VIA MEDICA
ORIGINAL ARTICLE
2011, Vol. 18, No. 5, pp. 538–545
10.5603/CJ.2011.0010

ISSN 1897–5593

Relationship between R-R interval variation and left ventricular function in sinus rhythm and atrial fibrillation as estimated by means of heart rate variability fraction

Maciej Sosnowski[1], Barbara Korzeniowska[1], Peter W. Macfarlane[2], Michał Tendera[1]

[1]3rd Chair of Cardiology, Unit of Noninvasive Cardiovascular Diagnostics, Medical University of Silesia, Katowice, Poland
[2]Division of Cardiovascular and Medical Sciences, Section of Cardiology, University of Glasgow, Royal Infirmary, Glasgow, Scotland, United Kingdom

Abstract

Background: *Reduced heart rate variability (HRV) is associated with a poor outcome in patients with sinus rhythm (SR) or atrial fibrillation (AF). However, cut-off points for HRV measures differ between SR and AF. We hypothesized that a global index of 24-hour HRV based on evaluation of scatterplot would describe HRV irrespective of cardiac rhythm.*

Methods: *407 patients with ischemic heart disease (317 male, 90 female, mean age 57 ± 9 years) were studied. 331 patients had SR and 76 patients had AF. 24-hour ECGs were recorded, and standard HRV indices were calculated. Scatterplots was used to determine the HRV fraction (HRVF, %). HRV measures were compared in respect to left ventricular ejection fraction (LVEF ≤ 35% or > 35%).*

Results: *Standard HRV measures were higher in AF-patients despite the mean RR interval was lower. In patients with LVEF ≤ 35%, standard HRV indices were lower in SR group, in AF group only SDNN and RMSSD were reduced. The HRVF was comparably reduced (SR 39.3 ± 15.3%, AF 37.3 ± 17.9%). In patients with LVEF > 35%, HRVF did not differ between SR (47.2 ± ± 10.5%) and AF (46.1 ± 12.1%). The HRVF correlated with SDNN and SDANN (~0.85) in SR. Correlations were weaker in AF (~0.6). Standard HRV indices and HRVF showed similar relations with LVEF, but only in AF at the same range.*

Conclusions: *The HRV fraction allows for HRV evaluation irrespective of cardiac rhythm. The index elicited a similar dependence of HRV on left ventricular function in SR and AF.* (Cardiol J 2011; 18, 5: 538–545)

Key words: heart rate variability, scatterplot, sinus rhythm, atrial fibrillation, left ventricular function

Address for correspondence: Maciej Sosnowski, MD, Unit of Noninvasive Cardiovascular Diagnostics, 3rd Chair of Cardiology, Faculty of Medicine, Medical University of Silesia, ul. Ziołowa 47, 40–635 Katowice, Poland, tel/fax: +48 322 52 39 30, e-mail: maciej.sosnowski@gmail.com

Received: 28.02.2011 Accepted: 27.06.2011

Introduction

Heart rate variability (HRV) is a complex phenomenon based mainly on parasympathetic control of the heart [1–5]. Its analysis is proposed for risk stratification in patients after myocardial infarction (MI) and in heart failure (HF). Most predictive HRV measures are complex and suffer from several limitations, and the common indices are still in use [5–11]. Numerous indices derived from non-linear dynamics have been introduced. But because physicians are less familiar with the algorithms used, their application in practice is limited [5, 12–14].

The presence of cardiac arrhythmias, especially atrial fibrillation (AF), practically excludes reliable HRV analysis [15] in an increasing proportion (~30%) of patients with HF or left ventricular (LV) dysfunction. The cut-off points for prognostic use of HRV indices are not definitely established in patients with sinus rhythm, and often lie within normal limits. However, in post-MI patients and in HF patients, different cut-off points have been suggested for SDNN (< 50, 65, 70 and 100 ms) and SDANN (< 44, 50, 65.3, 97, 100 and 120 ms), respectively [5]. The cut-off points are higher if AF is present [5].

At present, owing the limitations of available methods, neither HRV measure can be used practically at the bedside [5, 11]. Thus, the search for new HRV indices is important. The ideal index should estimate the neural cardiac control irrespective of the presence of arrhythmias. It should also show similar dependence of HRV on underlying factors like age, gender, mean R-R interval, and LV function [5, 16]. An achievement of these goals creates the basis of the present study.

