody>
</table>

AVNRT, atrioventricular node reentrant tachycardia.

Table 2 Response of VA Conduction to ATP in Each Group

<table>
<thead>
<tr>
<th>WPW</th>
<th>AP</th>
<th>AVN</th>
<th>DP</th>
<th>AVNRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA block (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATP ≤ 0.2 mg/kg</td>
<td>2</td>
<td>14</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>ATP &gt; 0.2 mg/kg</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>VA block (-)</td>
<td>26</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total (patients)</td>
<td>29</td>
<td>16</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

VA, ventriculoatrial; ATP, adenosine triphosphate; WPW, Wolff-Parkinson-White syndrome; AP, accessory pathway group; AVN, atrioventricular node group; DP, dual atrioventricular node pathway group; AVNRT, atrioventricular node re-entrant tachycardia group.

Fig 1. ATP-induced VA block over the AP with decremental conduction properties before catheter ablation. The first portion displays recordings during right ventricular pacing (130 beats/min) before ATP administration. The earliest atrial activation was recorded in the proximal coronary sinus catheter consistent with retrograde conduction over the left posteroseptal AP. The second portion shows VA block 13 sec after ATP administration. VA block appeared after prolongation of VA interval. V1, surface electrocardiographic leads; HRA, high right atrial; CSd,m,p, distal, mid, proximal coronary sinus; HBEd,p, distal, proximal His bundle electrogram.

Entrant tachycardia.

After ablation, dual AV node pathway newly occurred in 9 patients. The number of patients with dual AV node pathway increased to 18 (30.5%) after ablation. Of the 9 patients whose dual AV node pathway was unmasked after ablation, 7 showed pre-excitation and 2 had concealed APs. AV node echoes were induced in 3 cases, but AV node re-entrant tachycardia was not induced in any patient after ablation. Of the 18 cases complicated by a dual AV node pathway, 11 had a jump in the anterograde conduction alone and 4 had a jump in the retrograde conduction alone. The remaining 3 had bidirectional jump.

Response of VA Conduction to ATP in Each Group (Table 2 and Figs 2 and 3)

Effects of ATP on APs

In 29 patients who had VA conduction over the APs, rapid intravenous injection of ATP was carried out during right ventricular pacing. Although the VA conduction over the APs could not be blocked in 26 patients, it was transiently blocked in the remaining 3, including the following 2 patients in whom VA block was achieved at an ATP dose of 0.2 mg/kg or less: (1) 1 patient with left posteroseptal AP with decremental properties (Fig 1) and (2) 1 patient with left posteroseptal AP that recurred when isoproterenol
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was administered after ablation. The remaining patient had a left lateral AP that was blocked by an ATP dose of 0.3 mg/kg. The responses of the VA interval during right ventricular pacing were analyzed by comparing pre-ATP interval with the interval measured 10–20 sec after ATP dosing (ie, during maximal prolongation of the interval after ATP administration). In the patient with decremental AP, the interval was increased from 150 msec (before dosing) to 185 msec after dosing. In the others, there was no statistically significant differences between the pre- and post-ATP VA interval. The average VA interval in all patients was slightly longer (57±32 msec) after ATP than before (54±27 msec), with a prolongation rate of 3.7±6.6%. The prolongation rate in the AP group was significantly smaller than in the other 3 groups.

Effects of ATP on AV Nodes

When ATP was administered to 16 patients in the AVN group during right ventricular pacing, VA block occurred in 15 patients (including 1 patient in whom block appeared after a dose of 0.3 mg/kg), but did not occur in the remaining patient even at a dose of 0.3 mg/kg. In the DP group, ATP was administered to 11 of the 18 patients with a dual AV node pathway. The earliest retrograde atrial excitation of 11 patients occurred in the His bundle electrogram, and thus VA conduction was judged to involve the fast pathway. All of these patients showed VA block after ATP administration. In the AVNRT group, VA conduction over the retrograde fast pathway was blocked in 9 of the 14 patients, in contrast to the results for the fast pathway of the DP group. In the AV node, DP and AVNRT groups, the VA conduction time was significantly prolonged by ATP administration. The degree of prolongation averaged 28.3±22.6% in the AVN group (from 132±53 msec pre-ATP to 164±59 msec post-ATP at maximum), 41.5±32.1% in the DP group (from 122±53 msec to 167±66 msec) and 20.9±20.9% in the AVNRT group (from 66±11 msec to 79±12 msec). The prolongation rate of VA conduction time in the DP group was significantly greater.
than that in the AVNRT group, suggesting a difference in the conductivity of the retrograde fast pathway.

**Discussion**

**Complication of Dual AV Node Pathway**

An important sign of a dual AV node pathway is the appearance of interrupted AV conduction curves, which represent the jump in the AH or VA interval caused by premature atrial or ventricular stimulation. In patients with Wolff-Parkinson-White syndrome who have APs, a diagnosis of dual AV node pathway is difficult to make unless a drug is used or the AP is surgically ablated.

