A Unified Model of Atrioventricular Nodal Conduction Predicts Dynamic Changes in Wenckebach Periodicity

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The atrioventricular (AV) node responds in a complex fashion to changes in activation rate. A variety of approaches have been used to explain these dynamic AV nodal responses, but none has been able to account fully for AV nodal behavior. Three specific rate-dependent properties of the AV node have been described: 1) time-dependent recovery after excitation, 2) an effect of short cycles to advance recovery ("facilitation"), and 3) a gradual slowing of conduction in response to sustained, high-frequency activation ("fatigue"). We hypothesized that a model incorporating quantitative descriptors of all three processes might be able to account for a wide variety of AV nodal behaviors. Quantitative descriptors of AV nodal recovery, facilitation, and fatigue were developed based on AV nodal conduction changes during selective pacing protocols in seven autonomically blocked dogs. These descriptors were incorporated into a set of mathematical equations that define AV nodal conduction of any beat based on activation history. The equations were then applied to predict pacing-induced Wenckebach periodicity in each dog. Experimental data were obtained after nine to 19 step decreases in atrial cycle length into the Wenckebach zone in each animal. Observed behaviors included complex patterns of block, a progressive increase in the level of block over 5 minutes of rapid pacing, and periods of alternating patterns of block. The model accurately predicted the onset of AV block at each cycle length, the relation between conduction ratio and cycle length as a function of time, and the changing patterns of Wenckebach periodicity during sustained atrial pacing. All three terms of the model equation (describing recovery, facilitation, and fatigue) were essential to account fully for the observed behaviors. Elimination of AV nodal fatigue from the model resulted in failure to account for time-dependent changes in Wenckebach patterns, whereas exclusion of facilitation led to consistent overestimation of the degree of AV block at each cycle length. We conclude that a mathematical model incorporating terms to describe recovery, facilitation, and fatigue accurately predicts a wide range of Wenckebach-type behavior and that complex conduction patterns of the AV node can be fully accounted for by simple functional AV nodal properties. (Circulation Research 1991;68:1280–1293)

The atrioventricular (AV) node is the conducting link between the atria and the ventricles and subserves an important filtering function by virtue of its rate-dependent properties. A characteristic feature of AV nodal function is the diversity of responses observed during different atrial stimulation sequences. These include conduction slowing of single premature atrial impulses,1 variable conduction responses to accelerations in rate,2,3 and different patterns of conduction block seen during Wenckebach periodicity.4–7

Several mathematical models of AV nodal conduction have been described.6–20 However, no single model has yet satisfactorily explained the wide variety of possible AV nodal behavior. For example, the assumptions used to explain one type of behavior such as Wenckebach-type AV block may not correctly account for normal patterns of anterograde conduction of premature atrial impulses13 or may fail to explain time-dependent changes in the pattern of
second-degree AV block that are observed with prolonged atrial stimulation in humans. Moreover, experimental confirmation of theoretical predictions is often lacking or based on stimulation sequences that are closely related to the original manner in which the model was constructed. There is general agreement that the rate dependence of AV nodal conduction is due to at least two different phenomena. The first, termed AV nodal recovery, describes the progressive delay in AV conduction as single atrial impulses penetrate the AV node more prematurely. The second appears during prolonged stimulation at faster rates, resulting in gradual prolongation of AV nodal conduction time independently of changes in recovery interval. This process, termed fatigue by Lewis and Master, has been characterized more recently by Billette and coworkers, who found that its onset and dissipation follow a slow, symmetrical time course. A third rate-dependent phenomenon has also been described. Atrial impulses at premature recovery (HA) intervals show less conduction slowing when preceded by a premature atrial activation. This process, termed facilitation, reaches steady state after one cycle at a new rate and leads to a parallel shift of the recovery curve toward shorter recovery intervals. In addition to these intrinsic AV nodal properties, tachycardias may also cause reflex changes in autonomic tone that alter AV nodal properties over time.

The relation between individual functional AV nodal properties (like recovery, facilitation, and fatigue) and complex AV nodal conduction patterns is unclear. Wenckebach periodicity can be explained by the recovery properties of the AV node and the AV nodal recovery curve obtained by studying the response to single electrically induced premature beats can be used to predict complex AV conduction patterns. However, the AV nodal recovery curve itself is altered by changes in rate and predicted conduction patterns depend strongly on the rate at which the recovery curve is obtained. Furthermore, conduction patterns do not remain stable after the onset of Wenckebach periodicity at a given rate, but continue to change over the subsequent several minutes, a finding that cannot be explained by a simple recovery model. It is therefore uncertain whether the many rate-dependent behaviors of the AV node can be accounted for on the basis of simple underlying functional AV nodal properties. Although models based on recovery properties alone are not sufficient to explain such behaviors, this failure may be due to the lack of consideration of other properties such as facilitation and fatigue. If complex AV nodal responses resulting from rate change can be attributed to underlying functional properties, a mathematical model incorporating these properties and their interdependence should be able to predict a priori these complex patterns of AV nodal responses. The purpose of the present study was threefold: 1) to develop a mathematical model capable of predicting AV nodal conduction time on a single-beat basis by incorporating quantitative indexes of AV nodal recovery, facilitation, and fatigue; 2) to determine experimentally the parameters of this model; and 3) to apply this model to a situation in which AV nodal conduction changes on a beat-to-beat basis. For the last purpose, we selected second-degree AV nodal block (Wenckebach-type) occurring after an abrupt increase in atrial rate.

Materials and Methods

Finite Difference Equation Model for the AV Node

Previous studies of AV nodal conduction have shown that AV nodal conduction time is a function of the preceding recovery (VA or HA) interval, so the longer the recovery interval, the shorter the conduction time. This relation, called the AV nodal recovery curve, is well described by either hyperbolic or exponential functions. Because the exponential function is more convenient mathematically and provides excellent fits to the experimental data, we use it in the computations that follow. In the simplest case, the AV nodal recovery curve is

$$AV = \alpha + \beta \exp(-VA/\tau_{rec})$$  \hspace{1cm} (1)

where $\alpha$, $\beta$, and $\tau_{rec}$ are constant and VA is any recovery interval that exceeds the effective refractory period of the AV node (AVERP). It was first recognized by Mobitz and subsequently by many others, that once the AV nodal recovery curve is known it is possible to predict the effects of periodic stimulation by using an iterative process. However, assuming a static AV nodal recovery curve does not incorporate known time-dependent changes in AV nodal properties.

