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Function of Atrioventricular Node Conduction: Hyperbolic Model

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Twenty four patients were subjected to an electrophysiologic clinical procedure. The conventional extrastimulus test was applied to verify the relation between conduction time increase through the atrioventricular node of the extrastimulus beat (ΔAH), and its preceding interval (A_1A_2). Following the least square root method the parameters of the hyperbolic model $\Delta AH \cdot A_1A_2 = m \cdot \Delta AH + n$ were adjusted. The correlation coefficients obtained and tested in all cases were very high and significant. From this hyperbolic equation it was possible to determine the equations for the effective refractory period ($ERP_e = m$) and functional refractory period ($FRP_e = ERP_e + n$). The theoretical values for refractoriness approached very closely those of the actually measured ERP and FRP, in all cases.

This model proved to be, in respect to adjustments and especially in calculating refractory periods, at least as good as the exponential model proposed previously by other authors.

The relationship between the conduction time of the atrioventricular node (AVN) (A_2H_2 interval) and their corresponding coupling interval (A_1A_2) is known as the curve of the AVN function (9). Changing the coupling of A_1A_2 by means of atrial pacing, the resultant curve (A_2H_2-A_1A_2) has been described qualitatively in canine and human hearts by several authors (1, 7, 14, 17, 18).

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The quantitative study of this phenomenon was initiated by HEETHAR *et al.* (4), who studied the variations of the P-R interval in relation to prior P-P intervals in rat hearts, isolated or *in situ*, according to the equation

$$g_t - g_{\infty} = (g_0 - g_{\infty})e^{-\lambda t}$$

FERRIER and DRESEL (1, 2) also applied an exponential model to define AVN conduction in isolated canine hearts. This model has recently been applied by TEAGUE *et al.* (16) in studying the human heart with normal AV conduction, and by the authors in both normal and pathologic hearts (9, 11).

In the present study the viability of a different model, a hyperbolic model, was considered, based on the equation

$$(A_1A_2)(\Delta AH) = m(\Delta AH) + n$$

Materials and Methods

Subjects. The study was carried out in 24 patients of both sexes (9 female, 15 male) from 18 to 77 years of age, the same group in which the prior study using an exponential model was performed (11), and, as with the latter study, the subjects were divided into 3 groups of 8 patients each according to the AV conduction state: Group I, subjects with normal AV conduction; Group II, patients with complete block of one branch; Group III, patients with first-degree AV block (table I). None of our subjects had type III or truncated conduction (18), or evidence of dual pathway in the AV node.

Instruments and Recordings. The His bundle electrograms were recorded by means of multipolar electrode catheters, and the conduction intervals and refractory periods were measured according to standard methods (10) using a GRASS 88 stimulator, with SIU-5 stimulus isolator unit generating square waves of 2 ms duration, and pacing was carried out at double threshold voltage. Impulses were amplified with an EMT 12 Elema-Schonander amplifier and the resulting hisiogram was recorded on a Mingograph 34-42 Elema-Schonander polygraph. The lower right auriculogram and the D_2 and V_1 standard ECG derivations were recorded simultaneously. Rate of paper flow was 100 mm/second.

The following intervals were measured: A_1A_2, H_1H_2, A_1H_1 and A_2H_2, where A_1 and H_1 represent the auriculogram and His bundle electrogram of the last paced beat in the basic series of 10-12 regular stimuli, and A_2 and H_2 correspond to those of the extrastimulus, the coupling of which varied from the longest intervals with atrial «capture» to the shortest in which the atrium was refractory. The rate of basic train series was the minimum possible to capture the atrium during the entire study.

Calculations. As with TEAGUE *et al.* (16), the AH intervals were measured as a specific expression of AV node conduction time. To calculate the increments in this interval (ΔAH) in relation to the variable coupling of A_1A_2, the minimum AH interval (A_0H_0) determined after the longest A-A intervals of the entire study for each patient was taken as point of reference, whether in sinus rhythm or the post-extrasystolic beat, in the same manner as FERRIER and DRESEL (2), who denominated it «basal conduction time». That is, $\Delta AH = (A_2H_2) - (A_0H_0)$.

