J. theor. Biol. (1995) **173,** 79–91

Alternans and Period-doubling Bifurcations in Atrioventricular Nodal Conduction

JIONG SUN,† FARID AMELLAL,‡ LEON GLASS,†§ AND JACQUES BILLETTE‡

† *Department of Physiology*, 3655 *Drummond Street*, *Montreal*, *Quebec*, *Canada H3G 1Y6 and* ‡ *Département de physiologie*, *Faculté de Médecine*, *Université de Montréal*, *CP* 6128, *Succ C*, *Montréal*, *Québec*, *Canada H3C 3J7*

(*Received on* 14 *June* 1993, *Accepted in revised form on* 13 *September* 1994)

A theoretical model, formulated as a finite difference equation is proposed for rate-dependent conduction properties of the atrioventricular (AV) node. The AV nodal conduction time, which is defined as the time interval from the atrial activation to the activation of the bundle of His, depends on the history of activation of the node. The theoretical model, which incorporates physiological concepts of recovery, facilitation and fatigue, accurately predicts a variety of experimentally observed complex rhythms of nodal conduction. In particular, alternans rhythms, in which there is an alternation in conduction time from beat to beat, are associated with period-doubling bifurcations in the theoretical model.

1. Introduction

The sinoatrial node is the normal cardiac pacemaker in the mammalian heart. Excitation generated by the sinoatrial node travels through the atria, the atrioventricular (AV) node, the bundle of His and then to the ventricles through specialized conducting fibers. The resulting electrical excitation of the ventricles leads to ventricular contraction and pumping of the blood to the lungs and body.

The AV node is an essential anatomical link in this chain of events. It generates a delay between atrial and ventricular activation thereby favoring ventricular filling and increasing pumping efficiency. It also can act as a filter, blocking some excitation during abnormally rapid atrial activation (supraventricular tachycardia), thereby protecting the ventricles from too rapid activation. In AV nodal disease, atrial excitation may fail to propagate to the ventricles (AV nodal block) even at slow rates.

Interest in the dynamics of the AV node developed early this century with the clinical descriptions of AV heart block by Wenckebach (1899) and Mobitz (1924). If atrial excitations are blocked in their passage through the AV node, one obtains an $N{:}M$ heart block consisting of repeating cycles of N atrial activations and M ventricular activations, with $N > M$. Such rhythms are commonly called Wenckebach rhythms. The mathematical structure of these rhythms has led to a rich theoretical literature (Mobitz, 1924; Decherd & Ruskin, 1946; Roberge & Nadeau, 1969; Heethar *et al*., 1973; Levy *et al*., 1974; Keener, 1981; Glass *et al*., 1987; Shrier *et al*., 1987; Urushibara *et al*., 1987; Guevara, 1991; Talajic *et al*., 1991; Arnold, 1991).

An approach widely used to represent AV nodal dynamics relates the conduction time through the AV node (AH, atrial–His interval) to the recovery time since the last passage of excitation (HA, His–atrial interval). This relationship is based on the observation that the nodal recovery time is the main determinant of the ensuing conduction time due to the slow and progressive recovery of nodal cell excitability following nodal activation (Merideth *et al*., 1968).

A widely used approximation assumes

$$AH = f(HA), \tag{1}$$

where the function f is called the AV nodal recovery curve. If the recovery curve is assumed to be a monotonically decreasing function, the theoretical model predicts that Wenckebach rhythmicity will be

§ Author to whom correspondence should be addressed

observed during a periodic stimulation, provided the stimulation frequency is sufficiently high (Mobitz, 1924; Decherd & Ruskin 1946). In particular, calling the number of conducted impulses divided by the number of stimuli the conduction ratio, a plot of the conduction ratio as a function of the stimulation frequency assumes the form of a Cantor function (Keener, 1981; Glass *et al*., 1987; Shrier *et al*., 1987; Guevara, 1991; Arnold, 1991). This means that different types of AV nodal block will be found at different stimulation frequencies, where the conduction ratio decreases as the stimulation frequency increases.

Other arrhythmias of AV nodal conduction do not involve heart block. Particularly intriguing from a theoretical standpoint are alternans rhythms, in which the conduction time through the AV node alternates on a beat to beat basis. An early observation of alternans was made by Lewis & Mathison (1910) who recorded the electrocardiograms of cats during asphyxia (Fig. 1). On the electrocardiogram, the atrial activation generates the *P* wave, the ventricular activation generates the *R* wave and changes in AV nodal conduction time can be estimated from changes in the *PR* interval. Lewis and Mathison observed that asphyxia caused an initial acceleration of the atrial activation rate associated with a prolongation of the conduction time. Complex changes in the atrial rate and conduction time ensued eventually leading to heart block. They noted that "At or about the time when the heart appears to waver between a condition of 2:1 heart-block and regular sequential contraction accompanied by prolongation of the P-R interval, it not infrequently happens that passing into the latter state it exhibits a regular alternation of the P-R intervals". Subsequent workers have observed *PR* alternans in a variety of clinical and experimental settings (Barker *et al*., 1943; Segers, 1951; Langendorff, 1958; Spurrell *et al*., 1973; Sung & Styperek, 1979; Rinkenberger *et al*., 1980).

In non-linear dynamics, a period-doubling bifurcation is a phenomenon in which the period of an oscillation doubles. The observation of alternans in the AV conduction time suggests that a period-doubling bifurcation may occur in a mathematical model of the AV node (Guevara & Glass, 1982; Guevara, 1991). However, if the AV recovery curve in eqn (1) is a monotonically decreasing function, the theoretical model in (1) is not capable of giving alternans of the AV conduction time (Guevara, 1991).

The goal of this study is to investigate the dynamics of the AV node with particular emphasis on the conditions needed to develop alternans of the AV conduction time. Section 2 summarizes the nodal response to different experimental protocols. Two concepts, "facilitation" and "fatigue", introduced by Lewis and Master (1925) and recently redefined by Billette and co-workers (Billette, 1981; Billette *et al*., 1986, 1988, 1994; Billette & Métayer, 1989; Billette & Nattel, 1994), are helpful in describing nodal response during stimulation. Experiments in which the atria are stimulated at rapid rates lead to a variety of complex rhythms including alternans and heart block. In Section 3, we develop a theoretical model for the AV node that incorporates time-dependent terms to represent facilitation and fatigue. Section 4 provides analytic insight into the properties of the theoretical model and derives conditions leading to the onset of alternans during stimulation. In Section 5, we carry out simulations demonstrating that the model reproduces important qualitative features of the experimental results. Implications and limitations of the current formulation are discussed in Section 6.

2. Experimental Characterization of AV Nodal Properties

Experimental studies have shown that AV nodal conduction time depends on the stimulation history as well as the recovery time (Lewis & Master, 1925, Ferrier & Dresel, 1974; Merideth *et al*., 1968, Levy *et al*., 1974; Billette, 1981; Billette *et al*., 1986, 1988; Talajic *et al*., 1991). This dependence has been assessed with a wide variety of stimulation protocols. In the present theoretical model we have adopted concepts, introduced largely by Billette and co-workers, which dissect the nodal response into different subcomponents called recovery, facilitation and fatigue (Billette *et al*., 1988, 1994; Billette & Metayer, 1989; Billette & Nattel, 1994). These concepts are defined and measured using physiological experiments presented below. Once these concepts are represented mathematically (which we do in Section 3) the nodal response to any stimulation protocol can be determined.

Experiments were performed in six isolated, superfused rabbit hearts. This preparation gives long stable recordings in which conduction time can be accurately measured and stimulation delivered using computer driven stimulators under the control of custom written software. In brief, the preparation was obtained from heparinized and anesthetized rabbit. The preparation included the right atrium, the AV node area, and the upper part of the interventricular septum. It was fixed on a grid immersed in a tissue bath and superfused with oxygenated Tyrode solution. Stimuli were delivered using a bipolar platinum–iridium electrode placed near the sinus node.

