Rate-Dependent Properties of Adenosine-Induced Negative Dromotropism in Humans

Wen-Ter Lai, MD; Chee-Siong Lee, MD; Sheng-Nan Wu, MD, PhD

**Background** The antiarrhythmic effects of sodium channel and calcium channel blockers are known to be rate dependent. Little is known about the rate-dependent effect of adenosine on human atrioventricular (AV) nodal conduction. The purpose of this study was to determine whether the negative dromotropic effect of adenosine is dependent on heart rate.

**Methods and Results** Atrial pacing at 20-millisecond increments decreasing stepwise was performed, and the curves that relate the AH interval to the atrial pacing cycle length were analyzed. The change in AV nodal function was evaluated in three protocols: (1) In 8 group 1A and 6 group 1B patients, an intravenous infusion of adenosine at a dose of 140 and 320 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) was given, respectively; (2) a bolus injection of a fixed dose of adenosine was given to 12 group 2A patients without and 6 group 2B patients with propranolol (0.1 mg/kg) treatment; and (3) in 12 group 3 patients, the AV nodal function was evaluated after intravenous propranolol (0.05 mg/kg) and after subsequent intravenous aminophylline (loading dose, 5 mg/kg; maintenance dose, 0.9 mg \cdot \text{kg}^{-1} \cdot \text{h}^{-1}).

No significant depression of AV nodal function could be demonstrated during intravenous infusion of adenosine. The bolus injection of adenosine could prolong the AH interval, which was dependent on heart rate and more significant at a shorter pacing cycle length. Intravenous propranolol significantly depressed the AV nodal conduction and shifted the curves of the AH interval versus the pacing cycle length to the right. Subsequent intravenous aminophylline shortened the AV nodal conduction time, however, in a rate-independent manner.

**Conclusions** The negative dromotropic effects induced by intravenous bolus injection of adenosine became more pronounced at fast atrial pacing rates. These results indicate that adenosine causes rate-dependent prolongation of AV nodal conduction in humans. *(Circulation. 1994;90:1832-1839.)*

**Key Words** • adenosine • conduction • tachycardia • atrioventricular node

Adenosine is an endogenous nucleoside with potent cardiac electrophysiological effects on the sinus node and atrioventricular (AV) node.1,2 Clinically, intravenous adenosine depresses AV nodal conduction and can be used to terminate most of the supraventricular tachycardias that involve the AV node as part of the reentrant circuit.3,4 The negative dromotropic effects of adenosine are believed to be mediated mainly by a receptor-effector complex that links the adenosine A1 receptor to open the specific acetylcholine/adenosine-regulated potassium channels by the activation of inhibitory G protein.5 Ideally, a drug used to treat reentrant tachycardia will demonstrate maximal effects on conduction and refractoriness during tachycardia but will have minimal effects at slow heart rates.6 Previous studies in nerve and cardiac cells have characterized the use- or frequency-dependent action of local anesthetic agents,7-10 thereby leading to the evolution of the modulated receptor hypothesis.11,12 The characteristic frequency-dependent effects of calcium channel blockers13,14 and amiodarone15 in human AV nodal conduction have also been described. Recently, the effects of adenosine on rate-dependent AV nodal function were demonstrated by Nayebpour et al16 in rabbit and guinea pig heart preparations. Since the great interspecies variation of the effects of adenosine on AV nodal function was reported previously,17 little is known about whether its rate-dependent effects were present in humans.18 Because the antiarrhythmic agent adenosine has been used widely to treat tachyarrhythmias, a better understanding of its rate-dependent action is necessary and important. We therefore designed the present study to evaluate whether adenosine-induced negative dromotropism in humans is related to heart rate.

Change in heart rate affects many facets of AV nodal electrophysiological properties.19-22 A variety of approaches have been used to characterize the rate-dependent properties of the AV node.23-25 Since the negative dromotropic effects of intravenous adenosine are extremely short, the details of AV nodal properties cannot be examined thoroughly when an intravenous bolus injection of adenosine26 is applied. Therefore, we selected prolongation of the AV nodal conduction time (AH interval) as the indicator of negative dromotropism of adenosine. Our specific goal for this study was to determine the extent to which adenosine effects on AV nodal conduction are related to changes in heart rate.

