Prognostic Value of Heart Rate Variability Analysis in Patients with Depressed Left Ventricular Function Irrespective of Cardiac Rhythm

M Sosnowski[1], PW Macfarlane[2], R Parma[1], J Skrzypek-Wanha[1], M Tendera[1]

[1]3rd Division of Cardiology, Medical University of Silesia, Katowice, Poland
[2]Division of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

Abstract

A new index of heart rate variability – HRF Fraction – was developed and its value for risk stratification was evaluated in 480 patients with coronary heart disease. The main purpose to introduce the HRVF was to overcome one of the most important constraints – cardiac arrhythmia, especially atrial fibrillation – that limits use of HRV measurement as a routine clinical tool.

In 384 patients with sinus rhythm (SR) and 96 with AF HRV measurements from 24h ambulatory ECG were performed. Patients were followed for a median period of 28 months. The HRV indices in those who died were compared to those who survived.

Authors found that HRV Fraction and - among standard time-domain indices - only SDANN, possessed properties that allow HRV measurement to be applied for risk stratification studies in unselected population of patients with cardiac arrhythmia.

1. Introduction

Heart rate variability (HRV) analysis, in spite of high scientific interest, still suffers from a low applicability in routine clinical practice. A plethora of standard and non-linear HRV indices are proposed without clear indications about clinical use and many methodical limitations [1-3]. Usually, meticulous manual editing is necessary, various algorithms are used to exclude noisy data (some genuine data are missing), a minimum number of qualified beats to be acceptable for analysis differs from 70-99%, often unfavorable statistical properties [1,2]. Apart from methodical constraints, there are two main factors - presence of cardiac arrhythmia and abstract meaning for physicians – that hampered HRV measurement to become a routine clinical tool, as yet [2].

We developed a new index of HRV, namely HRV fraction, which is promising for clinical use by its properties that overcome these most important constraints.

2. Methods

480 patients aged 58 ± 10 years with stable coronary artery disease (105 females, 375 males) entered the study irrespective of cardiac rhythm (sinus rhythm, 384, SR), atrial fibrillation, 96, AF). Their clinical characteristics is given in Table 1.

Table 1. Clinical characteristics of studied patients

	No [%]
Hypertension	298 [61]
Hyperlipidaemia	253 [57]
Diabetes	93 [19]
Active smokers	106 [22]
Prior MI	320 [94]
NYHA Class III/IV	124 [26]
CCS Class I/II / III	331 [69] / 149 [31]
Coronary angiography	389 [81]
Stenosed vesssels (no).	
- 0	19 [5]
- 1	70 [18]
- 2	70 [18]
- 3 or more	230 [59]
Pts with EF < 35%	172 [36]
Pts with EDD ≥ 60mm	149 [31]
Prior interventions (no)*	
post CABG	216
post PCI/stenting	230
Medical treatment	
Beta-blockers	331 [69]
ACEI/ARB	418 [87]
Ca blockers	152 [32]
Diuretics	202 [42]
Digoxin	82 [17]
Antiarrhythmics	62 [13]

* some patients had more than one intervention

All patients had 24-hour ECG monitoring (Medilog-Excel 2, Oxford) and standard time-domain HRV parameters (SDNN, SDANN, SDNNI, RMSSD, pNN50) data of all heartbeats, irrespective of their classification, were counted after manual editing. Additionally, HRV Fraction (HRVF, %) was determined. Briefly, numerical data was transferred to a personal computer. The scatterplot, which is a plot of R-R intervals ($R\text{-}R_i$) against the following intervals ($R\text{-}R_{i+1}$) was obtained. The scatterplot area (from 0.2-1.8s by 0.2-1.8s) was divided into 256 boxes with each side of 0.1s interval. In each box, the number of paired R-R intervals was counted, and simplified 2D (fig.1) and 3-dimensional graph of density was plotted (fig.2).

