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Electrophysiology

Heart Rate Variability and Early Recurrence of Atrial Fibrillation After Electrical Cardioversion

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OBJECTIVES The study evaluated the role of the autonomic nervous system in atrial fibrillation (AF) recurrence.

BACKGROUND Early recurrence of AF after cardioversion (CV) is attributed to electrical remodeling. The possibility that an abnormal autonomic modulation might contribute to this phenomenon has not yet been adequately tested.

METHODS We analyzed short-term heart rate variability (HRV) in 93 patients with persistent AF and on chronic amiodarone treatment, after restoration of sinus rhythm by electrical CV.

RESULTS Two weeks later, 25 patients presented with AF. Spectral analysis of HRV revealed that patients with AF recurrence were characterized by significantly greater low/high (LF/HF) frequency ratio in comparison to those in sinus rhythm (5.8 ± 6.86 vs. 1.1 ± 1.7). At univariable analysis, no clinical parameter differentiated the two groups. Using logistic regression analysis, LF/HF ratio was significantly associated with AF recurrence, with an odds ratio of 1.97 (95% confidence interval [CI] 1.33–2.94). By using a cutoff value of ≥2, LF/HF ratio presented a sensitivity and a specificity of, respectively, 76% and 90%. AF recurred in 9% of the patients with LF/HF ratio <2 compared with 73% of those with an LF/HF ratio >2. No correlation was observed between LF/HF ratio and late AF recurrences.

CONCLUSIONS These data indicate that signs of increased sympathetic and reduced vagal modulation of sinus node characterized patients with an early AF recurrence and suggest that an abnormal autonomic control may contribute to electrical remodeling by facilitating intracellular calcium overload. (J Am Coll Cardiol 2001;37:157–62) © 2001 by the American College of Cardiology

Maintenance of sinus rhythm after electrical or pharmacological cardioversion (CV) of atrial fibrillation (AF) is a major clinical problem. Available data (1) indicate that, in most instances, 40% to 60% of patients have recurrence of AF after CV even in the presence of an appropriate anti-arrhythmic therapy. It is generally recognized that patients prone to recurrences have a more severe left ventricular dysfunction and a larger atrial size, as well as a longer history of arrhythmia. However, in many cases, reappearance of AF is almost unavoidable despite control of factors that may play a pro-arrhythmic role, such as hypertension or congestive heart failure.

More recently, attention has been paid for timing of recurrences. It was reported (2) that in more than one-third of cases, AF recurs within two weeks after CV. Thereafter, the probability of recurrence decreases and becomes more constant over time. Thus, identification of the factors involved in this early phase may facilitate an understanding of this phenomenon and guide a more appropriate anti-arrhythmic therapy.

Several reports have indicated that duration of AF is associated with major changes in cardiac electrical properties that may favor arrhythmia recurrence (1,3). Structural remodeling has also been considered as a critical pro-arrhythmic factor (4,5). Less emphasis has been attributed to a possible role of the autonomic nervous system. In the past, the term *vagal* or *sympathetic* AF (6) has been used to characterize the autonomic environment in which AF has been reported to occur. No attention was instead directed to the possibility that a specific autonomic pattern could facilitate AF recurrence after electrical or pharmacological CV.

We therefore used spectral analysis of short-term heart rate variability (HRV) to evaluate autonomic modulation of the sinus node after restoration of sinus rhythm in patients with persistent AF, and we correlated spectral parameters with the incidence of early and late AF recurrence in patients under chronic amiodarone treatment.

METHODS

From September 1997 to January 1999, 126 patients with persistent AF gave informed consent to participate to the study. After a complete physical examination and two-dimensional echocardiography, patients were started on amiodarone (oral load plus 200 mg/daily) and on warfarin if not already on anticoagulant therapy. In 38 patients, a transesophageal echocardiographic examination was also performed.

