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

By BERT K. BOOTSMA, M.D., ADRIAAN J. HOELEN, M.Sc., JAN STRACKEE, PH.D., AND FRITS L. MEIJLER, M.D.

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

From the Department of Cardiology, University Hospital, Utrecht, and the Laboratory of Medical Physics of the University of Amsterdam, The Netherlands.

Address for reprints: Dr. Frits L. Meijler, Department of Cardiology, University Hospital, Utrecht, The Netherlands.

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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 healthly 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:

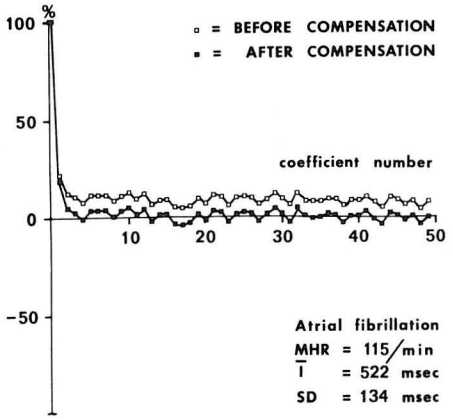

Figure 1

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 $r_{10}^{\pm}$ to and including $r_{19}^{\pm}$.

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

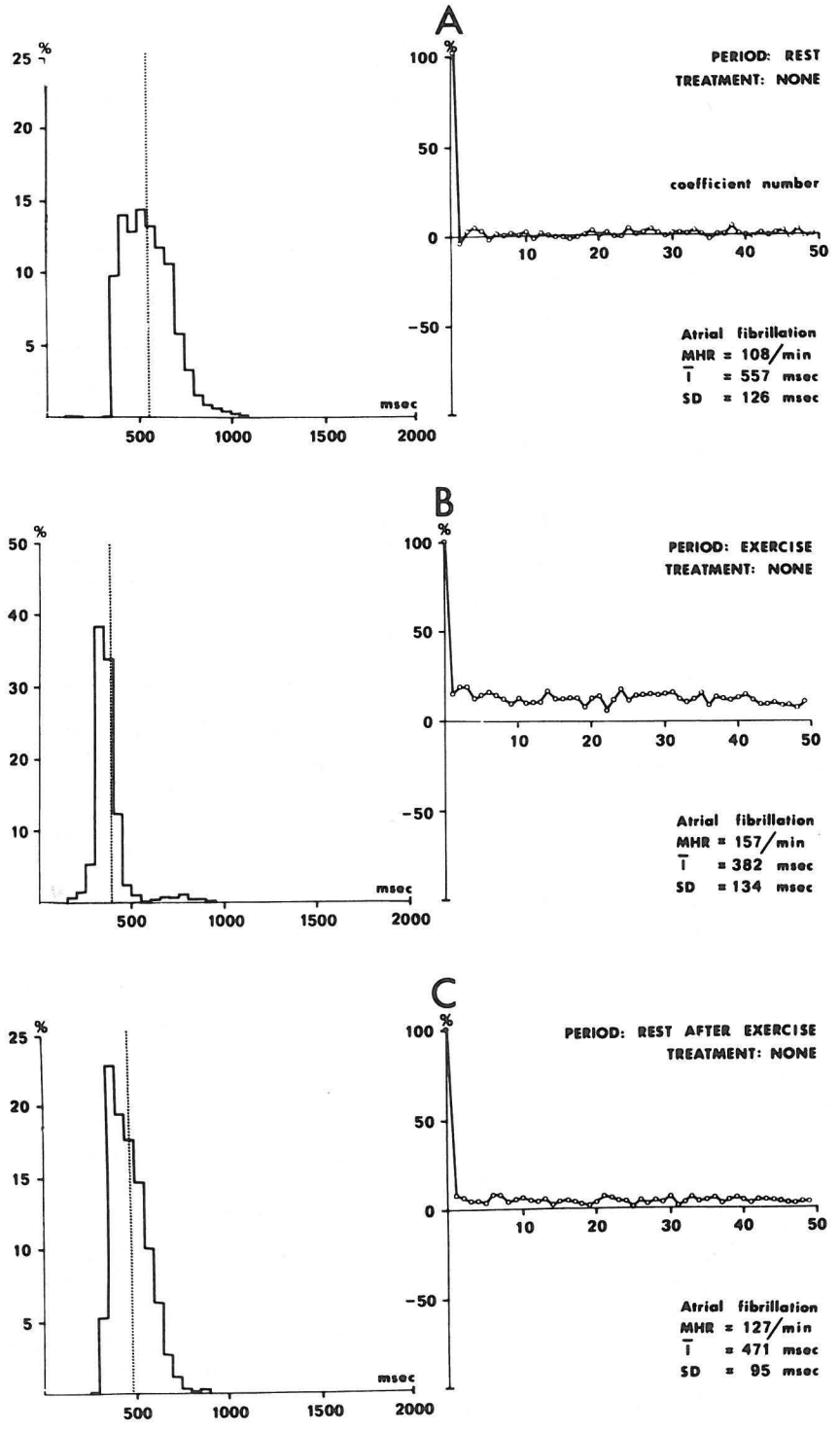

Figure 2

(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.

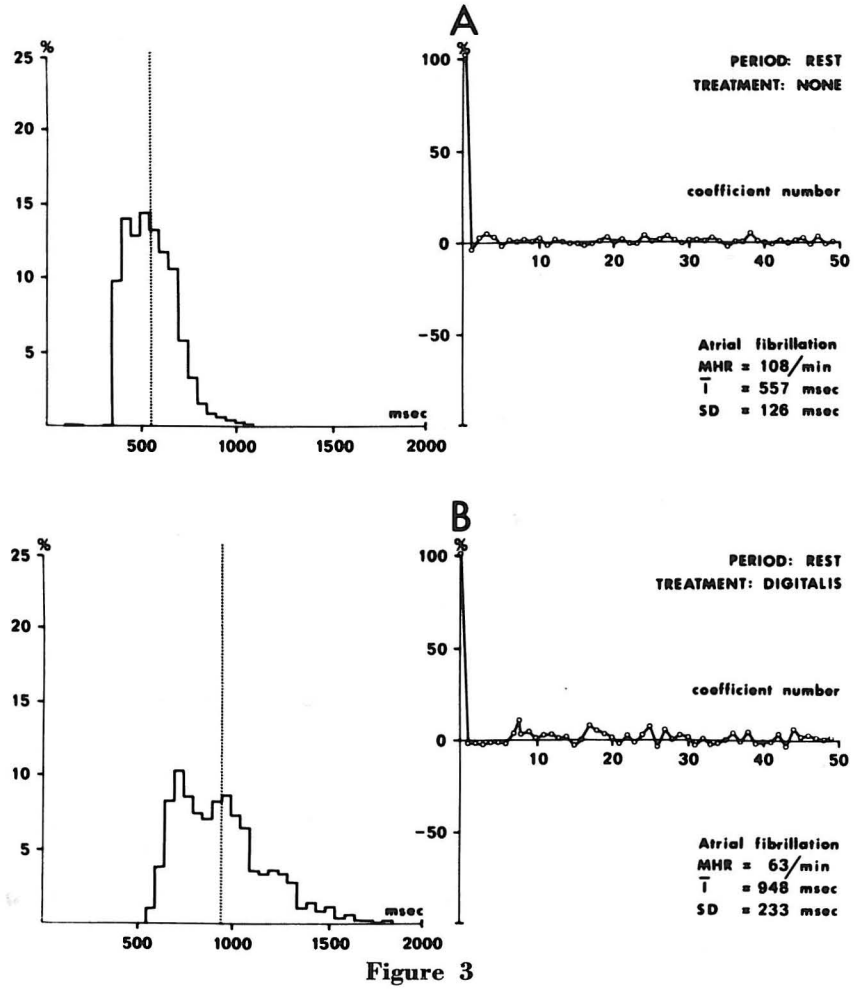

Figure 3

Histogram and autocorrelogram of the R-R intervals of a patient (table 1, R.N.) with atrial fibrillation at rest, receiving no medication (A) and during digitalis treatment (B). The autocorrelogram is unchanged, despite the change in form and the shifting to the right of the histogram.

median P_{50} of the coefficient distribution under this condition is $0.03 < P_{50} < 0.12$.

