Analysis of R-R Intervals in Patients with Atrial Fibrillation at Rest and During Exercise

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SUMMARY

Serial autocorrelation functions and histograms of R-R intervals in patients with atrial fibrillation, with and without digitalis, at rest and during exercise, were produced by a computer. At rest with and without digitalis the first and higher order coefficients did not differ from zero. During exercise (also with and without digitalis) only the first autocorrelation coefficient became slightly positive (in the order of 0.07) whereas the form of the histograms was profoundly altered by both exercise and digitalis. The change in form of the histograms reveals the change in electrophysiologic properties of the A-V conduction system. Since the serial autocorrelation functions were not influenced by digitalis and only slightly by exercise, the conclusion seems justified that the refractory period of, and the concealed conduction in, the A-V system cannot be (solely) responsible for the random nature of the ventricular rhythm in patients with atrial fibrillation. The effect of randomly spaced atrial impulses of random strength reaching the A-V node from random directions can explain these results.

Additional Indexing Words:
Digitalis — Concealed conduction — Random rhythm
Serial autocorrelation coefficients — Refractory period — A-V node

DESPITE increasing knowledge of the electrophysiologic properties of the A-V junctional tissue, the irregular pattern of ventricular rhythm in patients with atrial fibrillation is still not completely understood. Current opinions hold that (1) concealed conduction in and (2) changes of the effective refractory period of the A-V junction determine the irregular pattern of ventricular responses during atrial fibrillation.[1–3] The degree of concealed conduction of atrial impulses in the A-V junction is related to the refractory period of the A-V nodal tissue,[3–5] while the duration of the A-V nodal refractory period is related to the duration of the preceding R-R interval(s).[6, 7] At the same time the duration of the R-R intervals is related to the length of refractory period of the A-V nodal tissue as well as to the degree of concealment of atrial impulses in this tissue.

If these mutual relationships are to determine the R-R interval behavior in atrial fibrillation, at least some correlation between the duration of a R-R interval and that of its successors can be expected. This amongst others would imply that at least the first few serial autocorrelation coefficients of the R-R intervals would differ from zero. In a previous paper[8] we demonstrated that the ventricular rhythm of patients with atrial fibrillation at rest who did not receive any medication was random. These results were partly confirmed by others,[9, 10] whereas different results have also been published.[11–16]

If the electrophysiologic properties of the A-V node are responsible for the random pattern

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Received November 17, 1969; revision accepted for publication January 26, 1970.

of the ventricular rhythm, interventions like treatment with digitalis or exercise, or both, which change the electrophysiologic properties of the A-V junctional tissue should have a distinct effect on the R-R interval serial autocorrelation function.

This paper deals with the statistical analysis of R-R intervals in patients with atrial fibrillation at rest and during exercise with and without digitalis therapy. For comparison the effect of exercise determined by the same statistical methods was also studied in healthy subjects.

Methods

Patient Population

The case material consists of 41 subjects: 31 patients with atrial fibrillation and 10 healthy persons. The clinical situation of the patients is listed in table 1. Twenty patients were studied before, during, and after exercise; three of these patients were studied twice, one time without treatment and one time during digitalis therapy. Of the total of 23 exercise studies, 10 were on patients without treatment and 13 on patients receiving digitalis. The healthy persons all had sinus rhythm. They varied in age from 19 to 40 years. None of the healthy subjects received any medication.

Experimental Procedure

Before any recording was started, the patients rested for 30 min on a bench. Next the recording was made during another 30-min period of rest. The rest period recording was followed by a recording made during exercise. The subjects were exercised with a constant load on a hyperbolic bicycle ergometer in the sitting position for 17 min. The first 2 min of these recording periods were discarded. The last 15 min of this recording period were used for the analysis. The load applied varied according to the validity of the patient from 40 to 100 watts. As soon as possible after cessation of the exercise, the recording was continued in the recumbent position for another 30 min. In summary:

(1) 30 min rest (without recording)
(2) 30 min rest (recording)
(3) 2 min exercise (without recording)
(4) 15 min exercise (recording)
(5) 30 min rest (recording).

Data Handling

The electrocardiogram (leads V_4, V_5, and V_6) was recorded on an analog magnetic tape (Ampex FR 1300, tape speed 3¾ in/sec).

During each part of the experimental procedure approximately 2,000 consecutive complexes were recorded. For visual inspection of the recorded signals, the tape was played back on an oscilloscope and the lead with the most pronounced R waves was selected for further processing.

