Differences in Heart Rate Dynamics Before the Spontaneous Onset of Long and Short Episodes of Paroxysmal Atrial Fibrillation

Saila Vikman, M.D., Sinikka Yli-Mäyry, M.D.,
Timo H. Mäkikallio, M.D.,* K.E. Juhani Airaksinen, M.D.,†
and Heikki V. Huikuri, M.D.*

From the Division of Cardiology, Department of Medicine, University of Tampere, Finland;

**Division of Cardiology, Department of Medicine, University of Oulu, Finland; and*

†Division of Cardiology, Department of Medicine, University of Turku, Finland

Background: Altered heart rate (HR) dynamics precede the spontaneous onset of atrial fibrillation (AF), but the factors related to the perpetuation and duration of paroxysmal AF episodes are not well established. This study was designed to test the hypothesis that HR dynamics preceding the onset of (AF) may influence the duration of AF.

Methods: Traditional time and frequency domain HR variability indices, along with a short-term fractal scaling exponent (α_1) and approximate entropy (ApEn), were analyzed in 20-minute intervals before 92 episodes of spontaneous paroxysmal AF in 22 patients without structural heart disease. AF episodes were divided into two groups according to the duration of the arrhythmia episodes.

Results: The high-frequency (HF) spectral component in normalized units (nu) of heart rate variability was higher and low-frequency (LF) component lower before long (> 200 s, $n = 41$) compared to short (< 200 s, $n = 51$) AF episodes (HF nu; 40.1 ± 14.8 vs 31.5 ± 16.4 , $P < 0.0001$ and LF nu; 59.9 ± 14.8 vs 68.5 ± 16.4 , $P < 0.0001$). Short-term scaling exponent values also were lower before long compared to short AF episodes (e.g., α_1 ; 1.12 ± 0.21 vs 1.24 ± 0.23 , $P < 0.0001$). Women had a larger number of long AF episodes than men, but the duration of AF was not related to any other clinical or demographic features or antiarrhythmic medication.

Conclusion: Increased HF oscillations and decreased short-term correlation properties of R-R intervals, reflecting altered sympathovagal balance before the onset of AF, predispose to perpetuation of spontaneous arrhythmia episodes in patients with vulnerability to paroxysmal AF and without structural heart disease.

A.N.E. 2001;6(2):134–142

atrial fibrillation; heart rate; autonomic nervous system; maintenance

The autonomic nervous system has been proposed to play an important role as a trigger factor for the initiation of spontaneous episodes of paroxysmal atrial fibrillation (AF).^{1,2} However, clinical studies have not been able to document any consistent changes in the traditional time or frequency domain measures of heart rate (HR) variability before the onset of AF.^{3–5} On the contrary, two indepen-

dent studies have observed altered nonlinear HR dynamics, assessed by complexity and fractal analysis methods, to precede the spontaneous onset of AF,^{6,7} suggesting that autonomic regulation of HR may play an important role as a trigger for the onset of AF.

Animal models have documented the importance of cardiac autonomic regulation for the main-

Supported by the Medical Research Fund of Tampere University, the Finnish Foundation for Cardiovascular Research, and the Aarne Koskela Foundation.

Address for reprints: Saila Vikman, M.D., Division of Cardiology, Department of Medicine, University of Tampere. PL 2000, 33521 TAMPERE, Finland. Fax: 358-3-2474157; E-mail: saila.vikman@koti.tpo.fi

Table 1. Clinical Characteristics of the Study Population

Age, years	52 ± 11 (range 28–70)
Sex, male/female	11/11
Cardiac medication during recording (n = 26)	
β-blocking agents	11/26 (42.3%)
Digitalis	3/26 (11.5%)
Type IA antiarrhythmics	2/26 (7.7%)
Type IC antiarrhythmics	5/26 (19.2%)
No medication	13/26 (50%)

tenance of AF.^{8–10} However, there are only a few clinical reports concerning the factors related to the perpetuation of the paroxysmal AF episodes.^{11–13} This study was designed to test the hypothesis that alterations in HR dynamics before the onset of spontaneous episodes of AF may also predict the duration of AF episodes in patients without structural heart disease.