Hyperbolic Model. The starting hypothesis is that the curve relating the variable A_1A_2 intervals (abscissae) with the resulting A_2H_2 intervals (ordinates) is convex from the coordinate origin. For long A_1A_2 intervals it is almost parallel to the abscissae, and when the values for A_1A_2 exceed the functional refractory period (FRP) and approach the effective (ERP) the curve tends to parallelism with the ordinate axis, so that it seems to have two asymptotes (fig. 1), one at A_1A_2 = ERP and the other at $A_2H_2 = A_0H_0$. If this hyperbola is equilateral, the product of the coordinates of its asymptotes will be constant, i.e.

$$(A_2H_2 - A_0H_0)(A_1A_2 - \text{ERP}) = K$$

Equation I

If $\Delta AH = A_2H_2 - A_0H_0$ then

$$\Delta AH \cdot A_1A_2 = \text{ERP} \cdot \Delta AH + K$$

Equation II

Given that, in each case, the values for $\triangle AH$ and A_1A_2 can be determined, and thence their product ($\triangle AH \cdot A_1A_2$), these values would then correlate with those corresponding to $\triangle AH$ which is the mathematical form of the model to be verified.

If the values for $\triangle AH$ are determined for each variable A_1A_2 interval and their product is called y ($= \triangle AH \cdot A_1A_2$) and $\triangle AH$ x, then equation II *becomes* $y = mx + n$ corresponding to a straight line whose slope m coincides with the ERP. From this equation the estimated value of the functional refractory period (FRP) can also be deduced using the calculations explained in appendix I.

Verification of the Model. The model can be verified in the following ways:

a) by proving the accuracy of the linear adjustment between the pairs of values $\triangle AH \cdot A_1A_2$ and $\triangle AH$ in each case;

b) by checking the degree of linear correlation existing between the estimated FRP and ERP (FRP_e, ERP_e) according to the equation adjusted in each case, and its corresponding measured values (FRP_m, ERP_m). The more significant the preceding linear correlations are, the better the adjustment, and thus, the model.

Interpretation of results. The study of the correlations was carried out using Pearson's method, usual for this type of study (15).

Table I. *Values for the minimum AVN aconduction time (A_0H_0) and the AVN refractory periods in the 24 cases studied.*
Values are expressed in miliseconds. F = females. M = males.

Group	Sex	Age	ERPAVN	FRPAVN	A_0H_0
I: Normal					
1	F	46	290	390	65
2	M	50	325	350	54
3	M	55	385	512	95
4	F	44	280	440	80
5	M	18	285	405	75
6	M	34	410	500	54
7	F	47	345	470	64
8	F	22	260	420	59
II: Block of one branch					
9	F	45	365	405	68
10	M	62	330	510	119
11	M	77	285	462	95
12	M	77	492	592	72
13	F	68	360	540	109
14	M	69	390	440	69
15	M	29	495	512	64
16	M	53	270	380	78
III: AV block, first degree					
17	F	61	345	475	95
18	M	41	530	765	154
19	M	53	350	415	90
20	M	67	375	460	105
21	M	73	435	575	145
22	F	29	515	640	124
23	F	54	415	640	99
24	M	21	670	845	159

Results

The minimum AVN conduction time values (minimum AH interval = A_0H_0) and the AVN refractory periods (ERPAVN and FRPAVN) measured in the 24 cases studied are shown in table I.

The linear correlation between $\triangle AH \cdot A_1A_2$ ($= y$) and $\triangle AH$ ($= x$) was studied for the set of pairs of values (N) obtained in each case by causing A_1A_2 to vary between the widest possible margins. The results obtained for Pearson's linear correlation coefficient (r) and the probability that they are merely accidental (p), as well as the parameters of the linear regression equation (slope = m; ordinate at origin = n) are detailed in table II. Figure 1 illustrates one case of the series in which the perfect applicability of the hyperbolic function may be noted.

Table III-*A* is a summary of the mean and standard error values of the correlation and the regression coefficients in each of the three groups studied.

