Effects of Heart Rate and Isoproterenol on the Functional Refractory Period of the AV Node

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Abstract The effects of heart rate and l-isoproterenol on the functional refractory period (FRP) of the atrioventricular (AV) node were analyzed in anesthetized dog. A rectangular hyperbola was adopted to express the relationship between the AV conduction time of the premature beats and the atrial coupling intervals. FRP was shown to be expressed as $\text{FRP} = E + 2\sqrt{C - C/(T - E)}$. Thus, it is a function of the effective refractory period ($E$), basic cycle length ($T$), and $C$, a constant. A decrease in the basic cycle length caused a decrease in the effective refractory period as well as FRP; the minimum conduction time remained unchanged. As expected from the above equation, relationship of FRP to the basic cycle length was curvilinear. The above equation also indicates that changes in FRP produced by a change in the basic cycle length were to be ascribed to the change in the AV conduction time of the basic beats. Therefore, FRP under this condition cannot be equated with the refractory period in its true sense. In the paced hearts, l-isoproterenol hydrochloride caused a decrease in the effective refractory period, FRP, $C$ and the minimum conduction time, and the changes in FRP were shown to be correlated with the changes in the effective refractory period, indicating that the change in FRP attained in a given fixed cycle length may be due to a change in the effective refractory period.

The functional refractory period of the atrioventricular (AV) node (Krayer et al., 1951) has been used as an index of AV nodal conductivity and regarded as a measure of the functional refractory period (Preston et al., 1959). However, the meaning of the functional refractory period is not simple. For example, administration of epinephrine causes a decrease in both the effective refractory period and the functional refractory period (Krayer et al., 1951), and agents which inhibit the slow channel lengthen both of these refractory periods (Zipes and Fischer, 1974). An increase in heart rate prolongs the effective refractory period (Cagin et al., 1973), while it shortens the functional refractory period. On the contrary, a decrease in the effective and the functional refractory periods is also
observed in certain cases of increases in heart rate (DENES et al., 1974; ROSENBLUETH, 1958). Furthermore, FERRIER and DRESEL (1974) have reached the conclusion that the functional refractory period does not represent the refractory period in a true sense; the changes in the conduction time of the regular beats play an important role in a decrease in the functional refractory period associated with an increase in heart rate.

In the present study, an attempt was made to explore further into the meaning of the functional refractory period. To express the relationship between the conduction time of the premature beat and the atrial coupling interval, a rectangular hyperbola was adopted instead of an exponential function, as was used by FERRIER and DRESEL (1974). As that approach proved to be successful in elucidating the meaning of the functional refractory period, the effects on the functional refractory period of heart rate and isoproterenol were investigated.

In consequence of these analyses, it has become apparent that the change in the functional refractory period observed when heart rate is altered and that produced by administration of dromotropic drugs at a constant heart rate have quite different meanings.

MATERIALS AND METHODS

The experiments were performed on 9 mongrel dogs of either sex, weighing 7-12 kg. Animals were anesthetized with urethane (450 mg/kg i.v.) and chloralose (45 mg/kg i.v.) after premedication with morphine hydrochloride (1.5 mg/kg s.c.). Under artificial respiration the chest was opened at the 5th intercostal space. The heart was suspended in the pericardial cradle and the bipolar stimulating electrode was sutured to the epicardial surface of the right atrium near the site of the sinoatrial node. In all experiments the vago were cut and the heart was electrically driven with 3 msec rectangular pulses, twice the threshold voltage after crushing the SA node. The bipolar catheter electrode (Cordis Co., No. 370-110) was introduced into the right ventricle through the femoral vein to record the His bundle electrocardiogram. The atrial extra stimulus was delivered with an electronic stimulator (Nihon Kohden MSE-40) coupled with Digitimer Type 3290, and the AV nodal conduction curve was constructed, relating the AV conduction time of the premature beats to the atrial coupling intervals. Digitimer opened the gate of the waveform generator of MSE-40 (SW-1) for a given period, during which ten basic train of stimuli were delivered to trigger the pulse-generator (SP-1). Digitimer also triggered another SP-1 to generate test stimuli at decreasing intervals from the last basic stimulus. The basic and the test stimuli were mixed in a power amplifier (SA-1) and delivered through the same electrode. The recordings of the His bundle and lead II electrocardiogram were displayed on an ink-jet recorder (Elema-Schönander Mingograph 800) at the speed of 100 mm/sec.

