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The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death

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Abstract

Objectives: This study introduces new methods of non-linear dynamics (NLD) and compares these with traditional methods of heart rate variability (HRV) and high resolution ECG (HRECG) analysis in order to improve the reliability of high risk stratification. **Methods**: Simultaneous 30 min high resolution ECG's and long-term ECG's were recorded from 26 cardiac patients after myocardial infarction (MI). They were divided into two groups depending upon the electrical risk, a low risk group (group 2, $n = 10$) and a high risk group (group 3, $n = 16$). The control group consisted of 35 healthy persons (group 1). From these electrocardiograms we extracted standard measures in time and frequency domain as well as measures from the new non-linear methods of symbolic dynamics and renormalized entropy. **Results**: Applying discriminant function techniques on HRV analysis the parameters of non-linear dynamics led to an acceptable differentiation between healthy persons and high risk patients of 96%. The time domain and frequency domain parameters were successful in less than 90%. The combination of parameters from all domains and a stepwise discriminant function separated these groups completely (100%). Use of this discriminant function classified three patients with apparently low (no) risk into the same cluster as high risk patients. The combination of the HRECG and HRV analysis showed the same individual clustering but increased the positive value of separation. **Conclusions**: The methods of NLD describe complex rhythm fluctuations and separate structures of non-linear behavior in the heart rate time series more successfully than classical methods of time and frequency domains. This leads to an improved discrimination between a normal (healthy persons) and an abnormal (high risk patients) type of heart beat generation. Some patients with an unknown risk exhibit similar patterns to high risk patients and this suggests a hidden high risk. The methods of symbolic dynamics and renormalized entropy were particularly useful measures for classifying the dynamics of HRV.

Keywords: High resolution ECG; Heart rate variability; Non-linear phenomena; Sudden cardiac death

1. Introduction

Malignant ventricular arrhythmia, especially ventricular tachycardia (VT) and ventricular fibrillations, are in many cases the cause of sudden cardiac death (SCD) in patients surviving acute myocardial infarction. Despite various improvements in risk stratification after myocardial infarction, the detection of these high risk patients remains unsatisfactory.

One suitable method to detect high risk patients is the analysis of signal-averaged high resolution surface ECG. Ventricular late potentials are low level signals in the terminal portion of the QRS complex of the ECG. They are a sign of pathological changes of the conduction system and are strongly correlated with the occurrence of sustained ventricular tachycardia. However, the predictive accuracy is limited by the high incidence of false positives in inferior MI [1,9], especially of time domain late potential analysis in postmyocardial infarction.

Short-term and long-term fluctuations in the heart rate are partially modulated by the autonomic nervous system control of heart activity. Recent studies [7,18] have shown

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that a low HRV is related to an increased risk for severe ventricular arrhythmia and sudden cardiac death. These phenomena are associated with a decreased complexity of beat-to-beat interval dynamics.

Several time-domain measures of HRV have been applied for clinical and limited research purposes. These measures take little time to calculate but they provide only an overall HRV measure. Spectral analysis of the RR time series [15,23,29], which expresses HRV as a function of frequency, is a better representation of the different physiological sources of the heart beat generation. However, a precondition for applying spectral analysis is a strong periodicity of the numerous superimposed short- and long-term physiological oscillations. Neither the traditional techniques of data analysis in time and frequency domain, nor the most popular statistics in chaos theory, the fractal dimension, are suitable to characterize the dynamics of the heart beat generation.

In a preliminary study [34] we found a special pattern of dynamics in patients with high risk for sudden cardiac death with methods of non-linear dynamics, whereas parameters of time and frequency domain were not as accurate. Therefore we conducted this study to investigate the hypothesis that methods of non-linear dynamics could improve the accuracy of HRV analysis. We theorize that with help of statistical approaches and multiparameter analysis patients with an unknown risk could be better classified. Finally, the combination of HRV and HRECG analysis leads to an improved discrimination of different patient groups.

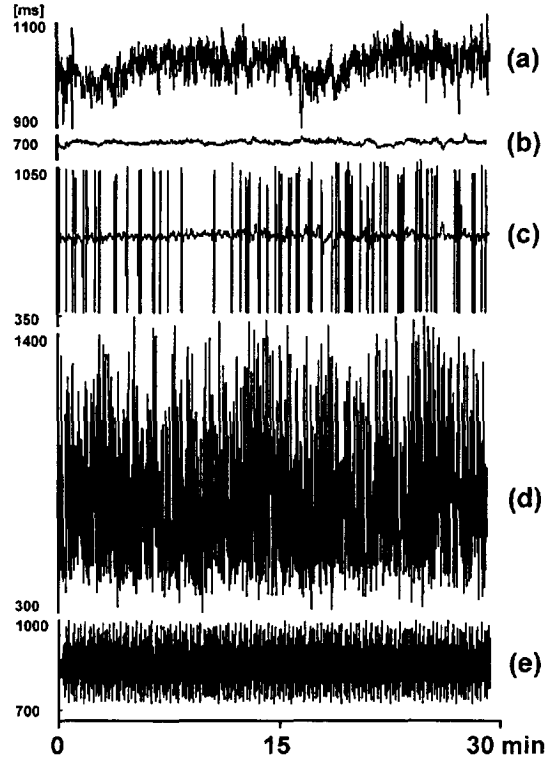

Fig. 1. 30 min tachograms from a healthy person (a), a patient with high risk for sudden cardiac death (SCD) (b), a patient with high risk for SCD with ventricular premature complex (VPC) (c), a patient with high risk for SCD with atrial fibrillation (d) and from a chaotic system with Roessler attractor (e).

2. Methods

2.1. Data recording and pre-processing

The sinus node is the central control element of the autonomic regulation. Its rhythm should be derived from the onsets of the P-waves. Since the P-wave signal cannot always be extracted the intervals between the R-peaks are chosen for further analysis. The error that occurs using the RR-interval instead of PP-interval detection amounts to approximately 4 milliseconds [12]. A pattern matching cross correlation method (as usually applied) extracts the RR-intervals from a 30 min high resolution ECG with a resolution of 0.5 milliseconds. This ECG was recorded under standardized conditions (rest, same time, place) for all patients and the control group. Simultaneously a second RR-interval detection was made by a commercial Holter system with a resolution of 8 milliseconds.

All usable methods of spectral estimations for calculating HRV power density spectra, such as the periodogram by means of the Fast Fourier Transformation (FFT), presuppose an equidistant (of equal, temporal intervals) sampled signal function. The RR time series (sequence of successive RR differences) is not equidistant in terms of time, but only in terms of the actual number of RR difference occurrences. Therefore, an equidistant series of this kind must be created by interpolation, in order to get a spectrum with frequency scaling. It is important to reject arrhythmias and artifacts (and if necessary the interpolation of the intermediate values with a special filter method that considers the basic variability), that would otherwise lead to a noticeable widening of the spectrum and thus blur the frequency bands. NN-intervals are the normal RR-intervals in the tachogram after filtering the RR time series.

2.2. Analysis of heart rate variability

2.2.1. Time domain measures

A tachogram is the graphic display of heart rate as a function of time. It shows the temporal development (x axes) either as registered time or interval number and the interval duration (y axis) of the RR or NN intervals as either ms values or beats per minute. The classic differences between healthy persons, patients with restricted or pathologically increased variability and patients with arrhythmias can often be recognized at this stage (see Fig. 1).From this time domain the following parameters [6,8,11,24–26,32,34] have been calculated: 'meanNN' — the mean value of the NN-intervals, 'sdNN' — standard deviation of the NN-intervals, 'cvNN' — the coefficient

of variation of the NN-intervals (quotient of standard deviation and mean value of the filtered tachogram), 'sdaNN1' — the standard deviation of mean values of successive 1 min NN-intervals, 'sdaNN5' — the standard deviation of mean values of successive 5 min NN-intervals, 'pNN50' — the percentage of NN-interval differences greater than 50 milliseconds, 'pNN100', 'pNN200' — the percentage of NN-interval differences greater than 100 (200) milliseconds, 'pNN110', 'pNN120', 'pNN130' — the percentage of NN-interval differences lower than 10 (20, 30) milliseconds, 'rmssd' — the root mean square of successive NN-interval differences, 'Shannon' — the Shannon entropy of the histogram (density distribution of the NN-intervals; see Appendix A), 'renyi2, renyi4' — the Renyi entropy of order 2 (4) of the histogram and 'renyi025' — the Renyi entropy of order 0.25 of the histogram.

