Considerations on the Nature of Irregularity of the Sequence of RR Intervals and the Function of the Atrioventricular Node in Atrial Fibrillation in Man Based on Time Series Analysis

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SUMMARY

Using sinus arrhythmia as a control, we elucidated the random nature of RR intervals during atrial fibrillation in man and determined the function of the atrioventricular (AV) node from the variability of RR intervals. The major difference between the characteristics of sinus arrhythmia and those of atrial fibrillation is the presence of a significant correlation between successive intervals in the former. Since the pattern of distribution of RR intervals in atrial fibrillation is unimodal and skewed to the right and so can be fitted to an Erlang distribution, atrial inputs can be considered to be summated to a certain threshold for ventricular activation in the N region of the AV node, the number of cumulative atrial inputs corresponding to this threshold being the phase of this Erlang distribution. The function of the AV node during atrial fibrillation is to transform an exponentially distributed input into an Erlang-distributed output. Loss of inputs occurs between the atria and the N region and the greater the loss of inputs the slower the ventricular response. However, the greatest loss occurs in the N region for summation of atrial inputs required to elicit ventricular activation.

Additional Indexing Words:
Arrhythmia Atrial fibrillation Atrioventricular node Block Concealed conduction Digitalis Dual AV transmission pathway Electrophysiology of the heart His bundle electrography Sinus arrhythmia
THE nature of the irregularity of the sequence of RR intervals in atrial fibrillation and the mechanism producing this irregularity have been studied by many investigators. For comprehensive references on these subjects, readers are referred to Brody\textsuperscript{1}) and Urbach.\textsuperscript{2}) We also studied these problems by rather different but more advanced methods of analysis.\textsuperscript{3}) Most important is the elucidation of the mechanism of input-output transformation at the atrioventricular (AV) node in atrial fibrillation. And also, the cause of varying lengths of RR intervals is of considerable interest. The output can be identified as an action potential recorded from the NH region or an R wave in the standard electrocardiogram. Although the interval between outputs is identical to the RR interval in the standard electrocardiogram, the corresponding input cannot be identified with certainty. As pointed out by Urbach,\textsuperscript{2}) there are many other inputs from the fibrillating atria. These inputs successively arrive at the entire atrio-AV nodal interface in addition to a particular input. Therefore, the argument that a particular atrial potential is the stimulus source for the AV nodal and ventricular beats is not tenable. From these considerations, the input-output relationship at the AV node in atrial fibrillation could not be clearly explained using the results of animal experiments conducted by microelectrode techniques. In this context, in studying the variability of the intervals between successive nerve impulses and the mechanism of neurons producing this variability, Stein\textsuperscript{4),5}) proposed that neuronal variability could be correlated with the mechanism of nerve impulse generation and intended to elucidate details of the mechanism by utilizing the statistical properties of the sequence of nerve impulse intervals or the sequence of outputs, where intracellular recording was impossible and the sequence of outputs might be the only available data. The situation postulated by Stein is very similar to that in the present study. Stein and Ten Hoopen\textsuperscript{6}) discussed the synapse model mathematically. Ten Hoopen\textsuperscript{7}) and the present authors\textsuperscript{3}) studied the irregularity of the sequence of RR intervals in atrial fibrillation by assuming that, in several respects, the AV node behaved functionally like a synapse. Although no corresponding anatomical structure is found in either humans or animals,\textsuperscript{8}) Cranefield\textsuperscript{9}) stated that transmission across the N cell layer in the AV node actually presents marked similarities to synaptic transmission. Hence, it is quite reasonable that mathematical procedures used in the analysis of the nerve impulse sequence can be equally well applied to the analysis of the RR intervals in atrial fibrillation. In the present paper, with the use of these mathematical procedures we intend to clarify the input-output relationship at the AV node in atrial fibrillation in reference to the electrophysiological experimental results reported by other investigators.
MATERIALS AND METHODS

Electrocardiographic records, consisting of 1,024 successive RR intervals, were obtained from 19 examinations of 7 patients with atrial fibrillation. These patients were studied before, during, and after digitalization, namely at rapid, intermediate, and slow ventricular rate, respectively. Before any recording was started, the patients rested for at least 10 min on a bed. The recording was then made during another 30 min period. In each case, the RR intervals were measured manually in msec and numbers corresponding to the length of 1,024 successive RR intervals were punched on cards. Once on cards, the data from each electrocardiographic record were subjected to mathematical analysis on a FACOM M-140 computer (Fujitsu Ltd, Tokyo).

