JACC Vol. 30, No. 7
December 1997:1778–84

Induction of Atrioventricular Node Reentrant Tachycardia With Adenosine: Differential Effect of Adenosine on Fast and Slow Atrioventricular Node Pathways

ANNE B. CURTIS, MD, FACC, LUIZ BELARDINELLI, MD, DAVID A. WOODARD, MD, CHRISTOPHER S. BROWN, MD, JAMIE B. CONTI, MD, FACC

Gainesville, Florida

Objectives. **This study sought to evaluate the sensitivity of fast and slow atrioventricular (AV) node pathways to incremental doses of adenosine in patients with typical AV node reentrant tachycardia.**

Background. **Although adenosine is known to depress conduction through the AV node, the relative sensitivity to adenosine of the anterograde fast and slow pathways in patients with dual AV node pathways and typical AV node reentrant tachycardia has not previously been studied.**

Methods. **Sixteen patients with dual AV node physiology and typical AV node reentrant tachycardia and 10 control patients were given incremental doses of adenosine during atrial pacing.**

Results. **In 14 of 16 patients with dual-AV node physiology, administration of small doses of adenosine during atrial pacing led consistently to transient block of impulse conduction in the fast pathway before block in the slow pathway, resulting in abrupt prolongation of the AH interval with continued 1:1 AV conduction. The mean (±SD) doses of adenosine required to cause conduction block in the fast and slow pathways were 2.7 ± 3.0 and 7.2 ± 4.7 mg, respectively ($p = 0.004$). In 9 of 16 patients, administration of low dose adenosine led to initiation of AV node reentrant tachycardia. The control patients showed no abrupt increases in AH interval with administration of adenosine during atrial pacing.**

Conclusions. **In most patients with dual AV node pathways and typical AV node reentrant tachycardia, the fast pathway is more sensitive than the slow pathway to the effects of adenosine.**

(J Am Coll Cardiol 1997;30:1778–84)

A great deal of evidence has accumulated from basic and clinical studies (1,2) that the compact atrioventricular (AV) node has dual inputs located anteriorly and posteriorly. In patients with AV node reentrant tachycardia, the anterior pathway in general is a rapidly conducting pathway with a long refractory period, whereas the posterior pathway is slowly conducting and has a shorter refractory period (3).

Adenosine is an endogenous nucleoside that slows the sinus heart rate (negative chronotropic effect) as well as impulse conduction through the AV node (negative dromotropic effect). Adenosine is highly effective in terminating supraventricular tachycardias in which the AV node is part of a reentrant circuit (4). In typical AV node reentrant tachycardia, previous studies (5) have shown that adenosine may terminate the tachycardia either by causing block in the anterograde slow pathway or in the retrograde fast pathway. Although observations in clinical studies (6) have suggested that adenosine is more potent in slowing anterograde than retrograde conduction through the AV node, the relative responsiveness of anterograde fast and slow pathway conduction to adenosine has not been investigated. The purpose of the present study was to determine whether the depressant effect of adenosine on the anterograde fast pathway is more pronounced than the effect on the slow pathway in patients with typical AV node reentrant tachycardia who have demonstrable dual AV node pathways. As a corollary to this first objective, the second aim of this investigation was to determine whether low doses of adenosine, by briefly blocking fast pathway conduction, could be used to initiate AV node reentrant tachycardia.

Methods

Protocol. All patients undergoing electrophysiologic studies for the diagnosis and radiofrequency ablation of supraventricular tachycardia were invited to participate in the study. The study was approved by the institutional review board of the University of Florida, and all patients gave informed consent. Patients were studied in the fasting state after all antiarrhythmic drugs had been discontinued for at least 5 half-lives. Three quadripolar catheters were inserted through sheaths in the femoral veins and advanced to the right ventricular apex, the high right atrium and the His bundle position,

From the Department of Medicine, University of Florida, Gainesville, Florida. Dr. Woodard was the recipient of a Research Fellowship from the American Heart Association, Dallas, Texas.