**Methods**

**Patient Population**

Patients referred for electrophysiological evaluation of symptomatic or suspected cardiac arrhythmias were selected.
Patients who had a normal distribution of both antegrade Wenckebach cycle length and effective refractory periods of the AV node and atrium as described by Josephson and Seides were included. Patients with any of the following characteristics were excluded from the study: dual AV nodal physiology during incremental atrial pacing or atrial extrastimuli, preexcitation during electrophysiological study, or symptomatic heart failure.

**Electrophysiological Study**

All studies were performed with patients in an unsedated, fasting state after informed consent had been obtained. None of the patients had received any antiarrhythmic agents or medications known to interfere with the effects of adenosine. By conventional methods, three 6F quadripolar electrode catheters were introduced into the right femoral vein and advanced to the high right atrium, right AV junction, and right ventricular apex for recording and stimulation. Intracardiac ECGs were filtered at 30 to 500 Hz, simultaneously displayed with three surface ECG leads (I, II, and V1) on a multichannel oscilloscope (Electronics for Medicine VR-16), and simultaneously recorded on photosensitive paper at 100 mm/s. Stimulation was performed with a programmable stimulator (Bloom Associates). Stimuli were delivered as rectangular pulses of 2-millisecond duration at 2x diastolic threshold. In addition to the routine electrophysiological study, the following study protocol was performed in all patients. Incremental high right atrial pacing for 2 minutes was performed at each pacing cycle length, starting at cycle lengths slightly shorter than the sinus cycle length and decreasing stepwise (at 20-millisecond increments) until AV block occurred. Between each stepwise pacing cycle length, there was a 3-minute interruption for recovery of AV nodal function. AV nodal conduction time (AH interval) was measured for three to five beats at 20 seconds before the end of the train of pacing at each pacing cycle length, and the average AH interval was obtained. The curves of the AH interval versus the cycle length were assessed.

**Electropharmacological Protocol**

Three study protocols in five separate groups of patients were performed as follows: (1) In 8 group 1A patients (3 men, 5 women; mean age, 40±16 years; male/female ratio, 3:5), intravenous infusion of adenosine at a dose of 140 μg·kg⁻¹·min⁻¹ was given through the right femoral vein after control electrophysiological evaluation. After 6 minutes of infusion, the same electrophysiological protocol was repeated during continuous intravenous adenosine infusion. Changes in AV nodal electrophysiological properties were observed. (2) In 6 group 1B patients (4 men, 2 women; mean age, 47±10 years), the same electrophysiological protocol as in group 1A patients was performed during continuous adenosine infusion at a dose of 320 μg·kg⁻¹·min⁻¹. Blood pressure, which was determined by auscultation with a mercury manometer in the control state and during intravenous adenosine infusion, was measured every 3 minutes. (3) In 12 group 2A patients (5 men, 7 women; mean age, 44±14 years), the incremental high right atrial pacing protocol was performed as described above. During each pacing cycle length, a bolus of a fixed dose of adenosine was administered rapidly through the right femoral vein and was followed immediately by a flush of 10 mL of NaCl (0.9%). The longest AH interval induced by intravenous bolus injection of adenosine at each pacing cycle length was measured. The curves of the AH interval versus each pacing cycle length were analyzed. The fixed dose of adenosine was determined by assessing the maximal dose of adenosine that could prolong the AH interval but still maintain 1:1 AV conduction when the pacing cycle length was just 30 milliseconds above the AV block cycle length. (4) For the purpose of attenuating the effects of sympathetic activation caused by bolus injection of adenosine as well as by rapid atrial pacing, the electrophysiological protocol performed in group 2A patients was performed in 6 group 2B patients (2 men, 4 women; mean age, 42±14 years) after propranolol treatment. Intravenous propranolol at a dose of 0.1 mg/kg was given at a rate of 1 mg/min. Ten minutes after propranolol injection, the incremental high right atrial pacing protocol in response to a fixed dose of adenosine injection was performed as described for group 2A patients. The curves of the AH interval versus each pacing cycle length were analyzed. (5) To determine whether endogenous adenosine plays a role in the genesis of nodal refractoriness effects on AV nodal conduction properties at fast pacing heart rates, the third study protocol was performed. In 12 group 3 patients (6 men, 6 women; mean age, 43.5±9 years), the electrophysiological properties of the AV node were studied in the control state and 10 minutes after intravenous propranolol injection at a dose of 0.05 mg/kg body wt; immediately after the propranolol study, amrinone (theophylline ethylendiamine) at a loading dose of 5 mg/kg was given intravenously for 5 minutes and was followed by a continuous intravenous infusion at a dose of 0.9 μg·kg⁻¹·h⁻¹. The electrophysiological study was repeated during the maintenance amrinone infusion. A blood sample was also taken to document theophylline serum concentration measured by fluorescence polarization immunoassay (TDX, Abbott Laboratories). The AH intervals at each different pacing cycle length were compared in the control state, after intravenous propranolol, and during amrinone infusion.

