Monitoring the Progression of the Atrial Electrical Remodeling in Patients With Paroxysmal Atrial Fibrillation —— Analysis of the f–f Interval During Ambulatory ECG Monitoring ——

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It is important to clarify how electrical remodeling develops in clinical cases of paroxysmal atrial fibrillation (PAF), because it has been suggested that this electrophysiological phenomenon promotes an increase in the frequency of PAF. In the present study, the f–f interval during PAF was analyzed from the ambulatory ECG recordings of 21 patients with PAF (total PAF duration >2/24 h with normal atrial size) to monitor the atrial electrophysiological changes. The patients were clinically followed-up for 6 months without any antiarrhythmic drugs. Before and after the follow-up period 24-h Holter monitoring was carried out and the duration of both the PAF and the f–f intervals during the PAF episode were evaluated. In selected cases, the atrial effective refractory period (ERP) was evaluated in an electrophysiologic study before and after the follow-up period. The total PAF duration was prolonged from 187±50 to 223±79 min (p=0.034) and the f–f interval was shortened from 0.14±0.03 to 0.12±0.02 ms (p=0.003). There was an inverse relationship between the changes in total PAF duration and f–f interval (p=0.027). The ERP was shortened from 214±15 to 194±5 ms (n=5, p=0.025) and there was a direct correlation between the changes in ERP and f–f interval (p=0.048). In clinical cases, the prolongation of the PAF was related to the shortening of the f–f interval during the PAF episodes and to the shortening of the atrial ERP. Electrical remodeling plays a role in promoting the development of the atrial fibrillation in patients with PAF.

Methods

Patients

The study population consisted of 21 patients with the frequent type of PAF (11 males, 10 females; mean age, 61±9 years). For the patient selection, the total PAF duration had to be longer than 2/24 h on Holter monitoring in

Electrical remodeling plays a role in promoting the development of the atrial fibrillation in patients with PAF.

Key Words: Atrial fibrillation; Atrial refractoriness; Electrical remodeling; Holter monitoring

Atrial fibrillation (AF) usually appears as paroxysmal (PAF) and progresses slowly to chronic AF with an increase in the frequency of the episodes of PAF. Progression of the basic organic heart disease (eg, mitral stenosis) may be one of the mechanisms that increases the number of PAF episodes, but a similar phenomenon occurs in cases of AF without organic heart disease (ie, lone AF). Although atrial electrical remodeling (ie, the shortening of the atrial wavelength caused by frequent atrial activation) has been suggested as another mechanism promoting the increase in PAF episodes, it has not been documented in clinical cases because it is difficult to monitor the atrial wavelength in that situation. In the present study, the f–f interval during PAF was analyzed in the ambulatory ECG recordings as the index of the atrial refractoriness in order to monitor the long-term change in the atrial electrophysiological property.

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order to achieve reproducible recording of the PAF episode in a few Holter recordings. Patients with atrial enlargement were excluded to avoid the influence of the progression of the basic heart disease on PAF frequency.

Holter Monitoring and the Electrophysiologic Study

The 21 patients were followed up for approximately 6 months without taking any antiarrhythmic medication, and 24–48 h Holter monitoring was performed before and after the follow-up period (Model 563 StrataScan, Del Mar Avionics Co Ltd, Boston, MA, USA). In the Holter recording, (1) the number of triggering atrial premature contractions (APC), (2) number of PAF episodes during 24 h, (3) total duration of PAF, (4) longest duration of an episode of PAF, (5) mean duration of PAF, and (6) the f–f interval during PAF were evaluated. For data analysis, the PAF episodes lasting more than 5 s were designated as PAF in the trend data of the Holter system (Fig 1). The appearance of the PAF episode was confirmed in the minimized ECG trace, and the total duration and the longest episode of PAF could be measured on the trend graph (Fig 1). The mean PAF duration was calculated by dividing the total PAF duration by the number of episodes. Fig 2 is a representative example of the analysis of the f–f interval during a PAF episode. Atrial deflection in the ECG trace was manually detected (arrows). The parts of the trace superimposed by the QRS or T wave were excluded from the measurement. The mean f–f interval in each measured trace was calculated dividing the total duration by the number of f–f interval in each part. The mean f–f interval was calculated from the measurements for 10–15 s. See text for discussion.

was selected from the later part of each PAF episode to eliminate the influence of increased sympathetic nervous tone at the beginning of a PAF episode. The measuring time point in the day was also selected from a similar time in the day before and the one after the follow-up period to avoid the influence of the autonomic nervous system. In 5 selected patients, an electrophysiologic study (EPS) was performed to evaluate the atrial effective refractory period (AERP) before and after the follow-up period. In these patients, cardiac catheterization was performed as another indication, such as the following up a coronary stenosis. Two 5F quadrupolar electrode catheters (USCI Division of C.R. Bard, Billerica, MA, USA) were positioned against the high right atrium and the His bundle electrogram recording area. The AERP was measured at the high right atrium. A single premature stimulus was delivered after the 8 basic drive train at a cycle length of 600 ms. The coupling interval of the premature stimulus was decreased by 2 ms steps. Electrical stimulation was delivered using a programmable cardiac stimulator (RCO30, Fukuda-Denshi Co, Tokyo, Japan) at twice the diastolic threshold with a 2 ms rectangular pulse. Intracardiac electrograms were recorded using a computer system (CardioLab, Pruka Co Ltd, Boston, MA, USA).

