영남의대학술지 제24권 제2호
Yeungnam Univ. J. of Med.
Vol.24 No.2 p216-231, Dec. 2007

□ 원저 □

Parasympathetic Modulation Plays a Key Role in Initiation of Paroxysmal Atrial Fibrillation

Won Jae Lee, Dong Gu Shin, Geu Ru Hong, Jong Sun Park, Young Jo Kim

Department of Internal Medicine,
College of Medicine, Yeungnam University, Daegu, Korea

-Abstract-

Background : An acceleration or deceleration of the heart rate (HR), which reflects autonomic effects, is observed before the onset of paroxysmal atrial fibrillation (PAF). The purpose of this study was to assess the discrepancy in the autonomic interactions before the onset of PAF for different patterns of change in the HR.

Materials and Methods : From 105 Holter tapes with the PAF recorded, 55 episodes (42 patients, 34 men, 58±12 years) of PAF (>5 min), preceded by a sinus rhythm for more than 1 hour, were selected and submitted to time-domain and frequency-domain HR variability analyses. Fifty-five episodes were divided into 2 groups: group A PAF (n=30) with acceleration of the HR during the last 2 minutes before the PAF and group B (n=25) with deceleration of the HR.

Results : A significant linear decrease in the mean R-R interval was observed in group A (924±30 to 835±28 ms, P=0.001) and an increase from 831±32 to 866±31 ms in group B PAF episodes (P=0.046). In the frequency-domain analyses, the LF/HF ratio exhibited a progressive linear increase before the PAF in group A (P=0.005). The HF normalized units (HFnu) and natural logarithm-transformed HF (*ln*HF) values decreased from 30.8±4.0 to 16.1±1.8 (P=0.003) and 4.49±0.25 to 4.07±0.22 (P=0.001), respectively. Contrary to the results in group A, a significant increase in the HF components (HFnu and *ln*HF) (from 22.6±3.2 to 30.2±4.0, P=0.005, and 4.27±0.27 to 4.75 0.33, P=0.001, respectively) and a resultant decrease in the LF/HF ratio were observed in group B PAF episodes. No significant changes were observed in the LF components in either PAF group.

책임저자 : 신동구, 대구광역시 남구 대명5동 317-1, 영남대학교 의과대학 내과학교실
Tel: (053) 620-3843, Fax: (053) 654-8386, E-mail: dgshin@med.yu.ac.kr

Conclusion : Autonomic stimuli leading to an acceleration or deceleration of the HR before the onset of AF are due to parasympathetic modulation. Parasympathetic modulation plays a key role in the initiation of PAF.

Key Words: Atrial Fibrillation, Autonomic Nervous System, Heart Rate, Variability

Introduction

Paroxysmal atrial fibrillation (AF) is an arrhythmia commonly encountered in clinical practice.[1] It is generally accepted that the autonomic nervous system functions to modulate the initiation of AF.[2] The analysis of the heart rate variability (HRV), just preceding the spontaneous onset of AF, is a noninvasive method for evaluating autonomic effects and provides a way to document them.[3, 4] An improved understanding of the mechanism of onset of PAF may help with patient management and preventive therapy.

Several studies have demonstrated the fluctuation in the autonomic effects before the onset of AF, however, the results have been inconsistent.[5, 6, 8-15] Coumel[2] classified AF into vagally mediated and sympathetically mediated types, based on the clinical history. Vagally mediated AF, was preceded by progressive bradycardia, whereas adrenergically mediated AF, was accompanied by an increased sinus rate, and was opposite to the vagal type in all aspects.

In previous studies to determine the autonomic mechanism underlying AF, PAF episodes were grouped and analyzed based on the AF onset time[5, 6] or the presence or absence of structural heart disease[8-10] in order to characterize and quantify the autonomic changes. Grouping of the PAF episodes by the timing of the AF onset or the presence of organic heart disease is too subjective. For example, daytime AF is not always sympathetically mediated AF and not always associated with organic heart disease. A more objective classification might improve the consistency of the study results. For example, the change in the heart rate, would be a more objective measure to study the autonomic effects before the onset of AF.

We hypothesized that the change in the autonomic effects before the spontaneous onset of AF would differ between AF preceded by bradycardia and AF adrenergically mediated with an increased sinus rate. No data are available regarding how the parasympathetic and sympathetic nervous system interact and cause changes in the heart rate before the spontaneous onset of AF. This study was undertaken to detect differences in the autonomic effects between the two types of AF, acceleration or deceleration of the heart rate, before the onset of AF.

Materials and Methods

Study Population

From 105 Holter recordings in which one or more PAF episode(s) were recorded, the PAF episodes were selected for analysis if the following criteria were met. : (1) The documentation of at least one episode of PAF (> 5 min), (2) The presence of noise-free normal sinus rhythm for > 60 minutes before PAF, and (3) no evidence of sinus node dysfunction or conduction disturbances. None of the patients were taking antiarrhythmics, such as amiodarone or β-blockers, at the time of the Holter recordings. The presence of structural heart disease was confirmed by the history, physical examination, ECG, echocardiography and exercise stress testing. Finally, 55 PAF episodes from 45 Holter recordings in 42 patients (34 men and 8 women, aged 58±12 years) without structural heart disease were suitable for the analysis.

The PAF episodes were divided into two groups according to the pattern of the heart rate change before the onst of PAF.: In Group A the mean heart rate for the 2-minutes of normal sinus rhythm immediately before the onset of PAF was faster than that of the prior 20 minute period (characterized by an acceleration of the heart rate before the AF onset). In Group B the heart rate decreased, (deceleration of the heart rate) just before the onset of PAF. The PAF episodes were further divided into two subgroups according to the time of PAF onset: from 7:00 A.M. to 9:00 P.M. (day-time AF) or from 9:00 P.M. to 7:00 A.M. (night-time AF).

