Noninvasive Diagnosis of Cardiac Arrhythmias Using Adenosine Compounds

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Known for more than 70 years,¹ the transient negative dromotropic effects of adenosine compounds on the atrioventricular (AV) node have been widely used in clinical practice.²⁻⁴ Both adenosine and adenosine triphosphate (ATP)—which mainly acts via its degradation to adenosine—have been shown to be highly effective in the termination of reentrant paroxysmal supraventricular tachycardia (PSVT) involving the AV node^{5,6} or in the transient slowing of ventricular rate of atrial tachyarrhythmias. In most countries, these compounds have supplanted verapamil for this indication.^{7,8} Recent studies, most originating from our laboratory, have shown that adenosine compounds can also be very useful in the noninvasive diagnosis of various cardiac arrhythmias. The purpose of this article is to review the diagnostic use of adenosine compounds in cardiac arrhythmias. The use of ATP in the investigation of patients with unexplained syncope, developed in a recent Task Force Report on Syncope from the European Society of Cardiology,⁹ is not discussed in this article.

DIFFERENTIAL DIAGNOSIS OF REGULAR, WIDE QRS TACHYCARDIA

Adenosine compounds do not affect the vast majority of sustained ventricular tachycardias (VT), especially those occurring in patients with healed myocardial infarction or with various cardiac diseases. Therefore, adenosine compounds were proposed many years ago¹⁰ to distinguish VT from SVT, postulating that termination or slowing of a wide QRS tachycardia with adenosine compounds

indicate a supraventricular origin whereas the lack of effects indicate a ventricular origin.¹¹⁻¹³ Although a study¹³ showed that a correct diagnosis of VT is made more often when based on the effects of adenosine (92%) than based on electrocardiographic criteria, we do not use systematically adenosine compounds for this diagnostic purpose for the following reasons: (1) some cases of VT, mostly those of idiopathic origin¹⁴⁻¹⁶ but also more exceptionally some occurring in postmyocardial infarction patients, do actually respond to adenosine compounds; at the opposite, a rare type of "PSVT" such as the one resulting from a reentrant mechanism involving an accessory pathway both in the antegrade and retrograde directions will not be terminated by adenosine compounds; (2) the administration of adenosine compounds in patients with VT can result (albeit rarely) in deterioration to ventricular fibrillation;¹⁷ also, such drug administration during reentrant tachycardia involving two accessory pathways may have deleterious consequences owing to adenosine-induced shortening of the atrial and accessory pathway refractoriness that can degenerate into atrial fibrillation and/or significant acceleration of the ventricular rate;^{18,19} (3) the routine use of adenosine compounds in the diagnosis of wide QRS tachycardia encourages intellectual laziness rather than stimulates systematic analysis of ECG tracings.

DIAGNOSIS OF LATENT FORMS OF PREEXCITATION

In the great majority of patients with the Wolff-Parkinson-White (WPW) syndrome, the diagnosis

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Figure 1. (A) Incomplete right bundle branch block without signs of preexcitation is present during sinus rhythm (PR = 0.14 s); (B) After administration of ATP (20 mg IV), slight slowing of sinus rate with obvious antegrade preexcitation over a right posteroseptal accessory pathway is observed and followed by atrial fibrillation and preexcited QRS complexes.

of ventricular preexcitation is manifest during sinus rhythm, based on the association of short PR interval, delta wave, and wide QRS complex. In some patients, a minor degree of preexcitation or no preexcitation at all are observed despite the presence of antegrade conduction over the accessory pathway (latent preexcitation).²⁰ The most typical case of latent preexcitation is represented by an accessory pathway located at the lateral free wall of the mitral valve annulus associated with enhanced AV nodal conduction and/or intraatrial

conduction disturbances. In that instance, the administration of adenosine compounds, by transiently delaying AV nodal conduction, can result in an increase of the degree of preexcitation, that allows an accurate location of the accessory pathway.²¹ Figure 1 shows a less frequently observed example of latent preexcitation over a right posteroseptal accessory pathway unmasked by administration of ATP. In the past, the ATP test was also used for enabling the assessment of the effects of pharmacologic agents (such as ajmaline) on preex-

Figure 2. (A) Before ATP administration: intermittent preexcitation (right anteroseptal accessory pathway) with only few preexcited complexes during sinus rhythm (80/min); (B) 20 seconds after administration of 10mg ATP, almost permanent preexcitation associated with increased sinus rate (100/min).

citation when the effects of these agents on preexcitation were not obvious.²²

REVELATION OF ACCESSORY PATHWAYS WITH INTERMITTENT CONDUCTION OR PHASE 3 BLOCK

In patients with intermittent preexcitation, antegrade conduction over the accessory pathway may disappear for undetermined, long periods of time. In such instances, adenosine^{23,24} and ATP (Fig. 2) may elicit the manifestation of the preexcitation, albeit transiently. The mechanism underlying this phenomenon seems to be related to the shortening of the action potential duration of the accessory pathway secondary to adenosine administration.¹⁸

In other instances, accessory pathways may exhibit during sinus rhythm a very long antegrade refractory period that overcomes the sinus cycle length, thereby preventing the diagnosis of ventricular preexcitation. In such patients, the marked sinus bradycardia following the administration of ATP may unmask the preexcitation.

