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Heart Rate Dynamics and Clinical Episodes of Atrial Fibrillation

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ACADEMIC DISSERTATION

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ABSTRACT

In animal models increased vagal outflow has been shown to play a major role in the initiation and the maintenance of atrial fibrillation (AF), but the role of the autonomic nervous system in the genesis and maintenance of clinical AF has not been well established. This research was designed to assess the role of the autonomic nervous system in the initiation, maintenance and recurrence of clinical AF episodes by measuring various indexes of heart rate (HR) variability in relation to the occurrence and duration of clinical AF episodes.

The study population consisted of patients for whom 24-hour ECG recordings were performed because of clinical reasons, and of 116 consecutive patients who were treated with transthoracic electrical cardioversion due to persistent AF (>3 month). HR variability was initially analyzed in 20-minute intervals before 62 episodes of AF in 22 patients with lone AF, and then in 15-minute periods both in patients with structural heart disease (n=35) and in patients with lone AF (n=28). HR variability was analyzed from the entire recording in 78 patients after restoration of sinus rhythm with cardioversion. HR turbulence after atrial ectopic beats located 0 to 60 min before the onset of AF episodes was compared with the means of HR turbulence after atrial ectopic beats by hour in the rest of the recording in 39 patients with structural heart disease and in 29 patients with lone AF.

Traditional time and frequency domain measures of HR variability showed no significant changes before the onset of AF. However, a progressive decrease occurred both in the approximate entropy (ApEn) ($p<0.001$) and short-term scaling exponent values (α^1) ($p<0.001$) before the AF episodes in patients without structural heart diseases.

In the analysis of possible relationship between the duration of AF and the HR variability preceding the AF, the high-frequency (HF) spectral component of HR variability was observed to be higher ($p<0.0001$) and low-frequency (LF) component lower ($p<0.0001$) before long (>200 s, n=41) compared to short (<200 s, n=51) AF episodes in patients with lone AF.

After restoration of sinus rhythm with cardioversion in patients with recurrence of AF during one month, all power spectral components except the ultra-low-frequency power were increased. An increased HF spectral component specifically predicted the early recurrence of AF.

Turbulence onset was significantly higher during one hour before the AF than during the other hours of the recording, both in patients with structural heart diseases and in patients with lone AF ($p<0.0001$ for both).

In conclusion, specific changes in HR variability patterns are related to spontaneous onset, maintenance and recurrence of clinical AF episodes: 1) a decrease in the complexity of R-R intervals is a common phenomenon preceding the spontaneous onset of clinical AF episodes; 2) altered HR variability, reflecting changes

in sympatho-vagal balance, predispose to perpetuation of AF episodes in patients with lone AF; 3) increased HR variability, reflecting enhanced vagal tone, is associated with recurrence of AF after cardioversion; and 4) R-R interval dynamics immediately after atrial ectopic impulses are blunted during one hour before the onset of spontaneous AF episodes compared to dynamics during the other hours of the recordings, suggesting that vagal inhibition in response to ectopic atrial excitation is absent, or even that a transient enhancement of vagal outflow occurs near the AF.

CONTENTS

ABBREVIATIONS

α^1	short-term scaling exponent of fractal-like correlations
β	slope of the power-law relations
AF	atrial fibrillation
ApEn	approximate entropy
ECG	electrocardiography
ERP	effective refractory period
HF	high frequency
HR	heart rate
LF	low frequency
SD	standard deviation
SDANN	standard deviation of average normal-to-normal RR intervals
SDNN	standard deviation of the normal-to-normal RR intervals
TO	turbulence onset
TS	turbulence slope
ULF	ultra low frequency
VLF	very low frequency

LIST OF ORIGINAL PUBLICATIONS

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INTRODUCTION

The autonomic nervous system has been proposed to play an important role in the genesis and maintenance of atrial fibrillation (AF) (Coumel 1992, Coumel 1994). Sustained AF is based on multiple reentrant wavelets wandering throughout the atria (Moe 1962). The wavelength of these wavelets, defined as the distance traveled by the depolarization wave during the duration of its refractory period (wavelength = conduction velocity x refractory period), is an important factor to determine the induction and maintenance of AF. The smaller the wavelength of the circulating wavelets, the more easily AF can be induced and maintained (Rensma et al. 1988).

Vagal activation causes a shortening of the atrial effective refractory period (ERP), increases the dispersion of ERP, and decreases the conduction velocity (Allesie et al. 1958, Geddes et al. 1996, Wang et al. 1996, Liu et al. 1997, Jayachandran et al. 2000), thus favoring induction and perpetuation of AF.

Analysis of heart rate (HR) variability has become an important noninvasive method for assessing cardiac autonomic regulation (Saul et al. 1988, Malliani et al. 1991, Huikuri et al. 1999). Some reports exist concerning changes in HR dynamics before AF episodes, but the results have been partly controversial (van den Berg et al. 1995, Dimmer et al. 1998, Herweg et al. 1998, Hnatkova et al. 1998a, Hnatkova et al. 1998c, Hogue et al. 1998, Huang et al. 1998, Wen et al. 1998, Fioranelli et al. 1999, Bettoni et al. 2002).

The present study was set out to evaluate possible alterations in HR turbulence and HR variability analyzed with traditional and new dynamical measures preceding spontaneous paroxysmal AF episodes in different clinical situations and to evaluate whether alterations in HR variability after cardioversion of persistent AF could predict further recurrence of AF.

REVIEW OF THE LITERATURE

Epidemiology and causes of atrial fibrillation

AF is the most common sustained arrhythmia that occurs in humans (Kannel et al. 1992). The incidence of AF increases with age; the prevalence of AF is reported to be 0.2-0.3% at age 25 to 35 years, 3-4% at age 55 to 64 years and 5-10% at age over 65 years (Kannel et al. 1982).

AF is usually a consequence of established heart disease. The majority of AF occurs in persons with hypertension and coronary heart disease, particularly in the setting of cardiac failure. AF also occurs in association with mitral valve disease, hypertensive cardiovascular disease, an enlarged left atrium, cardiomyopathy, and as a result of some extracardiac conditions. Cardiovascular disease increases the risk of AF three- to fivefold (Kannel et al. 1983).

In different studies, 2-40% of patients with paroxysmal, persistent, or chronic AF have no cardiovascular or extracardiac conditions precipitating AF (lone AF) (Leather et al. 1992). Patients with lone AF are more often men. These patients often have frequent paroxysms of AF occurring during night, but they seldom develop chronic AF. In these patients, ectopic foci which cause atrial firing have been found most often in the pulmonary veins (Jais et al. 1997, Haissaguerre et al. 1998, Chen et al. 1999a, Hsieh et al. 1999).

In small number of patients, genetic defects have also been found as a risk factor for developing AF (Brugada et al. 1997).

Mechanisms of atrial fibrillation

There have been three major concepts about AF mechanisms: ectopic activity with fibrillatory conduction; single circuit re-entry; and the multiple wavelet hypothesis.

Ectopic activity with fibrillatory conduction

In the beginning of the 20th century Winterberg surmised that AF was due to multiple rapidly-firing foci distributed throughout the atria (Winterberg 1907). Atrial ectopy clearly caused atrial tachycardias, but the efficacy of electrical cardioversion in terminating AF, and the infrequency of discrete atrial tachyarhythmias after cardioversion, made a role for ectopic foci in AF maintenance seem unlikely. However, AF is frequently initiated by atrial ectopic complexes (Bennett et al. 1970).

Atrial ectopy can trigger re-entry in the presence of a vulnerable substrate. Prolonged rapid atrial activation promotes AF via tachycardia induced remodeling of the atria (Wijffels et al. 1995). The ability of atrial ectopic complexes to induce AF depends on the presence of a vulnerable substrate and is related to their timing and location relative to electrical heterogeneity gradients (Lammers et al. 1990, Wang et al. 1996, Fareh et al. 1998).

Many sites: the vena cavae, the crista terminalis, the ligament of Marshall, ostium of the coronary sinus, atrial free wall, interatrial septum, and pulmonary veins, can give rise to ectopic activity that may be important as a trigger for AF initiation (Haissaguerre et al. 1996, Jais et al. 1997, Haissaguerre et al. 1998, Chen et al. 1999a, Chen et al. 1999b, Hsieh et al. 1999, Kim et al. 2000, Saksena et al. 2000, Tsai et al. 2000). Ectopic foci are significantly clustered within pulmonary veins, where 80 to 95% of the foci are identified (Jaïs et al. 2002). Elimination of the arrhythmogenic foci by radiofrequency catheter ablation has been shown to be effective for long-term elimination of AF (Haissaguerre et al. 1996, Jais et al. 1997, Chen et al. 1999b).

Single circuit reentry

As with rapid atrial ectopy, a single atrial reentry circuit can give rise to a temporally and spatially varying activation pattern consistent with AF by virtue of fibrillatory conduction away from the circuit to the remainder of the atrium. This kind of macroreentry is clearly responsible for atrial flutter (Waldo 1998). Patients with atrial flutter and apparent single-circuit macroreentry can be cured by a single linear lesion that transects the reentrant pathway (Cosio et al. 1996, Kottkamp et al. 1999, Wu et al. 2002). The same patients commonly experience both atrial flutter and AF (Biblo et al. 2001). The success of atrial flutter ablation in preventing AF (Katritsis et al. 1996) suggests that these two arrrhythmias may have a common pathophysiological mechanism. In animal models a single re-entrant circuit can act as a dominant generator of AF (Mandapati et al. 2000).

The multiple wavelet hypothesis

In the early 1960s Moe developed the multiple wavelet hypothesis to explain the characteristics of AF (Moe et al. 1959, Moe 1962, Moe et al. 1964). AF is maintained by the presence of a number of independent wavelets that travel randomly through the atrium around multiple islets of refractory tissue. Wavelets may collide with each other, divide, extinguish or combine with other wavelets. Each wavelet may also accelerate or decelerate when it encounters tissue in a more or less advanced state of recovery or excitability.

In 1985, Allessie et al. were able to provide the first demonstration *in vivo* of multiple propagating wavelets giving rise to turbulent atrial activity by mapping in dogs during rapid pacing-induced AF. During re-entrant rhythms the conduction time of the re-entrant impulse must be long enough to allow fibers ahead of the blockage

area to recover and become excitable again. The wavelength for circus movement has been defined as the product of the conduction velocity and the refractory period (Wiener et al. 1946). The smaller the wavelength of the circulating wavelets, the more easily AF can be induced (Rensma et al. 1988).

Maintenance of AF depends on the number of wavelets present in the atria (Allessie et al. 1994). With only a small number of wavelets, they may at a certain moment die or fuse into a single wavefront, leading to resumption of sinus rhythm or atrial flutter. Supporting this idea, termination of AF by class IC antiarrhythmic drugs has been shown to be preceded by a decrease in the mean number of wavelets (Wang et al. 1992, Wang et al. 1993). The wavelength must be significantly smaller than the size of the atrium. Thus, smaller circuits on larger atria favour the perpetuation of AF (Rensma et al. 1988).