In figure 5 the histograms and autocorrelograms of a healthy man, aged 20 years, with sinus rhythm before, during, and after exercise is shown. There is a considerable difference among the histograms and autocorrelograms of the healthy subjects. Figure 5 is a fair example of this group. During exercise the histograms become rather narrow (indicating an equalizing effect on the duration of the R-R intervals).

The effect of exercise on the value of the first serial autocorrelation coefficients of the R-R intervals in normal subjects with a sinus rhythm is shown in table 2C. The difference between sinus rhythm and atrial fibrillation is striking. Finally in figure 6 the effect of exercise on the compensated first serial autocorrelation coefficients and the relative standard deviation of the intervals is shown for all cases studied. On this basis a computer should be able to distinguish sinus rhythm from atrial fibrillation by using the R waves only.

Discussion

The serial autocorrelation functions, representing the statistical behavior of the R-R intervals, indicate a random distribution of the

Table 2

Data on Patients and Controls: At Rest and During and After Exercise

No.	Patient	Workload (watts)	Rest		Exercise		Rest after exercise	
			MHR	1st SAC (%)	MHR	1st SAC (%)	MHR	1st SAC (%)
A. Data on 19 patients with atrial fibrillation without treatment at rest and on 10 of them also during and after exercise								
1	J.P.	100	75	0.1	130	14.4	81	0.9
2	R.P.	75	60	−8.7	109	−5.5	63	−10.6
3	D.K.	100	81	−0.9	169	11.2	102	−5.0
4	D.N.	50	91	0.2	151	4.8	101	−6.3
5	J.B.	40	68	−2.1	194	15.8	78	1.6
6	S.O.	50	107	9.1	139	19.2	108	5.1
7	H.D.	50	139	−2.9	182	4.7	139	−7.2
8	L.G.	50	81	4.0	123	−1.7	85	6.0
9	J.S.	50	80	−10.2	124	10.0	85	−7.4
10	R.N.	50	108	−4.5	157	3.8	127	3.0
11	J.B.		83	−7.3				
12	J.K.		90	−0.5				
13	J.F.		62	−3.7				
14	A.O.		89	8.4				
15	C.K.		76	13.2				
16	C.M.		79	3.8				
17	W.J.		59	19.2				
18	N.L.		63	−2.8				
19	P.R.		70	1.6				
*B. Data on 17 patients with atrial fibrillation during digitalis treatment at rest and on 13 of them also during and after exercise**								
20	K.Z.	50	69	7.8	169	17.8	83	0.1
21	J.M.	50	58	−17.5	111	3.1	59	−18.6
22	G.K.	50	70	1.5	127	−26.1	81	0.2
23	C.G.	50	95	5.2	169	8.5	102	3.3
24	J.E.	50	61	−5.1	84	6.6	64	−1.3
9*	J.S.	50	82	−5.4	124	7.9	85	−2.9
25	P.O.	40	79	−4.1	115	5.7	83	−3.9
10*	R.N.	50	63	−5.1	115	11.0	77	1.1
26	B.H.	50	74	−4.2	106	−0.3	78	0.3
27	F.V.	50	67	−4.5	105	−1.2	72	−9.1
28	A.S.	40	75	−2.0	107	8.8	74	−2.9
6*	S.O.	50	78	5.0	107	11.6	78	7.2
29	J.V.	50	80	12.9	158	25.8	85	1.2
30	J.B.		72	6.5				
12*	J.K.		61	0.2				
31	L.K.		84	14.6				
13*	J.F.		78	2.9				
C. Data on 10 normal subjects at rest and during and after exercise								
32	W.R.	100	71	66.9	163	91.4	95	80.5
33	A.S.	75	53	38.9	108	87.3	60	26.5
34	C.B.	75	79	62.3	129	80.5	86	68.4
35	J.G.	75	70	25.9	108	59.1	71	15.0
36	K.B.	100	64	52.9	119	67.5	74	63.8
37	M.K.	75	51	−5.3	119	35.3	55	10.5
38	H.B.	100	61	52.6	125	84.3	72	63.5
39	F.F.	75	82	81.6	123	52.3	89	77.5
40	J.J.	75	69	43.1	133	89.3	74	46.2
41	J.H.	75	60	50.5	91	84.2	60	55.4

*Patients 6, 9, 10, 12, and 13 were also studied without treatment (see A in this table).

