AUTONOMIC ANTAGONISM UNDERLIES HEART RATE COMPLEXITY*

Zbigniew R. Struzik[a†], Ken Kiyono[b], Junihiro Hayano[c]
Shin Kwak[d], Yoshiharu Yamamoto[a]

[a]Graduate School of Education, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[b]College of Engineering, Nihon University, 1 Naka-gawara
Tokusada, Tamura-machi, Koriyama City, Fukushima, 963-8642, Japan
[c]Core Laboratory, Nagoya City University Graduate, School of Medical Sciences
Nagoya 467-8601, Japan
[d]Department of Neurology, Graduate School of Medicine, The University of Tokyo
Tokyo 113-0033, Japan

(Received December 20, 2011)

We investigate multiscale properties of intermittency of heart rate variability (HRV) through non-Gaussianity and through two-point one-scale magnitude correlations in HRV of patients with congestive heart failure (CHF) — both survivors (CHF–SV) and non-survivors (CHF–NS) — and of patients with primary autonomic failure (PAF). We confirm the sympathetic origin of the non-Gaussianity index elucidating its random character. We further confirm intermittency of the high frequency, fine scale firing of the parasympathetic nervous system branch, responsible for the multifractal complexity. We obtain further confirmation of the antagonistic function of the autonomic regulation of HRV, this time in terms of intermittency — heteroscedastic clustering of variance. In this context, we identify autonomic antagonism as the source of the mid to low frequency, intermediate scale intermittency observed at higher levels in CHF patients with elevated sympathetic activation and suppressed in the PAF patients — the case of neurogenic SNS dysfunction.

DOI:10.5506/APhysPolBSupp.5.181
PACS numbers: 87.19.Hh, 87.85.Xd, 89.75.Da, 05.40.–a

* Presented at the 8th European Conference on Mathematical and Theoretical Biology, Minisymposium "Modeling of Collective Phenomena in Biological Systems", Kraków, Poland, June 28–July 2, 2011.

† z.r.struzik@p.u-tokyo.ac.jp

1. Introduction

Human heart rate variability (HRV) has been shown to display intriguing characteristics, to a large degree defying satisfactory explanation. Starting with the seminal work by Kobayashi and Musha [1] demonstrating the evidence of $1/f$-like scaling (or rather $1/f^{\alpha}$, where α is close to one) of the power spectrum of healthy heart rate intervals, heart rate has become one of the key benchmarks of dynamical biological complexity [2,3]. While subsequent measures of complexity have added up to a picture of heart rate regulation as a highly non-trivial complex system [4,5,6], little has been revealed about the origins of this complexity. In this context, Struzik *et al.* [7] suggested that the dual antagonistic structure of the regulatory system, the parasympathetic (PNS) and sympathetic (SNS) branches of the autonomic nervous system are responsible for the $1/f$ type of fluctuations, while the PNS branch is uniquely responsible for the multifractal type of complexity. Further, Kiyono *et al.* demonstrated [8] that historical observations suggest that $1/f$ scaling, non-Gaussian PDF [4] and multifractality [5] produce one consistent picture of heart rate regulation which shares many of the characteristics of physical systems in the so-called critical state [3, 9, 10]. In particular, the unique scale invariance properties characterising the state of criticality govern the non-Gaussian PDF of a healthy heart rate in the state of usual daily activity — and exclusively in this state. A breakdown of this unique scale invariance reminiscent of continuous (second order) phase transition, emerges when the condition of autonomic imbalance is entered [11].

In this paper, we investigate multiscale non-Gaussianity and two-point one-scale magnitude correlations [12] of the HRV of patients with congestive heart failure (CHF) — both survivors (CHF–SV) and non-survivors (CHF–NS) — and of patients with primary autonomic failure (PAF). We show:

1. *sympathetic* origin of the non-Gaussianity of HRV at high frequencies, elevated in CHF, in particular in CHF–NS, but strongly decreased in PAF;

2. *parasympathetic* origin of the high-frequency heteroscedasticity. Heteroscedasticity, or intermittency is preserved in PAF at high frequencies, corresponding with the relatively intact vagal regulatory branch, while at lower frequencies *sympathetic* activation is the primary cause of the heteroscedasticity (relative comparison of PAF with CHF).