Table II. *Verification of the accuracy of the linear adjustement between the pairs of values $\triangle AH$.*

A_1A_2 and $\triangle AH$ in each case ($x = \triangle AH$; $y = A_1A_2 \cdot \triangle AH$; Technique: extrastimuli). Abbreviations: N = number of cases; r = regression coefficient; p = significativity. The values of «slope» express the slope and deviation of the slope.

Group	N	r	p	Slope	Ordinate
I: Normal					
1	12	0.96	< 0.001	249.3 ± 52.5	6,481
2	18	0.97	< 0.001	339.7 ± 46.5	528
3	18	1.00	< 0.001	381.0 ± 17.8	2,962
4	22	0.99	< 0.001	272.4 ± 21.3	6,683
5	26	1.00	< 0.001	266.4 ± 7.3	3,409
6	31	1.00	< 0.001	384.1 ± 9.0	3,509
7	17	0.99	< 0.001	236.7 ± 22.3	20,071
8	33	0.98	< 0.001	260.3 ± 19.3	5,074
II: Block of one branch					
9	19	0.99	< 0.001	351.6 ± 25.5	1,528
10	19	0.93	< 0.001	288.9 ± 59.2	18,703
11	18	0.99	< 0.001	254.9 ± 21.3	11,578
12	19	0.99	< 0.001	465.6 ± 38.0	6,967
13	23	0.94	< 0.001	327.1 ± 53.0	12,061
14	22	0.82	< 0.05	174.1 ± 57.5	27,469
15	24	0.97	< 0.001	405.0 ± 45.6	3,975
16	24	1.00	< 0.001	259.8 ± 10.2	2,813
III: AV block, first degree					
17	20	0.96	< 0.001	296.1 ± 41.0	10,931
18	7	0.80	< 0.05	435.6 ±377.8	58,501
19	23	1.00	< 0.001	326.9 ± 10.8	3,867
20	20	1.00	< 0.001	353.3 ± 16.7	4,999
21	30	0.99	< 0.001	409.9 ± 19.6	8,653
22	13	0.98	< 0.001	459.2 ± 62.3	16,263
23	35	0.99	< 0.001	412.1 ± 17.0	12,308
24	16	0.94	< 0.001	804.7 ±162.6	11,364

Table III. *Average of correlation parameters and verification of the accuracy of ERP and FRPAVN.*

Average values ± standard error. Abbreviations: y = measured value; x = estimated value; N = number of cases; r = linear correlation coefficient; p = significance of r in respect to zero; m = slope; n = ordinate at origin. * Where $\triangle AH$ = 200 m/s.

A) *Mean of correlation and linear regression parameters in each of three groups studied.*

Group	N	r	Slope	Ordinate
Normal	8	0.99 (± 0.01)	298.7 (± 21.2)	6,090 (± 2,120)
Block one branch	8	0.95 (± 0.02)	315.9 (± 32.6)	10,637 (± 3,143)
AV block first degree	8	0.96 (± 0.02)	437.2 (± 56.1)	15,861 (± 6,253)

B) *Linear regression and correlation coefficients between estimated and measured ERPAVN and FRPAVN values.*

y	x	N	r	p	m	n
ERP_m	ERP_e	24	0.88	< 0.001	0.71 ± 0.17	136
FRP_m	FRP_e	24	0.95	< 0.001	0.85 ± 0.12	126
ERP_m	ERP*	24	0.92	< 0.001	0.67 ± 0.13	116

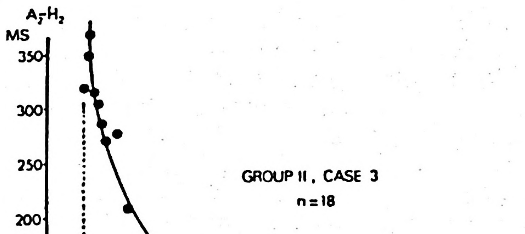

Fig. 1. *Relation between A_1A_2 (abscissae) and A_2H_2 intervals (ordinates) of one of the 24 cases studied selected at random (Case 3, Group II, 11), in which the measured ERP_m value (effective refractory period, measured) and the A_0H_0 value are represented as asymptotes, as well as the point corresponding to the FRP_m (functional refractory period, measured).*

If the values for ERP and FRP are calculated as described, starting from the linear regression equations (ERP_e and FRP_e), and these values are correlated with the corresponding measured values in each case, the results obtained are those shown in table III-*B*.