The HRV Fraction was calculated according to the formula [a]:

$$HRVF = \{1 - [(N1+N2)/(RR-RR50)]\} * 100\% \qquad [a],$$

where N1 and N2 are the two highest numbers of counts in any of the boxes, RR is the number of all heartbeats, and RR50 is the number of adjacent intervals differing by over 50ms [4,5].

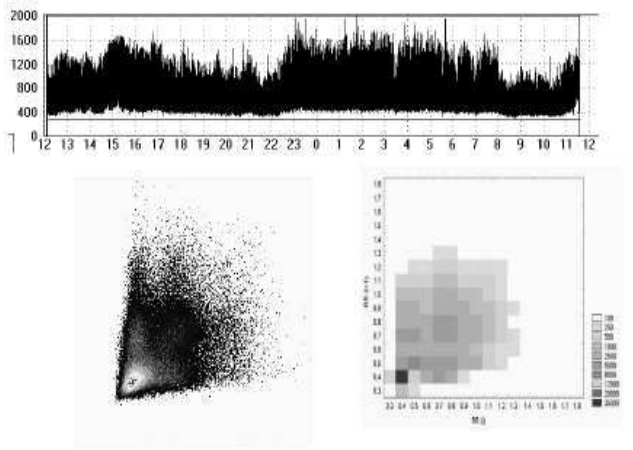


Figure 1. An example of HRV in a patient with AF. Typical tachogram of 24h R-R intervals on the top, left middle graph – automatically given scatterplot (only pattern can be described), right middle graph – a simplified 2D view of the scatterplot given by our method that allows for HRVF calculation.

Patients were followed for 36 months. Death for any reason was the only one clinical end-point. The cut-point of HRV indices for survival analysis and Cox hazard regression were chosen as the value of lower normal limit (SDNN<90ms, SDANN<80ms, and HRVF<35%), as reported previously in normal population of the same region [4].

3. Results

Over median period of 28 months, 70 patients (14.5%) died for any reason (18 among AF patients). Compared to those who alive, the victims had lower RRI (774 ± 134ms vs 849 ± 135ms, p<0.001), as well as depressed global standard time-domain HRV parameters (SDNN 111 ± 54ms vs 135 ± 48ms, and SDANN 83 ± 36ms vs 109 ± 38ms, p<0.001 both). SDNNI, RMSSD and pNN50 did not differ between alive and dead (so, these parameters were not included in further analysis). HRVF was significantly lower in those who died (33 ± 15%) than in those who survived (46 ± 12%, p<0.001). Separate analysis in patients with SR confirmed the above results. In contrast, among patients with AF only SDANN and HRVF showed ability for distinguishing patients who died and survived (92 ± 40ms vs 120 ± 52ms, p<0.05 and 33 ± 16% vs 43 ± 13%, p<0.001, respectively).

Even greater differences where found when HRV parameters were compared in respect to LVEF (Table 2). Lowest mean SDNN was found in patients with depressed LV function and SR who died during observation period. Meanwhile, in patients with AF and low EF, the mean SDNN value did not differ between those who survived and died. Furthermore, these values

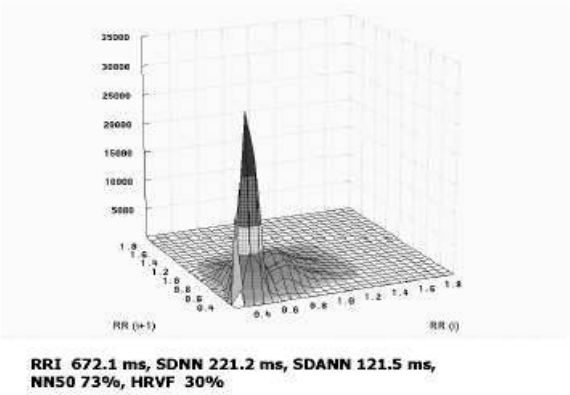


Figure 2. 3-dimensional graph showing peaked distribution of R-R intervals. Below values of the standard HRV indices and HRV are given (the same subject as in fig.1).

were almost twice greater compared to the mean SDNN in patients with SR.