The usual designations for the features of the electrogram recorded from the
His bundle were adopted. S is the stimulus artifact. A and H represent electrical activity in the atrial tissue adjacent to the His bundle and the proximal His bundle, respectively. The AH interval represents AV nodal conduction time. Symbols with primes, e.g., A' and H', are those of the premature beats.

To examine the effects on the AV conduction of a dromotropic agent, $l$-isoproterenol hydrochloride (Nikken Kagaku Co.) was infused through the cannula inserted into the femoral vein at the speed of 0.03 $\mu$g/kg/min. All the values were expressed as mean ± standard error of the mean. For the statistical analysis, Student's paired t-test was used.

RESULTS

Relationship between the functional refractory period and the effective refractory period

The atrioventricular nodal refractory period was determined using the atrial extrastimulus technique. A regular sequence of stimuli was terminated with a premature stimulus, and the interval between the last paced beat and the premature beat (coupling interval) is recorded from both the atrium and the His bundle.

Figure 1 shows the AV nodal conduction times of the premature responses (A'H') as plotted against the intervals between the last basic response of the atrium

![Graph](image)

Fig. 1. An example of the curvilinear fitting. Solid circles represent the relationship between the HH' intervals and the AA' intervals. Open circles represent the relationship between the A'H' intervals and the AA' intervals, i.e., AV nodal conduction curve. Both dotted curves correspond to the values calculated by Eq. (5) and/or Eq. (1). Data used were obtained from 5-1 in Table 2.

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and the premature atrial response near the AV node (AA', the coupling intervals to which the AV node responds). The intervals between the last basic response and the premature response of the His bundle (HH') are also shown in this figure.

As is well known, A'H' increases when AA' decreases. To treat this relationship mathematically, an exponential function was adopted by several investigators (FERRIER and DRESEL, 1974; TEAGUE et al., 1976). However, a rectangular hyperbola with the following equation was adopted in the present study:

\[(AA' - E)(A'H' - M) = C\]  \hspace{1cm} (4)

where \(E\) represents the effective refractory period and \(M\), the minimum conduction time, which is the AV conduction time at the infinitely long AA' intervals as is discussed in the THEORY section, and \(C\) is a constant. Then the functional refractory period can be expressed with the following equation:

\[\text{FRP} = E + 2\sqrt{C - M}/(T - E)\]  \hspace{1cm} (7)

where \(T\) is the basic cycle length.

The dotted curve in Fig. 1 (open circles) is a rectangular hyperbola, fitted to

**Table 1. Summary of AV nodal electrophysiological data and curvilinear-fitting parameters.** BCL 500 msec.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Index</th>
<th>S.E.*</th>
<th>(E) (msec)</th>
<th>(M) (msec)</th>
<th>FRP (msec²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-1</td>
<td>0.989</td>
<td>2.43</td>
<td>133</td>
<td>29</td>
<td>247</td>
</tr>
<tr>
<td>12-1</td>
<td>0.981</td>
<td>2.91</td>
<td>105</td>
<td>42</td>
<td>227</td>
</tr>
<tr>
<td>13-1</td>
<td>0.980</td>
<td>2.60</td>
<td>105</td>
<td>46</td>
<td>231</td>
</tr>
<tr>
<td>Mean</td>
<td>114.3</td>
<td>39.0</td>
<td>235.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.E.**</td>
<td>9.3</td>
<td>5.1</td>
<td>6.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: BCL = basic cycle length; Index: see APPENDIX; S.E.* = standard error of the estimate, see APPENDIX; \(E\) = theoretical effective refractory period; \(M\) = minimum conduction time; FRP = functional refractory period; S.E.** = standard error of the mean.

**Table 2. AV nodal electrophysiological data.** BCL 400 msec.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Index</th>
<th>S.E.</th>
<th>(E) (msec)</th>
<th>(M) (msec)</th>
<th>FRP (msec²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-1</td>
<td>0.990</td>
<td>1.38</td>
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<td>29</td>
<td>238</td>
</tr>
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<td>6-1</td>
<td>0.982</td>
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<td>100</td>
<td>28</td>
<td>195</td>
</tr>
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<td>40</td>
<td>244</td>
</tr>
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<td>8-2</td>
<td>0.970</td>
<td>5.42</td>
<td>100</td>
<td>44</td>
<td>218</td>
</tr>
<tr>
<td>11-1</td>
<td>0.977</td>
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<td>29</td>
<td>239</td>
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<td>39</td>
<td>214</td>
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*Abbreviations are the same as in Table 1.*