We have developed a method of global HRV evaluation, which introduces a simple and easy-to-understand index, namely the fraction of the density of selected areas of the return map (scatterplot, Poincare plot) in relation to the total number of R-R intervals differing from successive intervals by less than 50 ms. The methodology has already been introduced in normal individuals, patients with certain cardiac diseases and in AF [17–19].

Methods

Subjects

The study population consisted of 407 patients with angiographically documented ischemic heart disease (IHD) or with a remote MI. The 407 comprised 317 men and 90 women, mean age 57 ± 9 years, who were consecutively referred to our ECG laboratory. They were included if they gave informed consent and the Holter ECG recording lasted at least 21 hours including a whole night and the first four hours after awakening. Exclusion criteria were: recent (< three months) acute coronary syndromes (including unstable angina pectoris — CCS class IV), 2/3° S-A or A-V block, incessant tachycardia, an implanted pacemaker, any illness that required the use of beta-agonists or corticoids, or any other illness that might limit life expectancy.

Based on the rhythm detected, they were divided into two groups. The first included 331 patients with sinus rhythm (SR), and the second consisted of 76 patients with chronic AF. In each group, patients were categorized with respect to the LV systolic function expressed as an echocardiographically determined LV ejection fraction (LVEF). A reduction in the LV systolic function was recognized if a LVEF ≤ 35% was found. Characteristics of the groups are presented in Table 1. The study conformed to the principles outlined in the Declaration of Helsinki.

Standard HRV analysis

In each patient, a 24 hour ambulatory ECG recording was obtained using a three-channel solid-state recorder. The ECG recordings were processed with standard precision on a Medilog Excel 2 system (Oxford Instruments, Abingdon, UK). After careful manual editing and visual corrections, standardised time-domain indices of HRV were obtained using a commercially available software package. These included mean R-R interval (RRI), standard deviation of all normal R-R intervals (SDNN, ms), standard deviation of averaged means of normal R-R intervals over 5 min periods (SDANN, ms), mean of averaged standard deviation of normal R-R intervals over 5 min periods (SDNNI, ms), root mean square of successive differences (RMSSD, ms) and the percentage of neighbouring intervals differing by more than 50 ms (pNN50).

Calculation of HRV fraction

Data with labelled RRI were stored in the files and transferred to a personal computer (PC) for further processing using an in-house software package. Scatterplots and their evaluation were obtained using an algorithm written in MATLAB, implemented on a PC. The scatterplot is a plot of a given R-R interval ($R\text{-}R_i$) against the next RRI ($R\text{-}R_{i+1}$). In this way, a graphic two-dimensional presentation of beat-to-beat RRI changes is obtained. The scatterplot area (from 0.2 to 1.8 s by 0.2 to 1.8 s) was divided into 256 boxes each of 0.1 s interval (16 × 16, from 0.2–0.3, 0.3–0.4 and so on up to 1.7–1.8) [18].

Table 1. Clinical characteristics of patients with sinus rhythm (SR) and atrial fibrillation (AF).

Parameter\group	SR group (n = 331)	AF group (n = 76)
Age (years)‡	56 ± 10	63 ± 10
Gender (F/M)	67/264	21/55
CHD risk factors:		
Hypertension	190 (57%)	44 (58%)
Hyperlipidemia	174 (53%)	46 (61%)
Diabetes	56 (17%)	14 (18%)
Smoking (current or past)	266 (80%)	51 (78%)
Clinical status:		
NYHA class > II	101 (31%)	30 (39%)
CCS class:		
I/II	208 (62%)	52 (68%)
III	125 (38%)	24 (32%)
LVEF (%)†	43 ± 13	38 ± 13
LVEDD [mm]	57 ± 8	56 ± 8
Management (prior to the study)‡:		
After CABG/PTCA	232 (70%)	25 (33%)
Conservative	99 (30%)	51 (67%)
Medications:		
Beta-blockers†	203 (61%)	31 (41%)
ACE inhibitors†	194 (59%)	58 (76%)
Ca antagonists	108 (33%)	21 (28%)
Diuretics‡	128 (39%)	51 (67%)
Digoxin‡	39 (12%)	48 (63%)
Antiarrhythmics&	45 (14%)	9 (12%)
Antiplatelet agents/ /anticoagulants	271 (82%)	68 (89%)