Patient data are listed in Table I, and similar data from 3 cases of sinus

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Heart disease</th>
<th>Date</th>
<th>Mean ventricular rate per min</th>
<th>Mean RR interval (μ) (sec)</th>
<th>CV (%)</th>
<th>Phase of the distribution (ε)</th>
<th>Mean atrial input per sec (λ)</th>
</tr>
</thead>
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<tr>
<td>No. 1 FN</td>
<td>61F</td>
<td>hypertensive heart disease</td>
<td>1/11/77</td>
<td>111</td>
<td>0.54</td>
<td>20.1</td>
<td>25</td>
<td>45.6</td>
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<td></td>
<td></td>
<td></td>
<td>1/14/77</td>
<td>63</td>
<td>0.96</td>
<td>24.7</td>
<td>16</td>
<td>17.1</td>
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<td></td>
<td></td>
<td></td>
<td>1/19/77</td>
<td>73</td>
<td>0.82</td>
<td>23.9</td>
<td>18</td>
<td>21.3</td>
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<td>No. 2 SO</td>
<td>65F</td>
<td>hypertensive heart disease</td>
<td>3/31/77</td>
<td>100</td>
<td>0.60</td>
<td>20.2</td>
<td>25</td>
<td>40.9</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>4/ 4/77</td>
<td>91</td>
<td>0.66</td>
<td>21.2</td>
<td>22</td>
<td>33.6</td>
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<td></td>
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<td>4/ 5/77</td>
<td>60</td>
<td>1.00</td>
<td>28.2</td>
<td>13</td>
<td>12.6</td>
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<td>No. 3 KS</td>
<td>66M</td>
<td>combined valvular disease</td>
<td>12/29/76</td>
<td>86</td>
<td>0.70</td>
<td>18.4</td>
<td>30</td>
<td>42.5</td>
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<td>0.94</td>
<td>19.4</td>
<td>27</td>
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<td></td>
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<td>1/28/77</td>
<td>68</td>
<td>0.88</td>
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<td>75M</td>
<td>arteriosclerotic heart disease</td>
<td>2/18/77</td>
<td>69</td>
<td>0.87</td>
<td>21.8</td>
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<td></td>
<td>2/21/77</td>
<td>48</td>
<td>1.26</td>
<td>24.9</td>
<td>16</td>
<td>12.8</td>
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<td>No. 5 SF</td>
<td>69M</td>
<td>arteriosclerotic heart disease</td>
<td>2/23/77</td>
<td>65</td>
<td>0.92</td>
<td>27.0</td>
<td>14</td>
<td>15.0</td>
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<td></td>
<td>3/ 1/77</td>
<td>51</td>
<td>1.17</td>
<td>27.6</td>
<td>13</td>
<td>11.2</td>
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<tr>
<td>No. 6 YE</td>
<td>69M</td>
<td>arteriosclerotic heart disease</td>
<td>3/26/77</td>
<td>60</td>
<td>1.00</td>
<td>28.4</td>
<td>12</td>
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<td></td>
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<td>3/28/77</td>
<td>56</td>
<td>1.07</td>
<td>31.3</td>
<td>10</td>
<td>9.5</td>
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<td></td>
<td></td>
<td></td>
<td>4/ 1/77</td>
<td>52</td>
<td>1.16</td>
<td>30.4</td>
<td>11</td>
<td>9.3</td>
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<tr>
<td>No. 7 SK</td>
<td>31F</td>
<td>combined valvular disease</td>
<td>3/25/77</td>
<td>49</td>
<td>1.22</td>
<td>27.4</td>
<td>13</td>
<td>10.9</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>3/28/77</td>
<td>46</td>
<td>1.30</td>
<td>27.2</td>
<td>14</td>
<td>10.4</td>
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Table II. Data of the Patients with Sinus Arrhythmia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Heart disease</th>
<th>Date</th>
<th>Mean ventricular rate per min</th>
<th>Mean RR interval (sec)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 1</td>
<td>24M</td>
<td>YU</td>
<td>none</td>
<td>3/14/79</td>
<td>63</td>
<td>0.95</td>
<td>7.09</td>
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<tr>
<td>No. 2</td>
<td>14M</td>
<td>KK</td>
<td>none</td>
<td>5/21/79</td>
<td>65</td>
<td>0.92</td>
<td>9.05</td>
</tr>
<tr>
<td>No. 3</td>
<td>16M</td>
<td>TH</td>
<td>none</td>
<td>4/28/79</td>
<td>67</td>
<td>0.90</td>
<td>19.50</td>
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</tbody>
</table>

