ORIGINAL ARTICLES

Determinants of a Reduced Heart Rate Variability in Chronic Atrial Fibrillation

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Background: We aimed to evaluate whether clinical factors, which influence heart rate variability (HRV) in the presence of undisturbed sinus rhythm, have any associations with HRV in patients with permanent atrial fibrillation (AF).

Methods: One hundred ninety-seven consecutive patients with permanent AF were included (122 males, 75 females, aged 64 ± 11 years, range 25–85). In each patient a 24-hour electrocardiographic recording was performed and an HRV fraction (HRVF)—the index based on scatter plot numerical processing—was calculated. Additionally, standard HRV measures were analyzed. Reduced HRVF was defined as its value lower than lower normal limit. Demographic and clinical factors were examined for their association with a reduced HRVF by means of a univariate and multivariate logistic regression analysis.

Results: The reduced HRVF was associated with advanced age, clinical diagnosis of a previous MI or dilated cardiomyopathy, presence of diabetes, depressed left ventricular function, NYHA class > II, treatment regimen, use of digoxin, diuretics or antiarrhythmic agents, nonuse of beta-blockers, and increased heart rate. The independent determinants that sustained after multivariate analysis were: heart rate (per 10 bpm increase, odds ratio 2.77 [1.88–4.07]), age (per 5 years increase 1.43 [1.1–1.85]), depressed left ventricular EF (<30% vs higher 2.26 [1.19–4.31]), and presence of diabetes (3.45 [1.1–10.85]). The HRVF correlated moderately with standard HRV measures. This index showed also the strongest correlation with left ventricular ejection fraction.

Conclusion: We concluded that advanced age, left ventricular systolic dysfunction, increased heart rate, and presence of diabetes are cofactors of a reduced HRV in AF patients. Thus, the determinants of heart rate variability in the presence of atrial fibrillation are the same as those in sinus rhythm.

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Analysis of the heart rate variability (HRV) is a noninvasive clinically useful tool for risk stratification in patients after myocardial infarction and with heart failure.^{1–4} However, the use of standard HRV requires the presence of sinus rhythm.^{1,5} Accordingly, the presence of atrial fibrillation (AF) is listed among excluding criteria in most clinical studies. In such a way, numbers of patients with AF are rejected.⁶ This is of special importance in heart failure, where the proportion of AF patients varies between 10% and 50% depending on

the heart failure advance.^{7,8} Factors that determine HRV are well known only in the presence of sinus rhythm,^{9,10} while determinants of HRV in the presence of AF are less well recognized.

Only few clinical reports focused on factors that correlate to HRV in AF.^{11–15} Their results indicate that, as in sinus rhythm, HRV in AF is predominantly vagally mediated.¹⁴ It also depends on day-night rhythm, being higher during night hours.^{11,12,15} A work of Friedman indicated that HRV in AF is related to left atrial dimension and

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the HRV reduction correlates with an increase in left atrial size.¹⁵

The purpose of this investigation was to determine whether HRV in AF can be related to factors that are known to influence HRV in the presence of sinus rhythm.

METHODS

Subjects

The study comprised of 197 consecutive patients with symptomatic permanent AF who had at least 22-hour lasting ambulatory electrocardiographic (ECG) recordings analyzed for HRV. There were 122 male and 75 female of mean age 64 ± 11 years (range 25–85).

This population was divided into two groups based on values of an HRV fraction (HRVF)—the index based on numerical processing of a scatter plot.¹⁵ The first group consisted of 49 patients with HRVF lower than established lower normal limit (<5th percentile, <35%), and second, 148 patients with normal HRVF. The clinical characteristics of the groups are listed in Table 1. On the basis of an individual history or in-hospital records, information regarding the presence of main risk factors, symptomatology (NYHA and CS classes), etiology, management, and drugs was obtained. The left ventricular ejection fraction (LVEF) was assessed echocardiographically by using the Simpson's rule and left ventricular end-diastolic diameter (LVEDD) from the TM-mode recordings.

