Atrial fibrillation (AF) is often described as a disorganized phenomenon, but many features that qualitatively suggest an underlying order have recently been reported. The present study aimed to disclose this underlying order of AF in a quantitative manner, using a new method of mutual information (MI), which is a measure for gauging the general correlation between 2 time series. Frequency analysis and the MI method were used to analyze 5 epicardial potentials on both atria during AF induced by vagal stimulation (Vs) in 15 dogs. Unipolar electrodes were placed on the right atrial appendage (Rap), the high right atrium (HRA), and the left atrial appendage (Lap). The other 2 electrodes were placed equidistantly between HRA and Rap (RA1–RA2). The power spectrum of AF had a discrete peak around 17 Hz during Vs. After Vs was stopped, the discrete peak shifted from 17 Hz to 7 Hz on all epicardial leads. Taking RA2 as a reference, MI was calculated between RA2 and each of the other electrodes. The MI values (0.066±0.005) were greater than 0.047 (the critical value for correlated data) even during Vs. The MI values increased significantly from the highly active process of AF during Vs to the less active one (0.126±0.006) before termination of AF. In addition, the MI values increased more at the electrodes close to RA2 (RA1 and Rap) than at those far from it (HRA and Lap). These findings suggest that multiple wavelets, which are not random, progressively organize into a few major waves toward the termination of AF; therefore, AF is not a random phenomenon in this model. (Jpn Circ J 2001; 65: 111–116)

Key Words: Atrial fibrillation; Atrium; Frequency analysis; Nonlinear analysis

Canine Atrial Fibrillation by Mutual Information

Shuichi Shimizu, MD; Motohisa Osaka, MD*; Hirokazu Saitoh, MD; Hirotugu Atarashi, MD; Teruo Takano, MD

Frequency analysis is one of the most powerful tools for analyzing periodicity, but it has rarely been applied to the electrogram of AF11 On the other hand, frequency analysis is based on the assumption that the components of the signal are independent from each other, so that their individual amplitudes are not affected and new frequencies are not generated, an assumption known as linear superposition. The nonlinear characteristics of AF have been quantitatively examined by Hoekstra et al12 Thus, we considered that a method other than frequency analysis was essential for analyzing AF and so we used the mutual information method as well as frequency analysis.

Mutual information (MI), which will be defined precisely later, can measure the nonlinear as well as linear correlation of 2 variables. We have used it previously to measure the nonlinear relationship between each pair of the 3 variables: heart rate, blood pressure, and sympathetic nerve activity. In that study we found out that heart rate variability and sympathetic nerve activity are tightly coupled in the low-frequency range, although there has been controversy on this point13 We reported that the MI method was a powerful means of measuring correlations of physiological variables. Thus, in the present study, we assumed that MI could be used to assess the correlations between electrograms at different epicardial electrodes. Our goal was to clarify quantitatively the process toward the termination of AF in an experimental model in which AF is induced by vagal stimulation (Vs) with rapid atrial pacing.

Methods

General Procedure

The experimental protocol was approved by the Nippon Medical School Committee on Animal Care. Fifteen adult mongrel dogs of both sexes, weighing between 18 and 25 kg, were anesthetized by intravenous pentobarbital (30 mg/kg). Electrodes for the II lead were implanted in the right foreleg and both hind legs. After tracheal tube intubation, the dogs were placed on a positive pressure respirator. A cannula inserted from the right femoral artery was connected to a pressure transducer (Nihon Kohden Model TP-400T) to monitor blood pressure. A median sternotomy was performed, and the heart was suspended in the pericardial cradle. Bipolar atrial pacing electrodes were placed on the
right and left atrial appendages. Unipolar electrodes were placed on the right atrial appendage (Rap), the high right atrium (HRA), and the left atrial appendage (Lap). The other 2 electrodes were placed on a straight line from HRA to Rap, equidistant (approx. 15 mm) from these 2 points and from each other, at RA1 and RA2 (Fig 1). Signals from the 5 epicardial electrodes, the II lead and blood pressure were recorded on a computer through an A–D converter. The sampling rate was 2kHz.

The cervical vagus on each side was impaled by bipolar electrodes and wrapped with moistened gauze. Initial right and left vagal stimulations with a cycle length of 80ms (12.5Hz), an output of 7.0V and a stimulus duration of 0.1ms were delivered (Fig 2). We then dropped the voltage to reduce the heart rate to approximately 25–45% of that before the Vs. AF was induced by Vs and rapid right atrial (RA) pacing (10Hz, 8V). After the induction of AF, Vs was maintained for 120s without rapid RA pacing. Thereafter, AF was maintained spontaneously for 30s at the most, after which it spontaneously converted to sinus rhythm. The electrograms were recorded until the termination of AF.

