Noninvasive Diagnosis of Dual AV Node Physiology in Patients With AV Nodal Reentrant Tachycardia by Administration of Adenosine-5'-Triphosphate During Sinus Rhythm

Bernard Belhassen, MD; Roman Fish, MD; Michael Glikson, MD; Aharon Glick, MD; Michael Eldar, MD; Shlomo Laniado, MD; Sami Viskin, MD

Background—Atrioventricular nodal reentry tachycardia (AVNRT) represents the most commonly encountered type of regular paroxysmal supraventricular tachycardia. This study determined whether administration of adenosine-5'-triphosphate (ATP) during sinus rhythm may be useful in the noninvasive diagnosis of dual AV nodal pathways.

Methods and Results—During electrophysiological study, we intravenously administered incremental doses of ATP (from 10 to 50 mg) during sinus rhythm to patients with spontaneous and inducible sustained AVNRT (study group, n=42) and to patients with no evidence of dual AV nodal physiology or inducible AVNRT (control group, n=21). Signs suggestive of dual AV node physiology after ATP administration during sinus rhythm (“jump” of AH ≥50 ms between 2 consecutive beats, ≥1 AV nodal echo beat, or initiation of AVNRT) were observed in 32 (76%) of 42 study patients but in only 1 (5%) of the 21 control patients (P<0.001). Similar results were observed when only surface lead recordings (without intracardiac recordings) were evaluated. Signs suggestive of dual AV node physiology by the ATP test were observed in 29 (80.5%) of 36 patients who had electrophysiological demonstration of dual AV node physiology and in 3 (50%) of 6 patients without AV nodal duality (P=NS). Signs suggestive of dual physiology according to the ATP test disappeared in 11 (92%) of the 12 patients who underwent successful slow AV nodal ablation but persisted in 8 (62%) of 13 patients who underwent AV nodal modification.

Conclusions—Administration of ATP during sinus rhythm may be a useful bedside test for identifying patients with dual AV nodal pathways who are prone to AVNRT. This simple test should be considered as a screening test for patients with symptoms suggestive of paroxysmal supraventricular tachycardia but no documented arrhythmias or for patients with documented narrow complex tachycardia of unclear mechanism. (Circulation. 1998;98:47-53.)

Key Words: arrhythmia • tachycardia • electrophysiology

Adenosine 5'-triphosphate is a very effective drug for terminating atrioventricular nodal reentry tachycardia (AVNRT). The electrophysiological effects of ATP during AVNRT have been studied previously. ATP terminates the typical slow/fast form of AVNRT mainly due to antegrade block in the slow AV nodal pathway, with no or minimal effect on the fast retrograde nodal pathway. Less is known, however, about the effects of the administration of ATP during sinus rhythm in patients with AVNRT. Because the refractory period of the antegrade fast pathway is usually longer than that of the antegrade slow pathway, we speculated that (1) ATP would affect these two pathways differently during sinus rhythm, and (2) this difference in electrophysiological effects could prove to be useful in the noninvasive diagnosis of dual AV nodal physiology. Thus, we evaluated the effects of ATP administration during sinus rhythm in patients with typical AVNRT and compared them with those observed in a control group of patients without antegrade dual AV node physiology or inducible AVNRT. In addition, in a subset of patients who underwent radiofrequency catheter ablation or modification of the slow AV nodal pathway, we compared the effects of the administration of ATP during sinus rhythm before and after the procedure.

Methods

Patient Population
The study group consisted of consecutive patients with spontaneous paroxysmal supraventricular tachycardia (PSVT) referred for radiofrequency ablation who had inducible sustained AVNRT. All patients in the study group had the slow/fast form of AVNRT induced with no drug or after intravenous administration of isoproterenol. The control group consisted of consecutive patients who underwent successful radiofrequency ablation of an accessory pathway and who did not have inducible AVNRT or demonstrable antegrade dual AV node physiology by standard electrophysiological criteria (see be-
low). All patients were evaluated in the absence of antiarrhythmic drug therapy. None of the patients had a history of asthma, a contraindication for ATP administration, or were treated with drugs known to markedly interfere with ATP metabolism (e.g., aminophylline or dipyrindamole).

