Evaluation of renormalised entropy for risk stratification using heart rate variability data

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Abstract—*Standard time and frequency parameters of heart rate variability (HRV) describe only linear and periodic behaviour, whereas more complex relationships cannot be recognised. A method that may be capable of assessing more complex properties is the non-linear measure of 'renormalised entropy.' A new concept of the method, RE_{AR}, has been developed, based on a non-linear renormalisation of autoregressive spectral distributions. To test the hypothesis that renormalised entropy may improve the result of high-risk stratification after myocardial infarction, it is applied to a clinical pilot study (41 subjects) and to prospective data of the St George's Hospital post-infarction database (572 patients). The study shows that the new RE_{AR} method is more reproducible and more stable in time than a previously introduced method ($p < 0.001$). Moreover, the results of the study confirm the hypothesis that on average, the survivors have negative values of RE_{AR} (-0.11 ± 0.18), whereas the non-survivors have positive values (0.03 ± 0.22, $p < 0.01$). Further, the study shows that the combination of an HRV triangular index and RE_{AR} leads to a better prediction of sudden arrhythmic death than standard measurements of HRV. In summary, the new RE_{AR} method is an independent measure in HRV analysis that may be suitable for risk stratification in patients after myocardial infarction.*

Keywords—*Heart rate variability, Renormalised entropy, Risk stratification*

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1 Introduction

STANDARD TIME and frequency parameters of heart rate variability (HRV) only describe linear and periodic behaviour, whereas more complex relationships and interactions are not addressed. At the same time, modulation of sinus rhythm involves many non-linear elements. Thus it is not realistic to restrict HRV analysis only to linear methods. The application of non-linear methods in addition to the traditional ones seems to be promising in this respect (GOLDBERGER *et al*., 1988; VOSS *et al*., 1993; 1996; 1998; KURTHS *et al*., 1995; SCHREIBER, 1997; MAKIKALLIO *et al*., 1997; SCHÄFER *et al*., 1998; WESSEL *et al*., 2000). Nevertheless, many non-linear methods require rather long, stationary time series and are not easily applicable to the data of cardiac periods. However, non-stationarities may play an important role in arrhythmogenesis. Thus, HRV analysis should not be restricted to stationary epochs.

A method that may be capable of assessing more complex properties of cardiac periodograms is the non-linear measure of 'renormalised entropy'. The basic idea is to determine the complexity of cardiac periodograms based on a fixed reference. Based on general considerations in thermodynamics, KLIMONTOVICH (1991) suggested comparing the relative degree of order of two different distributions by renormalising the reference distribution to a given energy. SAPARIN *et al*. (1994) proposed a procedure for calculating this quantity from time series and applied it to the logistic map. They showed that the renormalised entropy allows the degree of order to be compared, not only between chaotic and periodic series, but also between different periodic and chaotic regimes. KOPITZKI *et al*. (1998) applied this method to the data of invasive electroencephalograph recordings. Their results suggested that renormalised entropy may be a useful procedure for clinical applications in this field, such as seizure detection and localisation of epileptic foci.

Applications of renormalised entropy to heart rate data based on the fast fourier transform (FFT) have been introduced previously (VOSS *et al*., 1993; 1996; WESSEL *et al*., 1994; KURTHS *et al*., 1995). However, this method suffers from a potential lack of reproducibility and time instability. To overcome these limitations, a new method was developed for the computation of renormalised entropy RE_{AR}, based on an autoregressive spectral estimation.

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In this study, we investigate the ability of the new RE_{AR} method to discriminate between different degrees of order in spectral distribution and the possibility of improving the risk stratification of patients surviving acute myocardial infarction.