Mapping studies in dogs (Kirchhof et al. 1993) , as well as in humans (Cox et al. 1991, Konings et al. 1994) have given support to the idea that multiple wavelets distributed randomly throughout the atria give rise to the seemingly chaotic activation patterns observed in the ECGs of patients with AF. The circulatory wavelets require a certain mass of atrial tissue in which to circulate, in order not to extinguish themselves in refractory tissue. Thus, a critical mass of atrial tissue is necessary for AF to be sustained. Surgical approaches to AF have been designed to test this hypothesis (Cox et al. 2000). In MAZE procedure multiple surgical lesions are created to compartmentalize the atria in regions presumably unable to sustain the multiple wavelets (Cox 1991). With this procedure chronic AF could be cured in some patients supporting the concept that multiple wavelets of activation are responsible for persistent AF in humans (Cox et al. 1991, McCarthy et al. 1993, Cox et al. 1996, Kawaguchi et al. 1996).

Heart rate variability

Arterial pressure and HR fluctuate from beat to beat, synchronous with respiration. Since the original report (Wolf et al. 1978), analysis of spontaneous variations of beat-to-beat intervals from electrocardiographic (ECG) recordings has become an important method for assessing cardiac autonomic regulation (Akselrod et al. 1981, Pomeranz et al. 1985, Pagani et al. 1986, Malliani et al. 1991, Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996).

Measurement of heart rate variability

Time domain measures of heart rate variability

The variations in HR may be evaluated by a number of methods. In time domain measures either the heart rate at any point in time or intervals between successive normal complexes are determined. All measurements require accurate timing of R waves and careful elimination of artefacts and ectopic beats.

The simplest variable to calculate is the standard deviation of the normal-to-normal RR intervals (SDNN) over a 24-hour period. This reflects all the cyclic components responsible for variability in the period of recording (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Another commonly reported measurement is the standard deviation of average normal-to-normal RR intervals (SDANN). This is the standard deviation of the 5-minute mean cycle lengths over the entire recording.

The second class of variables is based on the differences between adjacent cycles. These measuremants include rMSSD (the square root of the mean squared differences of successive normal-to-normal intervals), NN50 (the number of interval differnces of successive normal-to-normal intervals greater than 50 milliseconds) and pNN50 (the proportion of cycles where the difference is >50 milliseconds) (Task Force of the

European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996).

Time-domain variables are all positively correlated with each other, but the strength of correlation varies greatly. SDNN and SDANN have a correlation above 0.9. The variables calculated from the differences between the adjacent cycles (rMSSD, NN50 and pNN50) estimate high-frequency (HF) variations in HR, and thus are highly correlated (Kleiger et al. 1995).

Frequency domain measures of heart rate variability

The spectral method quantifies how the overall variance is distributed in different frequency contributions. The HR signal is decomposed into its frequency components and quantified in terms of their relative powers (Akselrod et al. 1981, Malliani et al. 1991).

Both a Fast Fourier transform algorithm (nonparametric) and an autoregressive model (parametric) have been used to transform RR interval signals into frequency domain measures (Öri et al. 1992). The autoregressive model requires an *a priori* choice of the structure and order of the model for the signal generation mechanism. Its advantages are smoother spectral components, an accurate estimation of power spectral density even on a small number of samples, and easy postprocessing of the spectrum. The advantages of the Fast Fourier method are the simplicity of the algorithm used and the high processing speed. In most instances, both methods provide comparable results (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996).

The power spectra are usually quantified by measuring the area in four frequency bands: ultra-low-frequency (ULF) <0.003 Hz, very-low-frequency (VLF) 0.003-0.04 Hz, low-frequency (LF) 0.04-0.15 Hz, and HF 0.15-0.4 Hz (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). The components estimate fluctuations with a periodicity of > 6 minutes, 25 s-6 min, 7-25 s, and 2.5-7 s, respectively. Total power is represented by the total area under the power spectral curve. The duration of the recording should be at least 10 times the wavelength of the lowest frequency bound by the spectral

components investigated. In addition, the linear trend should be removed by detrending and filtering the data to make the signal stationary (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). Spectral components are usually expressed as absolute units. LF and HF powers may be also expressed in normalized units by dividing the power of a given component by the total power, from which the power <0.04 Hz has been subtracted, and multiplying by 100 (Pagani et al. 1986, Malliani et al. 1991). The normalization tends to minimize the effect of the changes in total power on the values of the LF and HF components. The normalized units of HF and LF and the ratio between them have been used to describe the controlled and balanced behavior of the two branches of the autonomic nervous system (Pagani et al. 1986, Malliani et al. 1991, Pagani et al. 1997).

Non-linear measures of heart rate variability

Nonlinear dynamics studies systems in which output is not proportional to input. It is based on fractals and chaos theory (Goldberger et al. 1987, West et al. 1987, Goldberger et al. 1990). Fractals are complex shapes that are not simply lines, rectangular or cubes. Fractals are irregular, but their irregularity has an underlying pattern and the details seen under magnification resemble the outline of a larger structure (West et al. 1987). Chaos describes an apparently unpredictable behavior that may arise from the internal feedback loops of certain nonlinear systems (Goldberger et al. 1987, West et al. 1987, Goldberger et al. 1990). A chaotic process generates complex fluctuations that do not have a single or characteristic scale of time; rather, the signal varies in an erratic and unpredictable way.

A detrended fluctuation analysis technique quantifies the fractal correlation properties of the data. This method is a modified root mean square analysis of a random walk (Hausdorff et al. 1995, Peng et al. 1995b). The root-mean-square fluctuations of the integrated and detrended data were measured in observation windows of varying size and then plotted against the size of the window on a log-log scale. The scaling exponent (α) represents the slope of the line relating fluctuation (log) to window size (log) (Peng et al. 1995b). HR correlations can be defined

separately for short-term (<11 beats, α_1) and for long-term (>11 beats, α_2) fluctuations in the RR interval data (Peng et al. 1995a, Peng et al. 1995b, Mäkikallio et al. 1997).

The long-term power-law relation of R-R interval variability describes the distribution of the power-law density in the frequency range of 10^{-4} to 10^{-2} Hz. It reflects mainly fluctuations between ULF and VLF power from the spectra. The steeper the slope (β) of the power-law relationship is, the greater is the relative power of the ULF component compared to the VLF component in the spectra (Bigger et al. 1996).

Approximate entropy (ApEn) is a measure quantifying the regularity or predictability of time series data (Pincus 1991, Pincus et al. 1994). It measures the logarithmic likelihood that runs of patterns that are close to each other will remain close in the subsequent incremental comparisons. A time series containing many repetitive patterns has a relatively small approximate entropy; conversely, more random data produce higher values (Pincus 1991, Pincus et al. 1994).

Physiology of heart rate variability

HR and its variability comprise the cardiovascular response to broadly defined stimuli, these stimuli being physical, psychological or environmental. The beat-to-beat fluctuation of HR is a result of physical and autonomic nervous system activity, respiration, mental stress, thermoregulation, blood pressure regulation and possibly other unknown factors. HR variability represents the net effects of all of these inhibitory and excitatory influences.

Time and frequency domain measures of heart rate variability

Time-domain measures of HR variability show a linear relation with pharmacologically determined cardiac vagal tone (Eckberg 1983, Hayano et al. 1991). Short term HR fluctuation has been thought to be mediated by the modulation of autonomic inputs to the sinoatrial node. The magnitude of the HF component of the power spectra reflects the degree of respiratory modulation of vagal activity. The degree of this modulation augments linearly with the increase in the mean level of

vagal tone (Akselrod et al. 1981, Pomeranz et al. 1985, Hayano et al. 1991, Malliani et al. 1991, Pagani et al. 1997).

More controversial is the interpretation of the LF component, which has been considered as a marker of sympathetic modulation, especially when expressed in normalized units (Rimoldi et al. 1990, Malliani et al. 1991, Kamath et al. 1993, Montano et al. 1994). On the other hand the LF component is thought to be mediated by both the vagal and sympathetic outflow at this frequency range (periodicity of 7-25 seconds) (Akselrod et al. 1981, Pomeranz et al. 1985). In some conditions, like in heart failure which is associated with sympathetic excitation, a decrease in the absolute power of the LF component is observed (van de Borne et al. 1997). During sympathetic activation the resulting tachycardia is usually accompanied by a marked reduction in total power, whereas the reverse occurs during vagal activation. In normal subjects LF and HF expressed in normalized units have a circadian variation and reciprocal fluctuations, with higher values of LF in the daytime and of HF at night (Furlan et al. 1990, Malliani et al. 1991).

Although the VLF and ULF components account for 95% of the total power in long-term recordings, their physiological correlates are still unknown. VLF and ULF power is suggested to reflect both sympathetic and largely parasympathetic modulation as well as renin-angiotensin-aldosterone system and thermoregulation (Taylor et al. 1997). However, the vagal activity may also be a major contributor of these components, because a parasympathetic blockade abolishes almost all variations of HR (Akselrod et al. 1981, Pagani et al. 1986, Taylor et al. 1997).

Non-linear measures of heart rate variability

The physiological background of non-linear HR variability indexes is not well determined. Some evidence suggests that increased sympathetic activation is associated with an impairment of the fractal dynamics of HR. In a recent study, an increase in vagal outflow, together with increased circulating catecholamine levels, resulted in a reduction of short-term scaling exponent values (Tulppo et al. 2001b).

The long-term exponent (β) has been shown to be significantly steeper in a denervated heart, suggesting that it is mainly influenced by the autonomic input to the heart (Bigger et al. 1996).

ApEn has been shown to gradually increase during exercise after atropine (Tulppo et al. 1996). Complex R-R interval dynamics have also been shown to be associated with high levels of norepinephrine in patients with heart failure (Woo et al. 1994), suggesting that sympathetic activation may increase the values of ApEn.

ApEn, as well as both the short-term (α_1) and the long-term (β) scaling exponents, has been shown to decrease significantly during ageing (Kaplan et al. 1991, Mäkikallio et al. 1998, Pikkujämsä et al. 1999, Jokinen et al. 2001).

Heart rate turbulence

HR turbulence was introduced in 1999 by Schimdt et al. It describes the short-term fluctuation in sinus R-R intervals that follows an ectopic complex. Turbulence onset (TO) quantifies the brief phase of early acceleration after an ectopic beat. TO has been defined as the difference between the mean of the first two sinus R-R intervals after an ectopic beat and the last two sinus R-R intervals before an ectopic beat divided by the mean of the last two sinus R-R intervals before an ectopic beat (Schmidt et al. 1999).