In a previous work (11) the ERP was calculated using an exponential model, introducing the hypothesis that ΔAH usually reaches values of around 200 ms. If this figure is applied to the hyperbolic model studied here, the correlation and regression coefficients shown in table III-*B* are obtained for the effective refractory period calculated in this manner (ERP*).

Figure 2 represents the individual measured and calculated values of the refractory periods as well as the lines of identity (broken lines) and those which express the linear regressions (solid lines) shown in table III-*B*.

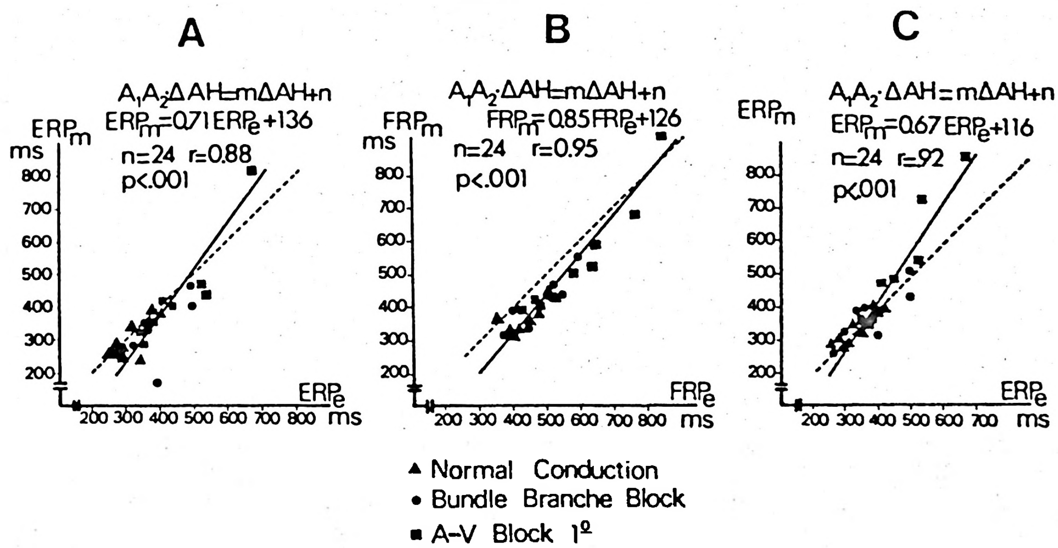

Fig. 2. *The points correspond to the pairs of values in each case of the parameters measured (ordinate) and estimated (abscissae) as explained in the text, and the straight line is the linear correlation.*

Broken line is the line of identity. *A* and *B* represent the regression $ERP_m \rightarrow ERP_e$ and $FRP_m \rightarrow FRP_e$ obtained by the hyperbolic model. In *C* the ERP_e was obtained by and exponential model, assuming that ΔAH = 200 ms (see text).

Discussion

HEETHAR *et al.* (4, 5), in studying AVN conduction time in isolated or *in situ* rat hearts, measured the ECG P-R interval and related this to the preceding P-P interval, showing that a sudden rise or fall of this interval produced a final lengthening of the P-R interval, preceded by several adaptation beats. This adaptation followed an exponential course. They also found that the responses to random atrial stimuli could be explained using this model.

FERRIER and DRESEL (1) used dog hearts and substituted the P-R interval for the A-H interval, which more accurately expresses AVN conduction time, and found that the relation between the delay produced in the AVN (ΔAH) and the prematurity of the stimulus (A_1A_2) can be expressed by an exponential equation of the following type:

$$\Delta AH = A \cdot e^{-B \cdot A_1A_2}$$

or its Napierian logarithmic equivalent,

$$\log_n \Delta AH = \log_n A - B \cdot A_1A_2$$

The latter equation is easier to manage, as it permits simple interpolation of the ΔAH and A_1A_2 relation by Pearson's method, easily establishing the correlation and regression coefficients. This requires the prior determination of ΔAH as a difference between A_2H_2 and the AH interval to be used as point of reference. The latter authors (1, 2) demonstrated that if this AH interval is the minimum possible (A_0H_0), the «frequency factor» which they denominate «fatigue») can be eliminated. The slope (B) and the ordinate at the origin ($\log_n A$) seem then to be related to the underlying functional conditions of the AVN, which would not be affected by other physiological conditions such as change in pacing frequency.

