Effects of β-Adrenergic Receptor Stimulation and Blockade on Rate-Dependent Atrioventricular Nodal Properties

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Recent work has shown that alterations in the dynamic atrioventricular (AV) nodal response to changes in heart rate can significantly modify AV nodal function. The present study was designed to evaluate the nature and potential importance of sympathetic regulation of the rate-dependent properties of the AV node. Selective stimulation protocols and mathematical formulations were used to independently quantify AV nodal recovery, facilitation, and fatigue in 12 morphine-chloralose--anesthetized dogs. Vagal effects were prevented by bilateral vagal transection and intravenous atropine, and the sinus node was crushed to allow a broader range of pacing cycle lengths. In seven dogs with sympathetic nerves intact, β-adrenergic receptor blockade increased the recovery time constant (τm) for the conduction of premature test beats from 47±2 (mean±SEM) msec (control) to 62±1 msec (p<0.001), whereas isoproterenol decreased τm to 38±1 msec (p<0.001). In addition, β-blockade increased the maximum amount of rate-dependent AV nodal fatigue from 7±2 msec (at a cycle length of 198±9 msec [control]) to 17±2 msec (p<0.001). In five dogs with decentralized stellate ganglia, τm was decreased from 71±3 msec (control) to 57±4 msec and 48±2 msec (p<0.001 for each) by left stellate ganglion stimulation at 5 and 10 Hz, respectively. Maximum fatigue was similarly reduced from 16±1 msec (control) to 12±2 msec (p=NS) and 8±1 msec (p<0.01), respectively. Stellate ganglion stimulation, isoproterenol, and β-blockade did not alter AV nodal facilitation. A mathematical model incorporating quantitative indexes of AV nodal function accurately accounted for tachycardia-dependent increases in the atrial–His activation interval, which were enhanced by β-adrenergic receptor blockade and reduced by isoproterenol. Furthermore, this model showed that β-adrenergic effects were increased by increasing heart rate, with the majority of the rate-dependent action being due to changes in the time course of AV nodal recovery. We conclude that β-adrenergic receptor stimulation alters functional properties that govern the AV nodal response to changes in heart rate. These changes in functional properties alter the ability of the AV node to conduct impulses during tachycardia and, as such, could play a major role in the ability of sympathetic stimulation to promote and β-adrenergic receptor blockade to prevent the occurrence of AV nodal reentrant arrhythmias. (Circulation Research 1992;70:902–911)

KEY WORDS • atrioventricular node • arrhythmias, atrial • electrocardiogram • calcium channels • sympathetic nervous system • isoproterenol

Atrioventricular (AV) nodal function determines the occurrence and consequences of a wide variety of cardiac rhythms. The likelihoods of intranodal AV block, AV nodal reentrant tachycardia, and orthodromic tachycardia in association with an accessory pathway, as well as the clinical consequences of atrial fibrillation and flutter, are highly related to AV nodal conduction and refactoriness.1-12 The ability of the AV node to respond to an atrial input with a propagated response is, in turn, related in a complex fashion to the activation history of the AV node.3-13 A number of discrete properties can be identified that relate activation history to AV nodal conduction. The conduction of extrasystolic impulses through the AV node is slowed increasingly as their prematurity increases.3,10,12-21 This phenomenon, AV nodal recovery, has a time constant in the range of 50–100 msec.8,12,18-21 On the other hand, an abrupt and sustained increase in atrial activation frequency results in a gradual slowing of AV nodal conduction, called “fatigue,” requiring minutes to reach steady state.4,8,11,22-25 Single premature AV nodal activations (A2) shift the relation between His bundle–atrial activation time (HA interval) and atrial–His activation time (AH interval) of a subsequent A2 beat to the left on the recovery time axis.4,16,18 This shift decreases the conduction time of premature activations for a given recovery interval and has been called AV nodal “facilitation.” The properties of recovery, fatigue, and facilitation can be characterized independently using specific stimulation protocols.15,18,24
The degree of sympathetic stimulation is an important regulator of AV nodal function. β-Adrenergic stimulation, via direct activation of the sympathetic innervation of the heart or by the exogenous administration of adrenergic agonists, accelerates AV nodal conduction. Changes in sympathetic input play an important role in baroreflex control of AV conduction.β The autonomic adjustments to upright posture facilitate the induction of sustained AV nodal reentrant tachycardia, and in some patients with AV nodal reentrant tachycardia, programmed stimulation fails to induce the tachycardia unless isoproterenol is infused. β Blockade slows AV nodal conduction and can prevent the induction of AV nodal reentry. The sympathetic nervous system thus plays an important role in regulating AV nodal function and determining the occurrence and manifestations of supraventricular arrhythmias.