The selected lead signal was band-pass filtered (approximately 5 to 30 Hz) in order to suppress T waves and noise, and fed into a Schmitt trigger. The discrimination level of the trigger and the filter characteristics were selected previously depending on the requirements of the signal but remained fixed during the actual R-wave detection. The trigger initiated a one-shot multivibrator. After the beginning of an output pulse the one shot was blocked for 200 msec. The

Table 1

Distribution of Patients by Age, Sex, Diseases, and Treatment

No.	Patient	Age (yr)	Sex	Diagnosis	Digitalis treatment
1	J.P.	49	M	RHD	−
2	R.P.	47	M	IHD?	−
3	D.K.	42	M	IHD?	−
4	D.N.	57	M	MI	−
5	J.B.	43	M	RHD	−
6	S.O.	52	M	IHD	−/+
7	H.D.	43	M	IHD?	−
8	L.G.	35	M	RHD	−
9	J.S.	62	M	IHD	−/+
10	R.N.	45	M	RHD	−/+
11	J.B.	58	M	IHD	−
12	J.K.	70	F	IHD	−/+
13	J.F.	49	M	RHD	+/−
14	A.D.	62	M	IHD	−
15	C.K.	50	F	RHD	−
16	C.M.	26	M	RHD	−
17	W.J.	50	F	RHD	−
18	H.L.	62	F	IHD	−
19	P.R.	63	M	IHD	−
20	K.Z.	43	M	RHD	+
21	J.M.	49	M	IHD	+
22	G.K.	31	F	RHD	+
23	C.G.	37	M	RHD	+
24	J.E.	36	M	RHD	+
25	P.O.	58	M	IHD	+
26	B.H.	47	M	RHD	+
27	F.V.	45	M	IHD	+
28	A.S.	45	M	CM	+
29	J.V.	53	M	IHD	+
30	J.B.	37	M	RHD	+
31	L.K.	56	M	IHD?	+

Abbreviations: RHD = rheumatic heart disease; IHD = ischemic heart disease; MI = mitral insufficiency; CM = cardiomyopathy.

output pulses of the multivibrator were recorded on a free channel of the analog tape. This procedure prevented spurious signals (e.g., eventual large T waves) to cause the incorrect detection of R waves.

In this way the original ECG was converted into a series of pulses, each pulse starting at the onset of an R wave. After inspection the tape was sent to the Dutch Scientific Data Center of IBM. Here the pulse signal was sampled at a sampling rate of 750/sec and a digital tape of the pulse-interval durations was produced by an IBM 1401 computer. From this tape an IBM 7094-II computer finally produced 50 serial autocorrelation coefficients together with the histogram of the R-R intervals.

Statistical Methods

I. Mean Heart Rate

The mean heart rate is computed from the reciprocal of the mean interval.

II. Serial Autocorrelation

The serial autocorrelation coefficients are approximated[17] by:

$$r_j = \frac{\sum_{i=1}^{N-j} (x_i - \bar{x})(x_{i+j} - \bar{x})}{\sum_{i=1}^{N} (x_i - \bar{x})^2} \cdot \frac{N}{N-j} \qquad (1)$$

where j = coefficient number (0, 1, 2, . ., 50)
r = correlation coefficient
x_i = duration of the i-th R-R interval
$\bar{x}$ = mean duration of the R-R intervals
N = number of subsequent R-R intervals (approximately 2000).

III. Trend Compensation

The serial autocorrelation procedure is only meaningful for stationary processes. However, the parameters of series of R-R intervals are seldom time-independent. For example, the heart rate may vary as a result of varying psychologic stress or in response to exercise.

For practical reasons these monotonic or more or less slow periodic changes of the heart rate, or both, have been called "trends" in this study. The serial autocorrelogram of a process with a superimposed trend is in general considerably different from the correlogram of the process itself (fig. 1). The degree of the distortion by the trend depends on the relation between the magnitude of the trend and the standard deviation of the uncontaminated data. So, even small trends give rise to large distortions if the variance of the data is also small. Undistorted correlograms can be computed after detection and classification of the trends, if any, and subsequent adjustments of the raw data.

Mostly the classification forms the bottleneck in this procedure. For many processes, however, it can safely be assumed that the correlation coefficients in a certain range of coefficient numbers are zero if trend distortion is not present. This property can be used to detect trend after the computation of a correlogram, while the degree of distortion can be used for trend compensation in the correlogram itself.[18] The trend compensation is accomplished according to the following formula:

$$r_i = \frac{r_i^{\mp} - \bar{r}}{1 - \bar{r}} \qquad (2)$$

where
r_i = the i-th coefficient after trend compensation
$r_i^{\mp}$ = the i-th coefficient before trend compensation
$\bar{r}$ = the mean value of a number of coefficients assumed to be zero (estimate for the trend distortion).