Statistics

All values are expressed as mean ± standard deviation. Statistical analysis was performed with one-way ANOVA or Pearson’s chi-square test. A p value <0.05 was considered significant.
Results

The mean number of APCs recorded during the Holter monitoring was 1,676±2,639 per day in the control state, and 1,452±1,590 per day after the follow-up period (NS). Table 1 summarizes the number of PAF, the duration of PAF and the f–f interval before and after the follow-up period. The total PAF duration and the mean PAF duration showed significant prolongation, whereas the f–f interval showed significant shortening after the follow-up period. Total PAF duration was increased in 16/21 patients and decreased in the remaining 5 patients. The mean measurements showed a significant increase in the total PAF duration (control 187±50 vs 6 months 223±79 min, p=0.034). Mean PAF duration was increased in 18/21 patients and decreased in the remaining 3 patients. The mean measurements showed a significant increase (control 9.2±3.1 vs 6 months 13.8±8.4 min, p=0.025).

Fig 4 shows the measurements of the f–f interval during PAF in all 21 patients, and the AERP in the selected 5 cases. The f–f interval during PAF was decreased in 13/21 patients and increased in the remaining 8 patients. The f–f interval was reproducible in individual patients and did not show significant change even during a relatively long PAF episode. The mean measurement showed a significant decrease in the f–f interval during PAF (control 0.14±0.05 vs 6 months 0.12±0.03 s, p=0.007).

The AERP was evaluated in 5 selected patients during an EPS. All 5 patients showed decreases in AERP, and the mean data also showed a significant decrease in the AERP (control 214±15 vs 6 months 194±5 ms, p=0.023). In these 5 patients, the f–f interval was shortened from 152±32 to 115±15 ms (p=0.042) and the total PAF duration was increased from 209±40 to 278±106 min (p=0.039). Fig 5 shows the relationship between ΔAERP and Δf–f interval in the 5 patients. These parameters were calculated by subtracting the control measurements from those after the follow-up period, so a positive number indicates an increase in the parameters. There was a significant relationship between these 2 parameters. See text for discussion.

Fig 6A shows the relationship between the total PAF duration and the f–f interval before the follow-up: no significant correlation can be seen. (B) Relationship between the change in total PAF duration (Δtotal PAF) and the f–f interval (Δf–f interval). These findings were calculated by subtracting the control measurements from those after the follow-up period, so a positive number indicates an increase in the parameters. There was a significant relationship between these 2 parameters. See text for discussion.
the follow-up period from those after the follow-up, so a positive number indicates an increase in each parameter. They showed a significant relationship; that is, the increase in the total PAF correlated with the decrease in the f–f interval during PAF. Fig 7A shows the relationship between the mean PAF duration and the f–f interval in the control state, during which there was no significant correlation between them, and Fig 7B shows the relationship between the change in the mean PAF duration (Δmean PAF) and the change in the f–f interval (Δf–f interval), which, similarly to the total PAF, showed a significant relationship.

Discussion

The present study evaluating the relationship between the PAF duration and the f–f interval during Holter monitoring has several interesting findings. First, the duration of PAF (ie, total PAF and mean PAF) was significantly prolonged during the follow-up period of 6 months in patients with the frequent type of PAF. Second, the f–f interval during a PAF episode was shortened during the follow-up period of 6 months, in addition to the shortening of the AERP in selected patients. Third, in those selected patients, ΔAERP and Δf–f interval showed a significant direct relationship. Finally, although the total or mean PAF and the f–f interval at the control state (ie, before the follow-up) did not show a significant correlation, Δtotal PAF or Δmean PAF and Δf–f interval during the follow-up period of 6 months showed a significant inverse relationship.

Electrical Remodeling in Clinical PAF Patients

Several experimental studies have documented that continuous and frequent atrial activation causes shortening of the AERP and a decrease in atrial conduction velocity, which is now widely known as electrical remodeling.2–7 This phenomenon leads to the shortening of the wavelength and results in the promotion of both the initiation and maintenance of AF. Electrical remodeling is considered to contribute to the PAF in clinical cases. Several investigators have documented that the AERP was relatively short immediately after the version of persistent AF, and this short AERP was progressively prolonged during a few days after the version.10–17 These clinical findings matched the findings in experimental studies. On the other hand, although electrical remodeling is considered to contribute to an increase in PAF duration in clinical PAF patients, it has not been documented in clinical cases because it is practically difficult to non-invasively monitor the long-term atrial electrophysiologic properties.18,19 In the present patients with the frequent type of PAF, there was significant prolongation in PAF duration during the follow-up period of 6 months and this prolongation in the total or mean PAF might be caused by an increase in the duration or number of PAF episodes itself (ie, electrical remodeling) because there was no progression of the basic organic heart disease in any of the patients. The study period of 6 months may be relatively short for observation of the increase in PAF episodes in clinical cases, but it occurred in the present study probably because the patients had the very frequent type of PAF.

