Effects of Adenosine on Rate-Dependent Atrioventricular Nodal Function
Potential Roles in Tachycardia Termination and Physiological Regulation

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Background. Adenosine is well known to depress atrioventricular (AV) nodal conduction, but the potential interactions between adenosine and functional AV nodal properties have not been explored. The purpose of the present study was to determine (1) whether exogenous adenosine modifies the rate-dependent properties of the AV node, (2) to what extent such changes underlie the actions of adenosine in an in vitro model of AV reentrant tachycardia (AVRT), and (3) the potential role of endogenous adenosine in rate-induced AV nodal responses.

Methods and Results. The functional properties of AV nodal recovery (defining the conduction delay of a single premature activation), facilitation (effect of short cycles on subsequent nodal recovery), and fatigue (slowly developing AV nodal delay at a rapid rate) were studied selectively in isolated, superfused rabbit and guinea pig cardiac preparations. Exogenous adenosine increased AV nodal fatigue and attenuated facilitation, resulting in tachycardia-dependent increases in AH interval and AV nodal effective refractory period (AVERP). In experimental AVRT, adenosine caused greater increases in tachycardia cycle length (T) and AVERP as tachycardia rate increased. AVRT was sustained when AVERP/T was <1, and adenosine suppressed AVRT by increasing the slope of the AVERP/T versus tachycardia rate relation, causing the critical ratio of 1 to be attained at slower rates. A mathematical model incorporating quantitative descriptors of recovery, facilitation, and fatigue accounted for changes in AH interval, AVERP, tachycardia cycle length, and AVERP/T under control conditions and in the presence of adenosine. In the absence of exogenous adenosine, 8-phenyltheophylline (10 μmol/L), an adenosine receptor antagonist, did not alter recovery or facilitation but significantly reduced rate-related fatigue (by 31±8%, mean±SEM, P<.05, in rabbit hearts; 46±5%, P<.01, in guinea pig hearts). Combined inhibition of adenosine deaminase (with erythro-9-[2-hydroxy-3-nonyl]-adenine hydrochloride, 5 μmol/L) and adenosine uptake (with dipiridamole, 1 μmol/L) increased fatigue in the absence of exogenous adenosine by 57±20% (P<.05).

Conclusions. We conclude that (1) exogenously administered adenosine increases AV nodal fatigue and reduces facilitation, without altering AV nodal recovery; (2) these changes cause rate-dependent AV nodal depression, which plays a role in adenosine's actions on experimental AVRT; and (3) endogenous adenosine receptor activation plays a role in physiological AV nodal fatigue. Adenosine's ability to terminate reentrant supraventricular tachycardia may be due, at least in part, to its ability to enhance the physiological conduction slowing that results from sustained increases in AV nodal activation rate. (Circulation. 1993;88:2632-2645.)

Key Words • adenosine • calcium channels • electrocardiography • arrhythmias • electrophysiology

The negative dromotropic actions of adenosine compounds have been recognized since the classic studies of Drury and Szent-Gyorgyi.12 Adenosine and related nucleotides have been shown to slow atrioventricular (AV) nodal conduction by binding to an extracellular receptor of the A1 type.3-6 Related experiments have shown that AV nodal conduction slowing during hypoxia5,7,8 and after defibrillation6 is due to adenosine release and can be antagonized by adenosine receptor blockers. Adenosine and adenosine-5'-triphosphate have received increasing clinical attention as highly effective agents in the treatment of AV nodal reentrant tachycardia,10-12 acting by purinergic induction of AV nodal conduction block.13 Improved understanding of the basic pharmacology of adenosine's actions on the AV node has resulted in new insights into the mechanisms of various clinical phenomena, and purinergic agents are now accepted as potential first-line therapy for reentrant supraventricular tachycardias involving the AV node as part of the reentry circuit.14-17

The AV node responds to changes in input rate in characteristic ways.18-28 A single premature AV nodal activation is conducted more slowly, a phenomenon that
is attributed to incomplete recovery of the AV node from preceding activation. Rapid stimulation shifts the steep portion of the AV recovery curve to the left, and a phenomenon that reaches steady state within one short cycle has been called "facilitation." Finally, a slow phase of AV nodal conduction slowing requiring hundreds of beats at a rapid rate has been defined and called AV nodal "fatigue."

Very little is known about the manner in which adenosine alters rate-dependent nodal properties. Experiments by Jenkins and Belardinelli demonstrated that an increase in activation rate causes an abrupt prolongation of AV nodal conduction time in guinea pig hearts, which is followed by the gradual development of further nodal conduction slowing. Endogenous production of adenosine was implicated in the latter, gradual phase of conduction slowing. The degree to which this effect can be attributed to changes in AV nodal recovery, facilitation, and rate-related fatigue, all of which could contribute to the observed action of the compound, has not been explored. Because these properties can account for a wide variety of nodal responses to changes in rate, such exploration is necessary to understand better the rate-dependent effects of the drug. A mathematical model incorporating quantitative descriptors of nodal recovery, facilitation, and fatigue is able to account for the steady-state rate dependence of AV nodal conduction time, a variety of Wenckebach block patterns, and the rate-dependent effects of cholinergic and adrenergic stimulation on AV conduction in anesthetized dogs. These mathematical descriptors can be used to quantify the effects of pharmacological interventions on individual AV nodal properties and to analyze the degree to which changes in such properties affect AV nodal conduction at different heart rates.

The present experiments were designed to analyze in detail adenosine's actions on rate-dependent AV nodal function by using the pacing protocols and mathematical approaches discussed above. Specific goals were (1) to analyze the effects of adenosine on the rate-dependent properties of the AV node, (2) to determine the potential contribution of these actions to adenosine's ability to terminate reentrant tachyarrhythmias involving the AV node in an experimental model, and (3) to evaluate the potential contribution of endogenous adenosine to rate-dependent AV nodal function.

**Methods**

**General Methods**

Experiments were performed in isolated, superfused rabbit and guinea pig cardiac preparations. We studied both species because of the known species dependence of adenosine action and receptor density. Only preparations that maintained stable AV nodal conduction for at least 1 hour before study were used. This was relatively straightforward for experiments with rabbits, and 25 complete experiments were obtained from the 25 that were attempted. The guinea pig preparation is well known to be more difficult to isolate and maintain in vitro, and we obtained complete results from only 5 of the 17 preparations studied. All data are from experiments in which complete results were obtained. The preparation, perfusion system, stimulation techniques, and recording system were similar to those previously described in detail by Billette and coworkers.