After four weeks of treatment, all patients were scheduled

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Abbreviations and Acronyms

AF = atrial fibrillation
CV = cardioversion
EGG = electrocardiogram/electrocardiographic
HF = high frequency component
HRV = heart rate variability
LF = low frequency component
ROC = receiver operating characteristic

for a 24-h hospital admission to perform electrical CV. In 13 cases spontaneous restoration of sinus rhythm occurred and patients were excluded. In the remaining ones, electrical CV was performed in the late morning hours under slight sedation (propofol 2 mg/kg) by means of DC shock delivered by commercial defibrillator (Codemaster XL, Hewlett Packard) with a starting energy of 200 J. In 52 subjects a second DC shock (360 J) was delivered. Restoration of sinus rhythm was obtained in 103 of 113 subjects (91%). Control visits with medical examination and 12-lead electrocardiogram (ECG) were scheduled at 12 to 15 days, one, three and six months post-CV. Thyroid function was evaluated before and six months after CV.

Analysis of short-term HRV. A 15-min ECG recording was obtained in all patients under resting conditions before hospital discharge (4 to 5 h after electrical CV). A second recording was collected at the time of first control visit (12 to 15 days after CV) if sinus rhythm was present. In both cases, the ECG signal was acquired on a personal computer at sampling rate of 1,000 Hz. Off-line analysis was then performed to compute parameters of short-term HRV. The principle of the software for data acquisition, QRS detection and spectral analysis has been previously described (7–10). After identification of each QRS complex, the program first calculates the numerical series of RR intervals. Each tachogram was then visually inspected so that irregularities due to artefacts or premature atrial or ventricular contractions could be recognized when the cycle interval became higher or smaller of a user-defined threshold. These irregularities were linearly interpolated based on the last and first cycle interval before and after the artefact, respectively, thus performing a low pass filtering procedure. Some 250 to 300 RR intervals were considered adequate for further analysis when editing was limited to no more than five events; otherwise, data were disregarded. As a result, 10 subjects were excluded from the study and data relative to 93 patients were considered. The clinical characteristics of the study population are presented in Table 1.

Autoregressive algorithms were used to provide the number, center frequency and associated power of the oscillatory components that characterize spectral analysis of short-term recording. Adequacy of analysis was verified by formal statistical criteria such as the Anderson test and the Akaike criterion. The order of model used to estimate power spectrum ranged between 9 and 14. As previously reported (7–10), spectral analysis of short-term recordings is characterized, in addition to a very low frequency component (VLF, 0 to 0.03 Hz), by two major components at low (LF: 0.03 to 0.15 Hz) and high (HF: 0.15 to 0.40 Hz) frequency. The LF component has been proposed (7) and utilized, particularly when expressed in normalized units (n.u.), as an index of sympathetic modulation, whereas HF, which is a measure of respiratory sinus arrhythmia, is used as an index of vagal activity. The ratio between the absolute power of LF component and HF component was also calculated, and the LF/HF ratio was used as an index of sympatho-vagal interaction (7,11,12).

Table 1. Clinical Characteristics of the Study Population (n = 93)

Age (yrs)	65 ± 9
Male gender	64
Underlying heart disease	
Hypertension	45
Valvular	13
Dilated cardiomyopathy	8
Ischemic	8
None	19
Duration of AF (months)	12 ± 18
Left atrial diameter (mm)	47 ± 7
Left ventricular ejection fraction	55 ± 11
Previous embolic events	5
Previous electrical cardioversion	21

AF = atrial fibrillation.

Statistical analysis. Differences between patients with or without AF recurrence were assessed by the Mann-Whitney *U* test for continuous variables, or by the chi-square and Fisher test exact test when categorical variables were concerned. Baseline predictors of subsequent AF recurrence were identified by logistic regression analysis. Variables showing a significant discriminatory effect at univariable analysis with $p \leq 0.15$ were included in the logistic regression analysis as candidate prognostic factors. This was the case for the LF/HF ratio. The AF duration, gender and left atrial diameter failed to achieve the threshold level of significance but were included in the analysis due to the prognostic value generally ascribed to them. Pearson's goodness-of-fit test was performed to assess the appropriateness of the logistic model.

To appraise the discrimination ability of the LF/HF ratio for the prediction of AF recurrence, a receiver operating characteristic (ROC) curve was constructed and the area under the curve calculated. The optimal cutoff point was identified as the LF/HR ratio value minimizing the total number of false results (13).