In the present study, 9 patients (15.3%) had a dual AV node pathway before ablation, but this number increased to 18 (30.5%) after the AP was ablated. Wolff-Parkinson-White syndrome is reported to be complicated by a dual AV node pathway in 10–21% of patients. The proportion (30.5%) in this study was higher than the reported figures, probably because our patients with Wolff-Parkinson-White syndrome had intractable tachycardia. Stable AV re-entrant tachycardia seems to be more likely to occur in the presence of slow pathways. This view is supported by the present study, in which patients with a dual AV node pathway showed AV re-entrant tachycardia (anterograde conduction over the slow pathway of the AV node and retrograde conduction across the AP). Although some investigators have reported that AV node re-entrant tachycardia develops after ablation of AP, the present study revealed atrial echoes in only 3 cases. These patients need to be followed up for longer periods than normal.

**Evaluation of VA Conduction Using ATP**

To use ATP to assess successful ablation of the AP, it is essential to confirm before ablation that ATP does not cause block of the AP. Before ablation, 2 of the 28 APs showed transient VA conduction block on ATP administration. Block of APs by ATP has also been reported in the literature. In such cases, evaluation using ATP alone is difficult. In this study, VA conduction over the AP that was modified by ablation was blocked by ATP. In this case, evaluation of VA conduction by ATP was not performed before ablation. However, the effective refractory period of this AP was prolonged compared with the preablation period, so this case seems to reflect the influence of ablation-induced injury. Some investigators have reported that ATP-induced block of APs is more frequently seen in patients with a prolonged effective refractory period whereas others have reported that it does not differ with the length of the effective refractory period. The ablation-injured AP has also been reported to show altered conduction characteristics or decremental properties, and some patients have been found to show increased sensitivity to ATP after incomplete ablation. It seems therefore to be important to consider the influence of ablation on APs when evaluating AP block. The results of previous studies in which APs showing decremental conduction properties were blocked by ATP were supported in the present study. In such cases, evaluation of the APs using ATP is probably impossible.

The use of ATP in evaluation of VA conduction which develops after ablation of the AP is based on the hypothesis that ATP blocks VA conduction over the AV node. Patients with AV node re-entrant tachycardia have been reported to show good VA conduction over the retrograde fast pathway, a small prolongation of the VA conduction time after an increase in the pacing rate, and high maximal 1-to-1 conductivity. Previously, we reported that the VA conduction over the fast pathway in patients with AV node re-entrant tachycardia is unlikely to be blocked by ATP. Thus, we analyzed normal AV nodes and retrograde fast pathways separately in the present study. In this study, ATP blocked VA conduction in all but 1 of the 27 patients (16 patients from the AVN group and
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11 from the DP group). Thus, VA block by ATP occurred more readily in the AVN and DP groups, even when these patients suffered the complication of a dual AV node pathway. This result differed markedly from that for patients in the AVNRT group, in whom VA block was unlikely to occur. This intergroup difference may be related to lack of patients with AV node re-entrant tachycardia in the DP group.

In the APs without decremental conduction properties, ATP had no significant influence on the VA conduction time. Two APs that were blocked by ATP also showed no prolongation of the VA conduction time. Therefore, if the VA block by ATP occurs without prolongation of the VA conduction time, it is necessary to consider the possibility that VA conduction may involve APs. In the control group (patients with AV node re-entrant tachycardia), the responses to ATP differed from those observed in the DP group, although both these group had a dual AV node pathway. In the AVNRT group, 5 of 14 patients showed no block in response to ATP administration and no prolongation of the VA conduction time. The prolongation rate of VA conduction time was significantly less than that observed in the DP group. It seems that these intergroup difference in the response to ATP are attributable to electrophysiologic differences in these pathways. Although the precise anatomic reason for the difference in these pathways is unknown, it seems possible that differences in the conductivity over retrograde fast pathways are related to the onset of AV node re-entrant tachycardia. Keim et al. reported that the occurrence of AV block after adenosine administration is evidence of successful AP ablation. Based on this finding, they concluded that the ATP method is useful. However, they also pointed out 2 problems with this evaluation method: the presence of adenosine-sensitive APs and changes in conductivity due to ablation. The present study revealed 2 additional problems: the high incidence of the complication of dual AV node pathway after ablation and the similarity of the response of retrograde fast pathways among the AVNRT group to ATP and the response of APs to ATP. These findings are important when responses to ATP before ablation are compared with those after ablation.

Conclusion

Observation of the response to ATP is a highly reliable and useful means of evaluating the success or failure of AP ablation. With this method, however, it is important to consider the possibility of the presence of ATP-sensitive APs and ATP-resistant retrograde fast pathways. The influence of ablation-induced injury has not been fully clarified. Therefore, it is essential to take into account various data, including a comparison of pre- and post-ablation data and analysis of the mode of VA conduction block.

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