Heart Rhythm Disturbances

Heart Rate Turbulence After Atrial Premature Beats Before Spontaneous Onset of Atrial Fibrillation

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OBJECTIVES
This study was designed to assess the temporal changes in vagal responses to atrial premature beats before spontaneous onset of atrial fibrillation (AF).

BACKGROUND
Enhanced vagal activity plays a major role in the onset and perpetuation of experimental AF, but the role of vagal activation in the onset of clinical AF episodes is not so well established.

METHODS
We calculated heart rate turbulence after atrial premature impulses occurring 0 to 60 min before the onset of AF (“prior to AF”) and compared it with the hourly means of the other hours of the 24-h electrocardiogram recordings (“non-AF hours”) in 39 patients with structural heart disease and 29 patients with lone AF. Traditional heart rate variability measurements and approximate entropy (ApEn) were also analyzed.

RESULTS
Turbulence onset (TO) was significantly less negative during the 1 h preceding AF than the average of the non-AF hours (0.71 ± 1.76 vs. −0.35 ± 1.46, p < 0.00001). Less negative TO before AF was observed among both the patients with structural heart disease (1.16 ± 1.73 vs. 0.07 ± 1.23; p < 0.0001) and those with lone AF (0.17 ± 1.67 vs. −0.85 ± 1.56; p < 0.0001). No significant difference was seen in the turbulence slope between the two periods, and none of the traditional frequency and time domain measurements differentiated between the periods; ApEn was significantly lower before AF than during the non-AF hours (p < 0.01).

CONCLUSIONS
Altered heart rate dynamics, suggesting transient enhancement of vagal outflow after premature atrial excitation, are temporally related to spontaneous onset of clinical AF. (J Am Coll Cardiol 2005;45:278–84) © 2005 by the American College of Cardiology Foundation

The pathophysiology of atrial fibrillation (AF) consists of both a triggering focal activator and changes in the atrial electrophysiologic properties capable of maintaining AF (1,2). Ablation of the ectopic pulmonary venous focus eliminates AF in many cases and emphasizes the importance of these triggers located in the muscular sleeves (3,4). Such sleeves are also present in the normal heart, and the reasons for the maintenance of triggering activity are largely unknown. Experimental studies have shown that parasympathetic stimulation dramatically shortens the atrial effective refractory period and, thereby, facilitates the onset and perpetuation of AF (5–7). The role of the parasympathetic nervous system in the genesis and maintenance of clinical AF episodes is not equally evident, however (8).

Analysis of heart rate (HR) variability has commonly been used to assess the cardiac autonomic regulation before the onset of AF episodes (9–14). Previous studies have shown alterations in some measures of HR variability before the occurrence of paroxysmal AF episodes, but the results have been partly controversial (11,12,14,15). This controversy may partly be due to methodological problems related to the assessment of changes in autonomic regulation by the traditional HR variability methods. Frequent ectopic beats, which often precede the onset of AF, cause a potential methodological bias, particularly for spectral analysis of HR variability (16).

Heart rate turbulence is a recently described method (17) that characterizes the short-term oscillations of HR after a premature impulse. In HR turbulence analysis, the presence of premature beats is a prerequisite rather than a harmful phenomenon in an analysis of temporal changes in autonomic regulation. Therefore, we set out to test the hypothesis that altered vagal responses to atrial premature beats may precede the onset of paroxysmal AF by analyzing the temporal changes in the measures of HR turbulence preceding the onset of AF.

METHODS
Patients. The 24-h electrocardiographic (ECG) recordings of patients who had paroxysmal episodes of AF were collected from the Tampere and Oulu University Hospitals in Finland during 1991 to 2001. Only recordings containing at least one episode of AF lasting >10 s, with at least 60 min of sinus rhythm preceding the AF episode, were included in the analysis. Patients >60 years of age with sinus pauses >2.5 s were excluded. Patients who had hypertension, coronary artery disease, or other structural
heart disease were included in the group of patients with structural heart disease, and patients who did not have hypertension, diabetes, or structural heart disease but had atrioventricular accessory pathways were included in the group of patients with lone AF.

