The Relationship between Atrioventricular Nodal Refractoriness and the Functional Refractory Period in the Dog

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SUMMARY We studied the relationship between the atrioventricular nodal functional refractory period (FRP) and refractoriness by mathematical analysis and by measurement during antegrade Wenckebach cycles in 16 dogs. The FRP relates directly to the conduction time of the control beat, and inversely to the coordinates of the point on the $A'\cdot H'$ vs. $A\cdot A$ refractory curve where the slope is $-1$. The FRP can vary without any change in refractoriness as measured by the effective refractory period (ERP) or the refractory curve. In 16 dogs the ERP and the FRP were measured during 4:3 Wenckebach cycles. Because of changes in the control conduction times, the FRP declined and did not reflect the progressive increase in refractoriness recorded during Wenckebach cycles. The FRP is a complex parameter and does not reliably measure refractoriness.

Since the original description by Krayer (1951), the functional refractory period (FRP) has been used as an index of refractoriness in the atrioventricular (AV) node (Moe et al., 1956 and 1965). Although changes in the FRP usually parallel changes in other measures of refractoriness, inconsistencies between the FRP and the effective refractory period (ERP) with cycle length changes have been reported (Cogin et al., 1973; Denes et al., 1974). Recently, we have studied AV nodal Wenckebach cycles and found that during Wenckebach cycles the AV node progressively increases its refractoriness in discrete steps (Simson et al., 1978). The FRP did not reflect changes in refractoriness as measured by conduction time or ERP. This paper evaluates the relationship between the FRP and other measures of refractoriness using theoretical analysis and experimental results recorded during Wenckebach cycles.

Methods

Experiments were performed in 16 adult mongrel dogs of either sex weighing 10-15 kg and anesthetized with sodium pentobarbital (30 mg/kg, iv). The dogs were ventilated by a positive pressure respirator, and a right thoracotomy was performed. Body temperature was maintained with a heating blanket. A 0.9% saline solution (10 ml/kg per hour) was administered throughout the experiment. The cervical vagi were cut and the stellate ganglia removed. Close bipolar plunge electrodes were used to record simultaneously from the low right atrial septum, the His bundle, and the low left ventricular septum at the site of earliest ventricular activation. The electrode amplifiers (Bloom Associates) had a 40-500 Hz bandpass and a noise level of less than 5 μV (rms). A lead II electrocardiogram was monitored continuously. Bipolar plunge electrodes were applied to the right atrial appendage to pace the hearts; the stimulus was 4 msec long and twice the voltage threshold.

The basic format of the experiments was to induce 4:3 Wenckebach periodicity by rapid atrial pacing and then to insert a test stimulus after various beats of the Wenckebach cycle. A stimulator was developed which could reliably insert a test stimulus after any preselected beat in the Wenckebach cycle as a substitute for the basic pacing stimulus. A detailed description of the stimulator has been published (Simson et al., 1978).

Computer-based instrumentation was developed to detect, time, and analyze statistically the electrophysiological signals on line while the experiment was proceeding (Simson et al., 1978). The instrumentation was based on a Hewlett-Packard 9820A computer and was capable of measuring electrophysiological signals with a resolution of 0.1 msec.

The analog data and the signals from the computer instrumentation were recorded on magnetic tape using a Honeywell 5600C FM tape recorder. The data were recorded later on 35-mm film at a film speed of 200 mm/sec and projected onto a Hewlett-Packard 9864A digitizer board. To verify the electronic data analysis system, appropriate samples of the data were analyzed with the digitizer board and computer. The resolution of this system was 50 μsec.

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Experimental Protocol

Before the experiments began, the stability of the electrogram configurations was tested by evaluating the reproducibility of A-H conduction intervals during atrial pacing at a basic cycle length of 350–450 msec. Electrodes were readjusted until reproducible and stable signals were obtained, and a standard deviation of less than 1% was achieved for 20 consecutive A-H intervals. Stability of the electrograms during premature beats was studied by recording them on the storage oscilloscope.