Briefly, the preparation, which included the right atrium, AV node area, and upper part of the interatrial septum, was mounted in a tissue bath perfused at 200 mL/min with a 6-L volume of oxygenated (95% O2-5% CO2) Tyrode's solution maintained at 37°C (pH 7.38). The composition of the superfusion solution was (mmol/L): NaCl, 128.2; KCl, 4.7; CaCl2, 1; MgCl2, 1; NaHCO3, 25; NaH2PO4, 0.7; and dextrose, 11.1.

A bipolar platinum-iridium stimulating electrode was positioned on the crista terminalis near the sinus node, and unipolar electrogrograms were recorded (using silver electrodes) from the sinoatrial node region, crista terminalis, nodal margin of the interatrial septum, and His bundle. Stimulation protocols were executed using custom-made software running on a PDP-1134-A computer interfaced with a D/A converter and a stimulus isolator. Electrogram signals were filtered (30 Hz to 3 kHz) and amplified by Grass Instruments 7P511 amplifiers (Quincy, Mass). Data were recorded on videotape with a Vetter 4000A recorder (Rebersburg, Pa) and, after A/D conversion, were analyzed off-line on an IBM 386 compatible computer.

**Stimulation Protocols Used to Quantify Recovery, Facilitation, and Fatigue**

Specific stimulation protocols were used, as previously described, to quantify the properties of AV nodal recovery, facilitation, and fatigue. To evaluate the basic recovery curve, the atrium was paced with a constant His-stimulus (HS) interval of 300 milliseconds, which corresponded to a basic cycle length of 380±6 milliseconds under control conditions and 390±6 and 400±11 milliseconds after dose 1 and dose 2 of adenosine, respectively. To construct the basic recovery curve, a single premature or delayed stimulus (S2) was introduced (Fig 1) after every 20 basic stimuli (S1). For consistency, the HS bundle electrogram preceding each test beat was designated HS1, and the atrial and His
responses to the test stimulus are $A_2$ and $H_2$, respectively. The relation between the conduction time of the test beat ($A_2H_2$) and the preceding recovery time ($H_1A_2$) was established and fitted to an exponential function as previously described.\textsuperscript{27-30}

To study facilitation, the recovery curve was constructed following a facilitation-inducing short cycle introduced after the last basic stimulus (Fig 1). The facilitating stimulus ($S'$) was inserted with a selected HS' interval (to be called the "facilitation interval" [FI]), and a test $S_2$ stimulus was applied to establish the effect of the HS' interval on the recovery curve relating the $A_3H_2$ conduction time to the $H_1A_2$ recovery interval (with $H_1$ again designating the His potential resulting from the stimulus preceding $S_2$). This procedure was repeated for six different values for the HS' facilitation interval between 40 and 200 milliseconds.

To analyze AV nodal fatigue, a series of tachycardias with a constant HS interval ranging from 40 to 200 milliseconds was initiated, and changes in AH interval over 5 minutes at a given HS interval were observed (fatigue 1 protocol in Fig 1). The changes in AH interval during such a tachycardia have been reported to result solely from the process of fatigue.\textsuperscript{22} The effect of steady-state fatigue at each rate on the AV recovery curve was studied as previously described.\textsuperscript{22,23,28} First, fatigue was established by 5 minutes of pacing at a rate faster than sinus rhythm. After every 20 cycles at the rapid rate, a facilitation-dissipating long cycle was introduced with an HS interval of 300 milliseconds. This has been shown to be sufficient to dissipate the effects of facilitation without diminishing the consequences of fatigue per se.\textsuperscript{22} A premature test pulse was then inserted at varying coupling intervals to establish the fatigue-affected recovery curve (fatigue 2 protocol in Fig 1). A recovery period of at least 5 minutes was allowed after each tachycardia for the dissipation of fatigue before the next tachycardia was initiated. AV nodal functional properties were completely assessed in six rabbit and five guinea pig preparations.

The functional and effective refractory periods of the AV node (AVFRP and AVERP, respectively) were measured with the extrastimulus technique. The AVFRP was defined as the shortest $H_1H_2$ output interval resulting from premature atrial stimulation, and the AVERP was defined as the longest $A_1A_2$ interval activating the atrial septum close to the AV node but failing to propagate through the bundle of His.

**Induction of Experimental AV Reentrant Tachycardia**

An experimental model of AV reentrant tachycardia (AVRT) was studied in a separate series of seven rabbit hearts, using an approach previously applied to the in situ dog heart.\textsuperscript{32,33} Each His bundle complex was detected by a signal detection unit, and a stimulus was delivered by the electrode located at the crista terminalis with a preselected HS interval delay. HS intervals...
endogenous superfusate were measured, thus initiated. The induction of AVRT was followed by a 5-minute recovery period. An average of five model AVRTs were induced in each preparation. AVRTs were considered to be sustained if they persisted for more than 2 minutes, at which time steady-state values of AH interval (AH_n) and cycle length (CL_w) were measured, and the AVERP was determined by the extrastimulus technique.

**Protocols to Study Effects of Exogenous and Endogenous Purinergic Stimulation**

Nodal properties were determined before and after two doses of adenosine in six rabbit preparations. Adenosine dose 1 and dose 2 were selected on the basis of the concentration necessary to increase the AH interval during spontaneous rhythm by 10 and 20 milliseconds, respectively. Dose 1 and dose 2 resulted in superfusate adenosine concentrations that averaged 150±27 µmol/L and 326±50 µmol/L, respectively. A series of seven additional preparations were studied to assess the effects of adenosine (at corresponding concentrations) on experimental AVRT. To study the role of endogenous adenosine on recovery, facilitation, and fatigue, these properties were characterized in a separate series of six rabbit hearts before and after superfusion with the adenosine antagonist 8-phenyltheophylline (8-PT; 10 µmmol/L). Adenosine was obtained from Sigma Chemical, St Louis, Mo, and 8-PT was purchased from Research Biochemicals Ltd, Natick, Mass). A stock solution (10 mmol/L) of adenosine was prepared in Tyrode's solution, and small quantities were added to the superfusate to achieve the desired concentration. The stock solution for 8-PT (10 mmol/L) was prepared in a 10-mmol/L solution of NaOH in absolute ethanol. The volume of stock solution added to produce the desired 8-PT concentrations in the superfusate was 0.05% of the total volume and did not alter the pH. In three experiments, addition of the diluent alone did not alter nodal conduction time or refractoriness. Finally, in some experiments, dipyridamole was added to the superfusate to achieve a concentration of 1 µmol/L to block adenosine uptake.

