Pacemaker Periodicity in Atrial Fibrillation

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Atrial fibrillation is a common and usually chronic atrial arrhythmia. Most descriptive accounts emphasize its irregularity but its mechanism is poorly understood, as shown, for example, by the number of theories that have been advanced to explain its genesis and perpetuation. Atrial electrical recordings, high speed atrial cinematography, and various techniques for the experimental production of this arrhythmia have not yet resolved the problem in favor of any single mechanism as the cause of the spontaneous atrial fibrillation in man.

The classic circus theory, as summarized by Garrey,1 describes a wave of depolarization traversing the atrium in a loop of sufficient temporal length to find excitable tissue before it. This wave then exists as a self-perpetuating pacemaker pathway and is a large scale example of a re-entry mechanism. The remaining atrial tissue not contained in the loop is then depolarized as "daughter" waves of excitation spread from the "mother" wave. Slowed conduction, shortening of the refractory period, local regions of block or depressed excitability and a pathway, that is sufficiently long geometrically and therefore temporally, are predicated to explain its perpetuation. Atrial flutter and fibrillation are considered to be explicable on the basis of such a re-entrant loop. Flutter is thought to be the result of a fairly constant loop path while the disorder of fibrillation is interpreted as being a result of spatial and temporal irregularity in the loop or loops.

The rapid ectopic focus theory explains the phenomenon of atrial fibrillation as the result of the inability of the atria to respond in an orderly manner to pacemakers with an excessively rapid rate. Prinzmetal2 observed large irregular contraction waves using atrial cinematography in surgical patients. The rate of these waves was between 250 and 400 and was correlated with large complexes of the direct atrial electrocardiogram. He concluded that the pattern of these waves with different rates at different sites in the atria at the same time were incompatible with circus movement theory.

Moe and associates3 have advocated the concept of a random wavelet, multiple scattered re-entry, type of pacemaking mechanism that depends upon the random distribution of refractory periods. Thus the wavefront of depolarization, not necessarily single and usually multiple, follows a path or paths determined by the refractory period characteristics and depolarization history of the tissue it encounters. Some constraints upon the randomness of this process would be determined by the geometry and mass of the tissue as well as by the distribution of recovery time of individual fibers.

This present investigation of atrial fibrillation is an attempt to examine certain statistical characteristics of an externally recorded atrial waveform in a single dimension. Methods are employed that establish the presence of periodic constituents, estimate the frequency of such components and examine the quantitative contribution of such regular elements to the over-all variance of the waveform. One may then examine current concepts of the mechanism of atrial fibrillation in the light of a fairly constant loop pathway while the disorder of fibrillation is interpreted as being a result of spatial and temporal irregularity in the loop or loops.
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of such numerical characterizations and place quantitative constraints upon certain postulated mechanisms. Further, numerical criteria for the recognition of this and other arrhythmias are prerequisites to computer analysis of electrocardiograms for these disorders.

Methods

A single bipolar transthoracic lead was recorded at high speed and high gain from twelve patients with chronic atrial fibrillation all of whom were receiving some form of digitalis. Electrodes were placed in positions corresponding to V1 and V9 in the conventional lead designations. A Sanborn 350-1600 EKG preamplifier was used as the first stage and its output was passed through a single stage high-pass RC filter with a time constant of 0.1 second. Clipping diodes were employed to limit excessive QRS excursions. This output was then recorded on a Sanborn no. 350 strip chart recorder at a paper speed of 100 mm/sec.

This tracing was digitized at 0.02 second intervals, with an arbitrary maximal value for the clipped QRS complex. These values were punched on IBM data cards for computer processing.

All subsequent computations were accomplished by programs written in basic FORTRAN for an IBM digital computer.

PREPROCESSING: REMOVAL OF VENTRICULAR COMPLEXES

An initial program was designed to accomplish the following: QRS peaks were recognized by their amplitude, the ST-T segment was subtracted out over the appropriate range following the QRS and the ventricular complex itself was simply deleted.

The average transients in the intervals, 0.40 to 0.06 second before and 0.06 to 0.44 second after the QRS peak, were calculated by appropriate summation of the values and division by the number of segments sampled. The average transient following the ventricular complex would represent the average ST-T deflection of ventricular repolarization if there were no atrial information contained therein. This would be approximately realizable for a finite number of beats if all significant atrial frequencies could be considered to have a random phase angle at the onset of QRS with all angles being equally probable. In those patients in whom the atrial deflections were fairly constant and separately identifiable, this relation could be estimated empirically. If the relationship were random, for a sufficient number of beats, this transient should be of low amplitude about the mean value of that region. By this criterion there were no patients exhibiting a fixed phase relationship between QRS and atrial waveforms. Additionally, in three patients tested, no simple linear regression between RR interval and phase angle could be detected.