NONINVASIVE DIAGNOSIS OF DUAL AV NODAL PHYSIOLOGY

Dual AV nodal physiology reflects the functional existence of two pathways in the AV nodal area, one "fast" and one "slow" which have different refractory periods with the fast pathway having a longer antegrade refractory period than the slow pathway. Such dual AV node physiology consti-

ATP 20 mg

Figure 3. Positive ATP test for antegrade dual AV nodal physiology in a patient with spontaneous and induced slow/fast AV nodal reentry tachycardia. About 13 seconds following the administration of 20 mg ATP, a sudden jump (+ 100 ms) of PR interval occurs on the third complex suggesting antegrade conduction block in the fast pathway with conduction over the slow pathway; on the 7th complex, the PR interval shortens suddenly suggesting resumption of conduction over the fast pathway.

utes the electrophysiological substrate of AV nodal reentry tachycardia (AVNRT) which is the most frequently observed regular PSVT in clinical practice. In 95% of cases of AVNRT, antegrade conduction proceeds via the slow pathway while retrograde conduction proceeds via the fast pathway (typical "slow-fast" form). Administration of adenosine or ATP during *sinus rhythm* in patients with such typical AVNRT was shown by our group and others to be highly effective in revealing dual AV nodal physiology, due to the higher sensitivity of the antegrade fast pathway to adenosine.²⁵⁻²⁷ In

about 75% of patients with inducible sustained slow/fast AVNRT, transient dual AV node physiology is observed about 10-15 seconds following drug administration and manifests as sudden PR prolongation or PR shortening by ≥ 50 ms on two consecutive sinus beats, followed or not by an AV nodal echo beat (Fig. 3). Induction of AVNRT, usually facilitated by atrial hyperexcitability triggered by adenosine compounds is observed in 7% of patients.²⁵ A relatively good correlation (72%) between the presence of dual AV node physiology by ATP test and electrophysiological testing was also

found by our group.²⁶ In addition, we surprisingly noted that the ATP test disclosed dual AV node physiology in 93% of patients who had *no* evidence of AV nodal duality during single atrial extrastimulation or incremental atrial pacing.²⁶ Such results confirm previous reports suggesting that two distinct components, representing both fast and slow pathways, are present in patients with AVNRT irrespectively of the existence of discontinuity of the AV nodal curves during atrial extrastimulation.²⁸ Finally, no significant relationship between the antegrade fast pathway refractoriness and the sensitivity of the fast pathway to ATP was found in two studies,^{25,26} suggesting that the ATP test has the potential to reveal dual AV node physiology in any patient with AVNRT and not only among those patients with prolonged fast pathway refractoriness.

NONINVASIVE ASSESSMENT OF THE RESULTS OF SLOW PATHWAY ABLATION

The ATP test is also useful in the noninvasive assessment of the results of radiofrequency ablation of the slow pathway. We showed that dual AV node physiology by ATP test disappeared in 96% of patients who underwent slow pathway abolition and in 60% of patients who underwent slow pathway modification.²⁶ In the patients who showed persistent dual AV node physiology by ATP test after slow pathway modification, a significant reduction (≥ 2 beats) in the number of beats conducted over the slow pathway was observed. Therefore, ATP testing would be useful in predicting recurrence of AVNRT after a successful radiofrequency ablation in patients who complain of palpitations. For example, the lack of dual AV node physiology following an ATP test in a patient who had dual AV node physiology before ablation would strongly suggest that the symptoms are unlikely to be related to AVNRT recurrence.

NONINVASIVE DIAGNOSIS OF CONCEALED ACCESSORY PATHWAY

The negative AV nodal dromotropic effects of ATP led us to hypothesize that the administration of ATP during *sinus rhythm*, by the means of the transient AV nodal conduction delay, could facilitate the occurrence of AV reentrant orthodromic

echo beats (AVRE) or AV reentrant tachycardia (AVRT) in patients with concealed accessory pathways. Therefore we evaluated the value of the intravenous administration of ATP during sinus rhythm in the noninvasive diagnosis of the presence of a concealed accessory pathway and associated dual AV node physiology in 33 patients with inducible sustained AVRT and in 27 control patients.²⁹ AVRE or AVRT were found in 24 (73%) study patients and in none of the control group (Fig. 4). ECG signs suggestive of associated dual AV node physiology were observed after ATP administration in 7 (21%) study patients and in none of the control group (Fig. 4). When extending our study group to 57 patients, we found a similar incidence of AVRE or AVRT (70%); however, the incidence of dual AV nodal physiology was much lower (14%) (unpublished data) and more in agreement with the incidence of dual AV node physiology in patients with concealed accessory pathways as found in the literature.