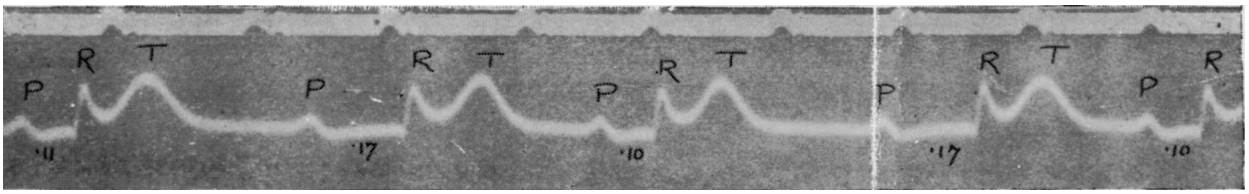

FIG. 1. Electrocardiogram from cats during asphyxia (Lewis & Mathison, 1910). Atrial activation corresponds to the *P* wave and ventricular activation to the *R* wave. Note that the *PR* interval, indicating the *AV* conduction time, alternates between 100 and 170 msec.

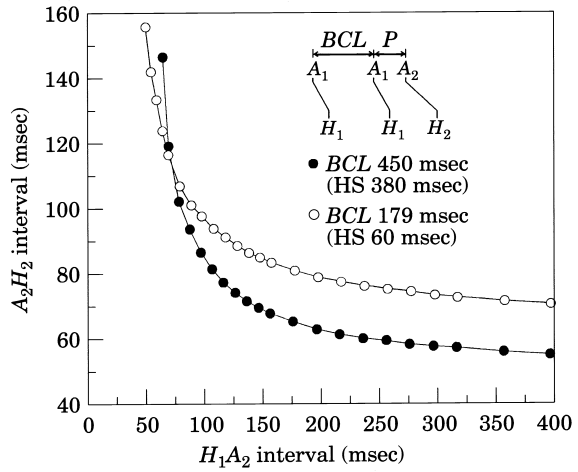

FIG. 2. Recovery curves obtained with premature stimulation performed at two basic cycle lengths (BCL) in an isolated rabbit heart preparation. *Inset*: Typical atrial and His bundle time relationship obtained during a basic cycle (left) and a premature cycle (right). Nodal conduction time (A_2H_2 interval) obtained during premature beats are plotted against corresponding recovery time (H_1A_2 interval). With the shorter BCL, the recovery curve is displaced upwards for long recovery times and to the left for short recovery times.

Activation times were determined with a precision of 0.2 msec. Nodal conduction time is given by the atrial–His (AH) interval measured from the low interatrial septum to His bundle. Nodal recovery time is given by the His–atrial (HA) interval measured from the His bundle complex, which marks the end of one nodal activation, to the beginning of next activation on the low interatrial septum.

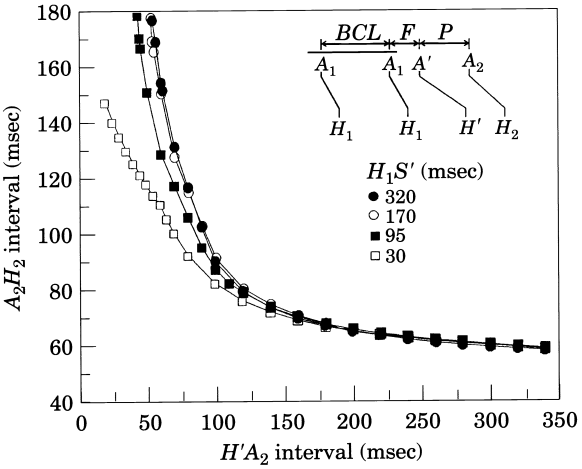

FIG. 3. Changes in the recovery curve associated with facilitation (A_2H_2 vs. $H'A_2$ interval) in one preparation. *Inset*: Stimulation protocol. BCL is maintained constant with an His–stimulus interval of 320 msec. The premature stimulation is repeated four times, each time inserting a conditioning H_1S' intervals (F) before each premature cycle. Note the increasing leftward tilt of the recovery curve with the shortening H_1S'.

PREMATURE STIMULATION

The atrium was paced at a fixed basic cycle length (BCL). After every 20 stimuli, a premature stimulus was delivered (see inset in Fig. 2). The plot of the nodal conduction time due to the premature stimulus (A_2H_2) as a function of the recovery time (H_1A_2) before the premature stimulus is called the recovery curve. The recovery curve can be measured using different BCLs. Figure 2 superimposes the recovery curves obtained at two different BCLs. The conduction time depends on both the recovery time and the BCL. However, for both BCLs, the recovery curve monotonically decreases as the recovery time increases. This reflects the progressive recovery of excitability of the AV node following the activation process. Similar results to those in Fig. 2 have also been observed in dogs (Talajic *et al*., 1991) and humans (Shrier *et al*., 1987).

FACILITATION PROTOCOL

The atrium was paced at a fixed BCL. After 20 basic stimuli we delivered a premature stimulus, S' that led to an activation of the atria A'. This was followed by a second stimulus that led to a second premature atrial activation A_2. While H_1A' was kept constant, the ($H'A_2$) interval was varied (see inset in Fig. 3). The plot of (A_2H_2) as a function of ($H'A_2$) not only depends on the preceding recovery time, $H'A_2$, but also on the value of (H_1A'). The shortening of the conduction time (A_2H_2) associated with the preceding short (H_1A') interval in the family of curves in Fig. 3 is called *facilitation*. Similar results have also been observed in dogs (Billette, 1981; Nayebpour *et al*., 1991; Talajic *et al*., 1991).

STIMULATION WITH A CONSTANT RECOVERY TIME

The preparation was first paced at a fixed BCL. After a stable conduction time was established, the atrium was stimulated with a fixed His–stimulus (HS) interval (Simson *et al*., 1981; Ross *et al*., 1982; Billette, 1988; Talajic *et al*., 1990). To do this, the time of activation of the His bundle was detected, and a fixed delay was imposed electronically before the atria were stimulated. The delay from His activation to atrial stimulation was held fixed for at least 1 min. This form of stimulation is used as a simple experimental model of re-entrant tachycardia, in which the activation passes anterogradely (from the atria to the ventricles) through the AV node, and retrogradely (from the ventricles to the atria) through the electronic component of the circuit. The electrical branch of the circuit therefore mimics an accessory pathway between ventricles and atria. This type of

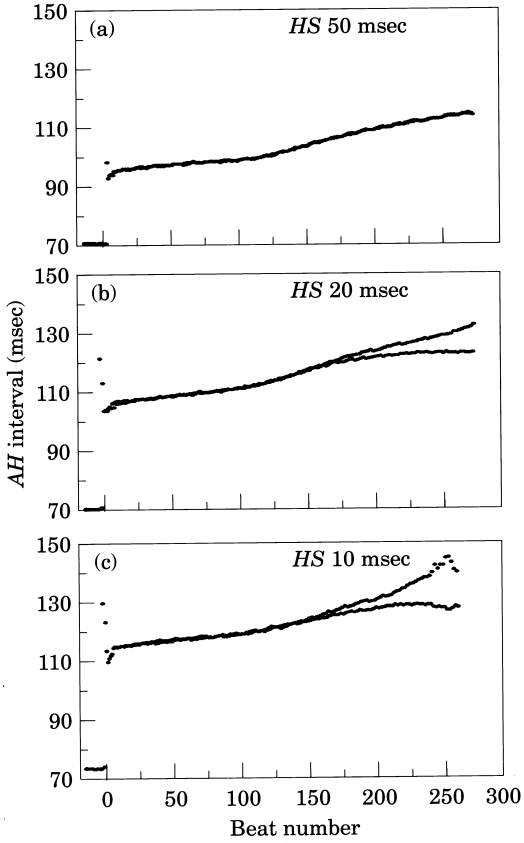

FIG. 4. Beat-to-beat changes in nodal conduction time (*AH* interval) observed at the beginning of fast rates imposed in the 1:1 conduction range with three different constant recovery times [His–stimulus interval: (a) 50 msec; (b) 20 msec; (c) 10 msec] in one preparation. Note the greater *AH* interval increase and occurrence of alternans at shorter His-stimulus intervals.