Equation 2 holds for linear trends (if N in equation 1 is large) and gives a negligible error for monotonic or low frequency trends, if:

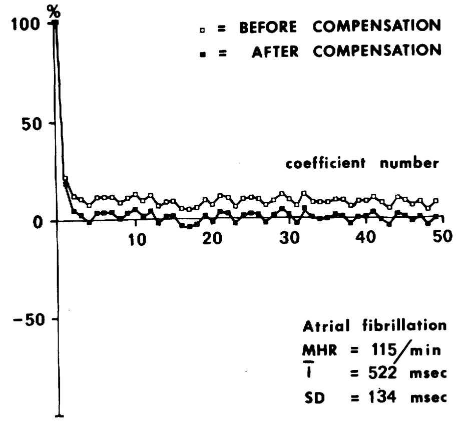

Figure 1

The serial autocorrelogram of the R-R intervals of a patient (table 1, R.N.) with atrial fibrillation during digitalis treatment in the exercise period. The effect of trend compensation on the correlation coefficients, bringing all values back to zero (except the first coefficient), is demonstrated. Abbreviations: MHR = mean heart rate; SD = standard deviation; Ī = average interval.

$$i_{max} >> n \quad (3)$$

where

i_{max} = the maximum length of lags in the computation of $\bar{r}$

n = the number of coefficients covering the duration of the smallest period in the trend.

It is important that i_{max} be sufficiently large to allow for a stable value of $\bar{r}$.

A previous study showed that in patients with atrial fibrillation at rest the first and higher serial autocorrelation coefficients of the R-R intervals did not differ from zero.[8] For normal subjects, without sinus arrhythmia, only the first few coefficients differ from zero. When sinus arrhythmia is present, the mean value of a series of the higher coefficients is still zero if the series contains one or more complete cycles of arrhythmia. With the above mentioned constraints in mind we have chosen $i_{max} = 19$, while the value of $\bar{r}$ is computed as the average of the values of the correlation coefficients $r^{\mp}_{10}$ to and including $r^{\mp}_{19}$.

IV. Shift of the First Coefficient

The sign-test is used to compare the influence of the experimental conditions on the first serial autocorrelation coefficients. This test is applied to the difference of the first correlation coefficients for each subject under two different conditions. Our null hypothesis is that the coefficients have the same value under both conditions. A 5% level of significance was chosen.

Results

The drawings of autocorrelograms in the figures are not compensated for trend except in figure 1 (see Methods). In figure 2 the histograms and the autocorrelograms of a representative patient with atrial fibrillation, preceding digitalis treatment before, during, and after exercise are shown. During exercise the mean heart rate increases from 108/min (at rest) to 157/min. The refractory period, as represented by the time between the Y axis and the beginning of the histogram, shortens from 350 to 250 msec. The decrease of the refractory period by exercise as represented by the time between the Y axis and the beginning of the histogram varied from 50 to 350 msec with a mean of 175 msec. Although a small trend can be noted (fig. 2B), the autocorrelograms of this patient remained uninfluenced by exercise. After the exercise the histogram more or less returns to the shape as in the period before exercise. The serial autocorrelation function after exercise is identical with that before exercise.

Figure 3 gives the histograms and the autocorrelograms of the same patient with atrial fibrillation as those in figure 2 now, before, and during digitalis treatment. The mean heart rate has diminished from 108/min to 63/min, and the refractory period as presented by the time between Y axis and beginning of the histogram has increased from 350 to 550 msec. It can be seen that as far as the histograms are concerned digitalis has an opposite effect to that of exercise. At the same time the autocorrelogram has remained virtually unchanged, all coefficients being zero before and during digitalis treatment.

Although digitalis tended to decrease the mean heart rate and had a distinct effect on the histograms at rest, the overall results of exercise were not influenced by digitalis. This is shown in figure 4. The digitalis histogram is also profoundly altered by exercise. The autocorrelograms of patients treated with digitalis are identical with those of patients without the drug. Although all the histograms had a general uniform appearance, being rather skew, each histogram differed from the other, showing a more or less typical form for each patient. In a number of cases the autocorrelograms showed a low frequency component, as shown in figures 1 and 4. The low frequency component coincides with a gradual increase of the mean heart rate during exercise in subjects with a small standard deviation.