Because of the well-known difficulty in obtaining stable, isolated guinea pig nodal preparations, the ef-
Effects of both adenosine (10 μmol/L) and 8-PT (10 μmol/L) were studied in five preparations, and AVRT was not evaluated in these animals. In all five preparations, recovery, facilitation, and fatigue were studied under control conditions, then in the presence of adenosine, and finally after adenosine washout and the addition of 8-PT.

In preliminary experiments with exogenous adenosine, very high concentrations were required to produce effects, and the latter were unstable, presumably because of the rapidity of adenosine degradation. We found, however, that coadministration of an adenosine deaminase inhibitor (erythro-9-[2-hydroxy-3-nonyl]adenine hydrochloride) (EHNA) along with adenosine resulted in more stable effects of the latter. EHNA was obtained from Sigma Biochemicals, St Louis, Mo, and a stock solution (1 mmol/L) was prepared in Tyrode’s solution to be added to the superfusate as necessary. In each experiment on the effects of exogenous adenosine, EHNA was added to the superfusate at a concentration of 5 μmol/L 20 minutes before adenosine administration, and superfusion with EHNA was continued along with that of adenosine. After ascertaining that EHNA itself produced no changes in AV nodal conduction at a long basic cycle length in each experiment, all control data were obtained in the presence of EHNA. AH intervals averaged 50±3 milliseconds before and 51±3 milliseconds (P=NS) 20 minutes after the onset of EHNA superfusion in the absence of adenosine. EHNA was not used when 8-PT was superfused to assess the effects of endogenous adenosine.

Data Analysis

Results are reported as the mean±SEM. Comparisons among multiple groups were made by two-way ANOVA with Scheffé contrasts.4 Comparisons between two groups of experimental data only were made with the Student’s t test. Two-tailed tests were used, and a probability of 5% was taken to indicate statistical significance. Nonlinear curve fitting was performed with Marquardt’s technique on an IBM AT compatible computer.

Results

Effects of Adenosine on Rate-Dependent AV Nodal Properties in Rabbit Hearts

AV nodal recovery. Basic nodal recovery curves in one rabbit heart preparation are shown in Fig 2. Adenosine shifted the basic recovery curve upward in a dose-dependent fashion. Each curve was well fit by a single exponential function (r always >.99). The mean time constant of recovery (τmc) averaged 44±4 milliseconds before adenosine compared with 47±6 and 46±7 milliseconds after dose 1 and dose 2 of adenosine, respectively (P=NS for each). Overall, adenosine increased the AVERP from 102±3 milliseconds to 123±4 milliseconds (dose 1, P<.01) and 137±6 milliseconds (dose 2, P<.001) and the AVFRP from 158±5 milliseconds to 182±3 milliseconds (dose 1, P<.01) and 193±3 milliseconds (dose 2, P<.001). Thus, although conduction and refractoriness were changed by adenosine, the time course of AV nodal recovery was not altered.

AV nodal facilitation. Fig 3 shows results from a representative experiment studying AV nodal facilitation. Data are shown for the basic AV recovery curve and four facilitation intervals because graphs showing all the data would have been too crowded to be interpretable. A conducted response resulting from a premature atrial stimulus (S’) resulted in a leftward shift (Fig 3A) of the AV recovery curve of a subsequent test beat without any changes in the recovery time constant (τmc) and the AH interval after full recovery (AHmin).

For example, at the shortest facilitation interval in each experiment, τmc and AHmin averaged 45±4 and 55±2 milliseconds, respectively, which was not significantly different from the corresponding values of 44±4 and 55±2 milliseconds for the basic recovery curve. Therefore, as previously shown in the dog,20,25 the effects of facilitation are represented by a leftward shift of the AV recovery curve of a subsequent beat. This facilitatory effect attenuates the conduction slowing of premature responses. The degree of the leftward shift depended on the length of the facilitation interval. Fig 3A shows a series of recovery curves obtained at varying facilitation intervals before adenosine infusion. The data in Figs 3B and 3C were obtained at the same facilitation intervals in the presence of dose 1 and dose 2 of adenosine, respectively. Adenosine reduced the amount of leftward shift induced by facilitation.
The degree of leftward shift caused by facilitation was quantified in two ways. First, as in previous research,25-30 we determined from the best-fit exponential relation for each recovery curve the HA interval associated with a standard AH interval (in these experiments, 115 milliseconds) and called it the HA115. The standard AH interval of 115 milliseconds was selected because this value was always on the steep portion of the recovery curve and was attained without block in all experiments. The magnitude of leftward shift is indicated by a decrease in the HA115. Second, we measured the AVFRP, a physiologically relevant variable that can be importantly modulated by facilitation.25 As shown in Fig 4, both HA115 and AVFRP were significantly decreased by short facilitation cycles under control conditions. Adenosine attenuated these decreases in a dose-dependent way.

**AV nodal fatigue.** An example of AH interval changes following the initiation of a tachycardia with a constant HS interval (to control the effects of recovery and facilitation) is shown in Fig 5. The process of fatigue is indicated by a time-dependent slowing of AV nodal conduction. The magnitude of the fatigue-induced conduction slowing increased as HS interval (and, consequently, cycle length) decreased. Adenosine increased the magnitude of rate-dependent conduction slowing resulting from increased rate. Mean data for the magnitude of steady-state conduction slowing due to fatigue are shown in Fig 6. Adenosine increased the effect of fatigue in a dose-related way, and this action was statistically significant for all rates.

**Effects of Adenosine on Rate-Dependent AV Nodal Function in Guinea Pig Hearts**

Fig 7A shows recovery curves obtained in a guinea pig preparation at a long basic HS interval (basic recovery) and in the presence of facilitation and fatigue. The recovery curve shown for facilitation was obtained at the shortest facilitation interval studied under both control and adenosine conditions, whereas the curve during fatigue was obtained at the shortest HS interval associated with 1:1 conduction under both control and adenosine conditions (fatigue 2 protocol in Fig 1). As in rabbit hearts, facilitation caused a parallel leftward shift in the recovery curve, whereas fatigue caused a parallel upward shift. The corresponding recovery curves after exposure to 10 μmol/L adenosine are shown in Fig 7B. Adenosine did not significantly alter the time constant of recovery (control, 38±9 milliseconds; adenosine, 47±6 milliseconds) but increased the magnitude of fatigue (from 18±3 to 29±2 milliseconds, *P*<.01) and attenuated facilitation (leftward shift, 17±4 milliseconds control, 5±2 milliseconds adenosine; *P*<.001).