Electrocardiographic Recordings

All subjects underwent 24-hour electrocardiographic recordings. The mean recording time of the Holter recordings was 22.9±1.3 hours. All measurements were obtained with a 3-channel digital recorder (SeerMc, Marquette Electronics Inc) with 125-Hz sampling and were processed by Marquette MARS 8000 equipment using MARS software version 4.0 (Milwaukee, Wisconsin, USA). Each beat was classified and labeled for the site of origin using template-matching techniques. An experienced observer manually reviewed and corrected all tracings if necessary. The Holter ECG data were then imported into a commercially available analysis program (WinCPRS, Absolute Aliens, Turku, Finland), and the R-R intervals were reviewed again to edit all premature beats and noise. All questionable portions were compared with the raw data from the Holter ECGs.

HRV Analysis

The 20 minutes of normal sinus rhythm preceding the onset of the sustained AF, was divided into 10 two-minute intervals (18 to 20 min, 16 to 18 min, 14 to 16 min, 12 to 14 min, 10 to 12 min, 8 to 10 min, 6 to 8 min, 4 to 6 min, 2 to 4 min, and 0 to 2 min preceding the onset of the PAF). Only the

segments with less than three ectopic beats and with no more than two beats occurring in succession, were included in the evaluation. All analyses of the R-R interval variability were performed with a commercially available program (WinCPRS software, ver. 1.157, Absolute Aliens, Finland).

The following time-domain HRV parameters were analyzed: the mean R-R interval (mean NN interval, ms), the standard deviation (SD) of all normal sinus R-R intervals (SDNN; ms), the root-mean-square of the successive normal sinus R-R interval difference (rMSSD, ms), and the percentage of successive normal sinus R-R intervals >50 ms (pNN_{50}, %).

We used an autoregressive method to calculate the spectral power of the R-R interval, as described previously.[16] The Akaike information criterion was used as an automatic model order calculation method. The spectrum was computed using all model orders from one to the value of the parameter Maximum model order. For each model order, the selected criterion was computed and the model order corresponding to the minimum value of the criterion was finally used to generate the spectrum.

The HRV indices in the frequency domain were analyzed over the same two-minute intervals, and the following parameters were calculated: very-low-frequency (VLF) components of <0.04 Hz, low frequency (LF) components of 0.04 to 0.15 Hz, high-frequency (HF) components of 0.15 to 0.40 Hz, and the LF/HFratio (LF/HF). The LF and HF components were analyzed both in absolute (ms^2) and normalized units (NU) obtained using the following formula:[3]

$$\text{Power (NU)} = 100 \text{ LF or HF power } (ms^2) / [\text{Total power } (ms^2) - \text{VLF power } (ms^2)]$$

Because of the skewed nature of the data with large values, the spectral power (ms^2) was transformed into the natural logarithm (ln) in the LF and HF bands before the statistical analysis.

Statistical analysis

Data are presented as the mean ± SEM for the HRV parameters and as the mean ± SD for the clinical and Holter data. Comparisons of the data obtained at different time intervals were performed using repeated measures ANOVA. A 2-tailed unpaired Student's *t*-test was used to compare the results of the HRV parameters between the different groups. Differences of categorical variables between the two groups were assessed using the Chi-square test or the Fisher exact test. A P value <0.05 was considered significant.

Results

The clinical characteristics of the study population are summarized in Table 1. Fifty-five episodes of paroxysmal AF fulfilled the inclusion criteria and were analyzed.

Table 1. Clinical characteristics of patients with group A and B PAF episodes (N=55)

Characteristics	Group A N=30	Group B N=25	P value
Age, years	57.6 ± 12.4	57.7 ± 11.5	NS
Male/Female	22/8	19/6	NS
Duration, minutes	208 ± 300	267 ± 340	NS
Day/Night time PAF	16/14	12/13	NS
Associated disease			
Hypertension	8	9	
DM	3	1	
IHD	1	4	
Hypertension & IHD	1	1	
Lone AF	17	10	NS
LA size, cm	3.70 ± 0.43	3.73 ± 0.47	NS
P wave duration*, msec	115.8 ± 2.3	112.1 ± 4.0	NS
LVEF, %	64 ± 10	65 ± 7	NS

Values are mean ± SD. PAF : Paroxysmal atrial fibrillation; DM : diabetes mellitus; IHD : ischemic heart disease; LVEF : left ventricular ejection fraction; NS : not significant; * : Filtered P wave duration measured by the signal-averaged ECG.

Baseline characteristics

Of 55 PAF episodes, acceleration of the sinus rate before AF onset was present in 30 episodes (55%, group A) and deceleration of the sinus rate was present in 25 episodes (45%, group B). The duration of the PAF episodes in groups A and B were 208 ± 300 and 267 ± 340 min, respectively, which was not statistically significant. No differences between the two groups were noted with regard to the filtered P wave duration using the signal-averaged ECG or by any of the echocar-

Table 2. Changes in the HRV parameters before the onset of PAF in the overall PAF episodes