METHODS

Patients

Twenty-four hour electrocardiographic recordings of patients with paroxysmal episodes of AF and without structural heart disease studied in Tampere and Oulu University hospitals in Finland were prospectively collected during 1991–1998. Recordings were done for clinical reasons. Only recordings containing one or more paroxysmal AF episode(s) lasting more than 10 seconds, with at least 20 minutes of sinus rhythm preceding the AF, were included in the analyses. Patients with structural heart disease, hypertension, diabetes, sick sinus syndrome, or with an atrioventricular accessory pathway were excluded from the study. Patients over 60 years of age with sinus pauses > 2.5 seconds were also excluded. The study population consisted of 22 patients from which 26 24-hour recordings were made, containing 92 episodes of AF. The clinical characteristics of the patients are shown in Table 1. Analysis of the trend of HR dynamics preceding the onset of AF episodes has been previously reported in the same population.⁶

Electrocardiographic Recordings

All two-channel 24-hour recordings were analyzed with the Medilog Excel (version 4.1c, Oxford Medical Ltd) electrocardiographic software system and also manually to detect and quantify arrhyth-

mias and artifacts. The data were sampled digitally and transferred to a computer for the analysis of HR variability.

Analysis of Heart Rate Variability

All R-R interval time series were first edited automatically deleting all ectopic beats and artifacts, followed by careful detailed manual editing. All questionable portions were compared with two-channel Holter electrocardiograms. Only segments with > 80 % qualified sinus beats were included. Details of this analysis and filtering method have been described previously.^{14,15} Analysis of HR variability was performed on 6 sequential 20-minute intervals starting 120 minutes before the onset of AF. In the final analysis all 20-minute intervals were included. All analyses of R-R interval variability were performed with a custom-made analysis program (Hearts, Heart Signal Co, Oulu, Finland); details of the methods have been described elsewhere.^{14–17}

The AF episodes were divided into two groups according to their duration. If there was < 5-minute sinus rhythm between subsequent AF episodes they were defined as one episode, and the duration of the AF was calculated by adding both episodes together because very early reoccurrence of arrhythmia describes also tendency to sustained AF. There were 31 episodes when arrhythmia reoccurred in 5 minutes, but only four episodes changed classification from short to long episode when adding subsequent episodes together.

The definition of short and long episodes was determined before the HR variability analysis by making a histogram from the logarithmic transformations of the durations of the arrhythmia episodes and then having the peak of the gaussian curve as a cutoff point. In that way, episodes shorter than 200 seconds were defined as short ones (n = 51) and those longer than 200 seconds as long AF episodes (n = 41).

Twenty-minute R-R interval data were then divided into two segments of equal size according to their beat count; a linear detrend was applied to those segments of 400–1000 samples to make the data more stationary. An R-R interval spectrum was computed over the 20-minute periods according to a previously described method.¹⁴ A fast Fourier transform method was used to estimate the power spectrum densities of the HR variability. The power spectra were quantified by measuring

the area in two frequency bands: 0.04 to 0.15 Hz (low frequency) and 0.15 to 0.40 Hz (high frequency). The ratio between low frequency (LF) and high frequency (HF) spectra was also calculated. Normalized units (nu) of LF and HF were calculated by multiplying the power of each spectra by 100 and then dividing it by the sum of the power of the LF and HF spectras. The standard deviation of the normal R-R intervals (SDNN) and the mean length of the R-R intervals in 20-minute segments were used as time-domain measures of HR variability.¹⁸