Ca — calcium; CHD — coronary heart disease; NYHA — New York Heart Association; CCS — Canadian Cardiovascular Society; LVEF — left ventricular ejection fraction; LVEDD — left ventricular end-diastolic diameter; CABG — coronary artery by-pass grafting; PTCA — percutaneous transluminal coronary angioplasty; F — female; M — male; &antiarrhythmics others than beta-blockers, digoxin and verapamil or diltiazem; *p < 0.05; †p < 0.01; ‡p < 0.001; χ^2 test and Student *t*-test were used as appropriate

In each box, the number of paired RRI was counted. In such a way, a matrix of numbers from 256 boxes was obtained and three-dimensional (3D) graphs of density were plotted (Figs. 1, 2).

The index was calculated according to the formula:

$$HRVFraction = (1 - \frac{N1 + N2}{TotalRR - RR50}) \times 100$$

where N1 and N2 are the two highest numbers of counts in any of the boxes, totalRR is the number of all RRI, and RR50 is the number of RRI that differ from successive RRI by more than 50 ms [18].

Statistical analysis

Means and standard deviations were calculated for each parameter. The student t-test or Mann-Whitney U-test was used for comparisons as appropriate (e.g. for age, RRI, HRV fraction and LVEF, as normally distributed, and for standard HRV indices, as not normally distributed, respectively). Discrete data were compared using the χ^2 test. Spearman rank correlation coefficients were calculated among all measured HRV parameters.

Results

The means of the analyzed HRV variables are shown in Table 2. The standard time-domain measures were statistically significantly higher in patients with AF, irrespective of the LV systolic function. Meanwhile, in the AF group, the mean R-R interval was significantly shorter than in the SR group, both in patients with low LVEF (764 ± 176 ms *vs* 825 ± 134 ms, respectively, $p < 0.05$) and in patients with preserved LVEF (802 ± 168 ms *vs* 868 ± 107 ms, respectively, $p < 0.01$).

The values of the new index, HRV fraction, did not show any significant difference between the SR patients and AF patients in corresponding groups based on LVEF. In the SR group with depressed LVEF, standard indices of global HRV (SDNN, SDANN and SDNNI) showed significantly lower values compared to those with preserved LVEF, while in the AF group, only SDNN and RMSSD were reduced significantly in patients with LVEF ≤ 35%. The HRV fraction was reduced in those with compromised LVEF irrespective of cardiac rhythm. Similarly, the values of the HRV fraction did not differ between SR and AF patients with LVEF > 35%.

The examples of reduced and normal HRV in patients with SR or AF are shown in Figures 1 and 2, respectively. As shown in these figures, the shape of the 3D view of the scatterplot of RRI of a patient with AF was comparable to that of a patient with SR. The HRV fraction indicated reduced HRV in both cases, while in the AF patients, the SDNN value was well within normal limits accepted for SR, while pNN50 was even above the normal limit. The only standard index reduced both in AF and SR patients was SDANN, but it still indicated greater RR variation in AF, whereas the HRV fraction was lower in this case. In Figure 2, the 3D scatterplots of patients with normal HRV showed comparable RRI and HRV fraction values, while standard indices were clearly higher in the case of AF.