Since the distribution of RR intervals was a subject for study, evaluation of the stability of data (stationarity) was first performed. Only for stationary sequences can relevant statistical procedures be legitimately and effectively applied to the data, but, in non-stationary sequences, the results of various statistical analyses do not necessarily provide mathematically significant information; it is meaningless to discuss the mechanism of ventricular irregularity in atrial fibrillation based on the results formally obtained from non-stationary data. There is no generally accepted method for quantitating the stationarity. The most elementary approach is first to divide the data into several equal parts, then to compute a mean value and standard deviation for each part and lastly to determine whether there is a statistically significant change among the mean values and standard deviations of these parts. Conversely, whether or not there appears a significant variability in the sequences of mean values and standard deviations following an increase in sample size may be tested. At a rather advanced level of study, the variability of histogram configuration produced by an increase in sample size may be compared.

For each electrocardiographic record, histograms with several bin widths were drawn and the means and standard deviations computed. The coefficient of variation (CV) indicates the ratio of interval variability to the length of the mean interval and therefore might be taken as an indicator of the irregularity of a given sequence of intervals. The serial correlation coefficients of intervals from the first to the 100th order and the spectrum of intervals were computed. The former is a measure of the degree of relationship between adjacent or non-adjacent intervals and the latter depicts the distribution of intervals by frequency composition of the data in terms of the mean square values of the data. The two form a Fourier transform pair. If the values of the former are not significantly different from zero throughout, the latter becomes constant; in this case, the sequence of intervals is independent.

Since the stationarity and independency of the sequence of RR intervals in atrial fibrillation can be proved as shown below, this sequence belongs to a renewal process. The Poisson, Erlang, and Weibull processes, which have
particularly simple properties, are the most commonly encountered renewal processes.\textsuperscript{10}

The distribution of intervals between events occurring according to a Poisson process is called exponential. Since the configuration of RR interval histograms in atrial fibrillation is unimodal and skewed to the right as shown below, the use of an exponential distribution must be ruled out, nor can a Weibull distribution be used in view of the results of goodness of fit (not described here). On the other hand, a Gamma distribution, which includes an Erlang distribution as a special case, has been frequently used to approximate the histogram of interspike intervals in neurophysiology.\textsuperscript{5,11}

Since the distribution of RR intervals in atrial fibrillation is unimodal and skewed to the right, fitting of the histogram by an Erlang distribution could be expected by successively changing the values of $\kappa$ called phase or order of the distribution. Denoting $x$ as a variable expressing the irregular RR interval and $\mu$ as its mean value, the probability density function of the Erlang distribution is

$$f(x) = \left(\frac{\kappa}{\mu} \right)^{\kappa - 1} x^{\kappa - 1} e^{-\kappa x / \mu} \frac{1}{\Gamma(\kappa)},$$

where $\Gamma(\kappa)$ is the Gamma function, and $\kappa$ is a positive integer. The mean, variance and CV of this distribution are $\mu, \mu^2 / \kappa$, and $1 / \sqrt{\kappa}$, respectively. This distribution arises as the sum of $\kappa$ independently and exponentially distributed random variables with a mean rate of occurrence of events $\kappa / \mu$. In applying this distribution to atrial fibrillation, it may be assumed that inputs to the AV node from the atria occur at times determined by a Poisson process with a mean rate of occurrence of events $\kappa / \mu$, the AV node firing due to a summed effect of $\kappa$ inputs. If the times between inputs are exponentially distributed, the time $x$ to the firing of the AV node is the sum of $\kappa$ exponentially distributed random variables. Consequently, $x$ has the probability density function described above.