Turbulence slope (TS) is defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus R-R intervals within the first 20 sinus R-R intevals after an ectopic beat (Schmidt et al. 1999). After an atrial ectopic beat HR turbulence has been shown to have a one-beat delay of initiation and a milder acceleration and deceleration than after a ventricular ectopic beat (Lindgren et al. 2003, Savelieva et al. 2003).

Physiology of heart rate turbulence

The precious mechanism behind HR turbulence is unknown. The drop of blood pressure because of compensatory pause after an ectopic beat causes arterial baroreceptor unloading. This decreases tonic vagal nerve activity, causing early acceleration of sinus rhythm immediately after an ectopic beat. After that there is an increase of blood pressure with subsequent baroreceptor loading. Then vagal nerve

activity is again increased, which causes a later deceleration phase of the sinus rhythm (Mrowka et al. 2000, Lin et al. 2002, Voss et al. 2002).

The relative contribution of the 2 limbs of the autonomic nervous system to turbulence measures is also unknown. However, the latency time and duration of heart responses to vagal activation is very short, while the sympathetic effects have a longer latency and duration (Hainsworth 1998). Thus the short and immediate acceleration phase may depend more on vagal withdrawal than on sympathetic recruitment. Atropine has been shown to abolish HR turbulence completely (Guettler et al. 2001, Marine et al. 2002). In the mathematical model betablocking agents reduced TS, but not TO (Mrowka et al. 2000). In patients without structural heart disease betablocking agents had no effect on HR turbulence (Lin et al. 2002). However, TS and TO are independent risk predictors (Schmidt et al. 1999, Ghuran et al. 2002) suggesting that HR turbulence is not a purely vagal phenomenon. Besides that, HR turbulence measures are only weakly related to HR variability indices (Koyama et al. 2002, Lindgren et al. 2003, Sestito et al. 2004), suggesting that other mechanisms than only autonomic influences may be involved in the mechanism of HR turbulence.

Abnormal HR turbulence has been found to predict mortality in post-myocardial infarction patients (Schmidt et al. 1999, Ghuran et al. 2002, Barthel et al. 2003), in patients undergoing coronary artery bypass grafting (Cygankiewicz et al. 2003), and in patients with chronic heart failure (Koyama et al. 2002). In patients with dilated cardiomyopathy more negative TO was a significant predictor of transplant-free survival (Grimm et al. 2003), and in patients undergoing primary percutaneous coronary intervention for a first myocardial infarction, improvement of HR turbulence after successful reperfusion has been reported (Bonnemeier et al. 2003).

Remodeling of the atrium

Chronic AF is often preceded by episodes of paroxysmal AF (Godtfredsen 1975, Kopecky et al. 1987). The transition from paroxysmal to chronic AF may be due to a further progression of underlying disease. However, experimental data have revealed that AF itself causes changes in the myocardium that favor its irreversibility (Morillo et al. 1995, Wijffels et al. 1995). Clinical studies have shown that conversion to and maintenance of sinus rhythm by pharmacological or electrical methods becomes more difficult with longer duration of AF (Lévy et al. 1998). These observations support the conclusion that AF by itself causes changes in atrial electrical function, contractile behavior, and structural composition, resulting in sustained AF.

Electrical remodeling

Experimental studies have shown that marked electrophysiological changes take place in the atria during AF, which favor the induction and perpetuation of AF. AF causes a shortening of refractoriness and a loss of rate adaptation (Morillo et al. 1995, Wijffels et al. 1995, van der Velden et al. 2000b). The shortening of atrial ERP promotes AF by decreasing the wavelength, thereby allowing the atria to accommodate a larger number of functional reentry circuits and decreasing the chance of AF termination (Rensma et al. 1988, Allessie et al. 1994). The reduction in rate adaptation of the ERP is also observed in patients with AF (Attuel et al. 1982, Boutjdir et al. 1986, Franz et al. 1997). In addition to changes in the absolute value of ERP, atrial tachycardia also affects the spatial distripution of ERP in animal models of AF (Satoh et al. 1996, Gaspo et al. 1997b, Jayachandran et al. 2000) and in humans with paroxysmal AF (Misier et al. 1992). The spatial heterogeneity of ERP appears to be an important determinant in the maintenance of AF (Wang et al. 1996, Liu et al. 1997, Fareh et al. 1998, Ramanna et al. 2000).

The ionic mechanisms underlying tachycardia-induced electrical remodeling have been studied both in animal models of AF (Gaspo et al. 1997a, Yue et al. 1997) and in humans (van Wagoner et al. 1997, Bosch et al. 1999, van Wagoner et al. 1999, Skasa et al. 2001). The most important impact of AF on the ion channels was a marked downregulation of the L-type Ca^{2+} channel. Secondary to this process, the reduced expression of several K^{+}channels may serve to adapt the myocardial cell to the high rate and counteract the shortening of ERP (Brundel et al. 2001, Dobrev et al. 2002).

Prolonged rapid atrial rates may also lead to a slowing of atrial conduction, but the results have been controversial (Morillo et al. 1995, Wijffels et al. 1995, Elvan et al. 1996, Gaspo et al. 1997b). Gap-junction proteins play an important role in the rapid and homogenous propagation of the wavefront in the heart (Elvan et al. 1997, van der Velden et al. 2000a). Changes in atrial gap junctions may cause a slowing of atrial conduction (Kanagaratnam et al. 2002), but the data presented on changes in intercellular connexins are not consistent (Elvan et al. 1997, van der Velden et al. 2000a). Spatial heterogeneities in the distribution of connexin have been reported, and this might create microscopic obstacles for conduction (van der Velden et al. 2000a, Kostin et al. 2002). It therefore remains a possibility that gap junctional remodeling is involved in the creation of a substrate for persistent AF.

Structural remodeling

In addition to electrophysiological, functional ion-current and ion-channel gene expression changes, AF is also associated with adaptive and maladaptive alterations in morphology (Bharati et al. 1992, Ausma et al. 1997, Thijssen et al. 2000). Cellular hypertrophy, alterations in connexin expression, disintegration of the contractile apparatus, glycogen accumulation, loss of the sarcoplasmic reticulum, and changes in mitochondrial size and shape have been noted in AF (Ausma et al. 1997, Elvan et al. 1997, Frustaci et al. 1997, van der Velden et al. 1998, Everett et al. 2000, Thijssen et al. 2000, Ausma et al. 2001). These changes resemble those observed in the hibernating myocardium of patients (Schotten et al. 2001b). In chronic lone AF, signs

of irreversible changes leading to cell death are absent (Dispersyn et al. 1999). The structural changes in response to AF might be considered as the consequence of a physiological adaptation to chronic Ca^{2+} overload and metabolic stress (Allessie et al. 2002). In patients with AF and atrial dilatation, degenerative changes and signs of apoptosis in atrial myocytes have also been found (Aime-Sempe et al. 1999, Thijssen et al. 2000). Furthermore, the degree of interstitial fibrosis is increased in patients with chronic AF (Frustaci et al. 1997, Wouters et al. 2001, Kostin et al. 2002). The normal atria has a heterogenous transmural and transseptal myoarchitecture (Ho et al. 2002). Atrial dilatation, fibrosis and other structural changes induced by AF are distributed nonuniformally in the atria, thus creating more three-dimensional structural heterogeneity which results in further inhomogenies in conduction and refractoriness.

Time course of remodeling

Atrial action potential duration (ADP) is abbreviated in a few minutes of high atrial rate, largely by causing inactivation of L-type CA^{2+}-channels (Courtemanche et al. 1998). During the first 24 hours of AF ERP shortens and loss of rate adaptation of ERP have been noted (Morillo et al. 1995, Wijffels et al. 1995, Elvan et al. 1996, Gaspo et al. 1997b), and the decrease of ERP can occur over a time interval as short as several minutes (Daoud et al. 1996). Further electrical remodeling takes place during the first days of AF, with ERP reaching a new steady state after 2 -3 days (Wijffels et al. 1995).

Structural remodeling of the atria is also a gradual, but much slower, process. During the first week of AF the first signs of structural remodeling occur, and in the time between 1 and 4 weeks several additional changes have been noted, such as a decrease of connexin, heterogenous distribution of connexin, an increase in the size of atrial myocytes, and a loss of sarcomeres (Allessie et al. 2002). When AF continues for longer than 1 month, further structural changes will occur (Morillo et al. 1995, Ausma et al. 1997, Li et al. 1999, Ausma et al. 2001).

Reversal of remodeling

After restoration of sinus rhythm ERP recovers quickly over the first few minutes to hours (Goette et al. 1996), and returns completely to normal within 1 week (Wijffels et al. 1995). A shorter duration of AF exhibits a faster recovery of the atrial ERP following conversion to sinus rhythm (Daoud et al. 1996). Lee et al. (1999) found regional differences in recovery from tachycardia-induced changes. In humans with persistent AF, reversal of electrical remodeling depends on the duration of sinus rhythm (Hobbs et al. 2000) and has been shown to be completely reversible within 3 days of sinus rhythm (Yu et al. 1999).

Reversal of the structrural changes caused by prolonged AF is a very slow process; a full recovery might not be possible at all. Everett et al. (2000) found no signs of recovery from atrial structural remodeling 2 weeks after cardioversion of AF, despite a complete reversion of electrical remodeling (Yu et al. 1999). After several months of sinus rhythm a lot of structural changes have been still present (Ausma et al. 2003), and atrial conduction disturbances have been detected even after 3 years of conversion to sinus rhythm (Nishino et al. 2000).

Autonomic nervous system

In the presence of a normal conduction system, HR is determined by the discharge rate of the sinoatrial node. The intrinsic discharge rate is affected by the metabolism of the pacemaker cells (Opie 1998). The sinus node is richly innervated with both parasympathetic and sympathetic nerve endings. Both divisions of the autonomic nervous system are continually active and regulate to an important extent the frequency of pacemaker discharge. Increased sympathetic nervous activity, with the released norepinephrine acting via the β-adrenergic pathway, increases the HR. Parasympathetic activity, which stimulates cholinergic receptors through the release of acetylcholine from vagal nerve fibers, diminishes the HR (Zipes 1997). The two branches of the autonomic nervous system work in a co-ordinated way, usually acting

reciprocally, but sometimes synergistically on HR. In resting conditions the sympathetic influence is minimal and the variations in HR are largely dependent on vagal modulation (Levy 1971, Chess et al. 1975). In the presence of stress or disease, β-adrenergic receptor control of HR is more important (Opie 1998). Several reflexes in the cardiovascular system help to control the HR. Regulation of cardiac neural activity is highly integrated and is achieved by circuitry at multiple levels. The intrinsic cardiac nerves and fat pads appear to provide local neural coordination independent of higher brain centers.

The baroreceptors in the carotid sinuses and aortic arch are among the major control systems responsible for changes in HR (Hainsworth 1995). Beat-to-beat fluctuation of HR is the result of a complex interaction between autonomic tone, sensory input, central influence, vasomotor regulation, and target organ responsiveness.