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Table 3. AV nodal electrophysiological data. BCL 320 msec.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Index</th>
<th>S.E.</th>
<th>E (msec)</th>
<th>M (msec)</th>
<th>FRP (msec²)</th>
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<td>228</td>
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<td>193</td>
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<td>23</td>
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<td>94</td>
<td>33</td>
<td>192</td>
</tr>
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<td>0.991</td>
<td>3.33</td>
<td>109</td>
<td>35</td>
<td>214</td>
</tr>
<tr>
<td>9-1</td>
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<td>4.00</td>
<td>115</td>
<td>36</td>
<td>223</td>
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<td>3.16</td>
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<td>40</td>
<td>229</td>
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<td>3.29</td>
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<td>176</td>
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<td>0.952</td>
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<td>39</td>
<td>224</td>
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<td>2.90</td>
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<td>207.3</td>
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<td>3.9</td>
<td>2.4</td>
<td>5.5</td>
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</table>

Abbreviations are the same as in Table 1.

Table 4. AV nodal electrophysiological data. BCL 250 msec.

<table>
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<th>Experiment No.</th>
<th>Index</th>
<th>S.E.</th>
<th>E (msec)</th>
<th>M (msec)</th>
<th>FRP (msec²)</th>
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<tbody>
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<td>91</td>
<td>33</td>
<td>183</td>
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<td>8-1</td>
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<td>220</td>
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<td>176</td>
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<td>164</td>
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<td>3.49</td>
<td>109</td>
<td>43</td>
<td>212</td>
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<td>98</td>
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<td>206</td>
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<tr>
<td>13-1</td>
<td>0.972</td>
<td>3.60</td>
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<td>192</td>
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<tr>
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<td></td>
<td></td>
<td>97.2</td>
<td>47.9</td>
<td>194.0</td>
</tr>
<tr>
<td>S.E.</td>
<td></td>
<td></td>
<td>3.9</td>
<td>1.8</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Abbreviations are the same as in Table 1.

the experimental data following the method described by RIGGS (1963) with modifications for application to a computer (General Electric Mark III, for details see the APPENDIX section). The values of E, M and C of this case are 129 msec, 29 msec and 3,741 msec², respectively.

All the computed results are summarized in Tables 1, 2, 3 and 4. As can be seen from these tables, the standard errors of estimates were small as compared with those of TEAGUE et al. (1976), who adopted an exponential function, indicating that a rectangular hyperbola is superior to the exponential in describing the relation between A'H' and AA'.

As shown in Eq. (7), the functional refractory period is the function of C as
well as of $E$ at a certain basic cycle length. However, when the functional refractory period was plotted against the effective refractory period ($E$) at each basic cycle length, a linear relationship was obtained as shown in Fig. 2. Since the scattering of the sample data did not seem to be different at each basic cycle length, all of them were grouped together and statistically analyzed. A correlation coefficient was 0.880, ($p<0.01$). The regression line drawn in the figure is obtained by the least square method, and is as follows:

$$FRP = 1.3E + 69.9$$

The Eq. (7) also demonstrates that the functional refractory period is independent of $M$. As shown in Fig. 3, the functional refractory periods were in fact independent of $M$ (a correlation coefficient $=0.195$, statistically insignificant), in agreement with the data obtained by Ferrier and Dreseel (1974).

**Relationship between the functional refractory period and the basic cycle length**

Figure 4 illustrates the effects of the basic cycle length ($T$) on the functional refractory period (FRP), effective refractory period ($E$) and the minimum conduction time ($M$), respectively. The decrease in the basic cycle length from 500 msec to 250 msec resulted in a decrease in the effective refractory period as well as the functional refractory period, while the minimum conduction time remained unchanged (also see Tables 1, 2, 3 and 4). The relationship between the functional refractory period and the basic cycle length was curvilinear. This corresponds to what is expected from Eq. (7) and is in agreement with the experimental results obtained by Mendez et al. (1956, 1964), Mendez and Moe.
Fig. 4. Effects on FRP(A), E(B) and M(C) of BCL. Each open circle represents the mean of 3 or 12 experiments, and vertical bar, standard errors of the mean.

(1972), and Møe et al. (1965). A decrease in the basic cycle length causes an increase in the absolute value of the third term of the right-hand side in the Eq. (7), causing a decrease in the functional refractory period. The third term in Eq. (7) corresponds to the conduction time of the regular beat (AH) minus the minimum conduction time (M, cf. Eq. (6) in Theory section). Therefore, it is to be concluded that the decrease in the functional refractory period induced by the decrease in the basic cycle length, (hence an increase in heart rate) is mainly due to the change in the conduction time of the basic beat.