	20-18	18-16	16-14	14-12	12-10	10-8	8-6	6-4	4-2	2-0 min	P value
Mean RR, msec	882±24	889±25	888±24	887±24	894±23	896±25	877±23	879±22	865±22	845±21	0.032
rMSSD, msec	23.7±2.8	21.3±2.1	21.9±2.0	22.0±2.1	23.4±2.1	21.9±2.0	20.9±2.0	22.4±1.9	21.0±1.9	24.3±3.0	0.983
pNN_{50}, %	5.09±1.59	4.22±1.35	4.72±1.44	4.67±1.40	5.98±1.50	5.53±1.55	4.54±1.21	5.70±1.53	5.18±1.51	5.61±1.45	0.488
LF, ms^2	405±113	269±40	312±61	317±51	350±55	298±52	321±63	319±61	285±75	359±56	0.848
LFnu, %	50.2±3.1	51.0±2.9	50.7±2.8	52.9±2.9	51.8±3.1	50.0±3.0	48.8±2.8	50.3±2.6	48.8±2.8	50.8±3.1	0.609
lnLF	5.00±0.19	5.00±0.17	5.04±0.17	5.06±0.18	5.12±0.19	5.01±0.17	4.87±0.20	5.04±0.17	4.87±0.17	5.27±0.17	0.724
HF, ms^2	210±67	145±33	161±32	171±33	196±36	174±37	149±27	181±36	156±35	179±99	0.586
HFnu, %	29.3±2.7	27.6±2.7	29.5±2.8	30.0±2.6	28.9±2.6	28.0±2.7	28.2±2.7	29.6±2.5	28.0±2.6	22.6±2.3	0.170
lnHF	4.36±0.17	4.26±0.16	4.37±0.16	4.41±0.16	4.46±0.18	4.32±0.17	4.23±0.18	4.42±0.17	4.18±0.18	4.35±0.20	0.661
LF/HF	3.61±0.64	3.68±0.64	3.86±0.72	3.32±0.51	3.48±0.53	3.44±0.54	2.98±0.34	2.68±0.26	3.26±0.42	4.31±0.69	0.741

Data are mean±S.E. rMSSD: root-mean-square of the successive normal sinus RR interval difference ; pNN_{50} :percentage of successive normal sinus RR intervals >50 ms ; LF and LFnu : low frequency power and it's normalized units; HF and Hfnu: high-frequency power and it's normalized units; ln: natural logarithm.

diographic parameters measured (Table 1).

Relation of the AF types to the AF onset time

With regard to the AF onset time, a nocturnal AF occurrence was observed in 14 of 30 (47%) PAF episodes in group A, and in 13 of 25 (52%) PAF episodes in group B. There was no significant difference in the incidence of a daytime or a nighttime onset of AF in comparisons between the two groups.

Time-domain HRV parameters

The HRV parameters are listed in Tables 2 and 3. No significant change in the mean RR interval, rMSSD or pNN_{50} before the onset of AF was observed when all PAF episodes were considered.

In group A, a significant and linear decrease in the mean R-R interval was observed over the 20 minutes preceding the onset of the AF (from 924±30 to 835±28 ms; P=0.001 Table 3, Fig. 2). The mean R-R interval peaked at 12 minutes and then linearly decreased from 951±28 to 835±28 ms in the

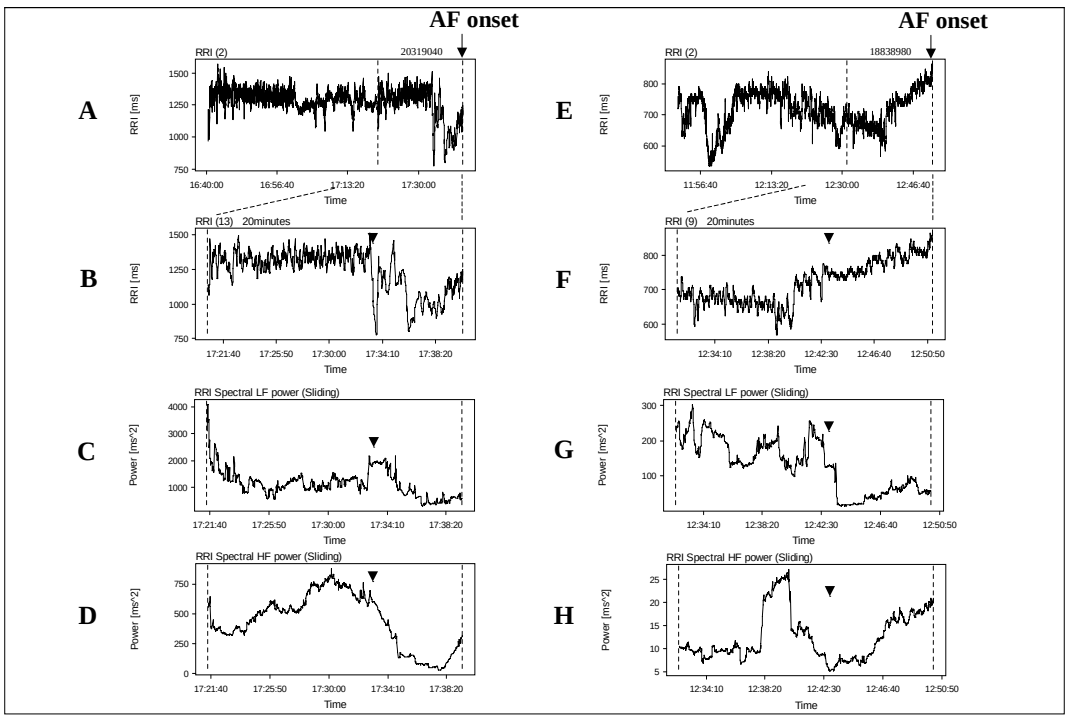

Fig. 1. Representative examples of one-hour (A) and 20-minute R-R interval tachograms (B) immediately before the onset of a group A PAF episode. A sliding spectra of the LF (C) and HF (D) powers, which were calculated using stepwise windows (120 second window width and 10 second steps), is shown. A decrease in the HF power, rather than an increase in the LF power, is noted around 8 minutes before the AF coinciding with an acceleration in the heart rate before the AF initiation. One-hour (E) and 20-minute R-R interval tachograms (F), sliding spectra of the LF (G) and the HF (H) power in a group B PAF episode are shown.