The actions of the intravenously injected adenosine were short and rapid; its effects may depend on speed of injection and the patient’s circulation time. To assess the intraindividual variation of adenosine effects, 6 patients (4 men, 2 women; mean age, 42±8 years) were studied as follows: Under compatible and constant pacing cycle lengths, intravenous bolus injection of adenosine at a fixed dose of 1 mg was given to each patient and followed by rapid saline flush. This procedure was repeated five times for each patient. The delay for each procedure was 5 minutes. The maximal prolongation of AH interval induced by adenosine was observed and compared for each procedure.

**Statistical Analysis**

The curves of the AH interval versus the pacing cycle length were assessed to determine whether the difference in AH intervals between drug and control curves was greater at the shorter pacing cycle length tested. Alterations in pacing cycle length result in a complex process that includes changes in drug dissociation between beats and in drug association occurring with successive activations. Therefore, in order to simply analyze the frequency dependency, two exponential processes, as described by Talajic and Nattel, were programmed on a personal microcomputer and calculated. The biexponential equation is

\[
\Delta \text{AH} = A_1 \cdot \exp(-x \cdot \tau_1) + A_2 \cdot \exp(-x \cdot \tau_2),
\]

where \(\Delta \text{AH}\) is the shortening of the AH interval, \(A_1\) and \(A_2\) are maximal shortening of AH interval, \(\tau_1\) and \(\tau_2\) are fast and slow time constants, and \(x\) is the pacing cycle length. For statistical analyses, the data were evaluated using repeated-measures ANOVA and Dunnett’s multiple range test for multiple comparisons. Data analyses were performed with STATPAK (Northwest Analytical, Inc). Results were considered significant when \(P<0.05\).

**Results**

**Effects of Intravenous Infusion of Adenosine (Groups 1A and 1B)**

Continuous infusion of adenosine at doses of 140 and 320 μg·kg⁻¹·min⁻¹ significantly shortened the basic sinus cycle length and 1:1 AV conduction cycle length (Tables 1 and 2). Although the functional refractory periods of the atrium precluded determination of the...
Table 1. Electrophysiological Effects of Intravenous Infusion of 140 μg · kg⁻¹ · min⁻¹ Adenosine

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<td>164.8</td>
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SCL indicates sinus cycle length; AVCL, atrioventricular conduction cycle length; ERP, effective refractory period; AVN, atrioventricular node; A, intravenous adenosine; and C, control.