Manuscript received June 11, 1997; revised manuscript received August 21, 1997, accepted September 2, 1997.

Address for correspondence: Dr. Anne B. Curtis, University of Florida, Box 100277, 1600 SW Archer Road, Gainesville, Florida 32610. E-mail: curtis.medcs0@shands.ufl.edu.

0735-1097/97/$17.00
PII S0735-1097(97)00386-0

respectively. A decapolar catheter was placed in the coronary sinus through a subclavian vein in selected patients. Baseline atrial, AV node and ventricular refractory periods were determined in each patient, and incremental atrial and ventricular pacing were performed. Supraventricular tachycardia was induced by using atrial or ventricular extrastimuli or by atrial burst pacing. The mechanism of the tachycardia was determined using standard criteria.

All patients who had consented to participate in the study and who had dual AV node pathways and typical AV node reentrant tachycardia underwent the adenosine protocol before radiofrequency ablation of the slow pathway. *Dual AV node pathways* were considered to be present when there was a sudden increase ≥50 ms in the AH interval for a 10-ms decrement in the A1–A2 coupling interval (7). Eligible patients received incremental doses of adenosine during atrial pacing at a cycle length that was determined by adding ~40 ms to the effective refractory period of the fast pathway to achieve steady state conduction over the fast pathway. Adenosine was administered at increasing doses of 1, 2, 4, 6, 9, 12 and 18 mg, or until AV block occurred. The adenosine was administered rapidly into a peripheral intravenous line, followed by an immediate saline flush. At least 2 min was allowed to elapse between injections of adenosine. In two patients in whom administration of low doses of adenosine during atrial pacing led to initiation of AV node reentrant tachycardia, atrial pacing was discontinued, and higher doses of adenosine were administered during the same episode of tachycardia to terminate it.

Intracardiac recordings were obtained throughout the period of administration of adenosine until the AH interval returned to baseline. The signals were filtered at 30 to 500 Hz and stored on an optical disk (Quinton Electrophysiology, Ontario, Canada) for later analysis. The longest AH interval achieved for each dose of adenosine was determined; in addition, any abrupt changes in AH interval were noted.

After the adenosine protocol was completed, all patients successfully underwent radiofrequency ablation of the slow pathway.

In addition to the patients with dual AV node pathways, 10 patients without known supraventricular tachycardia and with no electrophysiologic evidence for dual AV node pathways who were undergoing electrophysiologic studies for syncope or ventricular arrhythmias were also given incremental doses of adenosine during atrial pacing at cycle lengths of 50 and 100 ms longer than the Wenckebach cycle length.

Statistical analysis. Results are expressed as mean value ± SD. The Student paired *t* test was used to compare the mean doses of adenosine required to block the fast and the slow AV node pathways, with a p value ≤0.05 taken as evidence of a significant difference. Regression analysis was used to deter-

Table 1. Electrophysiologic Data

		Baseline			ERP (ms)			Adenosine Dose to Block (mg)	
Pt No./ Gender	Age (yr)	CL (ms)	AH Interval (ms)	Drive CL (ms)	Fast Pathway	Slow Pathway	WCL (ms)	Fast Pathway	Slow Pathway
Group 1									
1/F	42	709	72	400	337	<246	280	1	4
2/F	55	850	75	500	342	<278	360	12	≤12
3/F	35	713	41	400	302	<259	290	2	4
4/F	41	913	68	500	390	278	350	1	6
5/M	60	784	75	500	315	256	320	2	6
6/F	62	690	75	600	344	<282	370	1	4
7/F	47	780	69	500	396	323	AVNRT	2	6
8/M	62	891	62	600	482	293	AVNRT	1	3
9/F	39	534	54	400	263	<256	250	6	>18
Mean								3.1	7.0
±SD								±3.7*	±4.9*
Group 2									
10/F	75	713	81	500	363	<212	No	6	9
11/F	62	522	66	400	292	<220	Yes	4	ND
12/F	58	637	97	500	360	<280	No	1	ND
13/F	72	731	87	500	356	294	Yes	1	ND
14/F	34	694	72	400	281	262	Yes	1	ND
15/F	42	772	91	500	375	325	Yes	1	ND
16/F	83	734	103	500	308	<290	Yes	1	ND
*Mean†	54	729	74		344	272		2.7	7.2
±SD†	±15	±108	±16		±53	±31		±3.0	±4.7