Abbreviations: 1st SAC = first serial autocorrelation coefficient compensated for trend; MHR = mean heart rate.

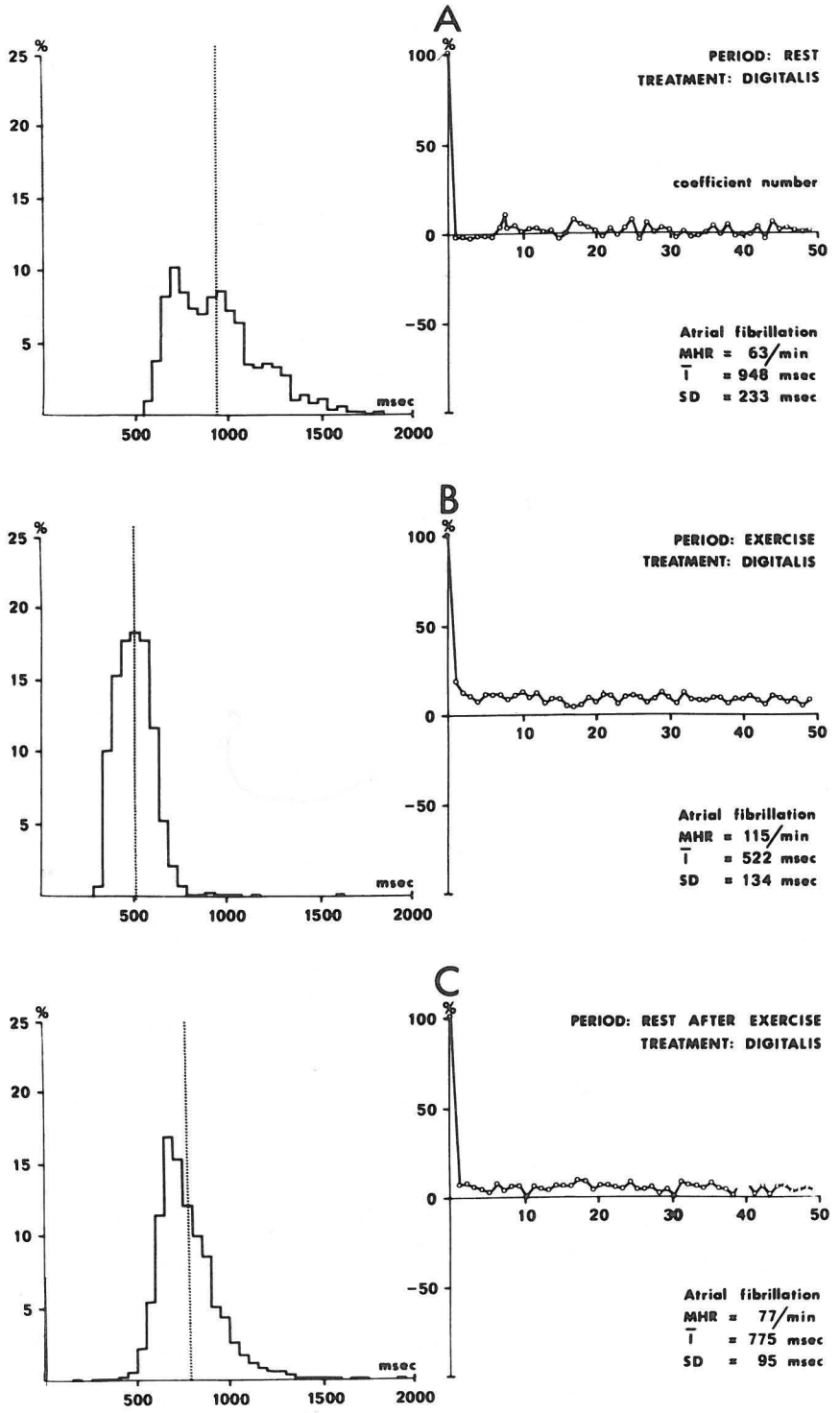

Figure 4

(A, B, and C) Histograms and autocorrelograms of the R-R intervals of a patient (table 1, R.N.) with atrial fibrillation during digitalis treatment at rest and during and after exercise. The almost identical patterns of the autocorrelograms, despite the change of histogram during exercise (B), is demonstrated.