Statistical analyses were performed using Stata Statistical Software (Release 6, Stata Corp., College Station, Texas). Standard deviations and 95% confidence intervals (CI) of the odd ratios (OR) were used to be reported in the text or in the tables as measures of variability. All analyses were two-sided.

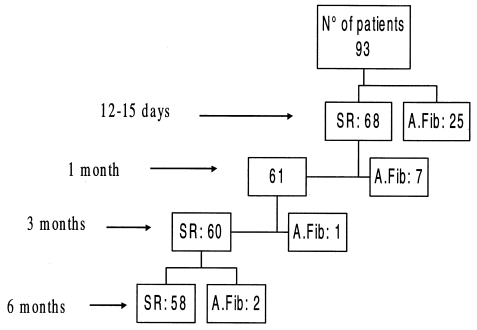

Figure 1. Schematic representation of atrial fibrillation (AF) recurrence during six-month follow-up period.

RESULTS

As illustrated in Figure 1, 68 patients were in sinus rhythm 12 to 15 days after CV. The clinical characteristics of this group as well as of patients with AF recurrence are presented in Table 2. There were no differences in relation to age, left atrial diameter, underlying heart disease, concomitant medical therapy, ejection fraction and duration of arrhythmia. Using logistic regression analysis, none of the above parameters was significantly associated with recurrence of AF.

The numbers of patients who maintained sinus rhythm one, three and six months after CV were 61, 60 and 58, respectively, with a total recurrence rate of 38%. No thrombo-embolic vascular event was observed.

Data concerning short-term HRV are presented in Table 3. In the entire group, LF component measured in either absolute or normalized units was relatively predominant over HF. As a result, the LF/HF ratio, which we used as an index of sympatho-vagal balance, was 2.36 ± 4.34. When we divided patients in relation to AF recurrence, mean RR interval and variance were similar in the two groups. In contrast, patients who relapsed presented a greater LF and a smaller HF component in comparison to those in sinus rhythm. This difference was even greater when considering the LF/HF ratio. Values ≥2 were observed in 24 patients. This parameter was significantly associated with AF recurrence with an OR of 1.97 (95% CI 1.33 to 2.94). To evaluate better the predictive value of the LF/HF ratio, an ROC curve was generated. The area under the ROC curve was 0.867 (Fig. 2). The LF/HR ratio value minimizing total number of false results in the prediction of AF recurrence was 2.2: using this value as the cutoff point, 87% of the patients would be correctly classified. By using instead a cutoff value of ≥2 (Figs. 2 and 3), the LF/HF ratio presented a 76% sensitivity and a 90% specificity, with a positive predictive value of 73%, a negative predictive value of 91% and an overall correct classification rate of 86%. Risk of AF recurrence was 73% and 9% in patients with LF/HF ratio values ≥2 or <2, respectively, with a risk ratio of 8.

Table 2. Clinical Characteristics of Patients With and Without Early Recurrence of Atrial Fibrillation

	Sinus Rhythm	AF	p Value
Number of patients	68	25	
Age (yrs)	65 ± 10	65 ± 8	1.0
Male gender (%)	72	60	0.31
Underlying heart disease (%)			
Hypertension	48	52	0.81
Valvular	12	20	0.32
Dilated cardiomyopathy	6	12	0.38
Ischemic	12	4	0.43
None	22	12	0.38
Duration of AF (months)	13.3 ± 20	8.4 ± 10	0.58
Left atrial diameter (mm)	47 ± 7	47 ± 8	0.95
Left ventricular ejection fraction (%)	55 ± 11	52 ± 13	0.36
Previous embolic events (%)	6	4	1.0
Previous electrical cardioversion (%)	19	32	0.26

AF = atrial fibrillation.

In contrast, no correlation existed between spectral parameters and, in particular, the LF/HF ratio measured after CV and AF recurrences occurring beyond two weeks after restoration of sinus rhythm.

When we considered recordings performed two weeks after cardioversion in 68 patients still in sinus rhythm (Table 4), there was a tendency of greater values of RR interval, variance and HF in 10 patients with late AF recurrence, whereas signs of sympathetic activation and of a reduced vagal modulation were not detectable in any of the two groups. Moreover, within the same patient who remained in sinus rhythm, spectral parameters of short-term HRV measured a few hours and two weeks after CV did not differ significantly.