2.2.2. Frequency domain measures

In the frequency domain the frequency bands 'ULF', 'VLF', 'LF', 'HF' [5–7] were calculated. The parameter 'ULF' represents the power in the frequency band from 0 Hz up to 0.0033 Hz, 'VLF' the power in the frequency band from 0.0033 Hz up to 0.04 Hz, 'LF' the power in the frequency band from 0.04 Hz up to 0.15 Hz, 'HF' the power in the frequency band from 0.15 Hz up to 0.4 Hz. The spectra were estimated by use of the Fast Fourier Transformation. To avoid the 'leakage' effect a Blackman Harris window function was applied. The following common ratios have been added: 'LF/HF' stands for the quotient of 'LF' and 'HF' and 'LF/P' for the quotient of 'LF' and the total power 'P'. Further, the measures 'HF/P', 'VLF/P', 'ULF/P', '(ULF + VLF + LF)/P' and '(ULF + VLF)/P' were calculated.

2.2.3. Measures of non-linear dynamics

Although partial processes in autonomic regulation (i.e. influence of respiration) can be described reliably well by linear methods [2,4,17,40], in view of the complexity of the total system of sinus node activity modulation, a more predominant non-linear characteristic has to be assumed [13,14,17,20]. The time and frequency methods described above were not sufficient in this case and in particular in the description of dynamic changes.

New parameters can be derived from methods of non-linear dynamics, also called chaos theory, which describe complex processes and their complicated interrelations. These methods should be able to record additional information about the state and temporal changes in the autonomic tonus. Therefore, we have applied several new measures of non-linear dynamics in order to distinguish different types of heart rate dynamics [21,34,35]:

2.2.3.1. Phase-space representation (Poincaré-Maps). Phase-space plots facilitate the visualization of beat-to-beat dynamics in the heart rate, independent of RR interval

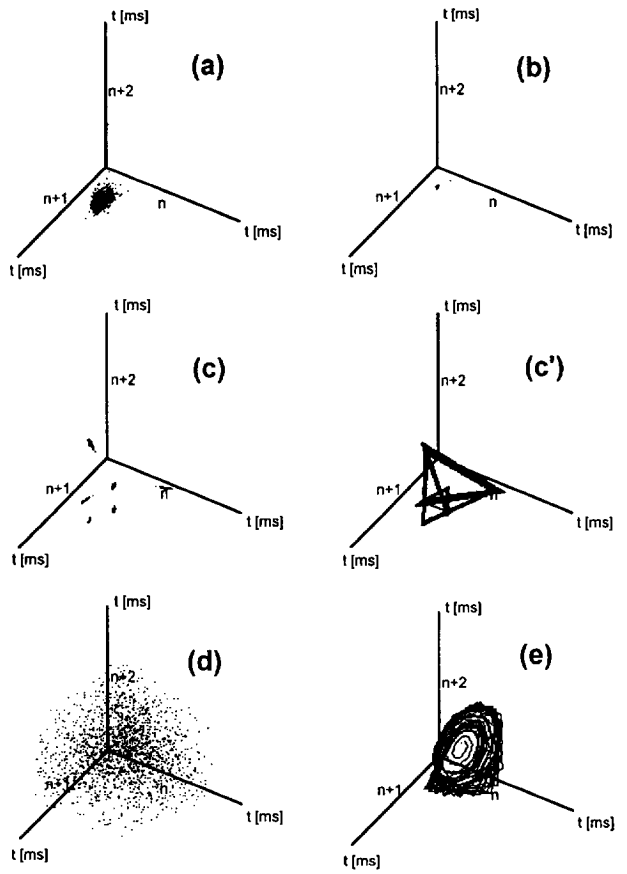

Fig. 2. 30 min phase space plots (derived from tachograms in Fig. 1) from a healthy person (a), a patient with high risk for SCD (b), a patient with high risk for SCD with VPC (c), the same patient, the successive RR intervals are connected via trajectories (c'), a patient with high risk for SCD with atrial fibrillation (d) and from a chaotic system with Roessler attractor (e).

standard deviation (difference plots). It is also possible, especially with 3-dimensional representation, to immediately record complex arrhythmias (see Fig. 2c) [30,34,36]. Phase space plots from healthy persons (see Fig. 2a) are quite different from those of patients with heart failure [39], i.e. high risk patients following myocardial infarction (see Fig. 2b, 2c, 2d). The phase space scatterplot displays the attractor of the heart beat dynamics. If the points in the phase space diagram are connected in temporal order, these connecting lines are known as the trajectories of the underlying system (see Fig. 2c, 2e).

The time series created by solving the Roessler differential equations is similar to the physiological heart rate data (see Fig. 1e). It is difficult to distinguish between this time series and that in Fig. 1a or 1d by means of only statistical standard measures like mean value or standard deviation. However, the phase space representation is a convenient method for a graphical characterization of such a non-linear system (see Fig. 2e).

2.2.3.2. Symbolic dynamics. Symbolic dynamics, as an approach to investigate complex systems, facilitates the

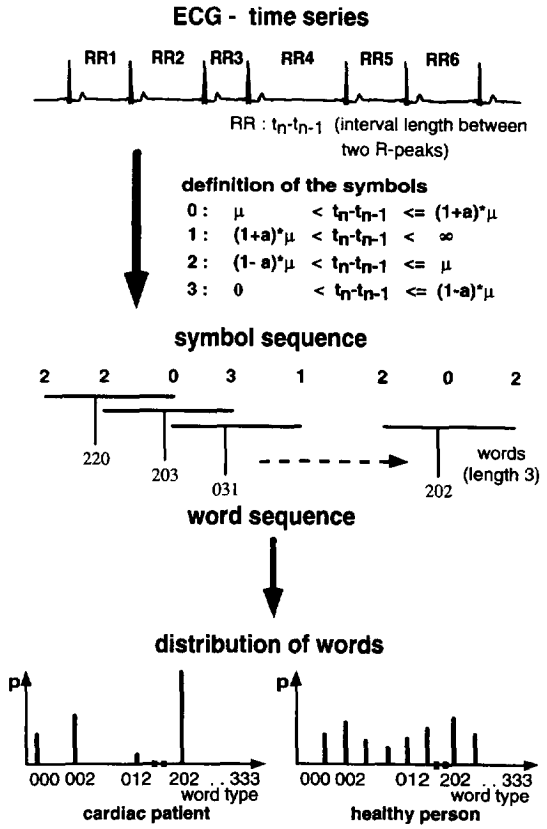

Fig. 3. The basic principle of symbolic dynamics that describes the extraction of symbols from an ECG time series, the extraction of word sequences from the symbol series for calculation of measures from the word distribution.

analysis of dynamic aspects of the HRV. The concept of symbolic dynamics is based on a coarse-graining of the dynamics [2,3,21,22]. The time series are transformed into symbol sequences with symbols from a given alphabet. Some detailed information is lost in the process but the coarse dynamic behavior can be analysed [16].

By comparing different kinds of such transformations, we found that the use of four symbols, as explained in Fig. 3, is appropriate for our purpose. The transformation into symbols refers to three given levels where μ refers to the mean RR-interval and a is a special parameter which is set to 0.1. It is important to note that small changes of the threshold values used here (a, μ) do not influence the results considerably. We verified this with various calculations (a in the range from 0.05 to 0.1). In these cases the result of the discrimination between the patient groups did not change.

