

# Computer Analysis of the RR Interval-Contractility Relationship during Random Stimulation of the Isolated Heart

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## ABSTRACT

Hemodynamic variability in patients with atrial fibrillation may originate from a direct influence of the variations in RR intervals on myocardial contractility. With the aid of a computer the serial autocorrelation function and the histogram of the RR intervals of patients with atrial fibrillation receiving no medication were produced. The RR intervals were randomly distributed and the histograms rather skew. Next, random rhythms with histograms matching those of the patients were produced with a radioactive source and a Geiger-Müller counter. These rhythms were used to stimulate isolated perfused rat hearts to study the relationship between the RR interval and a number of contractile parameters. The ECG and the isotonic contractions were digitized and processed by the computer. Serial crosscorrelation coefficients were computed between the RR interval on the one hand, and contraction height, contraction area, and maximum of the first derivative of the contraction on the other hand. The zero order crosscorrelation coefficient between the RR interval and contraction height was 0.6, between the RR interval and contraction area 0.8, and between the RR interval and maximum of first derivative 0.5. Although small, the first and second to approximately the tenth order coefficients were definitely negative. It is concluded that during a random rhythm the contractile parameters of an isolated heart are strongly related to the preceding RR interval. It is conceivable that this relation contributes to the variability of hemodynamic parameters during atrial fibrillation in man.

## ADDITIONAL KEY WORDS

Frank-Starling mechanism  
serial crosscorrelation coefficients  
serial autocorrelation coefficients

atrial fibrillation  
Poisson rhythm

RR intervals  
depotentialiation  
potentiation

■ Atrial fibrillation is a common rhythm disturbance of the heart in man. During this type of arrhythmia the ventricles beat very irregularly and, in general, each contraction differs from the preceding one and from the next.

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As early as 1915 Einthoven and Korteweg (1) published a paper on this subject. They demonstrated that the amplitude of the pulse wave was related to the duration of the preceding RR interval and to the amplitude of the preceding pulse wave. In the following decades the relationship between diastolic pause and pulse wave amplitude was explained by the effect of varying degrees of diastolic filling on the contractile force of the heart (Frank-Starling mechanism) (2-4). However, other investigations have shown that when changes in diastolic filling are absent, as in isolated hearts or myocardial strips, the contractile force is still dependent on the duration of the preceding RR interval (5-7). The question arises whether or not this

relationship between the RR interval and myocardial contractility (8) plays a role in the variability of hemodynamic parameters in patients with atrial fibrillation.

To avoid the influence of variations in diastolic filling we studied the relationship between interval and myocardial contractility in irregularly beating isolated hearts perfused through their coronary system. The irregularity which will be imposed on the isolated heart during this type of experiment should resemble as closely as possible that of a ventricular rhythm of a patient with atrial fibrillation receiving no medication. Although histograms of ventricular rhythms of patients with atrial fibrillation have often been described in the literature (9, 10), histograms together with the serial autocorrelation coefficients of those rhythms have, to the best of our knowledge, never been published. For most practical purposes, serial autocorrelation coefficients together with the histogram define the pattern of a rhythm.

Possible correlations between interval and contractility parameters by standard statistical techniques can be best assessed if the intervals of the applied rhythm are not inter-related. In other words, the serial autocorrelation coefficients of the intervals of such a rhythm should be zero (except the zero order coefficient). Hence, before the relationship between RR intervals and contractility in irregularly beating isolated hearts could be studied, a statistical analysis of the ventricular rhythm in patients with atrial fibrillation was needed.

This paper presents a statistical analysis of the ventricular rhythm of a patient with atrial fibrillation and an analysis of the relationship between the RR interval and contractility of isolated rat hearts stimulated with statistically defined irregular or random rhythms.