To describe the theoretical model given any stimulation history the following notation is convenient. Let us assume that each atrial impulse is conducted. Then the time interval from the $n$th atrial activation to the following ventricular activation is called $AV_n$, the time interval from the $n$th atrial impulse to the $(n+1)$st impulse is $AA_n$, and $VA_n = AA_n - AV_n$. Using this notation, we rewrite Equation 1 as

$$AV_n = \alpha + \beta \exp(-VA_{n-1}/\tau_{rec})$$  \hspace{1cm} (2)

Prior studies have shown that certain pacing protocols, which keep $VA_{n-1}$ constant, lead to changes in $AV_n$ thus demonstrating the inadequacy of Equation 2 alone. To account for these changes quantitatively we must assume that $\alpha$ and $\beta$ are not constant but depend on stimulation history.

Consider the conduction of the $n$th atrial impulse. Previous work has shown that if the recovery interval $VA_{n-1}$ stays fixed while the interval $AA_{n-2}$ is decreased, then $AV_n$ decreases. This process, called facilitation, reaches steady state after one cycle at a new rate. We have shown in a previous study that $\tau_{rec}$ and $\alpha$ of beat $n$ are unaffected by decreases in $AA_{n-2}$ and that the resulting leftward
shift of the recovery curve is exponentially related to $\Delta A_{n-2}$\textsuperscript{23} This shift can be expressed by relating $\beta$ to $\Delta A_{n-2}$

$$\beta = \beta_{\text{max}} - \delta \exp(-\Delta A_{n-2}/\tau_{\text{fac}})$$ \hspace{10mm} (3)

where $\beta_{\text{max}}$ and $\delta$ are constants, and $\tau_{\text{fac}}$ is the facilitation time constant. Equation 2 can therefore be generalized to apply in the presence of differing levels of facilitation by considering $\beta$ to be a variable that approaches a constant value ($\beta_{\text{max}}$) as $\Delta A_{n-2}$ becomes much greater than $\tau_{\text{fac}}$.

During prolonged atrial pacing, gradual increases in AV nodal conduction time occur independently of changes in recovery interval.\textsuperscript{21} We modeled this process (often called fatigue) by assuming that each AV nodal activation causes a conduction delay of all subsequent beats. Each activation is considered to add a constant amount of delay ($\gamma$), which decreases exponentially over time following that beat. Therefore, the magnitude of this increment caused by a single AV nodal activation at any time $(t)$ after that activation is given by $\gamma \exp(-t/\tau_{\text{fat}})$, where $\tau_{\text{fat}}$ is the fatigue time constant. Let us call the first AV nodal activation beat 0. The next AV nodal activation, beat 1, will be presented with fatigue produced by beat 0, resulting in conduction slowing given by

$$S_1 = \gamma \exp(-V_{A0}/\tau_{\text{fat}})$$

where $S_1$ is the conduction slowing of beat 1 resulting from fatigue, and $V_{A0}$ is the AV interval from beat 0 to beat 1. The next activation, beat 2, will have a component of fatigue resulting from beat 1 alone and equal to $\gamma \exp(-V_{A1}/\tau_{\text{fat}})$. In addition, beat 2 will also be exposed to residual fatigue resulting from beat 0, given by $\gamma \exp(-(V_{A0} + \Delta A)/\tau_{\text{fat}})$, where $V_{A0} + \Delta A$ is the time from distal AV nodal activation of beat 0 to the atrial activation of beat 2 (i.e., the recovery time from beat 0 to beat 2). Therefore, the slowing of beat 2 resulting from fatigue is given by

$$S_2 = \gamma \exp(-(V_{A0} + \Delta A)/\tau_{\text{fat}}) + \gamma \exp(-V_{A1}/\tau_{\text{fat}})$$

For $S_2=[\gamma \exp(-V_{A0}/\tau_{\text{fat}})] [\exp(-\Delta A/\tau_{\text{fat}})]$

But

$$\gamma \exp(-V_{A0}/\tau_{\text{fat}}) = S_1$$

so

$$S_2 = S_1 \exp(-\Delta A/\tau_{\text{fat}}) + \gamma \exp(-V_{A1}/\tau_{\text{fat}})$$

Similarly, for any beat $n$, the amount of slowing ($S_n$) caused by fatigue is given by the amount of fatigue introduced by the preceding beat, $\gamma \exp(-V_{A_{n-1}}/\tau_{\text{fat}})$, plus the fatigue resulting from all beats before the preceding beat ($S_{n-2}$), which has had an additional recovery interval $\Delta A_{n-2}$ and whose effect on beat $n$ is therefore given by $S_{n-1} \exp(-\Delta A_{n-1}/\tau_{\text{fat}})$. Because the process of fatigue is very much slower than facilitation or recovery, the influence of fatigue on a given beat can be expressed by an increase in the conduction time after full recovery ($\alpha$ in Equation 1), by an amount equal to $S_n$

We therefore assume that for any beat $n$

$$\alpha = AV_{\text{min}} + S_n$$ \hspace{10mm} (4)

where $AV_{\text{min}}$ is the AV conduction time after full recovery in the absence of fatigue, and $S_n$ is given by

$$S_n = S_{n-1} \exp(-\Delta A_{n-1}/\tau_{\text{fat}}) + \gamma \exp(-V_{A_{n-1}}/\tau_{\text{fat}})$$ \hspace{10mm} (5)

Equations 2–5 constitute the mathematical model of the AV node in this paper. Once the parameters are determined it is possible to compute the AV node dynamics for any stimulation protocol.

Block of atrial impulses occurs when the recovery interval of a beat in question is less than AVERP. However, the AVERP was difficult to determine using the extrastimulus technique, since the atrial refractory period was often greater than the AVERP. To incorporate AV nodal refractoriness into the model, we determined the maximum AV interval ($AV_{\text{max}}$) that could be recorded during periodic atrial stimulation. If the computed value of the AV nodal conduction time is greater than $AV_{\text{max}}$, the beat is assumed not to conduct. We have found experimentally, under conditions in which AV nodal refractoriness can be established directly, that this method establishes the AVERP within ±10 msec of directly measured values.

When an impulse failed to conduct, the nonconducted cycle length was added to the recovery interval of the next atrial input (i.e., an increased AV nodal recovery time was assumed to follow nonconducted atrial activations). In addition, only conducted atrial impulses were used to calculate $\Delta A_{n-2}$ during calculations of $\beta$ with Equation 3. Thus, during constant rate atrial pacing, the term $\Delta A_{n-2}$ equals the pacing cycle length for all beats except for the second beat following a blocked beat, for which a value equaling twice the pacing cycle length was used. All atrial activations were assumed to contribute to AV nodal fatigue, whether or not they were conducted.