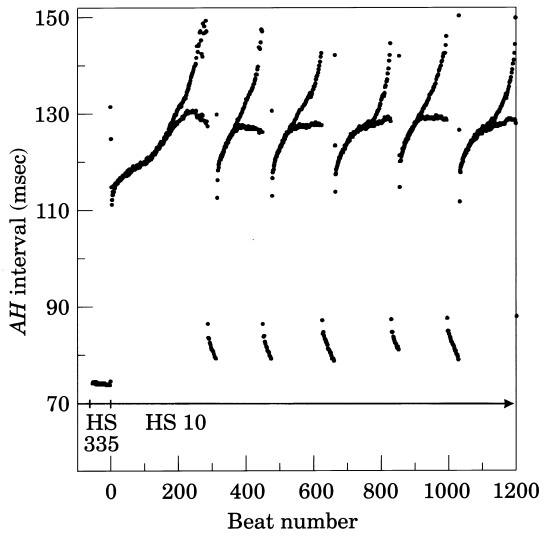

FIG. 5. Repetitive cyclic beat-to-beat changes in nodal conduction time (*AH* interval) observed during a stimulation with a constant His–stimulus interval of 10 msec in one preparation. Each of the six cycles illustrated shows a progressive increase in *AH* interval followed by increasing alternans and the occurrence of nodal blocks, which decreases the *AH* interval and resets the process.

accessory pathways in the intact heart can lead to supraventricular re-entrant tachycardia. If eqn (1) prevailed, the conduction time following each stimulus would be constant since the recovery time is constant. However, this was not the case.

Figure 4 shows experimental data of the conduction time obtained using stimulation at three different fixed HS intervals. In Fig. 4 (a), when the recovery time was held constant at 50 msec, there was a gradual increase in conduction time. This gradual increase is called *fatigue*. It develops with a slow time constant (of the order of 10–30 sec), and dissipates in a similar fashion (Billette *et al*., 1988). When the time delay was shortened to 20 msec [Fig. 4 (b)] there was initially a monotonic increase in the conduction time and then an alternation in conduction time developed. A further shortening of the HS delay to 10 msec led to a more rapid onset of the alternans [Fig. 4 (c)].

Striking rhythms are observed when the 10 msec HS interval was maintained for a longer period (Fig. 5). There was an initial increase in conduction time, followed by an alternation in conduction time. The alternation increased in magnitude, leading eventually to a conduction block. However, following the block the sinus node of the preparation started initiating spontaneous beats again. The first few atrial beats propagated to the His bundle with a progressively decaying AH interval, but the ensuing coupled stimulus delivered to the atria was blocked. The stimuli were soon again effective in driving the preparation and the re-entrant circuit was reinitiated.

STIMULATION WITH CONSTANT INTER-STIMULUS INTERVAL

A final experimental protocol for stimulation involves stimulation with a constant interval between stimuli. If the interval is sufficiently long, then for each stimulus there is a propagated conduction to the ventricles. When the interval between stimuli was shortened there can be complex changes in the dynamics such as Wenckebach rhythms. More complex rhythms were also observed. In our experiments, we observed that, prior to the establishment of blocked rhythms, there was usually some more complex periodicity, similar to the alternans rhythms just described. Although we have not yet carried out a complete study of this phenomenon, in Fig. 6 we show the results obtained both with a fixed HS protocol and a fixed inter-stimulus protocol in the same preparation. Both protocols showed complex fluctuations in the conduction time. Here, in contrast

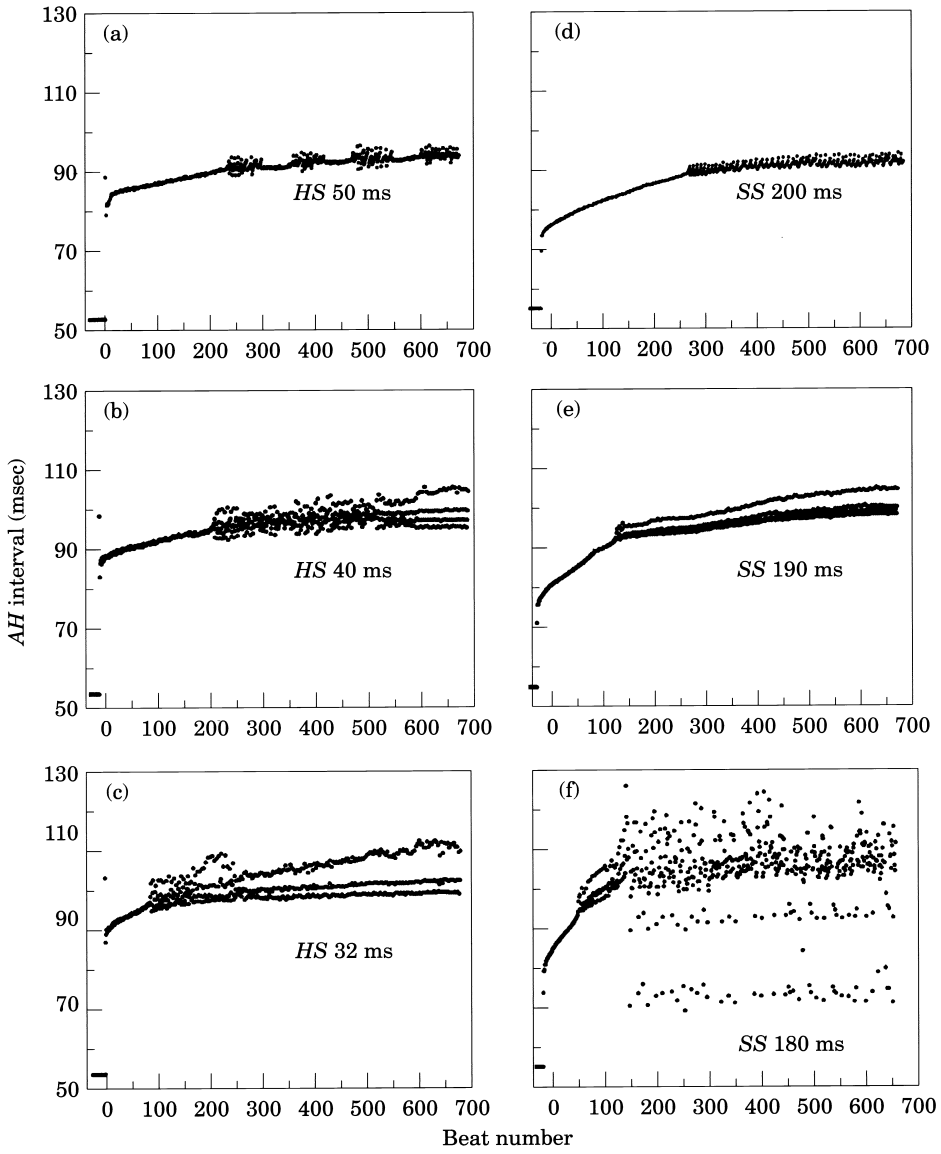

FIG. 6. Beat-to-beat changes in the *AH* interval observed in one preparation driven either with a constant His–stimulus interval [*HS* pacing, (a), (b), (c)] or a constant interstimulus interval (*SS* pacing (d), (e), (f)). Note that *SS* pacing results in greater changes in the *AH* interval and that complex rhythms can occur with both pacing modes.

to Figs 3 and 4, the conduction time fluctuated between several (three or four) levels. The fluctuation can be very small, of the order of a few milliseconds. However, this magnitude of fluctuation is significant since the normal level of beat-to-beat fluctuation of conduction time is only several tenths of a millisecond.

3. A Theoretical Model for AV Nodal Conduction Time

In recent years, progress has been made on formulating quantitative dynamical models, that can be used to predict AV conduction rhythms (Keener, 1981; Simson *et al*., 1980; Roberge & Nadeau, 1969; Glass *et al*., 1987; Shrier *et al*., 1987; Nayebpour *et al*., 1990; Guevara, 1991; Talajic *et al*., 1991). The majority of these models do not include time-dependent changes in parameters that are associated with the fatigue and facilitation effects described above, and therefore can not be used to model the complex dynamics described in Section 2. Although the paper by Talajic *et al*. (1991) develops a mathematical representation for fatigue and facilitation, it fails to give agreement with the alternans observed experimentally (Figs 3 and 4). In the present study, a simple modification of the model in Talajic *et al*. (1991)

successfully reproduces all the experimental observations in Figs 2–4. The model and its modifications are described below.