### Methods

#### ANALYSIS OF THE VENTRICULAR RHYTHM OF PATIENTS WITH ATRIAL FIBRILLATION

Lead II of the ECG from six patients with atrial fibrillation was recorded on magnetic tape (AMPEX FR 1300). Between 2,000 and 3,000 QRS complexes were registered, and the (ana-

log) signal was digitized with a converter at a sampling rate of 750/sec (IBM 9X12). After the conversion, a computer (IBM 7094) produced 50 serial autocorrelation coefficients together with the histogram, both derived from approximately 2,500 RR intervals.

#### RELATIONSHIP BETWEEN THE RR INTERVAL AND CONTRACTILITY OF ISOLATED RAT HEARTS DURING RANDOM STIMULATION

Random stimulation patterns were generated in the isolated hearts by a radioactive source and a Geiger-Müller counter. By scaling the impulses and introducing a constant dead time (refractory period), histograms matching those of the patients were obtained. In this way artificial rhythms of any desired mean rate and of completely random spacing were produced. These rhythms were stored on magnetic tape and could trigger a current source stimulator. This set-up has been called a Poisson generator because the histograms conform to higher order Poisson distributions. In addition to the stimulation patterns derived from the Poisson generator, the human ECG signal, also stored on magnetic tape, has been used to trigger the stimulator.

Isolated hearts from white rats weighing 250 g were perfused at 37°C using the Langendorff technique (11). The perfusion fluid was matched as closely as possible to the composition of the extracellular fluid. The hearts were stimulated via two ring-shaped platinum electrodes (diameter 2 mm) stitched to the epicardial surface overlying the area pretrabecularis of the right ventricle. To prevent interference with propagated sinus beats the atria of the isolated hearts were removed. The contractions of the heart were recorded by a 7 DCDT-100 Sanborn displacement transducer (weight approximately 1 g). In this way changes in length of the longitudinal axis of the left ventricle were measured. The displacement was calibrated with a micrometer screw. The ECG was obtained from a small ring-shaped electrode (diameter 2 mm) stitched to the epicardial surface of the lateral part of the left ventricle. Contractions and ECG were amplified with Sanborn preamplifiers and recorded on magnetic tape. After analog-to-digital conversion (sampling rate 750/sec), the contractions and ECG were processed by the computer, which selected from each contraction the height, the area, and the maximum of the first derivative; i.e., the contractility of the heart was expressed by these three parameters. Next the serial crosscorrelation coefficients between RR intervals, on the one hand, and contraction height, area, and maximum of the first derivative of the contraction, on the other hand, were computed. Serial crosscorrelation coefficients extend the concept of the correlation between two variables.