Physiology of the autonomic nervous system

The importance of the autonomic nervous system in the genesis of AF has been known for several years (Coumel 1992). Parasympathetic stimulation shortens the atrial ERP, increases the heterogeneity of ERP, and decreases the wavelength, thus favoring both the onset and maintenance of AF (Allesie et al. 1958, Geddes et al. 1996, Wang et al. 1996, Liu et al. 1997, Jayachandran et al. 2000). The occurrence of AF episodes has a unique circadian rhythm, so that the probability of maintenance is higher during nighttime than during daytime (Yamashita et al. 1997). In animal models vagal stimulation has been much more effective than sympathetic stimulation in promoting sustained AF (Geddes et al. 1996, Liu et al. 1997, Olgin et al. 1998). In dogs, catheter ablation of parasympathetic nervous input to the atrium can abolish vagally mediated AF (Schauerte et al. 2000).

The intrinsic neural network within the heart provides local, independent heart rhythm control (Randall et al. 1985, Chiou et al. 1998). Components of this innervation system reside within discrete fat pads. The cardiac fat pads and local cardiac regulatory systems are also of considerable clinical significance. The Maze procedure causes partial parasympathetic denervation, which may partly explain high

success rates in eliminating AF (Cox et al. 1996). In a recent ablation study, complete vagal denervation in the fat pads around and outside the pulmonary vein areas has been shown to significantly reduce recurrence of AF (Pappone et al. 2004).

Increased parasympathetic tone may also enhance ectopic firing, serving as a trigger of paroxysmal AF in subjects without evidence of other structural cardiac abnormality (Haissaguerre et al. 1998, Zimmerman et al. 2001). Experimental regional cardiac denervation has been shown to result in a regional shortening of atrial ERP, heterogeneity of atrial depolarization, and predisposition to induction of AF (Chen et al. 1998, Olgin et al. 1998, Jayachandran et al. 2000, Hirose et al. 2002). In goats a high vagal tone after restoration of sinus rhythm has been shown to attenuate the recovery of the atrial ERP (Blaauw et al. 1999).

AIMS OF THE STUDY

The purpose of the present work was to examine changes in HR dynamics preceding clinical episodes of AF by using conventional time and frequency domain measures of HR variability, as well as non-linear methods of HR variability. Alterations in responses to atrial ectopic impulses were also assessed by analyzing HR turbulence after atrial ectopic beats. The specific aims were:

1. To study the probable alterations in HR variability preceding spontaneous paroxysmal episodes of AF in patients with structural heart disease and in patients with lone AF.

2. To find out if the amount of ectopic beats increases before spontaneous onset of AF episodes.

3. To find out if alterations in HR variability before spontaneous episodes of AF could predict the perpetuation of AF episodes in patients with lone AF.

4. To evaluate whether vagal responses to atrial ectopic beats were different during one hour before the onset of AF episodes as compared to other hours of the 24-hour recordings.

5. To assess whether alterations in HR variability measures could predict the recurrence of AF after restoration of sinus rhythm with cardioversion.

SUBJECTS

The study population consisted of patients for whom 24-hour ECG recording was performed because of clinical reasons in Tampere or Oulu University Hospitals during 1991-2001, and of 116 patients who were treated with transthoracic electrical cardioversion due to persistent AF (>one month) in Tampere University Hospital during 1999-2001. From the 24-hour ECG recordings those 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 >60 years of age who had sinus pauses >2.5 seconds 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. Patients without hypertension, diabetes, structural heart disease, or atrioventricular accessory pathways were included in the group of patients with lone AF.

Only patients with lone AF were included in Studies I-II, while both lone AF patients and patients with structural heart diseases were included in Study III. The lone AF study population included in Studies I and II consisted of 22 patients from which 26 24-hour recordings were made, containing 92 episodes of AF. In Study III the study population consisted of 29 lone AF patients (21 of them were the same patients as in Studies I and II), for whom 33 24-hour recordings were made and of 39 patients with structural heart disease, for whom 40 Holter recordings were made. From the 116 patients who underwent electrical cardioversion, 98 achieved sinus rhythm. The final study group consisted of 78 patients; 20 patients were excluded because of signal artefacts, frequent ectopic beats or sick sinus syndrome. One patient was excluded because of early recurrence of AF 6 hours after cardioversion. The clinical characteristics of the study population are presented in Table 1.

The study protocol was approved by the Ethics Committee of the University of Tampere. Written informed consent was obtained from each of the cardioverted patients.

Table 1. Clinical characteristics of the study population.

	Lone AF patients	Patients with structural heart disease	Cardioverted patients
Number of patients	30	39	78
Age, years	52±15	64±10	63±13
Sex, male/female	15/15	20/19	55/23
Heart disease: n (%)			
Hypertension	-	28 (72)	37 (47)
Valvular	-	13 (33)	8 (10)
Dilated cardiomyopathy	-	3 (8)	4 (5)
Ischemic	-	17 (44)	10 (13)
None	30 (100)	-	25 (32)
Diabetes mellitus	-	12 (31)	10 (13)
Cardiac medication			
betablocking agents	13 (43)	21 (54)	63 (81)
IA antiarrhythmics	2 (7)	2 (5)	-
IC antiarrhythmics	7 (23)	4 (10)	6 (8)
digitalis	4 (13)	8 (21)	37 (47)
no medication	11 (37)	-	3 (4)
Duration of AF (months)			3±2
Left atrial diameter (mm)			45±6
Left ventricular ejection fraction (%)	63±6*	51±17†	60±12

AF, atrial fibrillation; *available from 20 patients; †available from 22 patients.

METHODS

All patients underwent a 24-hour ECG recording. Transthoracic echocardiography was performed for all patients who underwent electrical cardioversion, for 56% of the patients with structural heart diseases, and for 67% of the patients with lone AF.

ECG recordings

All two-channel 24-hour recordings were analyzed with the Medilog Excel (version 4.1c, Oxford Medical Ltd) ECG software system and also manually to detect and quantify arrhythmias and artefacts. The data were sampled digitally and transferred to a microcomputer for the analysis of HR variability.

Measurement of heart rate variability

After the ECG data were transferred to the microcomputer, the R-R interval series were first edited automatically, followed by careful detailed manual editing. In Studies I and II all ectopic beats and noise were deleted and in Studies III and IV the artefacts and ectopic beats were deleted and the formed gaps were replaced by the interpolation method described earlier (Huikuri et al. 1994, Salo et al. 2001). 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 (Huikuri et al. 1993, Huikuri et al. 1996b).

All analyses of R-R interval variability were performed with a custom-made analysis program (Hearts, Heart Signal Co, Oulu); the details of the methods have been described elsewhere (Huikuri et al. 1993, Huikuri et al. 1996b, Mäkikallio et al. 1996,

Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996, Mäkikallio et al. 1998). HR variability was analyzed from 2 hours preceding AF episode(s) in 20-minute segments in Studies I and II, from the entire recording in Study IV, and from the sinus rhythm in the whole recording, in 60-minute segments in Study III. In Study III HR variability was also analyzed in 15-minute segments from 60 minutes preceding AF episode(s). In Study I not all AF episodes had 2 hours of sinus rhythm suitable for analysis; the trend for HR variability measures was analyzed from episodes, which had at least 40 minutes of sinus rhythm preceding AF.

In Study II the AF episodes were divided into two groups according to their duration. If there was less than five minutes 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. 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 and those longer than 200 seconds as long AF episodes. The same cutoff point of 200 seconds was used in the Study III when comparing TO before long and short AF episodes.

Time and frequency domain measures of heart rate variability

Time domain and spectral measures of HR variability were analyzed according to the methods recommended by the task force (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). SDNN and the mean length of the R-R intervals were computed as time-domain measures.

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 four frequency bands: <0.0033 Hz (ULF), 0.0033 to 0.04 Hz (VLF), 0.04 to 0.15 Hz (LF) and 0.15 to 0.40 Hz (HF). ULF- and VLF spectral components were

computed over the entire recording interval. LF and HF components were computed from the segments of 512 R-R intervals and the average values of the entire recording or 60-minute periods were used.

Periods of 15 or 20 minutes were 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, and LF and HF spectral components were analyzed over the 15 or 20-minute periods. In addition to absolute units, normalized units (nu) of LF and HF were calculated by multiplying the power of each spectrum by 100 and then dividing it by the sum of the power of the LF and HF spectra. The ratio between LF and HF spectra was also calculated.

Nonlinear measurements of heart rate variability

The same pre-edited R-R interval time series that had been used for the spectral and time domain analysis of HR variability were also used for calculating scaling and complexity properties of R-R intervals by various indices.

A detrended fluctuation analysis technique was used to quantify short-term fractal correlation properties of the R-R interval data. HR correlations were defined specifically for short-term (<11 beats, α_1) fluctuations in the data (Peng et al. 1995b, Mäkikallio et al. 1997).

For overall complexity ApEn was computed. 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 accurate statistical validity (Pincus et al. 1992, Pincus et al. 1994). Analyses of approximate entropy and the short-term scaling exponent α_1 were also carried out from data where only noise was abolished and ectopic beats were not excluded. In the final analysis both edited and unedited data were used.

A long-term power-law relation of R-R interval variability was calculated from the frequency range of 10^{-4} to 10^{-2} Hz. The point power spectrum was logarithmically smoothed in the frequency domain, and the power was integrated into bins spaced 0.0167 log (Hz) apart. A robust line-fitting algorithm of log (power) versus log

(frequency) was then applied, and the slope of this line was calculated, yielding the long-term scaling exponent (β).

Effects of ectopic beats

The amount of ectopic beats by percentage was also analyzed. Because of the potential effect of ectopic beats on ApEn and scaling exponents, the effect of the ectopic beats on ApEn and on the scaling exponent α_1 was assessed in Study I by various experiments with real and artificial R-R interval data. Short and long time intervals resembling ectopic beats with a compensatory pause were added and the amount of replaced beats was increased progressively. First, ectopic beats with a constant coupling interval (500 ms) were added. The amount of replaced beats was then increased progressively from 0 to 40%. Second, the same procedure was repeated, but the time length of the coupling intervals was changed randomly within certain limits (350 to 800 ms). The tests were performed on real R-R interval data of a healthy subject with mean HR ~60 and SDNN 130 ms and also on artificial signals with 1/f signal properties, with a mean R-R interval length of 1000 ms and SDNN 160 ms.

Heart rate turbulence

Identification of atrial ectopic beats

Atrial ectopic beats were first identified automatically. The criterion for prematurity was at least a 20% shortening of the R-R interval. After that, careful manual editing was performed by checking simultaneously 2-channel Holter recordings and R-R interval tachograms. An ectopic beat was considered as an atrial ectopic beat if there was evidence of atrial depolarization in any of the Holter channels. Only isolated atrial

ectopic beats (preceded and followed by ≥20 normal sinus beats) with clear postectopic pause were included. The prematurity index for ectopic beats was calculated by dividing the coupling interval of the ectopic beat by the mean of two sinus R-R intervals preceding the coupling interval.

