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DETERMINISTIC MODEL OF THE CANINE ATRIO-VENTRICULAR NODE AS A PERIODICALLY PERTURBED, BIOLOGICAL OSCILLATOR

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ABSTRACT

The atrio-ventricular (AV) node may be regarded as a periodically perturbed, biological oscillator. In that case the ventricular response to atrial excitation can be described by a latency-phase curve. The phase is approximated by the time between a QRS-complex and an atrial stimulus S (R-S interval), the latency by the time between this stimulus and the following QRS-complex (S-R interval). This hypothesis was checked against results obtained in six anesthetized, pharmacologically denervated dogs. An exponential relationship between S-R and R-S intervals was obtained from normally conducted, premature atrial stimuli. This latency-phase relationship resulted in a deterministic model of the AV conduction system. Step increases and decreases in atrial stimulation rate yielded S-R intervals in the dog that corresponded to the intervals predicted by the model. These preliminary results support the hypothesis that not only the canine, but also the human AV node may function as a periodically perturbed, biological oscillator.

key words : atrio-ventricular conduction, biological oscillator, atrial stimulation

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INTRODUCTION

The AV node provides an appropriate delay between atrial and ventricular excitation and contraction (1). It is also of vital importance in supraventricular arrhythmias, like atrial fibrillation, because it protects the ventricles against high atrial rates (2,3,4). The AV node not just simply delays the atrial impulse to the ventricles. Transmission of impulses through the AV node is a non-linear phenomenon. This was shown among others by Strackee et al. (5), who studied the ventricular rhythm during artificial atrial fibrillation in dogs. Heethaar et al. (6) developed a mathematical model for AV conduction in the rat heart, in which AV conduction time was dependent on five preceding atrial stimulation intervals. In a previous study (7) we used a transfer function model (by means of time series analysis) to describe the relation between input and output of the AV node during random atrial stimulation in patients.

There are, however, two main objections against the latter two studies. Firstly, the use of the intervals between successive atrial stimuli as input for models describing the AV node-His behaviour may not be correct. Billette (8), for instance, demonstrated that AV nodal conduction time depends primarily on the time of arrival of the atrial impulse in the nodal recovery cycle (His-atrial time) rather than on the absolute atrial cycle length. Secondly, a restriction of the transfer function model is that it is only valid for random input. Describing the AV node as a biological oscillator removes these objections. Guevara & Glass (9) considered the AV node as a biological oscillator, the rhythm of which can be affected by periodic perturbation. They proposed that clinical cardiac arrhythmias can theoretically arise as a consequence of periodic stimulation of such an oscillator.

We developed a mathematical, deterministic model to describe AV conduction characteristics, using the concepts of a biological oscillator and a latency-phase curve. Model results are compared with results obtained in canine experiments.

MODEL : THEORY

The concept of a biological oscillator to describe AV nodal behaviour was chosen because of the similarities between AV nodal characteristics and properties of driven, non-linear oscillators (9,10,11,12,13), like an intrinsic natural frequency (cf. the intrinsic AV nodal rhythm) and the ability to be "forced" to oscillate at a wide range of frequencies (cf. synchronization at various atrial

stimulation rates). So called intermittent behaviour, a common condition of these oscillators, resembles Wenckebach periodicity in second degree AV block. Furthermore, when the frequency (f) of an impressed periodic force is increased beyond the range of automatic synchronization, frequency demultiplication (also called period-doubling) may occur, i.e. the oscillator synchronizes on a subharmonic of the impressed periodic force, for example on f/2, f/3, etc. (cf. various forms of second degree AV block). In addition to frequency demultiplication, irregular (random) noise (11) or chaotic dynamics (9,10,13) can be observed.

When the cycle length of a biological oscillator is perturbed by a stimulus, the phase of the oscillator (i.e. the time between the last reset of the oscillator and the moment of the stimulus) can be shortened or lengthened (phase advance or phase delay). Changing the phase of the oscillator by a stimulus also affects the latency (i.e the time between the stimulus and the next reset of the oscillator). When the cycle length is not perturbed by a stimulus, the sum of phase and latency equals the intrinsic period of the oscillator.