The study population consisted of 29 patients with lone AF who underwent 33 24-h recordings, and 39 patients with structural heart disease who underwent 40 24-h recordings. Five recordings from both patients with lone AF and patients with structural heart disease were excluded from the HR variability analyses because of signal artifacts. Thus, HR variability analyses were made on 63 recordings.

**Analysis of HR variability.** All of the two-channel 24-h recordings were analyzed both with the Medilog Excel ECG software and manually, to detect and quantify arrhythmias and artifacts. The 24-h ECG data were sampled digitally and transferred from the Oxford Medilog scanner (version 4.1c, Oxford Medical Ltd.) to a microcomputer for analysis of HR variability and HR turbulence. All R-R interval time series were first edited automatically, to detect all ectopic beats and artifacts, followed by careful manual editing for details. After automatic and manual editing, the artifacts and ectopic beats were deleted, and the gaps were filled using an interpolation method described earlier (19). All questionable portions were compared with filled using an interpolation method described earlier.

**Analysis of post-ectopic HR turbulence.** Heart rate turbulence was calculated as previously described (17). Briefly, turbulence onset (TO) was defined as the difference between the means of the first two sinus R-R intervals after a compensatory pause and the last two sinus R-R intervals before the premature beat. Turbulence slope (TS) was calculated as the maximum slope of the regression line over any sequence of five sinus R-R intervals within the first 20 sinuses beats after an ectopic beat. The means of TO and TS for all atrial ectopic beats occurring during the hour preceding an AF episode(s) were calculated. From the rest of the 24-h recording, the means of TO and TS for all ectopic beats were calculated by hour and compared with the means of the 1-h periods preceding the onset of AF.

To find out the possible correlation between the duration of AF episodes and the TO values, the AF episodes were divided into two groups based on their duration. The duration of the episodes was calculated as previously described, and we used the same cutoff value (200 s) to differentiate between short and long episodes of AF as in our previous work (23).

**Statistical analysis.** The results are presented as mean values ± SD. In the Kolmogorov-Smirnov test (z value >1), in addition to using the absolute values, a logarithmic transformation to the natural base was performed on the spectral components of HR variability, the SDNN_{TS} and the number of ectopic beats in the different periods, which made the data normally distributed. The paired-samples Student t test was used to evaluate the differences between the values of the hour preceding AF and the values of the
non-AF hours. Analysis of variance with repeated measures was performed to compare the differences between the 15-min periods preceding AF. Student t test was used to analyze the differences between the patients with structural heart disease and those with lone AF. Pearson’s correlation coefficients were used in the analysis of correlations between the continuous variables. A p value <0.05 was considered significant.

RESULTS

The clinical characteristics of the study population are presented in Table 1. The patients with lone AF were younger, and 39% of them had no medication, whereas all patients with structural heart disease had medication at the time of the recording.

HR turbulence after atrial premature beats. Table 2 presents the HR variability measures, the number of ectopic beats, the coupling interval, the prematurity index, and HR turbulence during the 1-h period(s) preceding AF and the hourly means of the rest of the recording. In the patients with lone AF, the number of ectopic beats was higher before AF than during the other hours of the recordings, and the ectopic beats were more premature during the 1-h period(s) preceding the AF episode(s) than during the rest of the recordings. The mean value for TS was not significantly different between the two periods. The mean values for TO, both in the patients with lone AF and in the patients with structural heart disease, were significantly less negative during the 1-h period preceding AF than during the non-AF hours of the recordings (Table 2, Fig. 1). The patients with lone AF also had more negative values of TO both during the 1 h before AF and during the other hours than the patients with structural heart diseases (p < 0.05 and p < 0.01, respectively).

Each 1-h period preceding an AF episode was divided into four 15-min periods, and TO was analyzed for the subgroup of patients who had at least one atrial ectopic beat in each of the 15-min periods. There were 17 recordings (11 from patients with lone AF and 6 from patients with structural heart disease) fulfilling these criteria. As shown in Figure 2, TO during the last 15-min period before AF was significantly less negative compared with the 60 to 45 min preceding the AF episode (1.67 ± 2.53 vs. −0.41 ± 2.46; p < 0.05 tested with the paired-samples Student t test).

