Effects of Intravenous Adenosine on Antegrade Refractoriness of Accessory Atrioventricular Connections

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Background. Several groups have suggested the use of intravenous adenosine or adenosine triphosphate in the diagnosis of regular broad complex tachycardias. However, the short half-life of these agents has precluded assessment of their effects on refractoriness of accessory connections, and their safety in preexcited arrhythmias has not been demonstrated.

Methods and Results. We examined the effects of intravenous adenosine on accessory atrioventricular (AV) connections in 30 patients with the Wolff-Parkinson-White syndrome. Intravenous adenosine (12 mg, rapid bolus) was administered to 14 patients (group 1) during continuous atrial pacing at a cycle length 20 msec below that required to cause 2:1 conduction block in the accessory connection (mean pacing cycle length 261±41 msec). After adenosine, transient 1:1 conduction occurred via the accessory connection in 12 of 14 patients, indicating a shortening of antegrade refractoriness. In three of seven patients, this effect was abolished after intravenous propranolol (0.2 mg/kg). Nineteen patients (group 2) received adenosine (0.17±0.04 mg/kg) during induced, preexcited atrial arrhythmias. The minimum RR interval during preexcited atrial fibrillation transiently decreased (252±44 msec to 224±35 msec, p<0.01) after adenosine, but no change in average RR interval was observed (360±59 msec to 357±60 msec, NS). The preexcited ventricular response to atrial flutter was transiently accelerated in five of eight patients (415±21 msec to 360±49 msec, p<0.05) due to shortening of flutter cycle length (207±10 msec to 180±24 msec, p<0.05). However, 2:1 accessory connection conduction was maintained in all eight patients. All effects were short lived, with the decrease in RR interval during atrial fibrillation occurring for a maximum of two RR intervals only. No patient suffered ventricular arrhythmias or hemodynamic deterioration.

Conclusions. Adenosine shortens antegrade refractoriness of accessory AV connections, and in some patients this action is mediated by β-adrenergic stimulation. Adenosine may cause acceleration of preexcited atrial arrhythmias, but these effects are transient and should not discourage the use of adenosine as a diagnostic agent in broad complex, regular tachycardias of uncertain origin. (Circulation 1991;84:1962–1968)

Broad complex tachycardias are frequently misdiagnosed and inappropriately treated both in North America and the United Kingdom. Patients with ventricular or preexcited arrhythmias are often incorrectly diagnosed as having supraventricular tachycardia with aberrant conduction to the ventricles via the atrioventricular (AV) node. It is not unusual for intravenous verapamil to be administered to these patients, with potentially fatal consequences. Recently, several groups have suggested the use of intravenous adenosine or adenosine triphosphate (ATP) as a diagnostic agent in these circumstances. Adenosine has been shown to be safe in patients with ventricular tachycardia, but safety in preexcited arrhythmias has not been demonstrated. The short half-life of adenosine has precluded assessment of its effects on antegrade refractoriness of accessory connections, and previous studies have been restricted to documenting the low incidence of adenosine or ATP-induced conduction block in accessory connections.

The aims of this study were 1) to determine whether adenosine is capable of shortening accessory connection antegrade refractoriness and 2) to examine the safety of adenosine when administered to patients during preexcited atrial arrhythmias.
Methods

Patient Selection

The study population consisted of 30 patients referred to our institution for electrophysiological assessment of the Wolff-Parkinson-White syndrome. Two groups of patients were selected for the study. Group 1 (14 patients) consisted of patients with persistent preexcitation in whom stable 2:1 antegrade conduction via the accessory connection could be maintained by atrial pacing at a site close to the insertion of the accessory connection. Group 2 (19 patients) comprised patients with preexcited atrial arrhythmias induced at electrophysiological study. Three patients were included in both groups 1 and 2. Eight of the patients in group 2 have been described briefly in a preliminary study.6