Nonlinear Analysis of R-R Data

The same pre-edited R-R interval time series that had been used for the spectral and time domain analysis of HR variability was also used for calculating approximate entropy and for the short-term fractal scaling exponent α_1 . Approximate entropy is a measure of complexity which measures the logarithmic likelihood that runs of patterns that are close to each other will remain close in subsequent incremental comparisons. A time series containing many repetitive patterns has a relatively small approximate entropy, and conversely, more random data produce higher values. Details of this method have been described previously.^{16,19,20} Two input values, m and r , must be fixed to compute approximate entropy, and $m = 2$ and $r = 20\%$ of the standard deviation of the data sets were chosen on the basis of previous findings of good statistical validity.^{19,20} A detrended fluctuation analysis technique was used to quantify fractal-like scaling properties of the R-R interval data. This method is a modified root mean square analysis of a random walk. In this study we used the scaling exponent α_1 , which measures the strength of the short-time (≤ 11 beats) correlation properties of R-R interval data. The details of this method have been described previously.²¹⁻²³

Statistical Methods

Results are presented as mean value $\pm$ SD. In the light of a Kolmogorov–Smirnov test (z value > 1), in addition to the absolute values, a logarithmic transformation to the natural base was performed on the spectral components of heart rate variability measures. The Pearson correlation coefficient was used to estimate univariate correlations. The unpaired Student's t test was used to analyze the differences between groups of short and long AF

episodes. The paired Student's t test was used to analyze the differences between short and long episodes in patients who had both episodes. A P value < 0.05 was considered significant.

RESULTS

Clinical Characteristics

The clinical characteristics of the study population are presented in Table 1. The mean duration of all AF episodes was 16 minutes 25 seconds (median 41 s; range 10 s–6 hours 2 min 16 s). Cardiac medication, time of the day, or age of the patients had no impact on the duration of AF episodes. However, women had a larger number of long episodes (54.9 %) than men (31.7 %) ($P < 0.0001$).

HR Variability before Long and Short Episodes of AF

The HF power analyzed in normalized units was significantly higher (Fig. 1) and the LF power was lower before long than short AF episodes (Table 2). Scaling exponent α_1 -values were lower before long episodes than the α_1 -values before short AF episodes (Fig. 1). ApEn-values did not differ significantly between long and short AF episodes. SDNN was somewhat lower before long AF episodes. No differences could be seen in the average R-R interval or in the amount of ectopic beats when compared between long and short AF episodes (Table 2).

The Influence of Medication or Ectopic Beats

When the same analysis was carried out in the subgroup of patients ($n = 11$) who had no medication during the recording, similar differences could be seen, so that the HF power was increased and the LF power decreased before long AF episodes as compared to short ones (Table 3). The scaling exponent α_1 -values also were significantly lower before long than short AF episodes (Table 3). Again, no differences could be seen in SDNN, average R-R interval, or ApEn values between long and short AF episodes.

Because the editing method itself may influence the results of the HR variability analyses in cases of frequent ectopy, the same analyses were also carried out in the subgroup of AF episodes with less than one percent of edited beats due to ectopy. All

Figure 1. High frequency spectral power in normalized units (mean $\pm$ SEM); left, is increased before long ($n = 41$) atrial fibrillation episodes when compared to short ($n = 51$) ones. Fractal scaling exponent α_1 values (mean $\pm$ SEM); right, are lower before long episodes than before short ones.

22 patients had at least one AF episode with no or only a few ectopic beats before the AF. The results remained the same in this subgroup of patients as compared to the results in the whole study group (Table 3).

In the whole group, 8 of the recordings had only short episodes and 8 recordings only long episodes. There were 10 recordings (from 8 patients) which had both long and short AF episodes. Also in this

subgroup of patients with both long and short AF episodes HF (nu) power was increased (Fig. 2), LF (nu) power decreased and SDNN reduced before the long episodes (Table 4). The scaling exponent α_1 -values were also reduced before long episodes (Fig. 2) as compared to short episodes (Table 4). Because women had a larger number of long episodes than men, the HR variability was analyzed separately for men and women. Practically, similar differences could be seen in the HR variability indices when the analyses were carried out for men and women separately (Table 5). Both genders had an increase in the HF power and a decrease in the LF power before long arrhythmia episodes, but this particular spectral pattern was more prominent in women than in men (Table 5). Women had generally lower short-term scaling exponent values than men, and the difference between long and short episodes was more prominent in women than in men.