**Experimental Methods**

General methods. Seven mongrel dogs were anesthetized with 100 mg/kg i.v. $\alpha$-chloralose and 2 mg/kg s.c. morphine. Femoral arterial and venous catheters were inserted and were kept patent with heparinized isotonic saline solution. Endotracheal tubes were inserted for mechanical ventilation via an animal respirator (Harvard Apparatus, South Natick, Mass.). Respiratory parameters were adjusted to ensure adequate oxygenation (SaO$_2$$\geq$90%) and physiological pH (7.35–7.45). A thoracotomy was performed through the fourth right intercostal space, and the heart was suspended in a pericardial cradle. Body temperature was monitored by a thermistor within the chest cavity and was maintained at 37–38°C by a homeothermic heating blanket.
Bipolar Teflon-coated stainless steel plunge electrodes were inserted into the lateral right atrium and high lateral right ventricle on either side of the atrioventricular ring and into the right atrial appendage. A bipolar electrode was inserted epidurally to record a His bundle electrogram. The electrodes located in the atrial appendage and lateral right ventricle were used to record atrial and ventricular electrograms, respectively. All stimulation protocols were carried out using 4-msec rectangular impulses at twice late diastolic threshold applied through the right lateral atrial electrode. The sinus nodal region was mechanically crushed to allow for a wide range of pacing rates.30,31

A Statham P23 ID transducer (Statham Medical Instruments, Los Angeles), electrophysiologic amplifiers (Bloom Ltd., Flying Hills, Pa.), and a paper recorder (model T-16, Siemens-Elema, Stockholm) were used to record blood pressure, six electrocardiographic limb leads, intracardiac electrograms, and stimulus artifacts.

Endogenous vagal and β-adrenergic effects were prevented to avoid changes in autonomic tone associated with mechanical ventilation and stimulation protocols. Vagal effects were prevented by surgical division of the cervical vagosympathetic trunks. This was followed by intravenous administration of 1 mg atropine to block the effects of acetylcholine released locally at the site of stimulation.32 β-Blockade was produced by intravenous administration of 0.5 mg/kg nadolol.33 Repeated doses of 0.5 mg atropine and 0.25 mg/kg nadolol were administered every 2 hours. We have previously demonstrated that α-adrenergic receptor activation or blockade has no effect on AV nodal conduction or refractoriness in vivo34 and that this experimental preparation results in stable AV nodal function over time.30,31,33

Experimental determination of the parameters in the model. Pacing protocols were adapted from prior published experiments.1,21–23,35 In each case, the lateral right atrium was paced at the basic cycle length (defined as the longest possible cycle length) for a minimum of 5 minutes before each pacing protocol. Results of these protocols were used to determine parameters defining the theoretical model. Several of the technical details are presented in the “Appendix.”

STEP 1: DETERMINATION OF \( \tau_{\text{rec}} \) AND \( AV_{\text{max}} \). Double atrial extrastimuli were delivered after every 20 basic stimuli (A1). The first or conditioning impulse (A1') was equal to the basic cycle length, while the coupling interval of the second, or test, impulse (A2) was set to an initial value equal to the basic cycle length and decreased until A2 failed to conduct (Figure 1A). This process was repeated with seven to 11 (10 ± 1.4, mean ± SEM) different A1'A intervals per experiment, varying from a value equal to the basic cycle length to just longer than the effective refractory period of the AV conducting system.

The AV interval of test beats (A2V2) was measured and plotted versus the preceding recovery interval (V'A2) for each selected conditioning impulse.

For each value of A1A', the data were fitted to the expression

\[
A_2V_2 = \alpha + \beta \exp(-V'A_2/\tau_{\text{rec}})
\]

to determine \( \alpha \), \( \beta \), and \( \tau_{\text{rec}} \). Average values for \( \alpha \) and \( \tau_{\text{rec}} \) were determined for all A1A' curves in each experiment. The average value of \( \tau_{\text{rec}} \) was the value used in the model. \( AV_{\text{max}} \) was the maximum value of A2V2 found for short V'A2.

STEP 2: DETERMINATION OF \( \beta_{\text{max}}, \delta, \) AND \( \tau_{\text{fac}} \). Nayebpour et al.23 have shown that facilitation does not alter \( \alpha \) or \( \tau_{\text{rec}} \). We therefore took the average values of \( \alpha \) and \( \tau_{\text{rec}} \) as calculated during step 1 and calculated \( \beta \) for each value of A1A'. \( \beta \) was then plotted as a function of A1A' and fitted to the equation

\[
\beta = \beta_{\text{max}} - \delta \exp(-A1A'/\tau_{\text{fac}})
\]

to find \( \beta_{\text{max}}, \delta, \) and \( \tau_{\text{fac}} \).
**Figure 2.** Characterization of atrioventricular nodal fatigue. Panel A: Pacing protocol. A tachycardia with a constant (VA) recovery interval was induced. The shortest VA interval with 1:1 conduction was tested in each experiment. Panel B: Atrioventricular intervals obtained in experiment 5 with the protocol shown in panel A are plotted vs. time. There is a slow increase in AV interval after the onset of tachycardia despite a constant recovery interval. The solid line represents the results of least squares nonlinear regression of the data points to Equation 8 (see text).

**Step 3: Determination of** $\tau_{fat}$. A sensing and pacing circuit was used to detect each ventricular activation at the right ventricular electrode and pace the right atrium through the lateral right atrial electrode after a preselected delay, resulting in tachycardia with a constant VA interval [34,36] (Figure 2A). The shortest VA interval that did not lead to AV block was tested in each experiment. Tachycardia was continued for 5 minutes and was then terminated by turning off the circuit. AV intervals were measured and plotted as a function of time after the onset of tachycardia.

Assuming the theoretical model for AV nodal conduction, an approximate theoretical expression for the time dependence of the AV interval during this tachycardia is given by

$$AV(t) = k_0 - k_1 \exp\left(-t/T_{fat}\right)$$

where $t$ is the time since the onset of the tachycardia, and $k_0$ and $k_1$ are constants. A derivation of this expression is in the “Appendix.” The data were fitted to this expression to find $\tau_{fat}$.

**Step 4: Determination of** $AV_{min}$ and $\gamma$. The right atrium was paced at a variety of steady-state cycle lengths ($AA_1$) between the basic cycle length and the shortest cycle length, which resulted in 1:1 AV conduction. Stimulation at each cycle length was continued for 5 minutes. Steady-state AV and VA intervals were measured at each cycle length ($AV_{ss}$ and $VA_{ss}$, respectively). In the “Appendix” we show that these values satisfy the equation

$$AV_{ss} = AV_{min} + \gamma \exp(-VA_{ss}/T_{fat}) + [k_{max} - \delta \exp(-AA_{ss}/T_{fat})] \exp(-VA_{ss}/T_{rec})$$

In this expression, only $AV_{min}$ and $\gamma$ are unknown. Steady-state values of $AV_{ss}$, $VA_{ss}$, and $AA_{ss}$ were used to determine these parameters with a nonlinear curve fitting routine.