2 Methods

2.1 *Concepts of renormalised entropy*

To compare the relative degree of order of two different distributions, the reference distribution is renormalised to a given energy. The complexity of any distribution in relation to a fixed reference distribution is estimated by solving an integral equation. Considering two tachograms (time series of beat-to-beat intervals) with the density distribution estimates $f_0(x)$ and $f_1(x)$ and using the estimate $f_0(x)$ as a reference, the renormalised density distribution $\bar{f}_0(x)$ of $f_0(x)$ is defined as

$$\bar{f}_0(x) := \frac{f_0(x)^T}{\int f_0(x)^T dx} \tag{1}$$

where T is the solution of the integral equation

$$\int \ln f_0(x)^{\left(\bar{f}_0(x)-f_1(x)\right)} dx = 0 \tag{2}$$

which is equivalent to

$$\int \bar{f}_0(x) \cdot \ln f_0(x)\, dx = \int f_1(x) \cdot \ln f_0(x)\, dx \tag{3}$$

The solution of eqn 2 or eqn 3 has to be found numerically.

The renormalised entropy (RE) of the distribution $f_1(x)$ is defined by the following interchanging algorithm. $S(f(x))$ is the Shannon entropy of distribution $f(x)$, that is

$$S(f(x)) = -\int f(x) \cdot \ln f(x)\, dx \tag{4}$$

Procedure:

(i) Calculate $\Delta_1 = S(f_0(x)) - S(\bar{f}_0(x))$, with the distribution $f_0(x)$ as the reference ($f_0(x)$ is renormalised). The value of T is noted $T_1 = T$.

(ii) Calculate $\Delta_2 = S(f_0(x)) - S(\bar{f}_1(x))$, with the distribution $f_1(x)$ as the reference ($f_1(x)$ is renormalised). The resulting T value is noted $T_2 = T$.

(iii) If $T_1 > T_2$, the distribution $f_0(x)$ is found to be the more disordered one (in the sense of renormalised entropy), and the renormalised entropy RE is defined as $RE = \Delta_1$. Otherwise ($T_1 < T_2$) $f_1(x)$ is the more disordered distribution (in the sense of renormalised entropy), and the $RE = -\Delta_2$.

2.2 *New RE_{AR} method*

Calculation of the renormalised entropy requires us to estimate the tachogram distributions. The previous approach, RE_{FFT} (WESSEL *et al.*, 1994), was based on FFT spectral estimation.

$$P_{FFT}(f) := \frac{1}{M \cdot \Delta t} \left| \Delta t \cdot \sum_{n=0}^{M-1} x_n \cdot \exp(-i \cdot 2 \cdot \pi \cdot f \cdot n \cdot \Delta t) \right|^2 \tag{5}$$

This method used the spectral distribution as the basis for further calculations. The estimation of a 30 min tachogram distribution was obtained as follows: from a filtered and interpolated ($\Delta t = 0.5$ s) tachogram, the spectrum of eight shifted windows of 2048 samples was estimated and averaged. The Blackman–Harris window function was applied to avoid the so-called 'leakage' effect. The non-zero part of the spectral density was the basis for the calculation of renormalised entropy.

The new algorithm for renormalised entropy, the RE_{AR} calculation, is based on autoregressive spectral estimation of a filtered and interpolated tachogram. The spectrum is estimated using an autoregressive model

$$X_t = \sum_{s=1}^{M} a_s X_{t-s} + Z_t \tag{6}$$

in which the order M is determined by a modified residual variance criterion (HAYKIN, 1983). For each tachogram, autoregressive coefficients of model order 1–100 are calculated, and the model order is chosen such that the variance $D^2 Z_t$ (see eqn 6) does not change significantly (that is the first index i, for which $\left|D^2 Z_t^{AR(i)} - D^2 Z^{AR(i-1)}\right| < \epsilon$ for a given ϵ, $\epsilon = 5$ used in this study). This modified criterion determines the model order of 30, which approximately corresponds to 15 beat-to-beat intervals ($\Delta t = 0.5$ s). The estimation of the spectral distribution is given by

$$P_{AR}(f) := \frac{a_0}{\left| 1 - \sum_{k=1}^{M} a_k \cdot (\exp(2 \cdot \pi \cdot i \cdot f \cdot \Delta t))^k \right|^2} \tag{7}$$

A known problem of autoregressive spectral estimations is the bias that can appear even in idealised circumstances. To overcome this problem, a sinusoidal oscillation with a fixed amplitude and frequency was added to the time series (VOSS *et al.*, 1992). The amplitude of 40 ms was chosen to obtain a dominant peak in the spectral estimation, and the frequency was set to 0.4 Hz, which is the upper limit of the high frequency band (TASK FORCE, 1996).