Electrophysiological Study

Diagnostic electrophysiological studies were performed in the fasting, nonsedated state after informed consent had been obtained. All antiarrhythmic therapy had been stopped for at least 48 hours before the diagnostic electrophysiology study, and no patients had been taking amiodarone. Four multipolar electrode catheters were inserted percutaneously and advanced under fluoroscopic guidance to the high right atrium, coronary sinus, right ventricular apex, and the AV junction to record the His potential. Bipolar intracardiac signals were recorded on paper simultaneously with at least four surface ECG leads (I, aVF, V1, V6). Atrioventricular–His (AH) and His–ventricular (H–V) intervals were measured by standard techniques.12 Programmed atrial and ventricular stimulation was performed with a programmable constant current stimulator that delivered rectangular pulses of 2-msec duration at two times diastolic threshold. Tachycardia induction was attempted by the introduction of progressively premature ventricular or atrial extrastimuli at two basic drive cycle lengths (usually 400 msec and 500 msec). If a single extrastimulus (atrial or ventricular) failed to induce tachycardia, then a second extrastimulus was introduced. Finally, induction of tachycardia was attempted by burst atrial pacing at a cycle length of 300 msec. Diagnosis of tachycardia mechanism was made according to standard criteria.12 The site of the atrial insertion of the accessory connection was defined as the site of earliest atrial activation (shortest VA interval) during AV reentrant tachycardia or ventricular pacing when retrograde atrial activation occurred via the accessory connection. Mapping of the mitral annulus was performed with a multipolar electrode in the coronary sinus, and mapping of the tricuspid annulus was performed using standard techniques.13 Antegrade and retrograde effective refractory periods of accessory connections were measured by the extrastimulus technique with an eight-beat atrial or ventricular basic drive train at a cycle length of 500 msec, an intertrain pause of 3 seconds, and 10-msec decrements in the extrastimulus coupling interval.

Study Protocol

Group 1. After the diagnostic electrophysiological study, the atrium was paced continuously at a site close to the atrial insertion of the accessory connection (see above). The initial pacing cycle length was decreased from an initial cycle length just below the sinus cycle length by 10-msec intervals until 2:1 conduction block occurred in the accessory connection. PACing cycle length was decreased by a further 20 msec, and pacing continued at this cycle length for 2 minutes to ensure stable 2:1 accessory connection conduction. At this point, adenosine was administered via a peripheral vein as a rapid bolus injection: Seven patients received an initial dose of 3 mg and then, after at least 1 minute, a further dose of 12 mg; in the remaining seven patients, the order of adenosine dosages was reversed (i.e., 12 mg followed by 3 mg). The response was recorded on paper at a speed of 100 mm/sec. In seven patients, this protocol was repeated after intravenous propranolol. Propranolol was infused at a rate of 1.0 mg/min to a total dose of 0.2 mg/kg in six of the eight patients. This dose of propranolol has been demonstrated previously to block the effects of β-adrenergic stimulation on the sinus rate.14 In two patients (patients 1 and 2), the total dose of propranolol was restricted to 10 mg (1.4 mg/kg and 1.5 mg/kg, respectively) because of development of sinus bradycardia suggestive of an adequate β-blocking effect.

Group 2. After induction of preexcited atrial arrhythmia and diagnosis of its mechanism, the tachycardia was allowed to continue uninterrupted for 5 minutes. In those patients with inducible atrial fibrillation, electrograms were analyzed (minimum and average RR intervals) over a period of 2 minutes before adenosine injection. Adenosine was administered via a forearm vein as a rapid (within 1 second) bolus dose of 0.05 mg/kg. Thereafter, incremental doses were given (increasing by 0.05 mg/kg up to 0.25 mg/kg) at 1-minute intervals until tachycardia was terminated, tachycardia was accelerated, or dosage was limited by symptoms. The response was recorded on paper at a speed of 100 mm/sec and was assessed by analysis of electrograms during the 60 seconds after adenosine injection.

Statistical Analysis

The effects of propranolol on the minimum RR interval during atrial pacing, the effects of adenosine on the minimum and average RR interval during atrial fibrillation, and the effects of adenosine on atrial flutter cycle length were analyzed by the paired t test. A value of p<0.05 was considered significant. All values are expressed as mean±1 SD.