More recently, TEAGUE *et al.* (16), in a study of 50 normal cases, showed that this exponential model is also applicable to the normal human heart, and that in this case it is not restricted to long coupling intervals, as HEETHAR *et al.* (4, 5) had assumed. This model has the advantage of being easy to interpolate by analytical methods (least square root) or even graphically, as the former authors suggest (16), using semilogarithmic paper on which the points are aligned along a straight line; once this line is plotted it is easy to estimate graphically its two parameters (B and $\log_n A$).

In an earlier study, the exponential model was applied to 23 subjects, both normal and pathologic (9), using as basal AH intervals those corresponding to the series of 10-12 regular beats preceding the extrastimulus; this model was again applied in the 24 cases of the present study, using the minimum AH (A_0H_0) for the entire plotting (11). In both studies the conclusion arrived at was that the model is applicable not only to human hearts with normal AV conduction but also to those to human hearts with normal AV conduction but also to those with pathologic AV conduction.

The model here presented is a hyperbola which correlates the same variables (ΔAH, A_1A_2), according to the equation

$$\Delta AH \cdot A_1A_2 = m(\Delta AH) + n$$

which also takes the form of a straight line, thereby offering the same advantage in regard to analytical and graphyc study as the logarithmic form of the exponential model.

All correlation coefficients in this hyperbolic model are statistically very significant and are slightly higher, compared with the coefficients of the exponential model obtained from the same data and subjects (11).

The parameters in current clinical use to define the properties of AVN conduction are conduction time (AH) and the functional and effective refractory periods (FRP and ERP). TEAGUE *et al.* (16) demonstrated that the FRP could be derived from the exponential model and found in 13 selected cases (out of a total of 50) that the estimated values (FRP_0) correlated significantly with the corresponding measured values (FRP_m) (mean $r = 0.85$; $p < 0.001$; $N = 13$). Subsequently, an even better correlation was obtained (9) using the same exponential model (mean $r = 0.78$; $p < 0.001$ for 21 of the 24 cases). This would seem to indicate that the FRP data is not always estimated to an acceptable degree of accuracy with the exponential model. In the hyperbolic model the coefficient of the linear correlation between FRP_0 and FRP_m is not only larger (mean $r = 0.95$; $p < 0.001$), but also includes all the cases ($N = 24$) (table III-*B*).

TEAGUE *et al.* did not determine the ERP directly from their model, as this is not possible. The present study utilizes the hypothesis that AH usually has a maximum value in the neighborhood of 200 ms, and assigns it this value in the equation, thereby rendering estimated values for ERP (ERP_0) which, in 23 out of 24 cases, correlated significantly with the actual measured ERP (ERP_m), giving a mean r coefficient of 0.78 ($p < 0.001$; $N = 24$) for the exponential model. In applying the same hypothesis to the hyperbolic model, coherent values were obtained in all 24 cases, and the linear correlation between the estimated and measured values was very significant ($r = 0.92$; $p < 0.001$; $N = 24$; table III-*B*). The hyperbolic model has the additional advantage of making possible a direct calculation of the ERP without the use of the 200 ms hypothesis, since the value of ERP_0 is that of the slope of the straight line ($ERP_0 = m$); thus the correlation of this value with the measured ERP gives an average $r = 0.88$ ($p < 0.001$; $N = 24$; table III-*B*). Consequently, the hyperbolic model may well be superior to the exponential model, particularly in the determination of values for refractory periods (ERP, FRP), calculable to a high degree of accuracy in all cases, proving that the hyperbolic model, particularly in the determination of values for refractory periods (ERP, FRP), calculable to a high degree of accuracy in all cases, proving that the hyperbolic model «contains» the information deducible from these parameters.