For the calculation of renormalised entropy, a spectral density estimation in the interval [0,0.42] Hz was used to include all physiological modulations as well as the calibration peak.

Calculation of the renormalised entropy RE_{AR} of a tachogram T based on a reference tachogram T_{REF} includes the rejection of arrhythmias and artefacts, the interpolation of the filtered tachogram and computation of normalised autoregressive spectral estimations $P(T)$ and $P(T_{REF})$, as well as the computation of renormalised entropy following the interchanging algorithm as in Section 2.1 ($f_0(x) = P(T_{REF})$ as the reference, $f_1(x) = P(T)$).

Using a reference tachogram from a healthy subject, with normal low- and high-frequency modulations, the RE_{AR} method is designed so that either a decreased HRV or a pathological spectrum leads to positive values of renormalised entropy.

2.3 *Length of time series and filter algorithms*

Both methods for the calculation of renormalised entropy require filtered time series free of noise and arrhythmic events. Consequently, the effects of three different filtering algorithms on both methods were studied. Further, to assess time stability and reproducibility, the effect of the length of time series was investigated. From a tachogram of a healthy person (see Fig. 1*a*), the coefficients of an autoregressive model of the order of 10 (residual variance criteria) were estimated. In a Monte-Carlo experiment, 50 time series were generated using these coefficients. On the basis of these simulated series, the influence of time series length and filtering algorithms on both methods RE_{AR} and RE_{FFT} were studied.

2.3.1 *Influence of length of time series:* The first 30 min of all simulated tachograms were analysed. Using the interchanging algorithm (Section 2.1), the most disordered distribution in the sense of renormalised entropy of all simulated time series was determined as the reference state (reference distribution belonging to the simulated time series, see Fig. 1*b*). Further-