Table 3. Changes in HRV parameters before the onset of PAF in Group A and B PAF episode

	20–18	18–16	16–14	14–12	12–10	10–8	8–6	6–4	4–2	2–0 min	P value
Group A PAF											
Mean RR, msec	924±30	937±31	930±30	935±28	951±28	950±30	921±28	909±36	883±27	835±28	0.001
rMSSD, msec	23.8±3.9	20.4±1.9	22.0±2.3	22.0±2.1	24.3±2.7	22.9±2.5	21.8±2.2	21.8±2.3	19.2±2.0	19.0±1.8	0.003*
pNN_{50}, %	3.95±1.31	3.66±1.12	4.53±1.40	4.33±1.51	6.42±2.07	5.46±1.72	4.11±1.21	4.51±1.61	3.47±1.22	3.12±0.95	0.036*
LF, ms^2	513±209	246±54	289±77	300±68	322±72	340±86	362±90	322±72	326±133	343±76	0.824
LFnu, %	50.6±4.3	50.3±3.8	48.4±3.7	51.4±4.0	50.7±3.7	48.5±4.1	49.2±3.9	51.0±3.7	49.6±4.0	51.4±4.0	0.936
lnLF	5.07±0.26	4.97±0.21	5.02±0.21	4.98±0.25	5.08±0.24	5.12±0.24	5.09±0.26	5.18±0.22	5.01±0.22	5.33±0.20	0.394
HF, ms^2	259±120	130±23	163±34	164±33	219±50	177±40	154±31	172±43	120±30	110±24	0.012*
HFnu, %	30.8±4.0	29.6±4.0	33.7±3.9	34.5±4.0	35.2±3.6	31.5±4.0	30.2±4.1	29.6±3.6	24.3±3.4	16.1±1.8	0.003
lnHF	4.49±0.25	4.34±0.21	4.55±0.21	4.54±0.21	4.69±0.24	4.56±0.22	4.49±0.21	4.52±0.21	4.11±0.23	40.7±0.22	0.001
LF/HF	3.09±0.54	3.04±0.54	3.12±0.99	2.63±0.53	2.28±0.38	2.92±0.57	2.83±0.46	2.79±0.39	3.75±0.63	5.31±1.19	0.005
Group B PAF											
Mean RR, msec	827±34	833±35	837±35	835±34	831±32	831±34	827±34	845±34	850±32	866±31	0.046*
rMSSD, msec	23.7±4.1	22.2±3.8	21.8±3.5	22.1±3.7	22.5±3.2	20.9±3.3	20.0±2.7	23.1±3.1	22.9±3.4	30.1±5.8	0.048*
pNN_{50}, %	6.33±2.99	4.83±2.55	4.94±2.61	5.03±2.43	5.49±2.22	5.61±2.68	5.00±2.17	6.98±2.67	7.03±2.85	8.30±2.76	0.022*
LF, ms^2	297±69	305±63	349±100	343±80	385±89	260±58	288±93	327±106	249±63	389±85	0.986
LFnu, %	48.9±4.7	51.8±4.8	53.2±4.5	53.4±4.2	51.6±5.2	50.1±4.7	47.4±4.3	48.9±3.9	47.3±4.1	49.2±5.0	0.233
lnLF	4.96±0.29	5.10±0.27	5.15±0.27	5.14±0.31	5.14±0.31	4.91±0.25	4.70±0.30	4.93±0.27	4.80±0.28	5.27±0.29	0.647
HF, ms^2	162±52	168±66	166±59	184±63	177±56	177±68	148±48	198±60	203±67	479±208	0.090*
HFnu, %	28.1±3.7	25.4±3.8	25.1±4.0	25.8±3.2	22.6±3.2	24.6±3.7	26.6±3.8	30.2±3.4	32.1±4.1	30.2±4.0	0.005*
lnHF	4.29±0.24	4.26±0.24	4.24±0.26	4.32±0.26	4.27±0.27	4.12±0.28	4.03±0.27	4.41±0.27	4.34±0.27	4.75±0.33	0.001*
LF/HF	4.17±1.24	4.49±1.25	4.76±1.10	3.90±0.90	4.40±0.93	4.00±0.98	3.02±0.52	2.48±0.35	2.72±0.56	3.13±0.60	0.035*

Data are mean ± S.E. Acronyms are the same as in Table 2.
* denote the variables having a significant change starting from 12–10 minutes before the onset of AF.

two minutes before the onset of the AF. A significant and linear decrease was observed for the rMSSD and pNN_{50} over the 12 minutes preceding the onset of the AF. In contrast to group A PAF episodes, in group B, a significant and linear increase in the mean R-R interval was observed over the 12 minutes preceding the onset of the AF episodes (from 831±32 to 866±31ms; P=0.046 Table 3, Fig. 2). A significant and progressive increase in the rMSSD and pNN_{50}, starting from the 12 minutes preceding the onset of the AF, was observed.

Frequency-domain HRV parameters

In the group A PAF episodes, a significant decrease in the HF power, starting from 12 minutes before the onset of the AF, was observed (from 219±50 to 110±24 ms2 P=0.012 Table 3, Fig. 2). The decrease was linear and the highest HF power was observed 12 to 10 minutes before the onset of the AF. Comparable results were observed for the normalized HF (HF_{nu}) and logarithmically