*P<.01.

effective refractory period of the AV node in five of eight group 1A and three of six group 1B patients, there is no tendency toward prolongation of the AV nodal refractory period after intravenous infusion of adenosine. The blood pressure also decreased significantly from 120±19/77±12 mm Hg in the control state to 116±25/75±12 mm Hg at 6 minutes after continued intravenous infusion of adenosine at a dose of 140 μg · kg⁻¹ · min⁻¹. In the control state and during intravenous infusion of adenosine, the AH interval increased as the pacing cycle length decreased; however, the curves of the AH interval versus the pacing cycle length were almost identical (Fig 1). The time constants for the slow and fast components of the control curve were 716±12 and 36±5 milliseconds, respectively, whereas those of the adenosine infusion curve were 720±10 and 39±6 milliseconds, respectively, in group 1A patients. Meanwhile, the time constants for the slow and fast components of the control curve were 725±11 and 35±7 milliseconds, respectively, whereas those of the adenosine infusion curve were 729±10 and 34±9 milliseconds, respectively, in group 1B patients. These results indicate that no significant modulation of the rate-dependent AV nodal conduction properties could be demonstrated during intravenous infusion of adenosine at the dose we used in this study. The higher dose of adenosine was limited by side effects that were not tolerated by patients. All six group 1B patients had chest tightness, nausea, and headache that subsided after adenosine infusion was terminated. One group 1B patient was noted to develop bronchial asthma that was reversed by intravenous aminophylline injection.

Effects of Intravenous Bolus Injection of Adenosine on AV Nodal Conduction (Groups 2A and 2B)

In the control state, AH interval increased as pacing cycle length decreased. The curves that relate the AH interval to atrial pacing cycle length were similar to those previously reported. The curves that relate the maximal AH interval induced by bolus injection of adenosine to atrial pacing cycle lengths for all group 2A patients are shown in Fig 2. No significant change could be demonstrated between the time constants for the slow components of the control and adenosine curves (952±20 versus 980±16 milliseconds, P>.05). However, the time constant for the fast component of the adenosine curve was significantly smaller than that of the control curve (21±3 versus 35±5 milliseconds, P<.05).

Table 2. Electrophysiological Effects of Intravenous Infusion of 320 μg · kg⁻¹ · min⁻¹ Adenosine

<table>
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<th>1:1 AVCL, ms</th>
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<td>SD</td>
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Abbreviations are the same as in Table 1.

*P<.01.
This result indicates that as the atrial pacing cycle length decreased, prolongation of the AH interval induced by adenosine injection increased more significantly. As shown in Fig 3A, compared with the control state, the mean maximal prolongation of the AH interval for all group 2A patients after bolus injection of adenosine was only 8.0±1.5 milliseconds at a pacing cycle length of 600 milliseconds. However, the mean maximal prolongation of the AH interval after bolus injection of adenosine increased to 43.0±5.0 milliseconds when the pacing cycle length was shortened to 380 milliseconds. As a result, the finding that the effects of bolus injection of adenosine on AV nodal conduction were more pronounced at rapid atrial pacings indicates that the effects of adenosine on AV nodal conduction were dependent on heart rate. The mean dose of bolus injection of adenosine for each group 2A patient was 27.6±11.5 μg/kg.

In group 2B patients, after propranolol injection the curves that relate the maximal AH interval induced by bolus injection of adenosine to atrial pacing cycle lengths were similar to those described for group 2A patients. As shown in Figs 3B and 4, prolongation of the AH interval induced by adenosine injection after propranolol treatment increased more significantly as the pacing cycle length decreased. These results indicate that in the presence of propranolol treatment, the effects of adenosine on AV nodal conduction were still dependent on heart rate. The mean dose of bolus injection of adenosine for each group 2B patient was 30.2±12.4 μg/kg.