Figure 1 shows a typical result of such processing. Tracing A is a short segment of the originally recorded ECG. Curve B is the computer estimated average ST-T deflection and curve C is the average transient preceding each QRS. Curve D represents the result of subtraction of the ST-T segment and the deletion of the QRS deflection with the resultant discontinuity replaced by a straight line segment. This initial program calculated a one-second autocorrelation function and caused the corrected curve of “pure” atrial information to be punched on IBM cards in a format suitable for further processing.

PRELIMINARY CONSIDERATIONS

Certain statistical techniques for the evaluation...
of periodic components of a waveform are suitable for analysis of the atrial waveform. Autocorrelation functions of such a time series express the covariance between values of the series separated by a temporal increment as a function of that increment. Thus the autocorrelation function of a sequence of values \( S_n \) is given by:

\[
R_{xx}(\tau) = \lim_{N \to \infty} \frac{1}{N} \sum_{n=1}^{N} S_n \cdot S_{n+\tau}
\]

where \( \tau \) is the temporal increment. The covariance of two variables divided by the product of their standard deviations is defined as the correlation coefficient; which will be numerically equivalent to the covariance if the standard deviations are unity.

Large values of the autocorrelation function at very small \( \tau \) will be expected in many functions as a reflection of finite limitation on the rate of change of the variable.\(^5\) For sufficiently large \( \tau \), however, any interdependence that is present must be the result of certain inherent properties of the function.

If a waveform is perfectly periodic and of fixed amplitude, its autocorrelation function will have the same period and a fixed amplitude. If the period and amplitude vary over a small range, the autocorrelation function will demonstrate the mean period but have decreasing amplitude with increasing \( \tau \). The autocorrelation function of random wide-band noise will rapidly approach zero amplitude with increasing \( \tau \). Typical autocorrelation functions are shown in figure 2. When a waveform is composed of a periodic function plus wide-band noise the only significant contribution to its phasic component at large \( \tau \) will be the autocorrelation function of the periodic component. Thus, autocorrelation can be useful in determining the presence of a periodic function, portraying its period and allowing assessment of its contribution to the over-all variance of the variable.

**Results**

Autocorrelation functions were generated from the atrial waveforms of twelve patients with chronic spontaneous fibrillation. Their routine electrocardiograms all had widely variant RR intervals and all had been interpreted as atrial fibrillation or atrial flutter-fibrillation on several tracings. No criterion except the presence of this arrhythmia and an infrequency of ventricular premature contractions was used in patient selection.

Atrial waveforms were extracted by the preprocessing routine and then subjected to autocorrelation analysis. The waveforms were adjusted to zero mean deflection and unity variance. Thus, the autocorrelation function generated at any \( \tau \) will be numerically equivalent to the correlation coefficient between points \( \tau \) distance apart in time in the range considered. Sufficiently large \( \tau \) was arbitrarily assigned as greater than twenty-four times the fundamental period as estimated from the short preliminary autocorrelation function.

Summation was done over fifty cycles of the atrial waveform. The peak values in the region between the twenty-fifth and fiftieth cycle of the autocorrelation function were selected as one-half the peak to peak value of the maximal amplitude repetitive waveform. This value will be referred to as the maximal covariance. \( R_{xx}(\tau) \) was calculated and plotted against \( \tau \) on an IBM 1401 printer.

Figures 3 and 4 show tracings of typical graphs of the autocorrelation function from two patients, one with a high and one with

**FIGURE 2**

Typical autocorrelation functions of a sine wave, narrow-band noise and wide-band noise.
a low maximal covariance in the region of interest. The basic period is clearly displayed in at least the first few beats in each case. A mean rate of 421 beats per minute was observed in this group of patients with a range of 346 to 528 and a standard deviation of 52 beats per minute. Data on individual patients are seen in table 1. Using the maximal covariance as a measure of orderliness allowed some observations upon the relation...
A coefficient of correlation of $\pm 0.51$ was obtained between rate in beats per minute and the maximal covariance value. For this small sample the correlation was not significant at the usual 95% confidence limits ($P = 0.09$) assuming the null hypothesis of a theoretical mean correlation of zero. It is limited evidence against the concept that disorderliness of the atrial waveform becomes more profound at higher rates.

A stochastic model was designed to compare the maximal covariance values that were obtained from the patients' records with what might be expected as the result of a circus type pacemaker. The minimal resultant deviation from regularity as a result of a variant loop pacemaker might be viewed as the production of a train of beats with their periods varying about some mean value. In this simple model we will ignore for the moment the effects that would result in the waveform recorded in one dimension by the variation in geometry of such a pacemaker trace in a three dimensional syncytial structure. A triangular waveform was chosen as the basic element for computational simplicity and a computer program generated a sequence of values representing a train of such impulses with their duration values normally distributed about a fixed mean value and their sequence assigned by a random number sequence. The waveform was of equal area with each beat and a succeeding beat was initiated immediately at the end of the preceding beat. An autocorrelation function was then generated in a manner identical to that used for the patient's atrial waveform.