Electrophysiological Study
After informed consent was obtained from patients, the electrophysiological study was performed with the use of standard techniques. Two 6F quadrupolar electrode catheters (Bard, USCI) were introduced percutaneously through the right femoral vein and positioned in the right ventricular apex and the His bundle area, respectively. A 6F decapolar electrode catheter (Bard, USCI) was introduced into the coronary sinus, usually after catheterization of a left antecubital vein. The baseline electrophysiological study included the following: (1) delivery of 1 to 3 extrastimuli during sinus rhythm from the proximal coronary sinus until the atrial or AV nodal refractory period was reached; (2) incremental proximal coronary sinus pacing up to the AV nodal block cycle length; and (3) incremental rapid ventricular apical pacing up to the ventriculoatrial block cycle length. If sustained tachycardia was not induced by use of this protocol, isoproterenol was administered at incremental dosage until the basic sinus rhythm increased by ≥20%, and the stimulation protocol was repeated.

Definitions
Dual AV node physiology was defined as a ≥50-ms increment in AsH value after a 10-ms decrement in A-As interval during single atrial extrastimulation (As) during sinus rhythm (cycle length AA) or a ≥50-ms increment in AH or AV value in consecutive beats after a ≤10-ms decrement in pacing cycle length during overdrive atrial pacing. Absence of AV node physiology was defined as the failure to demonstrate dual AV node physiology (defined as above) during coronary sinus pacing up to the AV nodal block cycle length or by atrial extrastimulation until AV nodal refractoriness was reached. In patients in whom the refractory period of the fast pathway could be determined during sinus rhythm, it was defined as the longest A-As interval that resulted in conduction over the slow AV nodal pathway.

Ablation Procedure
Radiofrequency ablation of the slow AV nodal pathway was performed according to a standard electrophysiological-anatomical approach. Ablation of the slow pathway was considered achieved when, after radiofrequency application, both of the following criteria were present: (1) dual AV node physiology could no longer be demonstrated and (2) neither AV nodal echo nor AVNRT could be induced despite multiple trials of atrial extrastimulation (with up to 3 extrastimuli) and multiple trials of rapid atrial pacing (repeatedly performed during a 10-minute period) with and without isoproterenol infusion. Modification of the slow pathway was defined as the persistence of dual AV node physiology but without inducible AVNRT (≥1 AV nodal echo beat) with and without isoproterenol.

ATP Test
This protocol was approved by our Ethical Committee, and all patients gave informed consent. The effects of ATP on AV nodal conduction were evaluated during sinus rhythm. ATP (Striadyne, Wyeth Laboratories) was injected through the right antecubital vein as a rapid bolus followed by a 20-mL flush of normal saline. The initial dose of ATP was 10 mg. Repeated doses (with 10-mg increments) were given at 2- to 3-minute intervals until one of the following prospectively defined end points was observed: (1) signs of dual AV node physiology during ATP administration (see below) or (2) second- or third-degree AV block. The test was discontinued if severe clinical intolerance or sinus bradycardia causing >3-second pause occurred. The latter patients were excluded from final analysis. Once one of the study end points (signs of dual AV node physiology or AV block) was achieved for a particular dose of ATP, the reproducibility of the test was assessed with the use of an identical dose of ATP. If the second dose of ATP failed to achieve the same end point, a third identical dose of ATP was tested, and the definite result taken for analysis was the one observed in 2 of 3 ATP tests. The results taken for final analysis were those associated with the more pronounced effects.

The ATP test was first performed after completion of the baseline electrophysiological study. Whenever isoproterenol administration was used during the baseline study, the ATP test was performed after discontinuation of isoproterenol infusion and return of the sinus rate to baseline.

The ATP test was repeated in a subset of patients who underwent radiofrequency ablation or modification of the slow pathway. Assessment of AV nodal conduction (for differentiation between slow AV nodal pathway ablation or modification) after the ablative procedure always involved infusion of isoproterenol. The ATP test performed after the ablative procedure was performed only after discontinuation of isoproterenol and return of the sinus rate close to the preinfusion sinus rate.

Definitions Used During the ATP Test
Signs of dual AV node physiology during ATP administration were considered to be present when ≥1 of the following events occurred after ATP injection: (1) AH interval increased by ≥50 ms between 2 consecutive sinus beats; (2) an AV nodal echo beat was considered to be present; or (3) AVNRT developed. Diagnoses of AVNRT and AV nodal echo beat were based on intracardiac recordings. In addition, to evaluate the diagnostic value of the ATP test performed as a bedside test (using surface ECG leads only), recordings of surface leads I, II, III, and V1 were subsequently analyzed by 2 investigators who were blinded to the patients’ group assignments and to the simultaneous intracardiac recordings. Single AV nodal echoes are often difficult to discern without the aid of intracardiac recordings. However, AV nodal echoes would be expected to reset the sinus firing rate. Therefore, AV nodal echoes were considered to be present when, after a sinus complex conducted with increased PR interval, a ≥70% increment in P-P interval was seen or retrograde P waves were seen at the end of the QRS complex.