Effects of isoproterenol

Figure 5 shows the effects of l-isoproterenol hydrochloride on the AV nodal conduction curve at the basic cycle length of 320 msec. Isoproterenol was infused continuously (0.03 µg/kg/min) through the cannula inserted into the femoral vein. Electrophysiological parameters of the AV node before and after administration of isoproterenol are listed in Table 5.

To assess the effects of isoproterenol on C, these values were calculated manually using the method described by Riggs (1963). Since 

\[(AA' - E)(A'H' - M) = C\]

the relationship between A'H' and \(1/(AA' - E)\) becomes linear, when the value of E chosen is appropriate. Therefore, the various values of E were tried, until a value was found which gave straight line with the greatest correlation co-

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Fig. 5. An example of the curvilinear fitting. Open circle and triangle represent the relationship of A'H' to AA' before and after isoproterenol (0.03 μg/kg/min i.v.), respectively. Solid circle and triangle represent the relationship of HH' to AA' before and after isoproterenol, respectively. Dotted curves correspond to the values calculated with Eq. (5) and/or Eq. (1). Data used were obtained from 9–2 (open and solid circles) and 9–2' (open and solid triangles) in Table 5.

Table 5. Effects on the AV nodal electrophysiological parameters of isoproterenol (0.03 μg/kg/min i.v.). BCL = 320 msec.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Index E (msec)</th>
<th>M (msec)</th>
<th>C (msec²)</th>
<th>FRP (msec)</th>
<th>Index E (msec)</th>
<th>M (msec)</th>
<th>C (msec²)</th>
<th>FRP (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>After</td>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
<td></td>
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<td>39.0</td>
<td>3436.2</td>
<td>208.7</td>
<td>104.4**</td>
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<td>2.8</td>
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</table>

These data were obtained by the method described by RIGGS (1963).
*: p < 0.05, **: p < 0.01.
efficient. The values of $C$ and $M$ are calculated as the slope of this line and the intercept on the A'H' axis, respectively.

Administration of isoproterenol resulted in decreases in the functional refractory period, effective refractory period, and the minimum conduction time by $6.7 \pm 1.7$ msec ($p<0.01$), $3.9 \pm 0.9$ msec ($p<0.01$) and $1.5 \pm 0.5$ msec ($p<0.05$), respectively. In Fig. 6, the changes produced by isoproterenol in the functional refractory period are plotted against the changes in $E$. A linear relation was found and the regression line obtained by the least square method was:

$$\text{FRP} = 1.66E + 0.13$$

which almost intercepted the Y axis at zero point.

**DISCUSSION**

As indicated by Ferrier and Dreseel (1973), it is in most instances impossible to determine the effective refractory period of the AV node as defined by Hoffman et al. (1957) experimentally. Since the functional refractory period of the atrium, which is the shortest possible interval for stimulation of the AV node, becomes longer than the effective refractory period of the AV node at longer basic cycle lengths, thus making it impossible to determine the latter with the atrial extra-stimulus method. This situation is schematically depicted in Fig. 7. Therefore,
it was not feasible to judge whether the computed effective refractory period of the AV node \( (E) \) was in accordance with that defined by HOFFMAN et al. (1957). However, it is apparent that the change in \( E \) in Eq. (4) anyhow reflects the shift of the actual AV conduction curve in the horizontal direction, and that the shift is connected with the change in the effective refractory period as defined by HOFFMAN et al. (1957). Thus, it may be reasonable to take \( E \) as a measure of the effective refractory period.

![Diagram](image)

**Fig. 7.** Relationship between the effective refractory period (ERP) of the AV node and FRP of the atrium. A, C and E are FRP of the AV node and the atrium (curve 1 and 2), respectively. D and F are ERP of the atrium. In curve 1 ERP of the atrium (C) is longer than ERP of the AV node (B). Therefore, the latter cannot be determined experimentally. In contrast, ERP of the AV node can be determined when heart rate is high, since AA' vs. SS' curve shifts downwards and to the left, making FRP of the atrium short enough for determination of ERP of the AV node (curve 2).