Results

Group 1 (14 patients). The clinical characteristics and response to adenosine of individual patients in this group are described in Table 1. Mean age was 33 years (range, 22–54 years), and nine were men. Nine
patients had experienced spontaneous episodes of orthodromic AV reentrant tachycardia and five had experienced spontaneous atrial fibrillation or flutter. All patients had a single accessory connection with nondecremental conduction properties. No patient had a history of intermittent preexcitation, and mean antegrade accessory connection refractory period was 299±44 msec in those patients in whom it could be measured by the extrastimulus technique. Atrial fibrillation was inducible in 13 of 14 patients, and mean shortest RR interval between preexcited beats was 267±46 msec. Mean shortest RR interval during atrial pacing was 291±41 msec. There was a strong correlation between minimum RR interval during atrial pacing and effective refractory period measured by the extrastimulus technique in these patients (Figure 1). After the administration of adenosine (12 mg) during atrial pacing and 2:1 accessory connection conduction block (mean pacing cycle length of 261±41 msec), transient 1:1 conduction occurred via the accessory connection in 12 of 14 patients, indicating a shortening of antegrade refractoriness (Figure 2). This response was seen in only one patient after the lower dose of adenosine (3 mg). The time to transition from 2:1 to 1:1 conduction varied from 10 to 20 seconds after injection and was immediately preceded by adenosine-induced symptoms of flushing and dyspnea in those patients who experienced these symptoms. The duration of the effect varied from 1.5 to 12 seconds, although in several of the patients atrial pacing was terminated shortly after the onset of 1:1 conduction because of poor tolerance of the increased ventricular rate.

Intravenous propranolol was administered to seven patients, all of whom had shown a shortening of accessory connection refractoriness after adenosine, and the protocol was repeated. There was no significant differ-

<table>
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<th>Patient</th>
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<th>Arrhythmia</th>
<th>AC location</th>
<th>AC ERP (msec)</th>
<th>Min RR in AF (msec)</th>
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AC, accessory connection; AF, atrial fibrillation; AS, anteroseptal; AVRT, atrioventricular reentrant tachycardia; ERP, antegrade effective refractory period; LFW, left free wall; Min RR, minimum preexcited RR interval; NI, noninducible; NP, nonpreexcited; PS, posteroseptal; RFW, right free wall.

FIGURE 1. Scatterplot showing correlation between minimum RR interval during atrial pacing (min RR) and accessory connection antegrade effective refractory period (ACERP) measured by the extrastimulus technique in patients of group 1. In two patients, ACERP could not be measured and in two patients, both minimum RR interval during atrial pacing and ACERP equaled 280 msec.
ence between minimum RR interval during atrial pacing before and after propranolol (297±55 msec versus 306±56 msec, respectively). After propranolol, the effect of adenosine (2:1 to 1:1 conduction) was abolished in three of the seven patients (43%). In the single patient in whom there was a 1:1 response to both doses of adenosine, the effect lasted for 5 seconds with the 3-mg dose and 12 seconds with the 12-mg dose in the absence of propranolol. After administration of propranolol, the effect was seen only after the 12-mg dose and lasted for 3 seconds only.

**FIGURE 2.** Tracings showing the effect of intravenous adenosine (12 mg) on the preexcited ventricular response to atrial pacing in patient 9. The preexcited response is converted from 2:1 to 1:1, indicating a shortening of antegrade refractoriness of the accessory connection. A, atrial electrogram; DCS, distal coronary sinus electrogram; ms, milliseconds; PCS, proximal coronary sinus electrogram; RA, right atrial electrogram; RV, right ventricular electrogram; S, stimulus artifact.

**Group 2 (19 patients).** Adenosine was given to 19 patients during induced preexcited tachycardia at a mean dose of 0.17 mg/kg (range, 0.1–0.25). The clinical characteristics and response to adenosine of these patients are described in Table 2. Mean age was 39 years, and 18 were men. All patients had a single accessory connection with nondecremental conduction properties. Mean accessory connection effective refractory period (ACERP) was 291±35 msec.

Ten patients had inducible atrial fibrillation with a preexcited ventricular response, with a mean shortest

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<th>Arrhythmia</th>
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<th>Adenosine dose (mg/kg)</th>
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ACERP, accessory connection antegrade effective refractory period; AF, atrial fibrillation; AFI, atrial flutter; AT, atrial tachycardia; RR\textsubscript{m}, average RR interval during AF; RR\textsubscript{mm}, minimum RR interval during AF; TCL, tachycardia cycle length.
RR interval of 252±44 msec. Eight of these patients had previously documented spontaneous attacks of atrial fibrillation, and four were known to have received intravenous verapamil during these episodes: One of these patients (patient 16) had become syncopal 90 seconds after verapamil injection during a previous spontaneous episode of atrial fibrillation. After adenosine, the average RR interval did not change significantly (360±59 msec to 357±60 msec) but the minimum RR interval decreased (252±44 msec to 224±35 msec, p<0.01; Figure 3). None of the 10 patients suffered clinical deterioration after adenosine and in those patients in whom minimum RR interval was reduced, this effect was evident for no more than two RR intervals.