The dependence of AV nodal function on heart rate and autonomic tone are well known, but the interactions between the latter two are poorly understood. We have recently shown that changes in the AV nodal response to heart rate change are a potentially important mechanism of vagal action. Walllice et al. have shown that heart rate influences the effect of sympathetic nerve stimulation on AV nodal conduction in dogs, and Prystowsky and Page have provided evidence for a similar interaction in humans. We have developed mathematical approaches to the quantification of individual AV nodal properties and have shown that these approaches can account for both the rate-dependent changes in AV nodal conduction time and the rate-dependent effects of the vagus nerve on AV conduction. The present study was designed to assess the possibility that sympathetic stimulation alters AV nodal conduction by changing the ways in which the AV node adapts to changes in heart rate. Specific goals were 1) to evaluate whether β-adrenergic receptor stimulation or blockade alter AV nodal recovery, facilitation, or fatigue and 2) to determine the extent to which changes in these rate-dependent properties account for alterations in AV nodal conduction as a function of heart rate.

Materials and Methods

General Methods

Mongrel dogs of either sex were anesthetized with morphine (2 mg/kg) and α-chloralose (100 mg/kg i.v.). Catheters were inserted into both femoral veins and arteries and were kept patent with heparinized saline solution (0.9%). Dogs were ventilated via an endotracheal tube using an animal respirator (Harvard Apparatus, South Naütic, Mass.). Tidal volume and respiratory rate were adjusted to ensure adequate oxygenation (SaO₂ ≥90%) and physiological arterial pH (7.35–7.45). A thoracotomy was performed through the fourth right intercostal space, and intrathoracic temperature was maintained at 37–38°C by a homeothermic heating blanket.

Bipolar Teflon-coated stainless-steel electrodes were inserted into the lateral right atrium, right atrial appendage, and high lateral right ventricle. A bipolar electrode was inserted epicardially to record a His bundle electrogram. The electrodes in the atrial appendage and right ventricle were used to record atrial and ventricular electrograms. The lateral right atrial electrode was used to apply 4-msec square-wave pulses at twice diastolic threshold, with timing controlled by a programmable stimulator (Digital Cardiovascular Instruments Inc., Berkeley, Calif.). Electrogram signals were filtered (30–500 Hz) and amplified (Bloom Instruments Ltd., Flying Hills, Pa.), with the amplified output led into a paper recorder and/or a sensing circuit of the stimulator. A Statham P23 ID transducer (Statham Medical Instruments, Los Angeles, Calif.), electrophysiological amplifiers, and a Mingograf T-16 paper recorder (Siemens-Elema, Ltd., Toronto) were used to record blood pressure; electrocardiographic leads II and AVR; atrial, His bundle, and ventricular electrograms; and stimulus artifacts. Recordings were obtained at a paper speed of 200 mm/sec (measurement accuracy, ±2.5 msec).

The sinus node was crushed to allow for a wide range of pacing rates. The vagus nerves were isolated in the neck, ligated, and divided. Atropine was given as an initial intravenous bolus of 1 mg, followed by 0.5 mg every 2 hours to produce sustained muscarinic receptor blockade.

Measurement of Electrophysiological Variables

Wenckebach cycle length was determined by decreasing atrial pacing cycle length by 10 msec every 10 beats until second-degree AV block occurred. The effective refractory period of the AV node and atrial effective refractory period were measured with the extrastimulus technique. The effective refractory period of the AV node was defined as the longest atrial (A₁A₂) interval failing to result in a His bundle deflection, and the atrial effective refractory period was defined as the longest (S₁S₃) interval failing to result in a propagated atrial response.

AV conduction was assessed from the His bundle electrogram, with the AH interval measured from the peak after the most rapid deflection in the atrial electrogram of the His bundle electrode to the peak after the most rapid deflection of the His bundle electrogram. The HV interval was the time from bundle of His depolarization to the onset of ventricular activation in the His signal. The HA interval was the time from the peak after the most rapid deflection in the His electrogram to the peak in the next atrial electrogram in the His recording.