HRV Analysis

In each patient, a 24-hour ECG recording was performed. The recordings were obtained with a Medilog-Excel 2 System (Oxford, Abington, UK) using a three- or two-channel recorders. Further analysis was performed by an independent investigator. After manual editing of the ECG data, numerical data of all beats were transferred to a personal computer. The scatter plot was obtained and the HRVF was calculated using an algorithm previously described.¹⁶ Briefly, a scatter plot, which is a plot of RR intervals (RR_i) against the following intervals (RR_{i+1}), was obtained. The scatter plot area (from 0.2–1.8s by 0.2–1.8s) was divided into 256 boxes with each side of 0.1 s interval. In each box, of $0.01s^2$ area, the number of paired RR intervals was counted, and 3-dimensional graph of density

Table 1. Demographic and Clinical Characteristics of the Compared Groups

Variable	Reduced HRVF N = 49	Normal HRVF N = 148	P-Value
Age, years	67 $\pm$ 9	62 $\pm$ 11	<0.05
Gender (male, %)	31 (61)	91 (63)	NS
Arterial hypertension, %	29 (68)	83 (67)	NS
Hyperlipidemia, %	15 (35)	41 (34)	NS
Diabetes, %	18 (42)	17 (14)	<0.001
Current smoker, %	3 (7)	11 (9)	NS
Etiology			
Dilated cardiomyopathy	1 (2)	6 (4)	
Previous MI	23 (47)	42 (28)	NS
Uncomplicated CAD	9 (18)	40 (27)	
Nonischemic	16 (33)	60 (41)	
Previous CABG	12 (24)	18 (12)	<0.05
Previous PTCA	10 (20)	18 (12)	NS
NYHA class >II, %	15 (36)	30 (20)	NS
CCS class > I, %	16 (33)	46 (31)	NS
LVEF, %	37 $\pm$ 12	47 $\pm$ 13	<0.001
LVEF < 30%, %	14 (29)	18 (12)	<0.001
LVEDD, mm	57 $\pm$ 9	55 $\pm$ 7	NS
Beta-blockers, %	23 (47)	48 (32)	NS
ACE inhibitors, %	13 (27)	42 (28)	NS
Calcium antagonists, %	11 (22)	43 (29)	NS
Digoxin, %	24 (49)	45 (30)	<0.05
Diuretics (NPS), %	33 (67)	77 (52)	<0.1
Antiarrhythmics, %	14 (29)	17 (11)	<0.01

was plotted with the use of an original algorithm written in MATLAB. The HRVF was calculated according to the formula:

$$HRVF = (1 - N1 + N2 / \text{TotalRR} - \text{RR50}) * 100$$

where N1 and N2 are the two highest numbers of counts in any of the boxes, TotalRR is the number of all heartbeats, and RR50 is the number of adjacent intervals that differ >50 ms.

Standard HRV analysis was performed by using a commercial software. Only QRS complexes labeled as "normal" (N) were included in the analysis. The following indices were obtained: RRI – mean NN interval [ms], SDNN [ms] – standard deviation of all normal heartbeats, SDANN [ms] – standard deviation of the average NN intervals calculated over 5 minutes SDNN index, [ms] – mean of the 5-minute standard deviations of NN intervals calculated over 24 hours, RMSSD [ms], the square root of the mean squared differences of successive NN intervals, and pNN50 [%], the proportion derived by dividing the number of interval differences of successive NN intervals greater than 50 ms by the total number of NN intervals.¹

Table 2. Standard HRV Indices in the Compared Groups

Variable	Reduced HRVF N = 49	Normal HRVF N = 148	P-Value
RRI [ms]	637 ± 114	816 ± 144	<0.001
SDNN [ms]	154 ± 43	212 ± 53	<0.001
SDANN [ms]	79 ± 37	130 ± 47	<0.001
SDNNI [ms]	130 ± 38	166 ± 40	<0.001
RMSSD [ms]	158 ± 48	196 ± 53	<0.001
pNN50 [%]	57 ± 11	66 ± 11	<0.001

Statistics

Continuous variables were summarized as mean ± SD, categorical variables were displayed as counts or proportions (%). The comparison between groups was performed using the Kolmogorov-Smirnov test for continuous variables and chi-square test for categorical variables. Demographic and clinical factors were examined for their association with a reduced HRVF by means of a univariate logistic regression analysis. The variables that resulted to be significant ($P < 0.1$) univariate predictors of a reduced HRVF were included in a multivariate logistic regression analysis. All analyses were performed using Statistica for Windows package (Stat-Soft, Tulsa, OK, USA). A two-sided value of $P < 0.05$ was considered to be statistically significant.