Analysis of heart rate turbulence after atrial ectopic beats

HR turbulence was calculated as previously described (Schmidt et al. 1999). According to Schmidt et al. (1999) TO is defined as the difference between the mean of the first two sinus R-R intervals after a compensatory pause and the last two sinus R-R intervals before the atrial ectopic beat, divided by the mean of the last two sinus R-R intervals before the atrial ectopic beat. TS was calculated as the maximum slope of the regression line over any sequence of 5 sinus R-R intervals within the first 20 sinus beats after an atrial ectopic beat. The mean of TO and TS for all atrial ectopic beats located one hour preceding AF episode(s) was calculated. From the rest of the 24-hour recording the mean of TO and TS for all atrial ectopic beats were calculated by hour and compared with the mean of the values for one hour preceding AF.

Statistics

The results are presented as mean value ± 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 HR variability, the SDNN, and the number of ectopic beats in different time periods. These logarithmic transformations of HR measures were used in statistical analyses in all studies. The differences in continuous variables from the same recordings were analyzed with the paired samples Student´s t test. When comparison was made between different groups, the independent samples Student´s t test was used. Differences between categorical variables were analyzed with an χ^2 –test. Pearson correlation coefficients were used in the analysis of correlation between the continuous variables. One-way ANOVA was

used to compare the changes of HR variability measures in 15-minute periods before AF. Twenty-minute periods preceding AF episodes had unbalanced data. Thus, in order to evaluate if there had been a significant change in different HR variability measures or in the amount of ectopic beats before the onset of AF, the linear mixed models were used. With these models it is possible to analyze unbalanced repeated-measure designs, which use different types of mean and covariance structures. The linear mixed models were fitted using PROC MIXED in the SAS System for Windows version 6.12.

In Study IV the continuous R-R interval variability measures were dichotomized. Because there are no well-defined cutoff values for the continuous R-R interval variability measures, they were dichotomized by counting tertiles for each variable. The most "abnormal" tertile was then used as the dichotomization cut point. Kaplan-Meier estimates of the distribution of the times from cardioversion to AF were computed and log-rank analysis was performed to compare the curves, which indicate the maintenance of sinus rhythm. Odds ratios and 95% confidence intervals were also calculated for univariate predictors of recurrence of AF. The sensitivity, specificity and predictive accuracy values of R-R interval variability measures for recurrence of AF were also calculated. The P value of <0.05 was considered significant.

RESULTS

Time and frequency domain measures of heart rate variability

None of the time and frequency domain measures analyzed in 15-minute (Table 2) or 20-minute periods (Table 3) showed any significant changes before the onset of AF episodes. When compared one hour before the onset of AF with other hours of the recording no significant changes in average R-R interval (984±185 vs 969±135 ms), SDNN (84±35 vs 79±27 ms), HF power (299±316 vs 261±235 ms^2) or LF power (491±460 vs 484±431 ms^2) were seen (p=NS for all).

Table 2. Changes in R-R variability before spontaneous onset of atrial fibrillation.

Time epoch before AF	60-45 min	45-30 min	30-15 min	15-0 min
All Patients n=63*				
Average RR interval (ms)	997±189	1000±181	998±192	972±201
HF power (ms^2)	358±584	308±395	262±249	289±334
LF power (ms^2)	556±608	522±535	473±460	471±496
LF/HF ratio	2.2±1.8	2.2±2.0	2.3±1.9	2.2±2.1
SDNN (ms)	64±31	71±30	60±26	70±34

*Number of recordings. Values are mean ± SD. LF, low frequency; HF, high frequency; SDNN, standard deviation of all RR intervals; P=NS for all.

Table 3. Changes in time and frequency domain heart rate variability measures before spontaneous onset of atrial fibrillation in 22 patients with lone atrial fibrillation.

Time epoch before AF	120-100 min	100-80 min	80-60 min	60-40 min	40-20 min	20-0 min
AF episodes (n)	31	34	42	51	62	62
Average RR interval (ms)	1033±158	1036±166	1023±169	1001±187	992±180	974±174
LF power (ms^2)	797±451	832±642	711±678	694±521	640±548	667±767
ln	6.5±0.6	6.4±0.8	6.2±0.9	6.2±0.9	6.1±1.0	6.0±1.0
HF power (ms^2)	444±476	543±830	464±633	388±459	353±417	319±361
ln	5.7±0.8	5.7±1.0	5.6±1.0	5.5±0.9	5.4±1.0	5.3±1.0
LF/HF ratio	2.9±2.7	2.7±2.2	2.5±1.9	2.8±2.2	2.7±2.1	2.9±2.5
SDNN (ms)	76±36	66±22	71±29	70±29	65±27	67±32
ectopics (%)	2.6±4.6	2.3±3.8	2.9±5.1	2.9±4.9	4.0±5.4	3.6±4.0

Values are mean ± SD; AF, atrial fibrillation; LF, low frequency; HF, high frequency; SDNN, standard deviation of all RR intervals. p=NS for the trend for all HR variables and $p<0.05$ for the trend for ectopics tested with the linear mixed model.

Before long episodes of AF the HF power (normalized units) was significantly higher, the LF power (nu) lower, and the ratio between LF and HF lower than before short episodes of AF (Table 4). Figure 1 presents the HF power in normalized units from the patients (n=8, 10 recordings) who had both short and long episodes of AF.

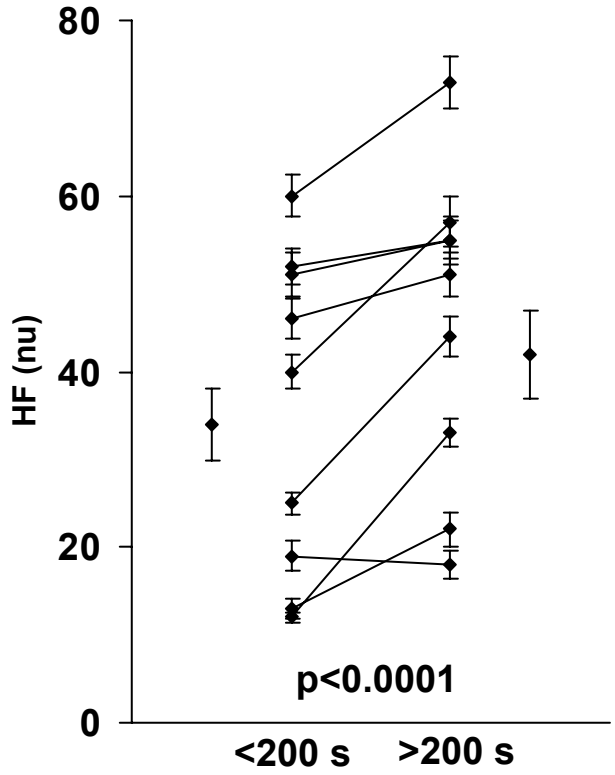

Figure 1. High frequency spectral power in normalized units (mean±standard error of mean) from patients who had both short and long episodes. High frequency power was almost regularly higher before a long episode than before a short episode in the same patient.

Table 4. Heart rate variability measures before short and long atrial fibrillation episodes in 22 patients with lone atrial fibrillation.

AF duration	< 200 s	> 200s
AF episodes, n	51	41
Average RR interval, ms	994±168	1008±175
SDNN, ms	70±27	63±30 *
HF power, ms²	381±559	404±428
NU	31.5±16.4	40.1±14.8 †
LF power, ms²	756±683	589±475 *
NU	68.5±16.4	59.9±14.8 †
LF/HF ratio	3.3±2.5	1.9±1.3 †
ectopics, %	2.6±3.2	3.4±4.2

* $p<0.05$, † $p<0.0001$. Values are mean ± SD. AF, atrial fibrillation; 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.

Table 5 presents time and frequency domain measures after restoration of sinus rhythm with transthoracic cardioversion. All power spectral components, except the ULF power, were significantly higher in patients who had relapse of AF during the one-month follow-up when compared with patients who remained in sinus rhythm. Increased HF and LF power were observed both during day- and night-time in patients with recurrence of AF. These patients had also higher SDNN and their mean HR was slower during night-time than in patients who remained in sinus rhythm.

Table 5. R-R interval variability of patients who had recurrence of atrial fibrillation and those who remained in sinus rhythm during the one month follow-up.

	Sinus Rhythm (n=51)	AF (n=27)
Mean R-R interval, ms	920±123	957±101
SDNN, ms	100±29	117±34 *
ULF power		
ms^2	6565±4135	8132±7196
ln	8.6±0.6	8.7±0.8
VLF power		
ms^2	872±618	1587±1095
ln	6.5±0.8	7.1±0.8 †
LF power		
ms^2	384±348	666±533
ln	5.6±0.9	6.2±0.8 †
nu	56±17	61±17
HF power		
ms^2	267±202	351±199
ln	5.3±0.7	5.7±0.6 *
nu	44±17	39±17
LF/HF ratio	1.61±1.01	2.08±1.32

* $p<0.05$, † $p<0.01$. Values are mean ± SD. SDNN ,standard deviation of all normal R-R intervals; ULF, ultra-low-frequency power; VLF, very-low-frequency power; LF, low-frequency spectral power; HF, high-frequency spectral power; ln, logarithmic transformation of power spectral measures; nu, normalized units of power spectral measures.

Figure 2 shows Kaplan-Meier curves from various dichotomized variables depicting the probality of remaining in sinus rhythm during the one-month follow-up after cardioversion. During the first week after cardioversion increased HF power was the most powerful predictor of recurrence of AF, with an odds ratio of 2.8 (95% confidence interval 1.0 to 8.0, $p<0.05$). However, later recurrence of AF was predicted most powerfully with increased VLF power, with an odds ratio of 3.3 (95% confidence interval 1.6 to 7.2, $p<0.01$).

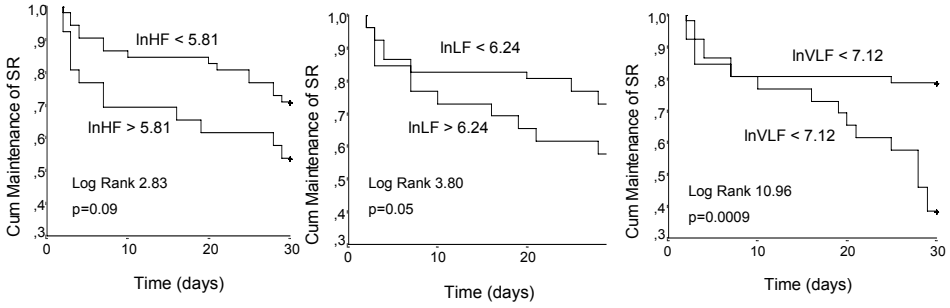

Figure 2. Kaplan-Meier curves depicting the probability of maintenance of sinus rhythm (SR) during 30 days after cardioversion of patients with natural logarithmic of high-frequency spectral component (lnHF) of < 5.81 and > 5.81, respectively (left); patients with natural logarithmic of low-frequency spectral component (lnLF) of < 6.24 and > 6.24, respectively (center); and patients with natural logarithmic of very-low-frequency spectral component (lnVLF) of < 7.12 and > 7.12, respectively (right).