There are several quantities that characterize such symbol strings. This study investigates the probability distribution of length 3 words (words which consist of three symbols from an alphabet {0,1,2,3}). In this way, one obtains 64 different types of words (bins). A 30 min ECG corresponds to about 1800 RR-intervals in the tachogram, so that there are about 28 words in each bin. Too few words per bin reduce the accuracy of the word distribution estimation. From results of several other investigations we defined on a heuristic basis 20 as the averaged minimal number of words per bin. For a 24-h analysis the number of symbols can be increased to 6 (word of length 4).

The Shannon and Renyi entropies calculated from the distributions of words ('fwshannon', 'fwrenyi025' — $a = 0.25$, 'fwrenyi4' — $a = 4$) are suitable measures for the complexity in the time series. Higher values of these entropies refer to higher complexity in the corresponding tachograms and lower values to lower ones. The definition of both entropies is given in Appendix A. A high percentage of words consisting only of the symbols '0' and '2' ('wpsum02') is a good measure for decreased HRV, conversely a measure of increased HRV ('wpsum13') would consist of a high percentage of all words which contain the symbols '1' and '3'.

A further measure of symbolic dynamics is the parameter 'wsdvar'. It measures the variability of the time series depending on a word sequence. The resulting word sequence $\{w_1, w_2, w_3...\}$ from Fig. 3 is transformed into a sequence $\{\bar{s}_1, \bar{s}_2, \bar{s}_3...\}$ in the following way:

$$\bar{s}_i(w_i) = \begin{cases} 3 \text{ if } n_{13}(w_i) = 3 \wedge s_{13}(w_i) = \backslash 1 \backslash' \\ 2 \text{ if } n_{13}(w_i) = 2 \wedge s_{13}(w_i) = \backslash 1 \backslash' \\ 1 \text{ if } n_{13}(w_i) = 1 \wedge s_{13}(w_i) = \backslash 1 \backslash' \\ 0 \text{ if } n_{13}(w_i) = 0 \\ -1 \text{ if } n_{13}(w_i) = 1 \wedge s_{13}(w_i) = \backslash 3 \backslash' \\ -2 \text{ if } n_{13}(w_i) = 2 \wedge s_{13}(w_i) = \backslash 3 \backslash' \\ 3 \text{ if } n_{13}(w_i) = 3 \wedge s_{13}(w_i) = \backslash 3 \backslash' \end{cases} \quad i = 1,2,3,...$$

where $n_{13}(w_i)$ represents the number of symbols '1' or '3' in the word w_i and $s_{13}(w_i)$ is that symbol '1' or '3' that occurs first in the word w_i. The word dynamics parameter 'wsdvar' is defined as the standard deviation of this sequence $\bar{s}i$.

Last, we counted the 'forbidden words' in the distribution of words with length 3. We calculate the number of words which seldom or never occur (in our case: probability less than 0.001). A high number of forbidden words stands for a steady behavior in the time series. If the time series is rather complex in the Shannonian sense, only a few forbidden words can be found.

An additional mode of symbolic dynamics for low or high variability analysis was developed. In this way we observed 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 beats lower than a special limit (5, 10, 20, 50, 100 ms) whereas '1' represents those cases where the difference between two successive beats exceeds this special limit:

$$\backslash 1 \backslash' : |t_n - t_{n-1}| \geq limit$$

$$\backslash 0 \backslash' : |t_n - t_{n-1}| < limit$$

Words consisting only of an unique type of symbol (either all '0' or all '1') were counted. These measures were called 'plvar5', 'plvar10', 'plvar20' (word type '000000'), 'phvar20', 'phvar50' and 'phvar100' (word type '111111'). As an example 'plvar10' represents the probability of the word type '000000' occurrence with the special limit of 10 ms. In contrast 'phvar100' represents the probability of the word type '111111' occurrence with the special limit of 100 ms.

2.2.3.3. Renormalized entropy. The renormalized entropy is a relative complexity measure, in which one can only measure the complexity of any state in relation to a reference state. In general, it makes no sense to compare in a direct way the Shannon entropies of two different systems states because their energies can differ considerably. In order to make these states comparable, the mean energy (Appendix B, equation 5) must be equalized (renormalized). That is why Klimontovich [19] suggested comparing the relative degree of order of the two different distributions (states) in such a way that the reference distribution is renormalized to a given energy.

Two 30 min tachograms were compared, one of the two tachograms is set to be the reference state, corresponding to the most disordered frequency distribution of a healthy person's tachogram [28]. To calculate the Shannon entropy from tachograms some pre-processing had to be done (see Fig. 4). At first all ectopic beats in the tachograms were removed by the above described filter algorithm. Then, the tachograms were interpolated and the trend subtracted. After filtering, interpolating and trend removal the power spectra were calculated [38]. From these spectral distributions the power in the interval [0 Hz, 0.4 Hz] was chosen. The algorithm of renormalization originated from thermodynamics and is described in Appendix B. The measure extracted from the difference of entropies is named 're_sar'.

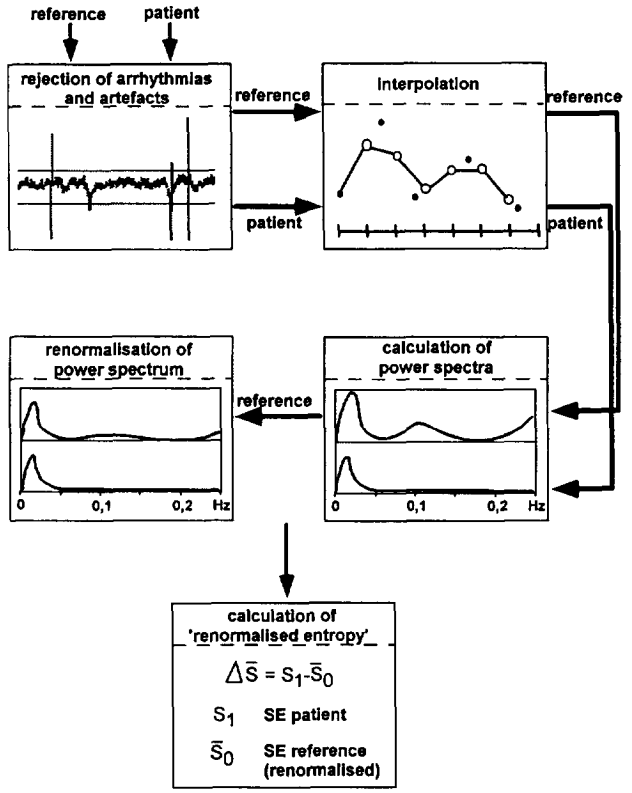

Fig. 4. The method of applied renormalization implies the rejection of arrhythmias and artifacts, the interpolation of the tachograms into equidistant time series, the calculation of power spectra, the renormalization of the reference power spectrum and the calculation of the renormalized entropy.

2.3. Analysis of high resolution ECG

A 30 min 4 channel high resolution ECG (Frank leads and an additional diagonal lead) with a sampling frequency of 2000 Hz and 16 bit resolution was recorded from all patients in a condition of rest. The software QRS detection algorithm was based on the usual applied cross correlation techniques. The Simson method [31] was used to calculate the sum vector magnitude from the three highly amplified and filtered (digital high pass filter, Butterworth characteristics 40 Hz) leads X, Y and Z. In the time domain the parameters 'rms40', 'rms50' (RMS-voltage of the last 40/50 ms of QRS), 'QRS-duration' and 'las40' (interval length beginning at the first point of the final part of QRS where the voltage has just fallen below 40 μV up to the end of QRS) were extracted from that vector.