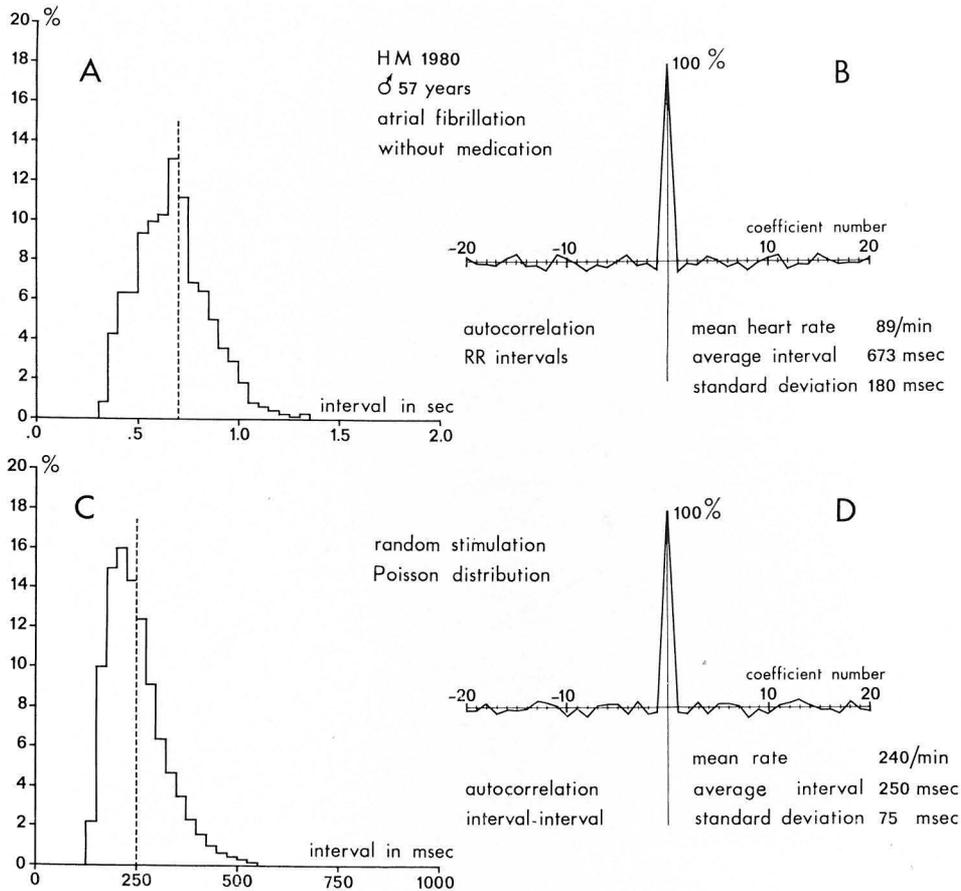


FIGURE 1

A: Histogram of the RR intervals of a patient with atrial fibrillation receiving no medication. B: Serial autocorrelation coefficients of the same RR intervals depicted in A. C: Histogram of intervals of the Poisson rhythm used to stimulate the isolated heart. The mean rate has been adjusted to the rat heart. D: Serial autocorrelation coefficients of the intervals of the same Poisson rhythm used in C. The similarity between the histograms in A and C and between the autocorrelograms in B and D should be noted.

**Results**

**ANALYSIS OF THE VENTRICULAR RHYTHM OF PATIENTS WITH ATRIAL FIBRILLATION**

The results presented here are from one patient and are representative of the six patients. Figure 1, A, gives the histogram of the RR intervals of this patient. This histogram is rather skew. The time from zero to the first bar is an indication of the shortest refractory period of the A-V conducting system. The last bar shows the longest intervals between the R waves. In Figure 1, B, the serial autocorrelation coefficients of the same RR intervals are shown. Besides the zero order coefficient,

which by definition equals one, the first and higher order coefficients did not differ from zero, indicating that the ventricular rhythm of this patient was completely random.

Since the aim of this paper is the study of the relationship between the RR interval and contractility of isolated hearts during random stimulation, we limit ourselves in presenting only those data of the rhythm analysis of patients which are relevant to this study.

For comparison, the rhythms derived from the Poisson generator were analyzed in the same way. C and D of Figure 1 demonstrate

