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Scale-specific and scale-independent measures of heart rate variability as risk indicators

Y. Ashkenazy[1,2](*), M. Lewkowicz[3,1], J. Levitan[3,1,4], S. Havlin[1,2], K. Saermark[4], H. Moelgaard[5], P. E. Bloch Thomsen[6], M. Moller[7], U. Hintze[7] and H. V. Huikuri[8]

[1] *Department of Physics, Bar-Ilan University - Ramat-Gan, Israel*
[2] *Gonda Goldschmied Center, Bar-Ilan University - Ramat-Gan, Israel*
[3] *Department of Physics, College of Judea and Samaria - Ariel, Israel*
[4] *Department of Physics, The Technical University of Denmark - Lyngby, Denmark*
[5] *Department of Cardiology, Skejby Sygehus, Aarhus University Hospital Aarhus, Denmark*
[6] *Department of Cardiology, Amtssygehuset i Gentofte, Copenhagen University Hospital Copenhagen, Denmark*
[7] *Institute of Clinical Research Cardiology, University of Southern Denmark Odense, Denmark*
[8] *Division of Cardiology, Department of Medicine, University of Oulu - Oulu, Finland*

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Abstract. – We study the correlation properties of heartbeat fluctuations using scale-specific variance (root-mean-square fluctuation) and scaling (correlation) exponents as measures of healthy and cardiac impaired individuals. Our results show that the variance and the scaling exponent are uncorrelated. We find that the variance measure at certain scales is well suited to separate healthy subjects from heart patients. However, for mortality prediction the scaling exponents outperform the variance measure. Our study is based on a database containing recordings from 428 individuals after myocardial infarct (MI) and on a database containing 105 healthy subjects and 11 heart patients. The results have been obtained by applying two recently developed methods (DFA —Detrended Fluctuation Analysis and WAV —Multiresolution Wavelet Analysis) which are shown to be highly correlated.

The study of heart rate variability (HRV) has been in use for the last two decades as part of clinical and prognosis work; international guidelines for evaluating conventional HRV parameters do exist [1]. The conventional parameters are power spectra [2] and standard deviation [3,4]. Recently new methods of analyzing heart interbeat interval (RR) time series have been developed, all of them showing signs of improved diagnostic performance. Two of these methods are: Detrended Fluctuation Analysis (DFA) [5–9] and Multiresolution Wavelet Analysis (WAV) [10–16]. The question which method and which measure yield better separation between cardiac impaired and healthy subjects has recently been debated [13, 14, 17].

(*) E-mail: ashkenaz@argento.bu.edu

In this letter we show that variance (root-mean-square fluctuation), which is a scale-specific measure, is well suited to separate between healthy subjects and heart patients. However, for the myocardial infarct (MI) group the scaling (correlation) exponent, which is a scale-independent measure, serves as a better risk indicator. Moreover, we show that the two above-mentioned methods for both variance and scaling exponent are correlated and converge to similar results while the variance and the scaling exponent are uncorrelated.

In our study we use two groups, the MI group, containing 428 heart patients after MI, and a control group, consisting of 105 healthy individuals and 11 cardiac impaired patients (9 diabetic patients, one diabetic patient after myocardial infarct, and one heart transplanted patient). Our analysis is based on 24 hour heart interbeat interval time series [18]. We applied the following methods.

The DFA method. The detrended fluctuation analysis was proposed by Peng *et al.* [5]. This method avoids spurious detection of correlations that are artifacts of nonstationarity. The interbeat interval time series is integrated after subtracting the global average and then divided into windows of equal length, n. In each window the data are fitted with a least-square straight line which represents the local trend in that window. The integrated time series, is detrended by subtracting the local trend in each window. The root-mean-square fluctuation, the standard deviation $\sigma_{\mathrm{DFA}}(n)$ of the integrated and detrended time series is calculated for different scales (window sizes); the standard deviation can be characterized by a scaling exponent α_{DFA}, defined as $\sigma(n) \sim n^{\alpha}$.

The WAV method. In the WAV method [13,14,16] one finds the wavelet coefficients $W_{m,j}$, where m is a "scale parameter" and j is a "position" parameter (the scale m is related to the number of data points in the window by $n = 2^m$ [18]), by means of a wavelet transform. The wavelet transform has the ability to eliminate higher-order trends from the data (trends which are not necessarily related to the cardiac activity). In this study we use discrete wavelet transform —the Daubechies 10-tap wavelet transform which excludes 4th order polynomial trends [19, 20]. The standard deviation $\sigma_{\mathrm{WAV}}(m)$ of the wavelet coefficients $W_{m,j}$ across the parameter j is used as a parameter to separate healthy from sick subjects. The corresponding scaling exponent is denoted by α_{WAV}.

