Autonomic Tone Variations Before the Onset of Paroxysmal Atrial Fibrillation

Marco Bettoni, MD; Marc Zimmermann, MD, FESC

Background—Mechanisms favoring the occurrence of paroxysmal atrial fibrillation (PAF) are complex and poorly defined. This study was designed to analyze dynamic changes in autonomic tone preceding the onset of PAF in a large group of patients.

Methods and Results—Holter tapes from 77 unselected consecutive patients (63 men and 14 women aged 58±12 years) with PAF were analyzed. A total of 147 episodes of sustained AF (>30 minutes) were recorded and submitted to time-domain and frequency-domain heart rate variability analyses; 6 periods were studied using repeated measures ANOVA: the 24-hour period, the hour preceding PAF, and the 20 minutes before PAF divided into four 5-minute periods. In the time-domain analyses, a linear decrease in mean RR interval from 925±16 to 906±16 ms (P<0.0002) was observed before the onset of PAF, together with a significant increase in the standard deviation of NN intervals from 65±4 to 70±4 ms (P<0.02). In the frequency-domain analyses, a significant increase in high-frequency (HF, HF-NU) components was observed before PAF (P<0.001 and P<0.0001, respectively), together with a progressive decrease in low-frequency components (LF, LF-NU) (P<0.0001 and P<0.004, respectively). The low/high frequency ratio showed a linear increase until 10 minutes before PAF, followed by a sharp decrease immediately before PAF, suggesting a primary increase in adrenergic tone followed by a marked modulation toward vagal predominance. No difference was observed in these heart rate variability changes between patients with “lone” PAF and patients with structural heart disease.

Conclusions—The occurrence of PAF greatly depends on variations of the autonomic tone, with a primary increase in adrenergic tone followed by an abrupt shift toward vagal predominance. (Circulation. 2002;105:2753-2759.)

Key Words: fibrillation ■ heart rate ■ nervous system, autonomic

Paroxysmal atrial fibrillation (PAF) is one of the most common arrhythmias in patients with and without structural heart disease.1,2 Atrial fibrillation (AF) is thought to be due to multiple wavelet reentry,3 and it has been shown recently that the trigger for PAF is often related to arrhythmogenic foci located at or near the orifice of the pulmonary veins, which can be successfully eliminated by radiofrequency catheter ablation.4–7 Moreover, the role of the autonomic nervous system in the genesis and/or in the maintenance of AF has been clinically recognized for many years.8,9 Autonomic fluctuations before the onset of PAF have been recognized in several studies10–12 but with conflicting results: a shift toward an increase in sympathetic tone or toward a loss of vagal tone has been observed before postoperative PAF,13 before the onset of atrial flutter,14 before PAF occurring during sleep,15 and in some patients with “lone” AF,16 whereas a shift toward vagal predominance was observed in young patients with lone AF and nocturnal episodes of PAF.17 Recently, observations made in patients with focal ectopy originating from the pulmonary veins have suggested a primary increase in adrenergic drive followed by marked modulation toward vagal predominance before the onset of PAF.12 To further improve our knowledge on the role of the autonomic nervous system in the genesis of PAF, we conducted a study designed to analyze dynamic changes in autonomic tone before the onset of sustained atrial arrhythmias in a large group of unselected patients with or without structural heart disease who presented with recurrent episodes of PAF.

Methods

Twenty-four-hour Holter tape recordings from 77 consecutive, unselected patients (63 men and 14 women aged 58±12 years) with PAF were prospectively collected between 1996 and 2000 and then analyzed. The clinical characteristics of the study population are summarized in Table 1. The presence and type of structural heart disease was assessed on the basis of medical history, clinical examination, 12-lead resting ECG, exercise stress testing, echocardiography and, in selected cases, coronary angiography. The diagnosis of lone AF was made in the absence of any structural heart disease in patients <60 years of age. In 15 patients, an electrophysiological study was performed together with radiofrequency catheter ablation of one or more arrhythmogenic foci (pulmonary vein foci in...
TABLE 1. Clinical Characteristics of the Study Population (n=77)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>58.4±11.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>63/14</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>5</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>4</td>
</tr>
<tr>
<td>Atrial enlargement, n (%)</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Left atrial diameter (echo), cm</td>
<td>3.9±0.2</td>
</tr>
<tr>
<td>Duration of symptoms, y</td>
<td>3.3±2.5 (0.3–12)</td>
</tr>
<tr>
<td>No. of PAF episodes per week</td>
<td>18±14 (1–50)</td>
</tr>
<tr>
<td>No. of drug trials per patient</td>
<td>2.5±1.6 (1–6)</td>
</tr>
<tr>
<td>History suggesting “vagally-mediated” PAF, n (%)</td>
<td>19/77 (24)</td>
</tr>
<tr>
<td>History suggesting “adrenergic” PAF, n (%)</td>
<td>7/77 (10%)</td>
</tr>
<tr>
<td>History with no evident predisposing factor, n (%)</td>
<td>51/77 (66)</td>
</tr>
</tbody>
</table>