*p = 0.009 for Group 1, p = 0.004 including Patient 10. †Values are from both Groups 1 and 2. AVNRT = atrioventricular (AV) node reentrant tachycardia; CL = cycle length; ERP = effective refractory period; F = female; Group 1 = fast and slow pathway responsiveness to adenosine; Group 2 = induction of AV node reentrant tachycardia with adenosine; M = male; ND = not done; Pt = patient; WCL = Wenckebach cycle length.

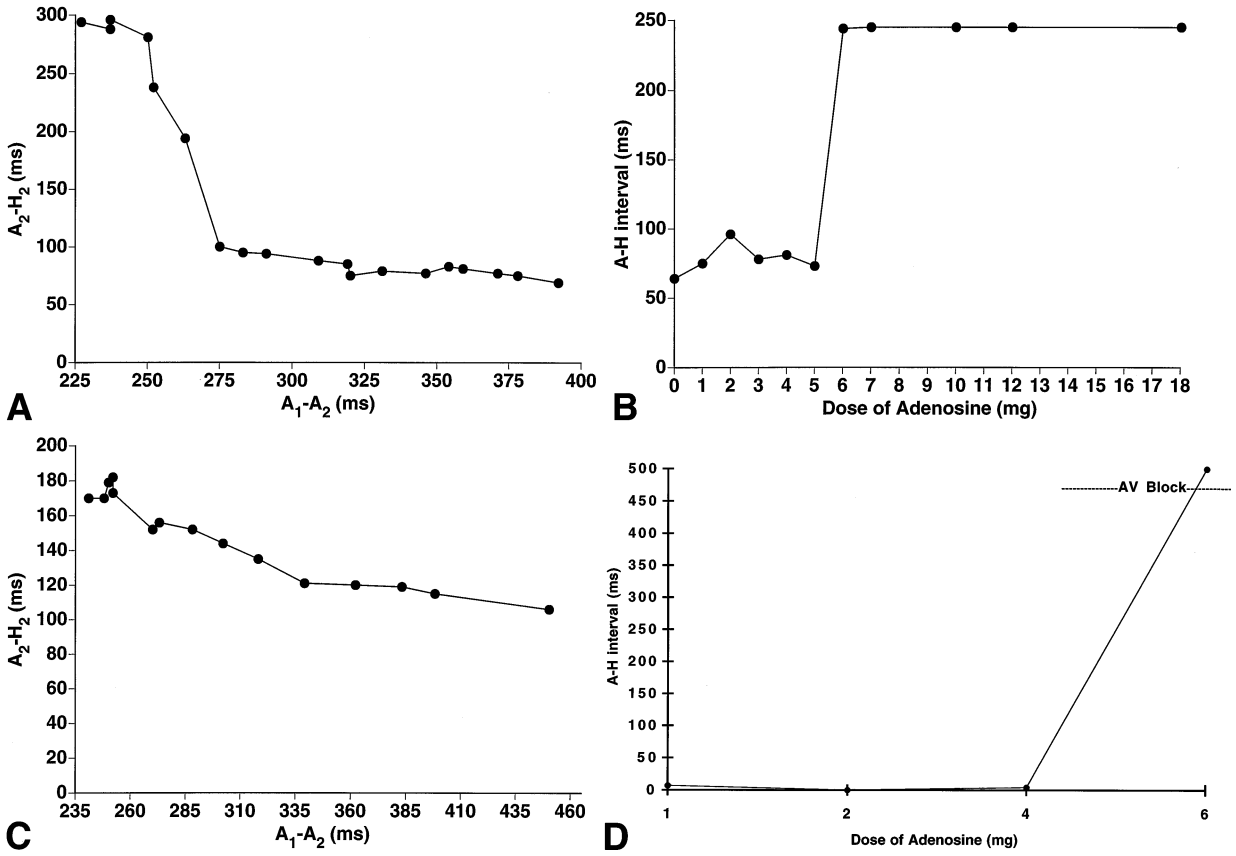


Figure 1. A, AV node refractory period determination demonstrating typical dual AV node pathways in Patient 9 (Group 1), with an abrupt increase of 94 ms in the AH interval at an A1–A2 coupling interval of 263 ms. At A1–A2 coupling intervals ≤252 ms, AV node reentrant tachycardia was induced. **B,** Relation between AH interval and dose of adenosine for the same patient during atrial pacing at a cycle length of 350 ms. For doses up to 5 mg, the AH interval ranged from 73 to 100 ms. At doses ≥6 mg, the AH interval abruptly increased to 245 ms throughout the time course of adenosine effect, then abruptly returned to the original value. Doses ≥10 mg led to the initiation of AV node reentrant tachycardia. AV block did not occur even with 18 mg of adenosine. **C,** AV node refractory period determination in a control patient, demonstrating a gradual increase in A2–H2 interval with decreasing A1–A2 coupling interval. **D,** Relation between AH interval and dose of adenosine for the same patient during atrial pacing at a cycle length of 450 ms. There is little change in the AH interval with increasing doses of adenosine, until AV block occurs at the dose of 6 mg.

mine the correlation between the dose of adenosine required to cause conduction block of the pathway and the effective refractory period of the fast and slow pathways.

Results