The first suggestion to use a scale-independent measure of the HRV as a separation parameter was by Peng *et al.* [5] who found that a critical value of the DFA scaling exponent α_{DFA} can distinguish between healthy individuals and heart patients. Thurner *et al.* [13] used the scale-specific WAV variance σ_{WAV} in order to better separate the same two groups. The debate on which method performs better was continued in two recent letters [14, 17]. Later on, another independent study on different database [16] yielded a better separation using the scale-specific σ_{WAV} measure. The question which measure is more suitable for bedside applications is important since: i) these measures may be used for diagnosis; ii) it may help to focus on the main difference between healthy and cardiac impaired regulation and thus may lead to better understanding the underlying mechanism of the heart regulation.

In fig. 1 we compare the conventional measures for HRV for the control group (105 healthy subjects and 11 heart patients): the variance (which is calculated for a fixed scale) for the WAV method (σ_{WAV}) and the scaling exponent (which is calculated for a range of scales) for the DFA method (α_{DFA}). In general, the heartbeat interval series is characterized by two scaling exponents —short-range scaling exponent (4-16 heartbeats) and long-range scaling exponent (16 up to thousands of heartbeats). Here we study the short-range scaling exponent (rather than the long-range scaling exponent) since it was shown to be the best for clinical use [5, 7, 8]. The variance measure is estimated at the crossover point between the short- and

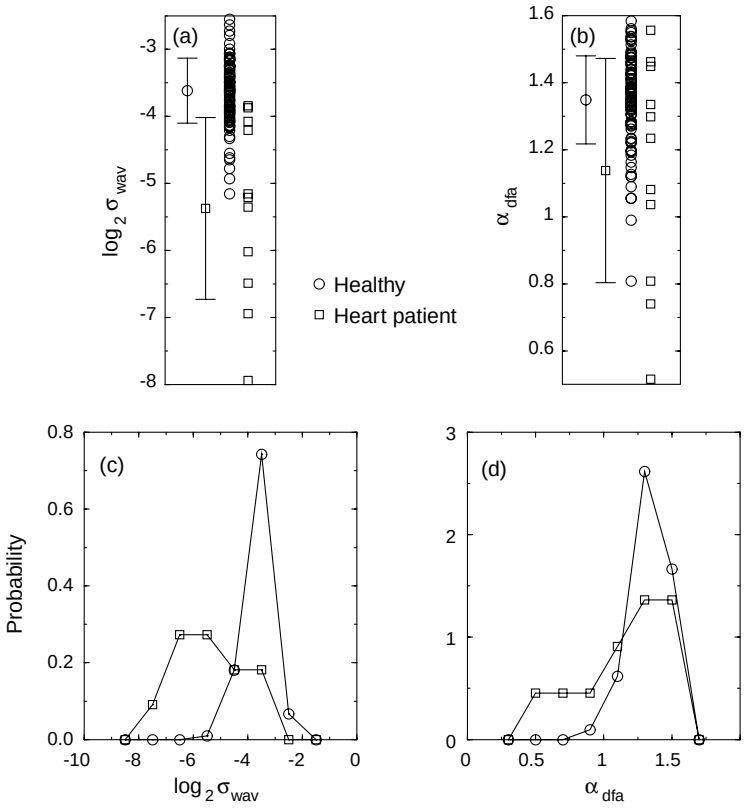

Fig. 1 – A comparison between different HRV methods (WAV and DFA). The 105 healthy subjects are denoted by ◯, while 11 heart patients are denoted by □. The error bars indicate the average ±1 standard deviation of each group. The σ_{WAV} is calculated at scale $m = 4$ ($n = 2^4 = 16$ heartbeats) and α_{DFA} for scales $1 \leq m \leq 4$ ($2^1 \leq n \leq 2^4$ heartbeats); it was previously reported that this choice of parameters yields the best separation between healthy group and heart failure group [5, 13]. (a) The scale-specific σ_{WAV} for the healthy and heart patient group; (b) the scale-independent α_{DFA}; (c) the probability distribution of (a); (d) the probability distribution of (b).

long-range scaling exponents ($m = 4$, $n = 2^4 = 16$ heartbeats) where the largest separation between healthy and heart failure was observed [5]. One notes that the scale-specific measure, σ_{WAV}, yields a nearly perfect separation between healthy and sick subjects (the p value of Student's t-test is less than 10^{-14}), compared with the scale-independent measure α_{DFA} which yields less pronounced separation (the p value of Student's t-test is less than 10^{-4}).