For every single lead the power spectrum (on the basis of the periodogram and the MES) has been calculated. To reject the influence of residual noise the variance subtraction method was applied, which is described in detail in Voss et al. [33,37]. The starting point of the time window with 100 ms length had been fixed at that time instant

Table 1
Investigated patient groups

Group	Type	n	EF [%]	Age	Gender	
					Female	Male
1	(healthy)	35	—	40.0 ± 15.8	7	28
	subgroup age-matched	12	—	58.8 ± 7.5	1	11
2	(MI, without VT)	10	50.4 ± 10.7	61.6 ± 5.2	0	10
3	(MI, with SUSVT)	16	50.9 ± 15.4	59.1 ± 8.4	2	14

EF, ejection fraction; MI, myocardial infarction; VT, ventricular tachycardia; SUSVT, sustained ventricular tachycardia.

within the final QRS where the signal amplitude had just fallen below 40 μV. From that point the analysis window was shifted into the ST-segment. The area under the power spectrum above 80 Hz 'sarea80fft', 'sarea80mes', the number of peaks above 80 Hz 'snbpeakfft' and 'snbpeakmes' were estimated to differentiate between normal and pathological spectra.

2.4. Patients (high risk stratification)

In the pilot investigation 61 patients were divided into 3 groups (see Table 1). The control group (group 1) consisted of 35 healthy persons. In this control group there was one subgroup (12 persons, age of 58.8 ± 7.5) for an age-related match. In the second group there were 10 patients after MI with a low electrical risk (no spontaneous ventricular tachycardia or fibrillation). Group 3 represents those 16 cardiac patients after MI who have documented life-threatening ventricular arrhythmias (i.e., sustained ventricular tachycardia 'SUSVT'); 10 of them are survivors of a SCD and therefore receive automatic cardioverters/defibrillators.

Group 2 and 3 consisted of patients who had had a MI more than 3 months earlier. None of the patients were medicated (considering the specific half-life) during the ECG recording. The mean age was similar, as well as the ejection fraction (EF). Therefore, groups 2 and 3 differed mainly in the degree of electrical risk.

2.5. Statistics

2.5.1. Counting method for HRV analysis

In a first statistical trial for HRV analysis we calculated parameter limits from the control group (minimum-maximum method). Then we compared all parameter sets of the patient groups with these limits. For every value outside the limits interval, simply one point was summed. The total number of points was used to discriminate between the control group and the high risk group, as well as to determine the degree of abnormality.

2.5.2. Counting method for HRV and HRECG analysis

Similar to the counting method described above, for every value outside a limit one point was summed. For the HRECG analysis in the time domain, the limits suggested by the Task Force Committee [10] were used. For the frequency domain we calculated limits as 95% intervals to reach a maximal discrimination between control group and high risk group. The total number of points from HRV and HRECG analysis was used to discriminate between the control group and the high risk group and to determine the degree of abnormality.

2.5.3. Discrimination function

Linear discriminant analysis is a statistical method to separate grouped objects. If a certain set of parameter values is given for each of the objects, a linear function of these variables is determined, the discriminant function. This function is calculated from a learning sample, that means from a set of objects with known group membership. A new object then can be classified in one of the categories with the help of its discriminant function value.

The main purpose of the statistical analysis was to find an optimal linear discrimination function between the parameters of a high risk group and an age-matched group of healthy persons derived from HRV analysis. We have applied this discrimination function to the group 2 parameter sets. In this way, one may classify the group 2 patients into clusters with almost the same characteristics.

In general, it is possible to use all 46 parameters calculated in this study for the discrimination analysis. This method will lead to an overestimation of some of the properties because of partly redundant parameters which cause numerical inaccuracies in the results due to the large number of variables. In practice, it may be rather expensive to calculate all these 46 values for each patient.

Therefore we tried to find a subset which would be able to discriminate the two groups without any misclassifications. There are different methods of variable selection.

The first way to reduce the number of parameters is to remove those that are particularly similar to others. The statistical method used was the hierarchical cluster analysis. This method identifies homogenous groups or clusters of objects based on their values. A second approach to variable selection is the use of stepwise methods in which parameters are sequentially entered and removed from the discrimination function based on specified criteria. For instance, the variable that minimizes the sum of the remaining unexplained variance for both of the groups is added at a certain stage. We executed this method with the help of the SPSS System.

The SPSS System also offers the possibility to use all variables simultaneously to discriminate between the groups. A tolerance test was performed before the discrimination analysis to minimize the influence of linear dependence of the parameter values. However, this tolerance test depends on the order of the parameters. We executed the SPSS procedure in the standard parametric order (that means an input in the order: time domain parameters, frequency domain parameters and parameters from NLD).

3. Results

This study examines the ability of methods from NLD to find a unique pattern in HRV time series that cannot be detected by traditional time and frequency domain parameters due to their non-linear sources. In this way, we introduced two new methods: symbolic dynamics and renormalized entropy.

The results from symbolic dynamics of the distributions of words of length 3 of a healthy person and of a patient can be seen in Fig. 5. The word distribution of a healthy person contains many different types of words, a characteristic of a normal HRV. The number of different kinds of words occurring represents high dynamics in the time series. The word distribution of a cardiac patient contains mostly eight different types of words. These are the words which consist only of the symbols '0' and '2' (e.g. the length 3 word '202') and describe only small differences in successive RR intervals. This pattern was typical for patients with decreased HRV. We emphasized two parameters that were suitable measures for the investigation of the dynamics in the time series. Both parameters indicated a strongly reduced HRV and a rapidly increased HRV (atrial fibrillation). The first effective criterion for the distinction of the patient and the healthy group was the parameter 'forbidden words'. In patients with high risk there are often more than 44 forbidden words. The second criterion was the Renyi entropy of order 0.25. A value of 'Renyi025' less than 3.6 best discriminated between the control group and the group 3 patients. To identify transient (and short) phases with reduced or increased variability we introduced the measures 'plvar5', 'plvar10', 'plvar20', as well as 'phvar20', 'phvar50' and 'phvar100'. These transients often cannot be detected by time or frequency domain parameters.

The calculation of renormalized entropy was based on the frequency components (0.0 to 0.4 Hz) in the power spectrum. By means of a special interchanging algorithm [38], the healthy person with the most disordered spectral distribution (the highest peak in the 'VLF'-band) has been calculated. This distribution was the reference for all further investigations. The choice of the reference state is very important for the classification of HRV time series. Fig. 6 shows the results of renormalization, if we compare

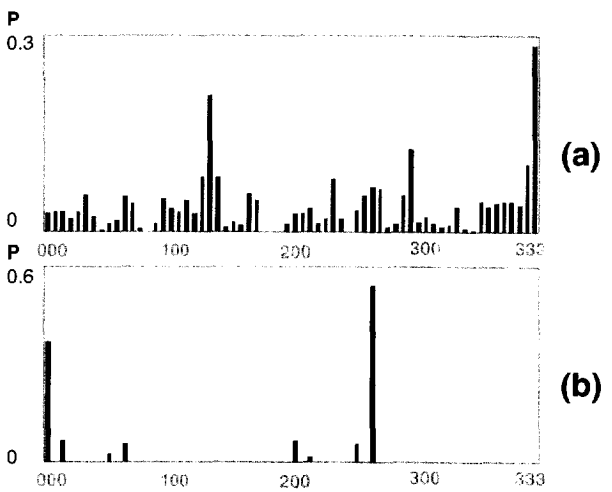

Fig. 5. The distributions of length 3 words formed from the alphabet {0, 1, 2, 3} according to the definition of symbols given in Fig. 3 from a healthy person (a) and from a sick person (b).

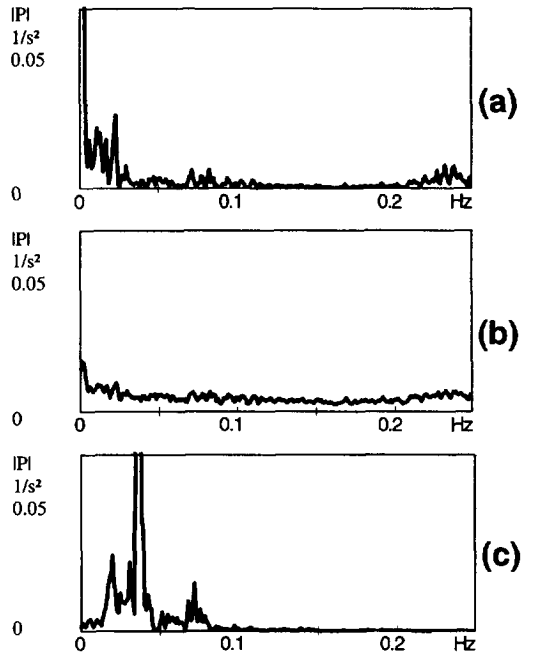

Fig. 6. The power spectrum distributions of the reference tachogram (a), of the renormalized reference tachogram (b) and of the patient tachogram (c).

this reference with a cardiac high risk patient. The reference distribution was in this case renormalized to a drastically changed distribution. If a healthy person was compared with the reference, then the renormalization caused only small changes in the spectral distribution. Healthy persons and groups with lower HRV and pathologically increased HRV could clearly be differentiated with the aid of the renormalized entropy.