Patient characteristics. A total of 26 patients were enrolled in the study (16 with dual AV node pathways and AV node reentrant tachycardia; 10 with no evidence for dual AV node pathways and no inducible supraventricular tachycardia). Among the 16 patients with dual AV nodal pathways (14 women, 2 men; mean age 54 ± 15 years), there was 1 woman with mitral valve prolapse 1 man with hypertrophic cardiomyopathy; the other 14 patients had structurally normal hearts. The 16 patients with dual AV node pathways were classified into two groups: Group 1 (n = 9) received incremental doses of adenosine until AV block occurred; Group 2 (n = 7) received increasing doses of adenosine only until fast pathway block occurred, with the primary aim of inducing AV node reentrant tachycardia. Baseline electrophysiologic data for both groups are summarized in Table 1. Two patients had repeated induction of AV node reentrant tachycardia with incremental atrial pacing, making it difficult to determine the Wenckebach cycle length.

Refractory periods and response to adenosine. Among the 16 patients with dual AV node pathways, the mean effective refractory period of the fast pathway was 344 ± 53 ms (range 263 to 482) versus an upper limit of 272 ± 31 ms for the slow pathway (range <212 to 325). In nine of the patients studied, the effective refractory period of the slow pathway could not be precisely determined because of atrial refractoriness. There was a significant difference between the mean doses of adenosine required to block conduction through the fast and the slow AV node pathways. In Group 1, conduction in the fast pathway blocked at a mean dose of 3.1 ± 3.7 mg (median dose 2.0), whereas conduction in the slow pathway blocked at a mean dose of 7.0 ± 4.9 mg (median dose 6.0). This difference was highly significant at p = 0.009. Among all the patients, the