This outcome is reversed when we applied the measures on the MI group. Since we have no diagnostics on this group, but rather do know the follow-up history for 328 individuals from the total 428 individuals of the larger group, we investigate the survival probability of these subjects as expressed through the so-called survival curve [21]. In these curves one divides the entire group by means of a specific value of the σ or α measure, called the critical value σ_{c} or α_{c}. Individuals with $\sigma > \sigma_{\mathrm{c}}$ (or $\alpha > \alpha_{\mathrm{c}}$) belong to the subgroup which is assumed to have higher survival probability while individuals with $\sigma < \sigma_{\mathrm{c}}$ (or $\alpha < \alpha_{\mathrm{c}}$) belong to the subgroup which is assumed to have lower survival probability. If the parameter (σ or α) is a good risk parameter, the survival probability of the first sub-group should be significantly

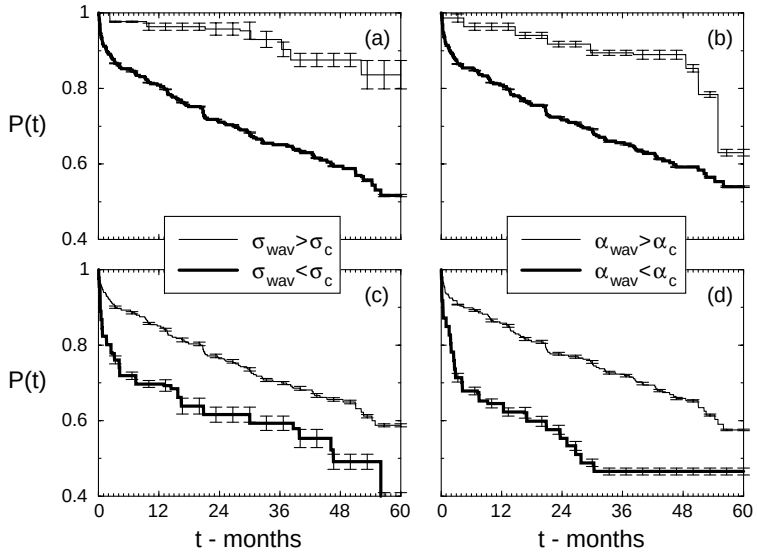

Fig. 2 – Cumulative survival probability curves using the WAV method. We divide the entire group of 328 individuals into two groups according to a critical value σ_c (or α_c) and calculate the survival probability for each subgroup. The survival curves shown in the figure are the average of 10 different, nearby, survival curves, corresponding to 10 different, nearby, critical values. We perform this average procedure in order to check the sensitivity to the critical value. The error bars indicate the standard deviation from the average. The average critical values (± standard deviation) are: (a) $\langle \log_2 \sigma_c \rangle = -3.749 \pm 0.02$; (b) $\langle \alpha_c \rangle = 0.68 \pm 0.008$; (c) $\langle \log_2 \sigma_c \rangle = -5.485 \pm 0.02$; and (d) $\langle \alpha_c \rangle = 0.135 \pm 0.008$.

higher than the second sub-group. On the other hand, if the parameter is not a good risk parameter, then the two subgroups will have similar survival probability. The cumulative survival probability is given by $P(t+\Delta t) = P(t)[1-\Delta N/N(t)]$, where $P(t)$ is the probability to survive up to t days after the ECG recording, $N(t)$ denotes the number of individuals alive at t days after the examination, and ΔN is the number of individuals who died during the time interval Δt. $P(t)$ is calculated recursively where the initial condition is $P(0) = 1$. In fig. 2 we show a comparison of survival curves where the separating measure in panels (a) and (c) is the critical standard deviation σ_c and in panels (b) and (d) the critical scaling exponent α_c. The upper panels of fig. 2 extract the subgroup with a high parameter value (high survival probability), whereas the lower panels extract the subgroup with a low parameter value (low survival probability). This comparison shows that the scale-independent scaling exponent α serves as a better prognosis predictor than the scale-specific variance σ (although fig. 2a and b are similar, the survival curves of fig. 2d are more separated than the survival curves of fig. 2c).

In fig. 2 we use the σ and α measures obtained through the WAV method. However, as we show below the two methods discussed above are highly correlated and no significant difference is noticeable in the survival curves when using the DFA measure.