Frequency Analysis

Each of the 5 electrograms recorded at each epicardial electrode was divided into segments of data length 1.024s (2,048 data points). Power spectra were calculated by fast Fourier transform (FFT) for 30 consecutive segments, which corresponded to the duration of 30.72s (1.024s×30) until the termination of AF (Fig 2).

MI Analysis

We calculated the MI values according to the algorithm proposed by Fraser and Swinney,\(^1\) the details of which are described in our previous study.\(^3\) The following is a simple outline. For a pair of time series: \(\{x(t)\} \) and \(\{y(t)\}\), we measured how dependent the values of \(y(t)\) are on the values of \(x(t)\). Their data lengths were the 12th power of 2 \(2^{12}\). We made the assignment \(s,q\}=\{x(t),y(t)\}\) to consider a general coupled system \((S,Q)\). MI is defined as the answer to the question, ‘Given a measurement of \(s\), how many bits on the average can be predicted about \(q\)?’:

\[
I(S,Q) = \int P_{s|q}(s|q) \log \left( \frac{P_{s|q}(s|q)}{P_s(s)P_q(q)} \right) ds dq,
\]

where (i) \(S\) and \(Q\) denote the systems, (ii) \(P_s(s)\) and \(P_q(q)\) are the respective probability densities at \(s\) and \(q\), and (iii) \(P_{s|q}(s|q)\) is the joint probability density at \(s\) and \(q\). If the value of MI for \((S,Q)\) is larger, it means that mutual dependence between \(S\) and \(Q\) is stronger. The data length was \(2^{12}\), that is 2.048s. If \(S=Q\), the correlation between them should be perfect. Then, \(I(S,Q)=n\), where the data length is \(2^n\), because the algorithm is developed to the discrete case. The MI value between the same 2 time series is \(n\). Hence, MI values were normalized by \(n\), in other words, these values were divided by \(n\) and a value of unity for MI means a perfect correlation. In the previous study we determined the threshold value for distinguishing correlated from noncorrelated data as 0.047.\(^1\) An MI value greater than 0.088 indicates a strong correlation.

We denoted 3 periods of data length 2.048s (4,096 data points) as Vs, IM (the intermediate period from the end of the vagal stimulation to the end of AF), and PT, respectively: (1) during Vs, (2) 6s before the termination of AF, and (3) just prior to the termination of AF (Fig 2). We took RA2 as a reference because it was situated midway between the other epicardial electrodes. We calculated MI \(IT(T)\) of \((S,Q)\); \(S\) is always a time series of RA2 and \(Q\) is another time series, for example, \(S=RA2(t)\) and \(Q=Lap(t)\) during each period.

Statistical Analysis

The values of the continuous variables are presented as means±1 standard error of the mean (SEM). We used one-way repeated-measures ANOVA (Fisher’s test) to test for statistical significance among the 3 periods (ie, Vs, IM and PT). In addition, we used one-way repeated-measures ANOVA to examine the relationship between changes of MI values and distances from RA2 to the other electrodes. A 2-tailed p<0.05 was considered significant.

Results

Observation of Recordings

Fig 3 shows the recordings of the II-lead electrocardiogram, blood pressure, and the 5 epicardial electrograms (HRA, RA1, RA2, Rap and Lap) between the 2s before and the 2s after the cessation of Vs (Fig 2). The artifact
spikes of Vs appear with a cycle length of 80 ms (12.5 Hz) in the II-lead electrocardiogram. During Vs the fibrillatory waves of right atrial potentials seem to be rather cyclic and faster than the stimulation spikes. The rate of these fibrillatory waves is approximately 17 Hz. The fibrillatory wave of Lap is slower than those of the right atrium and looks rather regular. After the cessation of Vs, the cyclic pattern appears in all epicardial electrograms, although the cyclic rate of the fibrillatory waves is slower than during Vs. In particular, the cycle length of fibrillation seems to be nearly equal in the right positions of the epicardial electrograms.

**FFT Analysis**

Fig 4 shows the time courses of the power spectra of 30 consecutive segments recorded at RA2. The vertical axis in the Figure shows the cessation of Vs. During Vs, the power at 17 Hz appears to be the most prominent. After the cessation of Vs, the peak power at 17 Hz gradually decreases, the power values at slower frequencies become more marked and the power around 7 Hz finally becomes the most prominent with some harmonics.

Fig 5 shows the time courses of the power spectra of 30 consecutive segments on each of the 5 epicardial electrograms. Note that the power around 17 Hz is conspicuous at the right atrial electrodes during Vs, whereas the power around 10 Hz is prominent at the left atrial electrode (Lap). In particular, the power around 17 Hz at HRA, RA1, and RA2 decreases at the time that Vs ceases, and the prominent power shifts from 17 Hz to 7 Hz.