Figure 5 shows a typical result of one such trial with a standard deviation of beat-to-beat period change of 28%. The solid dots of rate to this characteristic of the record.
in figure 6 are a plot of the standard deviation against the maximal covariance for repeated trials using this model. The patients’ covariance values and their average value are indicated by the horizontal lines to the right of the graph. One may estimate that the maximal variation of periods that would correspond to the average patient covariance value would have a standard deviation of slightly over 30%. This must be regarded as a maximal limit and probably represents a considerable overestimate. The variation in contour of the beats that would result in the atria as a result of the geometric variation of the pacemaker is ignored as is the probable lack of stationarity in mean rate that is likely to be present in the real situation. It is impossible to predict quantitatively the effects of low frequency average rate variations unless they could be specified as to magnitude and cycle length. Thus no definite numerical value can be established for the distribution of beat-to-beat cycle variation that would explain the characteristics of the patients’ atrial waveform but from these considerations it must be well under 30% and probably less than half that value.

Discussion

The finding of significant periodic components in these records is clearly at variance with any mechanistic explanation that would designate the pattern of established atrial fibrillation as chaotic. Thus the statement of Sano and Scher,9 based on the depolarization patterns from multiple direct atrial leads, that “. . . . . the situation during fibrillation is a completely chaotic one. . . . . .” cannot be accepted. Unduly pessimistic is their comment that “. . . . . the events during established atrial fibrillation may be too complicated to permit description by any technique.” They do not describe any attempts to search for statistical regularity in their recordings.

The amount of disorder implied by Moe and Abildskov3 in their description of the random wavelet mechanism would seem not compatible with the periodicities exhibited by our analysis. They envision such a mechanism not simply as an explanation of variability in conduction pathways in the atrium but as the self-sustaining, aperiodic pacemaker per se. They state: “Orderly spread of excitation will no longer be possible; the grossly irregular wavefront becomes fractionated as it divides about islets or strands of refractory tissue . . . . . its course, though determined by the excitability of surrounding tissue would appear to be as random as Brownian motion.”

It is possible that there is a preferential pathway in a random wavelet field, imposed by the geometry of the atria as demonstrated in the computer model of fibrillation by Moe and associates.9 This might then be a unitary pacemaking loop with some path variation in the pattern of daughter wave transmission. The random wavelet hypothesis in this special case would reduce to a mechanistic explanation of circus loop perpetuation and also allow for beat-to-beat alteration in the pathways of conduction.

Circus movement theory as initially proposed certainly admits the possibility of a central frequency and the periodicity demonstrated in this study is not evidence against such a mechanism. However, considerations detailed above would predict that a rather tight loop in the sense of transit time variation must be predicated for most patients in the group investigated.

It has been demonstrated that either a rapid focal pacemaker, produced electrically or chemically, or circus paths produced by mechanical intervention, can produce atrial fibrillation in the experimental animal. This certainly signifies that a circus loop is not necessary for the initiation of atrial fibrillation and its attendant irregular phenomena. No constant pattern of spread of excitation can be recorded from the atrial surface in established atrial fibrillation. Prinzmetal2 recorded not only irregularly distributed “heterorhythmic” large electrical puls but rapid disorderly small ones at a much higher frequency. Both the large and small waves had mechanical correlates in the cinematograph. The high frequency waves of small amplitude may be related to continuing re-entrant paths as a
fine structure of residual electrical activity over the atrial surface. This continuing activity may be of the type produced by random fields of re-entry in the manner suggested by the random wavelet hypothesis. However, the atria seem to be under the control of a periodic or nearly periodic pacemaker in atrial fibrillation in man.

If the random wavelet mechanism is viewed as the cause of variable pathways of atrial conduction without ascribing pacemaker function to these fragmented re-entry paths, a unifying synthesis of mechanisms is possible. As implied above, the demonstration of a periodic pacemaking mechanism by statistical methods cannot distinguish among a single cell focal pacemaker; a small, paucicellular re-entrant focus and a circus loop of relatively invariant path. It is proposed that pacemaker aperiodicity is not a significant contributor to the disorder of fibrillation. Rather, each response of the atrium is more or less similar in conduction pattern to succeeding and preceding response as a function of pathway modification by a random wavelet field. A wide range of beat-to-beat waveform variation might be expected if such a mechanism were operating; ranging from the almost periodic, though slowly changing patterns of "flutter-fibrillation" to a waveform in which pacemaker regularity is all but extinguished by the chaotic variation of the response pattern.

Summary

The presence of a periodic component in the atrial waveform of patients with chronic atrial fibrillation can be demonstrated by the use of autocorrelation techniques, and is interpreted as evidence for the presence of a periodic or almost periodic pacemaking mechanism. In twelve patients the average rate of this periodic element was 421 per minute with a range of 346 to 528. No correlation is present between increasing rate and disorder of the waveform.

The presence of persistent random wavelets modifying the beat-to-beat spread of excitation generated by a periodic focal pacemaker is proposed as a unifying hypothesis explaining the variability of the atrial waveform in atrial fibrillation in man.

References

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