The advantage of the scale-independent measure α over the scale-specific measure σ is also shown in fig. 3. Here we scan the possible critical values by the Receiver Operating Characteristic (ROC) analysis [22]; this analysis is usually used as a medical diagnostic test and also was the basic diagnostic test of ref. [17]. The idea of the ROC method is to compare the result of medical test (positive or negative) with the clinical status of the patient (with or without disease). The efficiency of the medical test is judged on the basis of its sensitivity

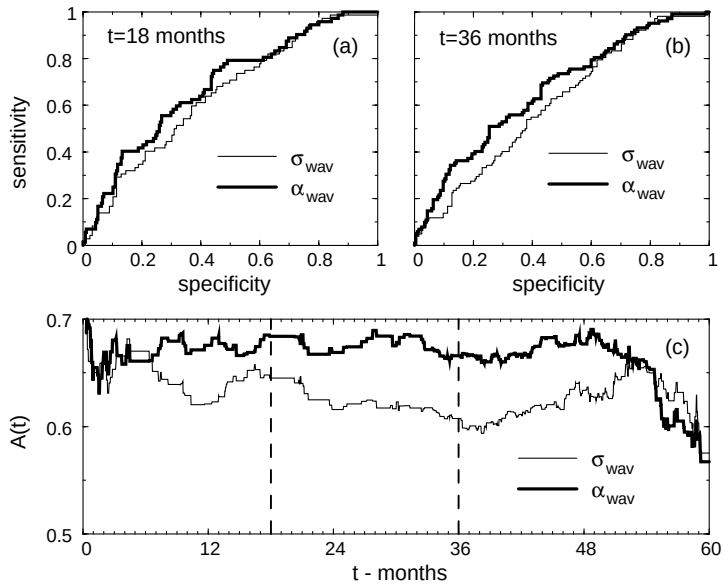

Fig. 3 – The ROC curves (sensitivity *vs.* specificity) of the scale-specific, σ_{WAV}, and scale-independent, α_{WAV}, measures. (a) $t = 18$ months, (b) $t = 36$ months, and (c) $A(t)$ —the area under the ROC curve— as a function of time. In all panels the scale-independent curve is located above the scale-specific curve. Thus, the scale-independent measure is more suitable for prognosis purposes. The fluctuations in panel (c) are due to changes in the ratio between the number of deaths and alives. Note that most of the time the curve for σ_{WAV} follows the curve for α_{WAV} and the distance between them remains relatively constant. In the present study σ_{WAV} is calculated at $m = 4$ ($n = 2^4 = 16$ heartbeats) and α_{WAV} for $1 \leq m \leq 4$ ($2 \leq n \leq 2^4$ heartbeats). For other choice of scales $A(t)$ drops toward 0.5 indicating less significant mortality prediction.

(the proportion of diseased patients correctly identified) and its specificity (the proportion of healthy patients correctly identified). The ROC curve is a graphical presentation of sensitivity *vs.* specificity as a critical parameter is swept. In our case the patient status is determined according to its mortality (death or survival up to time t) and according to its mortality prediction (a patient with parameter value smaller than the critical value is predicted to die while a patient with a parameter value larger than the critical value is predicted to survive). In fig. 3a and b we present two examples of the ROC curves in different times (18 months and 36 months). In both cases the ROC of the scale-independent (α_{WAV}) curve is located above the scale-specific (σ_{WAV}) curve; the larger the area under the ROC curve, the better the parameter [23]. In the ideal case a patient with small parameter value will die before the patient with higher parameter value. In this case the area under the ROC curve will be 1 (*i.e.*, 100% of the cases were correctly predicted). On the other hand, when there is no relation between the value of the parameter and the mortality of the patient the area under the ROC curve will be 1/2 (*i.e.*, 50% of the cases were correctly predicted). In fig. 3c we show the area under the ROC curves as a function of time ($A(t)$). Also here, the scale-independent (α_{WAV}) curve is located above the scale-specific (σ_{WAV}) curve. Thus, the scale-independent measure α_{WAV} is more suitable for prognosis.

In order to investigate if the two methods we use are correlated, we apply them on the larger MI group consisting of 428 subjects. Figure 4 shows that the variances (the scale-specific