Quantitative Assessment of Functional Rate-Dependent Properties of the AV Node

Specific stimulation protocols and analysis techniques were used as previously described to quantify selected functional AV nodal properties before and after interventions altering the level of cardiac β-adrenergic receptor stimulation. A brief summary of these protocols and techniques is given below.

AV nodal recovery. The atrium was paced at a basic cycle length (S₀S₀) of 500 msec, and a single premature or delayed stimulus (S₁) was introduced after every 15 basic stimuli. The relation between the A₂H₂ (AV nodal conduction time of the test impulse) and the H₂A₂ interval was established and fitted to a single exponential function.
AV nodal facilitation. The atrium was paced at a constant basic cycle length of 500 msec. A premature atrial impulse (S₃) was introduced to produce a selected A₁A₂ facilitation cycle after every 15 basic stimuli. A test impulse (S₄) was then applied after each S₃, and the AV nodal response to S₄ was monitored to generate an H₂A₃-A₃H₃ recovery curve. The latter curve was studied at seven values of (A₁A₂) facilitation cycle length (FCL) between 500 msec and 20 msec greater than the refractory period of the AV conduction system.

Each H₂A₃-A₃H₃ recovery curve was fitted by a monoeponential model, and the H₂A₃ value at which the A₃H₃ interval is 125 msec (to be referred to as the "H₃A₃" value for each curve. The H₃A₃ is an index of the position of the curve on the horizontal axis. Changes in H₃A₃ reflect the magnitude of parallel leftward shift resulting from facilitation and are an exponential function of FCL.⁴²

AV nodal fatigue. A pacing and pacing circuit was used to sense ventricular activation and to pace the right atrium with a given VA delay. Since the HV interval was constant, this caused a tachycardia with a constant HA interval. Tachycardia was initiated abruptly and maintained for 5 minutes, with the atrial cycle length before tachycardia set at 500 msec by using an activation-inhibited demand pacemaker at a rate of 120 beats per minute. After 5 minutes of tachycardia, the sense-pacemaker circuit was closed, and 5 minutes at the baseline cycle length (500 msec) was allowed for recovery before initiating tachycardia with a different HA interval. Fatigue was studied at a total of seven HA intervals in each experiment.

Experimental Protocol

AV nodal recovery, fatigue, and facilitation were characterized under control conditions as described above. Steady-state values for the AH interval were determined at various cycle lengths, with 5 minutes of pacing at each cycle length used to ensure steady-state conditions. Wenckebach cycle length was measured before and after each experimental protocol to confirm the stability of each preparation. Isoproterenol was then infused via an infusion pump (model 848, EDCO Scientific Inc., Chapel Hill, N.C.). The rate of isoproterenol infusion was selected to produce a 20–30-msec decrease in the Wenckebach cycle length, and the infusion rate was then kept constant in a given dog. Three dogs received an infusion of 2 μg/min, and four others received an infusion of 5 μg/min. Thirty minutes after the onset of isoproterenol infusion, the measurements obtained under control conditions were repeated. Isoproterenol was then discontinued, and 20 minutes were allowed for a return to baseline. When the Wenckebach cycle length had returned to control values, we administered 0.5 mg/kg nadolol, which we have shown causes sustained β-blockade for over 2 hours. Twenty minutes later, all measurements were repeated.

To compare the effects of endogenous sympathetic nerve stimulation with those of exogenous β-adrenergic receptor activation and blockade, an additional series of experiments was performed. The left stellate ganglion was decentralized by cutting its connections with the thoracic sympathetic chain and rami communicantes, and outflow from the right stellate ganglion was prevented by cutting both ansae. An insulated bipolar electrode (Dastre Electrode, Ealing Scientific Ltd., St. Laurent, Canada) was attached (anodal pole proximal) to the dorsal and ventral ansae, and stimulation was applied via an SD 9F stimulator (Grass Instrument Co., Quincy, Mass.). Square-wave stimuli of 2-msec duration, 6–10-V intensity, and 5- or 10-Hz frequency were used. AV nodal functional properties were studied in the absence of sympathetic nerve stimulation, and the measurements were repeated during continuous nerve stimulation, first at 5-Hz and then at 10-Hz frequency. Finally, nadolol (0.5 mg/kg i.v.) was given, and the measurements were repeated. Experimental protocols were approved by the animal care committee of the Montreal Heart Institute.