Table 2. HR Variability Measures Before Short and Long AF Episodes from All Patients ($n = 22$)

AF Duration	< 200 s	> 200 s
AF episodes, n	51	41
Scaling exponent α_1	1.24 $\pm$ 0.23	1.12 $\pm$ 0.21*
Approximate entropy	1.11 $\pm$ 0.22	1.16 $\pm$ 0.23§
Average RR interval, ms	994 $\pm$ 168	1008 $\pm$ 175
SDNN, ms	70 $\pm$ 27	63 $\pm$ 30†
HF power, ms ²	381 $\pm$ 559	404 $\pm$ 428
nu	31.5 $\pm$ 16.4	40.1 $\pm$ 14.8*
LF power, ms ²	756 $\pm$ 683	589 $\pm$ 475§
nu	68.5 $\pm$ 16.4	59.9 $\pm$ 14.8*
LF/HF ratio	3.3 $\pm$ 2.5	1.9 $\pm$ 1.3*
Ectopics, %	2.6 $\pm$ 3.2	3.4 $\pm$ 4.2

* $P < 0.0001$; † $P < 0.001$; ‡ $P < 0.01$, § $P < 0.05$. Data presented are mean value $\pm$ SD. SDNN, standard deviation of all RR intervals; HF = high frequency; LF = low frequency; nu = normalized units; ectopics = the amount of ectopic beats as a percentage from the total beat count.

DISCUSSION

The main finding of this study is that an increase in the HF spectral power and a decrease in the LF power of HR variability before the spontaneous onset of AF episodes predisposes to perpetuation and longer duration of paroxysmal AF episodes in patients without structural heart disease (Fig. 3). These findings concur with the animal data and suggest that cardiac autonomic regulation also

Table 3. HR Variability Measures Before Long and Short AF Episodes from Nonmedicated Patients (n = 11) and from Patients Who Had Less Than 1 Percent Edited Beats (n = 22)

AF Duration	Nonmedicated Patients		Patients Who Had Less Than 1% Edited Beats	
	< 200 s	> 200 s	< 200 s	> 200 s
AF episodes, n	27	18	16	11
Scaling exponent α_1	1.33 $\pm$ 0.21	1.11 $\pm$ 0.25*	1.27 $\pm$ 0.23	1.13 $\pm$ 0.23†
Approximate entropy	1.07 $\pm$ 0.23	1.16 $\pm$ 0.28	1.12 $\pm$ 0.22	1.22 $\pm$ 0.25§
Average RR interval, ms	941 $\pm$ 167	923 $\pm$ 171	991 $\pm$ 170	1013 $\pm$ 154
SDNN, ms	64 $\pm$ 17	63 $\pm$ 30	66 $\pm$ 22	57 $\pm$ 30‡
HF power, ms ²	214 $\pm$ 164	310 $\pm$ 205‡	273 $\pm$ 253	341 $\pm$ 333
nu	23.1 $\pm$ 13.3	38.0 $\pm$ 15.9*	29.5 $\pm$ 16.1	41.2 $\pm$ 16.1*
LF power, ms ²	715 $\pm$ 369	535 $\pm$ 367‡	665 $\pm$ 425	511 $\pm$ 420§
nu	76.9 $\pm$ 13.3	62.0 $\pm$ 15.9*	70.5 $\pm$ 16.1	58.8 $\pm$ 16.1*
LF/HF ratio	4.6 $\pm$ 2.6	2.2 $\pm$ 1.5*	3.7 $\pm$ 2.7	1.9 $\pm$ 1.4*
Ectopics, %	2.8 $\pm$ 3.3	2.6 $\pm$ 3.9	0.5 $\pm$ 0.5	0.6 $\pm$ 0.5

* P < 0.0001; † P < 0.001; ‡ P < 0.01; § P < 0.05. Abbreviations as in table 2.

plays an important role in the maintenance of AF in humans.