During studies of the Wenckebach cycles, a test atrial response (A') was evoked at different test intervals (A-A') which were longer or shorter than the basic cycle length. Refractory curves for all beats were recorded by successively inserting the same atrial test interval after each beat in the cycle and measuring the resulting atrial to His bundle (A'-H) conduction time for the test beat. For every test interval located after any given beat of the cycle, six A'-H' intervals were recorded. At least four control Wenckebach cycles were allowed between each test stimulus. Each beat of the Wenckebach cycle was tested with the same test interval before the test interval was changed.

The ERP, defined as the longest atrial test interval which was not conducted, was determined to the nearest millisecond. The test interval was incremented by 5 msec until the FRP was measured for all beats. The FRP is the minimal interval between the basic and test His bundle electrograms (H-H') achieved during testing. Further details of the protocol of these studies have been published (Simson et al., 1978).

The FRP also was studied with a computer simulation model, using a Hewlett-Packard 9825A desk top computer and a 9872A plotter. The refractory curve (A'-H' vs. A-A') for the AV node was modeled by the equation

\[ A'-H' = \frac{1000}{(A-A') - 230} + 60. \]

This equation approximated results achieved in the dog heart during testing with premature stimuli.

Statistical comparison were made by Student’s t-test and the Fischer exact test.

Results

Analysis of the Functional Refractory Period

The antegrade refractoriness of the AV node is determined by pacing at a basic cycle length, intermittently inserting a test atrial beat, and noting the resulting conduction time of the test beat through the AV node. The refractory curve is a plot of the conduction time of the test beat, the A'-H' interval, vs. the atrial test interval, the A-A' interval. Figure 1A represents a computer-generated curve in which a hyperbolic function, chosen to represent typical results recorded in the canine AV node, was used as a model for the refractory curve.

The ERP is the longest atrial test interval at which the test atrial beat fails to conduct. The FRP is defined as the minimal H-H' interval which is achieved during testing with premature atrial beats. The FRP is most easily seen by plotting the H-H' interval against the atrial test interval (A-A') as shown in Figure 1B. The FRP is the H-H' interval at the nadir, the point where the slope equals zero, or:

\[ \text{FRP} = H-H', \quad \text{when} \quad \frac{d(H-H')}{d(A-A')} = 0. \]  (1)

By definition, the H-H' interval equals the atrial test period (A-A') plus the conduction time of the test beat (A'-H') minus the conduction time of the control beat (A-H):

\[ H-H' = A-A' + A'-H' - A-H. \]  (2)

Differentiating Equation 2:

\[ \frac{d(H-H')}{d(A-A')} = \frac{d(A'-H')}{d(A-A')} + 1. \]

The first derivative of the control conduction time (A-H) is zero, since, by experimental design, it is constant. From the last equation, \( \frac{d(A'-H')}{d(A-A')} = 0 \), when \( \frac{d(A'-H')}{d(A-A')} = -1 \). Combining this result with Equation 1, and substituting in Equation 2:

\[ \text{FRP} = A-A' + A'-H' - A-H, \quad \text{when} \quad \frac{d(A'-H')}{d(A-A')} = -1. \]  (3)
FUNCTIONAL REFRACTORY PERIOD/Simson et al.

Expressing the FRP in this manner reveals that it occurs at an atrial test interval where the refractory curve has a slope of -1, as shown in Figure 1. One can graphically solve for the FRP from the refractory curve by noting the coordinates of the point where the slope is -1 and the control conduction time, which is the point on the curve where the atrial test interval equals the basic cycle length. Solving Equation 3 will then give the FRP.