Data Analysis

Results are reported as mean ± SEM. Comparisons between multiple groups were made by two-way analysis of variance with Scheffé contrasts.⁴⁷ Comparisons between two groups of experimental data only were made with Student’s t test. Two-tailed tests were used, and a value of p = 0.05 was taken to indicate statistical significance. Nonlinear curve fitting was performed with Marquardt’s technique on an IBM AT–compatible computer. The effects of exogenous β-adrenergic receptor stimulation with isoproterenol were evaluated in seven dogs, and the effects of sympathetic nerve stimulation were assessed in five dogs.

Results

General Effects of β-Adrenergic Receptor Stimulation and Blockade

Isoproterenol accelerated AV nodal conduction and decreased the Wenckebach cycle length (Table 1). β-Adrenergic receptor blockade had the opposite effects. The effective refractory period of the AV node was not measurable because it was exceeded by the atrial effective refractory period. Isoproterenol reduced diastolic pressure and tended to increase systolic pressure, whereas β-blockade significantly reduced both

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**Table 1. Effects of Isoproterenol and β-Adrenergic Receptor Blockade**

<table>
<thead>
<tr>
<th></th>
<th>WBCL (msec)</th>
<th>AERP (msec)</th>
<th>AH (msec)</th>
<th>Blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systolic</td>
</tr>
<tr>
<td>Control</td>
<td>167±8.8</td>
<td>132±6</td>
<td>57±5</td>
<td>136±7</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>146±10*</td>
<td>122±5</td>
<td>47±3†</td>
<td>142±10</td>
</tr>
<tr>
<td>β-Blockade</td>
<td>242±15‡</td>
<td>161±10*</td>
<td>92±6‡</td>
<td>103±7‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. WBCL, Wenckebach cycle length; AERP, atrial effective refractory period; AH, AH interval. All measurements other than WBCL were obtained at a basic cycle length of 500 msec.

*p<0.01, †p<0.05, and ‡p<0.001 compared with control.
systolic and diastolic pressure. The stability of the preparation is indicated by the consistent values of the Wenckebach cycle length obtained at the beginning, midpoint, and end of each experimental protocol (Figure 1).

Changes in AV Nodal Recovery

Typical recovery curves under control conditions, in the presence of isoproterenol, and after nadolol are shown in Figure 2. β-Adrenergic receptor blockade resulted in a slower time course of recovery, whereas isoproterenol slightly accelerated recovery. The mean time constant for all recovery curves averaged 47±2 msec under control conditions, compared with 62±1 msec (p<0.001) after β-blockade and 38±1 msec (p<0.001) in the presence of isoproterenol.

AV Nodal Facilitation

A premature AV nodal activation resulted in a leftward shift of the AV nodal recovery curve for a subsequent beat (Figure 3). The magnitude of the leftward shift for a given coupling interval was similar under all three conditions. To analyze changes in facilitation, each AV recovery curve was fitted to the equation

\[ AH_{HA} = AH_s + A \cdot \exp(-HA/τ_{rec}) \]  \hspace{1cm} (1)

where \( AH_{HA} \) is the AH interval at a given HA interval, \( AH_s \) is the AH interval after full recovery, \( A \) is a constant, and \( τ_{rec} \) is a recovery time constant. The magnitude of the leftward shift of the recovery curve was quantified by calculating the \( HA_{25} \) from Equation 1.

The \( HA_{25} \) decreased with decreased FCL under all three conditions (Figure 4). \( HA_{25} \) was greater in the presence of β-blockade, indicating that lesser degrees of prematurity were needed to attain an AH of 125 msec than under control conditions. Isoproterenol produced changes in \( HA_{25} \) qualitatively opposite to those resulting from β-blockade. However, the differences between \( HA_{25} \) under control compared with isoproterenol conditions were small and not statistically significant. Isoproterenol accelerated basal AV nodal conduction, as shown by \( AH_s \), whereas β-blockade had the opposite effect.