The starting point in earlier theoretical studies (Glass *et al*., 1987; Shrier *et al*., 1987; Guevara, 1991) was that the AV conduction time is related to the preceding recovery interval

$$f(HA) = \alpha + \beta \exp(-HA/\tau_{rec}) \text{ for } HA > \theta, \quad (2)$$

where α, β, τ_{rec} and θ are positive constants. The constant θ is called the refractory time and if $HA < \theta$ the conduction is blocked. Substituting this equation in (1) we find

$$AH_n = \alpha + \beta \exp(-HA_{n-1}/\tau_{rec}), \quad (3)$$

where AH_n is the AV nodal conduction time following the *n-th* stimulation, and α, β and τ_{rec} are constants. The recovery time HA_{n-1} following the $(n-1)$-th stimulation must be greater than the refractory time θ in order for conduction to occur. If this does not hold, then conduction will not take place until there is a new atrial stimulus occurring with a recovery time greater than θ.

To account for deviations of nodal conduction time different from that predicted by the recovery time alone, eqn (3) must be modified. We assume that the parameters α, β and θ in eqn (3) are not constant, but depend on stimulation history.

In order to represent the gradual increase in conduction time during rapid stimulation [Fig. 4 (a)] we assume that α increases. We use a formulation similar to that in Talajic *et al*. (1991). We assume that during every stimulation that leads to AV conduction, the AV conduction time is lengthened by a constant time interval γ, and this delay decays away exponentially with time, so that

$$\alpha = AH_{min} + S_n, \quad (4)$$

where

$$S_1 = \gamma \exp(-HA_0/\tau_{fat})$$

$$S_n = S_{n-1} \exp(-AA_{n-1}/\tau_{fat}) + \gamma \exp(-HA_{n-1}/\tau_{fat}), \quad (5)$$

where the parameters τ_{fat}, γ and AH_{min} are constants.

Facilitation is a shortening of the AV nodal conduction time as a consequence of a preceding short cycle. Referring to Fig. 3, the conduction time A_2H_2 decreases as $H'A_2$ decreases, even though the recovery time is held constant. Talajic *et al*. (1991) assumed the coefficient β was a function of A_1A'. However, this assumption does not lead to the alternation in conduction time observed in Figs 4 and 5. We assume that β is a function of the preceding nodal conduction time, so that in eqn (3)

$$\beta = \beta(AH_{n-1}) \quad (6)$$

where $\beta(AH_{n-1})$ is a monotonically decreasing function of AH_{n-1}.

Refractoriness is not constant, but depends on the stimulation history (Ferrier *et al*., 1974; Simson *et al*., 1981; Billette *et al*., 1989). In the experiments, the AV nodal conduction time reaches a maximum critical value AH_{cr}, beyond which block occurs (Talajic *et al*., 1991). From eqn (3), we find

$$\theta = \tau_{rec} \log\left(\frac{\beta}{AH_{cr} - \alpha}\right). \quad (7)$$

Therefore, we see that fatigue tends to increase the minimum refractory time of the AV node (since it increases α) while facilitation tends to decrease the refractoriness (since it decreases β). In order to guarantee a positive refractory time, we assume that the minimum value for θ is 3 msec in eqn (7).

With the theoretical model defined by eqns (3), (5), (6) and (7), we can determine the dynamics associated with any stimulation protocol using numerical iteration. However, certain theoretical results characterizing the behavior can be obtained from analytical computation.

4. Theoretical Analysis of the Dynamics

In order to carry out a theoretical analysis of the dynamics, it is convenient to make simplifications based on the magnitudes of time constants estimated from experimentally observed values. The time constant for the buildup and decay of fatigue is such that $\tau_{fat} \gg \tau_{rec}$. Consequently, α changes slowly during the course of the stimulation. This means that we can adopt a *quasi-steady-state* approximation in which we assume that, at any given time, eqn (3) applies using the current value of α based on stimulation history and β and θ defined from eqns (6) and (7). As a consequence of the stimulation, there will be small changes in α that will be reflected in changes in conduction time. In turn, the changes in the conduction time can lead to instabilities in the dynamics, as we show in Section 4.3 below. Therefore, in order to understand the dynamics, we must first understand the changes in α and then consider the influence of these changes on the dynamics.

4.1. STEADY STATE BEHAVIOR

We first consider stimulation using constant AA or HA with 1:1 conduction until a steady state is reached. At steady state, we designate the value of S_n

in eqn (5) as S_∞ and the value of the various intervals with the subscript *ss*. Then, eqn (5) can be rewritten

$$S_\infty = S_\infty \exp(-AA_{ss}/\tau_{fat}) + \gamma \exp(-HA_{ss}/\tau_{fat}). \quad (8)$$

Solving for S_∞, we obtain

$$S_\infty = \frac{\gamma \exp(-HA_{ss}/\tau_{fat})}{1 - \exp(-AA_{ss}/\tau_{fat})}. \quad (9)$$

Based on experimental data, $\tau_{fat} \gg AA_{ss} > HA_{ss} > 0$ we obtain the approximation

$$S_\infty = \frac{\gamma \tau_{fat}}{AA_{ss}}. \quad (10)$$

Substituting in eqns (3) (5) (6) we obtain

$$AH_{ss} = AH_{min} + \frac{\gamma \tau_{fat}}{AA_{ss}} + \beta(AH_{ss})\exp(-HA_{ss}/\tau_{rec}). \quad (11)$$

4.2 *AV* NODAL CONDUCTION TIME BUILD-UP

Previous studies have demonstrated that the buildup of the *AV* nodal conduction time often follows an exponential time-course (Billette *et al*., 1988; Nayebpour *et al*., 1991; Talajic *et al*., 1991). We now show that the theoretical model is in approximate agreement with an exponential build-up when the β-curve is a linear function of AH_{n-1} when *HA* is held constant.† We write the β-curve eqn (6) as:

$$\beta = b_0 - b_1 AH_{n-1} \quad (12)$$

where b_0 and b_1 are positive constants.

We will assume that the preparation is stimulated continuously with a constant BCL in the 1:1 conduction regime until a steady state is reached. At this point we switch to stimulation with *HA* fixed. We will assume that there is 1:1 conduction during the stimulation with *HA* fixed and will show that the *AH* interval evolves following an approximately exponential time course.

Equation (5) gives an iterative expression for the value of α during the course of stimulation. Under the assumption that all the cycle lengths are of equal length, $\overline{AA}$, the value of S_∞ can be explicitly computed using an iterative procedure (Talajic *et al*., 1991). We find that

$$S_n + S_0 \exp\left(-\frac{n\overline{AA}}{\tau_{fat}}\right) + \gamma \exp\left(-\frac{HA}{\tau_{fat}}\right)\left[\frac{1 - \exp\left(-\frac{n\overline{AA}}{\tau_{fat}}\right)}{1 - \exp\left(-\frac{\overline{AA}}{\tau_{fat}}\right)}\right], \quad (13)$$

where the initial condition, S_0, is found from eqn (10)

$$S_0 = \frac{\gamma \tau_{fat}}{BCL}. \quad (14)$$

A straightforward but tedious computation can now be carried out to find the time dependence of AH_n. Define

$$R = -b_1 \exp\left(\frac{-HA}{\tau_{rec}}\right)$$

$$R' = R \exp\left(\frac{\overline{AA}}{\tau_{fat}}\right) \approx R$$

$$\Delta = \gamma \tau_{fat}\left[\frac{1}{BCL} - \frac{1}{\overline{AA}}\right]$$

$$\kappa = AH_{min} + \frac{\gamma \tau_{fat}}{\overline{AA}} + b_0 \exp\left(-\frac{HA}{\tau_{rec}}\right). \quad (15)$$

From eqns (3), (5), (6) and (10) we compute that the buildup of AH_n is given by

$$H_n = \kappa\left[\frac{1 - R^n}{1 - R}\right] + R^n AH_0 - \Delta \exp\left(-\frac{n\overline{AA}}{\tau_{fat}}\right)\left[\frac{1 - R'^n}{1 + R'}\right]. \quad (16)$$

For parameters suitable for these experiments (see Section 5), $R \approx R' < 0.7$. Furthermore, $t + n\overline{AA}$ gives a measure of the length of time for the stimulation. Therefore, following a brief transient, the time-course of the *AH* interval is approximately given by an exponential with a time constant equal to τ_{fat},

$$AH(t) = \frac{1}{1 - R}[\kappa - \Delta e^{(-t/\tau_{fat})}]. \quad (17)$$

4.3. PERIOD-DOUBLING BIFURCATIONS AND ALTERNANS

The above computations make clear that during constant *HA* stimulation, there will be gradual changes in the *AV* nodal conduction time. The consequence of this is that there will be a period doubling bifurcation leading to an alternation of the *AH* interval provided the β curve in (6) has a sufficiently negative slope, and that the *HA* interval is sufficiently small. A schematic diagram showing the hypothesized mechanism is shown in Fig. 7.