Another explanation of this distribution is as follows: In the AV node during atrial fibrillation or in the neuron under physiological conditions, one may think of the cumulative action of $\kappa$ random inputs, each producing unit depolarization, whose integrated action produces a ventricular response or a neuronal firing as soon as their summed effect stored in the AV node or in the neuron without decay has reached threshold, or alternatively one may think that every $\kappa$-th input passes through the AV node and produces a ventricular activation. Although either explanation is applicable to the AV node, the former must be chosen; the latter cannot be accepted since summation of inputs in the AV node has been demonstrated as we shall see below.
Since the likelihood function, which fits the histogram to the Erlang distribution, is non-linear concerning the phase parameter $\kappa$, repeated computations are needed to obtain the optimum value of $\kappa$. Although the moment estimator $\bar{\kappa} = 1/(CV)^2$ is not a good estimator of $\kappa$, this is used as the initial value of the estimator for repeated computations.

For analysis of a stationary random process, there are two approaches, either or both of which may be required to characterize completely the process. The first of these is the interval process characterized by the times between successive events in an interval of time. A second form is the counting process that depicts the variability of the number of events as a function of elapsed time. Although these two processes correlate closely, they are not equivalent; in practice we used properties of both the counts and the times between events. Correlogram and spectrum of intervals are based on the concept of the interval process. In contrast, intensity function and spectrum of counts are major contributions from the counting process. The intensity function specifies the probability of encountering any event as a function of time after a given event. For a Poisson process, this function is constant and is equal to the mean rate of occurrence of events and, for a renewal process in general, the major departure from a Poisson process occurs at small times, and at larger times the function oscillates around the line corresponding to the mean rate of occurrence. An approximation of the spectrum of counts can be obtained by calculating the spectral density of a function which is assigned a value of one or zero according to whether or not an event occurs in each interval whose length is so small that at best one event is included. Since, actually, the length of each interval is to be assumed in the limit to tend to zero, the resolvability of the spectrum of counts can be considered greater than that of the spectrum of intervals. For a Poisson process, the spectrum of counts is constant.

**Results**

Table I shows the mean ventricular rate per minute, the mean RR interval, the CV of the RR intervals, the estimate of phase $\kappa$ of the Erlang distribution fitted by the maximum likelihood method and the mean atrial inputs per second. This rate of atrial input corresponds to the estimate of the rate of arrival in the underlying Poisson process when the distribution of RR intervals may be considered Erlang. The value of $\kappa$ becomes larger in the presence of a rapid ventricular response (these values are more than 40 when the mean ventricular rate per minute is over 100). Conversely, these values become smaller in atrial fibrillation with a slow ventricular response (these values are under 13 when the mean ventricular rate is below 60). Thus, the
Fig. 1. Test for stationarity of the sequence of RR intervals in atrial fibrillation. 3,072 consecutive RR intervals are equally divided into 3 parts, of which the first, intermediate, and last parts are called Cases 1, 2, and 3, respectively. This figure illustrates box-whisker plot (left panel), histograms of RR intervals (middle panel), and, for reference, spectrum of counts (right panel) in these 3 cases. The upper and lower sides of “box” indicate the upper and lower quartiles, and the line in the box indicates the median in each case. The upper and lower ends of the lines extending from the upper and lower sides of the box like “whisker” correspond to the maximum and minimum in each case. Normalized spectrum of counts is plotted against integer \( p \) or normalized frequency \( \omega \). The horizontal line is the theoretical spectrum for a Poisson process.

magnitude of \( \kappa \) depends on the mean ventricular response per minute. Although the frequency of atrial input correlates with the mean ventricular rate, this atrial frequency is much more dependent on the mean ventricular rate than on the value of \( \kappa \) because of the relation of \( \lambda = \kappa / \mu \).

Fig. 1 shows the behavior of RR intervals in Case 2 of atrial fibrillation. The sequence of 3,072 successive RR intervals was equally divided into 3 parts. From these 3 subsequences, each consisting of 1,024 successive RR intervals, box-whisker plot, histograms with bin width 25 msec, and, for reference, spectrum of counts were computed. Histograms of intervals with bin width 25 msec are selected here since the smaller the bin width the
more convenient the test for stationarity. The histogram configuration is skewed to the right, and although these histograms show multiple peaks, doubling of the bin width makes the histogram unimodal.