The latency-phase curve (LPC) (14) depicts graphically the effect of an atrial stimulus on the time until the next QRS complex. The time between the R-wave and the next atrial stimulus (R-S interval) can be considered as the phase(P). The time between the stimulus and the following R-wave (S-R interval) can be considered as the latency(L) (fig.1a).

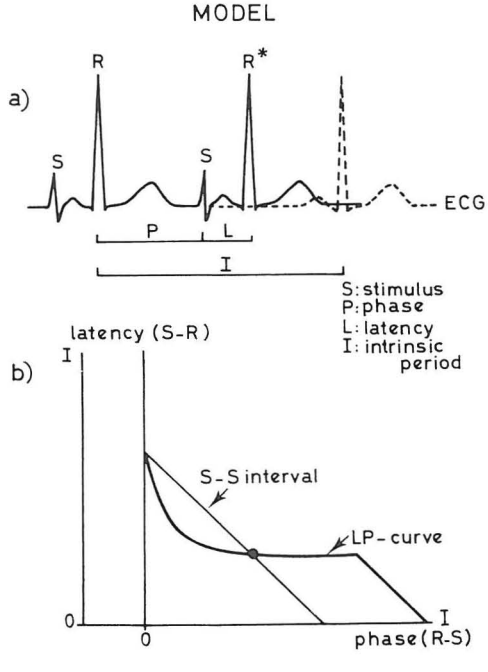

FIG. 1a
The effect of a stimulus S, applied after phase P, on the latency L, the time until the next QRS-complex. When the cycle length is not perturbed by a stimulus or when no stimulus is applied at all, the cycle length is equal to the intrinsic period I of the biological oscillator (dotted line).

FIG. 1b Latency-phase curve (LPC). The ordinate of● is the steady-state S-R interval to which (continuous) stimulation with a series of equal-length S-S intervals leads.

The LPC can be represented by plotting the R-S interval as the abscissa and the S-R interval as the ordinate in the latency-phase plane. Each R-R interval is equal to the sum of the R-S and corresponding S-R interval. Each S-S interval is equal to the sum of the previous S-R interval and the current R-S interval and can be depicted by a straight line with slope -1. The ordinate of the point of intersection of the LPC and the straight line indicating the length of the S-S interval (●) is the steady-state S-R interval to which sustained stimulation with these equal-length S-S intervals will lead (fig.1b). (In case of two points of intersection, the point where the clock-wise angle between the LPC and the straight line is smaller than 90 degrees corresponds always to stable 1:1 AV conduction.)

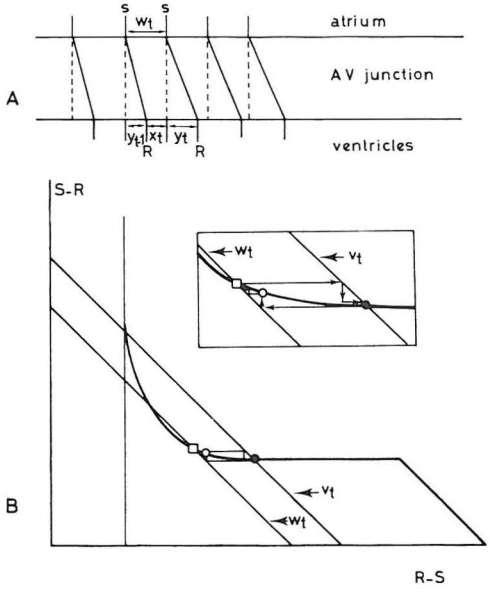

FIG. 2a
Schematic representation of the relation between S-S and R-R intervals.
w_t : S-S interval
x_t : R-S interval
y_t : S-R interval
y_{t-1} : preceding S-R interval
z_t : R-R interval

$z_t = w_t + y_t - y_{t-1}$
and
$z_t = x_t + y_t$
$(t=2,3,...)$

FIG. 2b MODEL
Adaptation of AV conduction time for step increase (w_t) and step decrease (v_t) in stimulation rate. The vertical line corresponds to the minimal R-S value (see also fig. 6 and text).