DISCUSSION

This study indicates that an abnormal autonomic modulation may play a major pro-arrhythmic role in the first days after electrical CV. Signs of enhanced sympathetic and reduced vagal modulation of sinus node characterized patients with greater incidence of early recurrence of AF.

Recurrence of AF after CV. Recurrence of AF after electrical or pharmacological CV is a frequent phenomenon, which is only partially affected by anti-arrhythmic treatment (14–18). In a recent Working Group report (1), an average six-month recurrence rate of 30% to 60% was observed in chronic or persistent AF. The percent rate was greater when no anti-arrhythmic drugs were used and smaller when 1c drugs or amiodarone was administered. In our study, almost all patients were treated with amiodarone for at least four weeks before electrical CV and maintained this therapy throughout the follow-up period. The observed recurrence rate at six months was 38%: a value in agreement with previous reports (1,17,18). However, the incidence of recurrence was already 27% two weeks after CV and then increased only slowly in the follow-up period.

A similar time course was recently reported by Tieleman et al. (2), who analyzed, by transtelephonic monitoring, the

Table 3. Spectral Parameters of HRV Measured Before Discharge in the Entire Group, in Patients With Early AF Recurrence and in Patients in Sinus Rhythm 12 to 15 Days After Cardioversion

	RR (ms)	Variance (ms^2)	VLF (ms^2)	LF (ms^2)	LF (nu)	HF (ms^2)	HF (nu)	LF/HF
All patients (n = 93)	930 ± 159	536 ± 655	352 ± 495	117 ± 222	41 ± 24	116 ± 316	41 ± 21	2.36 ± 4.34
AF recurrence (n = 25)	924 ± 199	505 ± 511	326 ± 366	201 ± 330	62 ± 22	49 ± 67	22 ± 16	5.79 ± 6.86
Sinus rhythm (n = 68)	932 ± 143	548 ± 703	358 ± 526	86 ± 158	33 ± 21	140 ± 365	48 ± 18	1.10 ± 1.7
p value	0.567	0.818	0.634	0.007	< 0.0001	0.013	< 0.0001	< 0.0001

AF = atrial fibrillation; HF = high frequency component; HRV = heart rate variability; LF = low frequency; VLF = very low frequency.

daily incidence of recurrence of persistent AF. These investigators reported that, of 35 relapses of AF during the first month after CV, 31 occurred in the first two weeks and 22 in the first five days. At variance with our study, calcium channel blockers were used in 80% of their patients. Among the mechanisms responsible for early recurrence, both short atrial refractory periods (19,20) and loss of rate-dependent adaptation of refractory period (21–23) have been observed in patients after electrical CV of chronic AF.

A correlation between higher tendency of AF recurrence and shortening of monophasic right atrial action potential was also described (19,20). It is therefore likely that changes in atrial refractory periods might play a critical role in causing electrical instability and favoring AF recurrence. In patients with chronic AF, these electrophysiological changes were considered to be dependent on a reduction in the density of I_{Ca} in atrial myocites (24). Moreover, it was also demonstrated that, in presence of adrenergic stimulation, a greater fraction of Ca^{2+} channels unavailable under basal condition could be recruited, thus contributing to calcium overload and to AF recurrence (24).

Our data, which indicate that an abnormal autonomic modulation and, in particular, an increased sympathetic and a reduced vagal modulation characterize patients with a higher rate of recurrences, are consistent with the above findings. The absence, in our study, of measures of atrial-effective refractory periods and conduction velocities prevents, however, a direct evaluation of the relationship between the observed changes in HRV and electrical remodeling.

The duration of this phase of atrial electrical instability appears short lived and is followed by a decline in recurrence rate in our study as well as in the Tieleman et al. study (2). In the goat model of AF, changes in atrial refractory periods were no longer evident one week after recovery of sinus rhythm (3). In patients after electrical CV, recovery of normal atrial mechanical function was reported to occur from one to four weeks following restoration of sinus rhythm (25,26). Thus, the time course of electrical and mechanical changes seems to parallel the observed changes in autonomic modulation and to be inversely correlated with vulnerability for AF recurrence.

