

Multiparametric Analysis of Heart Rate Variability Used for Risk Stratification Among Survivors of Acute Myocardial Infarction

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VOSS A., ET AL.: Multiparametric Analysis of Heart Rate Variability Used for Risk Stratification Among Survivors of Acute Myocardial Infarction. A multiparametric heart rate variability analysis was performed to prove if combined heart rate variability (HRV) measures of different domains improve the result of risk stratification in patients after myocardial infarction. In this study, standard time domain, frequency domain and non-linear dynamics measures of HRV assessment were applied to 572 survivors of acute myocardial infarction. Three parameter sets each consisting of 4 parameters were applied and compared with the standard measurement of global heart rate variability HRVi. Discriminant analysis technique and t-test were performed to separate the high risk groups from the survivors. The predictive value of this approach was evaluated with receiver operator (ROC) and positive predictive accuracy (PPA) curves. Results – The discriminant analysis shows a separation of patients suffered by all cause mortality in 80% (best single parameter 74%) and sudden arrhythmic death in 86% (73%). All parameters of set 1 show a high significant difference ($p < 0.001$) between survivors and non-survivors based on two-tailed t-test. The specificity level of the multivariate parameter sets is at the 70% sensitivity level (ROC) about 85-90%, whereas HRVi shows maximum levels of 70%. The PPA in the all cause mortality group is at the 70% sensitivity level twice as high as the univariate HRV measure and increases to more than fourfold as high within the VT/VF group. In conclusion, in this population, the multiparametric approach with the combination of four parameters from all domains especially from NLD seems to be a better predictor of high arrhythmia risk than the standard measurement of global heart rate variability.

heart rate variability, myocardial infarction, risk stratification, nonlinear dynamics

Introduction

Many concepts of non-linear dynamics have been applied to cardiovascular research in the past 15 years. Some have been related to heart rate variability (HRV)¹⁻⁵ and blood pressure variability (BPV).⁶ Most investigators favored traditional methods from chaos theory like Lyapunov exponents,² fractal dimensions^{2,6,7} or phase space representations.² These methods require a rather long and stationary time series and are sensitive to noise.

HRV in humans has been described as fractal.¹ Applying spectral analysis to the long term heart

rate time series, the so called inverse power law scaling $1/f$ can be obtained, if one plots the data as the log of spectral power versus log of frequency.^{3,7} One major problem of applying $1/f$ is the severe influence of non-stationarities (e.g. physical activity) occurring in most time series and leading to a falsified envelope.

To gain a higher level of robustness against influences of noise and non-stationarities several groups have developed other non-linear concepts. These methods have been based on different types of entropy estimation like approximate entropy¹ or entropies from distributions of symbolic dynamics.⁴ With surrogate techniques⁵ or discriminant analysis techniques³ several investigators demonstrated the origin contribution of non-linear measures.

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Among this variety of non-linear approaches there are only a few studies which assess the clinical usefulness of non-linear measures for high risk stratification based on HRV analysis.⁷⁻⁹ No extensive prospective study has been performed to show the efficacy of these new methods.

We recently evaluated a new concept of multiparametric HRV analysis in a pilot study⁸ attempting to classify risk in patients after myocardial infarction. We hypothesize that the four-dimensional multiparametric HRV analysis improves the result of risk stratification in patients after myocardial infarction.

Methods

Patients

HRV measures were applied to 572 survivors of acute myocardial infarction (AMI). All patients underwent 24-hour Holter monitoring before discharge from the hospital (5 to 8 days after AMI) and were followed up for 2 years. No patient received any antiarrhythmic treatment. Treatment with beta-adrenergic blocking agents was interrupted at least 48 h before the recording. During the follow-up 14 patients suffered from sudden arrhythmic death (SAD), 22 patients suffered from sudden death (SD), 34 patients from cardiac death (CD), 13 patients suffered from ventricular tachycardia or fibrillation (VT/VF) and 43 patients suffered from all cause mortality (ACM).