**Mutual Information**

Fig 6 compares the MI values between RA2 and each of the other epicardial electrodes in the Vs, IM, and PT periods. Each frame of Fig 6 shows a significant increase of MI values from Vs to PT through IM. The MI value on all epicardial electrodes during PT was 0.126±0.006. These
findings indicate that the correlations between RA2 and any one of the others became stronger as the highly active process of AF terminated. The MI values during Vs were all less than 0.088 and all those during PT were greater than 0.088, indicating that the correlations between RA2 and any one of the others were strong during PT, but not during Vs. However, note that the MI value (0.066±0.005) is greater than 0.047 (the critical value for correlated data) even during Vs, which indicates that the electrical potentials at RA2 correlate significantly with those at each of the other electrodes.

We calculated the differences between the MI values during Vs and those during PT (MI during PT–MI during Vs) at HRA, RA1, Rap, and Lap in order to examine the relationship between changes of MI values and distances from RA2 to the other electrodes. RA1 and Rap were closer to RA2 than HRA and Lap. Fig 7 shows one-way repeated-measures ANOVA between the difference of the MI values at RA1 (or Rap) and those at HRA and Lap. The difference of the MI values at Rap was significantly (p<0.05) larger than the differences of the MI values at HRA and Lap. The difference of the MI values at RA1 showed a tendency to be larger than those of the MI values at HRA and Lap. These results indicate that the MI values increase more at the electrodes close to RA2 (RA1 and Rap) than at those far from it (HRA and Lap).

Discussion

AF is often described as a disorganized phenomenon but recently many features that suggest an underlying order have been reported. Slocum et al showed that the power...
The qualities of AF do not seem consistent with spatially similar temporally periodic activity that were identified. Skanes et al demonstrated specific sequences of termination process of atrial fibrillation (AF). Atrial refractoriness is considered quantitative evidence for an underlying order in AF. It is consistent at all right atrial electrodes, which may be vagally induced AF had a discrete peak around 17Hz. After random activation, the power spectrum of AF had a discrete peak in the 4–9Hz band and Gerstenfeld et al demonstrated preferential routes of wave propagation during AF by showing transient linking of atrial excitation. In a recent high-resolution optical mapping study, Skanes et al demonstrated specific sequences of spatially similar temporally periodic activity that were identified during the complex patterns of activation seen in AF. These qualities of AF do not seem consistent with random activation.

The present study showed that the power spectrum of vagally induced AF had a discrete peak around 17Hz. After Vs was stopped, the discrete peak shifted from 17Hz to 7Hz consistently at all right atrial electrodes, which may be quantitative evidence for an underlying order in AF. It is considered that atrial refractoriness is shortened during Vs, which decreases the wavelength for reentry and promotes the occurrence of AF. Atrial refractoriness is considered to be minimized around a frequency of 17Hz, which is consistent with the 16.7Hz reported by Skanes et al in the isolated sheep heart. It would appear that the anatomy and electrophysiological characteristics of the atria are likely to constrain the patterns of wave propagation, resulting in some degree of underlying order.

Our findings from frequency analysis are quantitative evidence for some degree of underlying order in the frequency domain. In the present study, we used the MI method to reveal in a quantitative manner the spatio-temporal characteristics of the process in AF. The MI values were greater than 0.047 (the critical value for correlated data) even during Vs, which indicates that the electrical potentials at RA2 correlated significantly with those at each of the other electrodes. The MI values increased from the highly active process of AF during Vs to the less active one during PT, and increased more at the electrodes close to RA2 (RA1 and Rap) than at those further from it (HRA and Lap). These findings suggest that multiple wavelets progressively organized into a few major waves toward the termination of AF and are the first quantitative demonstration of an underlying order in the process of AF.

Here we summarize the findings from frequency analysis and MI analysis. The color maps of Fig 5 indicate some low peaks of less than 20Hz, which shift into a discrete peak around 7Hz from Vs to PT, suggesting that wavelets of various sizes during Vs organize into some larger waves, a process resulting from the lengthening of atrial refractoriness after stopping Vs. It can be considered that the closer wavelets organize more frequently and that AF terminates as the number of ‘mother’ waves sustaining it decreases (Fig 7).

Study Limitations
First, we used only 5 epicardial electrodes in total and only 1 of them was on the left atrium (Lap). Hence, we could not examine the process of AF in the left atrium. In the present study, power around 17Hz was conspicuous in the right atrium during Vs, whereas that around 10Hz was prominent in the left atrium. However, several studies in different models have demonstrated that activity is more rapid in the left atrium than in the right atrium. To solve this discrepancy, we need to use more epicardial electrodes on the left atrium.

Second, the power around 17Hz remained until the termination of AF, although it decreased gradually. We need to examine whether such high-frequency wavelets result from stable mother waves or an ectopic focus.

Third, we only examined a model of AF induced by Vs.

Conclusion
Quantitative evidence from frequency analysis and MI analysis demonstrated that AF is not a random phenomenon in this model.

References