Values are mean±SD (range) or n (%).

14 patients; right atrial focus in 1 patient; immediate success in all; early recurrence in 7 of the 14.

Holter tapes were eligible for analysis if the following criteria were met: (1) normal sinus rhythm during at least 70% of the recording period, (2) occurrence of one or more episode(s) of sustained (>30 minutes) AF, (3) presence of at least 1 hour of sinus rhythm before the onset of PAF, and (4) the presence of >80% of N-N intervals during the period of recording. For clinical and ethical reasons (rapid ventricular response during AF), it was not possible to withdraw all antiarrhythmic drugs during Holter recording in selected patients. Therefore, 9 patients (12%) were taking amiodarone, 18 (23%) were on β-blockers, and 10 (13%) were taking digoxin at the time of recording.

All 24-hour ambulatory recordings were performed using a 2-channel bipolar recorder (Recorder 8500, Marquette Electronics Inc) and analyzed using the MARS 8000 Workstation and software (Marquette Electronics Inc). Only high-quality recordings were considered for analysis. As described previously, all tapes were converted to a digitized format and reviewed by an experienced operator. All episodes of sustained atrial arrhythmias were manually identified, labeled, and printed out on paper (30 seconds per line at 25 mm/s). Ventricular and supraventricular ectopic beats, as well as the preceding and the following RR interval of each ectopic beat, were excluded from heart rate variability (HRV) analysis.

HRV was used as a indicator of autonomic activity in accordance with guidelines for standardization. Six time periods were selected for HRV: the 24-hour period of recording, the hour preceding the onset of sustained AF, and the 20 minutes preceding the onset of sustained AF, which were divided into four 5-minute periods (15 to 20 min, 10 to 15 min, 5 to 10 min, and 0 to 5 min preceding the onset of sustained AF). The following time-domain HRV parameters were analyzed: mean RR interval (mean NN interval, in ms), the standard deviation of NN intervals (SDNN; in ms), the standard deviation of 5-minute means of NN intervals (SDANN; in ms), the root-mean square of differences between successive NN intervals (in ms), and the proportion of adjacent NN intervals differing by >50 ms (%). HRV in the frequency domain (fast Fourier transform) was analyzed over the same 5-minute periods, and the following parameters were calculated: very-low-frequency components (VLF; <0.04 Hz), low-frequency components (LF; from 0.04 to 0.15 Hz), high-frequency components (HF; from 0.15 to 0.40 Hz), and the ratio of LF/HF. The LF and HF oscillatory components were analyzed both in absolute (ms²) and normalized units obtained using the following formula:

Power (normalized units) =

100×[power (ms²)/[total power (ms²)−power VLF (ms²)]]

Power indicates the power of LF or HF. Moreover, the power of each frequency band was logarithmically transformed to avoid the undue influence of extreme values; this was expressed in ln (ms²).

Statistical Analysis

Data are presented as mean±SD for clinical and Holter data. Comparisons of data obtained at different time intervals were performed using repeated measures ANOVA. An unpaired Student’s t test was used to compare the results of HRV parameters between different groups (patients with versus those without structural heart disease; nocturnal PAF episodes versus diurnal PAF episodes; patients with versus patients without β-blockers). P<0.05 was used as a cut-off for statistical significance.