To assess the reliability of NLD methods, we compared them with methods from the time and frequency domains. First, we applied simple counting statistics. The detection rate of the high risk patient differs considerably in the time domain, the frequency domain, and non-linear dynamics. The parameters of the frequency domain and NLD lead to a highly comparable positive result (69% and 75% respectively). The time domain parameters, however, show a rather low recognition of high risk patients (43%). The analysis of HRV produces no false positive result in the group of healthy persons. Combining the results of HRV analysis from frequency domain and from NLD increases the number of detected high risk patients to 88%. At the same time the number of pathological cases also increases in group 2 (from 30% to 50%).

The results of HRECG analysis (detected high risk patients) are in group 1; four of all 22 healthy persons (18%) show abnormalities either in time or in frequency domain parameters. In 12 of 16 (75%) patients in the high risk group (group 3) pathological changes were detected. This confirms various other studies where false positive results in healthy persons and in athletes had been reported. In addition, 50% of patients in group 2 have been

classified pathologically as well, due partly to false positive classification.

If we combine the results of HRECG and HRV analysis, the detection rate in group 2 decreases remarkably to 20% without changing the number of high risk candidates classified in group 3 (88%). No further abnormalities in the healthy group were found.

Then we applied advanced statistics based on discrimination functions to assess the reliability of HRV analysis methods from NLD. First the hierarchical cluster analysis was executed with SPSS. The distance measure we used was the squared Euclidean measure. All parameters had to be standardized before the analysis. The following clusters were created: {'shannon', '*renyi025*', 'renyi2', 'renyi4'}; {'cvNN', 'sdNN', '*sdaNN1*', 'sdaNN5', 'sdaNN10', 'wsdvar'}; {'fwshannon', '*fwrenyi025*'}; {'*sum*', 'wpsum13'}; {'pNN100', 'HF', '*rmssd*'}; {'*pNN50*', 'phvar20'}; {'pNN200', '*phvar50*', 'phvar100'}; {'*pNNl10*', 'plvar20'} and {'*pNNl20*', 'pNNl30'}.

The remaining 20 other parameters had no matched common clusters.

We chose one element from each cluster for the discrimination analysis (in italics). Three parameters failed a tolerance test performed by SPSS ('pNNl50', '(ULF + VLF + LF)/P' and '(ULF + VLF)/P'). Further analysis resulted in the fact that 'pNNl10', 'plvar5' and 'meanNN' could be ejected without loss of the complete separation. Thus it was possible to decrease the number of parameters to 23. The created subset was sufficient to discriminate the 35 healthy persons from the 16 high risk patients without any misclassification.

The 23 elements in this subset are 6 time domain measures (of 19), 10 frequency domain measures (of 13) and 7 NLD measures (of 14).

The second approach to variable selection was the use of stepwise methods, in which parameters were sequentially entered and removed from the discrimination function based on specified criteria. For example, the variable that minimizes the sum of the remaining unexplained variance for both of the groups was added at a certain stage. Again we executed this method with the help of the SPSS system. Applying stepwise methods of discrimination function calculation a subset of 19 parameters was created which separated healthy persons from high risk patients. The composition of this subset was as follows: 6 time domain measures ('sdNN', 'sdaNN1', 'pNN100', 'pNN30', 'renyi4', 'renyi2'); 7 frequency domain measures ('ULF', 'VLF', 'LF', 'LF/HF', 'LF/S', 'HF/S', 'ULF + VLF + LF)/P') and 6 NLD measures ('forbidden words', 'fwrenyi025', 'phvar20', 'phvar50', 'wpsum02', 're_sar').

The SPSS statistical software system explained above also offered the possibility to use all variables simultaneously to discriminate between the groups. A tolerance test was applied before the discrimination analysis and 14 parameters failed the tolerance test, so that only 32 variables were used in the analysis.

The results of the discrimination function analysis for different subsets of parameters are given in Table 2. The values in the group centroids column differentiate the mean values of the discrimination function values for both groups. A smaller value indicates a lesser separation be-

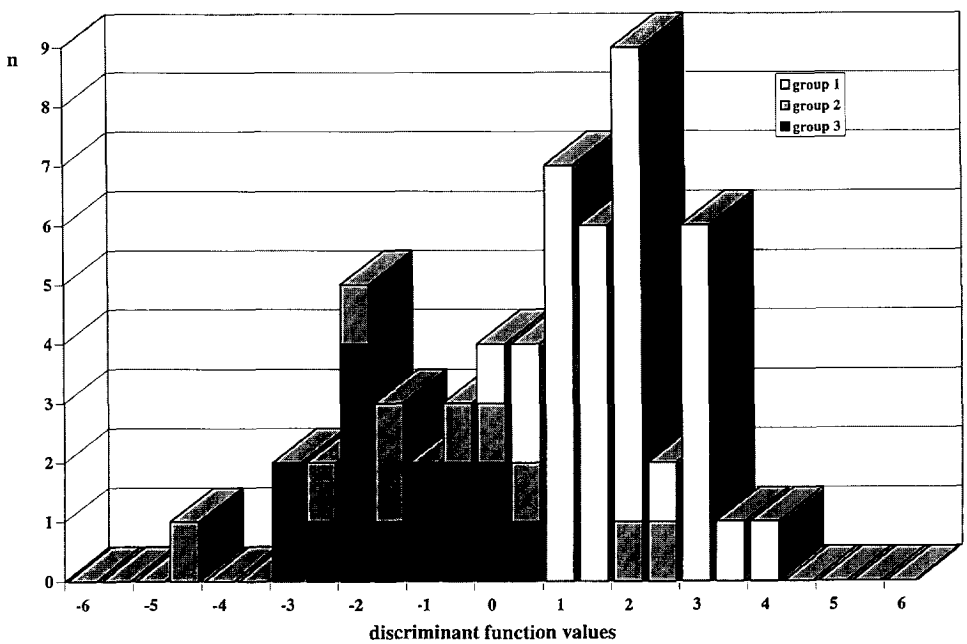

Fig. 7. Results of risk stratification (detection of pathological abnormalities) applying methods of HRV *time domain* analysis on the basis of discriminant function.