Intermittency, and increased heteroscedasticity has been found to emerge in a variety of complex phenomena such as turbulence, sunspot activity or population dynamics and in dynamical model scenarios [13,14,15,16], where it has also been shown to result from the operation at compromised stability [13, 14, 15].

Multiscale properties of non-Gaussianity [8] have previously been considered in reference to heteroscedasticity and complexity of heart rate fluctuations [17, 18]. In particular, we have demonstrated that the increase in the non-Gaussianity of high frequency, fine scale fluctuations of heart rate predicts mortality of patients suffering from CHF [18].

The magnitude correlations investigated in this work are a direct measure of heteroscedasticity and intermittency in time series and are more appropriate to be considered as a measure of complexity in such systems. Elevated intermittency and heteroscedastic behaviour suggest a more complex dynamics of the system under study in terms of a generally recognised — yet difficult to define and quantify — concept of "physical complexity" [19].

Furthermore, we investigate autonomic imbalance by using selective neurogenic suppression of the branches of the autonomic control system — sympathetic dominance in CHF and suppressed sympathetic stimulation in PAF. Indeed, PAF is clinically characterised as autonomic dysfunction, including orthostatic hypotension, impotence, bladder and bowel dysfunction and sweating defects, which primarily result from progressive neuronal degeneration of unknown cause. The main pathological finding related to autonomic dysfunction in PAF is severe loss of preganglionic and/or postganglionic sympathetic neurons, and it is, therefore, considered that this group serves as an example of relative and neurogenic SNS dysfunction. In contrast, CHF is characterised by elevated sympathetic activity and parasympathetic withdrawal.

2. Data

We analyse full day-long sequences of data, comprising over 80,000 data points, of the intervals between two successive R waves of sinus rhythm, *i.e.* HRV. To avoid the adverse effects of any remaining errors in the detection of the R wave, large ($> 20\%$) consecutive R–R interval differences were thoroughly reviewed until all errors were corrected. In addition, when atrial or ventricular premature complexes were encountered, the corresponding R–R intervals were interpolated by the median of the two successive beat-to-beat intervals.

2.1. Congestive heart failure patients; surviving (CHF–SV) and non-surviving (CHF–NS)

We evaluate a 24-hour Holter electrocardiogram of 108 CHF patients, of whom 39 patients (36.1%) died within four years of the follow-up period. The end point was all-cause death, but the majority (35/39) was cardiac death, including death from progressive heart failure, sudden death and acute myocardial infarction. For additional information on this data set, the reader is referred to Refs. [18, 17].

2.2. Neurogenic SNS dysfunction data: primary autonomic failure (PAF) patients

We analyse 24-hour ambulatory heart rate dynamics of 24 PAF patients, containing on average 10^5 heartbeats. The selection of the subjects and the collection procedures for the subjects in this data follow those described in Ref. [20] with an additional group of 14 subjects added subsequently.

3. Methods

For the purpose of studying intermittent fluctuations [8, 11], we analyse the scalewise behaviour of the sums of the process variable. Let us consider a stationary stochastic process in discrete time, $\{\xi(1), \xi(2), \ldots, \xi(i), \ldots\}$, with $\langle \xi(i) \rangle = 0$, $\langle \xi(i)^2 \rangle = \sigma^2$, where $\langle\rangle$ denotes the statistical average. Using integrated series of $\{\xi(i)\}$, $z(n) = \sum_{j=1}^{n} \xi(j)$, partial sums are obtained as,