**Effects of Intravenous Propranolol and Aminophylline (Group 3)**

Intravenous propranolol significantly prolonged the sinus cycle length (718±109 versus 672±120 milliseconds), the 1:1 AV node conduction cycle length (362±42 versus 329±21 milliseconds), and the effective refractory period of the AV node (310±37 versus 283±10 milliseconds). Compared with the effects of intravenous propranolol, intravenous aminophylline significantly shortened the basic sinus cycle length and the effective refractory period of the AV node (Table 3). Fig 5 illustrates the effects of atrial pacing on the AH interval in a patient who received intravenous propranolol and subsequent intravenous aminophylline infusion. In the control state, the AH interval progressively increased as the pacing cycle length decreased. After intravenous propranolol, the AH interval also progressively increased when the pacing cycle length decreased. Of note, prolongation of the AH interval after intravenous propranolol, relative to the control state, became more pronounced as the pacing cycle length decreased. On the other hand, during intravenous infusion of aminophylline, prolongation of the AH interval induced by propranolol was shortened. The curve that relates the AH interval to the atrial pacing cycle length was smoothly shifted to the left compared with the curve of intravenous propranolol. The mean changes in AH interval induced by intravenous propranolol and aminophylline of all group 3 patients during slow and fast pacing rates are displayed in Fig 6. After intravenous propranolol, compared with the control state, a greater increase in the AH interval (27.5±4.0 versus 7.7±2.5 milliseconds) was noted at a fast pacing cycle length (380 milliseconds) than at a slow pacing cycle length (600 milliseconds). During intravenous aminophylline infusion, compared with intravenous propranolol, the
AH interval was shortened. However, the decrease in the AH interval (8.2 ± 1.1 versus 6.2 ± 2.0 milliseconds, P = NS) was not accentuated at a fast pacing cycle length. These results indicate that intravenous propranolol prolonged AV nodal conduction time in a rate-dependent manner, with a larger increase of the AH interval at a fast pacing rate. On the other hand, intravenous aminophylline could partially shorten the prolongation of the AH interval induced by propranolol in a rate-independent manner. The mean serum aminophylline level in group 3 patients was 9.6 ± 1.6 µg/mL.

The mean maximal prolongation of the AH interval induced by adenosine among six patients at the first and fifth periods was 28 ± 3 and 29 ± 2 milliseconds, respectively (P > .05); i.e., the maximal prolongation of AH interval for each patient among various periods of adenosine bolus injection was not significantly different. Thus, the intraindividual variation of adenosine-induced AH prolongation in this study was insignificant.

Discussion

This is the first study that we know of to analyze the effects of exogenously injected adenosine on the rate-dependent properties of AV nodal conduction in humans. The most important finding of this study was that adenosine-induced negative dromotropism is obviously accentuated by an increase in heart rate. However, these rate-dependent effects of adenosine on AV nodal conduction were observed in patients who received intravenous bolus injection of adenosine but not in patients who received intravenous infusion of adenosine at a dose as high as 320 µg · kg⁻¹ · min⁻¹.

Effects of Intravenous Infusion of Adenosine

Previous studies have described the use- or frequency-dependent block of sodium channel–blocking agents⁹,¹⁰ and calcium channel–blocking agents¹³,¹⁴ in the human heart. The effects of β-adrenergic receptor stimulation, block and vagal stimulation on rate-dependent AV nodal conduction properties were also reported.⁵⁵,⁶ β-Receptor and vagal-stimulation effects on AV nodal properties were accentuated as the heart rate increased. In this study, two experimental protocols, i.e., intravenous infusion and bolus injection of adenosine, were used to demonstrate the adenosine modulation of the rate-dependent AV nodal conduction. Unexpectedly, during the recommended intravenous infusion dose of adenosine (140 µg · kg⁻¹ · min⁻¹)⁶⁷,⁶⁸ and an even higher dose (320 µg · kg⁻¹ · min⁻¹), the negative dromotropic effects of adenosine were not demonstrated on clinical electrophysiological study. In contrast, the heart rate and AV nodal conduction were slightly accelerated by intravenous adenosine infusion (Tables 1 and 2). Explanations for these findings include the following: (1) Adenosine-induced augmentation of sympathetic stimulation was most likely caused by vasodilatation in the peripheral vasculature⁷⁷ as well as chemoreceptor activation in the carotid body.⁶⁰ The sympathetic augmentation can mask the negative dromotropic and chronotropic effects of intravenous infusion of adenosine. This augmentation of sympathetic stimulation was compatible with the findings that the sinus cycle length and blood pressure decreased during intravenous adenosine infusion. (2) Adenosine, on intravenous infusion in this study, may have already been metabolized, thus becoming inactive before reaching the AV node, and as a result it may have been inadequate to produce a significant negative dromotropic response.⁶⁰ Further study may be necessary to determine the minimal intravenous infusion dose of adenosine required to produce sustained inhibitory effects on AV nodal conduction. In addition, to diminish the sympathetic reflex caused by adenosine, effects of intravenous infusion of adenosine might be studied under autonomic blockade. However, side effects and patient tolerance levels should be considered.
TABLE 3. Electrophysiological Effects of Intravenous Propranolol and Aminophylline

