

# The Adenosine Triphosphate Test: A Bedside Diagnostic Tool for Identifying the Mechanism of Supraventricular Tachycardia in Patients With Palpitations

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<b>OBJECTIVES</b>	This study assesses the value of the “ATP test” (injection of adenosine triphosphate [ATP] during sinus rhythm) for identifying patients with palpitations of unclear etiology who actually have atrioventricular (AV) nodal re-entry tachycardia (AVNRT) or AV re-entry tachycardia (AVRT).
<b>BACKGROUND</b>	Because AVNRT and AVRT can be cured with radiofrequency ablation, documentation of spontaneous AVNRT or AVRT usually prompts referral for electrophysiologic (EP) evaluation. However, these paroxysmal arrhythmias may elude clinical diagnosis. We recently showed that administration of ATP during sinus rhythm often reveals dual AV node physiology or a concealed accessory pathway (AP) in patients with documented AVNRT or AVRT. Thus, we postulated that the ATP test could identify patients with palpitations who actually have AVNRT or AVRT and would therefore benefit from EP evaluation.
<b>METHODS</b>	One hundred forty-six patients (54 with “palpitations without documented arrhythmias” and 92 with “documentation of arrhythmias of unclear mechanism”) underwent a noninvasive ATP test. ATP was injected during sinus rhythm using 10 mg increments. The ATP test was considered positive when prospectively defined signs of dual AV node physiology or concealed AP were disclosed in the electrocardiogram. These findings were correlated with the results of EP evaluation.
<b>RESULTS</b>	A positive ATP test predicted induction of AVNRT or AVRT with a positive predictive value of 93% (sensitivity 71%) but a negative predictive value of 37% (specificity 76%).
<b>CONCLUSIONS</b>	A bedside ATP test identifies patients with palpitations who are likely to have AVNRT or AVRT (and who are therefore likely to benefit from EP evaluation) with a high positive predictive value. (J Am Coll Cardiol 2001;38:173-7) © 2001 by the American College of Cardiology

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Atrioventricular nodal re-entry tachycardia (AVNRT) and atrioventricular re-entry tachycardia (AVRT) involving an accessory pathway (AP) are relatively common supraventricular tachycardias that can be cured with radiofrequency ablation (RF). Because of the high success rate and the low complication rates achieved with RF ablation in these particular arrhythmias (1), documentation of spontaneous AVNRT or AVRT generally leads to referral for invasive electrophysiologic (EP) evaluation (1-3). However, AVNRT and AVRT are paroxysmal (often short-lasting) arrhythmias that may repeatedly elude clinical diagnosis. Such patients often experience multiple episodes of rapid palpitations before a correct diagnosis is made. Also, palpitations may be caused by other arrhythmias (such as premature beats or atrial fibrillation) that are less amenable to RF ablation, or may be related to sinus tachycardia. Differentiation of patients with AVNRT or AVRT (from patients with arrhythmias for which RF ablation is less successful or is not indicated), using a noninvasive test, will

help to select patients for early referral to invasive EP studies.

We previously showed (4) that administration of ATP during sinus rhythm identifies the presence of dual AV node physiology in 76% of patients with documented and inducible sustained AVNRT. More recent data from our group (5) suggest that ATP administration during sinus rhythm may expose the presence of a concealed AP in 73% of patients with documented AVRT, and similar data exist for adenosine (6). Therefore, we postulated that the ATP test could be of use for identifying patients with palpitations who actually have AVNRT or AVRT.

## METHODS

**Patient population.** The study group consisted of consecutive patients referred for EP consultation because of palpitations of unclear etiology. On the basis of the initial evaluation, the study population was categorized into two subgroups. The first group consisted of patients without documented arrhythmias who were included if their clinical history was suggestive of a paroxysmal supraventricular tachycardia because the palpitations were rapid and started suddenly. Although a sudden termination of rapid heart

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**Abbreviations and Acronyms**

AP	= accessory pathway
ATP	= adenosine triphosphate
AVNRT	= atrioventricular nodal re-entry tachycardia
AVRT	= atrioventricular re-entry tachycardia
ECG	= electrocardiograms
EP	= electrophysiologic
NS	= not statistically significant
RF	= radiofrequency ablation

beat would probably increase the likelihood of a paroxysmal supraventricular tachycardia, this was not considered a requisite for inclusion.