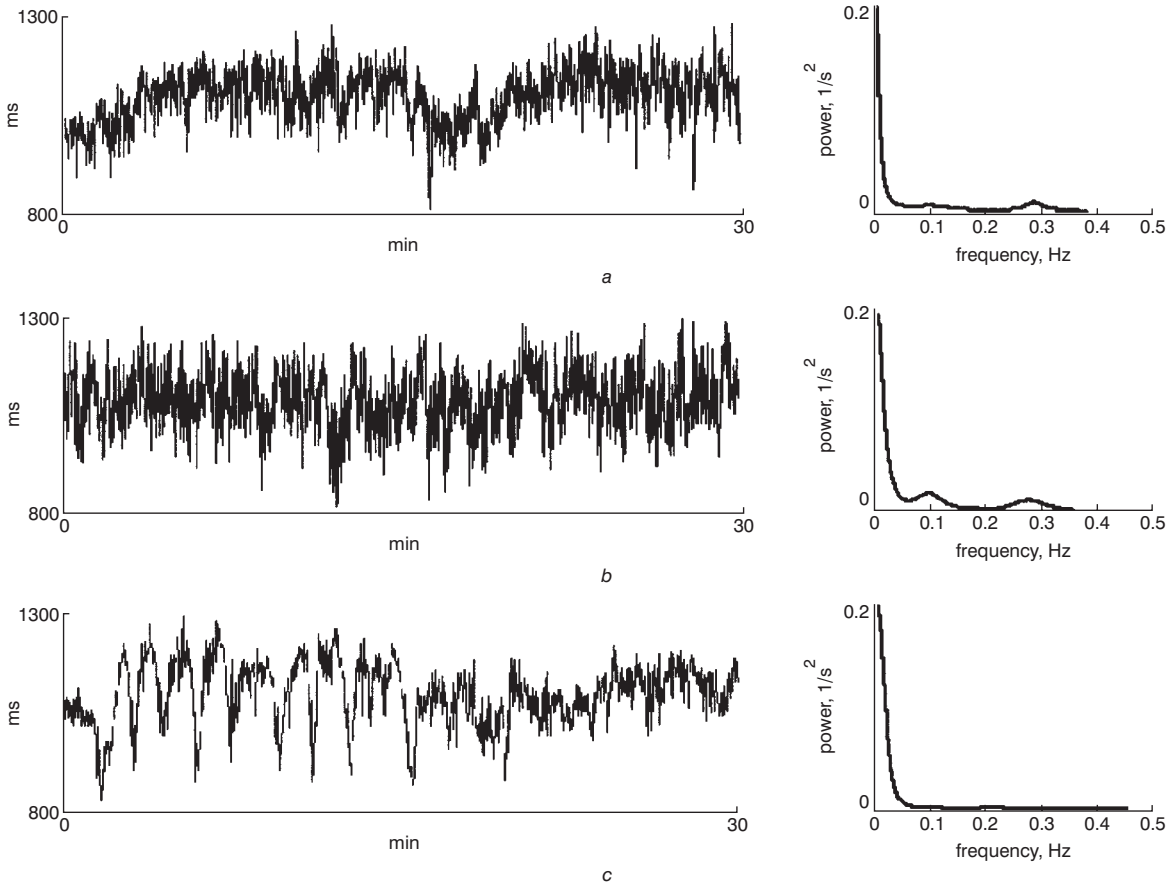

Fig. 1 *Influence of length of time series: tachograms and autoregressive spectral estimations (a) of original tachogram, (b) of most disordered simulated time series and (c) of an extremely disordered physiological time series*

more, the renormalised entropies of all simulated series were calculated using four different lengths of analysis (30, 28, 26 and 20 min). As the simulated series are stationary, their spectra should not change considerably for shorter durations. To compare the sensitivity of all methods, the cumulative error was calculated.

$$\Delta_{cum}(x) = \sum_{i=1}^{50} \left| RE_i(30) - RE_i(x) \right| \tag{8}$$

where $RE_i(x)$ is the renormalised entropy of the ith simulated series based on the analysis of x min.

In addition, an extremely disordered distribution (in the sense of renormalised entropy) was chosen as the reference state (physiological time series, see Fig. 1*c*) to investigate the time stability of both methods based on a more complex reference state.

2.3.2 *Influence of filtering algorithms:* The exclusion of ectopic beats and artefacts is essential for HRV analysis. To estimate the stability of our approach, the effects of three different filtering procedures were analysed based on 50 simulated series. Again, the first 30 min of each time series were analysed. The reference state was the same as described in the preceding Section (physiological time series). The renormalised entropies of all simulated series were calculated after being processed by three filtering methods: The original tachogram is filtered using a binomial-7-filter. Individual values t of the time series are accepted if

$$|t - m| \leq 3.5 \cdot sd \tag{9}$$

where m is the mean of the original tachogram, and sd is the standard deviation of the binomial filtered tachogram. The constant 3.5 was chosen empirically (WESSEL *et al.*, 1994). The three filtering methods differ in their ways of replacing t values that are not accepted, the original value t is

method 1 (F1): replaced by the respective value $\bar{t}$ of the filtered time series
method 2 (F2): replaced by linear interpolation
method 3 (F3): removed.

To compare the filtering methods, a cumulative error was again calculated

$$\Delta_{cum}(x) = \sum_{i=1}^{50} \left| RE_i - RE_i(x) \right| \tag{10}$$

where $RE_i(x)$ is the renormalised entropy of the ith simulated series processed by filter x ($x =$ F1, F2, F3; RE_i without filtering).

The cumulative errors for both methods based on different lengths of analysis and different filtering methods were compared using a two-tailed t-test.

2.4 *Clinical pilot investigation*

The RE_{AR} method was applied to data from 18 cardiac patients and 23 healthy subjects. The cardiac patient group consisted of survivors of myocardial infarction with documented life threatening ventricular arrhythmias, ten of them were survivors of cardiac arrest who had received automatic implantable defibrillators. For every subject, a standard bipolar high-resolution electrocardiogram of 30 min was recorded in supine rest conditions. The beat-to-beat intervals were extracted using a

pattern-matching algorithm based on a cross-correlation technique. From the group of healthy subjects, the most disordered tachogram (in the sense of renormalised entropy) was determined as the reference for each procedure (interchanging algorithm, Section 2.1), and renormalised entropies RE_{FFT} and RE_{AR} were calculated.