Equation 3 shows that the FRP is a complex parameter with multiple determinants. The FRP depends on the shape and configuration of the refractory curve for the test beat and on the conduction time of the control beat. The FRP does not accurately reflect refactoriness of the AV node as defined by the ERP or the refractory curve. A computer simulation experiment illustrates this point. Assume there is a hypothetical AV node whose refractoriness is constant under all experimental conditions, and is depicted by the refractory curve in Figure 2A. In Figure 2B are the H-H' curves for the AV node under two experimental conditions. Curve 1 was produced at the basic cycle length of 380 msec and curve 2 at a basic cycle length of 270 msec. Despite constant refactoriness of this hypothetical node, the FRP changes with different basic cycle lengths, reflecting a change in the control conduction time. At the longer basic cycle length, the FRP is longer (287 msec) than at the shorter basic cycle length (268 msec). Figure 2C depicts the result of determining the FRP over a range of basic cycle lengths. The curve is the inverse of the refractory curve (Fig. 2A), since the control conduction time is subtracted when the FRP is determined (Eq. 3).

The Functional Refractory Period during Wenckebach Cycles

The FRP was studied during antegrade 4:3 Wenckebach cycles produced in 16 dogs by rapid atrial pacing. Refractory curves were recorded by using a stimulator that could insert a test stimulus of variable timing after any preselected beat of the cycle. Figure 3A shows the results of a typical experiment. On the horizontal axis is the atrial test interval, the A-A' interval. On the vertical axis is the conduction time through the AV node for the test beat, the A'-H interval. Curve 1 was recorded when the test stimulus was inserted as the first beat of the cycle, that is, after the fourth beat of the preceding cycle. Curves 2, 3, and 4 were recorded when the test stimulus was inserted as the second, third, or fourth beat of the cycle, respectively.
third, or fourth beat of the cycle. Each point represents the mean of six observations.

Figure 3A demonstrates that the AV node becomes progressively more refractory as the 4:3 Wenckebach cycle proceeds. The conduction time increases from beat 1 through beat 4 for any given test interval shown on Figure 3A (P < 0.001). The ERP also increases as the cycle advances. The ERP after the blocked beat (the fourth beat) is shorter than the ERP for any subsequent beat. The ERP after the fourth beat lasts until the point on curve 1 which has the minimal A–A' interval; earlier test beats were blocked.

The ERP after the first conducted beat (214 msec) is longer than the ERP after the block beat (187 msec), and the ERP after the second beat is longer still (233 msec). The ERP following the third beat (246 msec) exceeds the basic cycle length (237 msec); hence the next beat falls within the ERP following the third beat, and it blocks. The fourth beat would conduct if the test interval were longer than the basic cycle length and the ERP after the third beat. Refractory curves were recorded in 16 dogs, and they were similar to the one depicted in Figure 3A.

In Figure 3B the H–H' intervals are plotted against the atrial test interval for the same experiment as shown in Figure 3A. Only three curves are shown since the fourth or blocked beat has no His bundle potential associated with it. The FRP is numbered after the preceding beat. Figure 3B demonstrates that the FRP decreases as the cycle proceeds. The FRP following beats 1, 2, and 3 are 264, 249, and 244 msec, respectively. In 4:3 Wenckebach cycles the AV node repetitively cycles through four distinct stages of increasing refractoriness as marked by the four refractory curves (Fig. 3A); the FRPs (Fig. 3B), recorded simultaneously, fail to reflect the increasing refractoriness.

In Figure 4A the relationship for all dogs between the ERP and the basic cycle length for each beat of the 4:3 Wenckebach cycles is shown. On the vertical axis, the ERP is normalized against the basic cycle length; the basic cycle length was subtracted from the ERP. On the horizontal axis is the beat number. After the blocked beat (the fourth beat), the ERP is shorter than after any subsequent beat. In every dog the ERP following beats 1–3 progressively increases. After the third beat the ERP is longer than the basic cycle length by a mean of 14.0 msec, and the next beat blocks.