The adaptation of AV conduction to an increase in frequency can be determined as follows (fig. 2a). Let w_t be the new S-S interval, then the new phase x_t (R-S interval) is equal to $w_t - y_{t-1}$. The corresponding latency y_t (S-R interval) can be derived as a function of this phase, $y_t = f(x_t)$. The next S-S interval leads to a new phase and latency, etc. until a new steady-state is reached. This adaptation process is depicted graphically in fig. 2b. From ●, a horizontal

line is drawn to the straight line depicting the new S-S interval (w_t). From the point of intersection of these two lines a vertical line is raised to the LPC. The abscissa of ○ is the new phase x_t, the ordinate the new latency y_t. In the same fashion the conduction time corresponding to the next S-S interval of length w_t can be determined and so on until a new steady-state AV conduction time is reached (ordinate of □). In case of a decrease in frequency from S-S intervals of length w_t to S-S intervals of length v_t, the adaptation of AV conduction time can be derived from fig. 2b also. A horizontal line is drawn from □ to the straight line depicting the S-S intervals of length v_t. From the point of intersection of the two lines a vertical line is dropped to the LPC leading to a new phase and latency. This can be repeated till steady-state conduction is reached again (●). The number of S-S intervals required to reach a steady-state S-R interval depends on the size of the step and is, in most cases, larger in a step increase than in a step decrease in frequency.

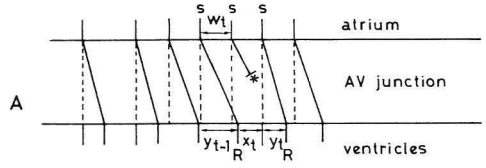

FIG. 3a
see legend of fig. 2a.
The stimulus S* is blocked.

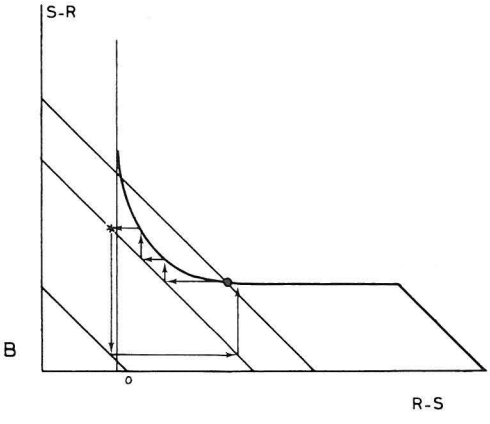

FIG. 3b MODEL
Increase of AV conduction time during sustained stimulation until a stimulus is blocked (*).

When there is no point of intersection between the curve and the straight line, i.e. when the (atrial) stimulation frequency is relatively high, no steady state (in terms of stable 1:1 AV conduction) can be reached (fig. 3a and 3b). Upon stimulation the R-S interval ultimately becomes shorter than the minimal R-S interval (the zero or reset point of the oscillator), i.e. the stimulus

drip of methadone (0.12 mg/kg/min) and dehydrobenzperidol (0.15 mg/kg/min). Ventilatory parameters were adjusted to keep the end-tidal CO_2 concentration at 4.7 %. The pH was 7.4. It was corrected with an 8.4 % sodium bicarbonate solution, if required. The heart was exposed through a right 5th intercostal space incision. Bipolar electrodes were sutured to the right and left auricle and to the left ventricular epicardium. The thorax was closed provisionally after positioning a thermistor in the pericardial space. Autonomic nervous influence had to be blocked pharmacologically to suppress periodic oscillations in the AV conduction time associated with the artificial ventilation by intravenous administration of atropine sulphate (0.2 mg/kg in 5 min), followed by propranolol (1.0 mg/kg in 10 min) (15).