There were 87 short (<200 s) and 63 long (>200 s) episodes of AF. In the whole group and in the patients with structural heart disease, TO values were not significantly different before short and long episodes (0.35 ± 2.65 vs. 1.04 ± 2.50, p = NS; and 1.15 ± 2.46 vs. 0.86 ± 2.41, p = NS, respectively). In the patients with lone AF, TO was significantly more negative before short than long episodes of AF (−0.39 ± 2.62 vs. 1.24 ± 2.63; p < 0.01).

HR variability measures. None of the traditional frequency and time domain measures showed any significant differences between the two periods. Both in the patients with lone AF and in the patients with structural heart disease, the values of ApEn were significantly lower before AF episodes than during the non-AF hours (Table 2).

No significant changes in HR variability measurements were found when the 1-h period(s) preceding AF episode(s) were divided into four 15-min periods and HR variability analyses were performed on these data segments (Table 3).

Turbulence onset did not correlate with SDNNi, or any of the frequency domain measures of HR variability (r < 0.3 for all), with ApEn (r = −0.19, p = NS), or with the prematurity of the ectopic beats (r = 0.07, p = NS). Turbulence onset correlated weakly with the mean length of R-R intervals (r = 0.36, p < 0.01) and had a weak inverse correlation with TS (r = −0.31, p < 0.01).

DISCUSSION

This study demonstrates that the immediate R-R interval responses to atrial premature impulses are blunted before the onset of AF compared with the other hours of the recordings in patients both with and without structural heart disease. The normal response of R-R intervals to both atrial and ventricular premature beats is a short-term acceleration of HR (i.e., a decrease of R-R intervals, which creates a negative TO). This acceleration was blunted, or even a slight deceleration of HR was observed after premature atrial beats during the 1-h period preceding the onset of AF. These blunted HR responses to atrial premature beats can be best explained by altered autonomic reflexes, such as the transient enhancement of vagal outflow that reduces HR changes in response to premature impulses in relation to the onset of AF.

Traditional measures of HR variability and onset of AF. Several studies have assessed the changes in cardiac autonomic regulation before the onset of AF by analyzing...
the spectral or non-spectral components of HR variability in patients with structural heart disease and with idiopathic AF (9–14,24). According to these reports, most of the AF episodes in patients with idiopathic AF are related to an increase in vagal tone, whereas most patients with organic heart disease are more sympathetically dependent (11,13,14). In many reports, however, it has only been possible to categorize a minority of AF episodes to be solely vagally or sympathetically driven, and the mode of onset of AF has also been inconsistent within individuals (24–27).

Bettoni and Zimmermann (12) found a primary increase in adrenergic tone followed by marked modulation toward vagal predominance before AF episodes both in patients with structural heart disease and in patients with idiopathic AF. In the present study, the power-spectral and time-domain measurements of HR variability were not different before the onset of AF compared with the corresponding values during the non-AF hours of the recordings. There are salient differences between these studies, which may explain the divergent results. Bettoni and Zimmermann (12) used 5-min periods for analysis, and the most marked changes in cardiac vagal regulation were observed within the last 5-min period before the onset of AF. Because of the random occurrence of atrial ectopic beats before the onset AF, the shortest time interval we could analyze here was 15 min. Thus, the lack of differences in spectral components between the periods may not exclude the occurrence of significant changes in the autonomic modulation of HR during the last few minutes before the onset of AF. Furthermore, the different numbers of premature complexes may partly explain the divergent results: there may be a potential bias caused by the replacement of ectopic beats and compensatory pauses by any of the interpolation methods in

Table 2. Changes in Heart Rate Variability and Heart Rate Turbulence Before Spontaneous Onset of AF