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C indicates control; P, intravenous propranolol; A, intravenous aminophylline; and other abbreviations are the same as in Table 1. *P<.01.

Rate Dependency of Adenosine Effects

With the protocol of intravenous bolus injection, we demonstrated that adenosine-induced changes in AV node functional properties became more pronounced at rapid heart rates in the control state and after propranolol treatment. Compared with previous studies, these tachycardia-dependent AV nodal depressant properties could apply to calcium channel–blocking agents and vagal stimulation.13,14,36 The intravenous bolus dose of adenosine used in this study was relatively small. Therefore, there were no significant negative dromotropic effects of adenosine at a slow heart rate. However, at a fast heart rate, the obvious AV nodal conduction delay could be demonstrated with the same dose of intravenous bolus injection of adenosine. If we chose the recommended bolus injection dose of adenosine (6 to 12 mg), AV nodal block would occur at slow and fast heart rates in most patients, and rate-dependent responses of AV nodal conduction to adenosine would not be able to be illustrated.

The results from group 2A and 2B patients showed that with or without propranolol treatment, the modulation of exogenously injected adenosine on AV nodal conduction was rate dependent. These findings may indicate that the rate-dependent modulation of AV nodal conduction by intravenous injection of adenosine was caused mainly by direct adenosine effects, whereas the indirect antiadrenergic action of adenosine appeared to be insignificant in this study.

![Fig 5. Plot of the AH interval vs the atrial pacing cycle length in a representative group 3 patient receiving intravenous propranolol and subsequent continuous infusion of aminophylline. The AH interval increases after intravenous propranolol, and the increase in AH interval is greater at shorter pacing cycle lengths. Intravenous aminophylline shortens the AH interval induced by propranolol and shifts the curve parallel to the left without showing a rate-dependent decrease of the AH interval at shorter pacing cycle lengths.](http://circ.ahajournals.org/)

![Fig 6. Bar graph shows the mean change in AH interval after intravenous propranolol and aminophylline in all group 3 patients. After propranolol, a further increase in the AH interval is noted at shorter pacing cycle lengths. Aminophylline shortens the AH interval; however, the decrease in the AH interval is not accentuated at shorter pacing cycle lengths. *P<.01.](http://circ.ahajournals.org/)
Role of Endogenous Adenosine

Previous study has shown that endogenous adenosine may play a role in the regulation of AV nodal accommodation and conduction.40 In this study protocol, endogenous adenosine released at fast pacing rates may have had an additive influence on the action of exogenously injected adenosine, and both effects may have contributed to the rate-dependent effects of adenosine on AV nodal conduction delay. Aminophylline, a theophylline derivative, has long been known to enhance human AV nodal conduction.41,42 The mechanisms attributed to the positive dromotropic effect of aminophylline are (1) the release of endogenous catecholamines from sympathetic nerve terminals and the adrenal medulla43 and (2) competitive antagonism of the adenosine action.44 To maintain the shortest 1:1 AV conduction cycle length after propranolol as close as possible to the control state, a relatively low dose of propranolol (0.05 mg/kg) was chosen. Since the sympathomimetic effects of aminophylline were not strong,45 we believe that the dose of propranolol used in this study was high enough to antagonize the sympathomimetic effects of aminophylline. As shown in Figs 5 and 6, intravenous propranolol shifted the AV nodal conduction curve to the right, and the more significant negative dromotropic effects of propranolol were also demonstrated at a fast heart rate. This rate-dependent change in AV nodal conduction induced by β-adrenergic blockade is compatible with previous reports.35 Of note, the finding that intravenous aminophylline shifted the AV nodal conduction curve to the left in a parallel pattern suggests that this left shift could be due to the antagonistic effects of endogenous adenosine and the sympathomimetic action induced by aminophylline. As reported by Belardinelli et al.,44 at a low concentration of aminophylline the effects of aminophylline-stimulated release of catecholamines were not significant in isolated perfused guinea pig heart, and the main action of aminophylline was the selective antagonism to adenosine effects. In this study, if the left shift of the AV nodal conduction curve caused by aminophylline had been attributed to the antagonistic effects of endogenous adenosine, the parallel left shift of the curve that was not more conspicuous at shorter pacing lengths may suggest that the contributory effects of endogenous adenosine on AV nodal conduction were not observed at fast pacing rates. When we applied this finding to the results of group 2 patients, there was more evidence to indicate that the rate dependency of the negative dromotropic effect of adenosine in this study was caused mainly by the action of the exogenously injected adenosine. However, since aminophylline possesses multiple electrophysiological and hemodynamic effects,41–43 it is difficult to draw conclusions about the role of endogenous adenosine in rate-dependent negative dromotropism according to the results of this study. A more specific adenosine receptor antagonist should be used to explore this event in a future study.