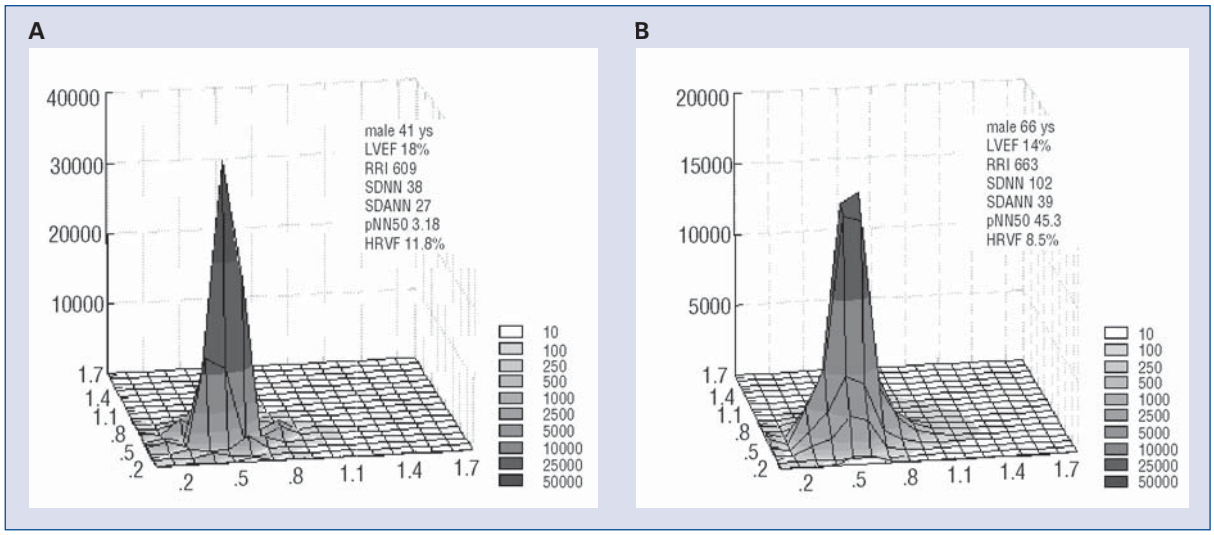

Figure 1. Examples of reduced heart rate variability (HRV) in patients with sinus rhythm (**A**) and atrial fibrillation (AF) **(B)** In both cases, some features of heart rhythm are similar, i.e. mean RRI, SDANN, HRV fraction, while common standard HRV indices differed substantially, i.e. SDNN or pNN50. Note that a reduction in HRV was even worse in an AF patient, as indicated by lower values of SDANN and HRV fraction.

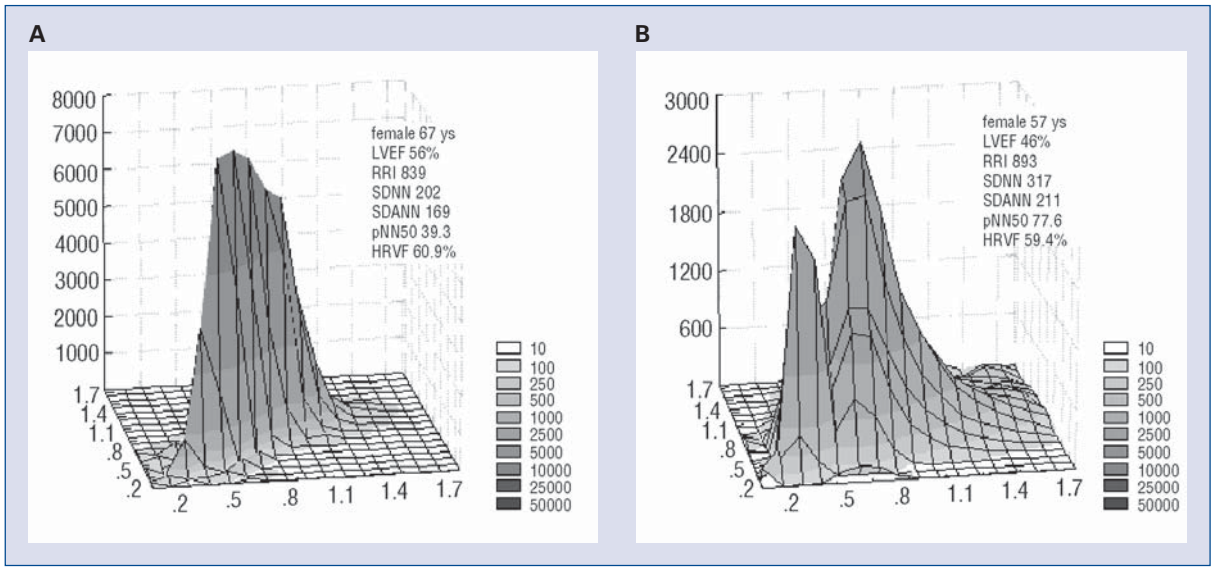

Figure 2. Examples of normal heart rate variability (HRV) in patients with preserved left ventricular ejection fraction with sinus rhythm **(A)** and atrial fibrillation (AF) **(B)**. In both cases, some features of heart rhythm are similar, i.e. mean RRI and HRV fraction, while common standard HRV indices differed substantially, being clearly higher in a patient with AF.