† The stimulation actually holds the interval *HS* fixed. However, for the theoretical model we will assume that the *HA* interval is equal to the *HS* interval. In the experiments there is a small difference between these two intervals due to the short time interval associated with the conduction from the stimulated impulse to the recording electrode.

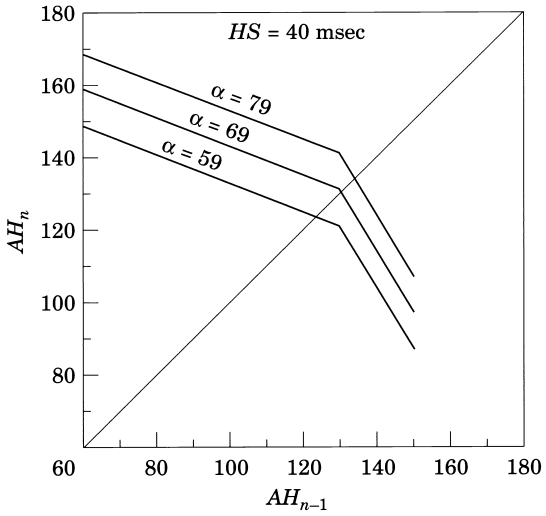

FIG. 7. Schematic representation of the theoretical model showing the origin of the instability leading to alternans. The three curves show AH_n as a function of AH_{n-1} during stimulation with fixed delay ($HS = 40$ msec). The three curves correspond to different times during stimulation. The vertical upward shift of the curves is due to an increase in α that is associated with fatigue as a consequence of stimulation. The three curves represent the quasi-steady-state approximation to eqn (3) following 20 stimuli ($\alpha = 59$), 100 stimuli ($\alpha = 69$), and 250 stimuli ($\alpha = 79$). The point of intersection of the curve with the diagonal gives the value of the nodal conduction time for the corresponding value of α. When the slope of the curve is more negative than -1 at the intersection point, there will be an instability leading to an alternation of the conduction time.

In Fig. 7 we show the relationship between AH_n and AH_{n-1} at three different times during stimulation at a fixed delay ($HS = 40$ msec). The three curves correspond to different times during stimulation. The vertical translation of the curves is due to increases in α that are associated with fatigue as a consequence of stimulation. The three curves represent the quasi-steady-state approximation to eqn (3) following 20 stimuli ($\alpha = 59$), 100 stimuli ($\alpha = 69$) and 250 stimuli ($\alpha = 79$). The point of intersection of the curve with the diagonal gives the value of the nodal conduction time for the corresponding value of α. As a consequence of the upward shift, the point of intersection is shifted to the right, corresponding to a larger value of the conduction time. If the slope at that intersection point is more negative than -1, there will be a loss of stability and a period-doubling bifurcation leading to an alternation in the conduction time.

The mathematical representation of the above mechanism is as follows. For the moment we assume that α is constant and β is as given in eqn (6). A computation of the stability can be carried out using the following steps. A quasi-steady-state value of nodal conduction time, designated AH^* is found from solving the equation

$$AH^* = \alpha + \beta(AH^*)\exp(-HA/\tau_{rec}), \qquad (18)$$

where the current value of α is determined from eqns (4) and (5).

Since β is a monotonically decreasing function of AH^*, as α increases, the value of AH^* increases. However, for any fixed value for HA, the asymptotic value AH_{ss} can be found from the analysis in the preceding section, so that for any experiment with stimulation with HA fixed, the maximal value that can be obtained for a 1:1 rhythm is AH_{ss}.

A period-doubling bifurcation will occur provided

$$\beta'(AH^*)\exp(-HA/\tau_{rec}) = -1, \qquad (19)$$

where

$$\beta'(AH^*) = \left.\frac{\partial\beta}{\partial(AH)}\right|_{AH^*}.$$

From this expression we see that if the negative slope of the β curve is sufficiently steep, then a period-doubling bifurcation can occur provided the conduction time is sufficiently large.

The above mechanism forms the basis for the current analysis. In non-linear dynamics, it is common to plot bifurcation diagrams in which the values of a variable are plotted as a function of control parameters. For systems displaying period-doubling bifurcations, the bifurcation diagram is similar to the plots in Fig. 4 (b) and (c). Therefore, it seemed plausible to assume that in the experiments, there was a gradual change in a parameter that could lead to bifurcations. Thus, the physiological concepts of recovery, facilitation and fatigue enable us to obtain a clear conceptual understanding of why plots of the conduction time as function of time in Fig. 4 (b) and (c) resemble bifurcation diagrams of maps displaying period-doubling bifurcations.

5. Numerical Simulations

In order to carry out numerical simulations of the theoretical model, it is necessary to determine the parameters. Here we use a "typical" set of parameters. We sketch out one method that can be used to set parameters based on the procedure in Talajic *et al.* (1991). In the current paper, detailed setting of parameters was not carried out for different preparations.

The recovery curves were determined using different BCL stimulation rates. The experimental data is fitted using non-linear regression to exponential functions of the form in eqn (5). In this manner, for each BCL, one can determine values of α, β, and τ_{rec}. The average value of τ_{rec} from the different BCLs is taken as the value of τ_{rec}. This method is successful because the

values of τ_{rec} at the different BCL rates differ by about 10% (Talajic *et al*., 1991; J. Sun, unpublished results). Using this value for τ_{rec}, the data can again be fitted to eqn (5) to determine α for different values of BCL. From, eqn (8), we can now estimate the values of AH_{min} and the product $\gamma\tau_{fat}$. The build-up of the nodal conduction is given approximately by eqn (17), so that the experimental data with stimulation with fixed delay can be used to estimate τ_{fat}.

This leaves open the determination of the β curve. We assume that the β-curve is a monotonically decreasing curve that is consistent with the qualitative features of the facilitation experiment. This form of the β-curve gives rise to alternans using either fixed-delay- or constant-period stimulation.

In the following computations, we assume

$$\begin{aligned} \tau_{rec} &= 70 \text{ msec} \\ \tau_{fat} &= 30 \text{ sec} \\ AH_{min} &= 33 \text{ msec} \\ \gamma &= 0.3 \text{ msec}. \end{aligned} \tag{20}$$

For the β-curve, we assume

$$\begin{aligned} \beta &= 201 \text{ msec} - 0.7\, AH_{n-1}, \\ &\qquad \text{for } AH_{n-1} < 130 \text{ msec} \\ \beta &= 500 \text{ msec} - 3\, AH_{n-1}, \\ &\qquad \text{for } AH_{n-1} \geqslant 130 \text{ msec}, \end{aligned} \tag{21}$$

where AH_{n-1} is the conduction time of the preceding beat expressed in msec. If the preceding beat is blocked then we assume that the conduction time for the last conducted beat is used to compute the appropriate value of β. Only the conducted beats lead to an increment of the conduction time by γ.