Eight patients had inducible atrial flutter with 2:1 conduction over the accessory connection. Four of these patients had previously suffered documented spontaneous attacks of this arrhythmia. After adenosine, flutter cycle length decreased in five of eight patients (207±10 msec to 180±24 msec, p<0.05), with a corresponding increase in ventricular rate (ventricular cycle length of 415±21 msec and 360±49 msec before and after adenosine, respectively, p<0.05). Two-to-one conduction block in the accessory connection was maintained in all eight patients, the increase in ventricular rate was for a few seconds only, and no patient suffered clinical deterioration. Changes in flutter cycle length were accompanied by changes in atrial electrogram morphology (Figure 4) and in three cases were followed (after 2 or 3 seconds) by termination of the modified atrial arrhythmia and resumption of sinus rhythm.

One patient had an intra-atrial reentrant tachycardia with 1:1 preexcited ventricular response. This patient had suffered repeated episodes of spontaneous atrial tachycardia and had been treated with intravenous verapamil on several occasions; administration of verapamil had been followed by hypotension and the requirement for emergency DC cardioversion. Tachycardia cycle length did not change after adenosine in this patient despite a dose of 0.25 mg/kg, and no clinical deterioration was noted.

**Discussion**

**Effect of Adenosine on Antegrade Refractoriness of Accessory Connections**

The major advantage of adenosine as a therapeutic and diagnostic agent in the management of cardiac arrhythmias is its extremely short duration of action (half-life less than 2 seconds\(^{15}\)). It is this property that, until now, has precluded assessment of the effects of adenosine on refractoriness of accessory AV connections. The conventional measurement of refractoriness of an accessory connection using the extrastimulus technique (i.e., ACERP) cannot be applied to changes that occur over such a short time. However, by administering adenosine during stable 2:1 AV conduction block in the accessory connection, we were able to demonstrate a decrease in the minimum RR interval during atrial pacing, suggesting an adenosine-induced decrease in antegrade refractoriness of the accessory connection. The dose-related nature of this effect, together with the
stability of 2:1 block before adenosine, is strong evidence against spontaneous change in refractoriness as a mechanism for this response. The abolition of this effect of adenosine in three of the patients by prior administration of propranolol suggests that in these patients, the shortening of accessory connection refractoriness was not a direct effect but was mediated by activation of the sympathetic nervous system. When given as a continuous infusion, intravenous adenosine is known to cause a sinus tachycardia in humans \( ^{16} \) that is absent in patients with autonomic dysfunction \( ^{17} \) and is associated with a doubling of plasma catecholamine levels. \( ^{17,18} \) A secondary sinus tachycardia also occurs after the direct sinus-slowing effect of an intravenous bolus dose of adenosine; similarly, this response is absent in patients with autonomic dysfunction. \( ^{17} \) Both exercise and administration of isoprenaline have been shown to reduce accessory connection refractoriness and decrease minimum RR intervals during atrial fibrillation in humans. \( ^{19,20} \) The decrease in accessory connection refractoriness seen with intravenous verapamil is also thought to be mediated via reflex activation of the sympathetic nervous system. \( ^{21} \)

The mechanism of the decrease in accessory connection refractoriness in the patients in whom it was not abolished by propranolol is unknown; it is possible that full β-blockade was not achieved in these patients, although all four received a dose of 0.2 mg/kg propranolol and experienced sinus bradycardia (≤55 beats per min) as a result. Alternatively, adenosine may reduce refractoriness by way of a direct action on the accessory connection. The electrophysiological properties of accessory connections are thought to be similar to those of unspecialized atrial myocardium, \( ^{22} \) and the reduction of accessory connection refractoriness by adenosine is consistent with the shortening of action potential duration and refractoriness of isolated atrial myocytes that has been demonstrated after this agent. \( ^{23,24} \) A third explanation is that the effects of adenosine are mediated via transient withdrawal of resting vagal tone. \( ^{25,26} \) It has recently been demonstrated that resting vagal tone exerts a direct depressant effect on accessory AV connections that does not require background sympathetic activity to be manifest. \( ^{27} \)

Further studies are required to determine the mechanism in such patients.