HRV-analysis

Short-term HRV measures from time and frequency domain were computed as mean values from successive 5-minutes periods (HRV short term 5 min - HRVST_{5min}) and from a 30-minutes stationary stage (HRV short term stationary - HRVST_{stat}). The non-linear measures used require longer time series with at least 1500 samples (that means approximately 20-30 minutes). Thus, the short term HRV based on non-linear parameters was calculated as the mean value of successive 30-minutes windows (HRV short term 30 min - HRVST_{30min}). Long-term HRV measures were

computed as parameters over the entire 24 hours (HRV long term HRVLT).

Using statistical procedures like hierarchical cluster analysis and stepwise discriminant function analysis⁸ we limited the parameter number to four, where the following three parameter sets turned out to be the most useful ones in risk stratification:

Parameter set 1 (PS1)

shannon (HRVST_{5min}), (vlf+lf)/p (HRVST_{5min}), wpsum02 (HRVST_{30min}), meanNN (HRVST_{stat})

Parameter set 2 (PS2)

plvar10 (HRVST_{5min}), renyi025 (HRVLT), shannon (HRVLT), lf/hf (HRVST_{stat})

Parameter set 3 (PS3)

hf/p (HRVST_{5min}), (vlf+lf)/p (HRVST_{5min}), fwshannon (HRVST_{30min}), meanNN (HRVST_{stat}).

A special filter method, which considers the basic variability in the time series, was used to filter out arrhythmias, missing beats and artifacts. From all corrected time series (NN time series) the following parameters were calculated:

The triangular index HRVi is a geometrical time domain parameter.^{10,11} It is the integral of the density distribution (number of all NN intervals) divided by the maximum of the density distribution. This measure expresses overall HRV measured over 24 hours and is mainly influenced by lower frequency processes. One major advantage of this parameter lies in its relative insensitivity to the quality of the investigated HRV time series.¹²

The parameter 'shannon' from the first parameter set PS1 denotes the averaged Shannon entropy of the histograms from successive 5-minutes intervals over the entire 24 hours. The parameter '(vlf+lf)/p' marks the averaged normalized low frequency component calculated from successive 5-minutes intervals of the 24h-tachogram ('vlf' represents the power in the frequency band 0.0033 Hz - 0.04 Hz, 'lf' 0.04 Hz - 0.15 Hz, 'p' is the total power). The spectra are estimated by use of the Fast Fourier Transformation. To avoid the 'leakage' effect a Blackman Harris window function was applied.

'wpsum02' is a nonlinear measure derived from symbolic dynamics.⁸ There are several quantities

that characterize symbol strings. For 30 minutes intervals we investigate the probability distribution of length 3 words (words which consist of three symbols from an alphabet $\{0,1,2,3\}$). In this way, one can obtain 64 different types of words (bins). A high percentage of words consisting only of the symbols '0' and '2' ('wpsum02') is a measure for an intermittent decreased HRV. Parameter 'meanNN' is the mean value of the NN-intervals calculated from the most 30 minutes stationary stage within the 24h-tachogram.

The first parameter from the second set PS2 'plvar10' is an additional mode of symbolic dynamics for transient low variability analysis. In this mode we observe 6 successive symbols of a simplified alphabet, consisting only of symbols '0' or '1'. Here the symbol '0' stands for a difference between two successive interbeat intervals lower than 10ms whereas '1' represent those cases where the difference between two successive interbeat intervals exceeds this special limit. Words consisting only of six zeros are counted, that means 'plvar10' represents the probability of the word type '000000' occurrence. The term 'renyi025' denotes the Renyi-entropy (order 0.25) of word distribution, calculated from a long term symbolic dynamics mode. The word distribution was formed of length-6 words of the alphabet $\{0,1,2,3,4,5\}$. In this way we get 7776 different word types containing different information about the dynamics in the time series. The parameter 'shannon' denotes the Shannon-entropy of the 24h histogram. That means, that only one histogram and one Shannon entropy are calculated. This parameter describes the global 24h HRV including all long term phenomena like circadian rhythms. Finally, 'lf/hf' is the well known low frequency to high frequency ratio¹ calculated from the most stationary phase.