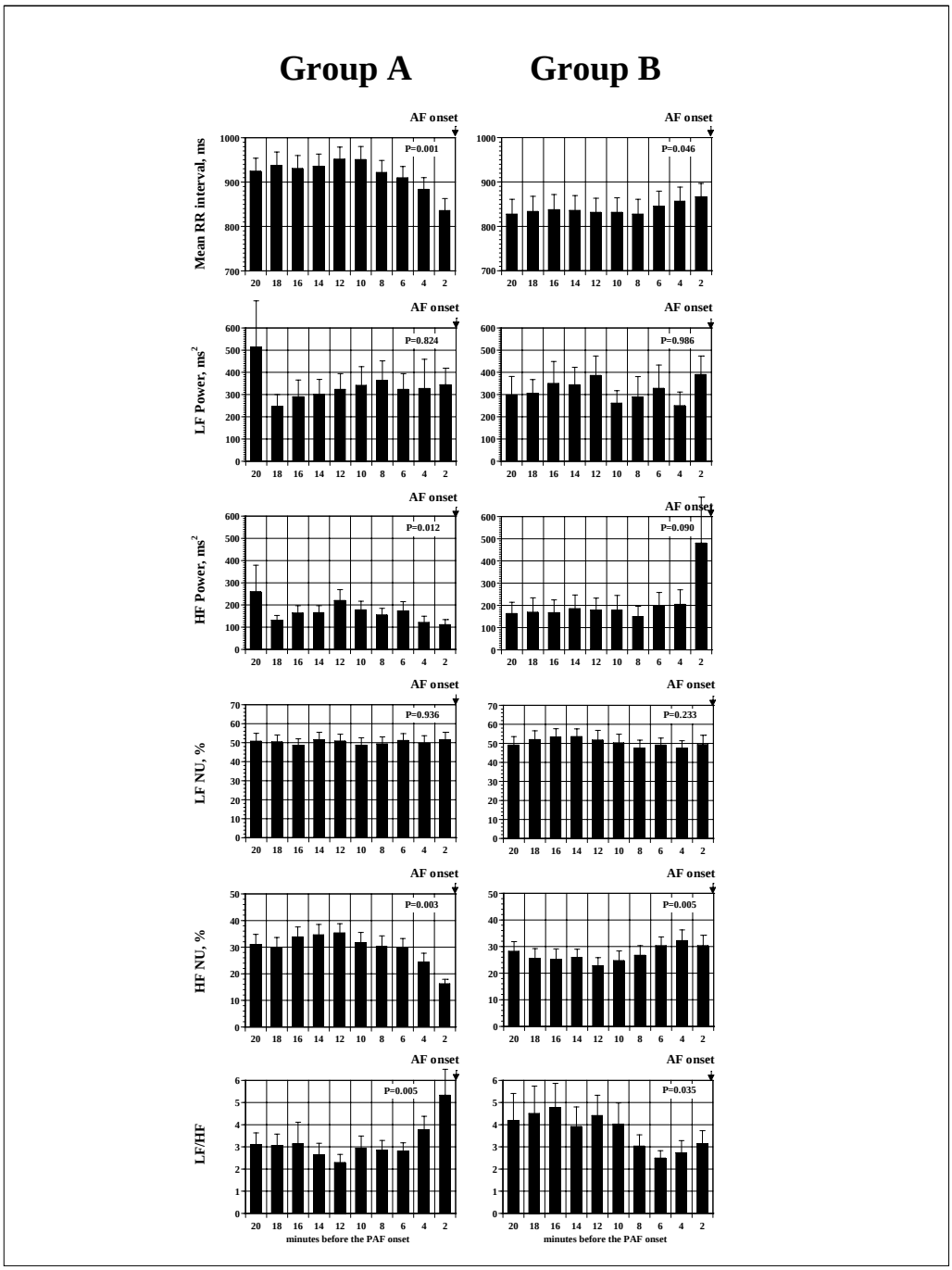

Fig. 2. Change in the time- and frequency-domain HRV parameters before the onset of AF in group A and B PAF episodes: mean RR intervals, LF and HF powers, normalized units (nu) of the HF and LF components, and the resultant LF/HF ratio before the onset of AF. See the text for the details. Data are expressed as mean ± SEM.

transformed HF powers (*ln*HF) (Table 3). There was no significant change in the LF power during the 20 minutes prior to the onset of AF. The highest LF power was noted 20-18 minutes prior to a significant gradual decrease in the HF power before the AF. The change in the normalized LF (LF_{nu}) and logarithmically transformed LF (*ln*LF) powers was also not significant. Furthermore, a significant linear increase in the LF/HF ratio was observed (2.28±0.38 at 12 min. to 5.31±1.19 two min. just before the AF, $P<0.005$) (Fig. 2). In group B PAF episodes, the HF powers during the 20 minutes before the onset of the AF had a tendency to increase ($P=0.090$) and a marked increase in the absolute HF power (from 203±67 ms^2 at 4-2 minutes to 479±208 ms^2 at 2-0 minutes immediately before the onset of AF) was observed. The HF_{nu} and *ln*HF exhibited a significant linear increase starting from 12-10 minutes before the onset of AF (Fig. 2, Table 3). A significant linear decrease in the LF/HF ratio was noted in group B PAF episodes ($P=0.035$). However, no significant decrease in the LF powers was observed during the 20 minute observation period before the onset of the AF ($P=0.986$). The results were the same as when the LF powers were normalized or logarithmically transformed.

No significant changes in any of the frequency-domain parameters, as with the time-domain parameters, were noted when all PAF episodes were analyzed (Table 2).

Discussion

The results of this study demonstrated an altered sympathetic/vagal balance before the onset of AF consistent with previous studies.

Main findings

The main findings of this study were that a significant decrease in the vagal tone ("vagal withdrawal"), rather than an increase in sympathetic activity, was the primary autonomic stimuli for AF initiation for the sympathetic type of PAF episodes in which the heart rate acceleration was observed before the onset of the AF. A significant increase in the vagal tone was observed in PAF episodes where a deceleration in the heart rate was noted before the onset of AF. However, no significant changes in the sympathetic activity were observed in either type of PAF episode. These results suggest that parasympathetic modulation plays a key role in the initiation of PAF regardless of the PAF onset type. Therefore, these results extend the work of previous studies and improve our understanding of the role of the autonomic nervous system in the initiation of PAF.