Results

Clinical Characteristics

PAF had been present for 3.3±2.5 years. History suggested an adrenergic dependence (AF provoked by exercise or stressful situations) in 10% of the cases, and vagally-mediated AF (AF occurring during sleep) in 24% of the cases. However, in most patients (51 of the 77; 66%) no clear-cut precipitating factor before AF onset could be deduced from the history (Table 1).

Holter Data

Among the 77 patients, a total of 147 episodes of sustained AF fulfilled the inclusion criteria and were submitted to analysis. The mean sinus rate was 78±15 bpm, (mean maximal sinus rate, 173±39 bpm; mean minimal sinus rate, 47±12 bpm), and the mean number of atrial premature beats per patient during sinus rhythm was 1484±2384. Nocturnal occurrence of PAF was observed in 95 of 147 episodes (65%) at the time of recording. Before the onset of PAF, a long-short sequence was observed in 98 of 147 episodes (67%), both with (73 of 147 episodes) and without (25 of 147 episodes) atrial bigeminy (mean duration, 6±5 s). Acceleration of sinus rate was present in only 5 of 147 episodes (3%).

Time-Domain HRV Parameters

HRV parameters can be found in Table 2. A significant and linear change in the mean RR interval was observed over the 20 minutes preceding the onset of sustained episodes of PAF (from 925±16 to 906±16 ms; P<0.0002; Figure 1A). The mean RR interval during the 5 minutes preceding the onset of AF was not significantly different from the mean RR interval of the 24-hour period of recording (906±16 versus 897±13 ms; P=0.39) or from the mean RR interval of the hour preceding AF (906±16 versus 916±15 ms; P=0.31). The mean SDNN value increased significantly over the 20 minutes preceding the onset of AF (from 65±4 to 70±4 ms; P<0.05), but the SDNN value of the 5 minutes preceding AF was significantly lower compared with the SDNN value of the hour preceding AF (70±4 versus 80±3 ms; P<0.001) or compared with the SDNN value of the 24-hour period of recording (70±4 versus 120±4 ms; P<0.001). The mean SDANN did not show any significant change before AF, but a trend toward a progressive increase was observed between the 20 minutes and the 5 minutes preceding AF (from 27±2 to 31±2 ms; P=0.09). However, the mean SDANN value was significantly lower during the 5 minutes preceding AF compared
with the SDANN value of the hour preceding AF (32±3 versus 51±3 ms; *P*<0.0001) or compared with the SDANN value of the 24-hour period of recording (32±3 versus 99±3 ms; *P*<0.0001). No significant changes were observed for the root-mean square of differences or for the proportion of adjacent NN intervals differing by >50 ms during the 20 minutes preceding the onset of AF.

### Frequency-Domain HRV Parameters

A significant increase in HF values (*P*<0.001) was observed before the onset of sustained AF (Figure 1B). This increase was linear, with the highest value of HF observed during the 10 to 5 minutes preceding the onset of AF. Comparable results were observed for normalized HF values or when HF values were logarithmically trans-
formed (Table 2). An initial linear increase in LF values was observed before the onset of AF, but it was present only until 15 minutes before the onset of AF and was then followed by a marked decrease (from 1315±309 to 935±124 ms; P<0.0001; Table 2 and Figure 1C). Com-

parable results were observed for normalized LF values or when LF values were logarithmically transformed. No significant change in the LF/HF ratio was observed (P=0.11), but there was a progressive increase in the LF/HF ratio until 10 minutes before AF, followed by a sharp decrease during the 5 minutes preceding the onset of
AF (from 4.9±0.3 to 3.9±0.3; Figure 1D). No significant changes were observed in VLF values before the onset of sustained episodes of PAF.

Comparison Between Patients With Lone AF and Patients With Structural Heart Disease
Except for the mean RR interval during the 24-hour period of recording (significantly shorter in patients with structural heart disease; 824±30 ms versus 912±15 ms; P=0.01), the various HRV parameters were not significantly different between patients with lone AF and those with structural heart disease (Table 3). The autonomic variations showed the same pattern in both groups, with a significant increase in LF followed by an increase in HF before the onset of PAF.