Measurements

The electrocardiogram was recorded using standard extremity lead II. Bipolar cardiac electrograms were recorded from the left auricle and the left ventricle to verify that changes in the interval between the stimulus artefact and the R wave were due to changes in AV conduction time. The temperature in the thorax was read at the start of each stimulation run. Arterial pressure from the aortic arch (Statham P23Db), the electrocardiogram, the stimulus pulses and the atrial and ventricular electrograms were recorded on an instrumentation recorder (Ampex 2000) and displayed on a multichannel ink-writer (Gould-Brush). Simultaneously, arterial pressure, electrocardiogram and stimulus pulses were digitized on-line (sampling frequency 1000 Hz) by a Hewlett-Packard computer (HP 1000 F) and the samples were recorded on a magnetic disc. Subsequently parameters were computed off-line as described earlier (16).

Stimulation protocol

The right auricle was stimulated by 2.0 ms pulses of 2 to 4 mA (twice threshold intensity). The basic stimulation interval (BCL) was 500 ms.

Step increase and step decrease in stimulation frequency : After 2 min of stimulation with the BCL, the right auricle was stimulated at intervals of 350 to 270 ms for 1 min, followed by stimulation with the BCL. Two frequency steps were applied: the highest frequency that allowed stable 1:1 AV conduction and an intermediate frequency that produced approximately half the increment in AV conduction time induced by the high frequency step.

Premature beats : Using the BCL of 500 ms, every eighth beat a test pulse was applied 150 to 400 ms after the basic pulse.

Estimation of the LPC

The LPC can be estimated from the experimental results of normally conducted premature atrial stimuli (extrasystoles). An exponential relationship between S-R and R-S intervals is fitted to the data by linear regression analysis (fig.6).

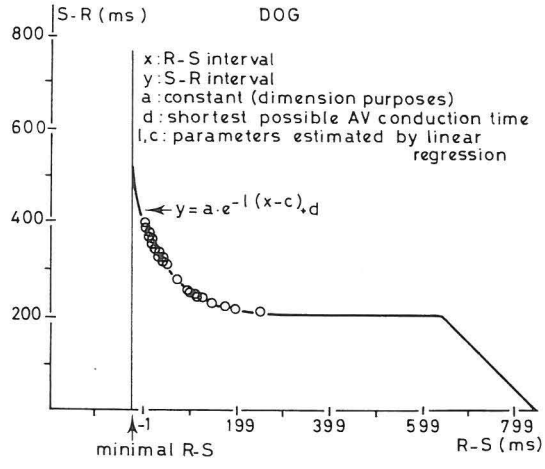

FIG. 6
Fitted LPC for normally conducted premature atrial stimuli. (for explanation, see text)

The natural logarithm is taken from the S-R interval decreased by the shortest possible AV conduction time. This is the dependent variable (the R-S interval is the independent variable) for linear regression analysis. The equation for the LPC then becomes

$$y = a \cdot e^{-l(x-c)} + d \qquad \text{(eq. 1)}$$

in which
- x: R-S interval [ms]
- y: S-R interval [ms]
- a: constant, needed for dimension purposes [ms]
  in our model a is equal to 1
- d: shortest possible AV conduction time,
  estimated from steady-state stimulation
  with the basic stimulation interval [ms]
- l: parameter estimated by linear regression [1/ms]
- c: parameter estimated by linear regression [ms]

R-S = 0 corresponds with an atrial stimulus applied on the moment of the R-wave resulting from the previous stimulus. A negative R-S value indicates that a stimulus is applied before the ventricular response of the previous stimulus has been generated. When a negative R-S value is smaller than the minimal

R-S value, a ventricular response does not occur. This minimal R-S value is estimated by -10 % of the shortest possible AV conduction time (d) (see discussion).