The second group consisted of patients with arrhythmia documentation, who were included if the mechanism of the documented arrhythmia could not be identified from the available electrocardiograms (ECG) (which consisted mainly of single-lead ECG recordings of the arrhythmia, Holter recordings, telemetry, portable monitors or transtelephonic recordings). Specifically, patients with documented supraventricular tachycardias that could be diagnosed from available ECGs were not included in this study. Patients were excluded if they had an antegradely conducting AP or if they had bronchial asthma (which is a contraindication for ATP administration). All patients gave informed consent to undergo the ATP test and EP study. Our Helsinki Committee approved the study protocol. Some patients included in the present study also appear in two reports dealing with different aspects of the electrophysiologic effects of ATP administration during sinus rhythm (5,7).

**ATP test.** The ATP test was performed as a bedside test during sinus rhythm. Adenosine triphosphate (Striadyne, Ayerst Laboratories, Paris, France) was injected through an antecubital vein as a rapid bolus, followed by a 20 ml flush of normal saline, during continuous ECG recording. The initial ATP dose was 10 mg. Repeated injections (using 10 mg increments, up to a maximum of 60 mg) were given until one of the prospectively defined end points allowed defining the ATP test as positive, negative or inconclusive (Table 1). An ATP test was positive when it revealed the presence of dual AV node physiology or a concealed AP, by demonstrating: 1) a sudden  $\geq 50$  ms increment (or decrement) in the PR interval of consecutive sinus beats, or 2) by triggering echo beats, AVNRT or AVRT (Table 1, Fig. 1). 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 node firing rate. Therefore, AV nodal echoes were considered to be present if when following a sinus complex conducted with increased PR interval, a  $>70\%$  increment in sinus node cycle length (P-P interval) was observed (even if a retrograde P wave at the end of the QRS complex could not be clearly identified) (Fig. 1A). We have found that a good correlation exists between these ECG criteria and the diagnosis of AV nodal echoes using endocardial recordings (4). Finally, the diag-

**Table 1.** ATP Test: Definitions\*

Test Interpretation	Outcome of ATP Injection During Sinus Rhythm
Positive ATP test	
Suggestive of DAVNP	A $\geq 50$ ms $\dagger$ PR increment in two consecutive sinus beats A $\geq 50$ ms $\dagger$ PR shortening in two consecutive sinus beats Occurrence of AV nodal echoes or AVNRT
Suggestive of concealed AP	Occurrence of AVR echo beats or AVRT
Negative ATP test	Occurrence of II $^\circ$ or III $^\circ$ AV block without any of the above
Inconclusive test	1) Failure to demonstrate any of the above despite incremental administration of up to 60 mg of ATP 2) Premature discontinuation of the test because of intolerance ( $\geq 3$ s of sinus arrest or patient refusal to continue)

\*All the definitions were prospective and all the adenosine triphosphate (ATP) tests were interpreted before the electrophysiologic evaluation. The ATP test was positive when any of the criteria suggestive of dual atrioventricular node physiology (DAVNP) or suggestive of a concealed accessory pathway (AP) were observed.  $\dagger$ The  $\geq 50$  ms change in PR value was selected to define DAVNP in analogy to the criteria used for defining dual physiology during electrophysiologic studies (16). Accordingly, a  $\geq 50$  ms PR increment, i.e., a "PR jump" following ATP injection, was considered to represent ATP-induced blockade of fast atrioventricular (AV) nodal conduction (unmasking a slow AV nodal pathway). Conversely, a sudden  $\geq 50$  ms decrement in PR (after gradual PR prolongation or AV block) was taken as representing resumption of fast AV nodal conduction.

nosis of AVR echoes and AVRT after ATP injection was made by consensus (by at least two electrophysiologists) based on electrocardiographic criteria. In other words, the atrial depolarizations observed after ATP injection were believed to be consistent with retrograde conduction over an accessory pathway in regards to the P' wave morphology and timing (within the ST segment) (Fig. 1B). The diagnosis was subsequently confirmed at the EP study.

**EP study.** The EP study was performed as previously described (4). Baseline evaluation included 1) delivery of one to three extra stimuli during high right atrial pacing at a cycle length of 600 ms until the atrial or AV nodal refractory period was reached; 2) incremental high right atrial pacing up to the AV nodal block cycle length; 3) delivery of  $\leq 2$  ventricular extra stimuli during ventricular pacing at a cycle length of 600 ms until the ventricular or ventriculoatrial refractory period was reached and 4) incremental ventricular pacing up to the VA block cycle length. If AVNRT or AVRT were not inducible with this protocol (even if other arrhythmias such as atrial tachycardia or atrial fibrillation were induced), isoproterenol was administered until the basic sinus rhythm increased by at least 20% and the stimulation protocol was repeated. Standard EP criteria for defining dual AV node physiology (4), AVNRT (4) or AVRT (8) were used. Whenever AVNRT or AVRT was induced, RF therapy was performed as previously described (4).