Comparison Between Nocturnal and Diurnal Episodes of PAF
HF values were significantly higher before nocturnal episodes of PAF, and the LF/HF ratio was significantly lower before nocturnal episodes, thus confirming a vagal predominance at night. An increase in HF values was observed before AF onset before both diurnal and nocturnal episodes, but this increase reached significance only in the nocturnal group (P<0.001 for HF in the nocturnal group; P=0.08 for HF in the diurnal group). No significant variation was observed for LF values in the diurnal group, whereas a significant increase in LF values was observed in the nocturnal group (P<0.0001) during the 20 minutes preceding AF onset.

Comparison Between Patients With and Without β-Blockers
As expected, the mean RR interval was significantly longer in patients treated with β-blockers, with higher values for SDNN and SDANN (Table 4). In the frequency-domain, HRV parameters were comparable between the 2 groups except for HF (normalized units) values, which were significantly lower in patients treated with β-blockers. The dynamic pattern of frequency-domain HRV parameters was comparable in patients with and without β-blockers (Tables 5 and 6), with a primary increase in LF until 15 minutes before AF followed by a sharp decrease immediately before AF onset (Figure 2).

Discussion
This study demonstrates significant changes in HRV parameters before the onset of PAF in patients with and without structural heart disease. The present data suggest a primary increase in adrenergic drive occurring over at least 20 minutes before the onset of PAF followed by a shift in the

<table>
<thead>
<tr>
<th>Parameter</th>
<th>24 h</th>
<th>1 h</th>
<th>15–20 min</th>
<th>10–15 min</th>
<th>5–10 min</th>
<th>0–5 min</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR, ms</td>
<td>1005±20</td>
<td>1008±24</td>
<td>1024±24</td>
<td>1020±25</td>
<td>1000±24</td>
<td>985±24</td>
<td>0.04*</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>135±8</td>
<td>94±8</td>
<td>78±9</td>
<td>78±8</td>
<td>85±8</td>
<td>86±8</td>
<td>0.0001*</td>
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<tr>
<td>SDANN, ms</td>
<td>112±7</td>
<td>58±6</td>
<td>37±6</td>
<td>32±4</td>
<td>42±7</td>
<td>41±7</td>
<td>&lt;0.0001*</td>
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<tr>
<td>rMSSD, ms</td>
<td>31±2</td>
<td>32±2</td>
<td>32±2</td>
<td>33±2</td>
<td>32±2</td>
<td>32±2</td>
<td>0.81</td>
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<tr>
<td>pNN50, %</td>
<td>9±1</td>
<td>10±2</td>
<td>10±2</td>
<td>13±3</td>
<td>10±2</td>
<td>11±2</td>
<td>0.28</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>114±32</td>
<td>265±56</td>
<td>391±101</td>
<td>392±149</td>
<td>345±65</td>
<td>330±59</td>
<td>0.01*</td>
</tr>
<tr>
<td>HF, NU</td>
<td>12±1</td>
<td>16±2</td>
<td>20±2</td>
<td>17±2</td>
<td>16±2</td>
<td>16±2</td>
<td>0.005*</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>444±114</td>
<td>992±225</td>
<td>1248±275</td>
<td>1988±952</td>
<td>1204±256</td>
<td>1180±250</td>
<td>0.13</td>
</tr>
<tr>
<td>LF, NU</td>
<td>38±2</td>
<td>43±3</td>
<td>51±3</td>
<td>51±3</td>
<td>46±3</td>
<td>43±4</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>3.6±0.2</td>
<td>4.1±0.4</td>
<td>4.7±0.6</td>
<td>5.2±0.8</td>
<td>3.9±0.4</td>
<td>4.1±0.5</td>
<td>0.053</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. Abbreviations as in Table 2.

*Significant.
Autonomic tone toward more vagal predominance immediately before the onset of PAF.

The role of autonomic tone in the genesis of atrial arrhythmias has been clinically recognized for many years, but characterization and quantification of these autonomic changes are extremely complex and are therefore difficult to define. The main tool in clinical cardiology to evaluate autonomic nervous system activity is the analysis of HRV parameters on continuous ECG recordings. Among them, frequency-domain HRV parameters obtained by spectral analysis are considered the most useful to document changes in the sympathetic/parasympathetic balance. The HF components are thought to reflect primarily vagal tone, whereas LF components are more complex but probably reflect sympathetic activity or the sympathovagal balance. Several studies have been conducted to analyze variations of autonomic tone before the occurrence of atrial arrhythmias, but conflicting results have been reported.