2.5 *Validation of RE_{AR} with prospective data*

RE_{AR} and eight time- and frequency-domain parameters were calculated from tachograms of 572 survivors of acute myocardial infarction. All these patients underwent 24 h Holter monitoring before hospital discharge (5–8 days after myocardial infarction) and were followed up for a minimum of two years. During the two-year follow-up, 14 patients succumbed to sudden arrhythmic death (SAD).

Recordings that were too short, as well as tachograms with more than 20% ventricular premature complexes or with atrial fibrillation, were excluded (VOSS *et al.*, 1998). In long-term tachograms, renormalised entropy was calculated as the mean of successive 30 min analyses. The time and frequency-domain parameters of HRV were determined from the filtered 24 h tachogram. The following time domain parameters were used:

(i) *HRVi*: the triangular index of the histogram
(ii) *meanNN*: the mean value of filtered time series
(iii) *sdNN*: the standard deviation of filtered time series
(iv) *rmssd*: the root mean square of successive interval differences.

The frequency spectra were estimated using FFT with a Blackman–Harris window function, and four frequency components were estimated: the ultra low-frequency domain (ULF) (0–0.0033 Hz); the very low-frequency domain (VLF) (0.0033–0.04 Hz); the low-frequency domain (LF) (0.04–0.15 Hz); and the high-frequency domain (HF) (0.15–0.4 Hz). The following frequency domain parameters were used in this study:

(*a*) *ULF* and *VLF*: the power in the frequency bands introduced above
(*b*) *LF*/*HF*: the ratio of *LF* and *HF* components
(*c*) *LF*/*p*: the ratio of *LF* and the total power *p* (0. . . 0.4 Hz).

For all parameters, the two-tailed *t*-test for equality of means was performed to distinguish between the SAD and the non-SAD group. Further, the Pearson correlation coefficients between renormalised entropy RE_{AR} and time and frequency domain parameters were calculated.

3 Results

3.1 *Computational stability*

The values of the cumulative error measures $\Delta_{cum}(28)$, $\Delta_{cum}(26)$ and $\Delta_{cum}(20)$ as the influence of the length of time series are given in Table 1. The differences between the RE_{AR} and RE_{FFT} methods with simulated reference are highly significant ($p < 0.001$). The RE_{FFT} method is more sensitive to time series length, as the value of Δ_{cum} increases rapidly with decreasing length of the analysis. In contrast, the cumulative error of the autoregressive method RE_{AR} does not significantly increase with decreasing length. The differences between the RE_{AR} and RE_{FFT} methods with physiological reference are also highly significant ($p < 0.001$). However, the value of Δ_{cum} increases more rapidly with decreasing length of analysis.

Table 1 Mean cumulative error: influence of length of time series

	$\Delta_{cum}(28)$	$\Delta_{cum}(26)$	$\Delta_{cum}(20)$
RE_{FFT}: simulated reference	3.30	6.09	13.08
RE_{AR}: simulated reference	0.30	0.38	0.67
RE_{FFT}: physiological reference	2.23	5.15	20.77
RE_{AR}: physiological reference	0.61	1.24	3.20

Table 2 Mean cumulative error: influence of filtering algorithms F1, F2 and F3

	$\Delta_{cum}(F1)$	$\Delta_{cum}(F2)$	$\Delta_{cum}(F3)$
RE_{FFT}	0.21	0.30	0.72
RE_{AR}	0.23	0.26	0.34

Table 2 shows the results of the cumulative errors $\Delta_{cum}(F1)$, $\Delta_{cum}(F2)$ and $\Delta_{cum}(F3)$ as the influence of different filtering algorithms. Both methods RE_{AR} and RE_{FFT} show comparable sensitivities to different filter algorithms. However, the cumulative errors for the different filters vary considerably. The first filtering procedure, based on the binomial-7-filter, showed the smallest errors ($\Delta_{cum}(F1)$); the global behaviour of the time series did not change. Linear interpolation of ectopic beats and artefacts led to approximately 20% higher cumulative errors ($\Delta_{cum}(F2)$). It is strongly recommended that the last filtering procedure is not used, because the cumulative error $\Delta_{cum}(F3)$ is more than three times as high as $\Delta_{cum}(F1)$ (RE_{FFT}). Summarising the results of filtering, we have to prefer the application of the first filtering procedure, which was used in the following.