**Effects of Adenosine in an Experimental Model of AVRT**

Under control conditions, the minimum HS interval at which AVRT was sustained averaged 33±5 milliseconds. Atrial refractoriness was the limiting factor in two of seven preparations. In the presence of adenosine, the minimum HS time permitting tachycardia was 61±5 milliseconds (*P*<.001 versus control) for dose 1 and 80±3 milliseconds (*P*<.001 versus control) for dose 2, with AV nodal refractoriness being the limiting factor in all cases. The tachycardia cycle length decreased nearly linearly with decreased HA interval under control conditions (Fig 8A). Adenosine increased tachycardia cycle length, with the increase becoming larger as the HA interval decreased (ie, as the tachycardia accelerated). Thus, the slowing effect of adenosine was more marked for faster tachycardias than for slower ones.

These rate-dependent changes in tachycardia cycle length were related to rate-dependent drug actions on AV nodal activation. Adenosine's prolonging effects on steady-state AV nodal conduction time (AH interval,
Fig 8. Plots of observed (mean±SEM) effects of adenosine on characteristic properties of experimental atrioventricular reentrant tachycardia (AVRT) in seven rabbit preparations, along with corresponding values calculated on the basis of the mathematical model (MM) presented in the text (continuous curves). A, Tachycardia cycle length (CL) as a function of HA interval observed when pacing with a constant "retrograde" activation delay to mimic an accessory bypass tract. B, AV nodal conduction time at steady state during tachycardia, as a function of tachycardia CL. C, AV nodal effective refractory period (AVERP) during tachycardia, as a function of tachycardia CL. D, Ratio of AVERP to tachycardia CL (T) as a function of tachycardia rate. Ado 1 and ado 2 indicate adenosine dose 1 and dose 2, respectively.

Fig 8B) and effective refractory period (Fig 8C) depended on tachycardia cycle length. As the tachycardia rate increased, the tendency of adenosine to increase these variables was enhanced.

Adenosine's effects on the ability of AVRT to be sustained depends on the balance between two opposing actions—a tendency to increase AVERP, which makes tachycardia less likely, and a tendency to slow the tachycardia by slowing AV nodal conduction, which makes it more likely that the tachycardia can sustain itself. The result of these opposing actions can be determined by applying the concept of wavelength, as first put forward by Mines35 and subsequently developed by Lewis.36 The wavelength (\(\lambda\)), equal to the minimum path length that can support reentry, was characterized by Wiener and Rosenblueth37 as

\[
\lambda = \theta \times RP
\]

where \(\theta\) is conduction velocity, and RP is refractory period. Like the reentry models considered in the elaboration of the concept of the wavelength,35,36 our experimental AVRT can be considered to represent reentry that is fixed anatomically, with antegrade conduction via the AV conducting system and retrograde conduction mimicked by the pacing circuit. While a "wavelength" as described by Mines does not truly exist since the impulse is traveling through diverse structures of different electrical properties, a functional wavelength can be defined in terms of mean conduction velocity (\(CV_a\)) and the longest refractory period (\(RP_L\)) in the circuit. The wavelength

\[
\lambda = CV_a \cdot RP_L
\]

must be shorter than the path length (PL) for the reentrant impulse if AVRT is to be sustained. Since \(CV_a=PL/T\), where \(T\) is time for one reentry circuit to be completed, and AVERP is always the longest refractory period in the circuit in the presence of adenosine,

\[
\lambda/PL = AVERP/T
\]

Adenosine would be expected to make sustained AVRT impossible by prolonging \(\lambda\) so that it exceeds PL, ie, by increasing AVERP/T so that it exceeds unity.

Fig 8D shows values for AVERP/T during various AVRTs in seven experiments. Adenosine increases AVERP/T with effects that are small at slow rates but increase importantly as tachycardia rate increases. The largest values of AVERP/T measurable during sustained tachycardias were close to 1. When AVRT initiation was attempted with HS intervals smaller than
those associated with AVERP/T < 1. block occurred in the AV node, and AVRT was not sustained. Under control conditions, AVERP/T increases as tachycardia rate increases. The same is true in the presence of adenosine, but the slope of the rate dependence is greater so the critical AVERP/T ratio of 1 is attained at a slower tachycardia rate. These data support the contention that the ability of adenosine to prevent sustained AVRT is related to its rate-dependent capacity to increase AVERP/T so that it exceeds unity.

Mathematical Analysis of Adenosine's Rate-Dependent Actions and Ability to Prevent Sustained AVRT

Rate-dependent effects on cycle length of experimental AVRT. Previously developed mathematical approaches were used to define AV nodal conduction time as a function of activation rate. The recovery curve of the AV node can be expressed as

\[ AH_{fast} = AH' + A^* \exp(-HA/\tau_{rec}) \]  

where \( AH_{fast} \) is the AH interval at a recovery interval \( HA_0 \), and \( AH', A^* \), and \( \tau_{rec} \) are constants. This equation can be written in a more explicit way so as to incorporate quantitative indexes characterizing the basic recovery, facilitation, and fatigue processes.

The equation for the basic recovery curve is first obtained from data acquired at the longest cycle length, as the solution to the equation

\[ AH_{fast} = AH + A^* \exp(-HA/\tau_{rec}) \]  

where \( AH \) and \( A \) are specific solutions for \( AH' \) and \( A^* \) at the long cycle length, and \( \tau_{rec} \) is the recovery time constant. The recovery time constant \( (\tau_{rec}) \) is not altered by facilitation or fatigue, and Equation 4 can be expressed in terms of the basic recovery Equation 5 with two modifiers, \( \Delta AH_{fast} \) and \( \Delta HA_{fast} \), as follows:

\[ AH_{fast} = (AH + \Delta AH_{fast}) + A^* \exp[-(HA + \Delta HA_{fast})/\tau_{rec}] \]  

In turn, \( \Delta AH_{fast} \) and \( \Delta HA_{fast} \) can be described in terms of equations fitted to the type of data shown in Figs 4C and 6, as follows:

\[ \Delta AH_{fast} = \Delta AH_{max} \exp(-D \cdot HA) + E \]  

\[ \Delta HA_{fast} = \Delta HA_{155} \exp(-F \cdot C) \]  

where estimates of \( \Delta AH_{fast} \) and \( \Delta HA_{fast} \) as shown in Figs 6 and 4C are used to obtain the empirical constants \( \Delta AH_{max} \), D, E, B, and C. The constants obtained from the curve fitting set each of experimental data are shown in Table 1.