$$\Delta_s z(i) = \sum_{j=i+1}^{i+s} \xi(j) = z(i+s) - z(i)\,. \tag{1}$$

In order to obtain a temporal representation of the heart rate intervals, the N–N interval time series are interpolated and resampled at a predefined sampling rate. Temporal resampling is more appropriate for the estimation of the non-Gaussianity parameter λ and for the correlation analysis, as the results can be interpreted in terms of frequency, commonly used in the spectral analysis of HRV. Thus, the time series of N–N intervals are interpolated with a cubic spline function and resampled at an interval (Δt) of 250 ms (4 Hz). After subtracting the average interval base, the integrated, "random walk" time series is obtained by integrating the interpolated time series $b(t)$ over the entire length,

$$B(t) = \sum_{i=1}^{t/\Delta t} b(i\Delta t) - b_{\text{ave}}\,. \tag{2}$$

The integrated time series are divided into overlapping segments of 2 [sec.] length, with 50% overlap, where s is the scale of the analysis ($s = 25$ [sec.] for $\lambda_{25\,\text{sec}}$). To remove the non-stationary trends, in each segment, the local trend is approximated by the d-degree polynomial $f_{\text{fit}}(t)$ (we use $d = 3$, as in our previous studies [8, 11, 17, 18]). The momentary deviation $\Delta_s B(t)$ at the observation scale "s" is then measured as the increment with a time lag t of the detrended time series $B^*(t) = B(t) - f_{\text{fit}}(t)$. For instance, in a segment from $T - s$ to $T + s$, the increments are calculated as

$$\Delta_s B(t) = B\left(t + \frac{s}{2}\right) - f_{\text{fit}}\left(t + \frac{s}{2}\right) - B\left(t - \frac{s}{2}\right) - f_{fit}\left(t - \frac{s}{2}\right)\,, \tag{3}$$

where $T - s/2 \leq t < T + s/2$ and $f_{\text{fit}}(t)$ is the polynomial representing the local trend of $B(t)$. The elimination of the trend assures the zero-mean probability density function, subject of the next step of the analysis.

To characterise the non-Gaussian property quantitatively, the standardised PDF (where the variance is set to one) constructed from all the $\Delta_s B(i)$s is approximated by the standardised Castaing model [21,22] P_λ

$$P_\lambda(x) = \frac{1}{2\pi\lambda} \int_0^\infty \exp\left(-\frac{\left(\ln\sigma + \lambda^2\right)^2}{2\lambda^2}\right) \exp\left(-\frac{x^2}{2\sigma^2}\right) \frac{d(\ln\sigma)}{\sigma}\,, \tag{4}$$

where λ is a single parameter to describe the non-Gaussian P_λ; the greater λ indicates the fatter non-Gaussian tail of the PDF. $\lambda \to 0$ corresponds with the Gaussian PDF shape. We estimate the non-Gaussian parameter λ using the moments method with $q \to 0.0$, which entails that λ is estimated from the mean of the log-amplitude of HRV. Details of this method are described elsewhere [22].

Let us define the log-amplitude, or magnitude, of $\Delta_s B(t)$ at a scale s, as

$$\hat{\omega}_s(t) = \log|\Delta_s B(t)|\,. \tag{5}$$

Further, the two-point, one-scale magnitude correlation function [11,12] is defined as

$$C(\tau, s) = \langle(\hat{\omega}_s(t) - \langle\hat{\omega}_s\rangle)(\hat{\omega}_s(t+\tau) - \langle\hat{\omega}_s\rangle)\rangle\,. \tag{6}$$

The long-range temporal correlations of the magnitude $\hat{\omega}_s$ (log-amplitude) indicate long persistent memory in the local variance, where large deviations are more likely to be followed by large deviations (and small by small deviations). This is consistent with increased heteroscedasticity — the phenomenon of the so-called variance clustering[1] such as that observed in intermittent behaviour in various complex phenomena. Such increased intermittency characterised by temporal correlations of the magnitude are independent of the non-Gaussian statistics of the time series. Indeed, non-Gaussianity does not characterise intermittency in terms of the non-stationarity of variance.

[1] Referred to as "volatitity clustering" in quantitative financial analysis — following the observation by Mandelbrot (1963), that "large changes tend to be followed by large changes, of either sign, and small changes tend to be followed by small changes".