The behavior of each part, including the spectrum of counts, is quite similar or almost identical from mere inspection; furthermore, means and standard deviations of each part are not significantly different. Thus, since the sequence of 3,072 successive RR intervals in atrial fibrillation was station-

![Fig. 2. Histogram, correlogram, and spectrum of intervals and counts in 3 cases of sinus arrhythmia. The upper, middle, and lower 2 panels show histograms, correlograms, and spectra of intervals and counts respectively. Horizontal lines in the correlogram are 5% significance bands. The spectrum of intervals smoothed by a Bartlett window is plotted against normalized frequency and the normalized spectrum of counts is plotted against integer p or normalized frequency ω. In the scale of the abscissa of the spectrum of intervals, for example, π corresponds to the frequency equivalent to the double of the mean RR interval, and, in the spectrum of counts, 2π corresponds to the frequency equivalent to the 2π/mean RR interval. The horizontal line in the lower 2 panels is the theoretical spectrum for a Poisson process.](image-url)
ary, the sequence of only 1,024 intervals was subjected to analysis on all the records.

Fig. 2 shows histograms of RR intervals with bin width 25 msec, correlograms and spectra of intervals and counts for 3 cases of sinus arrhythmia. The histogram configurations are quite different from one another. A common feature of the correlogram is the presence of a significant correlation between adjacent or non-adjacent intervals. In Cases 1 and 2, the adjacent intervals tended to be equal in length. Especially in Case 2, nearly equal intervals appeared successively for several beats. Long and short intervals tended to alternate in Case 3. Since the spectrum depicts large peaks in both intervals and counts, there are periodicities corresponding to these peaks in sinus arrhythmia and hence the sequence of RR intervals in this arrhythmia is not independent.

Fig. 3 shows correlograms and spectra for 2 cases of atrial fibrillation (Cases 1 and 2) before and after digitalization. Although some serial correlation coefficients slightly exceed the 5% significance bands for the estimates, almost all coefficients are within these bands. The spectrum of intervals can be considered constant. Therefore, the sequence of RR intervals in atrial fibrillation can be regarded as independent. However, since the spectrum of

![Fig. 3. Correlogram and spectrum of intervals and counts in 2 cases of atrial fibrillation before and after digitalization. From top to bottom, correlogram and spectrum of intervals and counts are shown. The left and right half of the figure depict the properties of Cases 1 and 2, and, in each case, the left and right panels correspond to the behavior before and after digitalization, respectively. The horizontal lines in the top panel are 5% significance bands. The horizontal line in the middle and bottom panels is the theoretical spectrum for a Poisson process.](image-url)
counts exhibits far greater peaks than those of the spectrum of intervals, the possibility that there is a hidden periodicity in atrial fibrillation could not be entirely excluded.

Fig. 4 shows intensity functions in sinus arrhythmia and also in atrial fibrillation. In sinus arrhythmia (top panel), the intensity function oscillates and its peaks far exceed the 5% significance bands, which indicates the presence of periodicities corresponding to these peaks. Since the intensity function during atrial fibrillation in general (bottom panel) rarely exceeds these significance bands, most cases of this arrhythmia can be characterized by an intensity function that is confined between the upper and lower significance bands except for small values of t, which indicates the absence of periodicity.

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Fig. 4. Intensity function in cases of sinus arrhythmia and atrial fibrillation. The intensity function of Cases 1 and 2 of sinus arrhythmia (top panel), and those of Case 1 of atrial fibrillation before and after digitalization (bottom panel) are shown. Horizontal lines are 5% significance bands. These functions that represent mean rate of occurrence (M. R. O.) of events (R waves) per msec are plotted against time (msec). The left and right half of the bottom panel show the behavior before and after digitalization, respectively.
It also tends to oscillate about the mean rate of occurrence of R waves; this feature is characteristic of a renewal process.

DISCUSSION

The present study was designed to elucidate the mechanism of transmission of atrial impulses through the AV node and the cause of irregular ventricular response in atrial fibrillation. In other words, the objective of the study was to develop a clear explanation of the mechanism of input-output transformation which is carried out by the AV node in such a way that irregular rapid inputs from the fibrillating atria are transmitted to the ventricle with an irregular but much slower rate.

In atrial fibrillation, details of the atrial inputs delivered to the AV node, including their frequencies and intra-atrial as well as intranodal conduction pathways, are quite unclear as discussed by Urbach. During this arrhythmia the AV nodal cells might be excited by a frequency corresponding to their functional refractory period since the atrial fibers are continuously depolarized with a high rate of excitation and the inputs from the fibrillating atria could be invariably and promptly utilized by the AV node immediately after its refractory period. However, neither the exact location of the impulse formation for ventricular activation in the AV node nor the mechanism controlling this impulse formation is clearly known.