As to the possibility that amiodarone might have influenced HRV parameters and recurrence rate, it must be recalled that this drug, at variance with other antiarrhythmic drugs and beta-blockers, is known to have small effects on short-term HRV parameters during resting con-

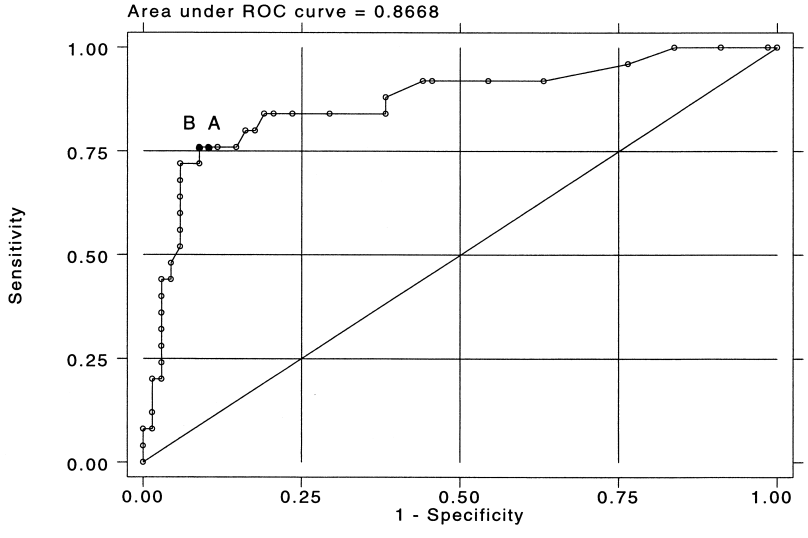

Figure 2. Receiver operating characteristic (ROC) curve for LF/HF ratio in prediction of atrial fibrillation recurrence. **Point A** indicates LF/HF ratio value equal to 2; **point B** (LF/HF ratio of 2.2) represents the value that minimizes classification errors. LF/HF = low frequency/high frequency.

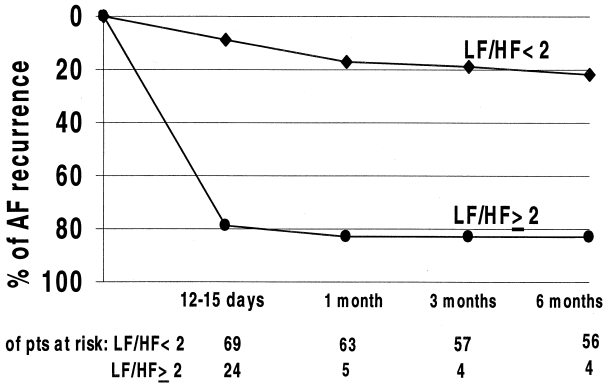

Figure 3. Percent (%) recurrence of atrial fibrillation (AF) in relation to the selected cutoff value of LF/HF ratio. Numbers of patients at risk for LF/HF ratio ≥2 and <2 are shown in the abscissa. LF = low frequency; HF = high-frequency component of heart rate variability.

trolled conditions (27,28), and it was given to all patients with and without arrhythmia recurrence.

Autonomic modulation and AF. Most of the data concerning the effects of autonomic nervous system and AF are related to the clinical environment in which this arrhythmia may occur (6). Vagal mechanisms have been indicated to be predominant when AF onset occurred after meals or during nighttime in absence of significant increases in heart rate, particularly in male patients without evidence of organic heart disease. In contrast, a pro-arrhythmic role of sympathetic activation was suspected when AF was initiated during exercise, emotion, or isoproterenol infusion. However, in most instances, recognition of a specific autonomic pattern is difficult; also, when HRV analysis was used to characterize the role of the autonomic nervous system before AF onset, contrasting results were noticed (29). The complexity of the problem might be partially explained by the fact that both sympathetic or vagal activation may exert a pro-arrhythmic action by affecting atrial action potential duration and conduction velocity (30,31); nonuniform autonomic innervation of the atria may also play a critical role (32).