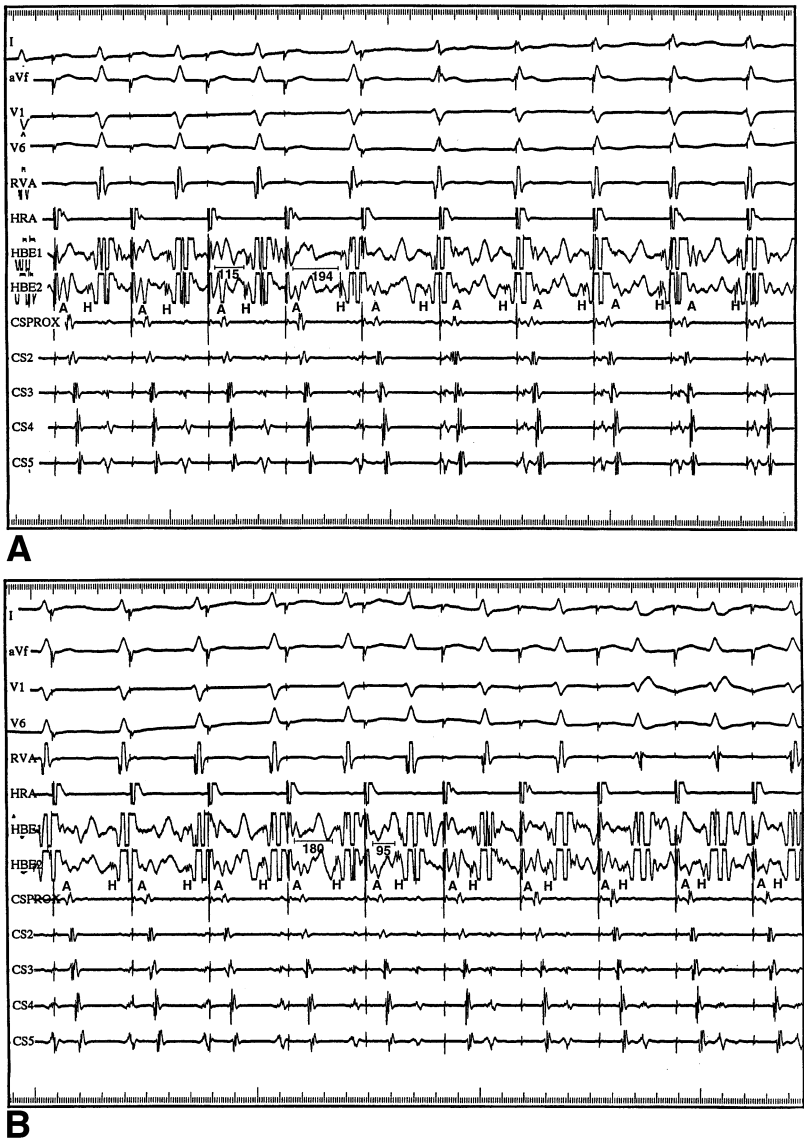


Figure 2. Representative recording of the effect of adenosine on AV conduction during atrial pacing in Patient 9 (Group 1). **A,** There is an abrupt increase in the AH interval from 115 to 194 ms after a 6-mg intravenous bolus injection of adenosine during atrial pacing at 350 ms. **B,** The AH interval abruptly shortens from 180 to 95 ms as the adenosine effect dissipates.

fast pathway blocked at a mean dose of adenosine of 2.7 ± 3.0 mg (median dose 1.0).

A representative example of a patient with dual AV nodal pathways and the effect of adenosine on the AH interval is illustrated in Figure 1. Fig. 1A depicts an abrupt increase in the AH interval at an A1–A2 coupling interval of 263 ms during the AV node refractory period determination. Figure 1B shows that in the same patient, the AH interval was 64 ms and changed little (73 to 100 ms) during administration of 1- to 5-mg doses of adenosine while pacing the atrium at a cycle length of 350 ms. At a dose of 6 mg, there was an abrupt increase in the AH interval to 245 ms that persisted for 14 s before abruptly returning to baseline. Higher doses of adenosine (i.e., 7 to 18 mg) also led to abrupt increases in the AH interval to 245 ms. When 10 to 18 mg of adenosine was given, AV node reentrant tachycardia was initiated. In this patient, AV block was not seen, even at the 18-mg dose of adenosine. Although the effect of adenosine on fast pathway conduction that was seen in this patient was typical of that observed throughout the study, this patient required markedly higher doses of adenosine to block conduction in the fast pathway than were necessary in the other patients (Table 1).