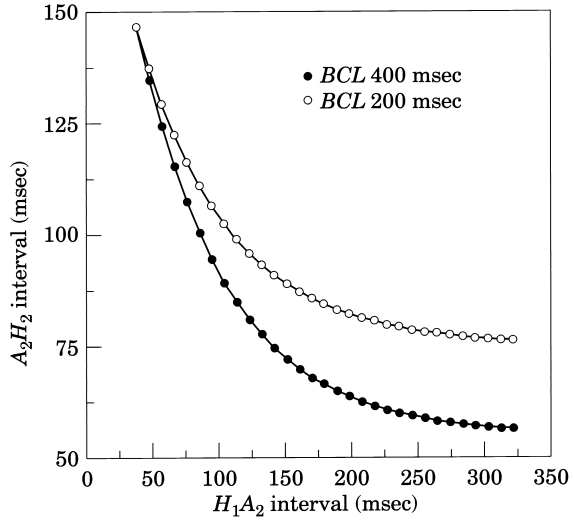

FIG. 8. Recovery curve obtained in response to premature stimulation performed at two basic cycle lengths (BCL) in the model.

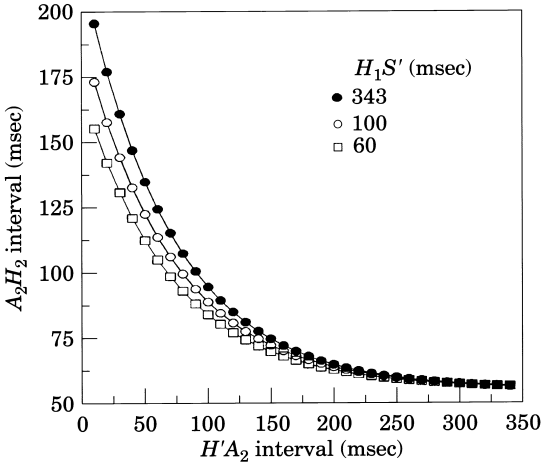

FIG. 9. The recovery curve obtained in the theoretical model using the same stimulation protocol in Fig. 3. Note progressive tilt of the curve to the left with the shortening of the H_1A' interval.

The theoretical model can now be tested by subjecting it to the various protocols described above. Figure 8 shows the simulation of the recovery curve at two different BCL. At the faster stimulation rate, the value of α increases. If β were simply constant, this would lead to a vertical translation up of the recovery curve. However, the functional dependence of β on AH_{n-1} in eqn (6) leads to downward shift of the recovery curve for small values of the recovery time in accord with experimental observations (compare Figs 2 and 8).

Figure 9 shows these recovery curves obtained using the facilitation protocol, assuming two different values for H_1A'. The theoretical model shows a decrease of the nodal conduction time associated with decreases in the H_1S' interval. This decrease arises as a consequence of the increase in the conduction time $A'H'$ as described by the β function in eqn (6).

Stimulation of the preparation with constant HA interval elicits dynamics dependent on α and β. For a broad range of HA interval, the numerical computations of the theoretical model show that the nodal conduction time increases during stimulation, and tends to a constant [Fig. 10 (a)]. This constant increases when the HA interval decreases. When the HA interval is further decreased, the theoretical model predicts the occurrence of a bifurcation leading to the alternation of the AH conduction time [Fig. 10 (b)]. For this choice of the parameters, using eqn (19) we find that a period-doubling bifurcation will occur if $HA < 57$ msec. For $HA < 57$ msec, the time from the

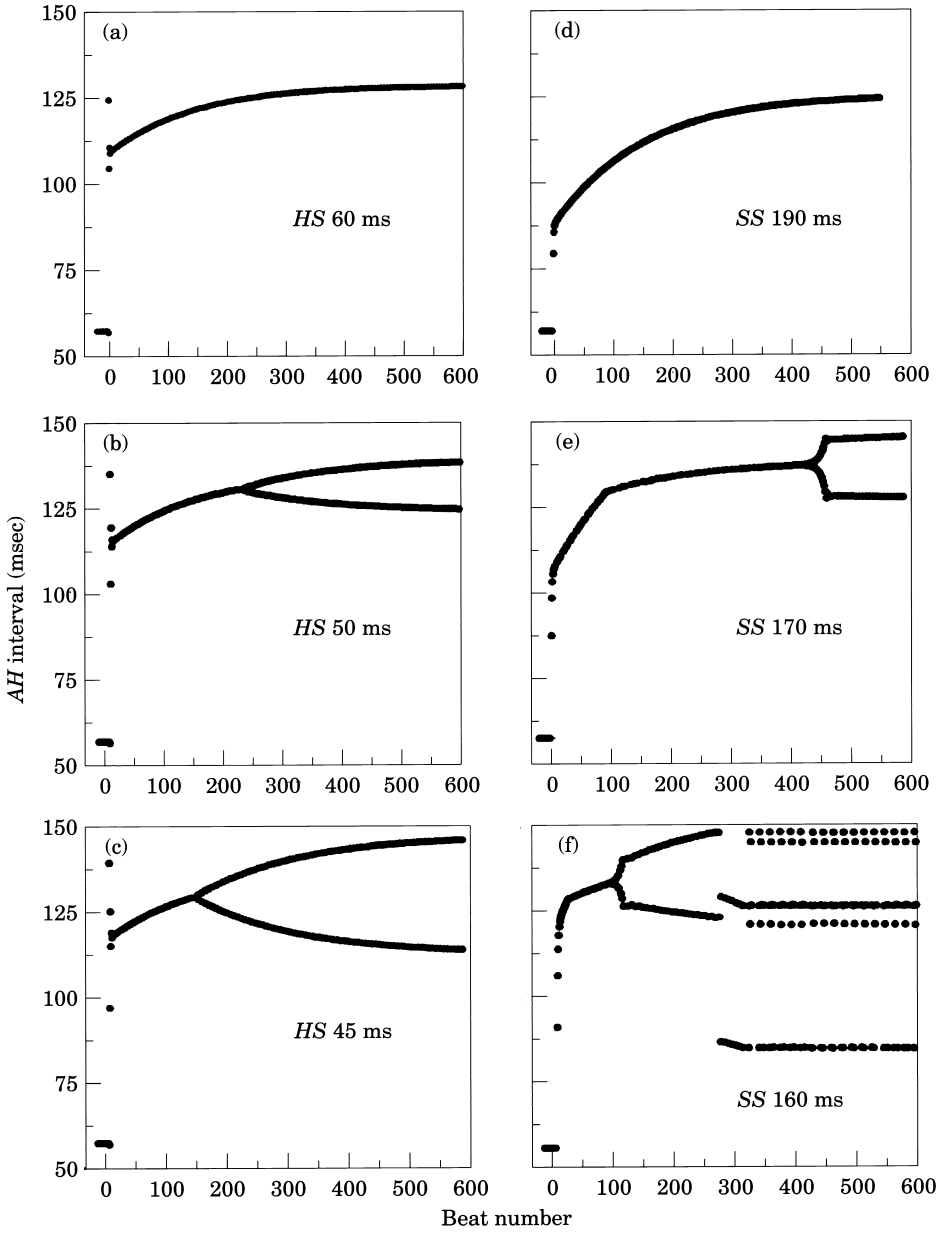

FIG. 10. Beat-to-beat changes in the *AH* interval obtained in the model with constant His–stimulus interval (*HS* pacing, left panels) and constant interstimulus interval (*SS* pacing, right panels). Note that the *SS* pacing results in steeper increase in the *AH* interval and greater instability than *HS* pacing. The initial condition is established by pacing with an *SS* interval of 400 msec prior to the start of the records.

onset of stimulation to the block decreases as *HA* decreases [Fig. 10 (c)].

In response to stimulation with a constant interstimulus (*SS*) interval, we see similar dynamics. There is initially a build-up in conduction time with no instabilities [Fig. 10 (d)]. With stimulation at a more rapid rate [Fig. 10 (e)], there is alternans. The theoretical analysis shows that for the parameters used here the alternans instability will occur for $SS < 175$ msec. At still more rapid stimulation rates, there is a more rapid onset of the alternans instability followed by conduction block [Fig. 10 (f)]. In Fig. 10 (f), the block occurs after approximately 250 stimuli. As a consequence of the blocked beat, there is a long recovery time so that the first *AH* interval following the blocked beat is shortened (to about 88 msec). The observation of alternans prior to the onset of conduction block during periodic stimulation parallels the observations of Lewis & Mathison (1910). Although the evolving nature of the preparation of this earlier work (the sinus rate was changing as a consequence of reflexes induced by the asphyxia) precludes any

definite conclusions, the current work provides the first theory for the pioneering observations of Lewis and Mathison.