4. Results

The magnitude correlation functions are shown in Fig. 1 for CHF survivors (CHF–SV) and CHF non-survivors (CHF–NS) recalculated from the study reported in Refs. [18, 17], and for PAF data [7]. Comparing the CHF survivors (Fig. 1 (a)) and non-survivors (Fig. 1 (b)), correlations in scales $s < 20$ [sec.] in the CHF non-survivors are marginally stronger than in survivors. An opposite tendency is observed in the characteristic scale-wise band of correlation around 30–40 [sec.] which appears to be marginally stronger in CHF–SV than in CHF–NS. For the PAF data, however, we observe the correlations to be substantially weaker throughout the magnitude correlation function (Fig. 1 (c)), except for the narrow band of elevated correlations in scales $s < 20$ [sec.] Such a scale-dependent increase of high frequency correlations in PAF is in stark contrast to the decrease observed in CHF (both SV and NS).

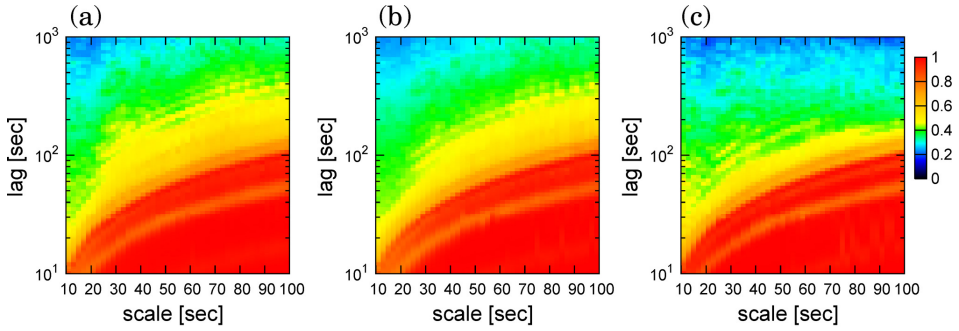

Fig. 1. Two-point, one-scale magnitude correlation functions, $C(\tau; s)/C(0; s)$, where τ is the time lag and s is the scale (in time units [sec.]). (a) CHF–SV (survivors); (b) CHF–NS (non-survivors); (c) PAF patients.

Such correlations of the log-magnitude, here revealed in a detailed, precise manner of temporal lag and scale indexed magnitude correlation function, reveal the complex structure of the clustering of variance, giving rise to the intermittent behaviour of multiscale character. Correlations of the log-magnitude are mathematically independent of the non-Gaussianity in the PDF, such as the scale overall increase of the non-Gaussianity parameter λ observed in particular in the CHF non-survivors [17, 18], and scale specific decrease markedly greater at the finest scales (*i.e.* highest frequencies) observed in PAF patients, as shown in Fig. 2.

For the purpose of validating the above observations, in Fig. 3 we provide pairwise differences of the intensity of the respective magnitude correlations between each of the analysed groups (CHF–SV, CHF–NS and PAF). While non-survivors have the λ index consistently higher than survivors,

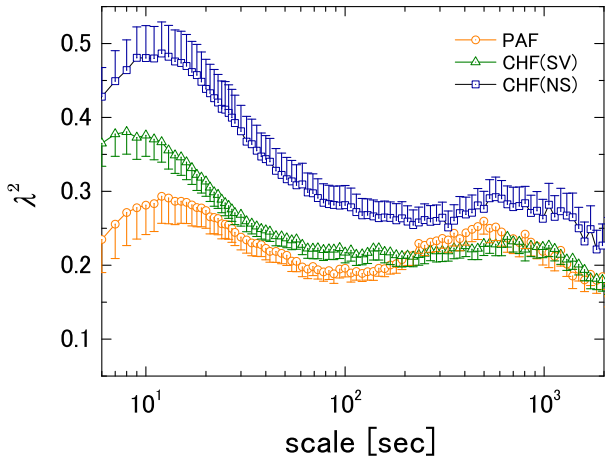

Fig. 2. Scale dependence of the non-Gaussian parameter λ^2 for the three patient groups PAF, CHF–SV and CHF–NS.