Differences in the Measures of HR Variability Before Long and Short AF Episodes

Spectral and time-domain analysis of HR variability have been most commonly used to describe the autonomic regulation of HR. An augmented cardiac vagal outflow is characterized by a shift of the LF-HF balance in favor of the HF component.²⁴

Both absolute and normalized units of power spectral components were used here in the assessment of cardiac autonomic regulation, and only the normalized units showed significant differences before long and short AF episodes. Although there is some controversy regarding the assessment of so-called "sympathovagal balance" by using normalized units,²⁵ the utility of the normalized spectral components to describe vagal and sympathetic outflow, respectively, has been recently verified by direct measurements of efferent muscle nerve activity in

Figure 2. High frequency spectral power in normalized units (mean $\pm$ SEM); right, and fractal scaling exponent α_1 (mean $\pm$ SEM); left, from patients who had both short and long episodes. High frequency power was almost regularly higher before a long episode than before a short episode in the same patient and the fractal scaling exponent α_1 values were lower before long than before short episodes.

Table 4. HR Variability Measures Before Short and Long AF Episodes from Patients Who Had Both Long and Short Episodes (n = 8)

AF Duration	< 200 s	> 200 s
AF episodes, n	34	28
Scaling exponent α_1	1.20 $\pm$ 0.24	1.10 $\pm$ 0.23†
Approximate entropy	1.12 $\pm$ 0.24	1.18 $\pm$ 0.25
Average RR interval, ms	1000 $\pm$ 149	953 $\pm$ 140§
SDNN, ms	67 $\pm$ 23	53 $\pm$ 23*
HF power, ms ²	309 $\pm$ 242	264 $\pm$ 206
nu	33.9 $\pm$ 17.3	41.5 $\pm$ 15.2*
LF power, ms ²	623 $\pm$ 393	389 $\pm$ 291
nu	66.1 $\pm$ 17.3	58.4 $\pm$ 15.2‡
LF/HF ratio	3.0 $\pm$ 2.3	1.9 $\pm$ 1.4†
Ectopics, %	2.6 $\pm$ 3.4	2.3 $\pm$ 3.3

* P < 0.0001; † P < 0.001; ‡ P < 0.01; § P < 0.05. Abbreviations as in table 2.

the subjects without structural heart disease.²⁶ Therefore, an increase in the normalized HF component can be interpreted to reflect an increase in the cardiac vagal outflow.

Traditional spectral and time-domain measures of HR variability may not uncover complex HR behavior. Therefore, new HR variability indices based on nonlinear dynamics have been developed to describe the features of HR behavior that are not detectable with traditional methods.^{20,22,27} Methods analyzing the complexity (ApEn) and fractal-like correlation properties of HR behavior have been most commonly used to detect abnormalities in R-R interval dynamics in various cardiovascular disorders.^{6,7,16,23,28,29} In the present study, the values of short-term fractal scaling exponent were

lower before long compared to short AF episodes. Reduced values of short-term scaling exponent have been previously observed to precede ventricular fibrillation in postinfarction patients²⁹ and the spontaneous onset of AF episodes in patients without structural heart disease.⁶ Although the physiological background for fractal correlation properties of HR variability is not well established, preliminary data suggest that an increase in vagal outflow together with increased circulating catecholamine levels results in a reduction of short-term scaling exponent values.³⁰ In this case, a reduced α_1 -value before long AF episodes may reflect an accentuated sympathovagal interaction, i.e., an increase in vagal tone together with high levels of a sympathetic transmitter.