In parameter set PS3 the measures '(vlf+lf)/p' and 'meanNN' are already described. The parameter 'hf/p' (0.15Hz - 0.4Hz) marks the averaged normalized high frequency component calculated from successive 5-minutes intervals of the 24h-tachogram. Finally, the parameter 'fwshannon' is also a measure from non-linear dynamics (symbolic dynamics). The same word definition for

this parameter as for 'wpsum02' is used. From these 64 different word types described above a word distribution is calculated. The Shannon-entropy of this special distribution describes the basic variability of the most stationary region.

Data quality control

Under clinical routine conditions the collected ECG records represent a typical mixture of good, average, and moderately poor quality long term recordings. Unfortunately, this quality inhomogeneity of ECG records leads to misclassifications and non-comparable results. Therefore, we had to develop an algorithm for automatic exclusion of those heart rate time series which are too short or including too many arrhythmias and artifacts.

A long term tachogram will be excluded if one of the following conditions holds:

- E1. The recording time deducting the measured artifact time is less than 19 hours (excludes recordings which are too short or which have too many artifacts).
- E2. The parameter 'sdaNN5' is greater than 120ms (excludes time series where the number of RR-interval misclassifications is beyond the selected limit).
- E3. The measure 'phvar20' is greater than 0.2 (reject all time series with long episodes of arrhythmias like atrial fibrillation or bigeminy).

Parameter 'sdaNN5' is the averaged standard deviation of the NN-intervals calculated from successive 5-minutes intervals of the 24h-tachogram. 'phvar20' denotes a long term measure for transient high variability analysis. We observe 6 successive symbols of a simplified alphabet, consisting only of symbols '0' or '1'. Here, the symbol '1' stands for a difference between two successive beats higher than 20 ms whereas '0' represent those cases where the difference is lower. 'phvar20' represents the probability of the word type '111111' occurrence. Applying these criteria to St. George's data base did reduce the number of included patients from 810 to 572.

MULTIPARAMETRIC ANALYSIS OF HEART RATE VARIABILITY

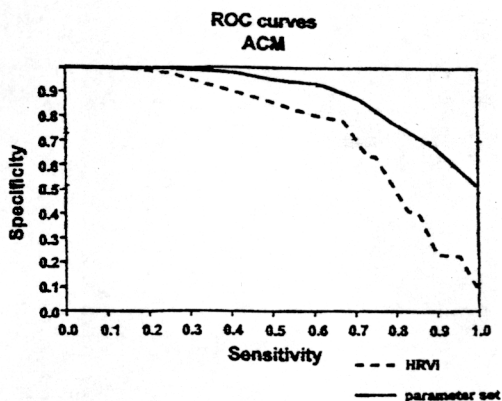


Figure 1. ROC curves of ACM group calculated for parameter HRVi and parameter set 1

Statistical analysis

The two tailed univariate t-test for equality of means is used to test whether the means of the non-survivor groups differ significantly from the survivor group. With discriminant function technique the degree of multivariate linear independence between these groups is calculated. To determine the maximum specificity for each value of sensitivity the receiver operator characteristics (ROC) were computed.¹⁴ To express the percentage of correctly positive classified patients in relation to all patients the positive predictive accuracy (PPA) was determined. ROC and PPA curves distinct between individual end points based on multivariate combination of the three parameter sets and on univariate HRVi.

Results

In recent studies we computed approximately 50 HRV analysis parameters. Using standard statistical procedures the parameter number was reduced to three sets each with four parameters.