Control patients. Ten patients without evidence of dual AV node pathways or a history of supraventricular tachycardia were studied as well. In these patients, administration of increasing doses of adenosine was associated with little change in the AH interval, until AV block occurred at a mean adenosine dose of 7.5 ± 1.7 mg. A typical example is illustrated in Figure 1, C and D.

Block of fast pathway conduction with adenosine. The abrupt prolongation of the AH interval caused by adenosine in the patients with dual AV node pathways is shown in Figure 2. Fig. 2A illustrates a sudden increase in AH interval within a single beat (from 115 to 194 ms), whereas the abrupt return of the AH interval to baseline (from 180 to 95 ms) as the effect of adenosine wore off is shown in Figure 2B.

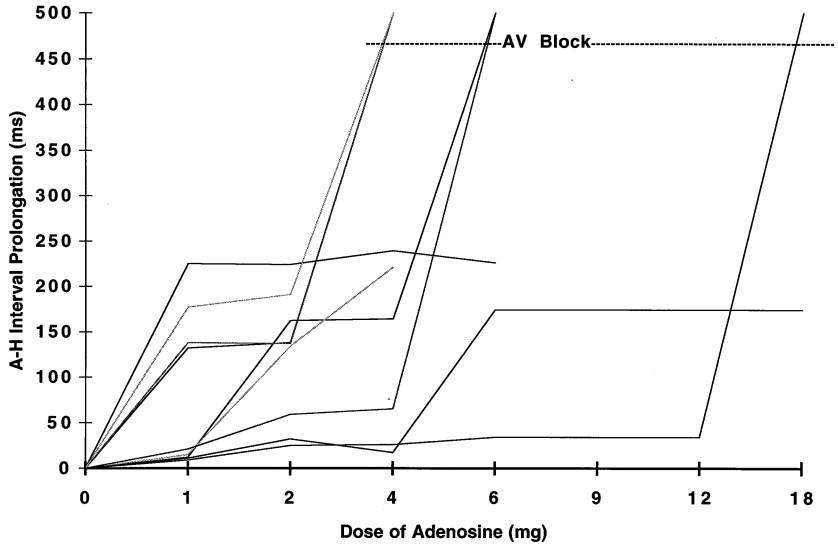


Figure 3. Relation between AH interval and dose of adenosine in Group 1 patients. In all except Patient 2, the fast pathway blocked with low doses of adenosine, whereas the slow pathway required higher doses.

The data for the patients with dual AV node pathways in Group 1 in whom both fast and slow pathway responsiveness to adenosine were tested are summarized in Figure 3. In eight of nine patients, conduction block occurred in the fast pathway before the slow pathway, as depicted by the abrupt increase in AH interval with a small increment in the dose of adenosine. This greater responsiveness of the fast than the slow pathway to adenosine was also observed in six of seven patients in Group 2 tested primarily to induce AV node reentrant tachycardia. Hence, adenosine caused fast pathway conduction block before slow pathway conduction block in 14 of the 16 patients studied. The two patients who did not show this pattern had clear evidence of dual AV node pathways at baseline, yet they showed only a gradual increase in AH interval with increasing doses of adenosine until AV block occurred at adenosine doses of 18 and 9 mg, respectively.

The relation between the dose of adenosine required to block conduction in the fast or the slow AV node pathway and the effective refractory period of each pathway is shown in Figure 4. There was a clear inverse correlation between the effective refractory period of the pathway and the dose of adenosine required to block the pathway, with a correlation coefficient of 0.94. That is, the longer the refractory period of the pathway, the lower the dose of adenosine required to cause block.

