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A TRANSFER FUNCTION MODEL FOR AV CONDUCTION IN THE HUMAN HEART

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1 INTRODUCTION

Contraction of cardiac muscle is triggered by depolarization of the cell membrane. The depolarization front is spread in a rapid coordinated fashion through the myocardium [1] and through a specialized conducting system of the heart. From the sinoatrial (SA) node, the normal pacemaker of the heart, the excitation wave spreads throughout the atria. At the base of the atria, the excitation wave enters a small group of specialized cells which form the atrioventricular (AV) node. This node and the bundle of fibres called the His bundle stemming from it, constitute the only conducting link between the atria and the ventricles. This ensures that excitation can only travel from atria to ventricles through the AV node. After leaving the AV node, the impulse travels along the bundle of His to the base of the papillary muscles and then spreads throughout the left and right ventricles. Little is known about the way the AV node conducts the impulses, about the possible influence of previous impulses and especially about the time intervals between these impulses. Earlier studies were done with isolated rat hearts (see Heethaar [2]) resulting in an empirical model that showed dependence of the time interval between a stimulus (S) and the resulting ventricular excitation (S-R interval) of, at most, five preceding stimulus intervals (S-S intervals). We made an effort to explain the conduction through the AV node during random stimulation by fitting a transfer function model to the S-S and S-R intervals.

2 METHODS

During cardiac catheterization and after informed consent, a patient's heart was stimulated via a bipolar stimulation catheter on the right atrium, thus eliminating the influence of the SA node. Time intervals between stimuli were random and followed a normal distribution. The mean and standard deviation of the chosen distribution were patient-dependent to avoid blocking in the AV node or escape beats from the SA node. Random intervals were chosen because of underlying clinical considerations that atrial fibrillation can be viewed as a series of random stimuli. The analog signals (stimulus and QRS complexes) were digitized with a sampling frequency of 400 Hz, stored on magnetic tape and analysed by computation of

- auto- and cross-correlation functions;
- transfer function models, according to Box and Jenkins [3].

Up till now three patients have been analysed, resulting in four series of observations.

3 STATISTICAL ANALYSIS

For the mathematical analysis the measured time intervals (in msec) were considered as equidistant events with amplitudes corresponding to the length of the intervals.

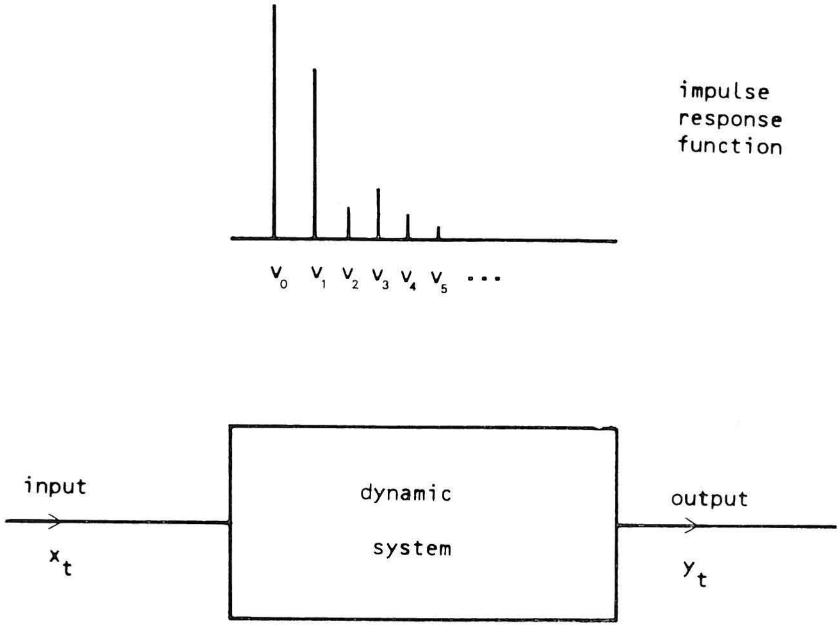

FIGURE 1 Input to, and output from a dynamic system.