NONINVASIVE DIAGNOSIS OF THE MECHANISM OF TACHYCARDIA IN PATIENTS WITH PALPITATIONS OR SVT OF UNDETERMINED MECHANISM

Based on the beneficial role of ATP in the noninvasive diagnosis of dual AV node physiology and concealed accessory pathway, our group also evaluated in 146 patients, the predictive accuracy of an ATP test for identifying patients with palpitations or supraventricular arrhythmias of unclear mechanism who would benefit from invasive electrophysiological evaluation.³⁰ The results of the ATP test were correlated with the results of a subsequent electrophysiological study. A positive ATP test predicted the presence of AVNRT or AVRT with a positive predictive value of 93% (sensitivity = 71%) but a negative predictive value of 37% (specificity = 76%). Moreover, signs of dual AV node physiology by ATP test predicted the induction of AVNRT with a predictive positive value of 92%. Therefore, an ATP test identified patients with palpitations who are likely to have AVNRT or AVRT (and therefore may benefit from electrophysiological evaluation) with a high positive predictive value. In addition, knowing in advance that the arrhythmia to be encountered at the electrophysiological study will be AVNRT might be important for some patients. For example, elderly

Figure 4. Positive ATP test for concealed accessory pathway and dual AV node physiology in a patient with spontaneous and inducible AV reentrant tachycardia involving a left posterior accessory pathway. About 15 seconds following the administration of 30 mg ATP, a sudden jump in PR interval by 80 seconds suggesting dual AV node physiology is observed on the second complex. A further increase of PR interval by 20 ms is noted on the third complex, followed by an atrioventricular echo beat with $RP' = 0.12$ seconds. The retrograde P wave is negative in aVF, positive in aVR and V_1 , and isodiphasic in aVL, consistent with a left posterior location of the accessory pathway.

patients, who might be at higher risk for complications during left heart catheterization can be reassured that a venous catheterization will most likely suffice to cure their arrhythmia if dual AV node physiology is revealed during an ATP test. Finally, ablation of AVNRT is often a short procedure (performed with only two catheters in our laboratory) and prediction of AVNRT by ATP test is useful when scheduling cases in a busy catheterization room.

DUAL AV NODE PHYSIOLOGY AT TERMINATION OF PSVT BY ATP

In a recent study from our laboratory (unpublished data), we found that 30 (36.5%) of 82 pa-

tients exhibited dual AV node physiology at the termination of AVNRT following administration of 10.6 ± 2.4 mg ATP. In contrast, only one (5.5%) of 18 control patients (with AVRT and no dual AV node physiology at electrophysiological study) showed slight (60 ms) PR jump after termination of AVRT with ATP. Thus, findings at termination of PSVT by ATP may be useful in the noninvasive diagnosis of the mechanism of the tachycardia.

SAFETY AND TOLERANCE

The administration of adenosine or ATP frequently results in side effects (dyspnea, malaise) which are almost always minor and transient, disappearing in < 1 minute. Sinus bradycardia and

high degree AV block, frequently observed, are exceptionally symptomatic due to their short-lasting duration. Adenosine compounds exert a proarrhythmic effect at the atrial level^{31,32} with atrial fibrillation observed in our experience in < 2% of patients when injected during sinus rhythm. Atrial fibrillation is usually short-lasting and uneventful; however, deleterious consequences can be observed when adenosine compounds are administered in patients having antegradely conducting accessory pathways (Fig. 1), especially those with a short refractory period. Finally, there have been a few reports of torsades de pointe occurring in patients with a long QT syndrome and treated with adenosine for terminating PSVT.^{33,34} In any case, these exceptional complications justify that the administration of adenosine compounds should be performed under strict cardiac monitoring and only by well equipped experienced medical personnel.

CONCLUSIONS

First used as a major agent in our therapeutic arsenal for terminating PSVT, adenosine compounds have gained importance as a bedside diagnostic tool in a variety of clinical settings, especially in the diagnosis of wide QRS tachycardia, and the noninvasive diagnosis of dual AV node physiology, latent or concealed accessory pathway. Further studies are required to assess the potential use of these agents in the noninvasive identification of other types of tachyarrhythmias, such as atrial fibrillation or the long QT syndrome.

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