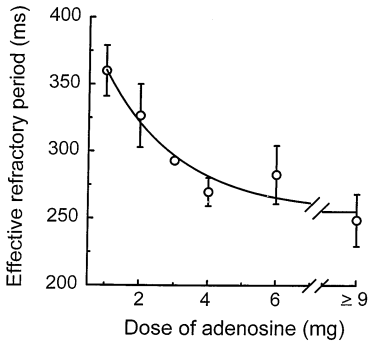
Induction of AV node reentrant tachycardia with adenosine. Of interest was the observation that in many patients, administration of doses of adenosine lower than those required to cause AV block actually led to the induction of AV node reentrant tachycardia. For instance, 9 of the 16 patients with dual AV node pathways developed AV node reentrant tachycardia with the administration of 1 to 10 mg of adenosine (mean 3.2 ± 2.9, ≤4 mg in all but 1 patient), respectively, whereas 1 additional patient showed single echo beats after administration of 2 and 4 mg of adenosine. In two of the patients, after adenosine was given during atrial pacing to initiate AV node tachycardia, atrial pacing was discontinued, and a higher dose of adenosine was given, which led to termination of the same tachycardia (Fig. 5).

Discussion

The results of the present study demonstrate that the fast and the slow AV node pathways are not equally responsive to adenosine. In most patients with dual AV node pathways, the anterograde fast pathway is more responsive to the effects of adenosine than the anterograde slow pathway. In addition, because of this differential responsiveness of the fast and slow pathways, adenosine can be used both to initiate and to terminate AV node reentrant tachycardia.

Effects of adenosine on anterograde and retrograde AV node conduction. Previous investigators (5) have shown that adenosine can terminate typical AV node reentrant tachycardia by causing conduction block either in the anterograde slow pathway or the retrograde fast pathway, or both. Other studies

Figure 4. Correlation between the effective refractory period of the fast and slow AV node pathways and the dose of adenosine required to block the pathway. There is an inverse correlation between the dose of adenosine and the refractoriness of the pathway, with a correlation coefficient r = 0.94.