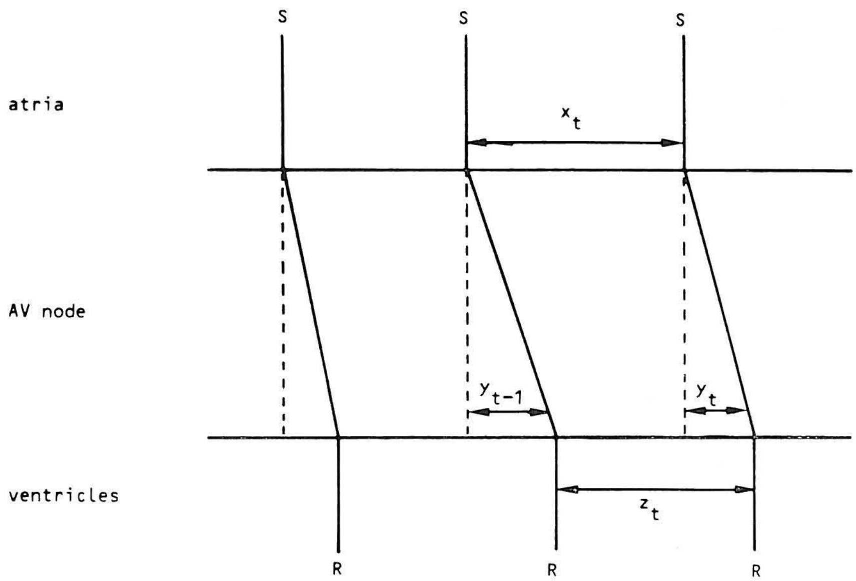

FIGURE 2 Schematic representation of AV conduction. x_t, S-S interval; y_t, S-R interval; y_{t-1}, preceding S-R interval; z_t, R-R interval.

3.1 *Auto- and Cross-correlation Function*

The auto-correlation function is a measure of the relation between succeeding observations of a variable. Likewise, the cross-correlation function measures the relation between succeeding observations of two variables.

3.2 *Transfer Function Model*

Suppose pairs of observations (x_t, y_t) are available of an input x and an output y for some dynamic system. x_t and y_t must be stationary processes, which can be derived by differencing of the series. If x_t and y_t are deviations from their respective means $\bar{x}$ and $\bar{y}$, the output deviation y_t can be represented as a linear aggregate of input deviations $x_t, x_{t-1}, x_{t-2}, \ldots$ in the form (Figure 1):

$$y_t = v_0 x_t + v_1 x_{t-1} + v_2 x_{t-2} + \ldots$$

or

$$y_t = (v_0 + v_1 B + v_2 B^2 + \ldots) x_t$$

or

$$y_t = v(B) x_t$$

(B is the backward shift operator, defined by $Bx_t = x_{t-1}$). The weights $v_0, v_1, v_2, \ldots$ are called the impulse response weights. When there is no immediate response of the output to the input, one or more of the initial v's will be equal to zero.

Theoretically, the impulse response function $v(B)$ is an infinite function and thus difficult to estimate. Therefore, and for reasons of parsimony of the parameters, the above mentioned relation between output and input can also be written as

$$\delta(B) y_t = w(B) x_{t-b}$$

in which

$$\delta(B) = (1 - \delta_1 B - \delta_2 B^2 - \ldots - \delta_r B^r)$$

$$w(B) = (w_0 - w_1 B - w_2 B^2 - \ldots - w_s B^s)$$

$$b = \text{lag parameter}$$

Now $v(B)$ is equal to the quotient of two finite functions $w(B)$ and $\delta(B)$ of the order respectively s and r, $v(B) = w(B)/\delta(B)$. These functions can be estimated (see Box and Jenkins [3]).

In practice, the system will be disturbed by noise, which corrupts the output y_t by an amount n_t. Thus, the model looks like:

$$\delta(B) y_t = w(B) x_{t-b} + n_t.$$

This noise n_t is assumed to be generated by an ARIMA-process (autoregressive integrated moving average process), statistically independent of the input x_t.