At first, one rather straightforward assumption is proposed: Atrial inputs arrive at the AV node in accord with a Poisson process. This possibility is not quite so artificial as it may appear because of the existence of a general theorem in the theory of queueing which states that, under fairly general conditions, the superposition of several independent series of simpler forms is indistinguishable from a Poisson process. If atrial inputs are transmitted to the AV node, especially to its N region, through several conduction pathways at different velocities or rates, the distribution of intervals between successive inputs may be regarded, as a whole, as exponential.

On the other hand, the output of the AV node should be regarded as an impulse that produces ventricular activation, so that this output corresponds to the R wave in the standard electrocardiogram or the ventricular electrogram in the electrophysiology of the heart. Several recent studies using micro-electrode techniques have revealed that, during atrial fibrillation, all impulses which reach the His bundle are transmitted to the ventricle without delay. In humans and animals with atrial fibrillation the His bundle electrogram shows the appearance of His deflection only and always before the QRS complex, and the HV interval remains the same as in normal controls.
Therefore, the action potential recorded from the NH region of the AV node can be regarded as the output of the AV node, and the interval between these outputs is identical to the interval between R waves in the standard electrocardiogram.

We demonstrated that the distribution of RR intervals in atrial fibrillation was Erlang; now we must elucidate the mechanism of transformation of exponentially distributed intervals between atrial inputs into Erlang-distributed intervals between outputs of the AV node.

Here, there are two approaches in analyzing the data. One approach is as follows: First, we formulate the probability density functions of both input and output sequences. Second, we model the AV node by accepting the simplest hypothesis that the cumulative action of atrial inputs produces a ventricular response as soon as their summed effects have reached a certain threshold. Last, we analyze the mechanism of input-output transformation at the AV node by using properties of these functions and elucidate mathematical implications of the model. The other is to use the so-called Monte Carlo method. After a suitable model of the AV node is simulated by a computer, various forms of input sequences are furnished to the computer, the resulting sequences of output are compared with the actual data, and thus the validity of the model can be tested.

We utilized the former approach since the probability density function of the output sequence is clearly determined and also that of the input sequence can be fairly reasonably assumed. Since the value of phase parameter $\kappa$ of the Erlang distribution is greater and the mean RR interval $\mu$ is smaller in atrial fibrillation with a rapid ventricular response than in atrial fibrillation with a slow or intermediate ventricular response, the frequency of the atrial input $\lambda$ increases with an increasing ventricular response in accord with the relation of $\lambda = \kappa / \mu$.

A theoretical model of neuronal behavior was proposed by Iso, who assumed that the probability of inhibitory input increased with membrane depolarization of the postsynaptic neuron. While the assumption of such an inhibitory input is somewhat unreasonable in the light of present-day neurophysiological data, its presence is necessary to approximate the exponential decay of membrane depolarization and to solve the model mathematically. In this model, when a random sequence of excitatory inputs of relatively low frequency is furnished, the mean output interval also becomes large and the distribution of intervals between outputs becomes exponential. Also, the greater the frequency of excitatory input, the greater the frequency of output and the smaller the interval between outputs. The distribution of intervals between outputs then becomes transformed to a Gamma distribution from the
exponentially distributed intervals between inputs; furthermore, as the mean rate of input increases, the distribution of output intervals is transformed to the Gamma distribution of correspondingly higher order. Since this model neuron is depolarized by an excitatory input to one unit, which, however, decays exponentially between successive inputs with a certain time constant, the model plausibly explains the empirical behavior of excitatory postsynaptic potentials.22)

In our model of the AV node during atrial fibrillation, only excitatory inputs from the atria are randomly delivered to the AV node where each input produces unit depolarization, these depolarizations are summed up without decay to threshold and finally the output for ventricular depolarization is transmitted to the ventricle. This output can be considered to be the action potential recorded from the NH region of the AV node.

The inadequacy of the model of Ten Hoopen7) results from the assumption that there is no decay of input and yet hypothetical inhibitory input is required for modeling.