**Induction of Wenckebach-type AV block.** Atrial pacing cycle length was abruptly decreased after pacing at the basic cycle length for 5 minutes. A value of 250 msec was chosen as the first short cycle length for study. After stimulation at this rate for 5 minutes the pacing cycle length was then returned to the basic cycle length for an additional 5 minutes. The protocol was then repeated at a fast cycle length 5–10 msec shorter than the initial cycle length tested. This procedure was repeated nine to 19 times per experiment to scan the zone between first appearance of Wenckebach periodicity and the point where 2:1 AV block appeared immediately.

**Prediction of Wenckebach periodicity by the AV nodal model.** We performed computer simulations of AV nodal conduction in each experiment with Equations 2–5, with the values of parameters that were derived experimentally (as described above). The effects of abrupt decreases in cycle length from the basic cycle length predicted by the model were computed for comparison with experimental results. Simulations were performed with custom software written in Turbo Pascal with a microcomputer (IBM compatible, 12 MHz). The results of computer simulations were expressed as the conduction ratio (defined as the number of conducted impulses divided by the number of atrial activations) versus pulse number after the onset of rapid pacing. The conduction ratio was taken to be characteristic of all the beats of a given cycle, for example, the conduction ratio for atrial impulses one to four of a 4:3 Wenckebach cycle would be 0.75.

**Data Analysis**

Electrogram and electrocardiographic recordings were obtained at 200 mm/sec paper speed during determination of functional AV nodal properties, whereas recordings for measurement of conduction ratios during induction of Wenckebach AV block were obtained at 25 mm/sec.

AV intervals were used as an index of AV conduction time in all experiments. As previously demonstrated, pacing protocols used in this study lead to changes in AH interval without changes in HV interval. This was confirmed by direct measurements of the HV interval in each experiment, justi-
TABLE 1. Results of Quantification of Rate-Dependent Atrioventricular Nodal Parameters

<table>
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<tr>
<th>Experiment</th>
<th>AV\textsubscript{min}</th>
<th>$\tau_{\text{rec}}$</th>
<th>$\beta_{\text{max}}$</th>
<th>$\delta$</th>
<th>$\tau_{\text{rec}}$</th>
<th>$\gamma$</th>
<th>$\tau_{\text{tot}}$</th>
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<tr>
<td>1</td>
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<td>73</td>
<td>233</td>
<td>211</td>
<td>209</td>
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</table>

Values for the eight parameters are expressed in milliseconds. All parameters are constants that were derived using selective pacing protocols (for details see text). These values were used in Equations 2–5 to predict sequential AV intervals during computer simulations.

fying the use of AV intervals as an index of AV nodal conduction time.

AV intervals were measured on-line using an analog to digital converter (model PDMA-16, Metabyte Corp., Taunton, Mass.) coupled to a microcomputer (IBM compatible, 16 MHz) and custom-written software. Atrial and ventricular electrograms, recorded from the His bundle and ventricular electrodes, respectively, were sampled at 1 kHz. Peak positive or negative amplitude was used to determine activation times, using one criterion consistently throughout each experiment. Reproducibility of AV intervals measured by this system was ±2 msec. In addition, direct comparisons between AV intervals determined manually (by using paper recordings at 200 mm/sec, accuracy of ±2.5 msec) and those measured by computer were obtained during two determinations of AV nodal recovery curves in each experiment. Correlation coefficients exceeding 0.99 were found in each experiment.

Results are reported as mean±SEM. All nonlinear curve fitting was performed with Marquardt’s technique and commercially available software (Statistical Graphics, Rockville, Md.). Statistical comparisons were made with Student’s $t$ test using the Bonferroni correction for multiple comparisons.37 Two-tailed tests were used for all statistical comparisons, and $p \leq 0.05$ was taken to indicate statistical significance. All animal care techniques followed recommendations of the Canadian Council on Animal Care, and the research protocol was approved by the Animal Care Committee of the Montreal Heart Institute.

Results

Quantification of Rate-Dependent AV Nodal Properties

AV nodal recovery and facilitation. The results of periodic atrial stimulation in experiment 4 are shown in Figure 1B. When the coupling interval of the conditioning impulse is equal to the basic cycle length (600 msec in this experiment), a curve describing the recovery characteristics of AV nodal function in the absence of facilitation is obtained. As the recovery interval (VA\textsubscript{2}) of test beats decreases, AV nodal conduction time (A\textsubscript{2}V\textsubscript{2}) increases in an exponential fashion. No evidence suggesting dual AV nodal path-ways, such as abrupt increases in AV nodal conduction time or AV nodal echoes, was found in any experiment.

When the conditioning impulse ($A'$) is introduced prematurely ($A_1A' = 300$ and 200 msec in Figure 1), the relation between recovery interval and AV conduction time of test beats shifts to the left. The results of nonlinear curve-fitting using Equation 6 are displayed in Figure 1B as solid lines. Excellent fits ($r>0.99$) were obtained in this and all other experiments. The leftward shift of the AV nodal recovery curve by premature conditioning impulses was reflected by a progressive decrease in the $y$-intercept of the fitted curve. Table 1 shows average values of $\tau_{\text{rec}}$ obtained from these curve fits along with maximum AV intervals observed (AV\textsubscript{max}) for each experiment.

![Figure 3](http://circres.ahajournals.org/Downloaded from /1285)

**Figure 3.** Quantification of atrioventricular nodal facilitation. Values of the $y$-intercept ($\beta$) obtained from curve-fitting of individual recovery curves (as described in Figure 2) are plotted vs. the coupling interval of the preceding conditioning impulse ($A_1A'$) in experiment 4. Note that there is a nonlinear decrease in $\beta$ as $A_1A'$ decreases. In this experiment, $\beta$ failed to decrease after a minimum value had been attained (indicated by the dashed line). The solid curve represents the results of at least squares nonlinear regression of all data points exceeding this minimum value along with the longest $A_1A'$ showing the minimum value to Equation 7 (see text).
Figure 3 shows $\beta$ obtained from curve-fitting of individual recovery curves plotted against the coupling interval of the preceding conditioning impulse in the same experiment. Note that $\beta$ decreases in a nonlinear fashion as $A_1A'$ decreases. Similar results were obtained in each experiment. Nonlinear regression of $\beta$ and $A_1A'$ to Equation 7 was performed and yielded estimates of $\beta_{\text{max}}$, $\delta$, and $\tau_{\text{fac}}$ (Table 1). Correlation coefficients averaged 0.99±0.01 for these mathematical fits. In three of seven experiments, $\beta$ reached a minimum value and failed to decrease further (as shown in Figure 3). In these experiments, points with values of $\beta$ exceeding this minimum value, along with the point with the longest $A_1A'$ having the minimum value, were used in nonlinear regression to determine $\beta_{\text{max}}$, $\delta$, and $\tau_{\text{fac}}$. During simulations, this minimum value was used (as $\beta$) in Equation 2 when $AA_{\text{ss}}<260$ msec (Figure 3).