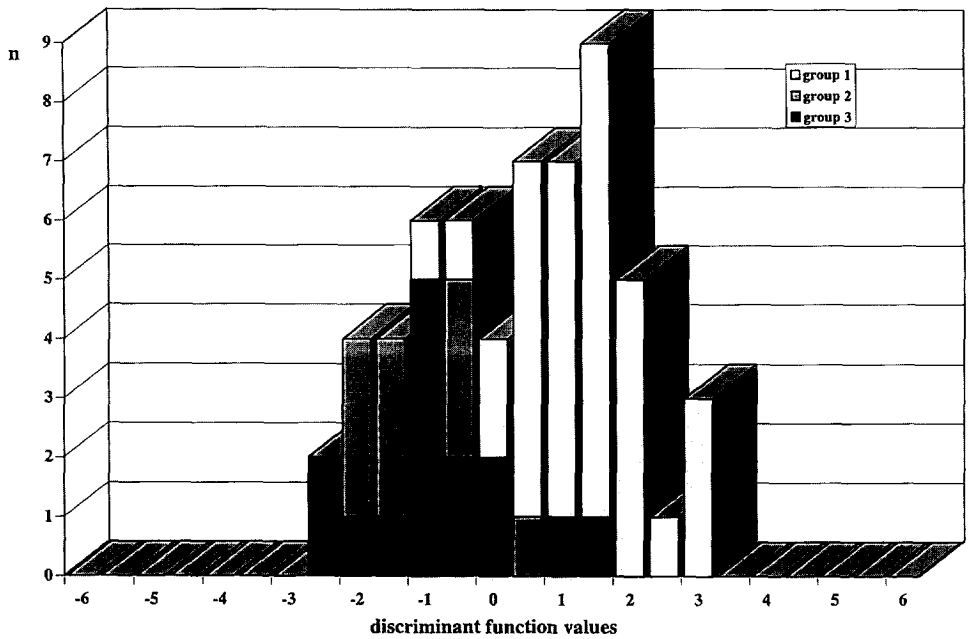

Fig. 8. Results of risk stratification (detection of pathological abnormalities) applying methods of HRV *frequency domain* analysis on the basis of discriminant function.

tween the two groups. This shows that the stepwise method provided the best results with a small number of parameters.

Separate analysis of all three parameter domains proved that none of them could lead to a complete discrimination of the different patient groups. Between the time domain, the frequency domain and non-linear dynamics the detection rate of the high risk patient differs considerably. Fig. 7, Figs. 8 and 9 show, respectively, the results of the time domain, frequency domain or NLD parameters only. While

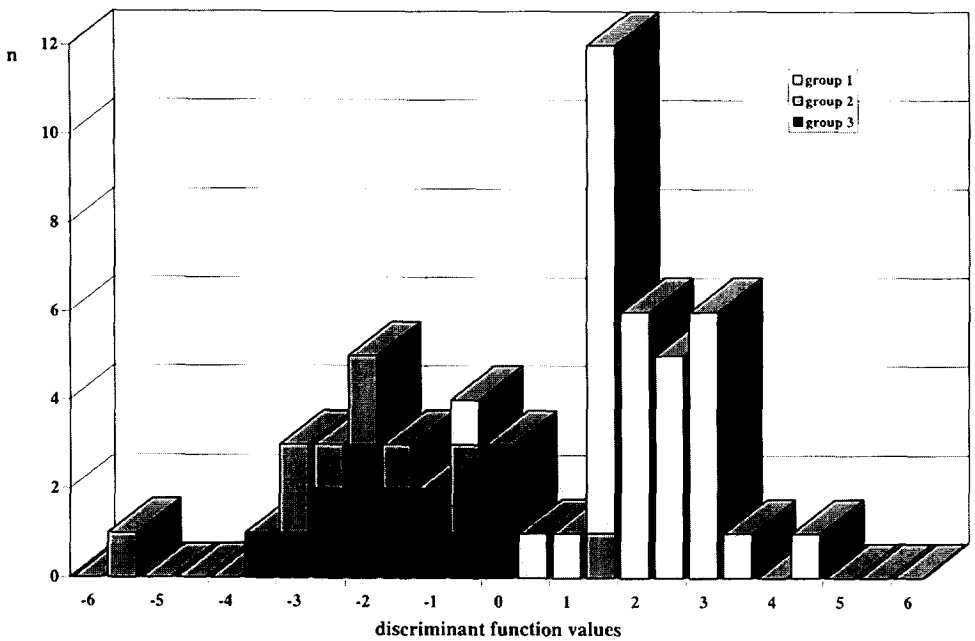

Fig. 9. Results of risk stratification (detection of pathological abnormalities) applying methods of *non-linear dynamics* on HRV analysis on the basis of discriminant function.

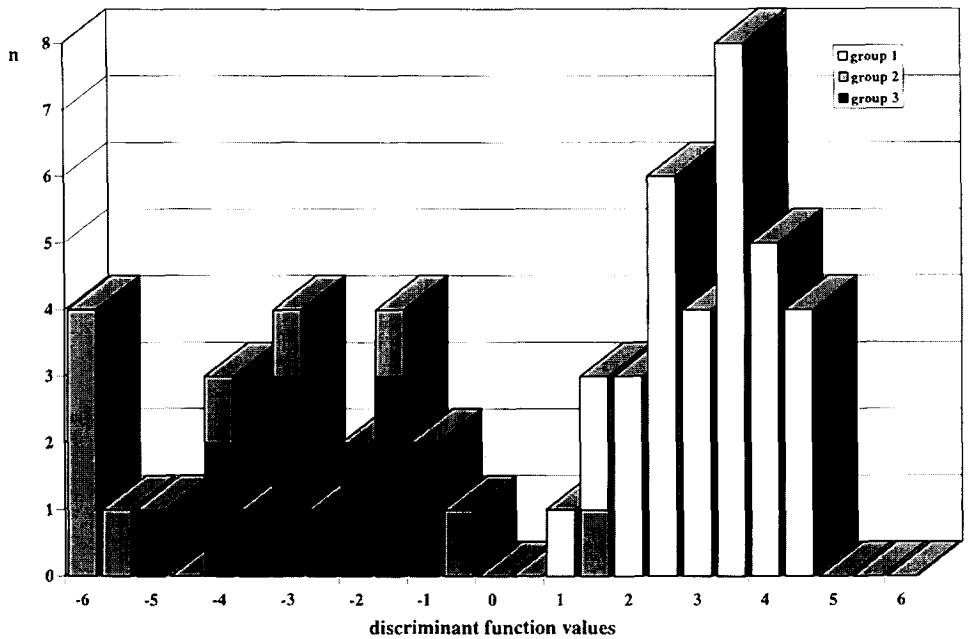

Fig. 10. Results of risk stratification (detection of pathological abnormalities) applying all methods of HRV analysis on the basis of stepwise discriminant function (19 parameters).

the time domain and the frequency domain parameters lead to a misclassification of more than 10%, the measures of NLD failed in only 4% of all patients.

It can be shown that the HRV analysis based on stepwise discrimination analysis and combination of the time domain, the frequency domain, and NLD optimizes the discrimination between the control group and the high risk patients (Fig. 10). With the same discrimination function the sets of group 2 are classified. Three patients of this group exhibit a similar pattern to the high risk patients and one similar to a healthy person. The remaining 6 generate a separate pattern that cannot be assigned to one of the two clusters. The discriminant analyses of the HRECG analysis (see Fig. 11) show more or less the same results as the counting method. A complete discrimination cannot be achieved (misclassification 20%). Finally, the combination of the extracted 19 parameters from the optimized discriminant function of HRV analysis with the parameters of

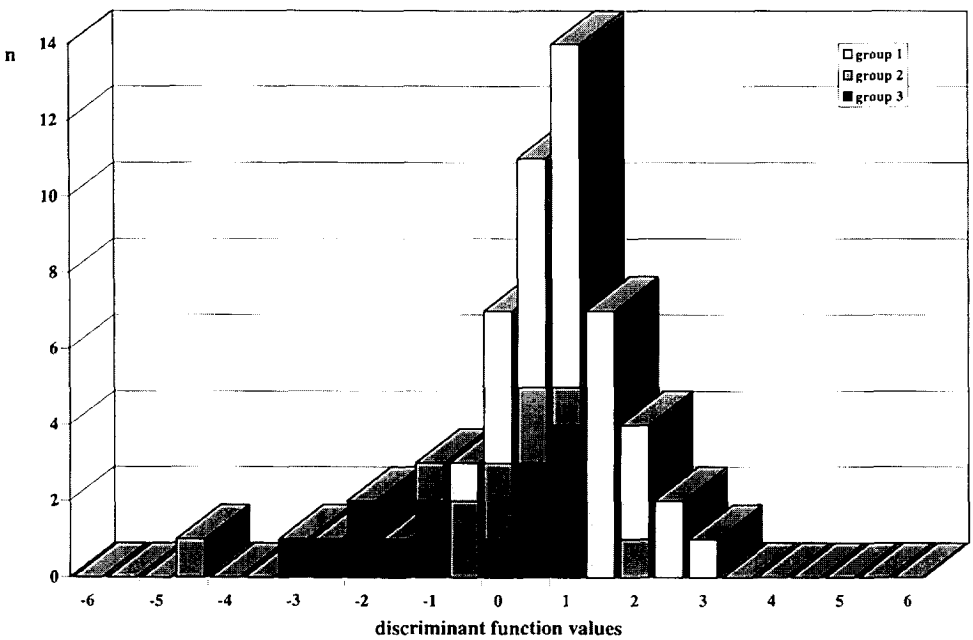

Fig. 11. Results of risk stratification (detection of pathological abnormalities) using different methods (time and frequency domain) of HRECG analysis on the basis of discriminant function.