Substitution of the mean constants into Equation 6 allows for the calculation of the model-predicted AH interval during AVRT as a function of the HA interval. The tachycardia cycle length can be estimated from the model as the sum of the HA interval and the calculated AH interval. The effect of adenosine in prolonging the cycle length of experimental AVRT was rate dependent. Adenosine-induced increases in AVRT cycle length at the shortest HA retrograde conduction interval permitting tachycardia averaged 31±6 and 52±6 milliseconds for dose 1 and dose 2, respectively (Fig 8A), compared with increases of 12±3 and 19±4 milliseconds (P<.01 for each) at the same doses during AVRT with the longest HA interval. The model-estimated relation between AH intervals and cycle length of AVRT, based on model-predicted AH intervals as a function of the HA interval of the AVRT, is in close agreement with experimental data as shown by the model-predicted curves in Figs 8A and 8B. Therefore, adenosine's rate-dependent effects on the cycle length of AVRT are well described by a model incorporating quantitative indexes of basic recovery, facilitation, and fatigue at each level of effect.

Suppression of AVRT. The ability of experimental AVRT to be sustained was closely related to the estimated AVERP/T ratio under each condition. The mathematical model described above provides good estimates of the AVRT cycle length as a function of the HA interval. We therefore attempted to adapt the mathematical model to estimate AVERP as a function of the HA interval of a tachycardia.

For all protocols under a given condition, we observed that the maximum AH interval (\( AH_{max} \)) for conducted beats during the determination of each recovery curve was relatively constant. To estimate the shortest HA interval permitting conduction for any set of basic recovery, facilitation, and fatigue conditions, Equation 6 was rearranged to solve for the shortest HA interval permitting conduction (\( HA_{s} \)) as follows:

\[ HA_s = -\tau_{rec} \cdot \ln([AH_{max} - AH_s - \Delta AH_{fast}]/A) - \Delta HA_{fast} \]  

where \( \tau_{rec} \), \( AH_s \), \( HA_{max} \), A, and \( \Delta HA_{fast} \) have the meanings indicated above, and \( AH_{max} \) is the longest AH interval attainable for conducted beats during the basic recovery protocol. Because the effective refractory period was estimated with 1-millisecond accuracy, the longest HA value at which conduction failed (\( HA_{ERP} \)) was estimated as \( HA_{s} = -1 \). This allows for calculation of the longest AA interval at which conduction fails (\( AVERP \)), by adding \( HA_{ERP} \) to the AH interval during the tachycardia from Equation 6 as described above. The solid curves in Fig 8C show the model-determined effects of adenosine on AVERP as a function of tachycardia cycle length. AVERP is prolonged by adenosine to a substantially greater extent as the AVRT cycle length decreases. There is good agreement between model calculations and observed data.

The mathematical model can now be used to estimate both tachycardia cycle length (Fig 8A) and AVERP (Fig 8C) for experimental AVRT at any HA interval and therefore to estimate the AVERP/T ratio as a function of tachycardia rate. Model estimates based on mean values of the parameters in Equations 6 through 9 are shown by the solid curves in Fig 8D. As tachycardia rate increases, AVERP/T increases under all conditions. In the presence of adenosine, the curves are displaced upward, indicating prolonged AV nodal refractoriness at all cycle lengths. Furthermore, the slopes of the curves increase with increasing adenosine concentration, showing that adenosine increases the rate dependence of AVERP/T. Experimental results agree well with model-predicted behavior, with sustained tachycardia no longer inducible at cycle lengths similar to those with a model-estimated AVERP/T > 1. Fig 9 shows the shortest AVRT cycle length observed from each condition, along with model-predicted values based on parameters from each experiment. Adenosine increased
TABLE 1. Values of Constants Characterizing Atrioventricular Nodal Recovery, Facilitation, and Fatigue

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<td>38</td>
</tr>
<tr>
<td>Mean±SEM</td>
<td>±3</td>
<td>±3</td>
<td>±5</td>
<td>±4</td>
<td>±6</td>
<td>±7</td>
<td>±19</td>
<td>±99</td>
<td>±86</td>
<td>±6</td>
<td>±6</td>
<td>±8</td>
</tr>
</tbody>
</table>

AH<sub>o</sub> indicates AH interval after full recovery at control basic cycle length; A₁, adenosine dose 1; A₂, adenosine dose 2; τ<sub>rec</sub>, recovery time constant; A, constant; B, constant equal to the change in the HA interval at a facilitation cycle length of 0; C, rate constant of facilitation; D, maximum changes in the HA interval due to fatigue; E, constant; and F, constant.

*P<.05, †P<.01, ‡P<.001 for value in the presence of adenosine versus control.

the minimum cycle length of sustained AVRT in a dose-dependent fashion, and experimental observations agree well with values obtained from the model.

Role of Endogenously Produced Adenosine in Rate-Dependent AV Nodal Function

Fig 10A shows AV basic recovery curves and recovery curves in the presence of maximum facilitation and fatigue in a rabbit preparation. The result of exposure to the selective A<sub>1</sub> receptor antagonist 8-PT is shown in Fig 10B. The magnitude of fatigue assessed by the same pacing protocol was reduced by 8-PT, but the AH intervals during spontaneous rhythm, basic recovery, and facilitation were unaltered. In six preparations, τ<sub>rec</sub> averaged 41±4 milliseconds under control conditions and 49±4 milliseconds (P=NS) after 8-PT. AH, (basal nodal conduction time) averaged 52±2 milliseconds under control conditions and 51±2 milliseconds after 8-PT. The maximum leftward shift in the recovery curve caused by facilitation averaged 17±4 milliseconds before and 23±3 milliseconds (P=NS) after 8-PT. Figs 10C and 10D show corresponding data from an experiment in an isolated guinea pig heart. In guinea pigs, τ<sub>rec</sub> averaged 38±9 milliseconds before and 40±6 milliseconds after 8-PT, whereas the leftward shift due to facilitation averaged 17±4 milliseconds before and 20±5 milliseconds after 8-PT. Fatigue was significantly decreased by 8-PT in both rabbit and guinea pig hearts (Fig 11). The mean decrease in fatigue by 8-PT averaged 31±8% and 46±5% in rabbits and guinea pigs, respectively.