The results in Fig. 10 (a), (b), (c) are very similar to the results observed experimentally in Fig. 4 (a), (b), (c). Experiments were not carried out in this preparation using a constant stimulation interval protocol. In another preparation, stimulation using both a constant HS and a constant SS were carried out (Fig. 6). Although there are many features of similarity between Figs 6 and 10, there are delicate issues that are not understood. Most important, at the moment we do not understand why the instability in the experimental data gives a splitting into several branches rather than just the two branches in the theoretical model. We discuss a possible mechanism in Section 6.

After the bifurcation in the nodal conduction time, the alternans increases in magnitude. Block occurs if the AV conduction time reaches the value AH_{cr}. In the stimulation we have assumed that $AH_{cr} = 150$ msec (see eqn (7)]. In response to prolonged stimulation, block will occur if the fixed stimulation delay is too short. In Fig. 11, we simulate the effects of block and restart of the stimulation using a fixed HS interval of 40 msec. After the block, we assume a time interval of 40 sec between the block and the restart of the stimulation. After 40 sec, the prolongation of conduction time associated with fatigue has significantly dissipated (since $\tau_{fat} = 30$ sec). In the model, following restart of the stimulation, the re-entrant circuit is re-established and there is again a period-doubling bifurcation leading to alternans.

These results are similar to the experiment shown in Fig. 5. However, in the experiment, there is a time interval of about 10–15 sec, before the re-entrant circuit is re-established. In the experimental system, this shorter time interval is adequate to dissipate the fatigue. Although there is qualitative agreement between theory and experiment, the origin of the quantitative differences requires further investigation.

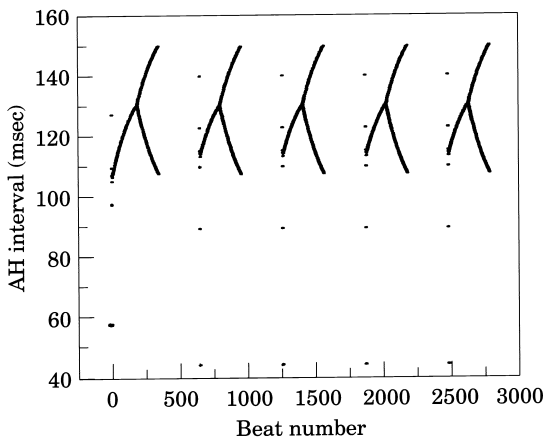

FIG. 11. Cyclic beat-to-beat changes in the AH interval obtained with a constant recovery time imposed with a His–stimulus interval of 40 msec. In each segment the conduction time increases followed by alternans, and eventually blocked conduction. Following the blocked conduction, an interval of 40 sec is assumed during which time the value of α decays.

6. Discussion

In this paper we have shown that alternans of AV nodal conduction can be associated with a period-doubling bifurcation in a theoretical model of AV nodal function. Although previous authors had suggested that AV nodal alternans might arise as a consequence of a period-doubling bifurcation, previous hypothesized mechanisms were the periodic forcing of a non-linear oscillator (Guevara & Glass, 1982) or supernormality (Guevara, 1991). In the current formulation, the origin of the alternans is predicted based on the mathematical representation of facilitation.

Our analysis contrasts with earlier mathematical models of AV nodal conduction during stimulation with a fixed retrograde conduction time (Simson *et al*., 1981; Ross *et al*., 1982; Talajic *et al*., 1990). In these earlier papers, the AV nodal conduction time was assumed to be a function of a preceding AA interval. Although this formulation did give agreement with data using a fixed retrograde conduction time, the theoretical formulation was not capable of displaying Wenckebach rhythmicity manifested by the progressive increase in AH conduction time and eventual block observed during rapid stimulation with fixed AA intervals. The current theoretical model incorporates physiological properties of recovery, facilitation and fatigue that have long been used to characterize AV nodal dynamics in response to a variety of different stimulation protocols. The theoretical formulation of Talajic *et al*. (1991) is consistent with the qualitative features of the dynamics during the facilitation and fatigue protocols, but it is not capable of showing the stable alternans during the fixed delay stimulation.

Our analysis may provide a mechanism for alternans of nodal conduction time observed in other settings, for example during asphyxia (Lewis & Mathison, 1910), during supraventricular tachycardia (Baker *et al*., 1943; Segers, 1951; Langendorf, 1958; Spurrell *et al*., 1979; Sung & Styperek, 1979), or following the administration of verapamil (Rinkenberger *et al*., 1980). Although it is sometimes assumed in the clinical literature that the observation of alternans of the PR interval in the electrocardiogram implies the existence of two anatomically distinct pathways for

conduction between the atria and ventricles (Spurrell *et al*., 1973), the current analysis shows that electrophysiological properties in a single pathway may also be consistent with a mechanism to generate alternans —see also Rinkenberger *et al*. (1980). Since the current approach provides definite rules that must be satisfied to observe alternans, a quantitative basis for further investigations of alternans in nodal conduction time has been set.

The theoretical analysis has helped us identify a number of experimental questions that bear closer examination. Most important of these are:

- *Independent measurement of the β curve*. Stimulation protocols can be carried out in which AH_{n-1} is varied with a fixed recovery time for various values of the BCL. Our theoretical model predicts that the different values of the BCL would lead to different values of α and consequent vertical shifts of the β curve—see eqns (3), (6) and Fig. 7. Since period-doubling bifurcations and the consequent alternans in conduction time are only observed if the β curve steepens sufficiently at large values of the preceding conduction time, it is important to measure independently the β-curve.
- *An analysis of the kinetics of build-up and decay of the fatigue effect with short fixed delay stimulation*. The results in Fig. 4 show an approximate exponential build-up of conduction time for long fixed delays. For shorter fixed delays, there is an initial exponential build-up followed by a more steeply rising segment, possibly indicating a secondary mechanism. In the situation in which there is repeated blocking and restarting of the tachycardia (Fig. 5), there appears to be a more rapid decay of the conduction than is predicted from the theory, but a careful analysis of this has not yet been carried out.
- *Determination of AV conduction time near the onset of conduction block during stimulation with a constant period*. During stimulation with a constant period, we observe fluctuations in the conduction time of the order of several milliseconds prior to the onset of the block [Fig. 6 (f)]. Most clinical analysis of AV block do not measure conduction time with such a fine accuracy. It is consequently intriguing to speculate that fluctuations in AV conduction time may be a common feature before the onset of AV block during stimulation at a fixed rate.
- *Reproducibility of the experimental results*. The protocols involved in these experiments are lengthy, and not all procedures have been carried out in all preparations. The stimulation with a constant recovery time was carried out in six preparations. In three preparations, there was a clear splitting of the conduction time into two branches. In one of these cases, the splitting tended to be transient, and decreased following prolonged stimulation. In a second case, the splitting sometimes evolved into more complex fluctuating rhythms during the stimulation. The third case is illustrated in Figs 3 and 4. In another experiment, there was an initial establishment of complex fluctuations of conduction time (Fig. 6) that was not a simple alternans. In the other two experiments, there was no striking fluctuations in conduction time. In the four experiments in which an instability leading to alternans or complex fluctuation of the conduction time was observed, the largest value of HS that was associated with the fluctuations was 20, 40, 40 and 100 msec.

There are many limitations of the current formulation. The formulation is based on phenomenological characterizations of the nodal conduction time. Despite the appeal of this way of conceptualizing nodal dynamics, it does not give a deep understanding of the various ionic currents that underlie the functional properties of the AV node. In order to study those aspects, detailed ionic models must be developed. The current studies will be useful in this regard, by providing a body of qualitative observations that must be accounted for in ionic models.

In developing theoretical models further, it is important to recognize that the AV node is not a homogeneous structure. Rather, there are several different anatomically and physiologically distinct regions of the AV node. We believe that the source of variability in the experimental results may be due to subtle anatomical and physiological differences between the different preparations, which play an important role when conduction breaks down. Moreover, the complex fluctuation in conduction time between several different levels (Fig. 6) may be due to heterogeneities in the AV node that are not accounted for in the current formulation.