The HRV fraction correlated significantly with standard time-domain HRV measures. In particular, there was a high correlation with SDNN (0.872), SDANN (0.835) and SDNNI (0.718) in patients with SR. However, in the presence of AF, these correlations became less close, although still statistically significant. The HRV fraction correlated positively with RRI in both groups (Table 3).

The HRV dependence on LV function was observed for most of the analyzed indices. However, the HRV fraction showed a similar strength of relationship in patients with SR (Spearman $R = 0.29$, $p < 0.05$) and with AF (Spearman $R = 0.26$, $p < 0.05$) at the same range (Fig. 3). Meanwhile, for the SDNN the coefficients of rank correlation were even better, but at quite different ranges for patients

Table 2. Means of the heart rate variability measures in the subgroups examined.

	Sinus rhythm		Atrial fibrillation	
	LVEF ≤ 35% n = 117	LVEF > 35% n = 214	LVEF ≤ 35% n = 41	LVEF > 35% n = 35
RRI	825 ± 134†	868 ± 107	764 ± 176*	802 ± 168**
SDNN	107 ± 33‡	124 ± 40	182 ± 55***†	212 ± 57***
SDANN	93 ± 35‡	110 ± 33	111 ± 45*	132 ± 49*
SDNNI	45 ± 22‡	51 ± 17	144 ± 47***	160 ± 41***
RMSSD	29 ± 24	28 ± 17	160 ± 56***†	184 ± 49***
PNN50	7.1 ± 10.9	6.2 ± 7.4	55.0 ± 12.4***	59.2 ± 8.7***
HRV fraction	39.3 ± 15.3‡	47.2 ± 10.5	37.3 ± 17.9†	46.1 ± 12.1

Mann-Whitney U-test was used. AF *vs* SR: *p < 0.05, **p < 0.01, ***p < 0.001, LVEF < 35% *vs* LVEF > 35%: †p < 0.05, ‡p < 0.001; abbreviations — see methods

Table 3. Correlations among standard time-domain heart rate variability (HRV) measures and HRV fraction in patients with sinus rhythm and atrial fibrillation.

	RRI	SDNN	SDANN	SDNNI	RMSSD	PNN50	HRVF
RRI		0.404	0.319	0.502	0.404	0.413	0.482
SDNN	*0.506*		0.958	0.728	0.485	0.521	0.872
SDANN	*0.409*	*0.843*		0.560	0.337	0.382	0.835
SDNNI	*0.536*	*0.825*	*0.550*		0.756	0.763	0.718
RMSSD	*0.554*	*0.759*	*0.468*	*0.889*		0.941	0.445
PNN50	*0.506*	*0.453*	*0.301*	*0.590*	*0.727*		0.482
HRVF	*0.571*	*0.590*	*0.591*	*0.528*	*0.486*	*0.523*	

Tables indicate Spearman rank coefficients. All coefficients with p < 0.001, except for pNN50 *vs* SDANN in the atrial fibrillation group (p < 0.01); right upper panel — patients with sinus rhythm, left lower panel (italics) — patients with atrial fibrillation; abbreviations — see methods