Because this was an in vivo human study, the possibility of release of catecholamines induced by aminophylline, although the serum concentration was in the low range, could not be totally excluded. Therefore, another interpretation of the left shift of the AV nodal conduction curve caused by aminophylline is that it was due to the effects of aminophylline-stimulated release of catecholamines, which in part reversed the depressive effects of AV nodal conduction induced by propranolol.

It is worth mentioning that the use-dependency phenomenon was seen primarily with drugs that were administered on a long-term basis. Interestingly, according to the results of our study, a drug such as adenosine that is rapidly metabolized after injection is still able to demonstrate rate-dependent effects on AV nodal conduction. The mechanisms through which adenosine induced negative dromotropism in a rate-dependent manner certainly need to be clarified further.

Study Limitations

Several limitations of this study should be mentioned: (1) The number of patients evaluated in the present study was relatively small. Nevertheless, intravenous bolus injection of adenosine was constantly found to produce rate-dependent effects. Repetitive injection of adenosine and its accompanying side effects were unendurable and hence did not allow us to analyze more patient samples. (2) Since bolus injection of adenosine has a short half-life, it is difficult to measure all the functional parameters of the AV node. Thus, only the AV nodal conduction time was analyzed as the indicator of AV nodal function. (3) The dependency of adenosine effects on the speed of injection, circulation time, and the hemodynamic effects of different pacing heart rates may affect the concentration of adenosine that reaches the AV node. However, since the present study was a clinical investigation and the intraindividual variation of adenosine effects on AH interval proved not to be significant, we believe that the present findings of rate-dependent effects of adenosine on AV nodal conduction are credible. (4) Because propranolol is not a total autonomic blocker, changes in autonomic tone may occur during different pacing heart rates and interfere with the AV nodal conduction induced by adenosine. Despite the presence of residual autonomic tone, rate-dependent effects of adenosine were demonstrated. Also, these results can be applied clinically because most of the patients who receive intravenous adenosine for supraventricular tachycardia exhibit autonomic reflexes.

Clinical Consequences

Intravenous bolus injection of adenosine is the drug of choice for terminating supraventricular tachycardias that involve the AV node as part of the reentrant circuit. In this study, we demonstrate the rate-dependent effects of adenosine on human AV nodal conduction. The characteristic augmentation by tachycardia of AV nodal conduction prolongation caused by adenosine could result in enhanced antiarrhythmic action of adenosine during supraventricular tachycardia. In addition, after conversion of tachycardia, the response in adenosine-induced AV nodal depression will be reduced due to the slowed heart rate, which may contribute to adenosine’s margin of safety in clinical application. Thus, an appropriate dose of adenosine might be available not only to terminate the sustained tachycardia but also to maintain proper AV nodal conduction without producing significant AV block or sinus pause after restoration of the sinus rhythm.
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