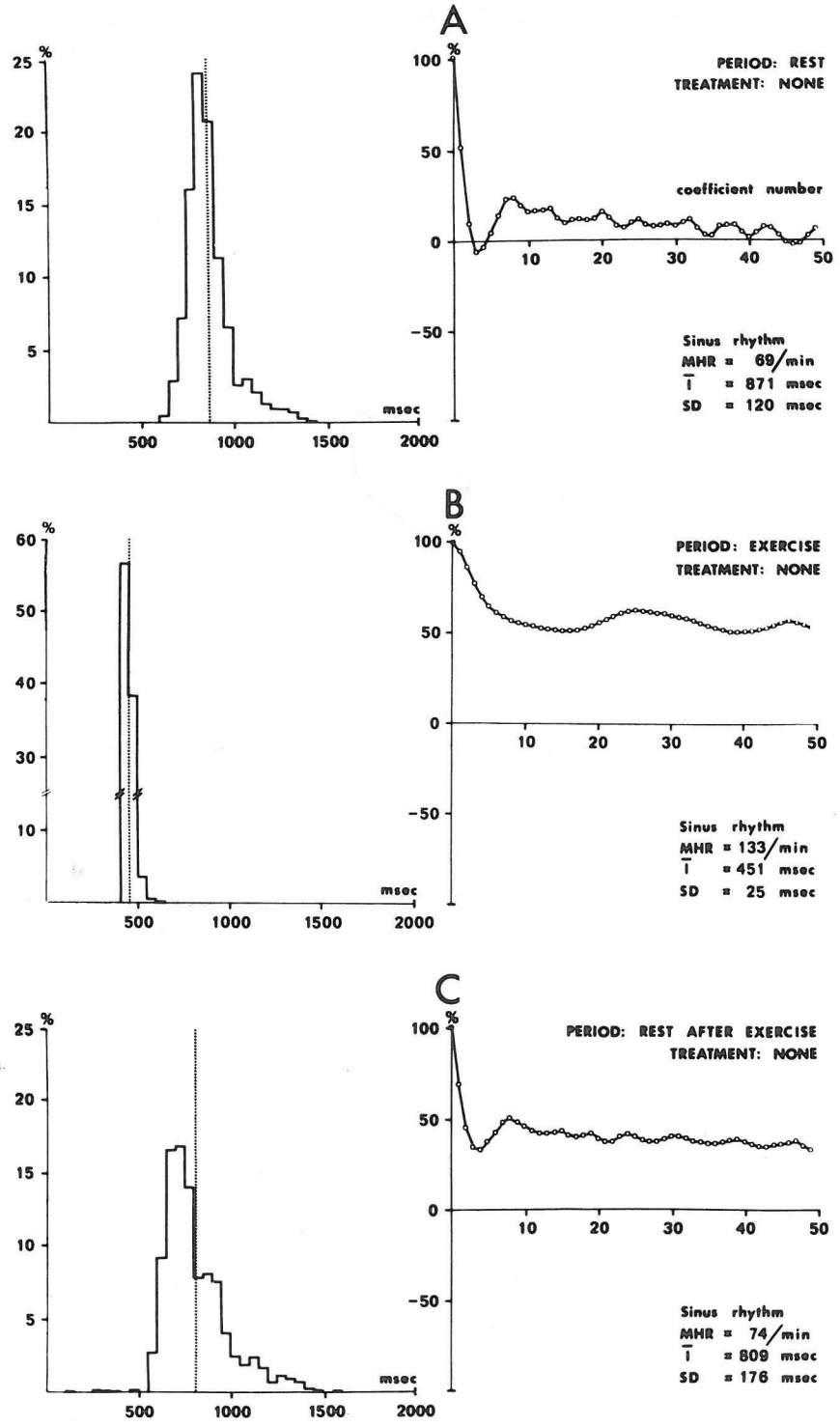

Figure 5

(A, B, and C) Histograms and autocorrelograms of the R-R intervals of a normal young man, 20 years old, with sinus rhythm at rest and during and after exercise. The use of a different scale in B should be noted. This figure should be compared with figures 3 and 4.

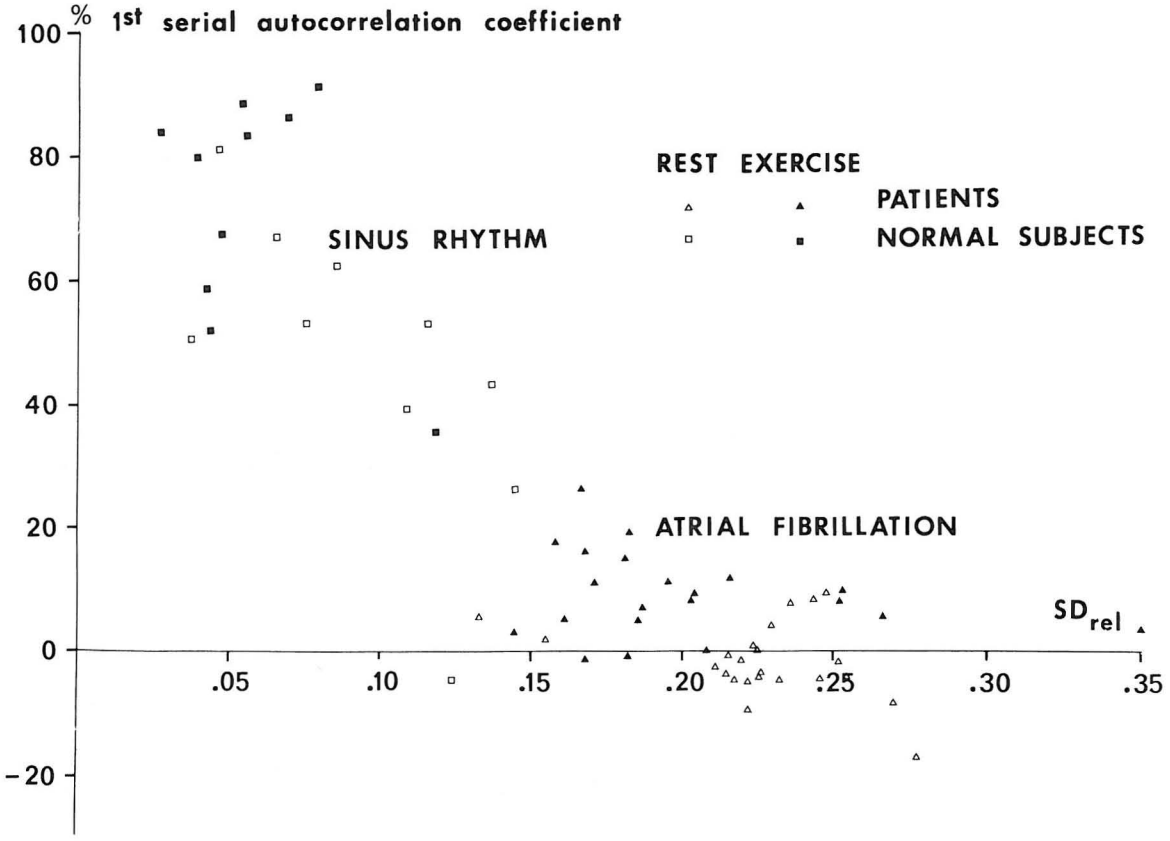

Figure 6

Scatter diagram of the first serial autocorrelation coefficients at rest and during exercise of 23 patients and 10 normal subjects. The values on the X axis represent the ratio of standard deviation to average interval. All coefficients have been compensated for trend. During exercise the first serial autocorrelation coefficients of the patients with atrial fibrillation became slightly positive.