For the same reason, the precise analysis of the effects of the basic cycle length on the effective refractory period is not easy, and the general agreement was not obtained till now. ROSENBLUETH (1958) has shown that his "Lim. AA'," which corresponds to the effective refractory period defined by HOFFMAN et al. (1957), decreases from 257 to 237 msec by the change in the basic cycle length from 1.8 to 0.81 sec. Figure 13 of MERIDETH et al. (1968) also shows that the decrease in the basic cycle length shortens the effective refractory period and causes the depression of the conductivity of the AV node. In contrast, CAGIN et al. (1973) and DENES et al. (1974) have shown that an increase in heart rate lengthens the AV effective refractory period, and FERRIER and DRESEL (1973) have found that in

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dogs the effective refractory period of the AV node changes little, as heart rate is increased. The results obtained in the present study support the conclusion obtained by Rosenblueth (1958) and Meredith et al. (1968). However, the effects on the effective refractory period of heart rate merit further study, since the conclusions drawn in the present study are based on the several assumptions.

As for the functional refractory period, it is well known that a decrease in the basic cycle length causes a decrease in this parameter (Cagin et al., 1973; Denes et al., 1974; Ferrier and Dresele, 1974; Neuss et al., 1975; Rosenblueth, 1958; Mendez et al., 1956, 1964; Mendez and Moe, 1972; Meredith et al., 1968; Moe et al., 1965); the functional refractory period is a curvilinear function of the basic cycle length (Mendez et al., 1956, 1964; Mendez and Moe, 1972; Moe et al., 1965). Ferrier and Dresele (1974) have recently shown that an important cause of the decrease in the functional refractory period that occurs when heart rate is increased is the change in the conduction time of the basic beats, and the changes in the functional refractory period observed under this condition cannot be equated to a change in a true refractory period. The important role of changes in the basic cycle length on the changes in the functional refractory period is explicit in Eq. (7).

However, it is also conceivable that the effective refractory period, if it does change, contributes to the change in the functional refractory period when heart rate is altered.

It is well known that the functional refractory period and the effective refractory period change in the same direction when agents with dromotropic action are administered at the constant basic cycle length (Krayer et al., 1951; Zipes and Fischer, 1974). This was also confirmed in the present study (Fig. 6). Furthermore, a linear relationship was observed between them, despite that the functional refractory period is not linearly related to $E$ as shown in Eq. (7). This may be due to the fact that the change in the third term of Eq. (7), i.e. $-C/(T-E)$, is negligibly small, because the change in $E$ is small as compared with the value of the basic cycle length ($T=320$ msec).

According to Eq. (7) the functional refractory period is also a function of $C$, and both of them were decreased, when isoproterenol was administered. However, biological meaning of $C$ is not clear at present.

In conclusion, the changes in the functional refractory period observed when heart rate is changed and those observed with dromotropic agents have a quite different meaning. The former is associated with the change in the conduction time of the regular beat, as has been shown by Ferrier and Dresele (1974), and possibly with the change in $E$, while the latter is mainly due to the change in the effective refractory period per se. Although Ferrier and Dresele (1974) contend that the changes in the functional refractory period do not represent those in the true refractory period, it is without doubt that they represent the changes in the refractory period when they occur at a given fixed basic cycle length.

Ferrier and Dresele (1974) have defined the minimum conduction time as
the conduction time of the premature beats at the long atrial intervals, and the basal conduction time as the shortest of the minimum conduction time which is obtained when heart rate is extremely slow (e.g., basic cycle length of 800 msec). They have also shown that an increase in heart rate lengthens the minimum conduction time, and administration of epinephrine shortens both minimum and basal conduction time. In the present study isoproterenol shortened the minimum conduction time. However, there was no change in the minimum conduction time when the basic cycle length was decreased. The discrepancy may be due to the difference in the definition, for the minimum conduction time in the present study ($M$) is defined as the conduction time at the infinitely long atrial coupling intervals. In other words, $M$ is asymptote of the rectangular hyperbola. Thus, the fatigue effects, which inevitably occur when heart rate is increased (FERRIER and DRESEL, 1974), are circumvented in the present study. Although the meaning of the minimum conduction time, or the basal conduction time, has not been clarified yet, it has been proved that it has no effects on the functional refractory period (FERRIER and DRESEL, 1974). In other words the parallel shift of the $A'H'$ vs. $AA'$ curves in the $A'H'$ direction does not affect the value of the functional refractory period. This is to be expected from Eq. (7), and is confirmed in the present experiment (Fig. 3). Thus, if conductivity of the AV node is taken as the change in the conduction time of the premature beats at given atrial coupling intervals, the functional refractory period can never be an index of the conductivity, and it is clear that the minimum conduction time or the basal conduction time must be determined, if the conductivity is to be discussed.

