Electrophysiologic effects of adenosine-5’-triphosphate on atrioventricular reentrant tachycardia

BERNARD BELHASSEN, M.D., AMIR PELLEG, PH.D., DAVID SHOŠHANI, M.D., BOAZ Gева, M.D., and SHLOMO LANIADO, M.D.

ABSTRACT The effects of adenosine-5’-triphosphate (ATP) on atrioventricular reentrant tachycardia (AVRT) were studied in 18 patients. Nine patients had AV nodal reentrant tachycardia and the remaining nine patients had AVRT with an accessory pathway for retrograde conduction. After electrophysiologic control study, ATP was administered (20 mg iv, rapid bolus) during sustained tachycardia and during right ventricular pacing (150 beats/min). ATP terminated the tachycardia within 16 sec of administration in eight of nine patients with AV nodal reentry and in all patients with accessory pathways. Termination of the tachycardia was related to a block in the antegrade slow pathway in patients with AV nodal reentry and to a block in the AV node in patients with accessory pathways. In one patient with AV nodal reentry, ATP resulted in a slowdown of the rate of the tachycardia due to delayed conduction in the slow antegrade pathway. No change in the conduction in the retrograde fast nodal pathway or in the accessory pathway was noted in any patient before termination of the tachycardia. The administration of ATP during ventricular pacing resulted in transient complete ventriculoatrial (VA) block or slight prolongation of VA conduction in five of nine patients with AV nodal reentry. VA conduction was not affected in four of nine patients with AV nodal reentry or in all patients with accessory pathways. Short-lived and benign side effects were commonly noted after administration of ATP. Transient episodes of second-degree or complete AV block and sinus bradycardia were noted in eight patients and did not require any treatment. These results suggest that intravenous ATP is a safe and effective drug for rapid termination of AVRT.

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FOR MANY YEARS adenosine-5’-triphosphate (ATP) has been successfully used in Europe to treat paroxysmal supraventricular tachycardia (PSVT) in adult patients.1–5 More recently ATP was established as a drug of first choice for quick termination of PSVT in infancy.6

In spite of the wide clinical use of ATP, information on its electrophysiologic effects in patients with atrioventricular reentrant tachycardia (AVRT) is rather limited. In this study we assessed the efficacy and safety of ATP and evaluated its electrophysiologic mechanism of action in patients with AVRT.

Material and methods

Patients. The criteria for patient selection were the following: (1) a history of documented recurrent PSVT, (2) inducible sustained AVRT during electrophysiologic study, and (3) no contraindication for the administration of ATP (asthma).3

The study group consisted of 18 patients, six women and 12 men, ages 25 to 72 years (49 ± 14). Fifteen patients had no evidence of organic heart disease and three patients had coronary heart disease. In seven patients (Nos. 3, 5, 8, 9, 14, 16, and 18) the tachycardias responded to vagal maneuvers, and in the remaining 11 patients pharmacologic intervention was required to terminate tachycardias.

Electrophysiologic studies. Electrophysiologic studies were performed with patients in the postabsorptive nonsedated state after informed written consent was obtained. All cardiovascular drugs were discontinued for at least five half-lives before the study. One bipolar and two quadripolar electrode catheters were introduced through the right femoral vein and placed at the high right atrium, right ventricular apex, and AV junction (for His bundle recording). When atrial activity during AVRT was not synchronous with the QRS complex (nine patients), left atrial activity was recorded with an electrode catheter positioned in the coronary sinus (seven patients) or the pulmonary artery trunk (two patients).7

Standard electrocardiographic (ECG) leads I, II, III, and V1, as well as the intracardiac electrograms, were simultaneously recorded on an eight-channel recorder (Mingograph Elemia 82). Stimuli of 2 msec in duration and approximately twice the diastolic threshold were delivered by a programmable stimulator (Medtronic Model 5325).

The study protocol was as follows: (1) atrial extrastimulation during sinus rhythm and during atrial pacing at several cycle lengths, (2) incremental atrial pacing up to a cycle length of 220

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mesic or until a second-degree AV block was obtained, (3) ventricular extravastimulation during sinus rhythm and during ventricular pacing at several cycle lengths as well as during tachycardia, and (4) incremental ventricular pacing up to a cycle length of 220 msec or until a second-degree ventriculointraventricular (VA) block was obtained.