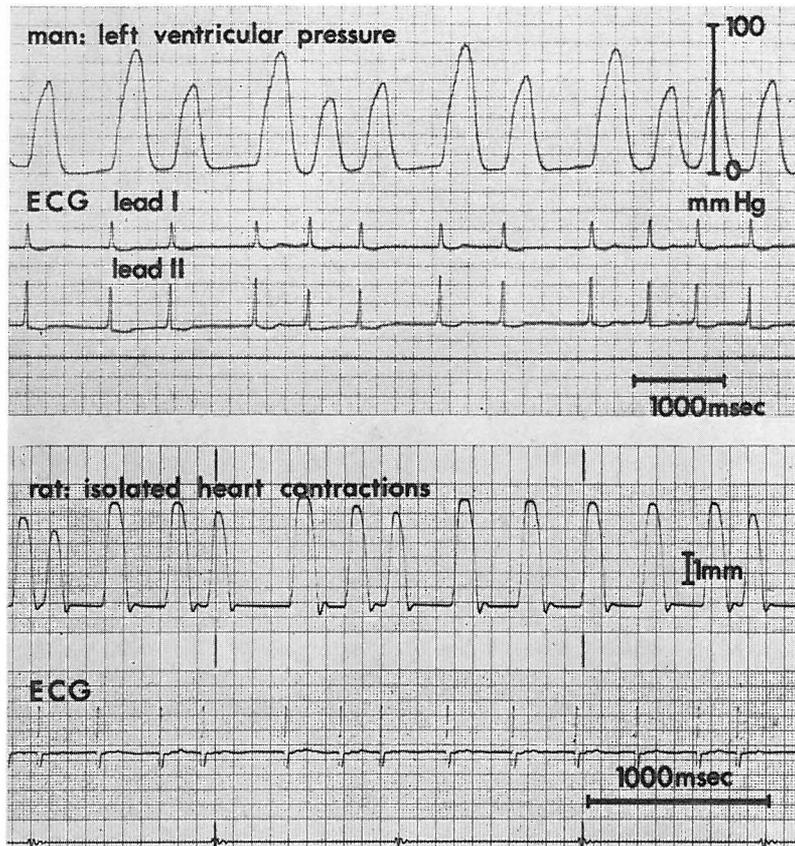


FIGURE 2

Left ventricular pressure curve of a patient with atrial fibrillation (upper curve) and isotonic contractions of an isolated rat heart stimulated with a rhythm derived from a patient with atrial fibrillation (lower curve).

respectively the histogram and the serial autocorrelation coefficients of such a rhythm. It should be emphasized that the mean rate of the Poisson rhythm was adjusted for the rat heart and therefore the mean rate is higher than that of the patient. The "refractory period" is the dead time introduced in the Poisson generator. As can be seen from comparison of B and D of Figure 1, the serial autocorrelation coefficients from the human

rhythm and the Poisson rhythm are identical. Thus both types of rhythm can be used for the interval-contraction study.

#### RELATIONSHIP BETWEEN THE RR INTERVAL AND CONTRACTILITY OF ISOLATED RAT HEARTS DURING RANDOM STIMULATION

Figure 2 demonstrates the similarity between the left ventricular pressure curve of a patient with atrial fibrillation (upper curve) and the contractions of an isolated rat heart stimulated with a rhythm obtained from a

FIGURE 3

Serial crosscorrelation coefficients between RR intervals and contraction parameters and their respective scatter diagrams of an isolated perfused rat heart stimulated with a random rhythm as outlined in C and D of Figure 1.

A: Serial crosscorrelation coefficients between RR intervals and contraction height. Coefficient zero is strongly positive, several of the following coefficients are negative. B: Scatter