Non-linear measures of heart rate variability

In patients with lone AF, ApEn analyzed in 20-minute segments from fully edited data and the real R-R interval data without excluding the ectopic beats decreased significantly before the onset of AF (Figure 3). The short-term scaling exponent α_1, analyzed from the real R-R interval data, also decreased progressively before the onset of AF (from 1.01±0.28 in 120-100 minutes to 0.89±0.28 in 20-0 minutes before AF, $p<0.05$). When α_1 was analyzed from the fully edited data no significant changes were found before AF.

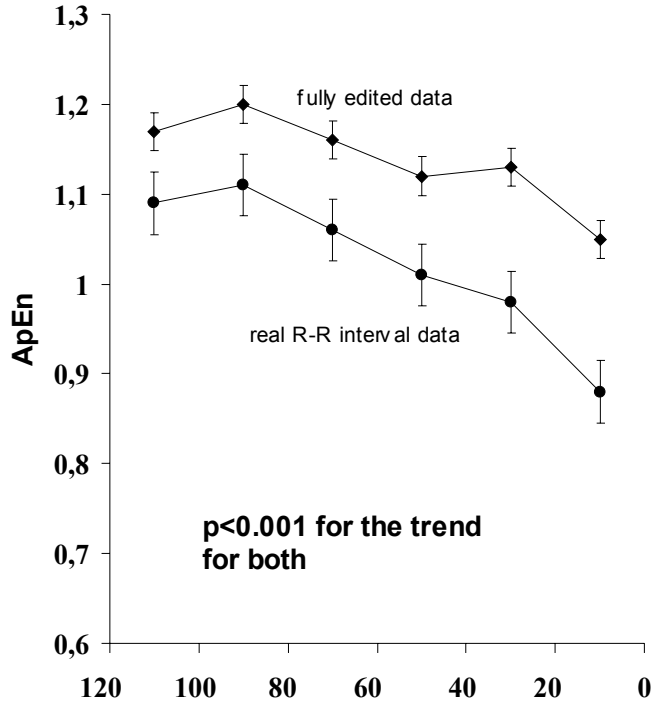

Figure 3. Approximate entropy before the onset of atrial fibrillation episodes in patients with lone atrial fibrillation.

When ApEn was analyzed in 15-minute periods from fully edited data no significant changes were found either in patients with lone AF or in patients with structural heart diseases. One hour before the onset of AF, ApEn analyzed from fully edited data was significantly lower when compared with the other hours of the recording, both in patients with structural heart diseases (0.94±0.26 vs 1.02±0.23, $p<0.05$) and in patients with lone AF (0.97±0.25 vs 1.09±0.21, $p<0.01$).

Before long episodes of AF, α_1 was significantly lower (1.12±0.21 vs 1.24±0.23, $p<0.0001$) and ApEn higher (1.16±0.23 vs 1.11±0.22, $p<0.05$) than before short episodes of AF. Figure 4 presents α_1 -values in patients who had both short and long episodes of AF. Also in this subgroup of patients α_1 was significantly lower before long episodes of AF than before short episodes of AF.

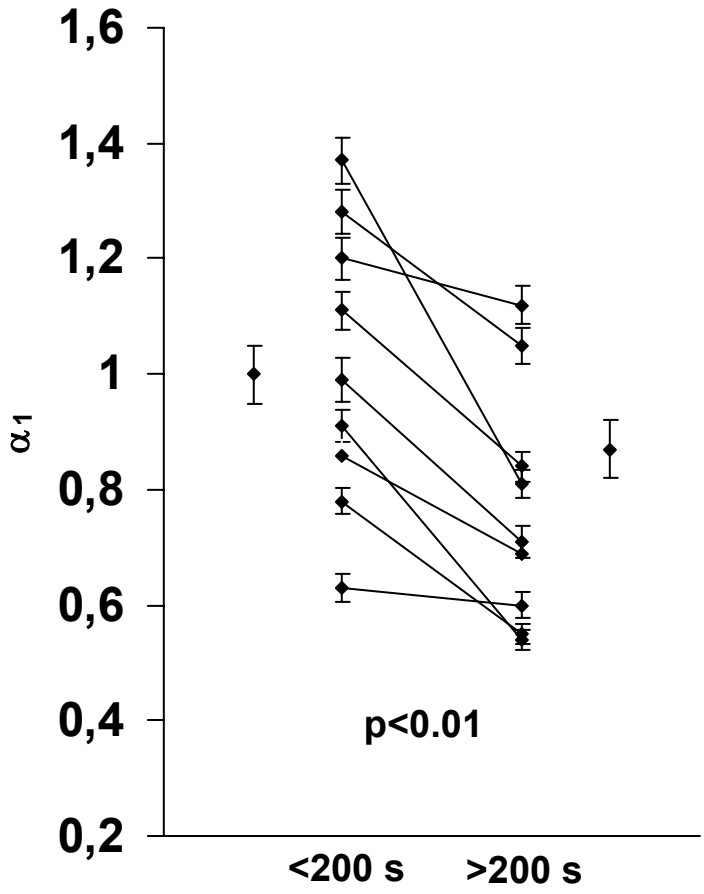

Figure 4. Scaling exponent α^1 (mean±standard error of mean) from patients who had both short and long episodes. The fractal scaling exponent α_1-values were regularly lower before long than before short episodes in the same patient.

After cardioversion, long-term power-law slope β differed significantly between the patients who remained in sinus rhythm during the one-month follow-up and who had recurrence of AF (-1.29±0.19 vs -1.19±0.20, $p<0.05$), while no differences in ApEn and α^1 were found. When these measures were analyzed from the patients who had relapse of AF during the first week after cardioversion no differences could be found in α^1 and β –values, but ApEn was lower in those patients who remained in sinus rhythm (0.99±0.22 vs 1.15±0.25, $p<0.05$).

Atrial ectopic beats

The amount of ectopic beats increased during the last 40 minutes preceding AF episodes in patients with lone AF (Table 3). One hour before the onset of AF episodes the amount of ectopic beats was higher than during other hours of the recording in patients with lone AF (Table 6). The atrial ectopic beats were also more premature near AF than far from AF (Table 6) in patients with lone AF. In patients with structural heart diseases no differences in the amount or prematurity of ectopic beats were found when compared between one hour before the onset of AF and the other hours of recording (Table 6). There was no difference in the amount of ectopic beats before the onset of AF episodes between short and long episodes of AF (Table 4).

The amount of ectopic beats in patients who had recurrence of AF after restoration of sinus rhythm with cardioversion was not different than in patients who remained in sinus rhythm during the one-month follow-up.

When the number of ectopic beats with constant coupling interval was added to real and artificial R-R interval data, ApEn decreased progressively (from 1.08 with no ectopics to 0.63 with 40% ectopics from real data). The opposite effect, with increasing values of ApEn, was noted when ectopic beats with randomly varied coupling interval were added (from 1.08 with no ectopics to 1.49 with 40% ectopics from real data). α_1 decreased when ectopic beats, either with constant or varying coupling intervals, were added to the real or artificial data.

Heart rate turbulence

During one-hour period(s) preceding the onset of AF episodes, TO values were significantly higher than the means of TO values by hour from the rest of the recording both in patients with lone AF and in patients with structural heart diseases. The mean value of TS was not significantly different between the two time periods (Table 6).

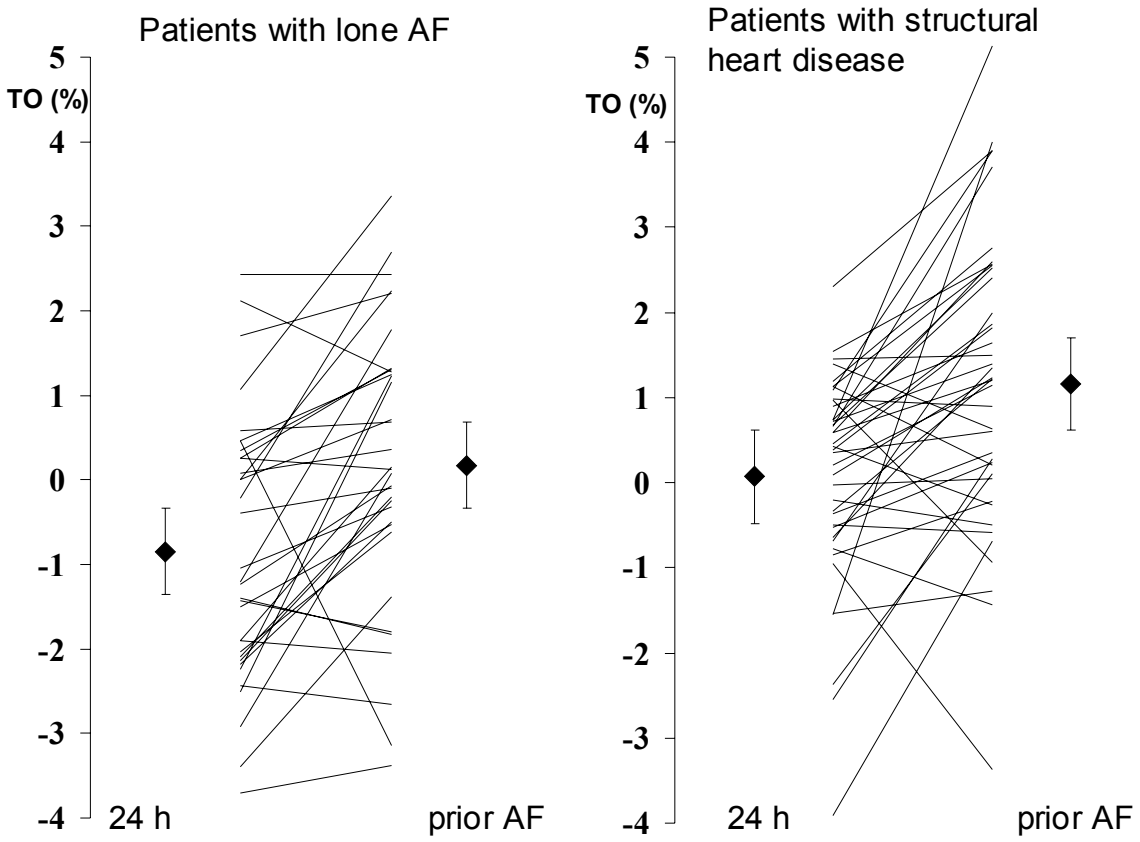

Figure 5. Heart rate turbulence onset (TO) after spontaneous atrial ectopic beats. The mean values of TO are significantly higher ($p<0.0001$) during one hour preceding atrial fibrillation (prior AF) than the mean values by hour from the rest of the recording (24 h) both in patients with lone atrial fibrillation (left) and in patients with structural heart diseases (right).