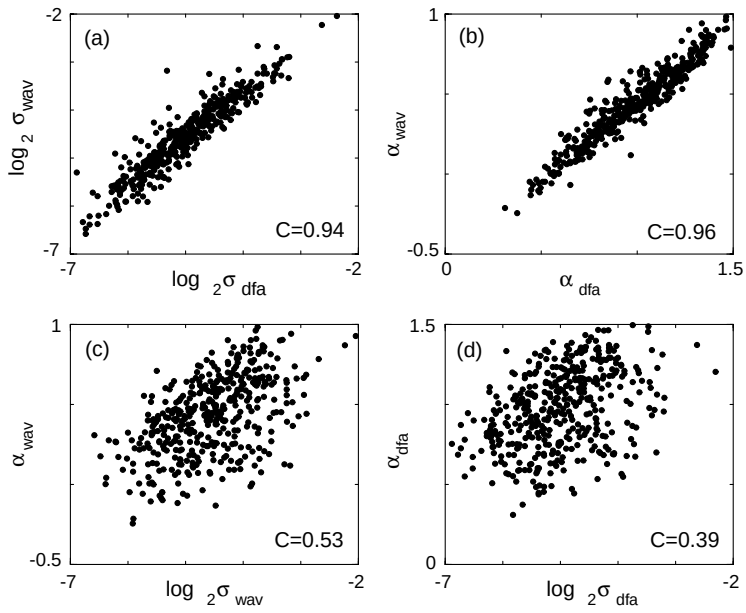

Fig. 4 – A comparison between different HRV methods using 428 individuals. The value C in each panel indicates the cross-correlation value between the different measures [24]. (a) σ_{WAV} *vs.* σ_{DFA}; (b) α_{WAV} *vs.* α_{DFA}; (c) α_{WAV} *vs.* σ_{WAV}; and (d) α_{DFA} *vs.* σ_{DFA}. The σ_{DFA} and σ_{WAV} are calculated at $m = 4$ ($n = 16$ heartbeats), α_{DFA} and α_{WAV} are calculated for $m = 1$ to 4 ($n = 2$ to 16 heartbeats). Note that $\sigma_{\mathrm{WAV}}(m = 4) \sim \sigma_{\mathrm{DFA}}(m = 4)$ and $\alpha_{\mathrm{WAV}} \sim \alpha_{\mathrm{DFA}} + \frac{1}{2}$.

measure) of the two methods (fig. 4a) as well as the scaling exponents of the two methods (fig. 4b) are highly correlated. These comparisons indicate that indeed the two methods yield the same results in terms of variance and scaling exponents. On the other hand, the lower panels of fig. 4 show that the scale-specific variance and the scale-independent scaling exponent are uncorrelated for the DFA methods and are only faintly correlated for the WAV method.

From this we conclude that the α and σ measures characterize the interbeat interval series in different ways; the variance, which is a measure in the time domain (and thus is almost invariant to shuffling [13]), performs better as a diagnostic tool, while the scaling exponent, which is a measure in the frequency domain, depends on the order of events and performs better as a prognosis tool. Thus we suggest that the scale-specific variance reflects changes in either the sympathetic or the parasympathetic activities of the neuro-autonomic nervous system [25] which affect the cardiac ability of contraction; the scale-specific variance may hint on the instant condition of the physical properties of the heart. From the above we also suggest that the scale-independent scaling exponent characterizes the memory interplay of the two competing branches of the autonomic nervous system (the sympathetic and the parasympathetic systems) and is thus an expression of the underlying mechanism of heart regulation (which influences the conventional power spectrum [2]) [26].

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[18] Note that our wavelet analysis is not restricted to series lengths which are powers of two; in the present study the maximum scale is $m = 4$ ($n = 2^4 = 16$) and thus the series length should be a multiple of 16.

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[21] We also performed a simpler test to verify whether the scale-independent measure is better than the scale-specific measure for making a prognosis. We divided the group of 328 subjects into two subgroups —a group of patients who survived and a group of patients who died. Then we used Student's t-test to compare between the two groups. For the scale-specific σ_{WAV} we obtained (average ± 1 standard deviation) for the alive group -4.47 ± 0.75 and for the dead group -4.79 ± 0.74 ($p < 0.0003$). For the scale-independent α_{WAV} we obtained for the alive group 0.46 ± 0.24 and for the dead group 0.34 ± 0.23 ($p < 8 \times 10^{-6}$). Thus, the scale-independent measure performs better prognosis.

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[23] The area under the ROC curve quantifies the separation between the two sub-groups. It is a nonparametric test for separation and serves as the p-value obtained by Student's t-test and other tests.

[24] Given two series ($\{x_i\}$ and $\{y_i\}$) with the same length, the cross-correlation value is $C = \sum[(x_i - \langle x\rangle)(y_i - \langle y\rangle)]/\sqrt{\sum(x_i - \langle x\rangle)^2 \sum(y_i - \langle y\rangle)^2}$, where $\langle \ldots \rangle$ indicates the average of the series.

[25] The sympathetic/parasympathetic system is the system which increases/decreases the heart rate.

[26] An increase/decrease in one of the activities is usually compensated by a decrease/increase in the other activity. In cardiac failure the regulation between the two activities breaks down.