Comparison with previous studies

The arrhythmic influence of vagal/sympathetic effects on atrial tissue is well known.[2, 17, 18] Coumel[2] originally identified two different patterns of PAF, suggesting a predominant

role of either the vagal or the sympathetic system as the determinants of the episodes. The clinical history is a reliable guide for determining which type of autonomic predominance contributes to the destabilization of the arrhythmogenic substrate. However, the analysis of the heart rate variability (HRV), just preceding the onset of the arrhythmia, provides a non-invasive method for evaluating the autonomic effects and permits documentation of the associated mechanism.[3, 4)]

Several studies have demonstrated fluctuation in autonomic activity before the onset of AF. However, the previous results were inconsistent.[5, 6, 8-15)] The provisional conclusion was that a shift toward a vagal predominance was observed essentially in patients with PAF and structurally normal hearts, especially in young patients with nocturnal AF[5, 6)] or in patients with PAF triggered by pulmonary vein foci.[12)] However, most patients with organic PAF were considered to have a more sympathetic dependent AF.[8-10)]

The inconsistent results from the prior studies suggest more than one mechanism ; complex changes in autonomic activity are likely responsible for the occurrence of AF. In previous studies attempting to identify the autonomic mechanism responsible for AF, PAF episodes were grouped and analyzed based on the time of AF onset[5-7)] (day-time vs. night-time onset), or the presence or absence of structural heart disease[8-10)] to characterize and quantify the autonomic changes. For example, the study reported by Bettoni and Zimmermann,[9)] suggested that the underlying autonomic mechanism could be explained by a primary increase in adrenergic activity over at least 20 minutes prior to the onset of the PAF followed by a shift in the autonomic activity toward a more vagal predominance immediately before the onset of the PAF. The mean RR interval decreased linearly before the onset of the PAF in their study. However, this is not always the case, because for some PAF episodes, such as the so-called vagal type, an increase in the mean RR interval can be observed as shown in our study. The results may vary depending on the composition of the PAF patient population. Therefore, one cannot generalize these results as autonomic mechanisms applicable to all PAF episodes. In addition, it is unclear whether PAF should be divided into daytime or nighttime groups or whether the presence of structural heart diseases, which can affect the autonomic nervous system, is sifnificant.

The identification of specific onset mechanisms may help guide the development of preventive therapy strategies. From the therapeutic perspective, analysis of the heart rate dynamics, before the onset of AF, should not be evaluated with all PAF lumped together, regardless of the AF initiation pattern. The autonomic interaction underlying the acceleration or deceleration of the heart rate just before the onset of AF has not been

fully investigated. Therefore, this study was designed to analyze the changes in the autonomic activity before the onset of AF, and to determine the differences in the vagal and sympathetic autonomic nervous system based on the presence of an acceleration or deceleration of the heart rate before the onset of AF.

An acceleration and/or deceleration of the heart rate can be observed before the onset of AF. We classified the PAF episodes into two groups according to the preceding heart rate dynamics and sought to study the change or interaction of the sympathetic and parasympathetic nervous systems before PAF initiation in the two groups. In the cases with PAF episodes where a significant increase in the heart rate was observed (group A), a linear decrease in the RR interval values with a decrease in the rMSSD and pNN50 (the parameters predominantly reflecting vagal modulation) was observed before the onset of the PAF. These findings imply an increase in sympathetic activity, and are compatible with the characteristics of the daytime PAF as described in prior studies. However, the power spectral analysis showed that a significant linear decrease in the vagal tone before the onset of AF was a major factor in the autonomic imbalance or shift to a sympathetic predominance. The observed upsurge in the LF/HF ratio is compatible with these dynamic changes in the autonomic activity. Though a minor increase in the sympathetic tone preceding a significant reduction in the vagal tone was observed, the change in the sympathetic tone was not significant. Therefore, the heart rate acceleration was caused by "vagal withdrawal", not by direct augmentation of the sympathetic tone.

It is known that abnormal atria react differently than normal fibers, with an enhanced sensitivity to adrenergic stimulation. There is a predominance of vagal effects in the normal atria, and vagal withdrawal is an early characteristic of damaged hearts that may precede an increase in the sympathetic drive.[2, 29] However, we did not find a higher incidence of organic heart disease in the PAF patients where an acceleration of the heart rate was observed before the onset of the AF. Whether the vagal withdrawal observed in our study is an abnormal vagal reaction because of enhanced sensitivity to sympathetic stimulation is unknown and requires additional investigation.

Contrary to the aforementioned PAF types, a significant linear increase in the HF power was observed from 12 minutes prior to the onset of the PAF episodes in group B where a deceleration in the heart rate was noted. A transient increase in the LF power preceding a significant increase in the HF power was observed, and that increase in the HF power was thought to be a vagal rebound due to the preceding enhanced sympathetic tone. A significant linear change in the sympathetic

tone during the 20-minute observation period was absent. Comparable changes were noted in the time-domain parameters: i.e., an increase in the mean RR interval, rMSSD and pNN_{50}. These PAF episodes were similar to the onset of PAF during the nighttime with regard to change in the heart rate before the onset of AF. There was no difference in the incidence of the AF onset time and the presence of structural heart disease between groups A and B and the PAF episodes observed in our study.

When all of the PAF episodes were analyzed, regardless of the pattern of the heart rate change, there was no meaningful change in the sympathetic or parasympathetic nervous system observed. Thus, the changes in the autonomic activity likely differ depending on the proportion of PAF types included in the analysis.