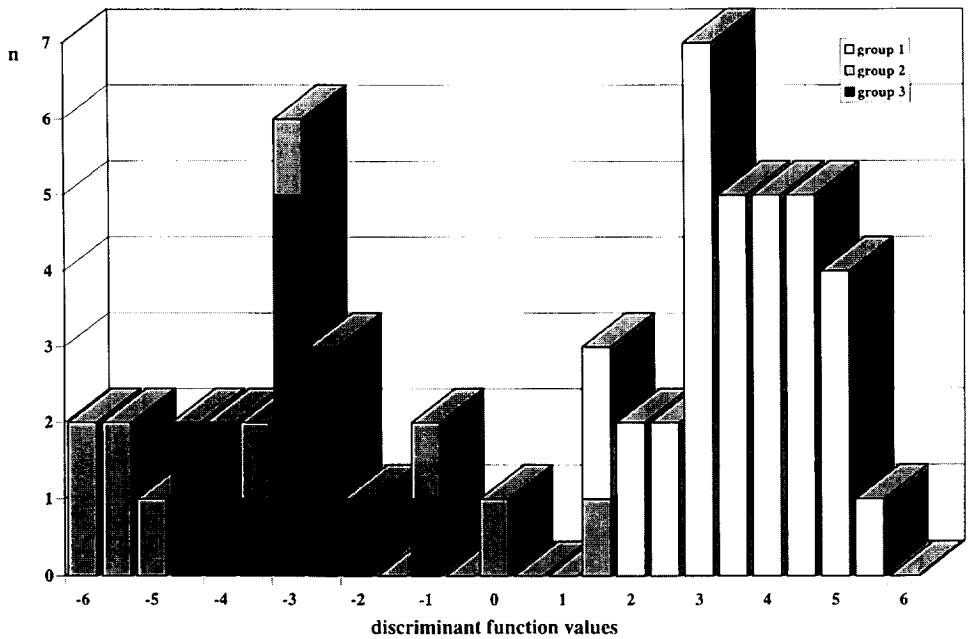

Fig. 12. Results of risk stratification (detection of pathological abnormalities) using the methods of HRV and HRECG analysis on the basis of stepwise discriminant function (24 parameters).

Table 2
Results of different discrimination methods between the control group and group 3 (a higher value represents a better separation)

Parameters included in the discrimination function analysis	Percentage of misclassifications	Distance of group centroids
Cluster analysis (23 parameters)	0.0	4.8179
Stepwise method (19 parameters)	0.0	5.6481
After SPSS tolerance test (32 parameters)	0.0	4.4738

HRECG analysis and repeated stepwise discriminant analyses improve the classification result (Fig. 12). The discriminant function values extend from 5.64 to 6.66, whereas the group classifications did not change.

4. Discussion

The HRV analysis provides, as a non-invasive diagnostic tool, important prognostic information on the individual risk following the survival of an acute infarction, which

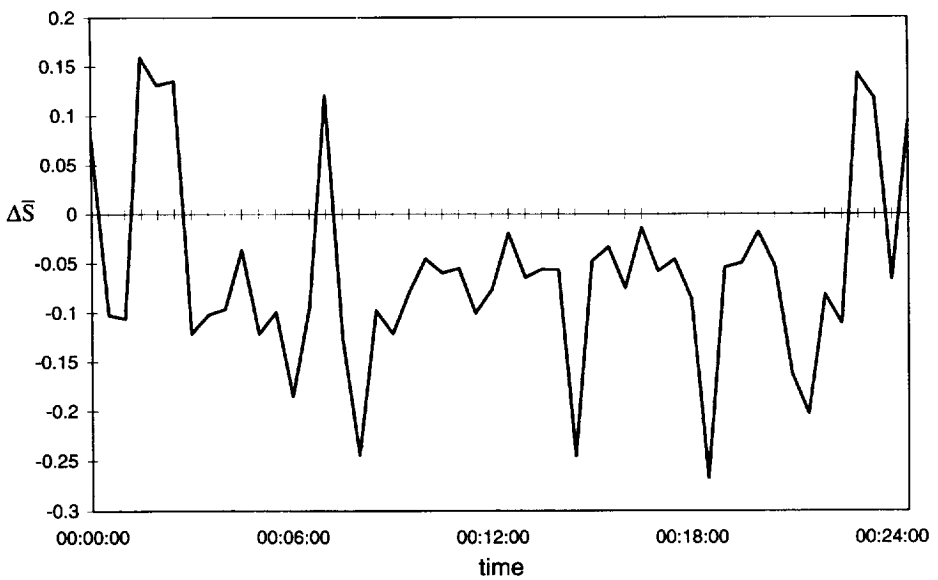

Fig. 13. Renormalized entropy of a healthy person over 24 h (with the exception during some phases of instationarity the value lies below zero).

clearly go well beyond the findings of Holter's classical arrhythmia analysis. The classical methods of the time domain HRV analyses are less accurate in classification of complex rhythm changes. However, the frequency domain measures and especially the introduced methods from NLD are highly accurate for determining the separation of different pathological states.

The method of symbolic dynamics is a useful approach for classifying the dynamics of HRV. By means of this method, the inner motions of the time series can be investigated. Parameters of the time and the frequency domain often leave these dynamics out of consideration. The optimized definition and number of symbols have to be validated on a more representative number of patients. It is necessary to check which symbol definition best describes the dynamics inherent in the time series. The specific symbol definition has to be adapted by applying symbolic dynamics to patients with atrial fibrillation. In comparison with all other methods of NLD for HRV analysis, symbolic dynamics is the method with the closest connection to physiological phenomena and is relatively easy to interpret.

The renormalized entropy, as a measure of relative degree of order, is a further suitable method for the detection of high risk patients threatened by SCD. A fundamental precondition is the choice of reference spectral distribution. For this reason, a more general strategy of reference selection should be found. Applying this method to 24 h Holter ECG's, one has to find stationary periods (i.e. during the night) in the time series. The influence of instationarities can theoretically lead to contradictory results. In our first results from the 24 h Holter analysis the global characteristics of the renormalized entropy in controls and in high risk patients were surprisingly stable (Figs. 13 and 14). Furthermore, it should be important to investigate the influence of errors caused by interpolations and normalization of the spectra. A model based on a spectral estimation procedure, such as autoregressive model, is probably more suitable for HRV analysis because of the lesser sensitivity to instationarities. An interesting aspect is the development of procedures of renormalized entropy with high order autoregressive models, independent of the influence of instationarities.

By applying discrimination functions with parameter reduction one achieves the best discrimination between patient groups with a minimum number of parameters. Because of the small number of patients the training set was also used for the final dicriminant function analysis.

A more or less multi-domain parameter selection best discriminates between normal and abnormal patterns. The parameters 'sdNN', 'sdaNN1', 'pNN30', 'phvar20' describe a reduced HRV. 'pNN100' and 'phvar50' are measures of a high HRV. 'renyi4' and 'renyi2' describe the morphology of the histogram. 'ULF', 'VLF', 'LF', 'LF/HF', 'LF/S', 'HF/S', 'ULF + VLF + LF)/P' include periodical processes influenced by the autonomic regulation. 'forbidden words', 'fwrenyi025', 'wpsum02', and 're_sar' classify the degree of complexity in the heart rate time series. In this way, each of the parameter sets represents a special characteristic of the heart beat generation and probably an underlying physiological process. At this time we do not know which special process or which process combination it is, but we do know that it is not noise and not random. Therefore, more basic research is necessary to improve our knowledge of these physiological phenomena.