After the electrophysiologic control study, AVRT was induced. When the tachycardia had lasted for 5 min, a bolus injection of 20 mg of ATP (Striadyne, Lab. Auclair, France) was administered rapidly through a femoral vein (slow administration is a definite cause of drug failure). A similar injection was given 10 min later during right ventricular pacing at a rate of 150 beats/min. In both instances the patients' symptoms were carefully monitored.

Electrophysiologic definitions. The mechanism of AVRT was defined as previously described.8,9 AV nodal reentry was diagnosed by a combination of the following criteria: (1) induction of tachycardia related to achievement of a critical AV nodal (AH) conduction delay, (2) demonstration of "discontinuous" A1A2, H1H2 curves with induction of tachycardia related to antegrade block in the fast pathway, (3) retrograde atrial activation synchronous with the onset of ventricular activation during tachycardia, (4) activation of the low right atrium during tachycardia and during ventricular pacing before other atrial sites, and (5) inability to preexcite the atrium during AVRT by premature ventricular depolarizations when the His bundle was refractory.

The involvement of an accessory pathway conducting retrogradely was diagnosed when the following were observed during AVRT: (1) eccentric retrograde atrial activation sequence, (2) increase in VA conduction interval when bundle branch block occurred ipsilateral to the accessory pathway, and (3) preexcitation of the atri by a ventricular extrastimulus delivered when the His bundle was refractory.

Antegrade conduction properties were determined by the longest atrial-paced cycle length that produced a second-degree block in the AV node and/or in the accessory pathway and by measurement of the effective refractory period of the AV node and/or the accessory pathway. Retrograde conduction properties were determined by the longest ventricular-paced cycle length that produced a second-degree block in the AV node and/or in the accessory pathway. The time from the earliest deflection of the QRS to the earliest high-frequency deflection of the high right atrial electro gram was taken as an approximation of retrograde conduction time during AVRT. A'H was defined as the time from the high-frequency deflection of the high right atrial electro gram and the His bundle activity, and it was taken as an approximation of AV nodal conduction during AVRT. VpA' was defined as the interval between the stimulus artifact of ventricular pacing at 150 beats/min and the earliest high-frequency deflection of the high right atrial electro gram.

Results

Electrophysiologic control data. In nine patients with normal AV and intraventricular conduction, the mechanism of AVRT was AV nodal reentry involving an antegrade slow pathway and a retrograde fast pathway. However, discontinuous AV nodal conduction curves suggesting dual AV nodal pathways were noted in only three patients (Nos. 1, 4, and 7). In the remaining nine patients the mechanism of AVRT involved a retrograde accessory pathway. Five patients had Wolff-Parkinson-White syndrome (type A) and four patients had a concealed accessory pathway with a normal resting ECG. Electrocardiographic and electrophysiologic data suggested a left free wall accessory pathway in all patients except one (patient 18), who had a left posterolateral accessory pathway associated with a right bundle branch block.

In all patients with AV nodal reentry, progressive prolongation of VpA' interval of variable magnitude was observed during incremental ventricular pacing and during ventricular extravastimulation. No significant change in VpA' interval was noted in patients with accessory pathways. During ventricular pacing at a rate of 150 beats/min, retrograde conduction occurred through the fast nodal pathway in patients with AV nodal reentry and through the accessory pathway in patients with accessory pathways.

Effects of ATP during tachycardia (Table 1). ATP terminated the tachycardias in all patients except one (patient 7) within 16 sec after the injection (figures 1 to 3). In patients with AV nodal reentry and in those with accessory pathways, termination of the tachycardia was related to a block in the antegrade slow pathway or a block in the AV node, respectively. Progressive variable prolongation of A'H interval was noted before the termination of tachycardias in all patients. In patient 7, the cycle length of the tachycardia transiently increased from 310 to 410 msec due to prolongation of A'H interval. No change in VA' interval was observed in any patient.

After termination of the tachycardias, transient (3 to 11 sec) second-degree AV nodal block was observed in four patients (Nos. 2, 3, 5, and 12) and complete AV nodal block in four patients (Nos. 4, 11, 14 and 15). Sinus arrest (5 sec) was observed in one patient (No. 16) and transient (6 to 10 sec) sinus bradycardia (cycle length 1100 to 1500 msec) in four patients (Nos. 10, 11, 17 and 18). In all patients the bradycardia did not require any intervention.

Preexcitation did not appear in patients with concealed accessory pathways after the restoration of sinus rhythm with ATP. In two of five patients with Wolff-Parkinson-White syndrome (patients 17 and 18), the preexcitation became transiently more pronounced. In the remaining three patients (Nos. 13, 14, and 16) no change in the degree of preexcitation was noted.