<table>
<thead>
<tr>
<th>Period</th>
<th>Non-AF h</th>
<th>One h Before AF</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 73)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average R-R interval (ms)†</td>
<td>969 ± 135</td>
<td>984 ± 185</td>
<td>NS</td>
</tr>
<tr>
<td>HF power (ms²)†</td>
<td>261 ± 235</td>
<td>299 ± 316</td>
<td>NS</td>
</tr>
<tr>
<td>LF power (ms²)†</td>
<td>484 ± 431</td>
<td>491 ± 460</td>
<td>NS</td>
</tr>
<tr>
<td>LF/HF ratio†</td>
<td>2.0 ± 1.3</td>
<td>2.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>SDNNₜ (ms)†</td>
<td>79 ± 27</td>
<td>84 ± 35</td>
<td>NS</td>
</tr>
<tr>
<td>ApEn†</td>
<td>1.05 ± 0.22</td>
<td>0.95 ± 0.25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Turbulence onset (%)</td>
<td>−0.35 ± 1.46</td>
<td>0.71 ± 1.76</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Turbulence slope (ms/R-R interval)</td>
<td>15.5 ± 7.4</td>
<td>15.0 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial ectopic beats (n)</td>
<td>3.2 ± 2.2</td>
<td>3.7 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Coupling interval (ms)</td>
<td>629 ± 102</td>
<td>615 ± 151</td>
<td>NS</td>
</tr>
<tr>
<td>Prematurity index</td>
<td>0.67 ± 0.07</td>
<td>0.65 ± 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Lone AF (n = 33)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average R-R interval (ms)†</td>
<td>979 ± 118</td>
<td>968 ± 182</td>
<td>NS</td>
</tr>
<tr>
<td>HF power (ms²)†</td>
<td>352 ± 305</td>
<td>376 ± 391</td>
<td>NS</td>
</tr>
<tr>
<td>LF power (ms²)†</td>
<td>675 ± 487</td>
<td>657 ± 528</td>
<td>NS</td>
</tr>
<tr>
<td>LF/HF ratio†</td>
<td>2.3 ± 1.3</td>
<td>2.5 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>SDNNₜ (ms)†</td>
<td>83 ± 25</td>
<td>91 ± 34</td>
<td>NS</td>
</tr>
<tr>
<td>ApEn†</td>
<td>1.09 ± 0.21</td>
<td>0.97 ± 0.25</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Turbulence onset (%)</td>
<td>−0.85 ± 1.56</td>
<td>0.17 ± 1.67</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Turbulence slope (ms/R-R interval)</td>
<td>18.8 ± 8.2</td>
<td>17.0 ± 8.3</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial ectopic beats (n)</td>
<td>2.9 ± 2.2</td>
<td>4.2 ± 4.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Coupling interval (ms)</td>
<td>611 ± 80</td>
<td>560 ± 129</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Prematurity index</td>
<td>0.64 ± 0.08</td>
<td>0.61 ± 0.09</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Patients with structural heart disease (n = 40)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average R-R interval (ms)†</td>
<td>961 ± 148</td>
<td>996 ± 188</td>
<td>NS</td>
</tr>
<tr>
<td>HF power (ms²)†</td>
<td>192 ± 128</td>
<td>239 ± 232</td>
<td>NS</td>
</tr>
<tr>
<td>LF power (ms²)†</td>
<td>337 ± 317</td>
<td>363 ± 356</td>
<td>NS</td>
</tr>
<tr>
<td>LF/HF ratio†</td>
<td>1.8 ± 1.2</td>
<td>1.9 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>SDNNₜ (ms)†</td>
<td>76 ± 28</td>
<td>78 ± 36</td>
<td>NS</td>
</tr>
<tr>
<td>ApEn†</td>
<td>1.02 ± 0.23</td>
<td>0.94 ± 0.26</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Turbulence onset (%)</td>
<td>0.07 ± 1.23</td>
<td>1.16 ± 1.73</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Turbulence slope (ms/R-R interval)</td>
<td>12.8 ± 5.5</td>
<td>13.5 ± 6.5</td>
<td>NS</td>
</tr>
<tr>
<td>Atrial ectopic beats (n)</td>
<td>3.4 ± 2.0</td>
<td>3.3 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>Coupling interval (ms)</td>
<td>644 ± 115</td>
<td>660 ± 155</td>
<td>NS</td>
</tr>
<tr>
<td>Prematurity index</td>
<td>0.69 ± 0.06</td>
<td>0.68 ± 0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Number of recordings; heart rate variability analyses obtained from 63 recordings (28 with lone atrial fibrillation [AF], 35 with structural heart disease). Values are mean ± SD. Statistical analysis made from the logarithmic transformation of HF and LF power, SDNNₜ, and the number of atrial ectopic beats.