The results of discrimination analysis showed a separation of the ACM and the survivor group of 80% for parameter set 1 and 2 and of 81% for set 3. Consequently all three parameter sets are suitable for a multiparametric HRV analysis.

Receiver operator and the positive predictive accuracy curves were computed to optimize the classification of patients after myocardial infarction.

Figure 1 shows the maximum achieved level of specificity at pre-selected levels 30%, 50% and 70% of sensitivity (ROC). At the 30% sensitivity level all multivariate parameter sets have a rather high specificity, the univariate parameter HRVi is slightly lower. Similar results have been obtained at the 50% level. The specificity level of the multivariate parameter sets is at the 70% sensitivity level about 85-90%, whereas HRVi shows maximum levels of about 70-75%.

In Table I the maximum achieved level of positive predictive accuracy at pre-selected levels 30%, 50% and 70% of sensitivity is presented. The maximum achieved levels of PPA varies at the 30% sensitivity level in the multivariate parameter sets from about 40% to 95%, whereas HRVi varies from about 5% to 50%. At higher levels of sensitivity the PPA is reduced. The PPA level of the multivariate parameter sets at the 70% sensitivity

Table I

The maximum achieved level of PPA at pre-selected levels of sensitivity related to the three parameter sets and HRVi

Sensitivity	30%				50%				70%			
	PS1	PS2	PS3	HRVi	PS1	PS2	PS3	HRVi	PS1	PS2	PS3	HRVi
PPA												
SAD	72%	96%	78%	48%	35%	21%	36%	8%	20%	10%	23%	8%
SD	47%	40%	50%	10%	29%	14%	22%	10%	16%	8%	15%	7%
CD	87%	71%	79%	43%	44%	35%	45%	20%	30%	20%	31%	17%
VT/VF	70%	85%	37%	6%	38%	23%	24%	6%	26%	12%	16%	6%
ACM	70%	59%	68%	38%	40%	33%	42%	22%	29%	20%	29%	15%

Table II

Basic statistics of HRV analysis performed with parameter set 1 (mean value $m \pm$ standard deviation s). The columns p show the different levels of significance (two sided t-test, survivors versus risk groups, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

	shannon		(vlf+lf)/p		wpsum02		meanNN	
	m \pm s	p	m \pm s	p	m \pm s	p	m \pm s	p
SAD	2.02 \pm 0.42	***	0.67 \pm 0.11	**	0.61 \pm 0.17	**	736.5 \pm 119.7	***
SD	2.12 \pm 0.42	***	0.66 \pm 0.11	***	0.59 \pm 0.17	**	798.8 \pm 156.5	***
CD	1.99 \pm 0.46	***	0.64 \pm 0.13	***	0.63 \pm 0.17	***	773.9 \pm 151.8	***
VT/VF	2.18 \pm 0.48	**	0.62 \pm 0.11	***	0.54 \pm 0.19	n.s.	842.5 \pm 170.4	*
ACM	2.02 \pm 0.44	***	0.64 \pm 0.12	***	0.63 \pm 0.17	***	798.7 \pm 164.4	***
Survivors	2.52 \pm 0.38		0.73 \pm 0.07		0.48 \pm 0.16		987.2 \pm 182.7	

level is about twice as high as the univariate HRVi.

Table II shows that the survivors have a higher Shannon entropy 'shannon' compared to non-survivors. A lower Shannon entropy reflects a more dominant peak in the density distribution and implies a more reduced variability. That means, their HRV is more complex, the dynamical behavior is increased. The normalized low frequency component '(vlf+lf)/p' is decreased in the risk groups. This finding is surprising, as we know from the literature that the low frequency components are increased in high risk patients after myocardial infarction.^{15,16} The measure 'wpsum02' shows higher intermittent low variability phases in all mortality groups. All high risk patients show a increased steady-state heart rate (during most stationary phase).