Decreases in \( HA_{25} \) produced by a premature beat at any FCL relative to the value at the basic cycle length of 500 msec (\( ΔHA \)) are an index of the magnitude of the facilitating effect at that FCL. 42,44,48 This index of facilitation was not altered by β-adrenergic stimulation or blockade (Figure 5). Changes in the HA interval can be fitted to an equation of the form

\[ ΔHA = K \cdot \exp(-FCL \cdot B) \]  \hspace{1cm} (2)

where \( K \) is a constant equal to the (theoretical) change in the HA interval at an FCL of 0 and \( B \) is a rate
constant. K and B were unaltered by \(\beta\)-adrenergic receptor stimulation and blockade (Table 2), further indicating that they did not alter AV nodal facilitation.

**AV Nodal Fatigue**

The initiation of a tachycardia with a constant HA interval results in gradual AH prolongation. Figure 6 shows the time course of changes in the AH interval from beat 2 of the tachycardia until a steady state has been achieved in a representative experiment. Since facilitation stabilizes within one cycle\(^{16,42}\) and the recovery variable HA is constant, such changes are due to fatigue alone. Changes in the AH interval were well fitted by an exponential relation of the form

\[
\Delta AH_n = \Delta AH_{in}[1 - \exp(-n/\tau_{fat})] 
\]

where \(\Delta AH_n\) is change in the AH interval due to fatigue for the nth beat, \(\Delta AH_{in}\) is steady-state change in the AH interval due to fatigue, and \(\tau_{fat}\) is the time constant for fatigue onset.

In the experiment illustrated in Figure 6, \(\beta\)-blockade increased the magnitude of fatigue (\(\Delta AH_n\)). This was a general finding in all experiments, as shown by the mean data in Figure 7. \(\tau_{fat}\) was not affected by \(\beta\)-adrenergic receptor stimulation and blockade, averaging 65±7 beats under control conditions, 84±18 beats in the presence of isoproterenol, and 47±3 beats after \(\beta\)-blockade (\(p=NS\)). The magnitude of AH change due to fatigue at any steady-state HA interval (\(\Delta AH_{HA}\)) was a function of HA, of the form

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

where \(\Delta AH_{max}, C,\) and D are constants. The dashed lines in Figure 7 show fits to the mean data using Equation 4 for each condition.

**Role of Changes in Rate-Dependent Properties**

The basic AV recovery equation (Equation 1) describes the effect of the coupling interval on AV nodal conduction but does not consider the role of facilitation or fatigue. It fails, therefore, to account for conduction changes when the level of facilitation or fatigue is changing.\(^9,12,48\) During sustained rate changes, alterations in both facilitation and fatigue occur. To evaluate the role of modulation of AV nodal properties at different heart rates, it is necessary to analyze the effects of changes in \(\beta\)-adrenergic receptor stimulation on all three rate-dependent AV nodal properties.

We have shown that the contribution of facilitation and fatigue can be incorporated into Equation 1.\(^{48}\) Facilitation is incorporated by considering HA to be modulated by the preceding cycle length (according to Equation 2), and AH\(_s\) is adjusted to account for the effect of fatigue (Equation 4). Equation 1 then becomes

\[
AH_{HA} = P + A \cdot \exp(-Q/\tau_{rec})
\]
 Estimates of the predicted effects of incomplete recovery alone (from Equation 1), of recovery modified by facilitation (Equation 2), of fatigue alone (Equation 4), and of all three processes functioning simultaneously (Equation 5). Values at each cycle length were subtracted from those at a basic cycle length of 500 msec, to estimate rate-dependent slowing at any cycle length due to the influence of each process.

The resulting curves are shown in Figure 8. Isoproterenol (middle panel) accelerates recovery, reducing the amount of conduction slowing due to incomplete recovery (dotted line) compared with control (top panel). β-Adrenergic receptor blockade (bottom panel) slows recovery and increases the effect of fatigue. These changes reduce total rate-dependent conduction slowing (solid line) in the presence of isoproterenol and increase rate-dependent conduction slowing in the presence of β-blockade. Experimental data (open boxes and error bars) agree well with the theoretical analysis.