as evidenced in Fig. 2, there is little difference in the correlations across the two groups — the actual variance clustering is at a comparable level in both non-survivors and survivors of CHF. In the highest frequency band; for scales < 25 [sec.] the correlations are slightly greater in non-survivors than in survivors but only for time lags greater than 100 [sec.] However, the PAF group, showing much lower non-Gaussianity at high frequencies than both survivors and non-survivors of CHF (Fig. 2), shows stronger correlations and therefore a higher level of intermittency in the highest frequency band. This confirms the previously established property of multifractality of PAF [7, 20]. Indeed, multifractality is a result of higher intermittency rather than non-Gaussianity. As shown in Fig. 2, the non-Gaussianity is low at high frequencies in PAF. Only in the highest frequency range (normally associated with the parasympathetic stimulus) the degree of correlations is higher in PAF. This confirms the known fact that parasympathetic nerves fire intermittently. In the lower frequency band (scales > 25 [sec.]), the intermittency is much lower in PAF than in CHF. A novel observation is that the sympathetic activity in PAF is not only impaired, as evidenced by the breakdown of correlations at scales greater than 25 [sec.], but also the firing of the sympathetic activity is much less intermittent in PAF than CHF/–SV/–NS, at comparable levels of non-Gaussianity Fig. 3. In contrast, this suggests that the lower frequency intermittent behaviour in CHF/–SV/–NS HRV records is due to sympathetic dominance. The effect of increased heteroscedasticity of CHF in comparison with PAF is particularly strong for scales > 60 [sec.] and time lags > 100 [sec.]

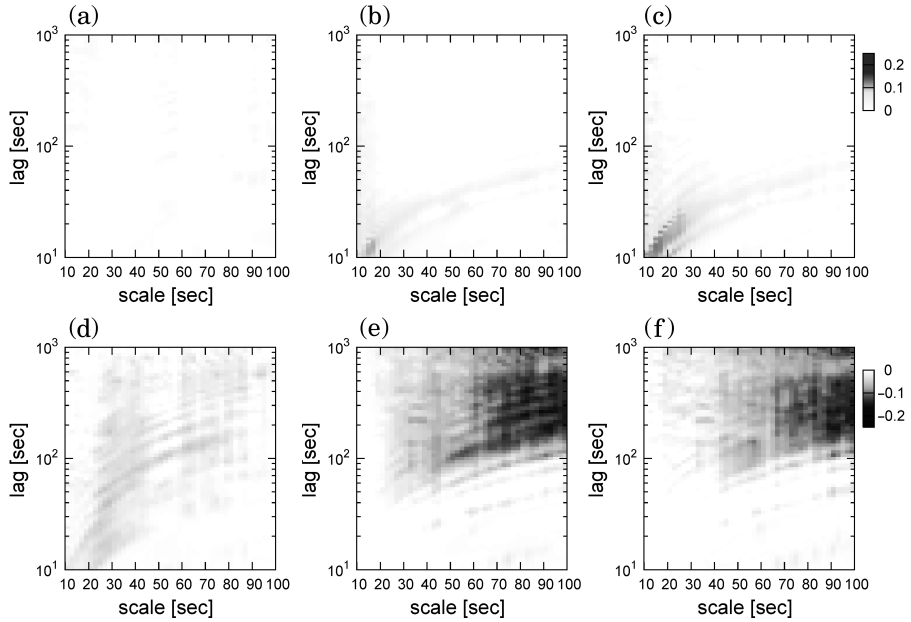

Fig. 3. The differences between pairs of the two-point, one-scale magnitude correlation functions $\tilde{C} \equiv C(\tau; s)/C(0; s)$, shown in Fig. 1, divided into positive (a)–(c) and negative (d)–(f) difference: *i.e.* the difference between Fig. 1 (b) and Fig. 1 (a); (b), (e) $\tilde{C}_{\mathrm{PAF}} - \tilde{C}_{\mathrm{CHF\ SV}}$, *i.e.* the difference between Fig. 1 (c) and Fig. 1 (a); (c), (f) $\tilde{C}_{\mathrm{PAF}} - \tilde{C}_{\mathrm{CHF\ NS}}$, *i.e.* the difference between Fig. 1 (c) and Fig. 1 (b), where τ is the time lag and s is the scale (in units of time [sec.]).