A reduction in the ApEn value, which quantifies the regularity and predictability of time series data, has been reported to precede the onset of AF episodes after cardiac surgery⁷ and before AF onset in subjects without structural heart disease.⁶ In the present study, no differences in ApEn values between short and long AF episodes could be found. These observations suggest that the trigger mechanisms of the onset of AF are different from the factors determining the perpetuation of AF episodes. A large body of recent data support the notion that ectopic foci in the pulmonary veins are of importance in triggering the onset of AF.^{31,32} Autonomic outflow to atrial tissue may then be of importance in perpetuation of the ectopic firing to a sustained AF. In contrast with the association between the length of AF episodes and changes in the power spectra of HR variability observed in the

Table 5. HR Variability Measures Before Long and Short AF Episodes Separately from Men (n = 11) and Women (n = 11)

AF Duration	< 200 s	> 200 s	< 200 s	> 200 s
	men		women	
AF episodes, n	28	13	23	28
Scaling exponent α_1	1.33 $\pm$ 0.20	1.24 $\pm$ 0.19‡	1.13 $\pm$ 0.21	1.06 $\pm$ 0.20§
Approximate entropy	1.09 $\pm$ 0.21	1.12 $\pm$ 0.24	1.13 $\pm$ 0.24	1.19 $\pm$ 0.22
Average RR interval, ms	981 $\pm$ 184	984 $\pm$ 165	1010 $\pm$ 143	1021 $\pm$ 179
SDNN, ms	69 $\pm$ 21	68 $\pm$ 33	72 $\pm$ 34	61 $\pm$ 29§
HF power, ms ²	246 $\pm$ 172	272 $\pm$ 148	559 $\pm$ 795	477 $\pm$ 508
nu	23.8 $\pm$ 12.2	30.4 $\pm$ 11.3*	41.5 $\pm$ 15.9	45.5 $\pm$ 13.8§
LF power, ms ²	763 $\pm$ 352	691 $\pm$ 446	747 $\pm$ 960	532 $\pm$ 484
nu	76.2 $\pm$ 12.2	69.5 $\pm$ 11.3‡	58.5 $\pm$ 15.9	54.5 $\pm$ 13.8
LF/HF ratio	4.3 $\pm$ 2.6	2.7 $\pm$ 1.3*	2.0 $\pm$ 1.8	1.5 $\pm$ 1.0
Ectopics, %	2.8 $\pm$ 3.4	3.6 $\pm$ 4.3‡	2.5 $\pm$ 2.9	3.3 $\pm$ 4.3

* P < 0.0001; † P < 0.001; ‡ P < 0.01; § P < 0.05. Abbreviations as in table 2.

Figure 3. Examples of power spectra of heart rate variability in a patient who had both short (15 s, left) and long (2 hours 19 min, right) episodes of atrial fibrillation during the same recording. Lower panels show the analysis of fractal scaling exponent before the same short (left) and long (right) episodes of atrial fibrillation. High frequency spectral band is increased and low frequency spectral band decreased before the long episode as compared to short episode. The fractal scaling exponent α_1 value is significantly lower before the long episode (right) compared to the short episode (left).

present study, no consistent changes in spectral measures were observed before the spontaneous onset of any paroxysmal AF episodes in a previous analysis.⁶

Previous Studies

There has been relatively little information on the factors influencing the duration of paroxysmal AF episodes. A unique circadian rhythm in the occurrence of AF episodes has been described, so that probability of maintenance is higher during nighttime than during daytime,¹¹ also suggesting to a concept that increased vagal tone may facilitate the maintenance of arrhythmia. Concurring with the present observations, women have been shown to have longer AF episodes than men. Interestingly, women also have reduced LF/HF ratio and reduced short-term scaling exponent of their HR variability compared to men.^{33,34} A similar spectral and fractal pattern of HR dynamics also preceded the longer AF episodes here. Advanced age has also been observed to be related to longer AF episodes in previous studies.¹² Many other factors besides autonomic nervous system, such as atrial enlargement and higher prevalence of undiagnosed structural cardiac abnormalities, may explain the association between the length of AF episodes and age.

Experimental AF can be induced and maintained through a shortening of the atrial refractory period by administration of acetylcholine.³⁵ In animal models of AF, vagal stimulation has been much more effective than sympathetic stimulation to promote sustained AF.⁸⁻¹⁰ A possible explanation is

that vagal stimulation increases the heterogeneity in the atrial refractory period, thus favoring maintenance of AF.⁸⁻¹⁰ These experimental findings can also well explain the present observations that enhanced vagal outflow plays an important role in the perpetuation of spontaneous AF episodes in subjects without structural heart disease. To our knowledge, this is the first time when the importance of vagal activity in sustained AF has been demonstrated in humans.