The effect of exercise on the mean heart rate and the value of the first serial autocorrelation coefficients of the R-R intervals in patients without treatment and during digitalis treatment is shown in table 2A and B and figure 6, respectively. In all cases trend compensation was applied to compensate for this low frequency distortion.

During exercise at a 5% level of significance (sign test) a positive shift in r_1 has been found. The 95% confidence level for the

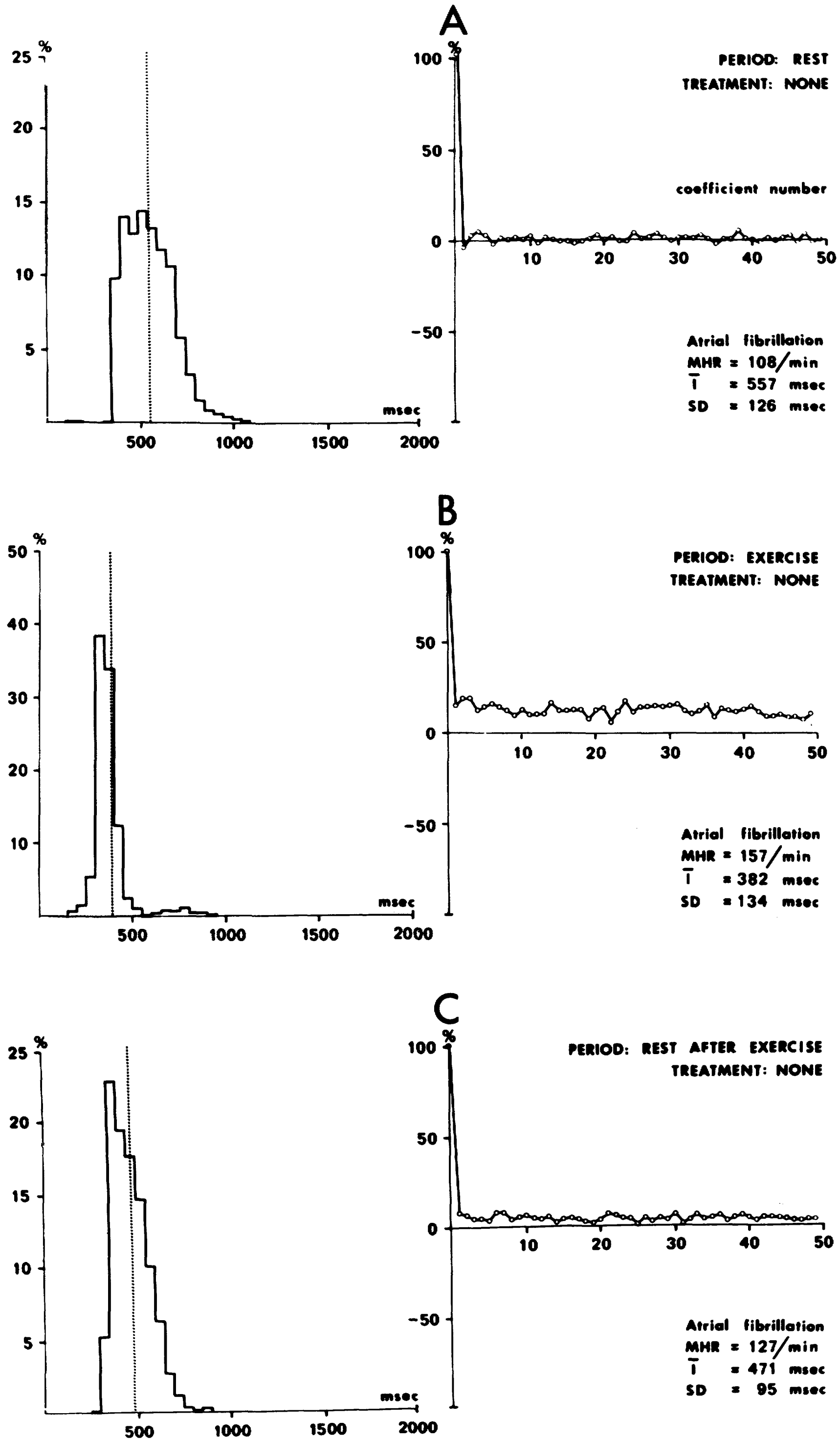

Figure 2

(A, B, and C) Histograms and autocorrelograms of the R-R intervals of a patient (table 1, R.N.) with atrial fibrillation who was receiving no medication: at rest, during, and after exercise. The use of a different scale in B should be noted. Despite the considerable change in the form of the histogram during exercise (B), the autocorrelogram is almost identical with those in A and C.

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