Our model of the AV node is identical to the following model of the neuron: Exponential decay of depolarization is negligible; the presence of artificial inhibitory input is not taken into account, the effects of inputs whose intervals are exponentially distributed are stored and the cumulative action of these inputs produces ventricular response whose intervals are Erlang-distributed. When inputs reach the AV node at high rates, the intervals between outputs become Erlang-distributed and the higher the rate of input, the greater the order of Erlang distribution regulating outputs. Therefore, although the behavior of our model is identical to that of Iso,20) neither unreasonable nor artificial assumptions are required except for the negligible decay of input.

Steps or notches on the rising phase of nodal action potentials were previously observed by several investigators and were ascribed to the presence of synapse-like structures in the AV node23)-25) and the prepotential which seemed to correspond to these steps or notches was considered to be a postsynaptic potential.26) However, neither a relevant anatomical structure similar to a synapse8) nor evidence for the presence of synaptic vesicles27) was observed.

Hoffman and Cranefield28) showed that action potentials recorded from the atrial part of the AV node characteristically show one or more notches or steps on the rising phase. Spear and Moore17) described notching as characteristic for some cells within the N region of the node. The genesis of steps or notches was ascribed to the electrotonic spread of excitation from the upstream cells.17),29) However, successive inputs to the AV node, each producing a certain depolarization without an absolute refractory period, should be
postulated since the upstroke probably corresponding to the next depolarization appeared immediately after the beginning of repolarization of the N region of the AV node. Hence, the absence of the absolute refractory period of the AV node is a matter of speculation and, if so, atrial inputs might be considered to invade successively the AV node irrespective of its refractory period; thus, the decay of input can be neglected and the assumption that, in our model, the effect of input is constant without decay would be reasonably tenable.

Salient features of transmembrane potentials recorded from the AV node are spatial and temporal summations of depolarizations. Although the location where summation occurs is not entirely evident, Hoffman and Cranefield described that, in the atrial part of the AV node, temporal summation is apparent and characteristic and spatial summation was demonstrated in the AN region by Watanabe and in the N region by Cranefield. Hoffman and Cranefield further stated that separate excitatory impulses arrive at a common point along separate converging pathways and that temporal summation of depolarization is apparent and results in excitation of the AV node in view of the presence of steps or notches. Recently, Cranefield pointed out that transmission across the N cell layer actually presents marked similarities to synaptic transmission. From these considerations, irrespective of the presence of anatomically proved synapse-like structures in the AV node, the N region of the AV node might be assumed to correspond in function to the synapse and the atrial inputs delivered to this region are subjected to summation so as to evoke action potentials for eliciting ventricular activation in the NH region. Hence, methods of analysis of the mechanism of input-output transformation performed by the neuron and those of neuronal variability can be effectively applied to explain the behavior of the AV node in atrial fibrillation.

Although excitatory inputs should be those which are delivered to the N region and are subjected to summation, details of these inputs are difficult to understand. Published simultaneous recordings of electrical activity in regions including the AV node in animals during atrial fibrillation displayed progressive loss of action potentials between the atrium and the ventricle and the greatest loss between these chambers was found to occur in Wenckebach rhythm. Atrial inputs transmitted through the atrio-AV nodal interface are further subjected to decremental conduction, inhomogeneous conduction and concealed conduction and block. If we postulate multiple intra-atrial and intranodal conduction pathways in addition to these observations, arrival of atrial input at the N region must be random and, hence, intervals between inputs might be considered ex-
ponentially distributed as indicated above. Dual or multiple AV transmission pathways are well known in both humans and animals. Dual or multiple AV transmission pathways are well known in both humans and animals. At least the upper part of the AV node is longitudinally divided into two or more pathways which communicate with a final common pathway, the position of which is also controversial. Mendez and his collaborators believed this pathway to be about halfway between the atrium and the His bundle, while Rosenblueth thought that it was much lower and could be considered as the His bundle. Since all inputs reaching the His bundle are propagated to the ventricle without delay and atrial inputs may be considered to be summated and integrated at the N region, the final common pathway could be assumed to start at the NH region.