The relationship between the fluctuations in the heart rate and the duration of the subsequent AF episodes continues to be debated.[19-21] Daytime AF episodes, which showed a significant increase in the heart rate, had longer (> 5 minutes) AF episodes.[19] However, there was no significant difference in AF duration in comparisons between the two groups; however, the episodes where a heart rate deceleration was observed tended to have a longer AF duration.

PAF episodes are preceded by runs of atrial premature beats or a solitary ectopic beat in more than half of the cases.[20] The count of premature beats is important in the analysis of the HRV. The amount of data distortion by preprocessing the R-R interval data contaminated with premature beats is not known. There are no specific recommendations in the literature for the maximum number of ectopic beats one can interpolate or accept. It is currently recommended that there should be no more than two or three ectopic beats in a short-term study (5 minutes), with no more than two beats occurring in succession.[23] We analyzed only the segments with less than two premature beats to avoid any distortion of the data. However, most prior studies included and analyzed segments with no more than 10 to 15% of ectopic beats.[5, 6, 8, 14]

The length of the segment duration for the calculation of the spectral power is important for detecting transient changes in the autonomic activity. A time interval ranging from five to 20 minutes before the onset of the AF is used in most studies. The difference in time intervals used for evaluation is one explanation for the inconsistency of the results of various studies on this topic. An analysis using a shorter time of less than 5 minutes would have better resolution for the temporal change in autonomic activity, because the vagal tone causes progressive heart rate slowing over a few hours or even a few beats, and a single vagal episode is sufficient to provoke AF.

Study limitations

Although the number of patients included in this study was relatively small, the number of AF episodes was large enough to analyze and draw conclusions. It is important to consider the sequence of the changes over time, because the autonomic interactions and the resultant imbalance is probably more important than the vagal or sympathetic activity alone. Vagal rebound generally results from primary adrenergic stimulation. We did not observe a significant variation in the sympathetic tone triggering a vagal rebound or withdrawal during our 20-minute observation period. The mechanisms explaining this abnormal sympathetic/vagal response might be explained at the cellular level.

We used the maximum entropy method (also called the autoregressive method) in this study. Though the fast Fourier transformation (FFT) method is the most widely used for calculating the spectral power; there is a high correlation between the spectral estimations obtained with the autoregressive and FFT techniques.[24] The autoregressive technique is useful for a very short time series.[3]

Summary

The results of this study demonstrated an altered sympathetic/vagal balance before the onset of AF, consistent with previous studies. A significant decrease in the vagal tone, rather than an increase in sympathetic activity, was the primary autonomic stimulus for AF initiation in the phenotypically sympathetic type of PAF episodes where heart rate acceleration was observed before the onset of AF. A significant increase in the vagal tone was observed in the PAF episodes where deceleration in the heart rate was noted before the onset of AF. No significant changes in the sympathetic activity were observed in either type of PAF episode. These results suggest that parasympathetic modulation plays a key role in the initiation of PAF regardless of the PAF onset type. These findings extend the understanding of the role of the autonomic nervous system in the initiation of PAF. Interventions to modify the parasympathetic input to the heart might be an effective treatment modality for PAF. Further study with the application of nonlinear methods might provide additional important information on the heart rate dynamics involved in the initiation of AF.[26]

Acknowledgments

The authors thank JM Lee, M.T. for her technical assistance with the data processing.

요 약

배경 : 자율 신경의 영향력을 반영하는 심박동의 가속 또는 감속은 발작성 심방세동의 시작 전 관찰된다. 본 연구의 목적은 심방세동 시작

전에 선행하는 두 다른 형태의 심박동의 변화가 자율 신경에 상호작용하는 차이를 평가하기 위함이다.

재료 및 방법 : 발작성 심방 세동이 기록된 105개의 홀터 결과 중에 5분 이상의 발작성 심방세동이 발생하기 전에 최소 한 시간 이상동안 정상 동율동을 보인 55개의 홀터 결과를 선택하여 심박동의 다양성에 대한 시간-우선 및 빈도-우선 분석을 시행하였다. 55개의 홀터 결과를 두 그룹으로 나누었는데, 발작성 심방 세동이 발생하기 전 마지막 2분 동안 심박동의 가속이 있었던 결과들을 그룹 A(n=30)로 분류하였고, 심박동의 감소가 있었던 결과들은 그룹 B(n=25)로 분류하였다.

결과 : 그룹 A에서 저명하게 비교적 균일한 평균 RR 간격의 감소(924 ± 30 to 835 ± 28ms, P=0.001)가 관찰되었고, 그룹 B에서는 평균 RR 간격의 증가(831 ± 32 to 866 ± 31ms, P=0.046)가 관찰되었다. 그룹 A는 빈도-우선 분석에서 LF/HF 비가 점진적으로 비교적 균일하게 증가하였다(P=0.005). 그룹 A에서 HF normalized units (HF_{nu})값은 30.8 ± 4.0에서 16.1 ± 1.8으로 감소하였고(P=0.003), natural logarithm-transformed HF (*In*HF) 값은 4.49 ± 0.25에서 4.07 ± 0.22로 감소하였다(P=0.001). 그룹 A와는 정반대로 그룹 B에서 HF_{nu} 값은 22.6 ± 3.2에서 30.2 ± 4.0으로 증가하였고 (P=0.005), *In*HF 값도 4.27 ± 0.27에서 4.75 ± 0.33으로 증가하였다(P=0.001). LF/HF 비도 그룹 B에서 결과적으로 감소하였다. 두 그룹 사이에 LF 구성요소의 저명한 차이는 관찰되지 않았다.

결론 : 발작성 심방세동이 시작되기 전에 선행하는 심박동의 가속과 감속을 유발하는 자율신경의 구동은 부교감 신경의 가감조절 때문이다. 부교감 신경의 가감조절이 발작성 심방세동의 시작에 중요한 역할을 하는 것으로 판단된다.