To further quantify the role of changes in rate-dependent properties, we determined the magnitude of AV conduction change attributable to changes in recovery and fatigue resulting from β-adrenergic receptor activation. AH intervals in the presence of isoproterenol were compared with those in the presence of β-adrenergic receptor blockade in order to contrast findings associated with a constant, enhanced level of β-adrenergic receptor stimulation (isoproterenol) with those associated with the absence of β-mediated effects. As shown in the top panel of Figure 9, β-adrenergic receptor stimulation results in a decrease in the AH interval, which becomes more marked as cycle length (or HA interval) decreases. Predicted changes are

### Table 2. Mean Values of Constants Characterizing Atrioventricular Nodal Recovery, Facilitation, and Fatigue in Seven Dogs

<table>
<thead>
<tr>
<th>Control</th>
<th>Isoproterenol</th>
<th>β-Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>( AH' ) (msec)</td>
<td>54±5</td>
<td>45±4*</td>
</tr>
<tr>
<td>A (sec)</td>
<td>1.5±0.3</td>
<td>1.0±0.3</td>
</tr>
<tr>
<td>( \tau_{\text{rec}} ) (msec)</td>
<td>43±5</td>
<td>35±2</td>
</tr>
<tr>
<td>K (msec)</td>
<td>317±59</td>
<td>425±114</td>
</tr>
<tr>
<td>B (msec⁻¹)</td>
<td>0.009±0.002</td>
<td>0.010±0.002</td>
</tr>
<tr>
<td>( \Delta AH_{\text{MAX}} ) (msec)</td>
<td>12±1</td>
<td>18±4</td>
</tr>
<tr>
<td>C (msec)</td>
<td>−1±1</td>
<td>0±1</td>
</tr>
<tr>
<td>D (msec⁻¹)</td>
<td>0.008±0.002</td>
<td>0.014±0.003</td>
</tr>
</tbody>
</table>

Values are mean±SEM. \( AH' \), AH interval after full recovery at a cycle length of 500 msec; A, constant; \( \tau_{\text{rec}} \), recovery time constant; K, constant equal to the (theoretical) change in the HA interval at a facilitation cycle length of 0; B, rate constant; \( \Delta AH_{\text{MAX}} \), maximum change in the AH interval due to fatigue; C and D, constants. \( AH' \), A, and \( \tau_{\text{rec}} \) were obtained by fitting recovery data at a cycle length of 500 msec to Equation 1 for each experiment and averaging the values obtained in all seven experiments. K and B were obtained by fitting facilitation data in each experiment to Equation 2. \( \Delta AH_{\text{MAX}} \), C, and D were obtained by fitting fatigue data from each experiment to Equation 4, as shown for the mean data in Figure 7.

*\( p<0.05, \) †\( p<0.01, \) and ‡\( p<0.001 \) compared with corresponding control value.

where P is \( AH' + \Delta AH_{\text{HA}} \) (AH′ is AH at a cycle length of 500 msec, and \( \Delta AH_{\text{HA}} \) is defined as in Equation 4) and Q is HA+ΔHA (for ΔHA as defined in Equation 2).

Data in each experiment were used to calculate the constants \( AH' \), A, \( \tau_{\text{rec}} \), K, B, \( \Delta AH_{\text{MAX}} \), C, and D. The mean constants for all experiments (Table 2) were substituted into the corresponding equations to obtain

### Figure 6. Graphs showing changes in the HA interval (ΔAH) as a function of beat number after the onset of tachycardia in a representative experiment. Solid lines show best-fit exponential curves. The time course of AH prolongation was similar under all three conditions, but its magnitude for a given HA interval was greatest in the presence of β-blockade, least in the presence of isoproterenol, and intermediate under control conditions.
Results


| Graph showing magnitude of fatigue (changes in the AH interval at steady state) for tachycardias produced by pacing with the fixed ventriculoatrial (VA) intervals shown. Results (mean ± SEM) were obtained from curve fits to the type of data presented in Figure 6. Dashed curves represent best-fit exponentials to mean data. **p<0.01 and ***p<0.001 compared with control values.

shown by the solid curve and agree well with experimental data. The mathematical analysis allows us to attribute the observed AH reductions to changes in underlying AV nodal properties. At cycle lengths >500 msec, the AH reduction caused by isoproterenol is attributed to a time-independent (tonic) action. As cycle length is reduced, the acceleration of recovery produced by β-adrenergic receptor stimulation becomes important and accounts for over half of the consequent acceleration in conduction at cycle lengths between 200 and 300 msec. Whereas a reduction of fatigue may also play a role at very rapid heart rates, it is predominantly the change in AV nodal recovery that accounts for the rate-dependent effects of sympathetic stimulation on AV nodal conduction.