**Statistics.** Data are expressed as mean  $\pm$  SD. Statistical analysis was performed using chi-square test. A value of  $p < 0.05$  was considered statistically significant.



**Figure 1.** (A) Positive adenosine triphosphate (ATP) test demonstrating dual atrioventricular (AV) node physiology in a 22-year-old male with palpitations. The PR and PP intervals are shown in ms. Following injection of ATP, there is gradual acceleration of sinus rate and sudden increment of the PR interval from 160 to 340 ms (arrow). This “PR jump” of 180 ms probably denotes ATP-induced blockade of fast AV nodal conduction with exposure of the slow AV nodal pathway. Moreover, an AV nodal echo (\*) is assumed to be present because of the sinus node resetting following the PR jump (the PP interval suddenly increases from 520 to 1,000 ms). This patient had inducible AV nodal re-entry tachycardia. (B) Positive ATP test unmasking a concealed accessory pathway in a 16-year-old male with palpitations. Note the AV re-entry echo beats (arrow heads), which were of identical morphology to the retrograde P waves observed during the atrioventricular re-entry tachycardia that was eventually induced during the electrophysiologic study. (C) ATP test in a 52-year-old male with a 20-year history of episodic palpitations. This ATP test was considered negative, according to our prospectively defined criteria, because II° degree AV block (\*) occurred without evidence of dual AV node physiology or a concealed accessory pathway. Interestingly, a few seconds after the onset of paroxysmal AV block, an atrial tachycardia (atrial rate 220 beats/min) ensued (small arrows). Provocation of nonsustained atrial tachycardia by ATP was reproducible. During the electrophysiologic study, this patient spontaneously developed an atrial tachycardia (with identical P-wave morphology) that was ablated in the left atrium.

## RESULTS

**Patient population.** The study group consisted of 146 patients with palpitations of unclear etiology. This group included 54 patients (27 men, 27 women, average age  $38 \pm 18$  years) with “palpitations without documented arrhythmias” and 92 patients (42 men, 50 women, aged  $44 \pm 16$  years) with “documentation of arrhythmias of unclear mechanism.” All these patients underwent the ATP test during sinus rhythm and then underwent EP evaluation.

**Results of the ATP test.** Five patients (3%) declined to continue with the study protocol after receiving 20 mg (three patients) or 40 mg (two patients) of ATP. These patients (three with palpitations without documented arrhythmias and two with arrhythmias of unclear mechanism) were the only patients with an inconclusive ATP test and were excluded from further analysis. One additional patient was excluded because the ATP test revealed the presence of

an antegradely conducting left lateral accessory pathway that was not recognized from the baseline electrocardiogram because pre-excitation was minor.

From the 140 patients who completed the study protocol, a positive ATP test was observed in 88 patients (63%) after injection of  $15.6 \pm 6$  mg of ATP (the actual doses needed were 10 mg in 55%, 20 mg in 28% and 30 mg to 40 mg in 17% of patients). The positive ATP test included disclosure of dual AV node physiology in 79 patients (57%) and disclosure of a concealed accessory pathway in nine patients (6%) (including one patient who also had disclosure of dual AV node physiology). This occurred in 30 patients (60%) with palpitations and no documented arrhythmias and in 58 patients (64%) with arrhythmias of unclear mechanism ( $p = NS$ ). A negative ATP test was observed in 52 patients (37%) following administration of  $14 \pm 5$  mg of ATP, including 10 mg in 23%, 20 mg in 55% and  $>20$  mg in 22% of

patients. Almost all patients reported flushing, nausea or chest discomfort after the ATP injection, but serious side effects never occurred.

**Correlation of the ATP test with the EP evaluation.** A positive ATP test was highly predictive of the results of EP evaluation: 73 patients (92%) with signs of dual AV node physiology according to the ATP test had inducible sustained AVNRT. Moreover, all nine patients who developed AV reentrant echo beats during the ATP test had inducible sustained AV re-entry tachycardia involving a concealed accessory pathway. The positive predictive value of a positive ATP test for predicting AVNRT or AVRT was 93% (sensitivity 71%).

Of the 52 patients with a negative ATP test, 29 patients had inducible AVNRT, four had AVRT, two had inducible sustained atrial tachycardia and 17 patients had no inducible arrhythmias. Of note, both patients with inducible atrial tachycardia had reproducible provocation of atrial tachycardia by ATP administration during sinus rhythm. The negative predictive value of the ATP test was 37% (specificity 76%).

In the subgroup of 50 patients with palpitations but no documented arrhythmias, the results of the bedside ATP test predicted the induction of sustained AVNRT or AVRT with a positive predictive value of 97%, a sensitivity of 78% and a specificity of 92%. The negative predictive value, however, was only 60%.