The primary results of this study show the effectiveness of NLD methods in the analysis of heart rate variability. They also show the advantage of combination with other HRV methods from the time and the frequency domains

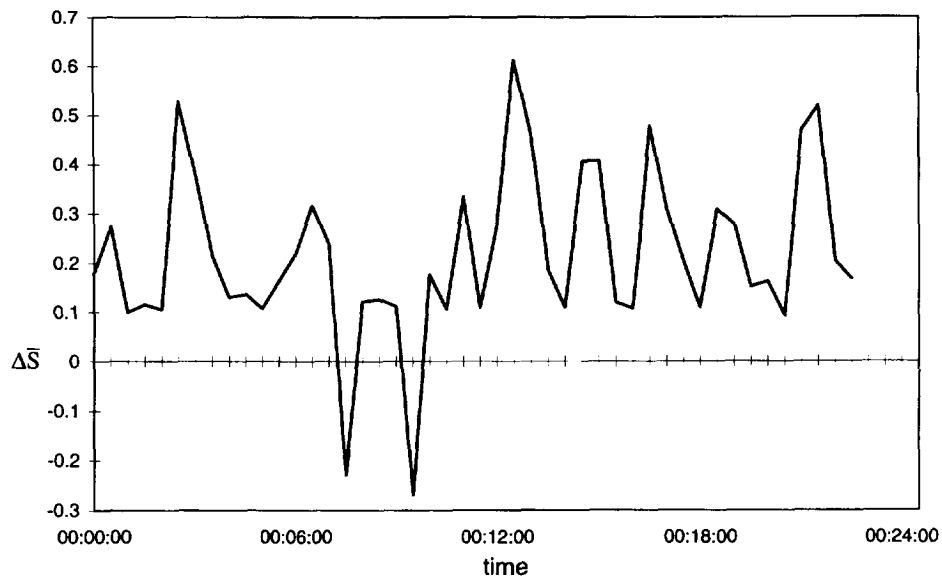

Fig. 14. Renormalized entropy of a cardiac patient from group 3 over 24 h (the value falls below zero only in two short periods of heavy instationarities).

and HRECG analysis to improve the precision of a high risk stratification. Finally they show the advantages of combining all HRV methods (NLD, time domain, frequency domain) with HRECG analysis in improving the precision of high risk stratification. These first positive results seem to confirm our hypothesis.

Due to the small number of subjects, these results need to be confirmed by a larger and especially a prospective clinical investigation. In addition we have to validate the results of the statistical discrimination with a separate training set.

It is interesting to note that one of the patients in group 2, who was classified by discrimination function into group 3 cluster, has already developed a ventricular tachycardia during the follow-up.

Acknowledgements

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Appendix A. Renyi and Shannon entropies

The Shannon entropy is the classical measure of information theory. It extracts the information contents of a symbol sequence. The Shannon entropy of order k is defined on the basis of the probability distribution p of length k words:

$$H_k = -\sum_{\omega \in W^k, p(\omega)>0} p(\omega) \log p(\omega)$$

where W^k denotes the set of all words of length k words.

The concept of Renyi entropy was introduced [27] as a generalization of Shannon's Ansatz:

$$H_k^{(q)} = \frac{1}{1-q} \log\left(\sum_{\omega \in W^k, p(\omega)>0} p(\omega)^{(q)} \right)$$

where q is a real number and $q \neq 1$.

This parameter q determines the manner in which the probabilities are weighted: if $q > 1$ those words of length k with large probabilities dominantly influence the Renyi entropy. This behavior is strengthened for large q-values. Vice versa, if $0 < q$ then words with small probabilities mainly determine the value of $H_k^{(q)}$. In this application we have taken both cases into account using $q = 0.25$ and $q = 4$.

Some basic properties of both measures are

(a) $H_k^{(q)}$ decreases with growing q.

(b) $H_k^{(q)}$ converges to H_k as $q \to 1$.

(c) In case of a periodic sequence with prime period m, $m < k$ one gets $H_k^{(q)} = \log m$.

(d) If the behavior of the sequence is such as white noise, i.e. completely uncorrelated, then these measures get their maximum values $H_k^{(q)} = H_k = k \log |A|$ and $|A|$ denotes the number of symbols used.

The calculation of H_k and $H_k^{(q)}$ for large k leads to some difficulties due to finite sequence lengths. Here, we only calculate these information measures for small values of k ($k = 1,2,3$), since the underlying word distribution can be reliably estimated.

Appendix B. Renormalized entropy

Provided that two sufficiently long realizations $x(t,a_0)$ (reference) and $x(t,a_0 + \Delta a)$ of a dynamic system $x'(t) = f(x(t,a))$ are given, with t for time and a for a control parameter (Δa denotes a small change of the control). From these time series the corresponding density distribution estimates $f_0(x) = f_0(x,a_0)$ and respectively $f_1(x) = f_1(x,a_0 + \Delta a)$ are calculated.

We are not able to compare in a direct way the Shannon entropies of two different systems states because their energies can differ considerably. In order to make these states comparable, Klimontovich suggested comparing the relative degree of order of the two different distributions (states) in such a way that the reference distribution is renormalized to a given energy.

From reference state '0' the so called *Hamilton function* $H_{\text{eff}}(x)$ of the system is calculated:

$$H_{\text{eff}}(x) := -\ln f_0(x). \tag{1}$$

We now renormalize the distribution $f_0(x)$ to a given value of $|H_{\text{eff}}(x)|$ in the following way: by definition the state '0' corresponds to the effective temperature $T_{\text{eff}} = 1$. The renormalized density $\tilde{f}_0(x)$ of $f_0(x)$ which corresponds to another effective temperature $T_{\text{eff}}(a_0 + \Delta a)$ is represented by:

$$\tilde{f}_0(x) = e^{\frac{\Phi(T_{\text{eff}}(a_0+\Delta a)) - H_{\text{eff}}(x)}{T_{\text{eff}}(a_0+\Delta a)}}, \tag{2}$$

where $\Phi(T_{\text{eff}}(a_0 + \Delta a))$ is the free effective energy and $T_{\text{eff}}(a_0 + \Delta a)$ the effective temperature. Equation (2) can be rewritten as

$$\tilde{f}_0(x) = C(T_{\text{eff}}(a_0 + \Delta a)) \cdot e^{-\frac{H_{\text{eff}}(x)}{T_{\text{eff}}(a_0+\Delta a)}}. \tag{3}$$

This equation involves two unknowns:

$$C(T_{\text{eff}}(a_0 + \Delta a)) \text{ and } T_{\text{eff}}(a_0 + \Delta a).$$

Since $\tilde{f}_0(x)$ is a distribution density, the integral of $\tilde{f}_0(x)$ with respect to x must be 1. That is why one gets from equation (3)

$$C(T_{\text{eff}}(a_0 + \Delta a)) = \frac{1}{\int e^{-\frac{H_{\text{eff}}(x)}{T_{\text{eff}}(a_0+\Delta a)}} dx}. \tag{4}$$

We get the effective temperature $T_{\text{eff}}(a_0 + \Delta a)$ from the additional condition that the mean effective energies of the two states are equal:

$$\int H_{\text{eff}}(x,a_0) \cdot \tilde{f}_0(x)\,\mathrm{d}x = \int H_{\text{eff}}(x,a_0) \cdot f_1(x)\,\mathrm{d}x. \quad (5)$$

The renormalized entropy is calculated in the following way

$$\Delta\bar{S} = S_1 - \bar{S}_0, \quad (6)$$

where $\bar{S}_0$ is the Shannon entropy of the renormalized reference state and S_1 is the Shannon entropy of the other state (patient).

The test for pathological or normal through the difference from the entropies of the frequency distribution can then take place [21,34,36,38].

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