4 RESULTS

Initially we looked at the auto-correlation function of R-R intervals. The problem, however, was that R-R intervals contain more information than can be explained as resulting from the AV node, because an R-R interval also depends on the preceding S-R interval, as it satisfies the equation (Figure 2):

$$z_t = x_t + y_t - y_{t-1}.$$

So we decided to leave R-R intervals and look at S-R intervals and their relation to preceding S-S intervals. The auto-correlation function of the S-R intervals shows a clear relation between succeeding intervals (see, e.g., Figure 3). When the cross-correlation function between S-S and S-R

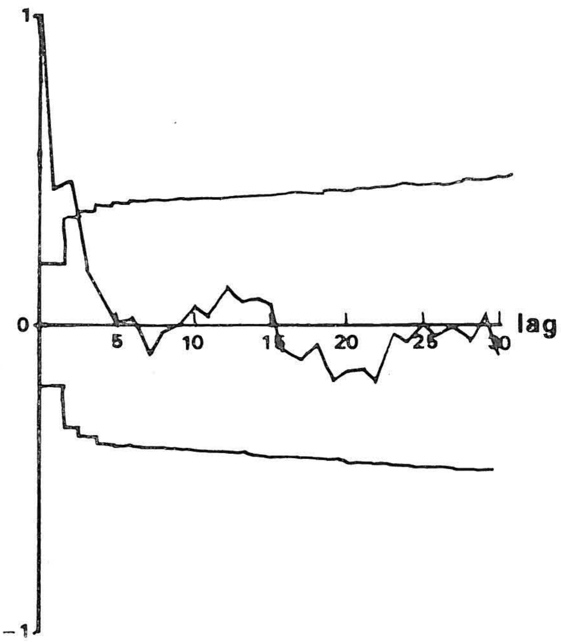

FIGURE 3 Autocorrelation function of S-R intervals with corresponding confidence bounds.

intervals is considered, a negative correlation coefficient can be seen at lag 0 and one or two less negative but significant coefficients at lags 1 and 2 (see, e.g., Figure 4).

These cross-correlation coefficients indicate a transfer function model with two or three impulse response weights and a lag parameter b equal to zero, i.e.,

$$y_t = v_0 x_t + v_1 x_{t-1} + v_2 x_{t-2} + n_t$$

Transfer function model identification and estimation of the four series of observations in all cases led to this type of model. Generally, we found n_t to conform to an autoregressive process of the form

$$\varphi(B) n_t = a_t,$$

in which a_t is uncorrelated white noise and $\varphi(B)$ is of the order two or three. For better understanding the above mentioned model can be rewritten as

$$\delta(B) y_t = w(B) x_t + n_t$$

or

$$\varphi(B)\delta(B) y_t = \varphi(B) w(B) x_t + a_t$$

and [after estimation of $\delta(B)$ and $w(B)$] as

$$\varphi(B) y_t = \varphi(B) v(B) x_t + a_t$$

In the case of two impulse response weights and two autoregressive noise parameters, this results in

$$y_t = \varphi_1 y_{t-1} + \varphi_2 y_{t-2} + v_0 x_t - (v_0\varphi_1 - v_1)\, x_{t-1} -$$

$$(v_0 \varphi_2 + v_1 \varphi_1) x_{t-2} - v_1 \varphi_2 x_{t-3} + a_t$$

Parameter values belonging to the four series can be found in Table I. Computer simulation of the model with the known stimulus series as input