Relative risk associated with the presence of HRVF<35% was 2.7 [95 %CI 1.2-6.0] in AF, 5.0 [3.0-8.3] in SR-patients, and 4.3 [2.8-6.6] in the entire population, while the respective values for SDANN <80ms were 3.2 [1.4-7.0], 4.2 [2.5-7.0] and 4.0 [2.6-6.1]. Other standard time - domain HRV parameters did not show prognostic value in patients with AF.

Kaplan - Meier analysis of survival showed that the

Table 2. Means of HRV measures depending on cardiac rhythm and LV systolic function

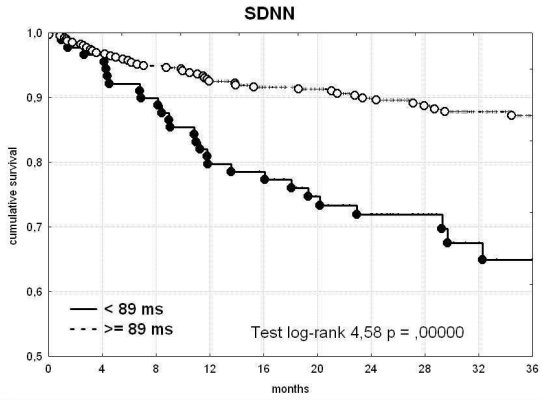
Outcome	Dead n=70				Alive n=410			
Rhythm	AF n=18		SR n=52		AF n=78		SR n=332	
EF [qual]	low	normal	low	normal	low	normal	low	normal
	n=12	n=6	n=35	n=17	n=34	n=44	n=91	n=241
RRI ms	715±168	796±182	762±128	828± 95	735±166	831±158	853±129	872±109
SDNN ms	159±47	190±54	78±32	117±37	165±49	210±58	115±35	124±34
SDANN ms	83±32	109±53	68±29	102±35	102±42	134±55	100±32	109±33
HRVF%	29±17	42±10	27±13	42±14	38±15	47±10	43±13	47±11

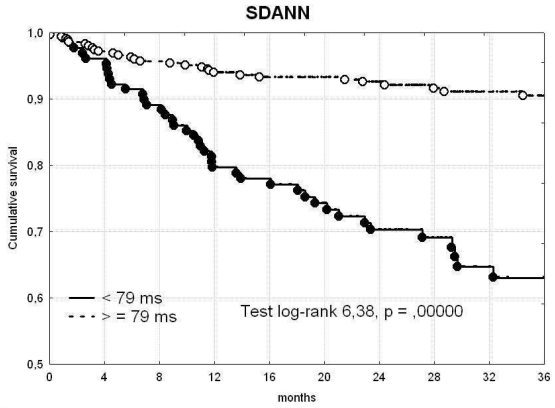
HRV Fraction appeared more sensitive prognostic index compared to SDANN, and especially SDNN (fig.3).

4. Discussion and conclusions

There are several findings in our report which should be emphasized.

First, the study populations was unique, as both patients with sinus rhythm and atrial fibrillation were included. The main exclusion criterion in most clinical HRV studies is atrial fibrillation. However, the more depressed LV function and older age, the proportion of patients with AF increases. It means that patients with a greater risk, carried not only by heart diseases itself, but also by the presence of impaired LV function and advanced age cannot be included in studies, in which a prognostic value of HRV is the objective.





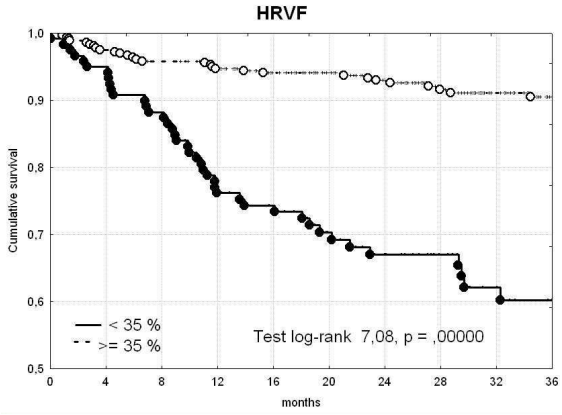


Figure 3. Kaplan-Meier curves of cumulative survival for SDNN, SDANN and HRVF.