To further explore the potential role of endogenously released adenosine in rate-related fatigue, we evaluated functional AV nodal properties in six additional rabbit hearts after the addition of EHNA alone, followed by EHNA and dipyridamole. EHNA alone did not significantly alter the recovery time constant, basal AV nodal conduction time (AH<sub>o</sub>), leftward shift of the recovery curve due to facilitation, or upward shift in the recovery curve caused by fatigue (Table 2). On the other hand, inhibition of both adenosine deamination (with EHNA) and uptake (with dipyridamole) significantly increased the upward shift in the recovery curve caused by fatigue by an average of 57±20%. Adenosine was then added (in the presence of EHNA and dipyridamole) in quantities sufficient to increase the AH interval during spontaneous rhythm by about 10 milliseconds, an effect equal to adenosine dose 1 as described in “Methods.”

The mean concentration required was 43±5 μmol/L. The addition of adenosine did not alter the time course of recovery but significantly attenuated facilitation and enhanced fatigue (Table 2). 8-PT (10 μmol/L) was then added, and it significantly reduced the magnitude of fatigue in the presence of EHNA, dipyridamole, and adenosine to the point that the change in AH interval due to fatigue was no longer significantly different than values obtained under control conditions.

Discussion

Our study shows that adenosine modifies the rate-dependent functional properties of rabbit and guinea pig AV nodes and that these actions contribute to adenosine’s ability to suppress AVRT in an experimental model. Furthermore, the ability of an adenosine receptor blocker (8-PT) to attenuate rate-induced AV nodal fatigue suggests a potential role for endogenous adenosine in mediating the latter property.

Relation to Previous Studies of Adenosine Action

Numerous previous studies have shown that adenosine slows AV nodal conduction (for detailed reviews,

Fig 9. Bar graph of shortest cycle length (CL) at which atrioventricular reentrant tachycardia (AVRT) was sustained in seven rabbit hearts. Open bars indicate experimental observations, and closed bars indicate results derived from the mathematical model described in the text (**P<.01, ***P<.001, for results observed in the presence of adenosine versus control). Ado 1 and ado 2 indicate adenosine dose 1 and dose 2, respectively.
see References 15 and 17). The current report presents the first detailed analysis of the effects of exogenous adenosine on rate-dependent AV nodal function. We found that adenosine attenuated AV nodal facilitation and substantially increased rate-related fatigue without altering the time course of nodal recovery in both rabbit and guinea pig cardiac preparations. A potential role for endogenously produced adenosine in the intrinsic development of fatigue is suggested by the effects of 8-PT on rate-dependent AV nodal function (Figs 10 and 11) and is supported by the ability of EHNA and dipyridamole to enhance AV nodal fatigue. These findings are in agreement with the observations of Jenkins and Belardinelli in isolated, perfused guinea pig hearts. These authors found that an adenosine antagonist (BW-A1433) improved AV nodal conduction selectively at very short atrial cycle lengths, whereas dipyridamole had the opposite effect. In the presence of hypoxia, BW-A1433 selectively attenuated the gradual increase in nodal conduction time following an abrupt decrease in cycle length. Although the latter, as measured by Jenkins and Belardinelli, is not identical to fatigue since AV nodal recovery and facilitation are not controlled, this process most likely reflects alterations in fatigue. Our research differs from that of Jenkins and Belardinelli in that although they studied the effects of endogenous adenosine alone on AV nodal accommodation, we evaluated the effects of both exogenous and endogenous adenosine receptor stimulation on specific AV nodal functional properties, and we analyzed the potential significance of such actions for adenosine’s antiarrhythmic properties.

Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>ΔAH_{max}, ms</th>
<th>Fatigue</th>
<th></th>
<th>ΔAH_{max}, ms</th>
<th>Fatigue</th>
<th></th>
<th>ΔAH_{max}, ms</th>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>A₁, A₂</td>
<td>Control</td>
<td>A₁, A₂</td>
<td>Control</td>
<td>A₁, A₂</td>
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<td></td>
</tr>
<tr>
<td>18</td>
<td>36</td>
<td>48</td>
<td>0.010</td>
<td>0.017</td>
<td>0.018</td>
<td>5.8</td>
<td>2.9</td>
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<td>40</td>
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<td>0.014</td>
<td>0.010</td>
<td>2.5</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>15</td>
<td>31</td>
<td>46</td>
<td>0.011</td>
<td>0.012</td>
<td>0.010</td>
<td>1.9</td>
<td>3.4</td>
<td>1.8</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>34</td>
<td>0.016</td>
<td>0.004</td>
<td>0.005</td>
<td>2.6</td>
<td>-3.5</td>
<td>-1.4</td>
</tr>
<tr>
<td>18</td>
<td>66</td>
<td>82</td>
<td>0.009</td>
<td>0.013</td>
<td>0.014</td>
<td>0.1</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>36</td>
<td>54</td>
<td>75</td>
<td>0.010</td>
<td>0.020</td>
<td>0.012</td>
<td>-1.3</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>23</td>
<td>42±6†</td>
<td>55‡</td>
<td>±0.014</td>
<td>±0.002</td>
<td>±0.002</td>
<td>2</td>
<td>1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>±5</td>
<td>±17</td>
<td>±8</td>
<td>±0.004</td>
<td>±0.002</td>
<td>±0.002</td>
<td>±1</td>
<td>±1</td>
<td>±1</td>
</tr>
</tbody>
</table>

Fig 10. Plots of examples of atrioventricular (AV) recovery curves (AVRCs) before and after 8-phenyltheophylline (8-PT) in rabbit (left) and guinea pig (right) preparations. The time constant of recovery was not changed, nor was the magnitude of leftward shift of the facilitation-affected curve compared with the basic AVRC. However, the magnitude of the fatigue-induced upward shift of the recovery curve was reduced by 8-PT. Identical pacing intervals were used to study facilitation and fatigue before and after 8-PT in each experiment.
Comparison With Other Studies of Drug Effects on Rate-Dependent AV Nodal Function