After the administration of ATP, tachycardia did not recur in any patient except one (patient 2) in whom atrial premature beats triggered a new episode of tachycardia.

Effects of ATP during ventricular pacing (Table 1). Administration of ATP during ventricular pacing in patients with AV nodal reentry resulted in transient (less
TABLE 1
Electrophysiologic variables before and after ATP

<table>
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<th>Pt</th>
<th>Sex/age</th>
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<th>Mechanism</th>
<th>CL</th>
<th>VA'</th>
<th>A'H</th>
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HD = heart disease; CHD = coronary heart disease; AVNR = atrioventricular nodal reentrance; AVR = atrioventricular reentrance; (C) = concealed accessory pathway; (M) = manifest accessory pathway; CL = cycle length; VA' = interval from the onset of the QRS complex to the retrograde high right atrial deflection; A'H = interval from the retrograde high right atrial deflection to the His bundle deflection; AVN = AV node; AP = accessory pathway; APCL = atrial paced cycle length that resulted in second-degree atrantegrade block; VPCL = ventricular paced cycle length that resulted in second-degree retrograde block; $V_pA'$ = ventricular stimulus to high right atrium interval; VP = ventricular pacing; CB = complete block.

Measurements were performed just before termination of the tachycardia; all measurements are in milliseconds.

than 10 sec) complete VA block, slight prolongation of $V_pA'$ interval, and no effect on retrograde conduction in three, two, and four patients, respectively (figures 1 and 4). No effect on the retrograde conduction was noted in all patients with accessory pathways.

Clinical tolerance of ATP. Side effects were frequently noted after the administration of ATP but they were short lasting (less than 1 min) and did not require any treatment. The most common side effects were flushing and a vague feeling of malaise (15/18 patients). Headaches, cough, and retching occurred in nine, three, and three patients, respectively. No major respiratory complication was noted.

Discussion

Early reports by Drury and Szent-Gyorgyi demonstrated that adenine compounds, in addition to their metabolic role, have a potent effect on the conducting system of the mammalian heart. Later studies in human subjects and animals established that ATP has powerful and selective negative chronotropic and dromotropic (AV node) effects. The exact mechanism of action of ATP remains obscure, due at least in part to contradictory results obtained in various species. For example, there is no agreement concerning the involvement of the vagus in the mode of action of ATP. Such an involvement was found in studies with human subjects, dogs, and cats. However, it was excluded in other studies with human subjects, dogs, and guinea pigs.

The vagomimetic properties of ATP led to its use as an antiarhythmic drug for the treatment of PSVT in many clinical studies. The results of the present study are in agreement with those of previous reports. ATP promptly terminated induced AVRT in 17 of our 18 patients and it slowed down the rate of the tachycardia in the other patient. In all patients termination or slowing of the tachycardia was due to block or slowing of conduction in the antegrade limb of the circus movement without any impairment of the retrograde limb, even in patients with AV nodal reentry. However, in the latter group, administration of ATP during rapid ventricular pacing depressed the retrograde conduction in five patients but ATP did not alter it in the remaining four.

The differential response of the retrograde conduc-
tion to ATP during AVRT and during ventricular pac-
ing, which has been previously noted with other antiarrhythmic drugs,\textsuperscript{19-21} is noteworthy. This could be related to the electrophysiologic properties of the final common pathway, which is assumed to be included in the AV nodal reentry mechanism. Since the HA' interval remained constant during tachycardia after admin-
istration of ATP, it is tempting to speculate that ATP had no effect on both the retrograde fast pathway and the antegrade final common pathway. Occurrence of VA block or delay during ventricular pacing after ATP could be best explained by conduction disorders located in the retrograde final common pathway. On the contrary, an intact VA conduction after ATP would suggest that the retrograde final common pathway was insensitive to ATP. Inability of ATP to alter the retro-
grade conduction in four patients with AV nodal reentry could indicate that the retrograde pathway was extranodal and composed of atrio-His bundle tracts.\textsuperscript{22} However, the decremental properties of the retrograde conduction in these patients actually suggest the in-
volvement, at least in part, of AV nodal structures.