Statistics
Statistical comparison of electrophysiological results in the study and control groups was performed by use of Fisher’s exact test. Data were expressed as mean±SD. A value of P<0.05 was considered statistically significant.

Results
Patient Population
Sixty-seven patients underwent evaluation of the effects of ATP during sinus rhythm. None of these patients had evidence of organic heart disease. Four patients (6%) (2 from the study group and 2 from the control group) were excluded because of intolerance to ATP. The remaining 63 patients completed the ATP test. The study group consisted of 42 patients (29 females, 13 males; age, 42±13 years) with inducible sustained, typical (slow/fast) AVNRT. The control group consisted of 21 patients (15 males, 6 females; age, 31±11 years) who had no evidence of dual AV node physiology or inducible AVNRT after radiofrequency ablation of an accessory pathway. Dual AV node physiology was demonstrated in 36 (86%) of the 42 study group patients and was not apparent (by atrial extrastimulation or overdrive pacing) in the remaining 6 (14%).

ATP Test
In the 63 patients who completed the ATP test, the ATP doses required to reach 1 of the end points in the study and control groups were 19.3±8.5 mg (range, 10 to 50 mg ATP) and 20.4±9.9 mg (range, 10 to 40 mg), respectively (P=NS). A
similar proportion of patients from the study group (27 of 42; 64%) and the control group (15 of 21; 71%) were given 20 mg of ATP. The effects of ATP typically began ~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 in AH interval (≥50 ms) after ATP injection during sinus rhythm was observed in 32 (76%) of the 42 patients in the study group (Fig 1A) but in only 1 (5%) of the 21 control patients (P<0.001) (Fig 2). The maximal AH increment between 2 consecutive beats was significantly greater in the study group (127±97 ms) than in the control group (17±14 ms) (P<0.001) (Fig 3). In the 32 patients who had an AH increment of ≥50 ms after ATP administration, this AH increment ranged from 50 to 400 ms (mean, 162±70 ms), and the number of beats with suspected conduction over a slow AV nodal pathway ranged from 1 to 17 (mean, 4.1±3.4) (Fig 1A). The single control patient who manifested an AH increment ≥50 ms had a 60-ms increment.

AV nodal echoes (range, 1 to 8; mean, 2.2±1.6 beats) after ATP injection were observed in 20 (48%) study patients (Figs 1A, 4B, and 4C) but in none of the control patients (P<0.001) (Fig 2). Interestingly, administration of ATP during sinus rhythm provoked episodes of sustained AVNRT (lasting >30 seconds) in 3 (7%) patients in the study group (Fig 4A). These episodes of AVNRT were triggered by premature atrial beats in 2 patients and initiated from sinus rhythm in the third patient.

Signs of dual AV node physiology (any of the above) were observed after ATP injection in 32 (76%) of the study patients. For comparison, only 1 (5%) of the 21 control patients had any signs suggestive of dual AV node physiology during the ATP test (P<0.001). Accordingly, the presence of dual AV node physiology (as suggested by the ATP test) correlated with the presence of inducible AVNRT with a sensitivity and specificity of 76% and 100%, respectively.

Similar results were obtained when only surface lead recordings, without intracardiac electrograms, were evaluated. All patients with a sudden ≥50-ms increment in AH 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 echoes were correctly identified.
with our prospectively defined ECG 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 PR). Although these ECG criteria led to misdiagnosis of AV nodal echoes in 2 study patients, other signs of dual AV node physiology after ATP injection were correctly identified with surface lead recordings in these patients. Thus, the sensitivity and specificity of the ATP test using surface leads only (without intracardiac recordings) for identifying patients with AVNRT were the same as those obtained with the aid of intracardiac recording.

### Correlation of ATP Test With Electrophysiological Data

Of the 36 study patients who had electrophysiological demonstration of dual AV node physiology, 29 (80.5%) had signs of dual AV node physiology suggested by ATP test. Of the remaining 6 patients in the study group who had no electrophysiological evidence of dual AV node physiology, 3 (50%) had signs of dual AV node physiology suggested by ATP test ($P=\text{NS}$). In patients with electrophysiological AV node duality, there was no correlation between the atrial pacing cycle length inducing block in the fast pathway and the results of the ATP test ($398\pm89$ ms, $n=29$ and $371\pm90$ ms, $n=7$ for patients with positive and negative ATP tests, respectively). Comparison between the refractory period of the fast pathway during sinus rhythm and results of the ATP test was not performed due to the small number of patients.