$AV$ nodal fatigue. Figure 2B shows the AV conduction time observed after the onset of a tachycardia with a constant VA interval in experiment 5. The tachycardia produced a slow, progressive increase in AV interval. Nonlinear curve-fitting with Equation 8 resulted in a fitted curve shown by the solid line in the figure. Similar methods were used to estimate $\tau_{\text{fac}}$ for each experiment (Table 1).

Figure 4 illustrates how values of $AV_{\text{min}}$ and $\gamma$ were obtained in experiment 5. Values of AV interval ($AV_{\text{sa}}$) during constant rate atrial pacing are plotted versus atrial cycle length ($AA_{\text{ss}}$) and recovery interval ($VA_{\text{ss}}$). The solid line represents the results of nonlinear regression of these data points to Equation 9 using values of $\tau_{\text{tec}}$, $\tau_{\text{tac}}$, $\tau_{\text{fat}}$, $\beta_{\text{max}}$, and $\delta$ determined as shown above for this experiment. Estimates of $AV_{\text{min}}$ and $\gamma$ were obtained from this regression in each experiment.

Table 1 lists the eight constants used in the final mathematical model to predict AV conduction on a beat-to-beat basis in each experiment. $\tau_{\text{tec}}$, $\tau_{\text{tac}}$, and $\tau_{\text{fat}}$ averaged $65\pm3$, $743\pm334$, and $17,385\pm2,602$ msec, respectively. Values of parameters derived from each experiment were used in subsequent simulations of Wenckebach periodicity. All of these constants were estimated by selective study of various AV nodal properties and then were applied to predict Wenckebach behavior. No post facto adjustment of constants to provide better agreement with observed Wenckebach behavior was permitted.

**Induction of Second-Degree AV Block**

Figure 5 illustrates the results of rapid atrial pacing in experiment 1. The right atrium was stimulated at a cycle length of 200 msec. AV conduction was 1:1 for approximately 2.4 seconds after the onset of pacing.
Second-degree AV block then developed with an initial 7:6 conduction pattern. In this example and in every other experiment, Wenckebach periodicity was found to be dynamic, with an increasing degree of block occurring with continued pacing. For example, by 30 seconds in the example shown, the pattern had changed to stable 4:3 conduction. The pattern became unstable after 1 minute, with 3:2 conduction alternating with 4:3, before a stable 3:2 pattern emerged and persisted until the end of the 5-minute pacing period.

Figure 6 shows the conduction ratio (defined as the number of conducted beats divided by the number of atrial activations) after the onset of rapid pacing in experiment 6. At each cycle length tested, a period of 1:1 AV conduction was followed by the development of Wenckebach periodicity. The degree of conduction block increased progressively in each case, with periods of alternating conduction noted at cycle lengths of 200 msec (0.75 alternating with 0.67 from beats 150 to 180) and 180 msec (0.75 alternating with 0.67 from beats 30 to 50, and 0.67 alternating with 0.5 from beats 100 to 120). The corresponding model predictions are shown to the right in Figure 6. In each case, the model predictions correctly accounted for the development of AV block and its evolution over time. In addition, the model showed periods of alternating conduction patterns at critical cycle lengths (seen here as alternation between 0.67 and 0.5 from beats 80 to 100 at a cycle length of 180 msec). Overall, there was no tendency for alternating conduction pattern to be observed more frequently experimentally or during simulations.

The observed and predicted conduction ratios for all cycle lengths in each experiment are displayed in Figure 7. The conduction ratios observed after 15 paced atrial complexes and after 5 minutes of pacing are plotted against the tested cycle length in each experiment. The corresponding model predictions are also plotted. In each experiment there was close agreement between experimental observations and model predictions.

To evaluate the role of individual processes, model simulations were also performed after excluding terms used to represent fatigue and facilitation in the final mathematical model. Fatigue was excluded by considering $\alpha$ to be constant (i.e., not including the term $S_\alpha$ as defined in Equations 4 and 5). Simulations without modifying $\alpha$ to reflect fatigue gave results identical to the initial model predictions shown as solid lines in Figure 7. However, this approach failed to predict changing Wenckebach periodicity over time. If facilitation was also excluded (by using a constant value of $\beta$ as determined when $A_1A'_1$ equaled the basic cycle length), a model based on recovery characteristics alone resulted. Predictions arising from this model are also plotted for each experiment in Figure 7 (dotted lines) and consistently overestimated the degree of block occurring at each cycle length.

Figure 8 shows the cycle length at which four common conduction patterns were observed. The mean cycle length at which 1:1 conduction disappeared or at which 4:3, 3:2, or 2:1 conduction patterns first appeared is displayed for initial and final experimental observations and corresponding model predictions. In each case, no statistically significant differences were observed between experimental data and model predictions, but initial and final values were consistently different. When experimental data were compared with the model incorporating only the recovery term (Figure 9), statis-
cally significant differences between recovery model predictions and experimental values were noted for 1:1, 4:3, and 3:2 but not 2:1 conduction patterns.

**Discussion**

This study demonstrates that a mathematical model based on rate- and time-dependent AV nodal properties can accurately predict AV nodal behavior on a beat-to-beat basis during pacing-induced second-degree AV block.

Classical Wenckebach AV block is characterized by AV intervals that progressively lengthen and RR intervals that gradually shorten until block of an atrial impulse occurs.\(^1,2\) Many variations of this de-

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**Figure 7.** Conduction ratio is plotted vs. pacing cycle length after the onset of rapid pacing for all experiments (protocol as in Figure 5). Results within 15 atrial activations after the onset of pacing (initial) and after 5 minutes of pacing (final) are shown along with corresponding model predictions (solid and dashed lines) and predictions using only recovery characteristics (dotted lines). Note the close agreement between initial and final model predictions and corresponding experimental data. A model based on recovery characteristics alone predicts a wide variety of conduction patterns but consistently overestimates the degree of block and fails to predict time-dependent changes.