The mean frequency of atrial input, which arrives at the N region and passes through this region after much modification, is smaller in atrial fibrillation with a slow ventricular response than in atrial fibrillation with a rapid or intermediate ventricular response. At the same time, the phase parameter decreases with a decrease in heart rate. If is regarded as the value of threshold and atrial fibrillation with a slow ventricular response results from an increase in threshold of the AV node, an extremely slow ventricular response must be evoked. Conversely, in atrial fibrillation with a rapid ventricular response, a very rapid ventricular rate must be brought about. Therefore, the presence of a small value of in atrial fibrillation with a slow ventricular response might be considered compensatory for a decrease in atrial input. In atrial fibrillation with a rapid ventricular response, an inverse relationship between these parameters holds. In summary, whether or not the ventricular response in atrial fibrillation is rapid depends upon the frequency of atrial input delivered to the N region of the AV node. Since the value of regulates the ventricular rate in atrial fibrillation, this phase parameter can be regarded as corresponding to the threshold value of the AV node.

Digitalis glycoside is the drug of choice in the treatment of atrial fibrillation, especially when this arrhythmia is associated with a rapid ventricular rate since the most significant effect of the drug on AV conduction is to depress the conductivity within the AV node, thus embarrassing the passage of impulses through the AV node. From the present study, the effect of this drug is to scale down the number of atrial inputs during their course of transmission from the atrium to the N region of the node. Watanabe and Drefus showed the N region of the AV node to be the major site of digitalis action on AV transmission. With their considerations and the above mentioned statement of Cranefield in mind, the atrial inputs which arrive at the N region and are probably summated to threshold can be assumed to be subjected to integration for firing the ventricle.
Hitherto, in the study of irregular ventricular response during atrial fibrillation, correlograms and/or spectral density functions of the sequence of RR intervals have been used for testing whether or not this sequence is independent. Despite a widespread use of autocorrelation techniques, contradictory results have been reported; one group of investigators found the periodicity in the sequence of RR intervals, but neither periodicity nor regularity was demonstrated by others.

Braunstein and Franke used a slightly different autocorrelation technique and the method utilized by Horbach was somewhat different from those of the other investigators.

Although the reason for this discrepancy in the results is difficult to understand, the length of recording time or the presence of a trend in the sequence plays some role in addition to that of the difference of analytical methods used by the investigators. In the study of Bootsma and associates who strenuously endeavored to eliminate the trend, neither periodicity nor dependency between intervals was observed. Hence, the sequence of RR intervals in atrial fibrillation can be considered independent.

Only our report was concerned with computation of the spectrum of intervals and in the present study we used related functions expressing the variability of the number of R waves as a function of elapsed time (spectrum of counts and intensity function). Although the behavior of the spectrum of counts is similar to that of the spectrum of intervals, there are small peaks in the spectrum of counts. Therefore, the presence of hidden periodicities in the sequence of RR intervals cannot be entirely excluded, but the intensity function is characteristic of renewal process. From these results, independence of the sequence of RR intervals is further confirmed. In cases of sinus arrhythmia used as controls, however, the behavior of the correlogram, the presence of large peaks in both the intensity function and the spectrum of intervals and counts all indicate a significant correlation between intervals and between counts, and also the presence of periodicity or rhythmicity in this arrhythmia. Therefore, the difference of irregularity between atrial fibrillation and sinus arrhythmia is intrinsic in nature; thus the assertion that the irregularity of RR intervals in atrial fibrillation results from respiratory arrhythmia is untenable.

The mechanism of slow ventricular response associated with atrial fibrillation and especially the cause of long RR intervals in this arrhythmia have been attributed to concealed conduction of atrial impulses in the AV node, or the role of the AV node scaling down the number of atrial inputs. The combination of these two theories is also possible.
In the present study, we demonstrated that the frequency of atrial input from the fibrillating atria decreased in atrial fibrillation with a slow ventricular response. In contrast, Hoffman and Cranefield\(^{28}\) stated that digitalis shortens the refractory period of myocardial tissue, from which Bootsma and co-workers\(^{48}\) postulated that digitalis may increase the number of atrial impulses that reach the AV node in a given time; in this situation, however, a slow ventricular response is thought to be caused by an increase in concealed atrial input. In this context, we concluded that slowing of the ventricular rate in atrial fibrillation with digitalis was caused by a decrease in the number of atrial inputs delivered to the AV node, especially to the N region of the node. These atrial inputs should be called “effective atrial inputs” which are delivered to the N region. The cause of the decrease in the number of inputs might be decremental conduction, inhomogeneous conduction, concealed conduction and their various combinations or interplays. Therefore, our conclusion is not necessarily incompatible with the results of Hoffman and Cranefield and of Bootsma and associates.

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