3.2 *Pilot assessment*

The results of renormalised entropy RE_{FFT} in the clinical pilot study are illustrated in Fig. 2. Only eight of 18 patients (44.4%) could be detected using the RE_{FFT} method. In comparison, the new RE_{AR} method of calculating renormalised entropy correctly classified 13 of 18 high-risk patients (72.2%; see Fig. 3).

3.3 *Prospective study*

In the validation study, the RE_{AR} method with the reference distribution of healthy person 16 from the clinical pilot investigation was calculated. Renormalised entropy RE_{AR}, as well as most time- and frequency-domain parameters, showed significant differences between the SAD and the non-SAD group

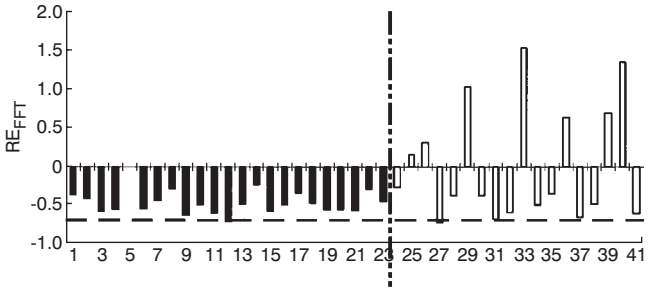

Fig. 2 *Results of renormalised entropy method RE_{FFT} in clinical pilot investigation: (■) healthy people; (□) high-risk patients. Subject 5 of control group showed most disordered distribution (in sense of renormalised entropy) and was chosen as reference for RE_{FFT} calculation. Only seven distributions of high-risk patients were more disordered than reference distribution and have RE_{FFT} value greater than zero. Considering values less than minimum value of renormalised entropy from healthy people, one further cardiac patient was identified; (– – – –) shows this border*

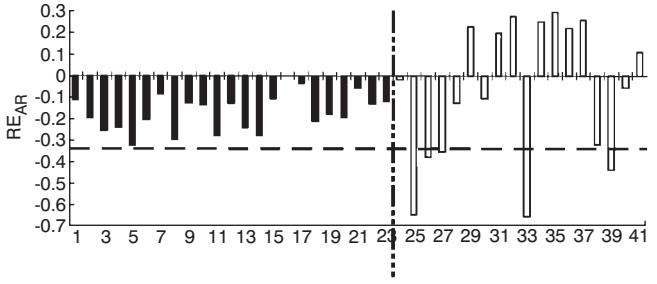

Fig. 3 *Results of renormalised entropy method RE_{AR} in clinical pilot investigation: (■) healthy people; (□) high-risk patients. Reference distribution was chosen from healthy subject 16. Eight patients had values greater than zero; five patients had RE_{AR} values less than minimum healthy RE_{AR} value (under broken line)*

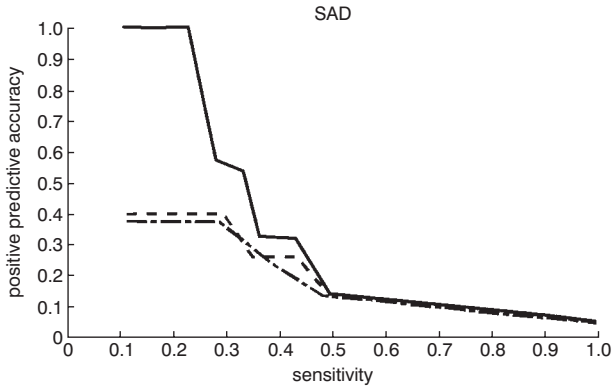

Fig. 4 *Positive predictive accuracy curves for univariate (– – – –) HRVi and (-·-·-) RE_{AR}, as well as for (——) combination of both methods. Enormous increase in positive predictive accuracy at 20% sensitivity level is also related to small SAD prevalence in investigated group*

(Table 3). To investigate the strength of the association between renormalised entropy RE_{AR} and time- and frequency-domain parameters, the Pearson correlation coefficients were calculated. The maximum absolute correlation coefficient between renormalised entropy and time and frequency domain HRV parameters was only 0.37. The slightly increased correlation values to $HRVi$, $meanNN$ and LF/p confirm the approach of renormalised entropy. Either an increased heart rate, which is connected with a decreased HRV, a depressed HRV, even at rest, or pathological spectra lead to positive values of renormalised entropy. Fig. 4 demonstrates that the combination of RE_{AR} and $HRVi$ improves the results of risk stratification. For sensitivity values of 10–40%, the positive predictive accuracy increases substantially.