The PPA in the all cause mortality group ACM is with PS1 at 70% sensitivity level twice as high as with the univariate HRV measure (Fig. 1) and this difference increases to a factor of more than 4 within the VT/VF group (Table I).

The specificity at 70% sensitivity level is in the univariate case (ROC ACM group) 68% and with PS1 85% (Fig. 2) and increases to 72% respectively 94% in the VT/VF group.

This study examines the capability of a multi-parametric all domain HRV analysis approach to increase the recognition of patients after myocardial infarction threatened by sudden cardiac death and severe tachyarrhythmias. The main result of this study in analysis of heart rate variability is a doubling of diagnostics precision.

Discussion

In the population of the St. George's hospital postinfarction data base, the combination of parameters from all domains especially from NLD is a better predictor of high arrhythmia risk than standard measurement of global heart rate variability. The favored parameter combination includes the measures 'shannon', '(vlf+lf)/p', 'wpsum02' and 'meanNN' - the mean heart rate during the most stationary phase.

This measure 'meanNN' reflects a steady state rest HRV excluding significant physical and mental stress influences and could be interpreted as basic autonomous status under a non (or normal) stimulated basic condition. A higher basic mean heart rate stands for a higher risk. There are several other attempts to emphasize the mean heart rate as a suitable risk predictor.¹⁷

Shannon entropy as a time domain parameter of the NN interval density histogram represents mainly the day-night time behavior as well as the range of variability during the whole day. In that way 'shannon' is rather similar to the St. George's 'HRVi'-measure.¹⁸ The main difference between 'shannon' and 'HRVi' is that 'shannon' includes all (weighted) information of the histogram while 'HRVi' considers only the height of the major (highest) peak and the derived basis.

Calculating the normalized frequency component '(vlf+lf)/p' we get an information about changes in lower frequency activity which is

modulated mainly by sympathetic activity as well as vagal activity.¹⁹ A decrease of lower frequency components in connection with an increase of higher frequencies could be a sign of autonomic imbalance with a more dominant vagal component. This result is in contrast to other findings¹⁶ showing a remarkable increase of sympathetic activity in high risk patients. One explanation for this phenomenon could be the clinical treatment. It is reported that angiotensin-converting enzyme (ACE) inhibitors,²⁰ β -blockers²¹ and antihypertensive drugs²² may decrease the LF component and increase the HF component. To answer this question, we have to investigate in further studies if the parameter '(vlf+lf)/p' might reflect the efficacy of a treatment and can be influenced by the therapy of the physicians (high risk patients get more of these drugs). In addition we should also consider a possible similar effect of the combination of different drugs.

'wpsum02' is a nonlinear measure of overall variance homogeneity. A high value of 'wpsum02' reflects a reduced HRV. This lack of variability may occur either as a general reduced HRV or as an intermittent reduced HRV. In opposition to any kind of standard deviation in time domain 'wpsum02' detects any epoch of reduced variability independently from the mean variability. That means, if a time series shows a relative high stan-

dard deviation interrupted with non regular short time phases of reduced variability, then the SDNN or SDANN are not able to detect these epochs of reduced variability and would not find any hint for an abnormal variability but 'wpsum02'. Since 'wpsum02' is a short time measure, we assume that a high value may imply a pathological depression of the vagal (pulmonary) mechanisms.

One limitation of this study is the relative small number of members in the different high risk groups. It implies a reduced number of measures for multiparametric HRV analysis.

The predictive value of HRV analysis performed only with one parameter is rather low. The important finding of this study is that the multiparametric analysis of HRV increases the prediction of risk in patients who survived a myocardial infarction. It is known that the combination of HRV with other (non HRV) risk factors increases the positive predictive accuracy.^{13,23} It is expected that a combination of multiparametric HRV analysis, as performed in this study, with other established clinical risk factors, like ejection fraction, New York Heart Association functional class, late potential analysis or inducible tachyarrhythmias by programmed electrical stimulation would lead to a further enhancement of risk stratification.

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