In our study both antegrade and retrograde conduction through the accessory pathways were not affected by ATP in any patient. These results contradict those reported by Perrot et al.,\textsuperscript{23, 24} who showed that ATP abolished antegrade preexcitation in seven of 15 pa-
ients with manifest preexcitation and that it abolished or prolonged retrograde conduction in five and three patients with manifest or concealed preexcitation, re-
spectively. The discrepancy between our results and those of Perrot might be due to the following: (1) a higher dose of ATP (40 mg) was administered by Per-
rot, (2) the accessory pathways in our patients had shorter refractory periods, (3) no evidence of associ-
ation of James and Mahaim fibers was found in any of our patients, and (4) the ATP-sensitive accessory pathways reported by Perrot might have included abber-
ant AV nodal tissue.

Frequent and uncomplicated side effects were noted after the administration of ATP in our study. These effects were short lasting, probably due to the rapid metabolism of ATP. Review of the literature revealed that not even a single death occurred in hundreds of patients treated by ATP. Symptomatic cardiac asystoles were rare and promptly responded to thoracic blows. However, the use of the drug should not be recommended in patients with sick sinus syndrome if cardiac pacing is not available. In addition, ATP should be used with caution in patients treated by pro-
pranolol, dipyridamole, and diazepam, since these drugs have been shown to potentiate the depressant

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Patient 1: Effects of ATP during AV nodal reentry tachycardia and during ventricular pacing (150 beats/min). Shown are ECG lead V\textsubscript{1} and electrograms of the AV junction (AV) and of the high right atrium (HRA). \textit{Top}, ATP slightly prolongs the cycle length of tachycardia (due to an increase in A'H interval by 15 msec) and within a few seconds terminates it. The termination of the tachycardia is related to a block in the antegrade slow nodal pathway with no change in the conduction in the retrograde fast nodal pathway. \textit{Bottom}, Administration of ATP does not affect the ventriculoatrial conduction (V',A' interval).}
\end{figure}
FIGURE 2. Effects of ATP during orthodromic AVRT in a patient (No. 18) with Wolff-Parkinson-White syndrome (type A) and a right bundle branch block. Termination of the tachycardia occurs 14 sec after the administration of ATP, which results in a block in the AV node after a progressive slight prolongation in A'H interval. Retrograde conduction through the accessory pathway (VA' interval) is not affected by ATP. The first two atrial beats after the termination of the tachycardia are ectopic beats. The subsequent atrial beats (not shown) were sinus beats (cycle length of 1500 msec during a 9 sec period) and had a pattern of major preexcitation. Abbreviations are as in figure 1.

FIGURE 3. Effects of ATP during AVRT in a patient (patient 10) with concealed left lateral accessory pathway. Termination of the tachycardia occurs 9 sec after the drug administration due to AV nodal block after a progressive increase in A'H interval. No significant change in conduction through the accessory pathway is noted. Sinus bradycardia at a cycle length of 1300 msec is subsequently present for 5 sec. PA = pulmonary artery trunk electrogram; other abbreviations are as in figure 1.
effects of ATP on the sinus node and AV node. Transient atrial and ventricular hyperexcitability have been noted after the administration of ATP and, therefore, the drug should not be recommended in patients with a history of atrial or ventricular tachyarrhythmias. A case of bronchospasm has been reported, suggesting that the drug should be contraindicated in asthmatic patients. Finally, although it has been safely used in coronary patients with PSVT (ref. 5 and unpublished data), it should be avoided in such cases because the drug has strong acetylcholine-like effects and acetylcholine has been shown to cause coronary vasoconstriction in man. The dose of ATP that was administered in the present study (20 mg) was similar to that used in numerous clinical reports. Since the success rate noted in our study was high, it is possible that a smaller dose producing fewer side effects would have been effective as well. However, it has previously been shown that doses of 15 to 30 mg were necessary to affect AV nodal conduction.

We conclude that ATP can be safely administered and, by selectively depressing AV nodal conduction, is a very effective drug for rapid termination of AVRT. Studies comparing its effectiveness with that of other antiarrhythmic drugs are required to establish its place in the short-term therapy of PSVT.

We thank Heschi Rotnensch, M.D., for his advice and encouragement. The donation of Striadyne by Lab Auclair (Mont-rouge, France) is gratefully acknowledged.

**FIGURE 4.** Effects of ATP on retrograde conduction in a patient (No. 4) with AV nodal reentrant tachycardia. ATP causes a complete VA block that lasts 5 sec. Note that V_p A' interval remains constant before and after occurrence of the block. Abbreviations are as in figure 1.

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