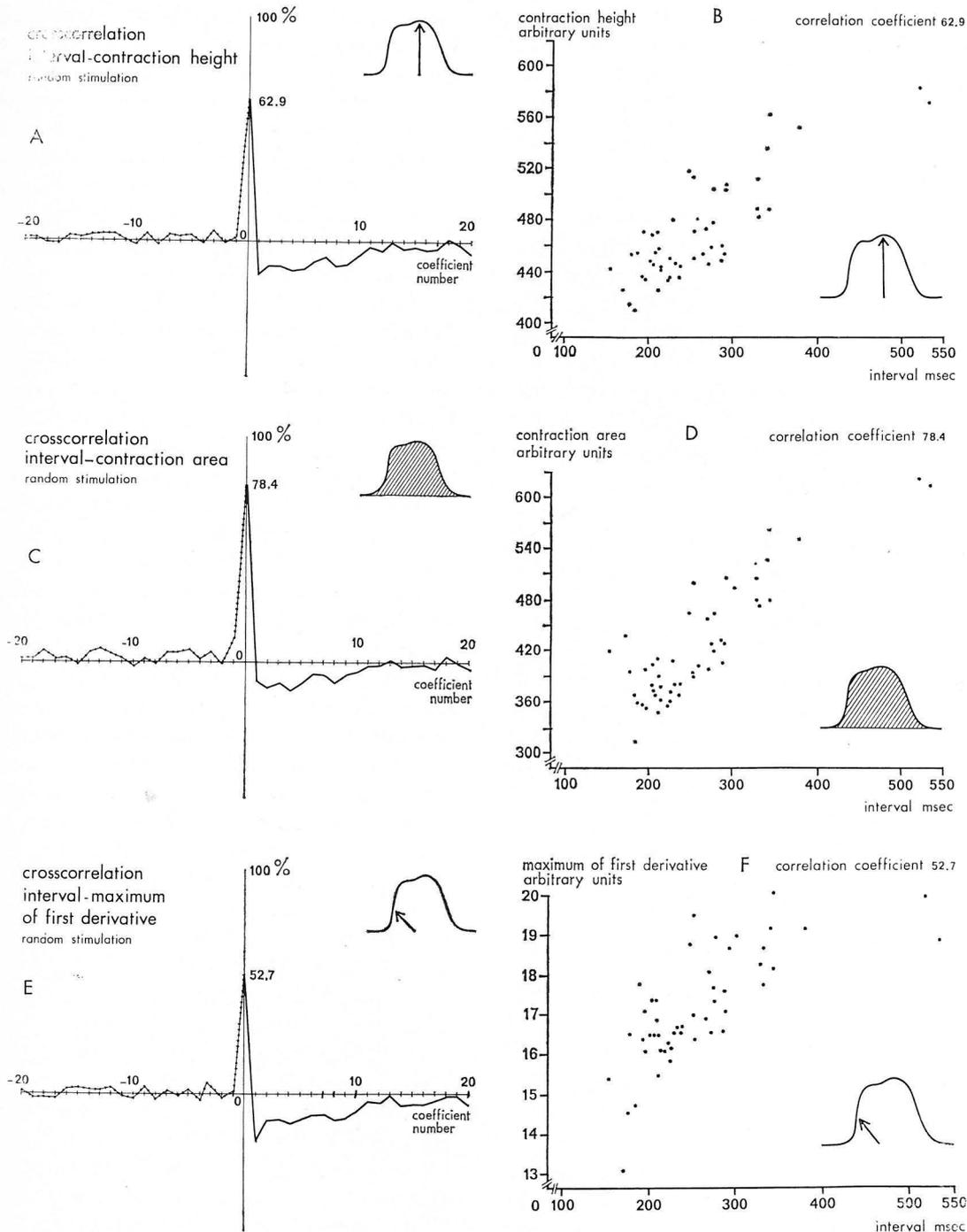


diagram of the correlation (coefficient zero of Fig. 3, A) between the RR interval and the height of the following contraction. C: Serial crosscorrelation coefficients between RR intervals and contraction area. D: Scatter diagram of the correlation (coefficient zero of Fig. 3, C) between the RR interval and contraction area. E: Serial crosscorrelation coefficients between RR intervals and maximum of the first derivative of the contraction. F: Scatter diagram of the correlation (coefficient zero of Fig. 3, E) between the RR interval and maximum of the first derivative of the contraction.

patient with atrial fibrillation (lower curve). The human left ventricular pressure curve and the rat heart contractions show a similar relation to the preceding interval. During these recordings the end-diastolic length of the isolated heart did not change.

Figure 3, A, shows the serial crosscorrelation coefficients between the RR intervals and contraction height of an isolated perfused rat heart, stimulated with a Poisson rhythm as outlined in Figure 1, C and D. The zero order coefficient (the correlation) between the RR interval and contraction height was about 60%. This correlation is depicted in another way in Figure 3, B, where the scatter diagram between the RR interval and contraction height (arbitrary units) is given. Similarly, the serial crosscorrelation coefficients and the associated scatter diagrams between RR intervals and the other contraction parameters (area and maximum of first derivative) are shown in Figure 3, C through F. The zero order coefficient between the RR interval and area was almost 80% and between the RR interval and maximum of the first derivative about 50%. However, it should be noted that from the first to almost the tenth order, all coefficients, though small, were negative.