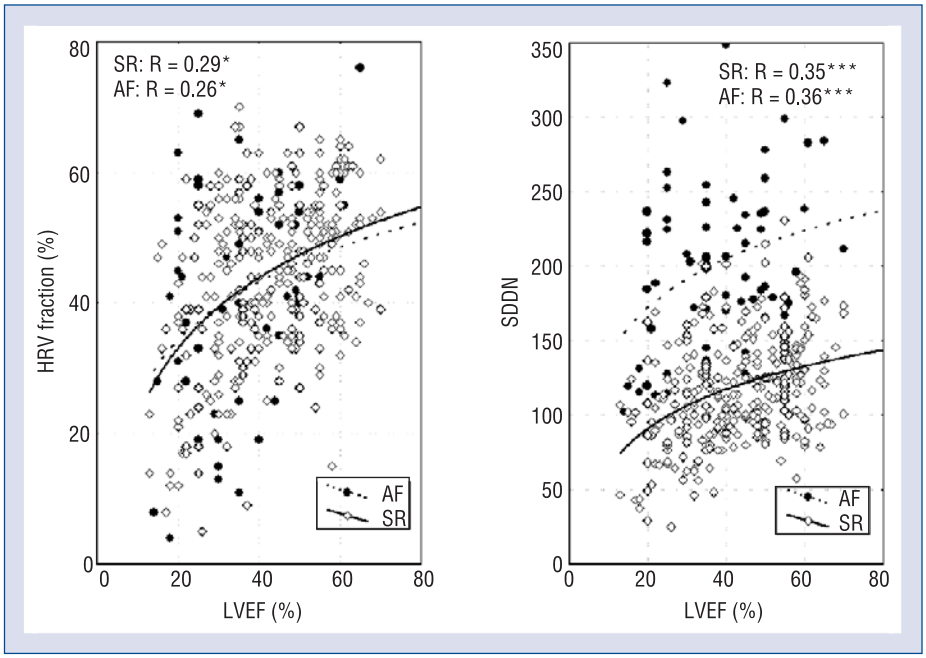

Figure 3. Heart rate variability (HRV) dependence on left ventricular systolic function. Both figures show combined scatterplots of HRV measures (HRV fraction and SDNN) against left ventricular ejection fraction (LVEF) in patients with sinus rhythm (SR) and atrial fibrillation (AF). Solid and dotted lines show the logarithmic relationship in SR and AF, respectively. Statistics: R — Spearman rank coefficient; *p < 0.05, ***p < 0.001.

with SR and AF. Thus, for example, the patients whose HRV fraction values were below 20% or above 50% may have either SR or AF. On the contrary, there were no cases of patients with AF who had SDNN below 80 ms, or of patients with SR with SDNN above 240 ms. These differences were clearly visible when comparing the curves of logarithmic fit. These curves were superimposed for HRV fraction, while clearly separated for SDNN (Fig. 3). Similar differences were seen for the other standard indices.

Discussion

The results of our study showed that a relatively simple HRV parameter can describe global RRI variation equally well in patients with SR and in patients with AF. Thus, an increasing number of patients with LV dysfunction or HF need no longer be excluded from trials which evaluate the prognostic value of a reduced HRV. At the same time, the standard time-domain HRV measures showed different ranges of RRI variation in patients depending on cardiac rhythm, being significantly lower in SR compared to AF. Stein et al. [20] found the cut-off value of the SDANN index lower than 141 ms helpful in distinguishing patients with AF at risk for mortality and cardiac surgery for non-ischemic mitral regurgitation. Clearly, the cited cut-off value lies well within normal limits in patients with SR. Using a more advanced technique, namely approximate entropy, allowed Yamada et al. [21] to evidence an increased risk of mortality in 107 patients with chronic AF with a reduced ventricular rate irregularity. In our previous one-center prospective study, we confirmed a prognostic value of HRV fraction in patients with coronary artery disease irrespective of the absence or presence of SR [19].

The HRV fraction is determined after numerical processing of a scatterplot. The analysis of the scatterplot has already been successfully used for HRV evaluation in patients with MI and HF, as well as to evaluate ventricular response to AF [22–26]. In an early paper by Woo et al. [22], a visual assessment of scatterplots identified four different patterns, of which the so-called 'complex pattern' carried high risk for subsequent death in patients with HF.

An idea for the calculation of density of 3D scatterplots has also been reported. Hnatkova et al. [23] determined the so-called 'compactness index', which expressed the density of pairs of neighbouring RRI. They showed that the compactness index was a better predictor of mortality after an acute MI than SDNN [23]. Again, only patients with SR were included. In addition, the compactness index showed higher values as HRV became smaller. The HRV fraction describes the density of RRI pairs in such a way that it gives greater values when there is higher RR variability, thus making understanding of the measurement easy.