**THEORY**

As is demonstrated by ROSENBLUTH (1958) and TEAGUE et al. (1976), the coupling intervals of the last regular beat and the premature beat can be related by the following equation:

$$AA' + A'H' = AH + HH'$$

or

$$HH' = AA' + A'H' - AH$$

Since the functional refractory period is defined as the minimum $HH'$ intervals obtainable when $HH'$ changes as a function of $AA'$, it can be calculated by taking the first derivative of Eq. (1) and setting the result equal to zero.

$$\frac{d(HH')}{d(AA')} = 1 + \frac{d(A'H')}{d(AA')} - \frac{d(AH)}{d(AA')} = 0$$

(2)

As $AH$ is the AV nodal conduction time of the regular beats and independent of $AA'$, $d(AH)/d(AA')$ is equal to zero. Thus Eq. (2) becomes

$$1 + \frac{d(A'H')}{d(AA')} = 0$$

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Several authors adopted an exponential function to treat the relation between AA' and A'H' mathematically (FERRIER and DRESEL, 1974; TEAGUE et al., 1976). However, a rectangular hyperbola as expressed by the following equation is adopted in the present study.

\[
(AA' - E)(A'H' - M) = C
\]  

or

\[
A'H' = C/(AA' - E) + M
\]

In this equation E corresponds to the effective refractory period, since A'H' is infinite (i.e., the excitation of the atrium cannot be conducted to the His bundle) when AA' is E. M is the AV nodal conduction time at the infinitely long AA' intervals and corresponds to the minimum conduction time defined by FERRIER and DRESEL (1974). And C is a constant. Combining Eq. (3) and Eq. (4), we obtain,

\[
d(A'H')/d(AA') = -C/(AA' - E)^2 = -1
\]

Therefore, HH' equals to functional refractory period, when

\[
AA' = E \pm \sqrt{C}
\]

Since AA' must be longer than the effective refractory period (E) for the atrial extrastimuli to be effective, one of the solution, i.e., AA' = E - C, must be discarded. Hence

\[
AA' = E + \sqrt{C}
\]

When AA' equals to the basic cycle length (T) of the regular beat, A'H' intervals become AH. Therefore, from equation (5),

\[
AH = C/(T - E) + M
\]

If Eq. (4), Eq. (5) and Eq. (6) are substituted into Eq. (1) and rearranged, the following equation is obtained to express the functional refractory period, i.e.,

\[
FRP = E + 2\sqrt{C - C}(T - E)
\]

APPENDIX

In general it is rather difficult to fit a rectangular hyperbola in the form of

\[(X - E)(Y - M) = C\]

or

\[Y = C/(X - E) + M\]
to the experimental data. Consequently, in the present study curvilinear fitting procedure was performed on the supposition that

\[ C = E \cdot M \]

then

\[ Y = \frac{C}{(X - E)} + M = (MX + C - E \cdot M)(X - E) = M \cdot X/(X - E) \]

If let both side of the equation be reversed, then

\[ \frac{1}{Y} = \frac{1}{M} - \frac{(E/M)}{(1/X)} \]

In this equation the relationship between \(1/Y\) and \(1/X\) is linear, and a slope of the line and intercept on the \(1/Y\) axis are expressed as \((-E/M)\) and \(1/M\), respectively. After the calculation of \(E\) and \(M\), INDEX and the standard error of estimate (S.E.) are calculated according to the following equations:

\[ \text{INDEX} = \frac{\sum(U - \overline{U})^2}{\sum(U - \overline{U})^2} \]

where \(U = 1/Y\), \(\overline{U}\) is the estimated value, and \(\overline{U}\) is the mean of \(U\).

\[ \text{S.E.} = \sqrt{\frac{\sum(Y - \hat{Y})^2}{(n-2)}} \]

where \(Y\) is the observed value, \(\hat{Y}\) is the estimated value and \(n\) is the number of observations. INDEX means the square of the correlation coefficient of the double-reciprocal plot (\(1/Y\) vs. \(1/X\)). All of the process of calculations are programed and computed on a computer (General Electric, Mark III).

The author is grateful to Professor S. Imai and Dr. K. Hashimoto for their pertinent suggestions. Analysis of the data on a computer were carried out by a friendly help of Mr. H. Takami, Information Services International Dentsu, Ltd.

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