The acceptance of the hyperbolic model as well as the exponential model suggests that AVN conduction (excluding cases with type III or truncated conduction, indicating possible dual pathway, in which the applicability of the models has not been studied), in spite of having been described as «inhomogenous» (17, 18), offers a general relation between input and output of AVN which 1) can be reproduced, 2) can be described mathematically in a simple manner and quantified using only two factors ($\log_n A$ and B in the exponential model; *m* and *n* in the hyperbolic model), and 3) can be employed to define any physiologic, pharmacologic, or pathologic effect, whether instantaneous or evolutional. A further advantage of the mathematical model is its role in the study of analogue simulators (3, 6, 8, 19).

Acknowlegment

We express our gratitude to Mr. V. Ruiz Ros for his inestimable technical collaboration.

APPENDIX I

Functional Refractory Period

The equation proposed is

$$\Delta AH \cdot A_1A_2 = m \cdot \Delta AH + n \qquad [I, 0]$$

where

$$\Delta AH = A_2H_2 - A_0H_0 \text{ and } m = ERP_0$$

By definition, the functional refractory period (FRP) is that period for which H_1H_2 is minimal. The function which defines H_1H_2 in respect of A_1A_2 is

$$H_1H_2 = A_1A_2 - A_1H_1 + A_2H_2 \qquad [I, 1]$$

If it is derived in respect of A_1A_2 and the H_1H_2 derivative is assigned a value of zero, the result is a condition wherein H_1H_2 is minimal. Since A_1H_1 is constant,

$$\frac{d(H_1H_2)}{d(A_1A_2)} = 0 = 1 + \frac{d(A_2H_2)}{d(A_1A_2)}$$

$$\text{or } \frac{d(A_2H_2)}{d(A_1A_2)} = -1 \qquad [I, 2]$$

Now, deriving [I, 0] in respect of A_1A_2,

$$\Delta AH + \frac{d(\Delta AH)}{d(A_1A_2)} \cdot A_1A_2 = m \cdot \frac{d(\Delta AH)}{d(A_1A_2)}$$

Substituting the value [I, 2]:

$$\Delta AH - A_1A_2 = -m$$

$$A_1A_2 = \Delta AH + m \qquad [I, 3]$$

From equation [I, 0] it can be deduced that $\Delta AH = \frac{n}{A_1A_2 - m}$, which value is substituted in [I, 3], and knowing that under these conditions $A_1A_2 = FRP_e$ and $m = ERP_e$, then

$$FRP_e = \frac{n}{FRP_e - ERP_e} + ERP_e$$

thence,

$$FRP_e^2 - 2ERP_e FRP_e + ERP_e^2 - n = 0$$

$$FRP_e = ERP_e \pm \sqrt{n} \qquad [I, 4]$$

of whose two resultant values the one corresponding to the branch of the hyperbola in question is

$$FRP_e = ERP_e + \sqrt{n}$$

Resumen

En 24 pacientes se realizó una exploración electrofisiológica clínica. Mediante el test del extraestímulo auricular se analizó la relación entre el incremento del tiempo de conducción del nodo auriculoventricular en el latido del extraestímulo (ΔAH) y el intervalo precedente (A_1A_2). Por medio del método de los mínimos cuadrados, se ajustaron los parámetros al modelo hiperbólico propuesto:

$$\Delta AH \cdot A_1A_2 = m \cdot \Delta AH + n$$

Los coeficientes de correlación obtenidos fueron en todos los casos, muy altos y significativos. De esta ecuación hiperbólica se pueden deducir las ecuaciones correspondientes al período refractario efectivo ($ERP_e = m$) y al período refractario funcional ($FRP_e = ERP_e + n$). Los valores teóricos así obtenidos alcanzan gran correlación con los ERP y FRP medidos, en todos los casos.

Este modelo se muestra al menos similar, en los ajustes y especialmente en la deducción de los períodos refractarios, al modelo exponencial previamente propuesto por otros autores.

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