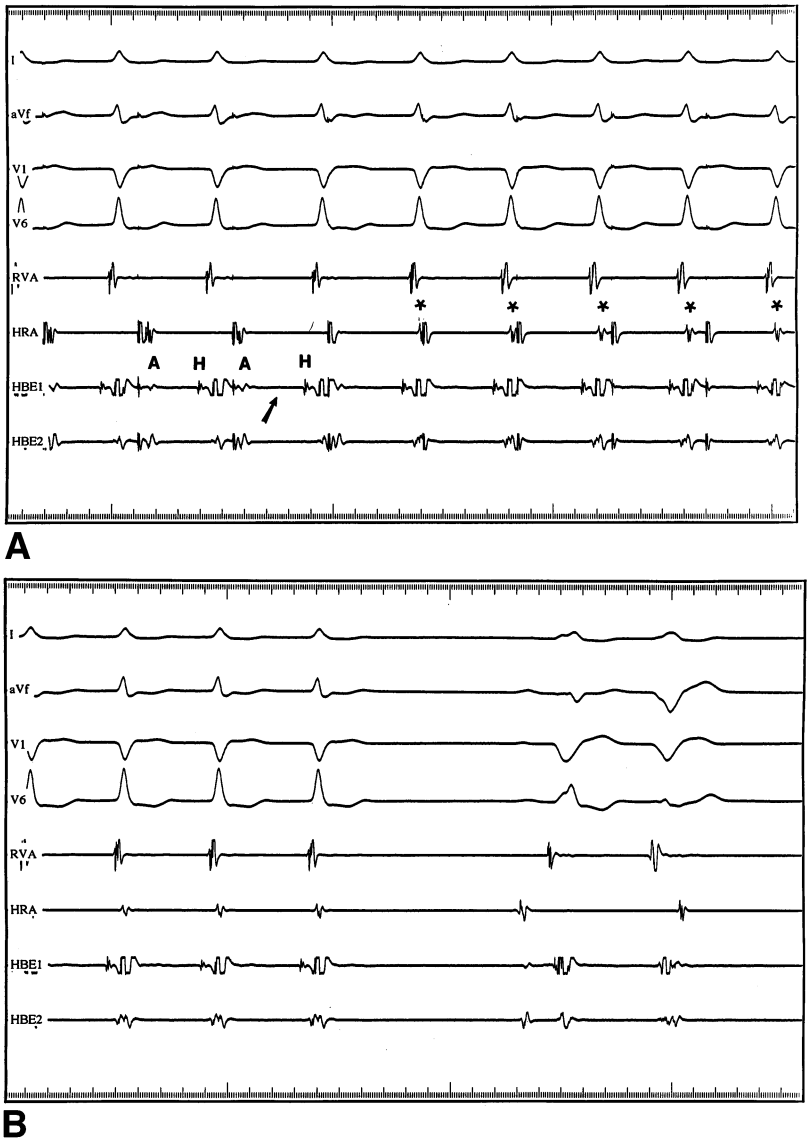


Figure 5. Initiation and termination of AV node reentrant tachycardia with adenosine in the same patient. **A,** During atrial pacing at a cycle length of 430 ms, after intravenous administration of 4 mg of adenosine, there is an abrupt prolongation of the AH interval (**arrow**), followed by initiation of the tachycardia (**asterisk**). The tachycardia persisted after pacing was discontinued. **B,** During the same episode of AV node reentrant tachycardia, intravenous administration of 12 mg of adenosine led to termination of the tachycardia by block in the slow pathway.

(6) have suggested that adenosine is more potent in blocking anterograde conduction through the AV node than retrograde conduction. Adenosine decreases the amplitude and duration of the action potentials of AN and N cells in the AV node, but not NH cells (8). The N zone of the AV node is the most likely site of conduction block caused by adenosine. Hence, the fact that adenosine markedly decreases the amplitude and shortens the action potential duration of AN cells but not NH cells is consistent with the observation that adenosine is more potent in blocking anterograde than retrograde conduction.

Effects of adenosine on anterograde fast and slow AV node pathways. Impulse propagation through the anterograde fast and slow AV node pathways enters into the compact AV node. Given the longer conduction time of the slow pathway than the fast pathway and the known site of action of adenosine in the AV node, it could be predicted that the slow AV node pathway would be more sensitive to the effects of adenosine than the fast pathway. Our results show just the opposite. It is thus possible that either the fast pathway involves the compact AV node to a greater extent than previously realized, or that the relative amount of input of each pathway into the compact AV node is irrelevant in explaining its responsiveness to adenosine.

A recent preliminary study (9) on the effect of adenosine on anterograde fast and slow pathway conduction found that a higher dose of adenosine was required to cause AV block before slow pathway ablation than after ablation was accomplished. This finding and the observation by the same investigators that administration of adenosine caused an abrupt increase in the AH interval without induction of AV block are both consistent with the results of our study.

Refractoriness and response to adenosine. An alternative explanation for the greater sensitivity of the fast pathway to adenosine may be that refractoriness of the pathway rather than conduction is the more important determinant of responsiveness to adenosine. This hypothesis is supported by our

finding that conduction through pathways with long effective refractory periods is blocked with lower doses of adenosine than pathways with shorter refractory periods. In support of this explanation, it is known that adenosine and A1 adenosine receptor agonists increase refractoriness in AV node tissue (10,11). However, it should be noted that the significant inverse relation between the refractory period of an AV node pathway and the dose of adenosine required to block conduction through that pathway does not in itself prove causality.

Mechanism of action of adenosine in AV node reentrant tachycardia. A hypothesis to explain the induction of AV node reentrant tachycardia with adenosine is that low doses of adenosine that selectively and briefly block fast pathway conduction allow conduction antegradely through the slow pathway only. Retrograde conduction up the fast pathway then sets up the reentrant circuit for AV node reentry. That induction of AV node reentrant tachycardia is not often seen clinically is simply due to the fact that large doses of adenosine are routinely administered that cause unselective conduction block of both AV node pathways and, thereby, termination of AV node reentrant tachycardia.

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