### Correlation of ATP Test With Ablation Results

Successful radiofrequency ablation or modification of the slow AV nodal pathway was achieved in all but 1 of the study patients. After completion of radiofrequency therapy, the ATP test was repeated in a subset of 25 consecutive patients, including 12 who underwent ablation and 13 who underwent modification of the slow AV nodal pathway. All these patients had signs suggestive of dual AV node physiology according to the ATP test performed at baseline (before the ablation procedure). After the ablation procedure, signs suggestive of dual physiology according to the ATP test disappeared in 11 (92%) of the 12 patients who had slow AV nodal ablation (Fig 1B) but persisted in 8 (62%) of 13 patients with AV nodal modification.

### Safety

Only 4 patients (2 from each group) were excluded from the study because of ATP intolerance. These patients developed...
intolerable dyspnea, before an end point was observed, after injection of 30 (1 patient) and 50 mg (3 patients) of ATP. In addition, transient complete AV block (lasting \(5\) seconds) occurred in 4 and 2 patients in the study and control groups, respectively. The bradycardia was well tolerated by all patients and did not require any intervention. Minor side effects (eg, flushing, tolerable dyspnea) occurred commonly but were self-terminating, lasting \(<1\) minute in all instances.

**Discussion**

**Main Findings**
Although spontaneous ECG manifestations compatible with dual AV nodal conduction are uncommon,\(^4\) we describe a noninvasive diagnostic test that uses administration of ATP to identify patients with dual AV nodal pathways who are prone to AVNRT. Administration of ATP during sinus rhythm revealed signs suggestive of dual AV node physiology in a high percentage (76%) of patients with inducible sustained AVNRT but in only 5% of the control group. Moreover, identification of patients with AVNRT could be performed with the same accuracy (sensitivity of 76% and specificity of 100%) when the ATP test was evaluated with surface ECG recordings (without intracardiac recordings). This suggests that the ATP test may be a useful bedside test for identifying patients prone to AVNRT.

**Study Population**
A sudden increment in AH interval of \(\geq 50\) ms after a 10-ms decrement during single atrial extrastimulation testing is considered indicative of the presence of dual AV node physiology.\(^5\) Extrastimulus testing is typically performed during atrial pacing (at \(\geq 1\) constant basic cycle lengths) and is performed from \(\geq 1\) atrial sites.\(^6\) In the present study, extrastimulus testing was performed only during sinus rhythm from a single pacing site (proximal coronary sinus). In addition, increase in AH interval of \(\geq 50\) ms for a 10-ms decrement in pacing cycle length was also taken as indicative of the presence of dual AV node physiology. When such definitions were used, the incidence of dual AV node physiology in our patients (86%) was similar to the 85% incidence found by Josephson in a review,\(^7\) suggesting that our study group is representative of the population of patients with typical slow/fast AVNRT.

**Diagnostic Value of ATP Test**
We prospectively defined a 50-ms increment in the AH interval between 2 consecutive sinus beats after ATP admin-
istration as suggestive of dual AV node physiology. Selection of this 50-ms value as a cutoff point may seem rather arbitrary. This definition, however, is analogous to the one used to define duality during electrophysiological testing. In fact, the magnitude of the jump in AH interval observed in patients with AVNRT after ATP administration was far more impressive in the majority of study patients. In other words, whenever the presence of duality was suggested after ATP administration, the jump was obvious (mean AH increment of 162±70 ms) and relatively long lasting (observed on a mean of 4 beats). Moreover, AV nodal echoes occurred in 62% of patients demonstrating a ≥50-ms jump, and even sustained episodes of AVNRT were triggered in a few patients after ATP injection. 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.

Electrophysiological Correlations
We found no correlation between the presence of duality (by ATP criteria) and the cycle length at which blockade of the fast AV nodal pathway occurred during atrial overdrive pacing, suggesting that the response to ATP does not depend on the antegrade refractoriness of the fast pathway. More interestingly, signs of dual AV node physiology were observed after ATP administration in 3 of our 6 study patients who did not have electrophysiological evidence of dual physiology. This observation is consistent with the report of Sheahan et al on the electrophysiological effects of radiofrequency ablation of the slow pathway in patients without discontinuous curves of AV nodal conduction who nevertheless have AVNRT. These workers concluded that the apparently “smooth” AV node refractory curve consists, in fact, of two distinct components representing both fast and slow AV node pathways, even when the typical discontinuity is absent.