The functional refractory period (FRP) of the AV node-His system yielded by the model can be derived from equation 1. If xc and yc are the coordinates of the point of contact of the tangent with slope -1 and the LPC, then

$$FRP = xc + yc$$

$$xc = (l * c + \ln(l)) / l \qquad \text{(eqs. 2)}$$

$$yc = a \cdot e^{-l(xc-c)} + d = a/l + d$$

(ln denotes the natural logarithm).

In our experimental set-up it was not possible to apply a stimulus at a fixed time after a QRS-complex, so we used the intervals between successive stimuli (S-S intervals) and the corresponding R-R intervals to compute R-S and S-R intervals according to the relations given in the legend to fig.2.

EXPERIMENTAL RESULTS

All dog experiments yielded similar results. For each dog the same model could be fitted with slightly different parameters. Model parameters for the six experiments are listed in table 1. For illustration purposes a representative experiment (dog A) was selected.

Step increase and step decrease in stimulation rate

Stimulation with intervals of 330 ms (fig.7b) took a longer time for AV conduction to become stable than stimulation with 350 ms intervals (fig.7a). No Wenckebach phenomenon was seen. In fig.7c the ordinates of □ and ○ depict the steady-state AV conduction times during sustained stimulation with intervals of 350 and 330 ms, respectively.

TABLE 1
Model Parameters for the Estimated Latency-Phase Curves

dog	l	l*c	c	d
A	0.0143	5.3594	374.78	201
n=24	(0.0141;0.0145)	(5.3381;5.3807)		
B	0.0137	5.5765	407.04	177
n=11	(0.0131;0.0144)	(5.5199;5.6332)		
C	0.0174	5.1911	298.34	154
n=22	(0.0168;0.0180)	(5.1536;5.2286)		
D	0.0158	5.1377	325.17	144
n=17	(0.0149;0.0166)	(5.0755;5.1999)		
E	0.0128	5.4197	423.41	150
n=15	(0.0122;0.0133)	(5.3496;5.4898)		
F	0.0142	5.5256	389.13	171
n=12	(0.0134;0.0151)	(5.4442;5.6069)		

TABLE 1
Model parameters for the estimated latency-phase curves in six dog experiments. n is the number of premature atrial stimuli used to estimate the latency-phase curve. (for explanation of the parameters l, c, and d, see text) Between parentheses the 95 % confidence intervals for the estimated parameters are given.

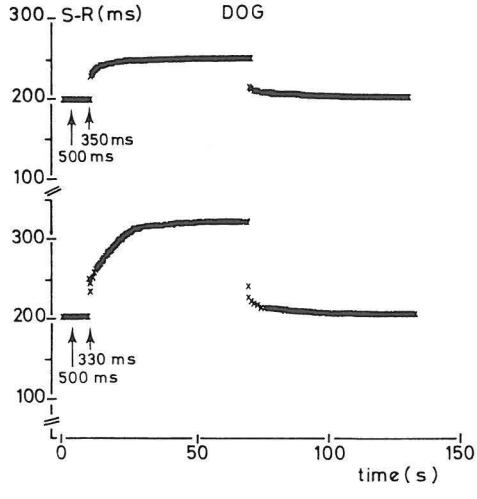

FIG. 7a DOG EXPERIMENT (top)
Adaptation of AV conduction versus time for step increase and decrease in stimulation rate. Step increase was to intervals of 350 ms and decrease to 500 ms.

FIG. 7b DOG EXPERIMENT (bottom)
Adaptation of AV conduction versus time for step increase and decrease in stimulation rate. Step increase was to intervals of 330 ms and decrease to 500 ms.