In conclusion, the present paper presents a theoretical model for the AV nodal conduction time. This model can reproduce reasonably well data obtained using different experimental protocols. When the recovery delay (HA) is constant, the model gives insight into the onset of alternans. For the stimulation period (SS) constant, the model predicts that there should exist zones in which fluctuations in conduction time occur during 1:1 conduction. In addition, AV nodal block rhythms that might appear to be simple Wenckebach rhythms may actually contain subtle

fluctuations in the timing of conduction. The model suggests that, from a mathematical perspective, there is an intimate relation between the proper representation of facilitation and the origin of the alternans.

This research has been partially supported with funding from the Natural Sciences Engineering and Research Council, Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (Québec) and the Medical Research Council. We thank Lise Plamondon for technical assistance.

REFERENCES

Arnold, V. I. (1991). Cardiac arrhythmias and circle mappings. *Chaos* **1,** 20–24.

Barker, P. S., Johnston, F. D. & Wilson, F. N. (1943). Auricular paroxysmal tachycardia with alternation of cycle length. *Am. Heart J.* **25,** 799.

Billette, J. (1981). Short time constant for rate-dependent changes of atrioventricular conduction in dogs. *Am. J. Physiol.* **241,** H26–H33.

Billette, J. Gossard, J. P., Lepanto, L. & Cartier, R. (1986). Common functional origin for simple and complex responses of atrioventricular node in dogs. *Am. J. Physiol.* **251,** H920–H925.

Billette, J. & Métayer, R. (1989). Origin, domain and dynamics of rate-induced variations of the functional refrectory period in rabbit atrioventricular node. *Circulation Res.* **65,** 164–175.

Billette, J., Métayer, R. & St-Vincent, M. (1988). Selective functional characteristics of rate-induced fatigue in rabbit atrioventricular node. *Circulation Res.* **62,** 790–799.

Billette, J., Amellal, F., Zhao, J. & Shrier, A. (1994). Relationship between different recovery curves representing rate-dependant *AV* nodal function in rabbit heart. *J. Cardiovasc. Electrophysiol.* **5,** 63–75.

Billette, J. & Nattel, S. (1994). Dynamic behavior of the atrioventricular node: a functional model of interaction between recovery, facilitation, and fatigue. *J. Cardiovasc. Electrophysiol.* **5,** 90–102.

Decherd, G. M. & Ruskin, A. (1946). The mechanism of the Wenckebach type of A-V block. *Br. Heart J.* **8,** 6–16.

Ferrier, G. R. & Dresel, P. E. (1974). Relationship of the functional refractory period to conduction in the atrioventricular node. *Circulation Res.* **35,** 204–214.

Glass, L., Guevara, M. R. & Shrier, A. (1987). Universal bifurcations and the classification of cardiac arrhythmias. *Ann. N. Y. Acad. Sci.* **504,** 168–178.

Guevara, M. R. (1991). Iteration of the human atrioventricular (AV) nodal recovery curve predicts many rhythms of AV block. In: *Theory of Heart*: *Biophysics*, *Biomechanics and Nonlinear Dynamics of Cardiac Function* (Glass, L., Hunter, P. & McCulloch, A., eds) pp. 312–358. New York: Springer-Verlag.

Guevara, M. R. & Glass, L. (1982). Phase locking, period doubling bifurcations and chaos in a mathematical model of a periodically driven biological oscillator: A theory for the entrainment of biological oscillators and the generation of cardiac dysrhythmias. *J. math. Biol.* **14,** 1–23.

Heethar, R. M., van der Gon, J. J. D., & Meijler, F. L. (1973). Mathematical model of A-V conduction in the rat heart. *Cardiovasc. Res.* **7,** 105–114.

Keener, J. P. (1981). On cardiac arrhythmia: AV conduction block. *J. math. Biol.* **12,** 215–225.

Langendorf, R. (1958). Alternation of A-V conduction time. *Am. Heart J.* **55,** 181.

Levy, M. N., Martin, P. J., Edelstein, J. & Goldberg, L. B. (1974). The A-V nodal Wenckebach phenomenon as a positive feedback mechanism. *Prog. Cardiovasc. Dis.* **16,** 601–613.

Lewis, T. & Master, A. M. (1925). Observations upon conduction in the mammalian heart. *A-V* conduction. *Heart* **12,** 210–269.

Lewis, T. & Mathison, G. C. (1910). Auriculo-ventricular heart-block as a result of an asphyxia. *Heart* **2,** 47–53.

Meredith, B. J., Mendez, C., Mueller, W. J., & Moe, G. K. (1968). Electrical excitability of atrioventricular nodal cells. *Circulation Res.* **23,** 69–85.

Mines, G. R. (1913). On dynamic equilibrium in the heart. *J. Physiol. Lond.* **46,** 349–382.

Mobitz, W. (1924). Über die unvolständige Storüng der Erregungsüberleitung zwischen Vorhof und Kammer des menschlichen Herzens. *Z. ges. exp. Med.* **41,** 180–237.

Nayebpour, M., Talajic, M. & Nattel, S. (1991). Quantitation of dynamic AV nodal properties and application to predict rate-dependent AV conduction. *Am. J. Physiol.* **261,** H292–H300.

Rinkenberger, R. L., Prystowsky, E. N., Heger, J. J., Troup, P. J., Jackman, W. M. & Zipes, D. P. (1980). Effects of intravenous and chronic oral verapamil administration in patients with supraventricular tachyarrhythmias. *Circulation* **62,** 996–1010.

Roderge, F. A. & Nadeau, R. A. (1969). The nature of Wenckebach cycles. *Can. J. Physiol. Pharmacol.* **47,** 695–704.

Ross, D. L., Dassen, W., Vanagt, E. J., Brugada, P., Bar, F. & Wellens, H. (1982). Cycle length alternation in circus movement tachycardia using an atrioventricular accessory pathway. *Circulation* **65,** 862–868.

Segers, M. (1951). L'alternance du temps de conduction auriculo-ventriculaire. *Arch. Mal. Coeur* **44,** 525–527.

Shrier, A., Dubarsky, H., Rosengarten, M., Guevara, M. R., Nattel, S. & Glass L. (1987). Prediction of complex atrioventricular conduction rhythms in humans with use of the atrioventricular nodal recovery curve. *Circulation* **76,** 1196–1205.

Simson, M. B., Spear, J. F. & Moore, E. N. (1981). Stability of an experimental atrioventricular reentrant tachycardia in dogs. *Am. J. Physiol.* 240 *Heart Circ. Physiol.* **9,** H947–H953.

Spurrell, R., Krikler, D. & Sowton, E. (1973). Two or more intra AV nodal pathways in association with either a James or Kent extranodal bypass in three patients with paroxysmal supraventricular tachycardia. *Br. Heart J.* **35,** 113–122.

Sung, R. J. & Styperek, J. L. (1979). Electrophysiologic identification of dual atrioventricular nodal pathway conduction in patients with reciprocating tachycardia using anomalous bypass tracts. *Circulation* **60,** 1464–1476.

Talajic, M., Papadatos, D., Villemaire, C., Glass, L. & Nattel, S. (1991). A unified model of atrioventricular nodal conduction predicts dynamic changes in Wenckebach periodicity. *Circulation Res.* **68,** 1280–1293.

Talajic, M., Villemaire, C., Papadatos, D., Lemery, R., Roy, D. & Nattel, S. (1990). Cycle length alternation during supraventricular tachycardia occurrence and mechanism in a canine model of AV reentrant tachycardia. *PACE* **13,** 314–325.

Urushibara, S., Kawato, M. & Nakazawa, K. (1987). Simulation analysis of conduction of excitation in the atrioventricular node. *J. theor. Biol.* **126,** 275–288.

Wellens, H., Tan, S. L., Bar, F., Duren, D. R., Lie, K. I. & Dohmen, H. M. (1977). Effect of verapamil studied by programmed electrical stimulation of the heart in patients with paroxysmal re-entrant supraventricular tachycardia. *Br. Heart J.* **39,** 1058–1066.

Wenckebach, K. F. (1899). Zur Analyse des unregelmässigen Pulses. *Z. klin. Med.* **37,** 475–488.