## DISCUSSION

The high therapeutic efficacy of ATP in terminating AVNRT or AVRT has been recognized for many years (8,9). Yet evaluation of adenosine compounds for diagnostic purposes has only recently been pursued (4-7,10-12). Adenosine triphosphate injection during sinus rhythm has been used to demonstrate the presence of an antegradely conducting accessory pathway in patients who have only minor pre-excitation during sinus rhythm (10,11). More recently, we described how ATP injection during sinus rhythm identifies dual AV node physiology in patients with documented spontaneous and inducible AVNRT. Evidence presented in that study (4) suggested that ATP exposes dual AV node physiology by preferentially blocking conduction along the fast AV nodal pathway during sinus rhythm. Finally, new data suggest that injection of ATP (5) or adenosine (6) during sinus rhythm will unmask the presence of a concealed AP in patients with documented AVRT (mainly by creating enough delay in antegrade AV nodal conduction to allow recovery of atrial excitability). In contrast, false-positive ATP tests (that is, ATP tests suggestive of the presence of dual AV node or concealed pathway conduction when electrophysiologic evidence of such conduction is absent) are only rarely observed (4,5,7). Our present study confirms that injection of adenosine compounds during sinus rhythm effectively discloses the presence of dual AV node physiology or a concealed AP.

Moreover, our results demonstrate that these observations have important clinical value because they identify many patients with curable arrhythmias among those with palpitations of unclear mechanism. As in previous studies (4,5,7), ATP was well tolerated and no serious side effects occurred during this bedside test.

**Patients with palpitations but no documented arrhythmias.** Palpitations are a commonly encountered complaint in outpatient clinics. Although the clinical history and baseline ECG provide important diagnostic clues, further testing is usually required to establish a definitive diagnosis (13). Ambulatory ECG monitoring (with Holter monitoring or event recorders) may provide useful information (13), but these tests are often negative even if performed repeatedly (14). Consequently, "palpitations without documented arrhythmias" may be erroneously ascribed to panic, anxiety or "stress" in up to 54% of patients (and in up to 65% of women) with AVNRT or AVRT (14). Our study suggests that administration of ATP during sinus rhythm may unmask the presence of dual AV node physiology or a concealed AP in these patients. By so doing, this ATP test may identify patients with palpitations who are most likely to benefit from early referral to invasive EP studies. Among the 50 patients with palpitations but no documented arrhythmias in our study, unmasking of dual AV node physiology or the presence of a concealed AP by ATP (at a bedside test) was highly predictive of the induction of AVNRT or AVRT at EP study (positive predictive value 97%). These results are comparable with those reported by Tebbenjohanns with adenosine administration during sinus rhythm in 30 patients with palpitations without documented arrhythmias (15).

**Patients with documented arrhythmias of unclear mechanism.** The mechanism of paroxysmal arrhythmias may not always be evident even when these are fortuitously recorded. This is especially true when only single-lead or poor-quality ECG recordings are available. It could be argued that patients with documented yet undiagnosed tachyarrhythmias will need an EP evaluation regardless of the results of the ATP test. Nevertheless, this test might provide useful information. Our study shows that demonstration of dual AV node physiology with the ATP test is highly predictive of AVNRT induction (positive predictive value 90%). Knowing in advance that the arrhythmia to be encountered at the EP study will be AVNRT might be important for some patients. For example, elderly patients, who might be at higher risk for complications during left heart catheterization (because of a higher incidence of atherosclerotic disease) can be reassured that a venous catheterization will most likely suffice to cure their arrhythmia if dual AV node physiology is revealed during the ATP test. Also, ablation of AVNRT is often a short procedure (performed with only two catheters in our laboratory). Therefore, prediction of AVNRT by the ATP test is useful when scheduling cases in a busy catheterization room.

**Study Limitations.** 1) The main limitation of the ATP test is its low negative predictive value. Although patients with a positive ATP test were likely to have inducible AVNRT or AVRT, a negative ATP test often failed to predict a negative EP study. Rather than invalidating our study, this suggests that protocol modifications are needed. For example, reducing the ATP dosage by 5 mg—after a 20-mg increment blocked the antegrade AV nodal conduction completely—could potentially increase the likelihood of selective blockade of the fast AV nodal pathway or could create just enough conduction delay to unmask a concealed AP. 2) Our patient population had a high rate of inducible arrhythmias. This reflects the careful selection of our patients, in the sense that their clinical history was suggestive enough of a supraventricular tachycardia to warrant further evaluation. Hence, the ATP test may not necessarily be as reliable when evaluating patients with more atypical symptoms.

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