Figure 4B shows the relationship between the FRP and the basic cycle length during 4:3 Wenckebach cycles. On the vertical axis is the FRP normalized against the basic cycle length. Only three beats are shown since there is no FRP following the fourth or blocked beat. In all dogs the FRP decreased from beat 1 to beat 2 (P < 0.001). In eight of 16 dogs, the FRP decreased from beat 2 to beat 3. In all experiments the progressive increase in refractoriness, as marked by an increase in the ERP as the cycle advanced, was not reflected in the FRP.

In Table 1 the changes in the FRP from beats 1 to 2 and beats 2 to 3 are analyzed in terms of the changes in the determinants of the FRP (Eq. 3). The A–A' interval and the A'–H' interval are the coordinates of the point on the refractory curve where the slope is $-1$. The A–H interval is the control conduction time. All results are mean values. There was an increase in the A–A' interval and a smaller increase in the A'–H' interval within both sets of beats; the increase in both parameters tends to cause an increase in the FRP. There was, however, a large increase in the conduction time of the control beats, and this caused a net decrease in the FRP within both sets of beats. For example, between beats 1 and 2 the A–A' interval increased 14 msec, and the A'–H' interval increased slightly, by 2.3 msec. Those increases, however, were offset by an increase in the control conduction time of 32.8 msec, which caused a decrease in the FRP of 16.5 msec. The ERP between the two beats increased by 13.5 msec. If the FRP were defined as an input parameter, that is, in terms of the atrial test interval (A–A') at which a minimal output period (H–H') was reached, then the FRP would have mirrored the changes in the ERP during the Wenckebach cycles (Table 1).

![Figure 4 A: The ERP normalized against the basic cycle length (BCL) for each beat of 4:3 Wenckebach cycles recorded in 16 dogs. The mean BCL was 240.2 msec. The mean ERP after beats 4, 1, 2, and 3 were 181.9, 220.7, 234.3, and 254.2 msec, respectively. B: The FRP normalized against the BCL for the same Wenckebach cycles. The mean FRP following beats 1, 2, and 3 were 267.7, 251.2, and 248.6 msec, respectively.]

Table 1: Analysis of Changes in Functional Refractory Period

<table>
<thead>
<tr>
<th>BEAT NUMBER</th>
<th>A A-A'</th>
<th>A A'-H'</th>
<th>A A-H</th>
<th>Δ FRP</th>
<th>Δ ERP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beats 1-2</td>
<td>14.0</td>
<td>2.3</td>
<td>32.8</td>
<td>-18.5</td>
<td>13.5</td>
</tr>
<tr>
<td>Beats 2-3</td>
<td>13.2</td>
<td>4.6</td>
<td>20.4</td>
<td>-2.6</td>
<td>20.0</td>
</tr>
</tbody>
</table>

The change in the FRP between beats 1 and 2 and between 2 and 3 are analyzed in terms of the changes (Δ) in the determinants of the FRP. The A–A' interval and the A'–H' interval are the coordinates of the point on the refractory curve where the slope is $-1$. The A–H interval is the control conduction time. All results are mean values in milliseconds.
For all beats in the Wenckebach cycles, there was a weak correlation between the FRP and the ERP ($r = 0.65$). It is clear from Figures 3A and 4A that the ERP is closely related to the basic cycle length during a Wenckebach cycle ($r = 0.79$). The FRP is also related to the basic cycle length ($r = 0.90$). During a Wenckebach cycle the basic cycle length intersects the refractory curves at their distal portions where the slope is rapidly increasing (Fig. 3A). The correlation between the FRP and the ERP reflects an underlying relationship between both parameters and a third variable, the basic cycle length. As is discussed above, changes in refractoriness as shown by changes in the ERP were not reflected in changes in the FRP.

**Discussion**

Traditionally, the definition of refractoriness in a conducting segment depends on the conduction time of a test beat. For a given stimulus intensity, a conducting segment is defined as more refractory when the conduction time of a test beat is longer than the minimal conduction time achieved at long test intervals (Brooks et al., 1955). The ERP is the longest test interval at which the conducting segment fails to conduct.