Summarizing, there exists a strong, positive correlation between the RR interval and the first following contraction, but a negative correlation between the RR interval and the second and several of the subsequent contractions. The first contraction after a short interval is small, but the second and the following contractions are increased. After a long interval, the first contraction is large and the second and following contractions are reduced.

### Discussion

The variations in hemodynamics in patients with atrial fibrillation have been mainly attributed to changes in end-diastolic pressure which were related to the variations in RR intervals typical in this type of arrhythmia (2-4). Since in previous studies of isolated perfused rat hearts (12) and isolated myocardial strips (13, 14) a close relationship between the RR interval and contractility was

found, we doubted that this explanation, however plausible and attractive, was the only solution. To exclude the role of varying degrees of diastolic filling we studied the isolated rat heart perfused through its coronary system using the Langendorff technique. Furthermore, we had to be sure that the irregular rhythm used for this study should not confuse the results because of mutual relations between the RR intervals.

The fact that all coefficients were zero seems to imply that no mutual relationship exists between consecutive RR intervals in patients with atrial fibrillation. We realize that our findings are different from those of Moe and Abildskov (15, 16), who found a certain pattern of interrelationship between RR intervals in dogs with experimental atrial fibrillation. The results shown here from the one patient are representative of the statistical behavior of RR intervals in the six patients with atrial fibrillation receiving no medication. Assuming that our statistical approach is comparable to that of Moe and Abildskov it would appear that the ventricular dysrhythmia in dogs with experimental atrial fibrillation differs from that in man with autochthonous atrial fibrillation. Goldstein and Barnett (17) found in 14 of their 28 patients a complete independence of successive RR intervals, and in the remaining patients RR intervals tended to be adjacent to RR intervals of nearly the same duration. Whether or not our findings are in agreement with the present explanation of the role of the conduction system in patients with atrial fibrillation is beyond the scope of this paper.

In Figure 3 the crosscorrelation between RR intervals and contractility of a single heart are shown. The variability between the different hearts studied in this way was negligible. However, marked changes in results can be obtained by various factors such as lowering of the calcium content of the perfusion fluid (unpublished observations).

Contractility is an ill-defined conception (18). Myocardial contractility in this study has been defined by three parameters: contraction height, contraction area, and maximum of the first derivative of the upstroke of

the contraction. Of course we do realize that these three parameters which present different aspects of one contraction are interdependent. The contraction area had the highest correlation with the preceding interval. From our findings (Fig. 3) it can also be concluded that during random stimulation the contractile behavior of an isolated heart is strongly related to the preceding RR interval, as demonstrated by the high, positive zero order crosscorrelation coefficient. Since the phenomenon is present in an isolated heart without diastolic filling and without appreciable changes in end-diastolic length, the Frank-Starling mechanism may indeed not be solely responsible for similar relationships between RR interval and hemodynamic parameters found in patients with atrial fibrillation (2-4).

The programs developed for this study will enable us to study similar correlations between RR intervals and hemodynamic parameters, such as left ventricular pressure, in patients with atrial fibrillation. Analog data of only a few patients have been collected so far. Although these data have not yet been processed by the computer, from inspection of the curves we are inclined to predict that the results will not differ too much from the data on isolated hearts presented in this paper. The fact that for each contraction parameter the first (and very often the second, third, and fourth) order crosscorrelation coefficient was definitely negative, demonstrates that potentiation and depotentiation mechanisms (7, 13, 19) are also present during random stimulation. The finding of negative correlation can possibly explain the relationship between the amplitudes of two subsequent pulse waves found by Einthoven and Korteweg (1) and by Dodge et al. (3).

It is conceivable that the RR interval-contraction relationship found in isolated rat hearts—and also present during random stimulation—contributes to the variations of hemodynamics during atrial fibrillation in man. So far this factor has not been taken into account for the explanation of “the variability of

the size of the pulse in cases of auricular fibrillation” (1).

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