In the present study, we observed that a specific HRV spectral pattern characterized by an LF/HF ratio ≥2 distinguished patients prone to early AF recurrence. By using this cutoff value, we were able to identify correctly the outcome of 86% of our patients. Moreover, preliminary results of an ongoing study at our institution show a marked reduction of incidence of early recurrence (12%) in six consecutive patients who presented an LF/HF ratio ≥2 and received beta-blocker therapy after CV.

The mechanisms causing this autonomic imbalance remain, however, to be understood. It is our opinion that the values of LF/HF ratio ≥2 observed after CV may indicate the persistence of an increased sympathetic and a reduced vagal activity directed to the heart in response to the mechanical and hemodynamic changes induced by AF. An abnormal sympatho-vagal balance may contribute directly and indirectly, through high atrial rate, to intracellular calcium overload, which is known to be a determinant component of electrical remodeling process and of vulnerability to AF recurrence (33). Alternatively, one may speculate that the hemodynamic consequences of restoration of sinus rhythm might have altered autonomic balance in a subgroup of patients who subsequently became more vulnerable to AF recurrence. The absence of a significant difference in resting heart rate, left atrial diameter, left ventricular ejection fraction and arrhythmia duration between patients with and without recurrence makes, in our opinion, this possibility less likely.

Of interest was the finding that spectral parameters of HRV recorded about two weeks after CV were substantially within the normal range and incapable of distinguishing patients with and without late AF recurrence, an observation that limits the predictive value of HRV analysis to the early post-CV period. Moreover, in patients who maintained sinus rhythm for six months, no changes occurred in HRV parameters measured a few hours and two weeks after CV, thus excluding the possibility that electrical CV, by itself, could have directly affected HRV.

Spectral parameters of HRV as markers of autonomic modulation. In the present study, we used spectral analysis of short-term HRV to obtain information on autonomic modulation of sinus node (7–12,34). The use of LF/HF ratio in our logistic regression model was based on the fact that this parameter may provide a more comprehensive evaluation of autonomic modulation than individual spectral components (10). The choice of 2 as the cutoff value for LF/HF ratio derives from previous evidence in the literature indicating that values of ≥2 were consistently associated

Table 4. Spectral Parameters of HRV Measured Two Weeks After Cardioversion in Patients Who Were in Sinus Rhythm at Time of First Control Visit and Did or Did Not Develop AF During the Follow-up Period

	RR (ms)	Variance (ms^2)	VLF (ms^2)	LF (ms^2)	LF (nu)	HF (ms^2)	HF (nu)	LF/HF
All patients (n = 68)	997 ± 181	762 ± 1071	390 ± 591	138 ± 272	36 ± 24	121 ± 234	39 ± 20	1.8 ± 2.7
AF recurrence (n = 10)	1106 ± 193	1286 ± 1604	518 ± 452	118 ± 178	26 ± 17	241 ± 370	41 ± 20	0.9 ± 0.8
Sinus rhythm (n = 58)	982 ± 175	688 ± 971	371 ± 609	141 ± 283	38 ± 24	104 ± 208	39 ± 20	1.9 ± 0.4
p value	0.063	0.091	0.085	0.359	0.234	0.062	0.920	0.466

AF = atrial fibrillation; HF = high frequency component; HRV = heart rate variability; LF = low frequency; VLF = very low frequency.

with a shift of sympatho-vagal balance toward a sympathetic activation and a reduced vagal tone (7–12,35). Moreover, analysis of the discrimination ability of LF/HF ratio using the ROC approach showed that this value was in close proximity to the cutoff point, minimizing the total number of prediction errors.

Conclusions. This study indicates that an abnormal autonomic modulation characterizes patients with a greater incidence of early AF recurrence after electrical CV despite anti-arrhythmic treatment. The analysis of short-term HRV appears, therefore, of clinical value to characterize autonomic tone after CV, to identify patients at higher recurrence rate and, if preliminary observations will be confirmed, to encourage the use of adjunctive beta-blocker therapy to prevent early AF recurrence.

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