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**Figure 8.** Mean cycle length at which first disappearance of 1:1 atrioventricular conduction or first appearance of 4:3, 3:2, or 2:1 conduction patterns were documented. Results (observed and predicted) within 15 beats after the onset of rapid pacing (initial) and after 5 minutes of pacing (final) are shown. No significant differences between experimental data and model predictions were found. **p<0.01, ***p<0.001 for results at 5 minutes vs. initial data after onset of pacing.

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**Figure 9.** Mean cycle length at which first disappearance of 1:1 atrioventricular conduction or first appearance of 4:3, 3:2, or 2:1 conduction patterns were documented. Initial predictions of the model incorporating all three rate-dependent processes are shown along with predictions based on recovery characteristics alone (recovery). Statistically significant differences were noted between mean cycle lengths predicted with the recovery model and experimental data for conduction ratios 1:1, 4:3, and 3:2. *p<0.05 for recovery model compared with observed data.
cription have been described, sometimes with alternative mechanisms proposed to explain the variant. For example, multilevel AV block has been invoked to account for alternating Wenckebach sequences. As can be seen in Figures 5 and 6, this type of behavior is frequently observed and is predicted by our model at critical atrial cycle lengths without a need to assume multiple levels of block.

Interaction of AV nodal recovery properties and atrial rate has been used to explain Wenckebach periodicity by several investigators. Mobitz used iterative techniques and theoretical AV nodal recovery curves to demonstrate how second-degree AV block might result from such an interaction and others have shown that complex alternating patterns of AV block can also result, depending on the atrial rate chosen. Using experimental methods in dogs, Levy and coworkers also concluded that feedback between AV nodal output and subsequent nodal input accounted for AV nodal Wenckebach periodicity.

More recently, Shrier and coworkers tested this hypothesis in humans in a quantitative manner and found that a model based solely on AV nodal recovery characteristics could account for a wide variety of conduction patterns observed during second-degree AV block, including alternating and atypical sequences. However, the AV nodal recovery curve is dependent on background pacing rate, and the predictions obtained by Shrier et al varied substantially depending on the basic cycle length at which the recovery curve was obtained. Observations were well predicted only when the recovery curves at rapid rates, close to the cycle length for Wenckebach AV block, were used. In addition, it was noted that the degree of block during constant rate atrial pacing increased over time, a finding not explained by their model or by previous models of Wenckebach periodicity.

The present paper is the first to incorporate time-dependent processes other than recovery into a single unified AV conduction model. The present model accurately predicts the wide range of conduction behavior observed after abrupt changes in atrial rate, including dynamic changes in Wenckebach periodicity.

The incorporation of a function describing the facilitating effects of premature atrial impulses significantly improves the accuracy of the model. This process explains why a model based on recovery characteristics alone consistently overestimates the degree of block observed experimentally and may also explain why the largest increase in conduction time typically occurs with the second atrial beat of a Wenckebach cycle. In the present model, facilitatory effects change on a beat-to-beat basis and depend on the coupling interval of the preceding conducted atrial beat. As a result, the atrial cycle length used to calculate the term \( \beta \) in Equation 3 for the second impulse after a blocked beat is equal to double the pacing cycle length, and the recovery curve for beat 2 during a Wenckebach cycle is shifted to the right. This agrees with the findings by Simson and coworkers that the recovery curve (plotted as AH versus HA) of beat 2 during a stable 4:3 Wenckebach pattern lies to the right of the curves of subsequent beats (see Figure 6 of Reference 18). Simson et al interpreted this observation as evidence against a model based on a positive AV nodal feedback mechanism because the AH-HA relation did not change in a predictable way. However, as shown in Figures 1 and 3, this relation is predictable and can be incorporated into a quantitative model. The dependence of the facilitatory process on prior conducted beats is also illustrated by the fact that a model based on recovery characteristics alone was most accurate during more advanced degrees of block (see Figures 7 and 9). During 2:1 rhythms, the atrial cycle length used to calculate \( \beta \) in Equation 3 would be double the rapid pacing cycle length for every conducted beat and, therefore, similar to the cycle length at which the recovery curve was obtained. Thus, the amount of facilitation modulating the conduction of these beats would be small, and the conduction pattern would resemble predictions of a recovery model that does not consider facilitation. Although the effect of fatigue is quantitatively small and has a slow time course, the inclusion of AV nodal fatigue was essential to account for the time-dependent changes in Wenckebach periodicity that were observed experimentally.

Underlying Mechanisms

The cellular mechanisms underlying AV nodal recovery, facilitation, and fatigue have not been firmly established. AV nodal cells remain partially refractory up to 200 msec after repolarization, resulting in slow conduction of premature activations within the nodal region of the node. An electrically silent period occurs between activation of N and NH cells and increases in duration as N cells become activated more prematurely. This silent period, possibly caused by slow activation across an electrotonically coupled gap, is responsible for most of the additional delay in AV conduction resulting from premature atrial impulses and may account for AV nodal recovery properties. The recovery of slow inward current in the central AV node is an important determinant of this delay and may explain why the AV nodal recovery time constant is similar to the time constant for recovery of slow inward current in vitro.

Less is known regarding the mechanism of AV nodal fatigability or facilitation. AV nodal fatigue, first noted by Lewis and Master, has been characterized as a progressive decrease in the excitability of AV nodal cells when stimulated repetitively at faster rates. Whether this process is related to extracellular accumulation of an ion or metabolite or is intrinsic to AV nodal cells is unknown. Our estimates of its time course in an in vivo preparation are consistent with recent observations in vitro. The underlying mechanism of AV nodal facilitation remains obscure. Action potentials recorded from the distal AV node shorten with premature stimulation, offering a potential mechanism. Our finding that blocked atrial
beats do not facilitate conduction of a subsequent beat (supported by the experimental findings of Simson et al\cite{18}) suggest that the intranodal site at which facilitation occurs is distal to the site of impulse block during Wenckebach cycles.