**Effect of Adenosine on Minimum RR Interval During Atrial Fibrillation**

This study has demonstrated a transient reduction in the minimum RR interval (but not the average RR interval) during preexcited atrial fibrillation after adenosine. This may be due to reduction of accessory connection refractoriness discussed above, a reduction in concealed retrograde conduction into the accessory connection, \( ^{28} \) or a combination of both factors. Such a reduction in minimum RR interval might be thought to increase the likelihood of progression to ventricular fibrillation in vulnerable patients, although this was not observed in the current study. The fact that the decrease in minimum RR interval was only present for a maximum of two RR intervals suggests that any increased risk will be present only transiently and will be considerably less than that of verapamil administration under these circumstances.

Sharma et al \( ^{8} \) have recently shown a similar reduction in minimum RR interval during preexcited atrial fibrillation after ATP, although in the latter study average RR interval was also reduced. The reason for the discrepancy in the effect on average RR intervals is not known. Dosages of adenosine (mean, 0.14 mg/kg) and ATP (20 mg or 0.28 mg/kg, assuming mean weight of 70 kg) used in the two studies are thought to be equivalent in terms of potency of action on the AV node. \( ^{29} \) It is possible that ATP produces a greater degree of secondary sympathetic activation than adenosine but, as far as we are aware, there is no study that has directly examined this question.

**Effect of Adenosine on Atrial Flutter**

The marked reduction in atrial flutter cycle length after adenosine demonstrated in this study has not been described previously. DiMarco and coworkers \( ^{30} \) reported no change in atrial activity after adenosine in four patients with nonpreexcited atrial flutter. However, in their study, AV nodal conduction block was an end point and lower doses were given than in the current study (mean, 0.11 mg/kg compared with 0.19 mg/kg). The fact that the decrease in flutter cycle length is associated with changes in atrial electrogram morphology suggests that the mechanism of the cycle length decrease is not related simply to an effect of adenosine on atrial conduction time. It is possible that reduction in refractoriness of atrial myocardial cells may cause a decrease in flutter cycle length by allowing incorporation of alternative, shorter routes for reentrant atrial activation. The stability of the resulting modified atrial flutter/fibrillation is likely to be variable, and this may explain the subsequent tachycardia terminations that were observed after shortening of the flutter cycle length. It is possible that sustained atrial fibrillation may result from administration of adenosine under these circumstances, although this was not observed in the present study. It is of interest that 2:1 AV conduction block in the accessory connection was maintained after adenosine in all eight patients during atrial flutter. The shortening of flutter cycle length in these patients is likely to have negated any tendency to 1:1 conduction that may have occurred as a result of simultaneous shortening of accessory connection refractoriness.

**Limitations of the Study**

The effects of adenosine on refractoriness of accessory connections were examined in the antegrade direction only. The effects on retrograde refractoriness were thought likely to be much less relevant in terms of management of preexcited arrhythmias.
Clinical Implications

This study has demonstrated that adenosine is capable of causing a temporary increase in the ventricular rate of preexcited atrial fibrillation or flutter. These effects were brief and no patient suffered clinical deterioration as a result. This is in marked contrast to the effects of intravenous verapamil given under these circumstances, the administration of which frequently results in hemodynamic deterioration and occasionally in death.31

In addition, the current study has demonstrated that, despite shortening of accessory connection refractoriness by adenosine, the risks associated with inadvertent administration during preexcited atrial flutter are small and should not discourage the use of adenosine as a diagnostic agent in broad complex regular tachycardias of uncertain origin. Although not observed in this study, it is possible that conversion of atrial flutter to sustained atrial fibrillation may occur, and it should be emphasized that, as with administration of all antiarrhythmic agents, continuous electrocardiographic monitoring and availability of DC cardioversion is a necessary precaution during administration of adenosine. This study supports the further evaluation of adenosine as a diagnostic agent in broad complex, regular tachycardia in the setting of the emergency room.

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