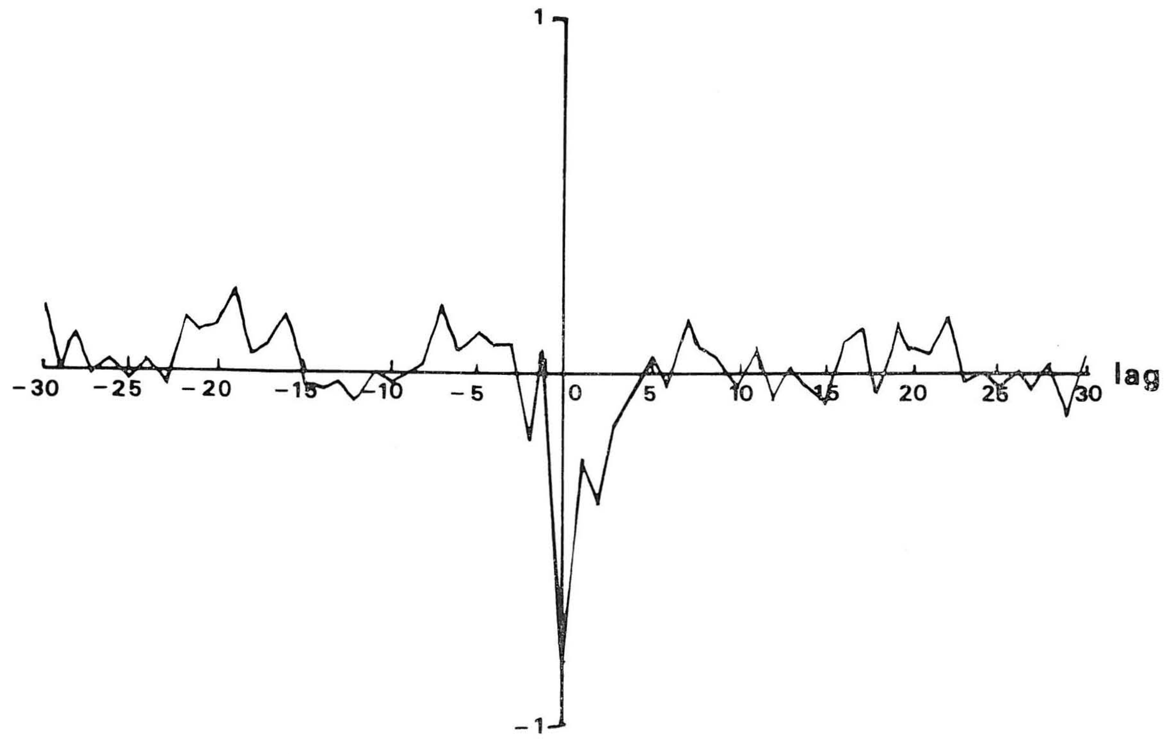

FIGURE 4 Crosscorrelation function of S-S and S-R intervals.

TABLE I
Parameters for the fitted transfer function models (3 patients; 4 series of observations)

Patient nr.	empirical S-S	empirical S-R	impulse response weights	noise parameters	stand. dev. of a_t
1 (n=106)	$\bar{x}$ =493.05 s_x = 56.38	$\bar{y}$ =253.01 s_y = 15.18	v_0=-0.2213 v_1=-0.0832 v_2=-0.0480	φ_1=0.5746 φ_2=0.3005	s_a=3.64
2 (n=202)	$\bar{x}$ =523.70 s_x = 32.84	$\bar{y}$ =289.61 s_y = 19.74	v_0=-0.4196 v_1=-0.1609 v_2=-0.0512	φ_1=0.7079 φ_2=0.2128	s_a=5.90
3^A (n=201)	$\bar{x}$ =458.72 s_x = 79.04	$\bar{y}$ =225.61 s_y = 4.57	v_0=-0.0387 v_1=-0.0270	φ_1=0. φ_2=0.2800 φ_3=0.2234	s_a=2.49
3^B (n=224)	$\bar{x}$ =480.44 s_x = 81.29	$\bar{y}$ =237.80 s_y = 5.30	v_0=-0.0527 v_1=-0.0244	φ_1=0. φ_2=0.1473 φ_3=0.	s_a=2.66

yielded theoretical S-R and R-R intervals with the same mean and standard deviation as the empirical found intervals.

5 DISCUSSION

By fitting a transfer function model to explain the relation between S-S and S-R intervals and thereby the conduction through the AV node in case of random stimulation, a model is fitted with known statistical properties. This is a great advantage over empirical models. The four series of observations belonging to three patients showed a relation between an S-R interval, one or two preceding S-R intervals and one or two preceding S-S intervals. Patient no. 3 (series 3a and 3b) shows a smaller range of S-R intervals than patients 1 and 2 and two impulse response weights instead of three. Nevertheless, the two series satisfy the same type of model. When we look at the residuals (i.e., the difference between the empirical and theoretical S-R interval), there still exists a slightly negative correlation between residuals and theoretical S-R intervals. This could possibly be explained by the knowledge that a long S-S interval in general will be followed by a short S-R interval and vice versa.

Further studies will concern more patients, as well as dogs and isolated rat hearts and also step response weights in transfer function models.

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