4 Discussion

On the basis of the simulated time series from the Monte-Carlo experiment, the two methods, RE_{AR} and RE_{FFT}, were compared. It was shown that the new renormalised entropy method RE_{AR} is more reproducible and stable in time. This could be achieved, on the one hand, by calculating autoregressive spectral estimations to obtain smooth spectra or, on the other hand, by comparing amplitude-adjusted spectra using calibration signals. Further, an optimum filtering procedure for data preprocessing was validated.

The replacing of artefacts and arrhythmias by the respective value of the binomial filtered time series seems to be the most suitable method of those used in this study. However, the filtering procedure used here is probably improvable; the dependence of renormalised entropy on different preprocessing algorithms needs to be investigated in future studies. The results of the clinical pilot investigation showed that the new RE_{AR} method is a better risk predictor than the RE_{FFT} method. The diagnostic results (see Figs 2 and 3) were improved significantly, probably as a consequence of the different spectral estimation methods and the associated different reference selection.

The renormalised entropy method RE_{AR} is designed in such a way that tachograms with a normal variability and typical periodograms have negative values of RE_{AR}. Either a decreased HRV or pathological spectra lead to single-peak spectral distributions and thus to positive values of RE_{AR}. Pathological spectra are periodograms with dominant ULF, VLF or LF peaks. Dominant ULF or VLF peaks are seen in tachograms without any respiratory modulations and without any influence of blood pressure regulation. Dominant LF peaks are recognisable in the absence of vagal modulations for a significant part of the recording. The results with the St George's Hospital post-infarction database study confirmed that, on average, the survivors have negative, whereas the high risk patients have positive, values of renormalised entropy. This means that the survivors have comparable spectral estimations with the spectrum of the reference series, whereas the high risk patients do not show this behaviour. Further, it could be shown that the combination of HRV index and RE_{AR} leads to a better prediction of sudden arrhythmic death than standard measurements of global heart rate variability. This is a hint that a multivariate approach, with different HRV parameters, as well as the combination of HRV measures with clinical parameters may be promising in risk stratification.

Calculating renormalised entropy assumes a fixed reference distribution. In this study, the reference distribution was selected using the interchanging algorithm applied to the data of 23 healthy people. It remains to be investigated whether a general or

Table 3 For non-SAD as well as SAD group, mean values μ and standard deviations σ of all calculated parameters are given. p values represent significance of two-tailed t-test for equality of means of both groups. Pearson correlation coefficient r was calculated between renormalised entropy and parameters from time and frequency domain

		HRVi	*meanNN*	*sdNN*	*rmssd*	*ULF*	*VLF*	*LF/HF*	*LF/p*	*RE*
Non-SAD	μ	27.6	871.9	96.8	32.4	62.7	14.7	3.0	0.05	−0.11
	σ	10.3	157.8	36.0	23.3	46.5	12.9	1.8	0.04	0.18
SAD	μ	16.7	687.8	57.2	23.1	26.2	6.5	2.2	0.04	0.03
	σ	6.4	103.3	20.2	15.1	16.4	6.6	1.4	0.04	0.22
	p	<0.01	<0.01	<0.01	not significant	<0.01	<0.02	not significant	not significant	<0.01
	r	0.32	0.37	0.24	0.21	0.26	0.18	0.02	0.27	1

a disease-dependent reference distribution should be considered in future studies. More generally, it is imaginable that the methodology of renormalised entropy could be improved in such a way that a reference series becomes unnecessary.

In summary, the new method of renormalised entropy RE_{AR}, which is a measure of relative degree of order, is an independent parameter in HRV assessment that seems to be potent for risk stratification of patients after myocardial infarction.

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Author's biography

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