A shift toward vagal predominance was observed essentially in patients with PAF and a structurally normal heart, especially in young patients with nocturnal AF or in patients with PAF triggered by pulmonary vein foci. Several observations suggest that most patients with idiopathic PAF are clearly vagally dependent, with a heightened susceptibility to vasovagal cardiovascular response, whereas most patients with organic PAF are more sympathetic dependent. Vagal stimulation has been shown to shorten the atrial refractory period and to facilitate reentry, and this effect has been used to induce or maintain AF in experimental models. Recently, Schauerte and coworkers showed that transvascular atrial parasympathetic nerve system modification by radiofrequency catheter ablation could abolish vagally-mediated AF, thus proving the major role played by the parasympathetic tone on the induction and/or maintenance of AF. However, some authors have suggested an increase in sympathetic tone (or a loss of vagal tone) before the onset of PAF in certain subsets of patients.

In the present study, spectral analysis of HRV showed a complex interaction, with an increase in adrenergic tone and an increase in vagal tone: the increase in HF components before the onset of PAF suggests a vagal rather than an adrenergic predominance immediately before the onset of PAF, whereas the increase in LF components occurring 20 to 5 minutes before the onset of PAF suggests an increase in adrenergic tone preceding the increase in parasympathetic tone. The pattern observed for the LF/HF ratio (Figure 1D) is compatible with these dynamic changes in autonomic tone. The complex fluctuations of autonomic tone occurring before the onset of PAF are underlined by the results of time-domain HRV analysis: a linear decrease in RR interval values was observed before the onset of PAF, suggesting an increase in sympathetic tone together with an increase in SDNN, a parameter predominantly reflecting vagal modulation. Others have reported similar results in patients with lone AF and in patients with “focal” AF.

**Figure 2.** Dynamic changes in HF components, LF components, and LF/HF ratio before onset of PAF in patients taking β-blockers (A, B, and C) and those not taking β-blockers (D, E, and F). See text for details. Data are expressed as mean±SEM.
Some studies have suggested that in patients with structural heart disease, there is no change in vagal activity before the onset of AF.\textsuperscript{11,16} In the present study, we found no statistical difference in HRV parameters between patients with lone AF and AF patients with structural heart disease: in both groups, the same fluctuations of autonomic tone were observed, suggesting that vagal influences are not only preponderant in patients with normal hearts. The only parameter significantly different between these 2 groups was the mean RR interval over the 24-hour period of recording, indicating a higher basic sinus rate in patients with structural heart disease. Finally, as pointed out by others,\textsuperscript{3} long-short sequences were frequently observed before the onset of AF (67%), with or without atrial bigeminy of usually short duration (50% of the cases).

Study Limitations

HRV is only an indirect measure of cardiac autonomic tone and therefore interpretation concerning the exact mechanism underlying the present observation should be cautious. Analysis of time-domain HRV parameters is less accurate in short-term recordings, and therefore data concerning SDNN (estimate of overall HRV) and SDANN (estimate of long-term components of HRV) should be interpreted with caution.\textsuperscript{18} Results of this study may not be applicable to all patients with PAF because the number of patients with structural heart disease included in this study was relatively small. However, the number of AF episodes is large enough to draw conclusions about fluctuations in autonomic tone before PAF. Only sustained (>30 minutes) episodes of AF were analyzed, and no conclusion can be made for shorter episodes of AF. For technical reasons, patients with numerous premature beats during the period of recording had to be excluded, and our conclusions may not be applicable to this subset of AF patients. Many patients were on medication during Holter recording, which may have influenced the measures of HRV. However, results were comparable in patients taking and those not taking measures of HRV. However, results were comparable in patients taking and those not taking measures of HRV.

Conclusions

The present study suggests that PAF episodes are preceded by fluctuations in autonomic tone, with a primary increase in adrenergic drive followed by a marked modulation toward vagal predominance. Such variations are observed in both patients with structural heart disease and those with lone AF, and they do not seem to be influenced by \( \beta \)-blockers. These data provide important information about the complex role of the autonomic nervous system as a modulating factor for the initiation and/or maintenance of AF.

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