The FRP is the minimal output period between two conducted beats (Krayer et al., 1951). The FRP represents a compound interaction of the conduction time of the test beat and the conduction of the control beat. The FRP relates (1) inversely to the conduction time of the control beat, and (2) directly to the conduction time of the test beat and to the test interval at the point where the refractory curve has a slope of $-1$, that is, the point where the conduction time of the test beat increases at the same rate that the test interval decreases (Eq. 3) (Rosenblueth, 1958; Ferrier and Dresel, 1974).

The FRP is an unreliable index of refractoriness primarily because it is inversely related to the conduction time of the control beat. In the AV node, changing the cycle length of testing causes the FRP to vary, even if the refractoriness of the AV node is constant in terms of the conduction times for test beats and the ERP. The changes in the FRP reflect the changes in the conduction time of the control beat (Fig. 2).

In 4:3 Wenckebach cycles the AV node repeatedly and precisely steps through 4 distinct stages of refractoriness as the cycle proceeds. The increase in refractoriness is marked by an increase in the ERP and an increase in conduction time for any given test interval as the cycle advances (Fig. 3A) (Simson et al., 1978). The FRP decreases as the cycle proceeds, predominantly because the control conduction time increases in successive beats of the cycle.

Previous investigators have noted inconsistencies between the FRP and the conduction time and ERP of the AV node with cycle length changes (Cagin et al., 1973; Denes et al., 1974; Ferrier and Dresel, 1974; Moe et al., 1964). Ferrier and Dresel (1974) deduced an inverse relationship between the FRP and the control conduction time. Denes et al. (1974) reported that the ERP increases but the FRP decreases with shorter cycle lengths of testing in man; we suggest that the major cause for the discrepancy may have been the increase of conduction time for the control beat at the shorter cycle length.

Many agents, such as epinephrine or atropine, shift the ERP and the FRP in the same direction (Krayer et al., 1951; Moe et al., 1965; Ferrier and Dresel, 1974; Damato et al., 1975). Epinephrine, for example, decreases refractoriness in the AV node, and moves the refractory curve to the left and downward (Ferrier and Dresel, 1974). As a result, all three parameters which influence the FRP decrease, and the net result is a decrease in the FRP. Paradoxical changes in the FRP and ERP have been seen with quinidine, procainamide, and cycle length changes (Damato et al., 1975). Because of the multiple determinants of the FRP, it must be kept clearly in mind that an agent may increase refractoriness, as measured by conduction time or the ERP, and yet leave unchanged or reduce the FRP. Conversely, a change in the FRP does not indicate the direction of a change in refractoriness.

The FRP is a useful measure since it represents the minimal output period which the AV node can present to more distal segments of the conduction system. If the FRP is shorter than the ERP of the distal conduction segment, then block can occur in the distal segment (Moe et al., 1965; Damato et al., 1976). With earlier atrial input intervals, the output interval of the AV node (the $H-H'$ interval) increases, and the distal conducting segment may resume conduction, giving rise to "gap" phenomena (Moe et al., 1965; Damato et al., 1976). The conduction "gap" centers around the atrial test interval at which the refractory curve of the AV node has a slope of $-1$, that is, the atrial test interval associated with the FRP.

The analysis of the FRP, performed in this paper for the AV node, is generally applicable to any segment of the conduction system. The analysis is directly applicable to conducting segments with refractory curves where the slope reaches or exceeds $-1$; an example of such a segment would be the His-Purkinje system during retrograde transmission (Josephson and Kastor, 1978). For segments that have a minimal increase in conduction time with premature beats, such as the His bundle (Wit et al., 1970), the analysis can be applied if one assumes that the conduction time, and hence the slope of the refractory curve, become infinite at the ERP; in those cases the FRP will closely follow the ERP. Discontinuous refractory curves, such as those representing dual pathways of the AV node, can be directly analyzed; in those cases, several
FRPs would be predicted where each curve passes through a slope of $-1$, and these have been reported (Rosen et al., 1974).

References


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