Potential Limitations

Because medication or ectopic beats even after editing could have potential influence on heart rate variability measures, we carried out the same analysis from the subgroup of nonmedicated patients and also from the subgroup of AF episodes with less than one percent of edited beats. The results remained essentially the same, suggesting that neither medication nor confounding effects of edited ectopic beats had major effects on the observed findings. Also the amount of ectopic beats were same before short and long episodes.

A conceptual problem of measurement of HR variability as a predictor of AF episodes is that all HR variability measures describe the output of the autonomic nervous system only at the level of sinus node. Cardiovascular autonomic effects may be qualitatively and quantitatively different on the atrial tissue where the arrhythmias arise, either directly, or indirectly as a consequence of neurohumoral activation. However, a recent study of patients with ectopic atrial tachycardia showed

that the cardiac autonomic regulation is similar in the ectopic atrial pacemakers as in the sinus node,³⁶ suggesting that assessment of the dynamics of sinus node activity also reflects the autonomic regulation of atrial tissue outside the sinus node.

CONCLUSIONS

Increased HF oscillations of HR, reflecting enhanced cardiac vagal outflow, precedes long AF episodes. A decrease of temporal correlation properties of short-term R-R intervals also precedes long AF episodes, suggesting an increase in vagal outflow at the time of high circulating levels of a transmitter of sympathetic activity. These observations support the hypothesis that cardiac autonomic regulation plays an important role in the perpetuation of AF episodes in patients without structural heart disease. HR dynamics facilitating the onset and perpetuation of AF seem not to be similar, suggesting that the triggers of initiation and maintenance of paroxysmal AF episodes are different. A better understanding of the physiologic background for these differences may help in the development of new treatment strategies for the prevention of long episodes of paroxysmal AF.