ventricular responses in atrial fibrillation. As an explanation for this random nature of the ventricular rhythm in atrial fibrillation we may suggest that randomly spaced impulses of random strength reach the A-V node from random directions. At this moment there is insufficient electrophysiologic support to be sure about the random spacing and random strength of the atrial fibrillation. However, in a recent paper Janse[19] has demonstrated that the direction from which an atrial wave front approaches the A-V node is an additional factor determining the successful or unsuccessful passage of an atrial impulse.

Our results also demonstrate that the form of the histograms of the R-R intervals in patients with atrial fibrillation is profoundly altered by digitalis as well as by exercise. The random distribution of the R-R intervals remained virtually unchanged. The change in form of the histograms reveals a change in the electrophysiologic properties of the A-V conduction system. Despite the electrophysiologic changes of the A-V nodal tissue, the random behavior of the R-R intervals was not influenced by digitalis and hardly, if at all, by exercise.

Recently Urbach and co-workers[16] have described a method of finding A-V junctional rhythms in atrial fibrillation. Our patients did not show the same high, isolated peaks in their histograms expressing the occurrence of a relatively large number of R-R intervals within the same class. In contrast with nine of

the 10 patients of Urbach and associates,[16] our patients were all in a good physical condition. Moreover, it should be realized that Urbach and associates assumed that a number of ventricular responses may originate from nonfibrillatory pacemakers. On the basis of this assumption they developed a method of detecting eventual sequences of these regularly spaced ventricular responses.

In contrast with the findings of Goldstein and Barnett,[10] who used the same statistical methods as we did, we have not been able to find any interrelation between R-R intervals in patients with atrial fibrillation at rest. This may be due to a different way of handling the patient. We allowed the patient 30-min rest before starting the rest period recording. We are inclined to state that one is only allowed to speak of an irregular ventricular rhythm due to true atrial fibrillation if that rhythm indeed has a random nature. In agreement with Urbach and associates[16] we feel that peaks in a histogram or a nonrandom distribution of a part of the R-R intervals may point to A-V junctional rhythms, the existence of atrial flutter, or other ventricular tachycardias or rhythms.

During exercise most of our patients showed a slightly positive first serial autocorrelation coefficient. These values of the first serial autocorrelation coefficients of the R-R intervals in patients differ substantially from those of the first serial autocorrelation coefficients of the R-R intervals in the normal subjects during exercise. A definite explanation for this slight positivity of the first autocorrelation coefficients during exercise in atrial fibrillation cannot be offered. We may suggest the possibility of a mutual relationship between a small number of sequential atrial impulses, which reach the A-V node. Since exercise shortens the refractory period of the A-V node, this mutual relationship may influence the randomness of the ventricular rhythm. No information is available about the influence of exercise on the activation pattern of the atrial muscle in patients with atrial fibrillation. Shortening of the refractory period of the atrial myocardial tissue in a normal subject during exercise, as shown by Carleton and associates,[20] would suggest that more atrial impulses are formed and may reach the A-V node. This effect would increase the occurrence of concealed conduction; however, the accompanying shortening of the refractory period of the A-V nodal tissue during exercise would decrease the occurrence of concealed conduction.

The effect of digitalis on the ventricular rate in atrial fibrillation is originated by lengthening of the short intervals (increase in refractory period of the A-V node), but also, and this is important, by an increase in numbers of long intervals of which the length is also increased by digitalis.

Long intervals in atrial fibrillation are contributed to concealed conduction.[1, 2] If this is true, during digitalis treatment more atrial impulses are being concealed. Digitalis shortens the refractory period of myocardial tissue.[4] Thus digitalis may increase the number of atrial impulses that reach the A-V node in a given time which may give rise to an increase of atrial concealed impulses.

In summary, the short R-R intervals are made longer by digitalis by increasing the refractory period of the A-V system and the long intervals are made longer by digitalis by increasing the number of concealed atrial impulses that originate from a decrease of the refractory period of the atrial myocardium. This is an easier explanation of the digitalis effect in atrial fibrillation than the so-called vagus effect.