Correlations With Ablation Results
Successful radiofrequency ablation of the slow pathway is associated with either total elimination of antegrade conduction over the slow pathway or its “modification.” The last term is used to denote the fact that despite the persistence of antegrade slow pathway conduction, no more than a single AV nodal echo beat can be induced, even after isoproterenol administration. In the present study, the results of the ablation procedure correlated with the results of the postablation ATP test. Signs of dual AV node physiology after the ATP test disappeared in 11 (92%) of 12 patients after elimination of the slow pathway but persisted in 8 (62%) of 13 patients after modification of the slow pathway. Rather than repeating the ATP test after each radiofrequency application, we performed a second ATP test only at the end of the electrophysiological study, whenever either complete elimination or at least modification of slow AV nodal conduction was thought to have been achieved. Therefore, we have no data on the value of the ATP test to predict unsuccessful ablation (persistence of inducibility of AVNRT).

Safety
The safety of ATP administration during PSVT is well established.1,2 Recently, Flammang et al provided data on the safety of ATP injection during sinus rhythm. In this study, cardiac pauses lasting ≥10 seconds were observed in 3 (6%) of 51 healthy control subjects who received a single injection of 20 mg of ATP. Although 41 (67%) of our patients received ATP at dosages of ≥20 mg, pauses lasting >5 seconds were never observed. The difference in the definition of “pauses” used in the different studies should be noted. Flammang et al ignored single escape beats and measured the total pause between conducted sinus beats, whereas we measured the longest pause between ventricular complexes (sinus beats or escape beats). Moreover, acute interventions were never required after ATP-induced pauses in either of the 2 studies. Nevertheless, the ATP test should always be performed under close ECG observation.

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

Clinical Implications
ATP has already been successfully used in the noninvasive diagnosis of several arrhythmia disorders, such as the differential diagnosis of wide QRS complex tachycardia. ATP has also been used during sinus rhythm to establish the diagnosis of Wolff-Parkinson-White syndrome in patients with a minor degree of preexcitation or to assess the results of an ajmaline test in patients with preexcitation. More recently, injection of ATP was recommended to select treatment in patients with severe vasovagal syndrome. The results of the present study suggest that ATP may also be useful in the noninvasive diagnosis of dual AV node physiology in patients prone to AVNRT. Although the diagnosis of the slow/fast form of AVNRT is usually easy when a good-quality 12-lead ECG, recorded during a spontaneous episode, is available, it may be difficult if the tracing is of poor quality or if only 1 or 2 ECG leads (for example, from Holter or telemetry recordings) are available. The ATP test may be useful in the latter case, and additional studies are warranted to test this possibility. Another potential field of research on the ATP test may be the group of patients with normal resting ECGs and undocumented palpitations suggestive of PSVT. Because AVNRT is by far the most common mechanism of PSVT, the results of the test may help in selecting patients for diagnostic electrophysiological study and radiofrequency therapy. Our study did not include patients with other forms of narrow complex tachycardia. Thus, we cannot elaborate on the value of this test for identifying or excluding other arrhythmia mechanisms. Obviously, a negative ATP test would not exclude the possibility that other arrhythmias (such as AV reentry involving a concealed bypass) are responsible for the patient’s symptoms.
Nevertheless, a positive ATP test would be valuable because radiofrequency therapy of AVNRT is generally less time consuming than evaluation and radiofrequency therapy of patients with other arrhythmias. Accordingly, patients with a positive ATP test could be allotted less time when the electrophysiological laboratory is scheduled. Finally, although the electrophysiological effects of ATP in humans are in great part due to adenosine, the final product of the degradation of ATP, our results are only applicable for ATP. Because of conflicting data regarding the involvement of the vagus nerve in the mechanism of action of ATP in the human heart, one cannot exclude that a vagal component involved in ATP effects in humans played a role in our findings. Because adenosine rather than ATP is commonly used in the United States for the treatment of PSVT, additional studies of the effects of adenosine in the noninvasive diagnosis of dual AV node physiology are warranted.

References

Noninvasive Diagnosis of Dual AV Node Physiology in Patients With AV Nodal Reentrant Tachycardia by Administration of Adenosine-5′-Triphosphate During Sinus Rhythm
Bernard Belhassen, Roman Fish, Michael Glikson, Aharon Glick, Michael Eldar, Shlomo Laniado and Sami Viskin

Circulation. 1998;98:47-53
doi: 10.1161/01.CIR.98.1.47
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/98/1/47

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/