Effects of Sympathetic Nerve Stimulation

To determine whether graded sympathetic nerve stimulation alters the rate-dependent properties of the AV node, an additional five dogs were studied. The effects of sympathetic nerve stimulation on recovery in a typical experiment are shown in Figure 10. Overall, sympathetic nerve stimulation reduced \( \tau_{rec} \) from 71±3 msec (control) to 57±4 msec (p<0.001) at a stimulation frequency of 5 Hz and 48±2 msec (p<0.001 versus control) at 10 Hz. In keeping with the decentralization of sympathetic cardiac nervous input, \( \tau_{tot} \) in the presence of β-blockade (65±3 msec) was not significantly different from control values.

Figure 11 shows results for fatigue-induced conduction slowing in the presence of varying degrees of sympathetic tone. Sympathetic stimulation caused a graded reduction in the magnitude of fatigue, which was statistically significant only for a VA interval of 50 msec during 10-Hz stimulation. In contrast, facilitation was not altered by sympathetic stimulation, with the maximum shift of the recovery curve averaging 45±9 msec under control conditions, 35±4 msec during 5-Hz sympathetic stimulation, 36±8 msec during 10-Hz stimulation, and 30±3 msec after β-blockade (no statistically significant differences).

Discussion

We have shown that the degree of β-adrenergic receptor activation can control the processes that govern the AV nodal response to changes in heart rate. Enhanced receptor activation reduces the conduction slowing effect of increases in heart rate, whereas β-adrenergic receptor blockade enhances the negative dromotropic effect of supraventricular tachycardia.

![Figure 8](http://circres.ahajournals.org/lookup/suppl/doi:10.1161/01.RES.70.5.908/-/DC1/FIG08A.pdf)

**Figure 8.** Graphs showing predicted rate-dependent changes in the AH interval (ΔAH) due to incomplete recovery, recovery modified by facilitation, and fatigue as a function of basic cycle length (BCL). Mean characterizing constants determined experimentally (Table 2) were substituted into Equations 1, 2, and 4, respectively (see text), to obtain predictions shown. As BCL decreases, incomplete recovery is expected to increase the AH interval to an extent indicated by the dotted lines. Facilitation attenuates the effects of recovery, and when this action of facilitation is incorporated, the AH slowing is predicted by the dashed lines. Changes due to combined recovery and facilitation were added to those resulting from fatigue alone to obtain the total rate-dependent AH prolongation predicted (solid lines). The latter are in close agreement with experimentally observed values (mean ± SEM).
Comparison With Previous Studies of Sympathetic Effects on the AV Node

Sympathetic nerve stimulation,\textsuperscript{26-28} exogenous $\beta$-agonists,\textsuperscript{8,29,30} and baroreflex-mediated increases in sympathetic tone\textsuperscript{31,32} all enhance AV nodal conduction by activating $\beta$-adrenergic receptors. Ferrier and Dresel\textsuperscript{8} showed that basal AV nodal conduction time at rapid heart rates is reduced by epinephrine, suggesting a reduction in AV nodal fatigue. Wallick et al\textsuperscript{38} showed that the acceleration of AV conduction caused by sympathetic nerve stimulation is magnified by tachycardia. The AH interval shortening produced by isoproterenol infusion in humans similarly depends on the atrial activation rate.\textsuperscript{49} Although the processes underlying rate-dependent responses of the AV node have been extensively characterized with selective pacing protocols,\textsuperscript{5,13,16,18,24,50} their modulation by sympathetic tone has not been analyzed.

We found that $\beta$-adrenergic receptor blockade increased the amount of rate-dependent fatigue in dogs with intact sympathetic nerves. In addition, $\beta$-blockade slowed the recovery of AV nodal conduction after preceding activation. $\beta$-Adrenergic receptor stimulation decreased fatigue and accelerated recovery. $\beta$-Adrenergic receptor activation produced qualitatively similar effects whether caused by the intravenous infusion of an exogenous agonist (isoproterenol) or by electrically stimulating the nervous outflow from the left stellate ganglion. The effect of isoproterenol was quantitatively smaller. It is possible that larger doses of isoproterenol might have been more effective, but preliminary studies suggested that the doses used produced near-maximal changes in the AH interval. The lesser effects of isoproterenol were more likely due to the high level of resting sympathetic tone in open-chest dogs with sympathetic nerves intact.
The effects of β-adrenergic receptor blockade support this contention. Nadolol had a large effect on AV nodal conduction in sympathetically intact dogs but a small and statistically nonsignificant effect in dogs with stellate ganglion outflow decentralized.