As indicated by the regression analysis, in patients with SR the HRV fraction was highly positively correlated with SDNN and SDANN. In the setting of AF, however, these correlations were weaker. This is possibly because standard time-domain measures took into account mainly the magnitude of HRV. The new index quantifies both the magnitude and distribution of RRI. In this case, the HRV fraction is similar to the triangular index, the second most commonly used index of HRV [27–29]. However, this index is especially suitable for in-hospital clinical studies, with stable environment and limited physical activity [27], since it is strongly dependent on the distribution of RRI in the density histogram. Therefore, in cases with bi-modal distribution, calculation of the triangular index may lead to incorrect assessment of HRV from 24 hour ECG. The bi-modal distribution of the RRI histogram is commonly seen in healthy subjects and in patients during out-of-hospital 24 hour ambulatory ECG recordings. It is the result of day/night difference, as well as physical and mental activity, which is usually greater in uncontrolled out-of-hospital conditions. The HRV fraction is independent of the distribution, because a sum is taken from the two boxes with the highest number of counts, not necessarily lying close to each other. Thus, a bi-modal distribution, which may influence calculation of the triangular index, does not affect the calculation of the HRV fraction.

The calculation of the HRV fraction takes into account the influence of HR itself. Thus, at the same level of HRV variability indicated by the value of SDNN, but faster HR, HRV fraction is lower. This feature of the HRV fraction is of special importance, since HR is one of the fundamental determinants of HRV [28]. A positive relationship between RRI and its variation has been shown to be closer in patients with advanced HF [28]. This explains why Copie et al. [29] found increased HR itself an independent predictor of cardiac mortality, the sensitivity, specificity and positive predictive value being practically the same as those of the triangular index. We observed a closer correlation between any HRV index and HR also in the setting of AF. The unique property of the HRV fraction results from calculation of a sum from any two boxes with the greatest number of counts, while the interval (side) of each box is the same, irrespective of R-R

interval length. Therefore, the probability of finding the highest number of counts is greater for boxes lying in the region of short RRI on the scatterplot and so the probability is greater at faster HR. In this way, the HRV fraction combines both HR and its variability. A more detailed explanation of the HRV fraction rationale has been described elsewhere [18].

As indicated in our results, low values of standard time-domain measures were found in AF patients with depressed LVEF, who also had shorter mean RRI. But mean values of these indices were still higher than in SR-patients with preserved LVEF. At the same time, the HRV fraction values were lower in AF patients with abnormal LVEF, as well as in SR patients with compromised LVEF. This was in part due to a faster HR in patients with LV dysfunction. The distribution of RRI was therefore more compact, and most RRI lay within two boxes, from which the numbers had been used in the HRV fraction calculation. Therefore, the distribution of the remaining RRI has a smaller influence on HRV fraction measurement, but it significantly affects the calculation of the standard indices.

A reduced HRV in patients with low LVEF and AF should be expected, since similar or even greater neurohormonal derangements were evidenced in studies which compared levels of catecholamines and several biologically active peptides in patients with AF and SR [30, 31]. These humoral factors mainly affect long-wave HR oscillations, which are usually assessed by the indices of global 24-hour HRV. The same factors could influence long-term spectral components, which were found to be indistinguishable in patients with AF or SR in a study by Hayano et al. [32]. The HRV fraction allows simple evaluation of the dynamics of the regulatory process underlying the long-term HRV component, which may be common, irrespective of cardiac rhythm.

A reduced HRV has been shown to carry a worse prognosis in studies performed separately in SR patients and AF patients with HF [5]. Thus, it might be expected that similar results would be obtained if a single, theoretically-derived index was used. HRV fraction seems to be a good candidate, allowing HRV evaluation in a combined population of patients with SR and AF simultaneously.

It should be noted that HRV fraction (and other HRV measures) accounted for somewhat different features of ventricular rate in the presence of SR and in AF. Accordingly, while SR is preserved, the HRV fraction provides information similar to standard global HRV measures that in fact reflect mainly parasympathetic cardiac control at the level of sinus node. However, in the presence of AF, when parasympathetic cardiac control at the level of atrio-venticular node predominates, ventricular rate irregularity must not reflect autonomic nervous control of the sinus node.

Conclusions

Our study has evaluated a simple and easily understood index of HRV that permits assessment of HRV irrespective of cardiac rhythm. The index shows a similar dependence of heart rate variation on LV function in patients with SR or AF. Its usefulness requires further studies to validate its prospective role in risk stratification in a population of cardiac patients.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

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