A variety of pharmacological interventions, including vagus nerve stimulation,29 β-adrenergic receptor stimulation and β-adrenoceptor blockade,30 and the administration of calcium channel blockers,38 have been shown to alter rate-dependent AV nodal properties. Detailed analyses of changes in recovery, facilitation, and fatigue have been obtained in anesthetized dogs at various levels of activation of cardiac muscarinic29 and β-adrenergic30 receptors. Like vagus nerve stimulation29 and β-adrenoceptor blockade,30 adenosine slows AV nodal conduction in a rate-dependent way. The changes in AV nodal properties responsible for rate-dependent conduction slowing, however, vary among these interventions. All three enhance AV nodal fatigue. Although β-blockade and vagal stimulation slow AV nodal recovery,29,30 adenosine does not alter the recovery time constant (Fig 2 and Table 1). Both vagal stimulation and adenosine attenuate facilitation, but β-adrenergic receptor stimulation and blockade have no effect on facilitation.30

Relation to previous analyses of rate-dependent AV nodal properties. The mathematical approach used in this study to characterize kinetic properties of the AV node has been shown to account for intrinsic responses of the AV node to changes in input frequency27,28 as well as for modifications in response to autonomic interventions29,30 in anesthetized dogs. In the present study, we show that similar methods can be successfully applied to characterize the response of the AV node in isolated rabbit and guinea pig heart preparations.

This report presents the first application of this mathematical approach based on quantitative descriptors of recovery, facilitation, and fatigue to account for the behavior of a model of AVRT. Simson et al32 analyzed the beat-to-beat changes in AVRT caused by a transient perturbation. Their experimental model of AVRT was similar to ours, but their studies were performed in vivo in dogs. They used a hyperbolic function to approximate the relation between AV nodal recovery time (which they took to be represented by the AA interval) and AV conduction time, and they used an empirical, single observed value for the refractory period. Their model is applicable only under conditions during which refractoriness is relatively stable and the AV nodal response is dominated by AV recovery alone. In fact, they noted discrepancies between the predictions of their model and experimental observations, which they explained on the basis of rate-dependent changes in refractoriness.

Our approach was successful in accounting for changes in AH interval, AVRT rate, AVERP, and ability for AVRT to sustain itself for tachycardias with a wide range of retrograde HA times (Figs 8 and 9). Furthermore, our analysis accounted for the effects of adenosine on the properties of experimental AVRT. Extension of the model to account for beat-to-beat conduction changes following the onset of AVRT, to account for the response to other drugs, and to predict the response of clinical AVRT in humans would be of interest. Because a variety of interventions used clinically to terminate AVRT, such as vagal maneuvers30-42 and calcium antagonists,43-45 significantly alter rate-dependent AV nodal properties,27,29 such an analysis would seem pertinent.

Potential Physiological Significance and Underlying Mechanisms

The mechanisms underlying rate-dependent AV nodal properties remain incompletely understood. It is probable that the time-dependent recovery of calcium channels from inactivation plays a major role in determining the AV nodal recovery curve.38 Changes in action potential duration in the distal AV node are likely involved in facilitation.46,47 Although the importance of AV nodal fatigue in mediating AV nodal conduction slowing during tachycardia has not been clearly established, our findings suggest that the rate-dependent changes in AV nodal recovery could contribute significantly to the occurrence of AVRT.

![Graph](https://via.placeholder.com/150)

**Fig 11.** Bar graph of magnitude of fatigue at the shortest HA interval associated with 1:1 conduction under both control and 8-phenyltheophylline (8-PT) conditions in rabbit and guinea pig preparations. Mean basic cycle length (CL) for the establishment of fatigue is shown at the bottom and was much less in rabbits. 8-PT substantially reduced fatigue in both preparations, with a larger effect in guinea pigs (*P<.05, **P<.01, 8-PT versus control).

<table>
<thead>
<tr>
<th>Preparation</th>
<th>$T_{m0}$ (ms)</th>
<th>$AH_{m}$ (ms)</th>
<th>$\Delta A H_{15}$ (ms)</th>
<th>$\Delta A H_{41}$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Control</td>
<td>44.6±4.5</td>
<td>52.1±3.9</td>
<td>10.3±0.9</td>
<td>6.8±1.3</td>
</tr>
<tr>
<td>B. EHNA (5 μmol/L)</td>
<td>39.3±4.8</td>
<td>54.3±3.7</td>
<td>11.3±1.4</td>
<td>7.0±1.0</td>
</tr>
<tr>
<td>C. EHNA (5 μmol/L) + dipyridamole (1 μmol/L)</td>
<td>41.8±3.9</td>
<td>55.9±3.8</td>
<td>11.3±1.7</td>
<td>9.6±1.0*</td>
</tr>
<tr>
<td>D. EHNA + dipyridamole + adenosine (5 μmol/L)</td>
<td>44.4±3.5</td>
<td>66.5±3.5</td>
<td>7.8±0.8*</td>
<td>11.6±1.5‡</td>
</tr>
<tr>
<td>E. Chemicals in preparation D + 8-PT (10 μmol/L)</td>
<td>46.0±3.2</td>
<td>58.8±2.0†‡</td>
<td>9.2±1.0</td>
<td>8.0±1.3‡</td>
</tr>
</tbody>
</table>

$T_{m0}$ indicates time constant (in ms) of basic recovery curve; $AH_{m}$, AH interval at a long cycle length (see Equation 5 in text); $\Delta A H_{15}$, leftward shift (in ms) of the recovery curve caused by facilitation with the shortest $S_{1}S_{2}$ (facilitation) interval possible under all conditions (Equation 8); $\Delta A H_{41}$ is the magnitude of the upward shift in the recovery curve (in ms) caused by fatigue (fatigue 2 protocol in Fig 1, at the fastest rate obtained under all conditions); and EHNA, erythro-9-(2-hydroxy-3-nonyl)-adenine hydrochloride. Results are mean±SEM from data obtained in six preparations.

*P<.05, †P<.01, ‡P<.001 vs control; §P<.01 vs value under condition D (EHNA, dipyridamole, and adenosine).
Adenosine has long been recognized, the underlying mechanisms have remained elusive. Results of the present study, along with the previous observations of Jenkins and Belardinelli, suggest that adenosine effects may account for a significant proportion of the fatigue-induced conduction slowing at rapid rates. Jenkins and Belardinelli suggested that tachycardia may increase endogenous cardiac adenosine production as a result of increased metabolic requirements and that this process could act as a protective mechanism by promoting AV block at very rapid supraventricular rates, thus limiting the degree of tachycardia to which the ventricles are exposed.