ApEn = approximate entropy; HF = high-frequency; LF = low-frequency; SDNNₜ = standard deviation of all R-R intervals.
the spectral analysis of HR variability (16). The frequency of premature atrial beats often increases before the onset of AF, as also observed here among the patients with lone AF.

**Nonlinear HR variability and onset of AF.** Methods of analysis derived from nonlinear dynamics have been developed to describe the features of HR dynamics that are not detectable with traditional methods (21,28,29); ApEn is a measurement that quantifies the regularity and predictability of time series data. Reduced complexity of HR dynamics has been seen in many cardiovascular disorders (19,30–32). Consistent with the present observation, reduced ApEn has been shown to precede AF episodes in patients after coronary artery bypass grafting and in patients without structural heart disease (10,26). The physiologic determinants of ApEn have not been well defined, however.

**HR turbulence.** Heart rate turbulence was first described to occur in response to ventricular premature beats with a typical short-term early acceleration and subsequent deceleration of HR after premature beats. Early acceleration has been shown to result from transient vagal withdrawal caused by baroreflex-mediated inhibition of vagal outflow (33–35). Recent pacing and Holter studies have shown that the modulation of R-R interval sequences is also present after atrial premature impulses (36,37). However, there are quantitative differences in the HR dynamics after ventricular and atrial premature complexes, the latter showing blunted early acceleration of HR immediately after the compensatory pause. A similar phenomenon was also observed here after atrial premature complexes. However, significant interindividual and time-dependent intrindividual differences were observed in these responses. The patients with structural heart disease tended to have even a more blunted acceleration of HR after the compensatory pauses than the patients with lone AF.

In accordance with a previous study (37), TO after atrial premature complexes was not related to the other HR variability indexes and correlated only weakly with TS, suggesting that mechanisms other than autonomic effects alone may also be involved in the modulation of R-R interval dynamics immediately after premature atrial impulses. One plausible mechanism is the sinus node resetting, which has been described to occur in response to atrial premature complexes (38). However, TO was not related to the prematurity of atrial impulses, suggesting that the changes in the resetting of sinus activity may not be the predominant factor influencing the temporal changes of TO. Most likely, vagal effects, which have short latency and duration, and the electrophysiologic resetting phenomenon together determine the immediate R-R interval length after premature atrial complexes.

The mechanism explaining the temporal relationship between the altered TO after atrial premature beats and the onset of AF could be explained by changes in vagal responses. It can be assumed that sinus node automaticity and its resetting after premature beats remain relatively stable in a given individual. Thus, enhanced vagal activity in response to premature excitation of the atrium could explain both the onset of AF and the prolongation of the first R-R intervals after the premature impulses shortly preceding the onset of AF.

**Study limitations.** All the patients with structural heart disease and many of the patients with lone AF were receiving medication at the time of the Holter recordings, which may have influenced the measurements of autonomic tone. However, the patients served as their own controls, and the results remained unchanged (data not shown) in the subgroup of patients with lone AF who were not receiving medication, which suggests that the cardiac medication itself had no major effect on these observations. The group of patients was relatively small, and the results should naturally be confirmed in larger patient series before they can be generalized.

![Figure 1. Heart rate turbulence onset (TO) after spontaneous atrial premature beats. The value of TO is significantly less negative during the 1 h preceding atrial fibrillation (AF) than the hourly mean values of the non-AF hours of the recording both in patients with lone AF (left) and in patients with structural heart disease (right).](image1)

![Figure 2. Heart rate turbulence onset (TO) after spontaneous atrial premature beats in 15-min periods during the 1 h preceding atrial fibrillation (AF) episode(s). In the subgroup of patients (n = 15; 17 recordings) with at least one atrial ectopic beat in each 15-min period during the hour preceding an AF episode, TO is significantly less negative during the 0- to 15-min period before AF than during the 45- to 60-min period preceding AF.](image2)
Conclusions. The R-R interval dynamics immediately after atrial premature impulses are blunted near the onset of spontaneous AF episodes compared with the dynamics during the non-AF hours of the recordings. The data suggest that vagal inhibition in response to premature atrial excitation is absent, or even that transient enhancement of vagal outflow occurs before AF. The documentation of a direct causal relationship between these phenomena warrants more experimental work.

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REFERENCES