RESULTS

AF patients with reduced HRVF were older and more frequently suffered from diabetes or oral glucose intolerance (Table 1). They were more likely to have a history of previous MI and coronary revascularization procedures. They had also more damaged left ventricle as indicated by lower mean LVEF (Table 1). Almost one-third of all AF patients with low HRVF had LVEF < 30%. They received digoxin, nonpotassium-sparing diuretics, and antiarrhythmic drugs more frequently (Table 1).

Table 2 summarized results of standard time-domain HRV indices in the two groups. All analyzed HRV indices were significantly lower in patients with the reduced HRVF. The values of RRI were within limits observed in subjects with sinus rhythm. Other indices had their mean values lying well within (SDNN) or far above (SDNNI,

RMSSD, pNN50) normal limits. In the AF patients with reduced HRVF the mean value of SDANN was just within lower normal limit, while in the AF-patients with normal HRVF, this value lied within normal range. Examples of abnormal HRVF in the AF patients with impaired LVEF are shown in Figure 1.

In a univariate analysis the following covariates with $P < 0.1$ were chosen as determinants of HRV in AF: age, presence of diabetes, clinical diagnosis of a previous MI or dilated cardiomyopathy, treatment regimen (CABG vs others), depressed LVEF, higher NYHA heart failure class, use of digoxin, nonpotassium sparing diuretics and antiarrhythmic agents, lack of treatment with beta-blockers and increased mean heart rate (Table 3).

The determinants that sustained after multivariate analysis were: age, presence of diabetes, depressed left ventricular EF, and heart rate (Table 4).

The HRVF correlated negatively with HR (Pearson $r = -0.537$) and positively with LVEF ($r = 0.356$) (Fig. 2A,B). It correlated moderately with standard HRV measures and the strongest correlation was found between HRVF and SDNN ($r = 0.610$) (Fig. 2C).

DISCUSSION

The present study showed that among entire population of patients with AF there is a substantial proportion (~25%) of those, in whom the scatter plot-based index, HRVF, revealed a reduction in the global heart rate variability in contrast to a high heartbeat variation indicated by standard time-domain HRV indices. Our attempts to define a reduction in HRV are based on the original index taking into account the distribution of all heartbeats over 24-hour. In the analysis of HRV from 24-hour recording in patients with AF we applied the lower normal limit (5th percentile) that has been established earlier in subjects with sinus rhythm.¹⁶ The same approach is impossible by using the standard time-domain HRV indices, since their lower normal limits established in the presence of sinus rhythm are not applicable in AF at all. A different way to solve the problem of the recognition of a reduced HRV in AF has also been proposed.¹⁵ However, in this study, comprised of 38 patients with AF, none of the standard time-domain HRV measured correlated with other factors than the average RR interval.

Figure 1. Examples of a reduced HRV fraction in patients with permanent AF and depressed LV function. M = male; K = female; other abbreviations as in the text. The lowest value of the HRVF can be noticed in the upper graph, with a severe LV dysfunction, despite the mean 24-hour HR (60/RR1) of ~90 bpm, while the higher HRVF can be seen in the lower graph in a male with less advanced LV dysfunction, despite substantially higher 24-hour HR of 125 bpm. One has to consider quite different behavior of the standard HRV time-domain measures, with the SDNN values within normal limits in all three cases, lower SDANN in the two, and extremely high values of the pNN50, never seen in sinus rhythm. Grey scale on the right side of each graph indicates number of heartbeats within certain 0.1*0.1 seconds squares. (from M. Sosnowski Ph.D. Thesis).

Table 3. Determinants of the Reduced HRVF in a Univariate Analysis

Variable	OR	95 CI	P-Value
Age ^a	1.22	1.02–1.46	0.030
Diabetes	4.56	2.05–10.14	0.00024
Previous MI or DCM	2.00	1.03–3.88	0.040
Previous CABG	1.64	0.92–2.93	0.093
LVEF ^b	2.51	1.60–3.95	0.00009
NYHA class ^c	1.60	1.04–2.46	0.030
Beta-blocker (no)	1.87	0.91–3.82	0.089
Diuretic (yes)	2.14	0.92–4.95	0.077
Digoxin (yes)	2.29	1.11–4.72	0.025
Antiarrhythmic agent (yes)	3.11	1.36–7.11	0.0076
HR ^d	2.50	1.82–3.42	0.00000

^aFor a 5-year increase from 45 years of age; ^b<30% vs higher; ^c>II vs lower; ^dfor a 10 bpm increase from a 60 bpm. OR = odds ratio; CI = confidence interval.