REFERENCES

- Coumel P. Neural aspects of paroxysmal atrial fibrillation. In Falk RH, Podrid PJ (eds): Atrial fibrillation: Mechanisms and management. New York, Raven Press, 1992, pp.109–125.
- Coumel P. Paroxysmal atrial fibrillation: A disorder of autonomic tone? *Eur Heart J* 1994;15:9–16.
- Huang JL, Wen ZC, Chang MS, et al. Changes of autonomic tone before the onset of paroxysmal atrial fibrillation. *Int J Cardiol* 1998;66:275–283.
- Fioranelli M, Piccoli M, Mileto GM, et al. Analysis of heart rate variability five minutes before onset of paroxysmal atrial fibrillation. *Pacing Clin Electrophysiol* 1999;22:743–749.
- 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;82:22–25.
- Vikman S, Mäkilä TH, Yli-Mäyry S, et al. Altered complexity and correlation properties of R-R interval dynamics before the spontaneous onset of paroxysmal atrial fibrillation. *Circulation* 1999;100:2079–2084.
- Hogue CW Jr, Domitrovich PP, Stein PK, et al. R-R interval dynamics before atrial fibrillation in patients after coronary artery bypass graft surgery. *Circulation* 1998;98:429–434.
- Olgin JE, Sih HJ, Hanish S, et al. Heterogenous atrial denervation creates substrate for sustained atrial fibrillation. *Circulation* 1998;98:2608–2614.
- Geddes LA, Hinds M, Babbs CF, et al. Maintenance of atrial fibrillation in anesthetized and unanesthetized sheep using cholinergic drive. *Pacing Clin Electrophysiol* 1996;19:165–175.
- Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. *Am J Physiol* 1997;273:H805–H816.
- Yamashita T, Murakawa Y, Sezaki K, et al. Circadian variation of paroxysmal atrial fibrillation. *Circulation* 1997;96:1537–1541.
- Hnatkova K, Waktare JEP, Murgatroyd FD, et al. Age and gender influences on rate and duration of paroxysmal atrial fibrillation. *PACE* 1998;21:2455–2458.
- Hnatkova K, Waktare JEP, Sopher SM, et al. A relationship between fluctuations in heart rate and the duration of subsequent episodes of atrial fibrillation. *PACE* 1998;21:181–185.
- Huikuri HV, Valkama JO, Airaksinen KEJ, et al. Frequency domain measures of heart rate variability before onset of nonsustained and sustained ventricular tachycardia in patients with coronary artery disease. *Circulation* 1993;87:1220–1228.
- Huikuri HV, Seppänen T, Koistinen MJ, et al. Abnormalities in beat-to-beat dynamics of heart rate before the spontaneous onset of life-threatening ventricular tachyarrhythmias in patients with prior myocardial infarction. *Circulation* 1996;93:1836–1844.
- Mäkilä TH, Seppänen T, Niemelä M, et al. Abnormalities in beat to beat complexity of heart rate dynamics in patients with a previous myocardial infarction. *J Am Coll Cardiol* 1996;28:1005–1011.
- Mäkilä TH, Ristimäe T, Airaksinen KEJ, et al. Heart rate dynamics in patients with stable angina pectoris and utility of fractal and complexity measures. *Am J Cardiol* 1998;81:27–31.
- Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurements, physiological interpretation, and clinical use. *Circulation* 1996;93:1043–1065.
- Pincus SM, Goldberger AL. Physiologic time-series analysis: What does regularity quantify? *Am J Physiol* 1994;226:H1643–H1656.
- Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci USA* 1991;88:2297–2301.
- Mäkilä TH, Seppänen T, Airaksinen KEJ, et al. Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. *Am J Cardiol* 1997;80:779–783.
- Peng CK, Havlin S, Stanley HE, et al. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos* 1995;5:82–87.
- Mäkilä TH, Høiber S, Køber L, et al. and the TRACE Investigators. Fractal analysis of heart rate dynamics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. TRACE investigators. TRAndolapril Cardiac Evaluation. *Am J Cardiol* 1999;83:836–839.
- Malliani A, Pagani M, Lombardi F, et al. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991;84:482–492.
- Eckberg DL. Sympathovagal balance. A critical appraisal. *Circulation* 1997;96:3224–3232.
- Pagani M, Montano N, Porta A, et al. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation* 1997;95:1441–1448.
- Goldberger AL, West BJ. Applications of nonlinear dynamics to clinical cardiology. *Ann N Y Acad Sci* 1987;504:155–212.
- Ho KKL, Moody GB, Peng CK, et al. Predicting survival in heart failure cases and controls using fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. *Circulation* 1997;96:842–848.

29. Mäkikallio TH, Koistinen MJ, Jordaens L, et al. Heart rate dynamics before spontaneous onset of ventricular fibrillation in patients with healed myocardial infarcts. *Am J Cardiol* 1999;83:880–884.
30. Tulppo MP, Mäkikallio TH, Seppänen T, et al. Heart rate dynamics during accentuated sympathovagal interaction. *Am J Physiol* 1998;274:H810-H816.
31. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–666.
32. Haissaguerre M, Jais P, Shah DC, et al. Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. *Circulation* 2000;101:1409–1417.
33. Pikkujämsä SM, Mäkikallio TH, Sourander LB, et al. Cardiac interbeat interval dynamics from childhood to senescence: comparison of conventional and new measures based on fractals and chaos theory. *Circulation* 1999;100:393–399.
34. Huikuri HV, Pikkujämsä SM, Airaksinen KEJ, et al. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. *Circulation* 1996;94:122–125.
35. Nahum LH, Hoff HE. Production of auricular fibrillation by application of acetyl-beta-methylcholine chloride to localized region of the auricular surface. *Am J Physiol* 1940;129:428–436.
36. Huikuri HV, Poutiainen AM, Mäkikallio TH, et al. Dynamic behavior and autonomic regulation of ectopic atrial pacemakers. *Circulation* 1999;100:1416–1422.