Usefulness of the f–f Interval in the Surface ECG to Monitor the Atrial Electrophysiologic Properties

According to the wavelength theory, the f–f interval during PAF in the local atrial electrogram reflects the local ‘wavelength’, which is defined as the product of the atrial refractory period and the conduction velocity20–22 The actual functional reentrant circuit is considered to have an excitable gap probably because of the influence of multiple anatomical obstacles (ie, vena cava, coronary sinus, pulmonary veins etc), in addition to the existence of post-repolarization refractoriness.3–25 However, the local f–f interval during AF has been confirmed to have a good relationship with the local atrial refractoriness, although the AF reentrant circuit may involve an excitable gap to varying degrees. In our previous studies, we used the f–f interval in the surface ECG during PAF as an index of the complexity of the multiple AF reentrant circuits with the result that the f–f interval in the surface ECG showed a good direct relationship with the local f–f interval in the atrial electrogram. The atrium in AF may have several simultaneous reentrant wavefronts, so the ECG trace in the surface lead may include all these activations in one ECG trace for analysis. Some of these activations may not appear on the surface lead, even though they exist, because of the voltage or the direction of the activation vectors, causing an underestimation with the former and an overestimation with the latter of the actual f–f interval. Although these influences may vary depending on the ECG recording (ie, body size, obesity etc), as well as the amplitude of the atrial signals, the analysis of the f–f interval was reproducible in each patient. Therefore, in total, the mean f–f interval in the surface
The f–f Interval as the Monitoring Index of Electrical Remodeling in PAF Patients

It was unclear whether electrical remodeling played a role in increasing the total or mean PAF duration during the present follow-up period of 6 months because the f–f interval does not directly reflect atrial refractoriness. However, there was a significant correlation between the AERP shortening and the increase in PAF duration in the 5 patients studied, although the number of patients was very limited. The f–f interval in the surface ECG trace can be considered an indirect index of atrial refractoriness; but it did not show a significant relationship with PAF duration, at least during the control state (ie, before the follow-up period). A partial explanation of this result is that PAF duration should be determined by not only the AERP but by other factors as well, and that the measurement of the f–f interval itself (ie, the recording of the f-wave in the surface ECG) is influenced by individual factors, such as body size, obesity etc. However, these 2 parameters showed a significant correlation when they were evaluated as changes during the follow-up (ie, f–f interval vs total PAF or mean PAF), which suggests that the f–f interval can be a useful index of atrial refractoriness, at least in individual patients, and might become a simple and feasible index of electrical remodeling in clinical cases.

Interestingly, in the present study the total PAF and the mean PAF showed a significant relationship with the f–f interval, but the max PAF did not. The reason of this difference was not clear, but probably the total PAF or the mean PAF duration reflects the mean arrhythmogenicity of the whole atrium. In contrast, the max PAF duration reflects just a single episode of PAF with the longest duration and so might not reflect the mean electrophysiologic property of the whole atrium. Because the number of triggering APCs was relatively large and unchanged during the follow-up period in the present patients, the shortening of the wavelength (ie, the atrial electrical remodeling) might have influenced the number of PAF episodes and resulted in prolongation of the total PAF duration.

Study Limitations

This study, evaluating the relationship between PAF duration and the f–f interval, has several important limitations. First, although patients with the frequent type of PAF (ie, >24 h/day) were selected, there may have been day-to-day variation in the PAF frequency itself during Holter recording. Second, the f-wave in the surface ECG trace is very small and so low voltage can lead to an underestimation and the recording noise can cause an overestimation of the number of f-waves. Although the f–f interval data was obtained from several measurements, the reproducibility of the data might be limited. Third, the influence of the autonomic nervous system was not evaluated. Finally, the change in the f–f interval in an individual PAF episode was not fully evaluated. These limitations should be solved in future studies with larger numbers of patients.

Conclusions

Patients with the repetitive type of PAF were followed up for 6 months and the PAF duration, AERP and f–f interval during a PAF episode was evaluated.

(1) Total PAF and mean PAF were significantly prolonged whereas the AERP and the f–f interval were shortened after the follow-up period.

(2) There was no significant relationship between the total PAF or the mean PAF and the f–f interval during the control state; however, there was a significant relationship between total PAF or mean PAF and f–f interval.

The f–f interval during a PAF episode can be a simple and useful method of predicting the change in PAF duration in clinical cases and may become an index of the progression of atrial electrical remodeling in individual patients.

References