Conclusion

We thus have demonstrated that interventions that change the electrophysiologic properties of the A-V junctional tissue hardly, if at all, influence the irregularity of the ventricles in atrial fibrillation. This would imply that the present explanation for the irregular ventricular rhythm using only the refractory period of, and the concealed conduction in, the A-V node cannot hold for the random pattern of ventricular rhythm in atrial fibrillation. The conclusion seems inevitable that the cause for the ventricular irregularity should be looked

for somewhere else than in the A-V system. We would like to offer the hypothesis that randomly spaced atrial impulses of random strength reaching the A-V node from random directions are responsible for the renewal process of the R-R interval sequence, the (otherwise essential) role of the A-V system in atrial fibrillation being limited to scaling the atrial impulses.

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References

1. Abildskov JA, Moe GK: Ventricular response in atrial fibrillation. *In* Mechanism and Therapy of Cardiac Arrhythmias, edited by LS Dreifus and W Likoff. New York, Grune & Stratton, Inc, 1966, p 135
2. Moe GK, Abildskov JA: Observations on the ventricular dysrhythmia associated with atrial fibrillation in the dog heart. Circulation Research **14**: 447, 1964
3. Hoffman BF, Cranefield PF, Stuckey JW: Concealed conduction. Circulation Research **9**: 194, 1961
4. Hoffman BF, Cranefield PF: Electrophysiology of the heart. New York, Blakiston Division, McGraw-Hill Book Co, 1960
5. Langendorf R, Pick A, Katz LN: Ventricular response in atrial fibrillation: Role of concealed conduction in the A-V junction. Circulation **32**: 69, 1965
6. Lewis T, Master AM: Observations upon conduction in the mammalian heart: A-V conduction. Heart **12**: 209, 1925
7. Mendez C, Gruhnit CC, Moe GK: The influence of cycle length upon the refractory period of the auricles, ventricles, and AV-node in the dog. Amer J Physiol **184**: 287, 1956
8. Meijler FL, Strackee J, Van Capelle FJL, et al: Computer analysis of the RR interval-contractility relationship during random stimulation of the isolated heart. Circulation Research **22**: 695, 1968
9. Jordan H: Die zeitliche Schwankungen der Herzschlagintervalle bei absoluter Arrhythmie. Arch Kreislaufforsch **21**: 40, 1954
10. Goldstein RE, Barnett GO: A statistical study of the ventricular irregularity of atrial fibrillation. Computers Biom Res **1**: 146, 1967
11. Arnoldi W: Die Ermittlung von dominierende Rhythmen sowie der Schwere der Rhythmusstörung bei Kranken mit Arrhythmia perpetua. Klin Wschr **6**: 1946, 1927
12. Söderström N: What is the reason for the ventricular arrhythmia in cases of atrial fibrillation? Amer Heart J **40**: 212, 1950
13. Macrez C: Essai d'analyse de l'irrégularité ventriculaire dans l'arythmie complète. Presse Med **68**: 607, 1960
14. Horan LG, Kistler JC: Study of ventricular response in atrial fibrillation. Circulation Research **9**: 305, 1961
15. Braunstein JR, Franke EK: Autocorrelation of ventricular response in atrial fibrillation. Circulation Research **9**: 300, 1961
16. Urbach JR, Grauman JJ, Straus SH: Quantitative methods for the recognition of atrioventricular junctional rhythms in atrial fibrillation. Circulation **39**: 803, 1969
17. Kendall MG: The Advanced Theory of Statistics, vol 3. London, Griffin, 1966, p 362
18. Hoelen AJ, Strackee J: Unpublished data
19. Janse MJ: Influence of the direction of the atrial wave front on AV nodal transmission in isolated hearts of rabbits. Circulation Research **25**: 439, 1969
20. Carleton RA, Graettinger JS, Bowyer AF: Parasympathetic influence on the atrial myocardium and atrio-ventricular node of man. J Lab Clin Med **66**: 413, 1965