**Comparison With Previous Models of AV Conduction**

Several prior mathematical models of AV nodal conduction have been reported. Heethar and colleagues\cite{8} used the time course of change in AV nodal conduction during abrupt increases in atrial rate and the conduction time of four preceding atrial beats to predict the AV conduction time of random atrial impulses. They did not, however, attempt to apply their model to experimental observations of different types of AV nodal behavior. Other models have considered the AV node as a perturbed biological oscillator,\cite{9-11,17} as the site of a single step delay,\cite{12,20} or as a one-dimensional cable of excitable and electrotonically modulated elements.\cite{19} The present description of AV nodal conduction differs from these prior models by its basis on known time-dependent AV nodal properties. Furthermore, many of these models were not tested by applying them to predict experimentally observed behaviors.\cite{13-15,19}

Our approach differs from previous models based on iteration of the recovery curve\cite{5-7} in our inclusion of a detailed mathematical treatment of the consequences of facilitation and fatigue. In a sense, this results in a generalization of the recovery curve concept so the recovery curve on which any beat lies can be defined based on previous activation history. The changing properties of AV conduction during different stimulation patterns are therefore understood as reflecting changes in the AV recovery curve on a beat-to-beat basis, as defined by the system of model equations (Equations 2–5). This is consistent with the observations of Billette et al.\cite{50} who noted that AV intervals occurring during divergent atrial stimulation sequences fall within a narrow crescent-shaped zone when plotted versus their preceding VA intervals.

**Significance of the Present Study**

The present study suggests that intricate behaviors of the AV node can be understood if three functional AV nodal properties are considered. It does not, of course, provide proof for the fundamental nature of these properties. Our equations characterizing the rate-dependent properties of the AV node are certainly not a unique solution, and other systems of equations may well exist that predict the same responses. Nonetheless, this work indicates that these properties, described extensively in vivo and in vitro by many investigators, can accurately account for very complex observed forms of AV nodal response.

The present model is formulated in a way that can be applied to any type of atrial input pattern. We have presented preliminary evidence that a similar approach accurately predicts AV nodal conduction during steady-state atrial pacing with 1:1 AV conduction.\cite{50} Billette and colleagues have shown that the interdependence of AV nodal recovery, facilitation, and fatigue accounts for rate-dependent changes in the AV nodal recovery curve\cite{51} and functional refractory period,\cite{35} ideas that are consistent with predictions of the present model. It will be interesting to assess the ability of the model to explain other observed forms of AV nodal behavior, such as those occurring in response to ramp changes in activation rate,\cite{52} during multiple step changes in atrial rate in the 1:1 conduction zone,\cite{2} and during more complex stimulation sequences.\cite{53}

**Potential Limitations**

Autonomic blockade was used in these experiments to evaluate the importance of intrinsic AV nodal properties and to prevent a major source of variability. Autonomic tone alters these properties\cite{23,28,54-56} and so would be expected to modify the types of responses observed. Although autonomic tone would change the values of the constants used in the proposed model, this should not alter the applicability of the model per se.

The current model relies on three functional AV nodal properties and ignores several other known determinants of AV nodal conduction. For example, the direction of input into the node also affects AV nodal conduction time.\cite{57-59} To avoid this confounding factor, all atrial stimulation was carried out from the same site. The effects of blocked atrial beats on the conduction of a subsequent impulse (concealed conduction) was not included in the current model. This would be expected to alter the AV conduction time of the first beat during a Wenckebach sequence but might not be expected to affect overall conduction ratios since this first beat falls on a relatively flat part of the AV recovery curve.\cite{60,61}

The current study used the VA and not the AA interval to define AV nodal recovery characteristics. It was not designed to test the superiority of either approach. Levy and colleagues\cite{16} have shown that clamping the VA interval during tachycardia prevents AV nodal block at rates at which Wenckebach block is observed when AA is kept constant. This suggests that there is a causal relation between the VA interval and the succeeding AV interval and that the progressive decreases in VA interval observed during Wenckebach cycles are not purely coincidental.\cite{16} However, these authors also showed that the AA interval also affected AV conduction independent of the VA interval (similar to how AA was used to define AV nodal facilitation in this paper). Definitive resolution of this problem will require detailed microelectrode experiments, and it may be that both AA and VA intervals contribute to the determination of AV nodal recovery under different conditions.

**Conclusion**

In conclusion, incorporation of three time-dependent variables into a single mathematical model can accurately account for many features of Wenckebach...
bach-type AV block. Future studies to assess the ability of this model to predict AV nodal behavior during other atrial input patterns and in other species (including humans), as well as cellular studies of underlying mechanisms, are needed to improve our understanding of AV nodal function.

**Appendix**

We provide justification for the methods used to derive some of the parameters in the theoretical model. During prolonged stimulation, it is possible to estimate the dynamics of the slow increase in the AV conduction time during stimulation with constant VA or AA intervals.

The derivations use the power series expansion of \( e^x \). Recall that

\[
e^x = 1 + x + \frac{x^2}{2} + \ldots
\]

so that provided the absolute value of \( x \) is much less than 1, the first two terms of the power series expansion provide a good approximation. Thus \( e^{0.3} \) is about 1.35 or about a 4% error from the approximate value of 1.3 found using the first two terms of the power series expansion.

For the sake of completeness, we repeat the four main equations that constitute the theoretical model; all terms are as defined in the text:

\[
\begin{align*}
AV_n &= \alpha + \beta \exp(-VA_{n-1}/T_{rec}) \\
\beta &= \beta_{\text{max}} - \delta \exp(-AA_{n-2}/T_{fac}) \\
\alpha &= AV_{\text{min}} + S_n \\
S_n &= S_{n-1} \exp(-AA_{n-1}/T_{fac}) + \gamma \exp(-VA_{n-1}/T_{fac})
\end{align*}
\]  

(A1)

(A2)

(A3)

(A4)

We first consider stimulation using either constant AA or VA until a steady state is reached. At steady state we designate the value of \( S_n \) in Equation A4 as \( S_s \) and the value of the various intervals with the subscript ss. Then, Equation A4 can be rewritten as

\[
S_s = S_s \exp(-AA_{ss}/T_{fac}) + \gamma \exp(-VA_{ss}/T_{fac})
\]  

(A5)

Solving for \( S_s \), we obtain

\[
S_s = \frac{\gamma \exp(-VA_{ss}/T_{fac})}{1 - \exp(-AA_{ss}/T_{fac})}
\]  

(A6)

Substituting in Equations A1–A3 for steady state when \( AV_n = AV_{n-1} = AV_{ss} \), \( AA_n = AA_{n-1} = AA_{ss} \), and \( VA_n = VA_{n-1} = VA_{ss} \), we obtain

\[
\begin{align*}
AV_{ss} &= AV_{\text{min}} + \gamma \exp(-VA_{ss}/T_{fac}) \\
&+ [\beta_{\text{max}} - \delta \exp(-AA_{ss}/T_{fac})] \exp(-VA_{ss}/T_{rec})
\end{align*}
\]  

(A7)

which has been used in step 4 to compute \( AV_{\text{min}} \) and \( \gamma \). This expression cannot be used to simultaneously determine \( \gamma \) and \( T_{fac} \). Since \( T_{fac} > AA_{ss} > VA_{ss} > 0 \), we can apply the power series expansion for \( e \) in Equation A6 to obtain the approximation

\[
S_s = \frac{\gamma \tau_{fac}}{AA_{ss}}
\]  

(A8)

Since \( \gamma \) and \( \tau_{fac} \) appear as a product here, only one of them can be independently estimated from the steady-state experimental data.