Adenosine is believed to alter AV nodal function via mechanisms similar to those underlying acetylcholine action: Binding to a specific receptor causes GTP-biding protein (G,)-mediated opening of a sarcomlemal potassium channel. There is evidence that the same set of channels is activated by both adenosine and acetylcholine, and the corresponding current has been designated . It is likely that under basal conditions in normal hearts, interstitial adenosine concentrations are not sufficient to affect AV nodal conduction, as indicated by the lack of change in basal nodal conduction time (AH) on exposure to 8-PT or the combination of EHNA and diprydamole. At rapid rates, however, adenosine production is increased, presumably resulting in gradual interstitial adenosine accumulation and AV nodal conduction slowing, which manifests as AV nodal "fatigue." Adenosine administration would be expected to have effects similar to those of acetylcholine, which also increases AV nodal fatigue and reduces facilitation. The precise mechanisms of the latter actions are unknown. Vagal stimulation slows AV nodal recovery in the dog, whereas in the present experiments in rabbit hearts, adenosine did not alter the AV nodal recovery time course. Whether these differences are due to species-specific responses or to differing actions of adenosine and acetylcholine on recovery per se remains to be determined.

Potential Clinical Importance of Adenosine’s Effects on Rate-Dependent AV Nodal Properties

Our results indicate that adenosine can modulate rate-dependent AV nodal properties. Dipyridamole increases plasma adenosine concentrations in humans by an average of 60% and can thereby significantly increase the AH interval and Wenckebach cycle length as determined in the clinical electrophysiology laboratory. These observations indicate that endogenous adenosine concentrations are sufficient to modulate AV nodal conduction in humans and may play a role in determining the clinical response of the AV node to changes in heart rate. Endogenous adenosine production may thus in some cases "set" the rate at which AV nodal reentrant tachycardias can be sustained and may determine the occurrence of such tachycardias in some patients. A proportion of the antiarrhythmic actions of intravenous adenosine and ATP may be due to rate-dependent AV nodal depression, which is maximized in the presence of tachycardia. We have presented preliminary data that support this concept. The well-known transience of adenosine’s effect after an intravenous bolus is in large part due to rapid cellular uptake and metabolism of the compound, but reduced AV nodal depression due to the greatly slowed heart rate following conversion of a tachycardia may also contribute to the drug’s margin of safety.

The ability of adenosine to modulate rate-dependent AV nodal function may extend beyond the direct actions of the compound demonstrated in the present study. Adenosine antagonizes a wide variety of responses to adrenergic stimulation, apparently by reducing β-adrenergic activation of adenyl cyclase. Because β-adrenergic stimulation modifies rate-dependent AV nodal properties by accelerating recovery and attenuating fatigue, adenosine may produce additional rate-dependent AV nodal conduction slowing by preventing the conduction-enhancing effects of background adrenergic tone. In the presence of stressful situations, such as a clinical tachycardia, this may represent a significant additional action.

Potential Limitations

The great interspecies variation in the response to adenosine makes extrapolation from animal studies difficult. Because of this, we performed experiments in both rabbit and guinea pig preparations and we obtained similar results. We also attempted to perform similar experiments in anesthetized dogs, but we were unable to achieve significant AV nodal conduction slowing without excessive hypotension, even with intracoronary adenosine administration. These findings are consistent with previous observations of very limited negative dromotropic effects of adenosine in dogs. The isolated, superfused preparation allows for very stable, precise measurements and excellent control of the recovery variable by coupling atrial stimulation to His bundle activation. A disadvantage of this approach is the difficulty of obtaining viable preparations from guinea pig hearts. Although we succeeded in a relatively small percentage of attempts, the successful preparations were highly stable over time and had conduction properties and responses to adenosine similar to those reported in the literature for isolated, retrogradely perfused guinea pig hearts. An additional disadvantage of the isolated preparation is that it is functionally denervated. Potentially significant actions of adenosine (eg, antiadrenergic effects) may not be seen in such a system.

Very high adenosine concentrations were required to slow conduction in rabbit preparations. These results are consistent with prior findings in the literature. Because we found that the effects of adenosine on AV nodal functional properties were qualitatively similar at equipotent doses in rabbit and guinea pig preparations, it is likely that adenosine-induced changes in such properties are not species specific. The response to 8-PT, suggesting a role of endogenous adenosine in physiological fatigue, is somewhat difficult to interpret for rabbit preparations. It is unlikely that tachycardia can cause interstitial adenosine concentrations to exceed 100 μmol/L in the range that we used to produce AV conduction slowing in rabbit preparations. On the other hand, the concentration-response curve for adenosine-induced conduction slowing is quite flat in the rabbit, suggesting that appreciable changes may occur at much lower concentrations. Furthermore, hypoxia-induced AV conduction slowing in the rabbit is substantially attenuated by adenosine receptor blockade, indicating that physiological stimuli can cause sufficient
accumulation of endogenous adenosine in the rabbit to slow AV nodal conduction.

Our experimental model of AVRT involved an electrocircuit coupling stimulation of the atrium to activation of the His bundle. This is different from clinical AVRT, in that atrial activation is coupled to ventricular activation by a relatively constant VA conduction interval via an accessory pathway. Because HV time is relatively fixed, however, the only difference between our model and one coupling atrial to ventricular activation is a constant interval (the HV time). Of course, other aspects of clinical AVRT, such as refractoriness of the accessory pathway, are not simulated by our model. Because adenosine does not generally alter bypass tract properties, this may not be a major limitation.

The final limitation of these studies is that the range of frequencies that can be studied is limited by relatively rapid spontaneous automaticity. Despite removal of the sinus node area, spontaneous cycle lengths rarely exceeded 500 milliseconds. It was therefore impossible to follow the recovery process to completion, obtaining complete separation from facilitation and fatigue. The mathematical descriptions of these processes must therefore be considered to be reasonable working models that describe adequately the phenomena observed over the range of frequencies obtainable although as limited depictions of absolute processes.

Conclusions

We have shown that adenosine enhances fatigue and decreases facilitation in isolated rabbit and guinea pig preparations, slowing nodal conduction without altering the time course of recovery. These actions result in rate-dependent depression of conduction in the AV node that contributes to adenosine’s ability to suppress sustained AV reentry in an experimental model. Mathematical descriptors of recovery, facilitation, and fatigue account for the rate-dependent conduction and refractoriness properties of the in vitro rabbit AV node in both the absence and presence of adenosine. Finally, adenosine receptor blockade attenuates rate-dependent fatigue, suggesting a role for endogenous adenosine in mediating this physiological process.

Acknowledgments

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M Nayebpour, J Billette, F Amellal and S Nattel

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