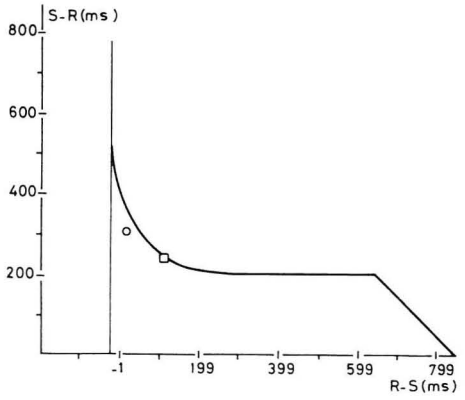

FIG. 7c DOG EXPERIMENT
□ : steady-state during stimulation with 350 ms;
○ : steady-state during stimulation with 330 ms. The solid line is the fitted LPC (fig. 6).

Postextrasystolic intervals

In fig. 8a, the ordinate of ○ is the AV conduction time for the extrasystolic stimulus and the ordinate of □ is the postextrasystolic AV conduction time. The postextrasystolic stimulation intervals are the intervals following the premature atrial stimulation intervals for which the LPC was derived. Their length is equal to the basic cycle length. In fig.8b S-R intervals are plotted versus R-S intervals for the postextrasystolic intervals.

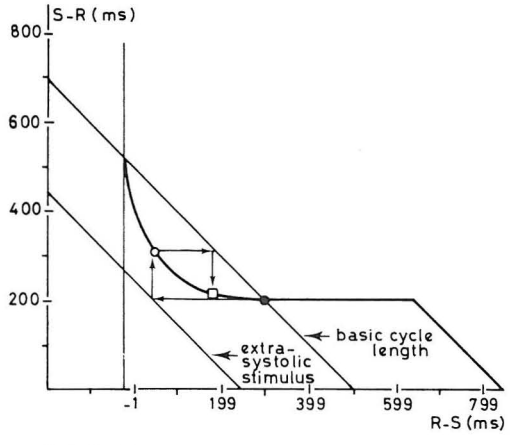

FIG. 8a DOG EXPERIMENT
○ : phase and latency for the extrasystolic stimulus;
□ : phase and latency for the postextrasystolic stimulus.

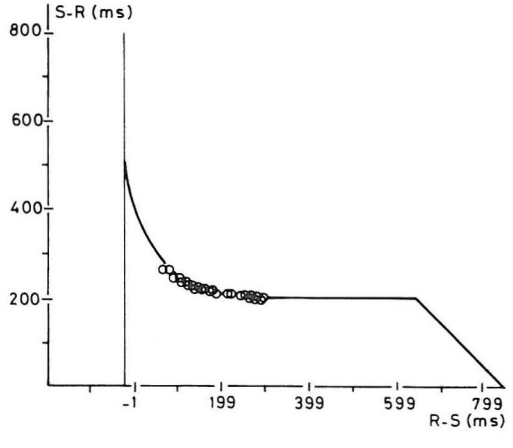

FIG. 8b DOG EXPERIMENT
S-R intervals versus R-S intervals for the postextrasystolic intervals (S-S = 500 ms).

R-R intervals versus R-S intervals

In fig.9 R-R intervals are plotted versus R-S intervals for the extrasystolic (●) and postextrasystolic (○) stimuli.

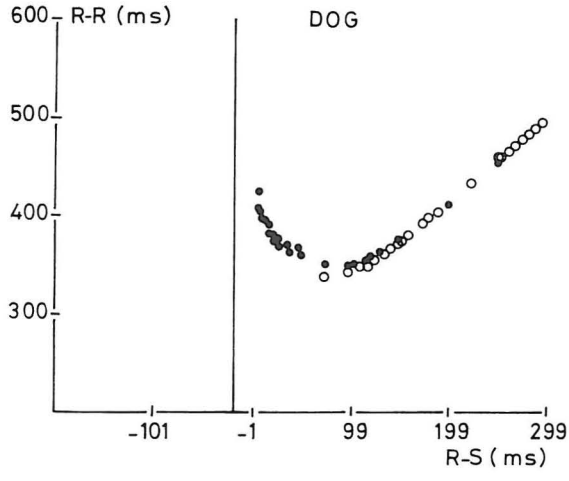

FIG. 9 DOG EXPERIMENT
R-R intervals versus R-S intervals for the extrasystolic (●) and postextrasystolic (○) stimuli.