Second, we found that among standard time-domain HRV measures derived from 24h-ECG only SDANN could sufficiently distinguish patients at risk from those with a good prognosis irrespective of cardiac arrhythmias. As the proportion of patients excluded from HRV studies varies between 5-25%, it seems obvious that commonly used index, SDNN, cannot be used in a substantial number of patients. This suggests that SDANN should probably replace SDNN in HRV prognostic studies without necessity of exclusion a substantial proportion of patients with AF, especially with heart failure.

Third, we showed that HRV Fraction performed not inferiorly compared to SDANN. However, in contrast to the latter index, the HRV Fraction possesses better empirical and statistical properties than SDANN [5]. As introduction of a new index should always be justified by clinical reasons, it cannot be disregarded that HRV Fraction is expresses as a percentage. Such a metric is quite well understandable for all physician.

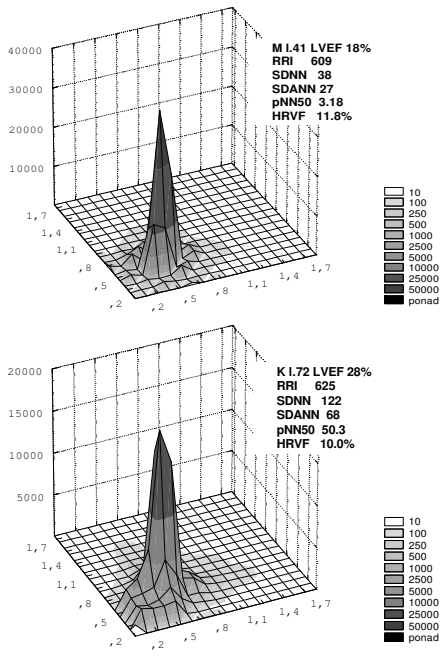


Figure 4. Two examples of R-R interval distribution in patients with depressed LV systolic function. Upper graph from a patient with sinus rhythm, lower – with AF. Values of HRV Fraction, as well as mean R-R interval are comparable, while SDNN was three times higher in AF-patient, reaching value far above the lower normal limit.

As illustrated in fig.4. global R-R variation can be equally well evaluated in patients with sinus rhythm and atrial fibrillation by using a measure which takes R-R intervals distribution into account. Previous studies confirmed usefulness of a scatterplot analysis for risk assessment in sudden infant death syndrome [6] and heart failure [7,8]. Hnatkowa et al. [9] were first who suggest applicability of a numerical analysis of the scatterplot, however, the compactness index they proposed still could not be used in patients with atrial fibrillation. Our proposal – which in this context – was similar to that of Hnatkova et al., would allow use of scatterplot analysis in patients with cardiac arrhythmias.

Fourth, the results of our study confirmed earlier observational study regarding prognostic value of HRV analysis in patients with AF [8]. Nevertheless, putting AF in exclusion criteria in most clinical studies, that formed current opinion on HRV applicability in cardiology, did not allow to draw evidence-based conclusions in a real-life settings. It seems important, as there are evidences for similar determinants of this phenomenon in atrial fibrillation [10].

In real-life population of patients with coronary artery disease presenting with various cardiac rhythm (sinus rhythm or atrial fibrillation) HRV fraction and SDANN are suitable for risk stratification. HRVF expression as percentage seems to be promising in HRV analysis use in clinical settings, especially in patients with depressed left ventricular function and heart failure, in whom cardiac arrhythmias are more prevalent.

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Address for correspondence

Maciej Sosnowski MD, PhD
3rd Division of Cardiology, Medical University of Silesia, Ziolowa St 47, 40-635 Katowice, Poland
maciej.sosnowski@gmail.com