References

1. Kopecky SL, Gersh BJ, McGoon MD, et al. The natural history of lone atrial fibrillation. a population-based study over three decades. N Engl J Med 1987;317:669-74.
2. Coumel P. Paroxysmal atrial fibrillation: a disorder of autonomic tone? European Heart Journal 1994;15 (Supplement A):9-16.
3. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996;93(5):1043-65.
4. Lombardi F, Malliani A, Pagani M, Cerutti S. Heart rate variability and its sympatho-vagal modulation. Cardiovasc Res 1996;32:208-16.
5. Herweg B, Dalal P, Nagy B, Schweitzer P. Power spectral analysis of heart period variability of preceding sinus rhythm before initiation of paroxysmal atrial fibrillation. Am J Cardiol 1998;82(7):869-74.
6. Tomita T, Takei M, Saikawa Y, et al. Role of autonomic tone in the initiation and termination of paroxysmal atrial fibrillation in patients without structural heart disease. J Cardiovasc Electrophysiol 2003;14(6):559-64.
7. Sopher SM, Hnatkova K, Waktare JE, Murgatroyd FD, Camm AJ, Malik M. Circadian variation in atrial fibrillation in patients with frequent paroxysms. Pacing Clin Electrophysiol 1998 Nov;21(11 Pt 2):2445-9.

8. Huang JL, Wen ZC, Lee WL, Chang MS, Chen SA. Changes of autonomic tone before the onset of paroxysmal atrial fibrillation. Int J Cardiol 1998;66:275-83.
9. Bettoni M, Zimmermann M. Autonomic tone variations before the onset of paroxysmal atrial fibrillation. Circulation 2002;105:2753-9.
10. Klingenheben T, Grönefeld G, Li YG, et al. Heart rate variability to assess changes in cardiac vagal modulation before the onset of paroxysmal atrial fibrillation in patients with and without structural heart disease. Ann Noninvas Electrocardiol 1999;4:19-26.
11. Tomoda Y, Uemura S, Fujimoto S, et al. Assessment of autonomic nervous activity before the onset of paroxysmal atrial fibrillation. J Cardiol 1998;31(1):11-7.
12. Zimmermann M, Kalusche D. Fluctuation in autonomic tone is a major determinant of sustained atrial arrhythmias in patients with focal ectopy originating from the pulmonary veins. J Cardiovasc Electrophysiol 2001;12: 285-91.
13. Dimmer C, Tavernier R, Gjorgov N, et al. Variations of autonomic tone preceding onset of atrial fibrillation after coronary artery bypass grafting. Am J Cardiol 1998;82:22-5.
14. Fioranelli M, Piccoli M, Mileto GM. Analysis of heart rate variability five minutes before the onset of paroxysmal atrial fibrillation. Pacing Clin Electophysiol 1999;22:743-9.
15. Dimmer C, Szili-Torok T, Tavernier R, Verstraten T, Jordaens LJ. Initiating mechanisms of paroxysmal atrial fibrillation. Europace 2003; 5:1-9.
16. Kay SM, Marple SL. Spectrum analysis: A modern perspective. Proc IEEE 1981; 69:1380-419.
17. Smeets JLRM, Allessie MA, Lammers WJEP, et al. The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium: the role of the heart rate, autonomic transmitters, temperature, and potassium. Circ Res 1986;58:96-108.
18. Ninomyia I. Direct evidence of nonuniform distribution of vagal effects on dog atria. Circ Res 1966;19:576-83.
19. Hnatkova K, Waktare JEP, Sopher SM. A relationship between fluctuationsin heart rate and the duration of subsequent episodes of atrial fibrillation. Pacing Clin Electrophysiol 1998;21:181-5.
20. Hnatkova K, Waktare JEP, Murgatroyd FD, et al. Analysis of the cardiac rhythm preceding episodes of paroxysmal atrial fibrillation. Am heart J 1998;135:1010-9.
21. Vikman S, Yli-Mayry S, Makikallio TH, Airaksinen KE, Huikuri HV. Differences in heart rate dynamics before the spontaneous onset of long and short episodes of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 2001;6(2):134-42.
22. Lok NS, Lau CP. Abnormal vasovagal reaction, autonomic function and heart rate variability in patients with paroxysmal atrial fibrillation. Pacing Clin Electrophysiol 1998;21:386-95.
23. Kamath MV, Fallen EL. Power spectral analysis of heart rate variability: a noninvasive signature of cardiac autonomic function. Crit Rev Biomed Eng 1993;21:245-311.
24. Cowan MJ, Burr RL, Narayanan SB, Buzaitis A, Strasser M, Busch S. Comparison of autoregression and fast fourier transform techniques for power spectral analysis of heart period variability of persons with sudden cardiac arrest before and after therapy to increase heart period variability. J Electrocardiol 1992; 25:234-9.
25. Wen ZC, Chen SA, Tai CT, et al. Role of autonomic tone in facilitating spontaneous onset

of typical atrial flutter. J Am Coll Cardiol 1998; 31:602-7.

26. Vikman S, Makikallio TH, Yli-Mayry S, et al. Altered complexity and correlation properties of R-R interval dynamics before the spontaneous onset of paroxysmal atrial fibrillation. Circulation 1999;100:2079-84.
27. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM for the CHS collaboratory Research Group:Prevalence of atrial fibrillation in elderly subjects (The Cardiovascular Health Study). Am J Cardiol 1994;74:236-41.
28. Andresen D, Bruggemann T. Heart rate variability preceding onset of atrial fibrillation. J Cardiovasc Electrophysiol 1998;9:S26-9.
29. Coumel P. Autonomic influences in atrial tachyarrhythmias. J Cardiovasc Electrophysiol 1996 Oct;7(10):999-1007.