DISCUSSION

The concepts of a biological oscillator and a LPC have been used to describe the conduction of impulses through the canine AV node.

A few remarks must be made with respect to the model. Firstly, the model yields expected or mean results ("expected" in statistical sense). Any "noise" caused by physiological phenomena (respiration, blood pressure, etc.) can not be simulated by the model in its present form. For that reason in the actual dog experiments the effects of fluctuations in autonomic influence were blocked. Secondly, during the experiments the dog's condition may change and this can cause changes in model parameters. And thirdly, the model describes the short-term adaptation of AV conduction time only.

Billette et al. (17) showed that cycle-length-dependent AV nodal delay occurs in the small N zone (18,19). Thus, the N cells may probably be considered as the part of the AV node that actually behaves as a biological oscillator.

Phase-transition curve versus latency-phase curve

Guevara & Glass (9) used a phase-transition curve (PTC) as a graphical representation of AV nodal response to atrial stimulation. In a PTC the new phase following a stimulus is plotted versus the old phase preceding the stimu-

lus. Normally, in both a PTC and a LPC, phase and latency are dimensionless units between 0 and 1. In this way different experiments as well as results derived with varying basic cycle lengths can be easily compared. Because our figures represent results from one dog in which only one basic cycle length has been applied, we used a LPC with phase and latency expressed as real time intervals. Thus, we are able to depict clearly the stimulation lines. Furthermore, such a LPC may be better understood in a cardiological environment. Nevertheless, a PTC and a LPC can be easily converted into each other.

Model parameters

In the present form of the model we chose the minimal R-S value equal to -10 % of the shortest possible AV conduction time. This estimate corresponds to the activation time of the NH cells (about 10 % of total AH time (18)). Because increment in conduction time and AV block occur in the N cells, the minimal R-S value can be thought to vary.

The maximal R-S and S-R values are determined by the intrinsic AV nodal rate, which we estimated to be two-thirds of the intrinsic rate of the sinus node (19). In the representative dog experiment we estimated the intrinsic AV nodal rate at 69.6 beats/min.

Step increase and step decrease

Step increase and decrease in stimulation rate yielded the same adaptation pattern of AV conduction times in the model and canine experiments, although the model reached a new steady-state faster. The observed Wenckebach phenomenon in the model results may be viewed as a form of intermittent behaviour of the oscillator (13). This phenomenon has not been observed in the dog experiment. An explanation could be a shortening of the refractory period of the AV node-His system as a result of the higher stimulation frequency (20).

R-R intervals versus R-S intervals

The plot of perturbed cycle length (R-R) versus phase (R-S) for the extrasystolic and postextrasystolic stimuli (fig. 9) is similar to those in forced biological oscillators as described by Glass et al. (21). We see a shortening of the cycle length relative to the intrinsic period of the AV node-His system. We were not able to stimulate sufficiently early in the phase to derive a possible lengthening of the cycle. The minimum of the curve corresponds with the functional

refractory period of the AV node-His system as derived in eqs. 2.

Conclusion

A deterministic, biological oscillator model of the canine AV node was able to describe and predict the ventricular response to extrasystolic and postextrasystolic atrial stimuli and to an increase and decrease in atrial stimulation frequency. The LPC is a useful graphical representation of the model. We expect that the human AV node may also behave as a periodically perturbed, biological oscillator.

ADDENDUM:

Some forms of ventricular tachycardias show a property resembling entrainment (22,23). Entrainment is the synchronization of the spontaneous frequency of a biological oscillator to a periodic influence of relatively small amplitude. This property was demonstrated for the sino-atrial node and the AV node in isolated rat hearts (24). The concept of the biological oscillator (relaxation oscillator) may contribute to understanding the origin of some ventricular arrhythmias.

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