Table 6. Changes in heart rate turbulence before spontaneous onset of atrial fibrillation

Time epoch	Non-AF hours	One hour prior to AF
All Patients n=73*		
Turbulence onset (%)	-0.35±1.46	0.71±1.76 ‡
Turbulence slope (ms/RRI)	15.5±7.4	15.0±7.5
Atrial ectopic beats (n)	3.2±2.2	3.7±3.2
Coupling interval (ms)	629±102	615±151
Prematurity index	0.67±0.07	0.65±0.09
Lone AF n=33*		
Turbulence onset (%)	-0.85±1.56	0.17±1.67 ‡
Turbulence slope (ms/RRI)	18.8±8.2	17.0±8.3
Atrial ectopic beats (n)	2.9±2.2	4.2±4.2 †
Coupling interval (ms)	611±80	560±129 †
Prematurity index	0.64±0.08	0.61±0.09 †
Patients with structural heart disease n=40*		
Turbulence onset (%)	0.07±1.23	1.16±1.73 ‡
Turbulence slope (ms/RRI)	12.8±5.5	13.5±6.5
Atrial ectopic beats (n)	3.4±2.0	3.3±2.0
Coupling interval (ms)	644±115	660±155
Prematurity index	0.69±0.06	0.68±0.08

*Number of recordings; Values are mean ± SD. † $p<0.05$, ‡ $p<0.0001$

Patients with lone AF had lower values of TO than patients with structural heart diseases both during one hour before AF and during the rest of the recording ($p<0.05$ and $p<0.01$, respectively) (Figure 5). There were 17 recordings (11 from patients with lone AF and 6 from patients with structural heart diseases) in which there was at least one ectopic beat in each 15-minute time epoch during the last hour before the onset of AF. Among this subgroup of patients TO values from the ectopic beats located 0-15 minutes preceding the AF episode was significantly higher than the TO values from the ectopic beats located 45-60 minutes before the onset of the AF episode (Figure 6).

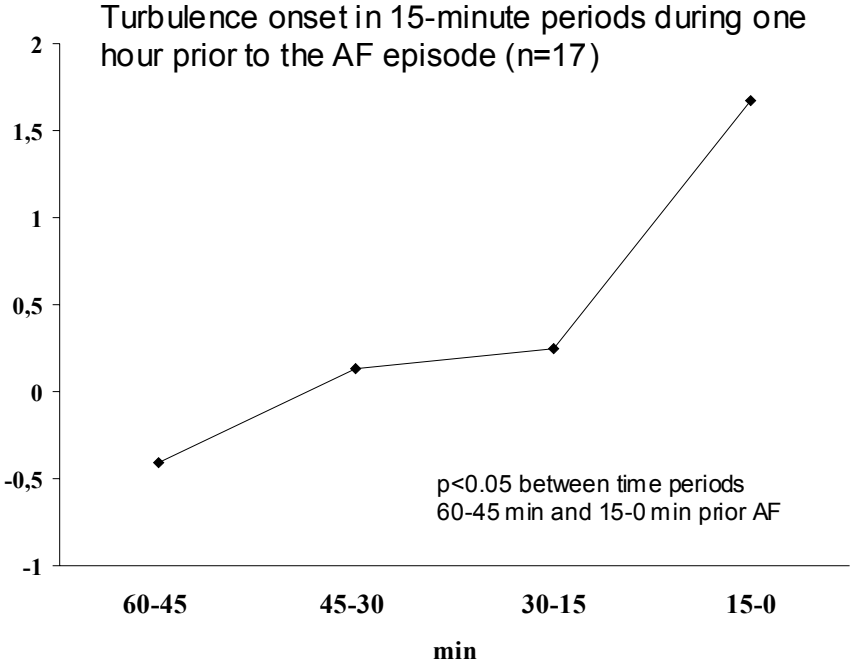

Figure 6. Heart rate turbulence onset after spontaneous atrial ectopic beats in 15-minute time epochs during the one-hour period preceding atrial fibrillation (AF) episode(s). In the subgroup of patients (n=15; 17 recordings) having at least one atrial ectopic beat in each 15-minute period during the last hour before atrial fibrillation episode, turbulence onset is significantly higher during the 0-15 minute period before atrial fibrillation than during the 45-60 minute period preceding atrial fibrillation.

There were 87 short (<200 seconds) and 63 long (>200 seconds) episodes of AF. In the whole group and in the patients with structural heart disease TO values were not significantly different preceding 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 patients with lone AF, TO was significantly lower before short than long episodes of AF (-0.39 ±2.62 vs 1.24±2.63; $p<0.01$).

DISCUSSION

The main findings of the Study are that there are alterations in HR variability before spontaneous onset of AF episodes, and that these alterations may predict the perpetuation of AF episodes and recurrence of AF after cardioversion. Furthermore, vagal responses to atrial ectopic beats were different during one hour before the onset of AF episodes as compared to other hours of the 24-hour recordings.

Time and frequency domain measures of heart rate variability

The role of autonomic tone in the genesis and maintenance of AF has been clinically recognized for many years (Coumel 1992, Coumel 1994, Chen et al. 1998). Activation of the vagus nerve shortens the atrial ERP, decreases the wavelength, and increases the dispersion of refractoriness, thus favoring the onset and maintenance of AF (Allesie et al. 1958, Geddes et al. 1996, Wang et al. 1996, Liu et al. 1997, Jayachandran et al. 2000). The main tool in clinical cardiology to evaluate cardiac autonomic regulation is analysis of HR variability from continuous ECG recordings (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996).

Before spontaneous onset of atrial fibrillation episodes

Several reports have been published about changes in spectral and non-spectral components of HR variability before the onset of AF episodes both in patients with

lone AF and in patients with overt cardiac disease (van den Berg et al. 1995, Dimmer et al. 1998, Herweg et al. 1998, Hnatkova et al. 1998a, Hnatkova et al. 1998c, Hogue et al. 1998, Huang et al. 1998, Wen et al. 1998, Fioranelli et al. 1999, Bettoni et al. 2002, Dimmer et al. 2003, Tomita et al. 2003). According to these reports, most episodes of AF in patients without structural heart disease are related to increased vagal tone, while in patients with structural heart disease AF episodes have been preceded by increased sympathetic tone.

However, even though dynamic changes in autonomic tone prior to AF have been demonstrated, the frequency, character, time frame, and degree of change vary considerably from study to study. In many reports only a minority of episodes could have been categorized to be purely related to parasympathetic or sympathetic tone and the mode of onset has also been inconsistent within individuals (Hnatkova et al. 1998a, Fioranelli et al. 1999, Dimmer et al. 2003, Tomita et al. 2003). Nonstationarity of the data and the replacement of ectopic beats and compensatory pauses by any interpolation method are the major problems in the spectral analysis of HR variability during uncontrolled conditions. In the present study there were no changes in traditional time and frequency domain measures before the onset of AF either in patients with lone AF or in patients with structural heart disease.

The lack of change in the spectral components of HR variability prior to AF may not exclude significant changes in autonomic tone before the onset of AF episodes, because it appears that the relative sympathovagal balance is as important, or more important, than the absolute vagal or sympathetic tone. It has been shown that regional cardiac sympathetic denervation can result in a relative increase in parasympathetic tone without a change in absolute vagal tone. This causes regional shortening of the atrial ERP, thus creating a heterogeneity of atrial depolarization, which predisposes the onset of AF (Chen et al. 1998, Olgin et al. 1998, Chang et al. 2001, Hirose et al. 2002).

Predicting perpetuation of atrial fibrillation episodes

Spatial dispersion of functional properties such as refractoriness has been shown to be an important factor contributing to the maintenance of AF (Geddes et al. 1996, Liu et

al. 1997, Olgin et al. 1998). In animal models vagal stimulation has been more effective than sympathetic stimulation for providing sustained AF (Geddes et al. 1996, Liu et al. 1997, Olgin et al. 1998).

There are not much data about factors related to the perpetuation of paroxysmal AF episodes in humans. The maintenance of AF episodes has been shown to follow a unique circadian rhythm, so that the probability for perpetuation of AF is higher during night-time, suggesting the importance of vagal tone in the maintenance of AF (Yamashita et al. 1997). Fukiji et al. (2003) found that an abrupt increase in fibrillation cycle length occurred before spontaneous termination of AF, which might be explained by the shift towards vagolytic autonomic balance. Concurrent with these findings increased HF power and decreased LF power preceding long AF episodes were noticed in this study.

Predicting recurrence of atrial fibrillation after electrical cardioversion of persistent atrial fibrillation

Maintenance of sinus rhythm after cardioversion is a major clinical problem. Even in the precence of an appropriate antiarrhythmic therapy, 40% to 60% of patients have a recurrence of AF (Coplen et al. 1990, van Gelder et al. 1997, Lévy et al. 1998). In this study 35% of patients had a recurrence of AF during one month, and in agreement with other studies (Tieleman et al. 1998, Lombardi et al. 2001, Boriani et al. 2003) the majority of recurrences occurred during the first week after cardioversion.

AF itself causes electrical and structural changes in the atria, favoring the maintenance of AF both in animal models and in humans (Attuel et al. 1982, Boutjdir et al. 1986, Wijffels et al. 1995, Franz et al. 1997). Characteristic features of atrial tachycardia induced electrical remodeling include decreased atrial ERP and decreased conduction velocity (Morillo et al. 1995, Wijffels et al. 1995, Gaspo et al. 1997b). Along with these electrical changes, loss of atrial contractility occurs during only a few minutes of AF (Schotten et al. 2001a). Remodeling is spatially heterogeneous, which also contributes to AF vulnerability (Gaspo et al. 1997b, Fareh et al. 1998). After restoration of sinus rhythm the reversal of AF-induced electrical remodeling takes only a week, even after prolonged periods of AF (months to years) (Yu et al. 1999).

In the present study, different patterns of HR variability predicted the recurrence of AF early during the first week after cardioversion and later during the one-month follow-up. During the first week after cardioversion, when the atria are in a vulnerable state, increased HF power, reflecting mainly cardiac vagal outflow, was the most powerful predictor of recurrence of AF.

In line with the present observations, experimental data have shown that vagal stimulation increases the heterogeneity in the atrial ERP, thus increasing vulnerability to the onset of AF (Geddes et al. 1996, Liu et al. 1997, Olgin et al. 1998). Furthermore, in an animal model high vagal tone during recovery of the atrial ERP has been shown to be associated with a short atrial ERP and an attenuated recovery of electrical remodeling of the atria (Blaauw et al. 1999). The time for recovery of ERP after reversion to sinus rhythm varies regionally, which creates heterogeneity favoring early recurrence of AF (Lee et al. 1999). Previously correlation between a higher tendency of AF recurrence and the shortening of monophasic right atrial action potential have been described (Olsson et al. 1971, Cotoi et al. 1972).