**Possible Ionic Mechanisms of Adrenergic Effects on AV Nodal Recovery and Fatigue**

The precise ionic mechanisms of AV nodal recovery and fatigue remain unknown. It is likely that AV nodal recovery is related to the time required for reactivation of L-type calcium channels.52-46,48 β-Adrenergic stimulation accelerates the recovery of slow channel action potentials51 and promotes the reactivation of calcium current in single guinea pig ventricular myocytes.52 An acceleration of the recovery of calcium current from inactivation is thus a probable explanation of the more rapid recovery of AV nodal conduction during β-adrenergic receptor stimulation. AV nodal fatigue may be related to ion accumulation or depletion, metabolic dysfunction, or electricogenic transport mechanisms. If extracellular potassium accumulation plays a role in AV nodal fatigue, it is possible that the ability of β-adrenergic stimulation to stimulate Na+, K+-ATPase activity53,54 accounts for its fatigue-attenuating properties.

**Potential Limitations of Our Findings**

We studied several levels of adrenergic tone in our dogs: resting basal tone in an open-chest, anesthetized preparation; a constantly increased level of β-adrenergic receptor stimulation resulting from either continuous iso-proterenol infusion or graded left stellate ganglion stimulation; and the absence of β-adrenergic stimulation resulting from β-blockade with nadolol. We have not examined the complex changes in rate-dependent AV nodal properties that may occur with continuously changing levels of sympathetic activity.55-58 Although such studies would have been interesting, they are beyond the scope of the present article. Direct membrane actions of β-blockers can be a complicating factor in electrophysiological studies. Nadolol, however, is devoid of any direct membrane actions,57 and all of its effects can be safely attributed to β-adrenergic receptor blockade.

We used the HA interval as an index of AV nodal recovery time. The relative merits of the HA interval and the AA interval as indexes of the AV nodal recovery period have been disputed, and resolution of this issue is beyond the capability of the methods used in this study. Levy et al46 have shown that the HA interval determines AV nodal conduction independent of basic cycle length, and Billette and Métayer58 have reported that consideration of the HA interval can explain complex properties of AV nodal functional refractoriness.

**Potential Significance**

Autonomic tone is well known to regulate AV nodal conduction. The present investigation, along with our previous study of vagal influences,42 indicates that the autonomic nervous system controls processes, particularly AV nodal recovery and fatigue, that determine the AV nodal response to changes in heart rate. Although there are data in the literature suggesting that the magnitude of sympathetic effects on AV nodal function is heart rate dependent,28 our work is the first to establish the changes in functional properties of the AV node that underly this rate-dependent action. Furthermore, we have been able to demonstrate quantitatively that an increase in the rate of recovery after activation is the most important contributor to the actions of β-adrenergic receptor activation on AV nodal conduction at rapid rates.

Changes in AV nodal functional properties are potentially important mechanisms of autonomic nervous system action. It is well known, for example, that 1:1 AV conduction is maintained during exercise at cycle lengths much shorter than the Wenckebach cycle length measured by rapid atrial pacing. Our results suggest that the acceleration of AV nodal recovery and attenuation of fatigue resulting from increases in sympathetic tone and decreases in vagal tone may contribute to the physiological maintenance of 1:1 conduction during exercise. The acceleration of AV nodal recovery and lessening of fatigue caused by β-adrenergic receptor stimulation may account for the role of sympathetic activation in the occurrence of AV nodal reentry.33,35,36 On the other hand, enhancement of fatigue and slowing of AV nodal recovery may contribute to the salutary effects of β-adrenergic receptor blockers in supraventricular arrhythmias.38-41

**Conclusions**

We have shown that the degree of β-adrenergic receptor activation modulates discrete rate-dependent properties of the AV node. These actions decrease AV nodal conduction slowing by tachycardia when sympathetic tone is high and increase the negative dromotropic effects of tachycardia in the presence of β-adrenergic receptor blockade. The accommodation properties of the AV node to changes in heart rate are under reciprocal control of both limbs of the autonomic nervous system and constitute a heretofore little-recognized target for autonomic regulation of AV nodal function. Further work needs to be done to clarify the underlying mechanisms of dynamic AV nodal properties and of the autonomic effects on them.

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