Table 4. Independent Predictors of the Reduced HRVF

Variable	OR	95 CI	P-Value
Age ^a	1.43	1.10–1.85	0.007
Diabetes (yes)	3.45	1.10–10.85	0.034
LVEF ^b	2.26	1.19–4.31	0.013
HR ^c	2.77	1.88–4.07	0.000

^aFor a 5-year increase from 45 years of age; ^b<30% vs higher; ^c– for a 10 bpm increase from a 60 bpm. OR = odds ratio; CI = confidence interval.

Our study confirmed earlier observations on strong dependence of the HRVF on mean heart rate. Mean heart rate was the most significant and independent predictor of HRVF in AF and the strength of this relation was actually the same as previously described in sinus rhythm.^{10,17}

In our population of AF patients the HRVF dependence on age was found, similarly as in sinus rhythm.^{9,10} This observation has never been described earlier in AF. A small number of the AF-patients did not allow Friedman to show a similar relation.¹⁵ HRVF was not found to differ between women and men with AF. The possible explanation might relate to the age of patients with AF, most of them being older than 60 years, as it is suggested that the gender-related differences disappear in older subjects,⁹ however conflicting data exist.⁶

Figure 2. Plots of HRVF relationship with heart rate, LVEF, and SDNN.

We confirmed the significant influence of diabetes mellitus on the HRV in patients with AF. An association of a reduced HRV and diabetes has been previously described in sinus rhythm,^{1,10} and a reduction of HRV may even be the clinical hallmark of diabetic autonomic neuropathy.¹⁸ The importance of the HRV dependence on diabetes was highlighted by the observations of Stein and coworkers,¹⁹ who found that inclusion of patients with diabetes mellitus decreased the association between HRV and mortality after myocardial infarction. As the HRV reduction in diabetes was shown to increase risk for all-cause and cardiovascular mortality in patients with sinus rhythm,^{20,21} we suggest that the use of HRVF in a subpopulation of AF patients with diabetes may help to stratify risk. Such a possibility was confirmed in our previous study in patients with left ventricular dysfunction.²²

Our results clearly show that the reduced HRVF is associated with left ventricular systolic dysfunction. LVEF was found as the independent factor determining the global HRV in patients with AF. The relationship between LVEF and HRVF might also be explained on the basis of a reverse mechanism. Accordingly, reduced HRVF together with shorter RR intervals negatively influence the performance of left ventricle, as it has been already noticed.²³ These results resemble those described in patients with sinus rhythm.¹⁷

Taken the data together we found that the independent factors that determine the global heart rate variability in patients with AF are similar to those previously found in patients with sinus rhythm. This indicates that variation of heartbeats in AF cannot be considered random.²⁴ There are only few data dealing with this problem. Stein and coworkers stated that in AF the RR intervals sequence was not completely unpredictable.²⁴ Hayano et al. found that long-term heartbeat fluctuations in AF are similar to that in sinus rhythm.²⁵ There are many others observations indicating that HRV in AF is vagally mediated, depends on posture, physical activity, and shows diurnal variation.^{11–14,26} Additionally, the prognostic value of the analysis of HRV in AF was previously reported.^{27,28} It should be also stressed that the determinants of low HRVF in AF are the same as the predictors of mortality in a community described by the Framingham Heart Study investigators.²⁹ Accordingly, the significant independent cofactors affecting HRV have to be considered obligatory before any prognostic HRV analysis in AF is going to be undertaken.

We are aware that not all factors potentially influencing HRV were controlled for. Therefore, effects of factors not specifically examined in this study might warrant clarification in further investigations. However, as reviewed by Sosnowski,⁶ numerous modifiable factors influence HRV in a negligible manner if considered in a cohort or cross-sectional studies.

In summary, we found that determinants of HRV in patients with AF are actually the same as those in sinus rhythm. The independent determinants of a reduced HRV in AF patients are advanced age, left ventricular systolic dysfunction, faster heart rate, and diabetes mellitus.

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