In agreement with this study Kanoupakis et al. (2000) have found significantly higher vagal activity in patients who had a relapse of AF than in patients who remained in sinus rhythm following cardioversion. However, they used only time-domain measures of HR variability.

Lombardi et al. (2001) have reported increased LF spectral power among patients with AF recurrence. They found that increased LF/HF power due to concomitant reduction in HF power was a powerful predictor of AF recurrence during the first two weeks after cardioversion. In accordance with their results, this study showed increased LF variability as well as increased LF/HF ratio in patients with recurrence of AF later during the one-month follow-up. However, in this study HF power was higher in patients with a relapse of AF, while Lombardi et al. (2001) reported lower HF spectral power among patients with a recurrence of AF. There are some salient differences between these studies. Amiodarone was used in all patients in the study by Lombardi et al. (2001), while none of the patients in this study were on amiodarone treatment. However, 80% of patients in the present study received beta-blocking agents during recordings. Amiodarone has been shown to reduce HR variability in all major spectral bands (Rohde et al. 1998). Conversely beta-blocking agents increase the HF spectral components, but has only a minor effect on the lower spectral components

(Cook et al. 1991, Lucini et al. 1993, Niemelä et al. 1994, Keeley et al. 1996). Besides that, 24-hour data recordings were used in this study, whereas 15-minute recordings were used in the previous study (Lombardi et al. 2001), which may cause subtle differences particularly in the lower spectral components.

Non-linear measures of heart rate variability

New non-linear measures of HR variability are based on fractals and chaos theory (Goldberger et al. 1987, West et al. 1987, Goldberger et al. 1990). These measures of HR variability reflect different aspects of HR dynamics compared with traditional measures of HR variability. They do not indicate the magnitude of HR fluctuations around its mean value, but rather the scaling characteristics and other features of behavior. They may reveal subtle abnormalities in HR dynamics which may not be covered with traditional time- and frequency-domain measures (Ho et al. 1997, Mäkikallio et al. 1997, Hogue et al. 1998, Mäkikallio et al. 1998, Mäkikallio et al. 1999).

Before spontaneous onset of atrial fibrillation episodes

In this study ApEn decreased significantly before the onset of AF episodes both in patients with lone AF and in patients with overt cardiac disease. In lone AF patients the short-term scaling exponent α_1, analyzed from real R-R interval data, decreased prior to AF, but no change was observed in α_1 values in pure sinus interval data. The decrease of ApEn has been previously found to precede AF episodes in patients after coronary bypass surgery (Hogue et al. 1998). Reduced values of α_1 have been previously reported to precede ventricular fibrillation in postinfarction patients (Mäkikallio et al. 1998). In selected patient populations the loss of the fractal nature of HR variability has been associated with a higher risk of for arrhythmic events and has predicted a poor prognosis (Mäkikallio et al. 1999, Huikuri et al. 2000, Tapanainen et al. 2002). However, the physiological correlates of ApEn or the short-term scaling exponent α_1 have not been well defined.

Predicting perpetuation of atrial fibrillation episodes

The short-term scaling exponent α_1 was lower before long than before short episodes of AF. It has been shown that vagal blockade leads to increased α_1 -values (Penttilä et al. 2003), and coactivation of cardiac vagal outflow at the time of a high level of a circulating sympathetic transmitter results in a reduction of short-term scaling exponent values (Tulppo et al. 2001b). The short-term scaling exponent has been shown to correlate with the LF/HF spectral ratio in controlled conditions (Tulppo et al. 2001a). The precise mechanisms behind altered fractal dynamics are not known. In the present study no differences in ApEn before short or long AF episodes could be seen, suggesting that the triggers for initiation and maintenance of atrial fibrillation may be different.

Predicting recurrence of atrial fibrillation after electrical cardioversion of persistent atrial fibrillation

From the non-linear HR variability measures, only the long-term power-law slope β differed between patients who remained in sinus rhythm and those who had a recurrence of AF during the one-month follow-up. The long-term power-law slope β was steeper among the patients who remained in sinus rhythm. A steep slope reflects a high relative power of the ULF component compared to the VLF component in the spectra (Bigger et al. 1996). Non-linear measures of HR variability did not provide any additional predictive power for the recurrence of AF as compared to conventional HR variability measures.

Clinical factors

Related to maintenance of atrial fibrillation episodes

In the previous study, advanced age was associated with longer AF episodes (Hnatkova et al. 1998b). In the present study, cardiac medication, time of the day, or

age of the patient had no impact on the duration of AF episodes. The overall HR variability and especially the LF power and α_1 have been shown to decrease with ageing (Jokinen et al. 2001), but many other factors besides the autonomic nervous system, such as enlargement of the atrium, increased atrial fibrosis, and higher prevalence of structural cardiac abnormalities, may explain the association with age and the length of the AF episodes. As also shown previously (Hnatkova et al. 1998b), women had more long episodes than men. Women also have lower LF/HF ratios and reduced short-term scaling exponents than men (Huikuri et al. 1996a, Pikkujämsä et al. 1999).

Related to recurrence of atrial fibrillation after electrical cardioversion

Various clinical factors have been shown to affect the recurrence of AF, mainly left atrial dimension or function, sex, age, AF duration, and the presence of coronary, pulmonary, or mitral valve disease (Ewy et al. 1980, Höglund et al. 1985, Brodsky et al. 1989, Dittrich et al. 1989, Zehender et al. 1992, Reimold et al. 1995, Alt et al. 1997, van Gelder et al. 1997, Duytschaever et al. 1998, Frick et al. 2001). However, in accordance with the results in the present study, many recent reports could not find any differences in clinical or echocardiographic parameters between patients with a relapse of AF and patients who remained in sinus rhythm (Brodsky et al. 1987, Kanoupakis et al. 2000, Lombardi et al. 2001, Maounis et al. 2001, Wozakowska-Kaplon et al. 2003).

Heart rate turbulence after atrial ectopic beats

The replacement of ectopic beats is a major problem in HR variability analysis. With any of the interpolation methods, ectopic beats may themselves cause a potential bias in HR variability analysis (Salo et al. 2001). The amount of ectopic beats often increases before the onset of AF (Kolb et al. 2001, Dimmer et al. 2003, Guyomar et al. 2003), which was also observed in the present study among patients without structural heart disease.

HR turbulence is a novel method, which is based on a simple expression of fluctuations of sinus rhythm cycle length after a single ectopic beat. It was first described to occur in response to ventricular ectopic beats with a typical short-term early acceleration and later deceleration of HR after an ectopic beat (Schmidt et al. 1999). Abnormal HR turbulence has been shown to be a strong risk predictor for total mortality and for fatal and nonfatal cardiac arrest in patients after myocardial infarction (Schmidt et al. 1999, Ghuran et al. 2002, Jokinen et al. 2003).

Recent pacing and Holter studies have shown that atrial ectopic beats also affect the postectopic HR (Lindgren et al. 2003, Savelieva et al. 2003, Schwab et al. 2004). However, there are differences in the HR response to ventricular and atrial ectopic beats, the latter showing a blunted early acceleration phase immediately after atrial ectopic complexes (Lindgren et al. 2003, Savelieva et al. 2003, Schwab et al. 2004).

In this study the immediate R-R interval responses to atrial ectopic beats were different during one hour before the onset of AF as compared to the other hours in the 24-hour ECG-recordings. Early acceleration has been shown to result from the sudden drop in blood pressure with the ectopic beat, resulting in vagal withdrawal and sympathetic recruitment, both of which accelerate sinus rate (Lin et al. 2002, Voss et al. 2002). After that, there is an increase of blood pressure with subsequent baroreceptor loading; vagal nerve activity is again increased, leading to a late deceleration phase of cardiac rhythm (Davies et al. 2001, Guzik et al. 2002). The early acceleration phase, quantified by TO, has been thought to be mainly due to the rapid parasympathetic modulation of heart rate (Mrowka et al. 2000). However, in agreement with a previous study (Lindgren et al. 2003), TO was not correlated to HR variability measures and was only weakly correlated to TS, suggesting that besides autonomic influences on the HR, there may be other mechanisms involved in the immediate response of the HR to atrial ectopic impulses.

Sinus node resetting has been shown to occur in response to atrial ectopic beats (Hadian et al. 2002). In accordance with other studies TO was not related to prematurity of atrial impulses (Watanabe et al. 2002, Schwab et al. 2004). Thus, the changes from resetting sinus node activity may not be solely responsible for the temporal changes in TO. It seems that the sinus node resetting, together with the rapidly-acting vagal withdrawal, determine the immediate R-R interval length after the compensatory pause of the atrial ectopic beat. In the same individual, sinus node

resetting after an atrial ectopic beat could be assumed to remain relatively stable, leading to the conjecture that observed changes in TO near AF depend on enhanced vagal activity.

SUMMARY AND CONCLUSIONS

This study showed that there are alterations in HR variability preceding spontaneous paroxysmal AF episodes both in patients with structural heart disease and in lone AF patients. Moreover the immediate response to atrial ectopic beats was different during one hour before the onset of AF as compared to the other hours of the 24-hour recordings. The HR dynamics facilitating the onset of AF, predicting the recurrence or the perpetuation of AF episodes, do not seem to be similar, suggesting that the factors related to recurrence, maintenance, or initiation of paroxysmal AF episodes are different. The specific findings were as follows:

I. An alteration of short-term, fractal-like, correlation properties and a reduced complexity of R-R interval data precede the onset of AF episodes. None of the traditional time and frequency domain measures showed any significant changes before the onset of AF.

II. The amount of ectopic beats increases before the spontaneous onset of AF in patients without structural heart disease.

III. The HF spectral power, reflecting enhanced cardiac vagal outflow, is increased before the onset of long episodes of AF. A decrease in short-term correlation properties also precedes long episodes of AF, suggesting an increase in vagal outflow at the time of high circulating levels of a sympathetic transmitter.

IV. Sinus rhythm fluctuation immediately after atrial ectopic beats are different during one hour before the onset of AF episodes as compared to R-R interval dynamics after atrial ectopic beats during other hours of the 24-hour recordings, both in patients with structural heart diseases and in patients with lone AF. The data suggest that vagal inhibition due to ectopic atrial complexes is absent, or that even transient enhancement of vagal outflow occurs during one hour before the onset of AF episodes.

V. Patients with a recurrence of AF after restoration of sinus rhythm with electrical cardioversion have increased HR variability compared to patients who remain in sinus rhythm during a one-month follow-up. During the first week after cardioversion increased HF spectral power, reflecting enhanced cardiac vagal outflow, was the most powerful predictor of the recurrence of AF. The fractal and complexity measures of HR variability did not show any additional predictive power for recurrence of AF when compared to traditional frequency domain measures.

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