We use the dynamics of the buildup of the AV conduction time during repetitive stimulation with a constant VA to estimate \( \tau_{fac} \). Prior work23 showed that under this stimulation protocol the buildup of AV conduction time is well fitted by the expression

\[
AV(t) = AV_{ss} - \Delta \exp(-t/\tau_{fac})
\]  

(A9)

Here, \( AV_{ss} \) is the final steady-state value of the AV conduction time and \( \Delta \) is the total change of the AV conduction time during the course of the stimulation. What is not obvious is that the \( \tau_{fac} \) here is the same time constant as in Equation A4. The strategy of our derivation is to assume that it is the same and to show that this leads to a self-consistent expression for Equation A9, derived using the model.

Let us first consider the time evolution of \( \beta \). We know that

\[
AA(t) = AV(t) + VA
\]  

(A10)

so substituting Equations A9 and A10 in Equation A2 we obtain

\[
\beta = \beta_{\text{max}} - \delta \exp(-AA_{ss}/T_{fac}) \exp(-VA_{ss}/T_{fac})
\]  

(A11)

where we have taken advantage of the fact that because \( T_{fac} > AA_{ss} \), \( AA_{ss} \) is approximately equal to \( AA_{n-2} \). This equation can be rewritten as

\[
\beta = \beta_{\text{max}} - \delta \exp\left(\frac{-AA_{ss}/T_{fac}}{\tau_{fac}} + \gamma \exp(-VA_{ss}/T_{fac})\right)
\]

and

\[
\beta = \beta_{\text{max}} - \delta \exp\left(\frac{-AA_{ss}}{\tau_{fac}}\right) \exp\left(\frac{\Delta \exp(-VA_{ss}/T_{fac})}{\tau_{fac}}\right)
\]

But since \( 0 < \Delta < T_{fac} \), we can carry out the power series expansion of \( \exp[\Delta \exp(-VA_{ss}/T_{fac})/\tau_{fac}] \) to obtain

\[
\beta = \beta_{\text{max}} - \delta \exp\left(\frac{-AA_{ss}}{\tau_{fac}}\right) \exp\left(\frac{\Delta}{\tau_{fac}}\right)
\]

(A12)

Rearranging,

\[
\beta = \beta_{\text{max}} - \frac{\delta \exp(-AA_{ss}/\tau_{fac})}{\tau_{fac}} \exp\left(\frac{-t}{\tau_{fac}}\right)
\]
This equation can be rewritten as

\[ \beta = \kappa_0 - \kappa_1 \exp(-t/\tau_{\text{fat}}) \]  
(A12)

where

\[ \kappa_0 = \kappa_{\min} - \delta \exp(-AA_{\text{ad}}/\tau_{\text{fat}}) \]  
(A13)

and

\[ \frac{\delta \Delta \exp(-AA_{\text{ad}}/\tau_{\text{fat}})}{\tau_{\text{fat}}} \]  
(A14)

This shows that the change in \( \beta \) follows the same exponential time course as the change in AV in Equation A9.

We now consider the time-dependent changes in \( \alpha \). To carry out the computation, we use the observation that the sum, \( s \), of \( n \) terms of a geometric progression is

\[ s = a \frac{(1-r^n)}{(1-r)} \]  
(A15)

where the first term is \( a \) and the common ratio is \( r \). Taking into account the detailed changes in AA during constant VA stimulation leads to an intractable mathematical problem. However, a good approximation for the changes in AV during the stimulation can be obtained by assuming a constant value of AA_{ad} for the AA interval during the course of the stimulation. This leads to a slight underestimate (from numerical studies for typical values of the parameters this is at most 10% or less than 1 msec) for \( S_n \) for small values of \( n \) and the correct long-term behavior for large \( n \). From the definition of \( S_n \) we find that \( S_n \) is a geometric progression with \( n \) terms with a common ratio \( \exp(-AA_{\text{ad}}/\tau_{\text{fat}}) \) and a first term \( \gamma \exp(-VA/\tau_{\text{fat}}) \). Thus we find that

\[ S_n = \gamma \exp(-VA/\tau_{\text{fat}}) \frac{1-\exp(-nAA_{\text{ad}}/\tau_{\text{fat}})}{1-\exp(-AA_{\text{ad}}/\tau_{\text{fat}})} \]  
(A16)

Note that as \( n \to \infty \) we obtain Equation A6. Since the \( n \)th stimulus occurs approximately at a time of \( nAA_{\text{ad}} \) after the beginning of stimulation, we can substitute back into Equation A3 to obtain

\[ \alpha = \lambda_0 - \lambda_1 \exp(-t/\tau_{\text{fat}}) \]  
(A17)

where

\[ \lambda_0 = AV_{\text{min}} + \frac{\gamma \exp(-VA/\tau_{\text{fat}})}{1-\exp(-AA_{\text{ad}}/\tau_{\text{fat}})} \]  
(A18)

and

\[ \lambda_1 = \frac{\gamma \exp(-VA/\tau_{\text{fat}})}{1-\exp(-AA_{\text{ad}}/\tau_{\text{fat}})} \]  
(A19)

This shows that \( \alpha \) in Equation A3 can also be approximated by an exponential of the form in Equation A9. Thus we have shown that in the stimulation protocol with constant VA both \( \alpha \) and \( \beta \) in Equation A1 can be approximated by the same exponential function with a time constant of \( \tau_{\text{fat}} \), and this is the justification for the use of Equation A9 in deriving \( \tau_{\text{fat}} \) from the experimental data.

By using a similar strategy, it is also possible to show that the buildup of the AV conduction time is described by Equation A9 during stimulation with a constant AA interval. In this case, the VA changes during the course of the stimulation. Provided \( 1 > \Delta(\tau_{\text{fat}}) > 0 \), a power series expansion of the exponential function in Equation A1 is possible and we once again derive Equation A9 from Equations A1–A4. In six of seven experiments it was possible to derive \( \tau_{\text{fat}} \) from Equation A9 using both the constant AA and constant VA stimulation protocols. With both techniques there was agreement to within 5.9±2.0%. This close agreement is further justification for the theoretical model and for the methods used to determine the parameters in it.

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**KEY WORDS** • atrioventricular nodal conduction • mathematical model • atrioventricular block • Wenckebach periodicity
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