5. Discussion and conclusions

Compared with HRV of PAF patients suffering neurogenic SNS dysfunction, heart rate fluctuations in CHF patients, especially those in non-survivors, are characterised by a scale specific increase of non-Gaussianity in the short scale (< 25) [sec.][2], Fig. 2. It is evident that this non-Gaussianity increase is of sympathetic origin, and it is also evident that this non-Gaussianity increase in CHF, both SV and NS, is of *random, uncorrelated* character, due to loss of correlations in sympathetic breakdown in PAF; see Fig. 3 (b),(c). One possible implication of the increased short scale random non-Gaussianity in CHF patients, particularly non-survivors, is a selective breakdown in the short-term neural regulation of heart rate (*i.e.* baroreflexes). Insufficiency or instability in the negative feedback control may lead to HRV dynamics with unresponsive quiescent phases of random duration giving rise to cardiac congestion and interwoven with sympathetic firing at randomly high rates.

[2] Roughly corresponding with 40 beats, referred to in Refs. [18,17].

Although the physiological origin of the short-term non-Gaussianity is still undetermined, in Kiyono *et al.* [11] we suggested that the underlying cause may be revealed by studying clustering of variance in HRV dynamics by analysing magnitude correlations. Here we have further investigated the underlying mechanism, also comparing the CHF subjects, generally suffering from the elevated sympathetic activity, with newly obtained results for the primary autonomic failure (PAF) patients with sympathetic deficiency. In summary, we confirm the sympathetic origin of the non-Gaussianity index, previously identified in Refs. [17, 18], elucidating its random character. We further confirm intermittency of the high frequency, fine scale firing of the parasympathetic nervous system branch. We obtain another confirmation of the antagonistic function of the autonomic regulation of HRV, this time in terms of intermittency — heteroscedastic clustering of variance. In this context, we identify autonomic antagonism as the source of the mid to low frequency, intermediate scale intermittency observed at higher levels in CHF patients with elevated sympathetic activation and suppressed in the PAF patients — the case of neurogenic SNS dysfunction.

REFERENCES

[1] M. Kobayashi, T. Musha, *IEEE Trans. Biomed. Eng.* **29**, 456 (1982).
[2] H.E. Stanley, *Physica A* **285**, 1 (2000).
[3] T. Mora, W. Bialek, *J. Stat. Phys.* **144**, 268 (2011) `arXiv:1012.2242v1 [q-bio.QM]`.
[4] C.-K. Peng *et al.*, *Phys. Rev. Lett.* **70**, 1343 (1993).
[5] P.Ch. Ivanov *et al.*, *Nature* **399**, 461 (1999).
[6] P.Ch. Ivanov *et al.*, *Chaos* **11**, 641 (2001).
[7] Z.R. Struzik *et al.*, *Phys. Rev.* **E70**, 050901 (R).
[8] K. Kiyono *et al.*, *Phys. Rev. Lett.* **93**, 178103 (2004).
[9] P. Bak, C. Tang, K. Wiesenfeld, *Phys. Rev. Lett.* **59**, 381 (1987).
[10] H.E. Stanley, *Introduction to Phase Transitions and Critical Phenomena*, Oxford University Press, 1971.
[11] K. Kiyono *et al.*, *Phys. Rev. Lett.* **95**, 058101 (2005).
[12] A. Arneodo, E. Bacry, S. Manneville, J.F. Muzy, *Phys. Rev. Lett.* **80**, 708 (1998).
[13] E. Floriani, D. Volchenkov, R. Lima, *J. Phys. A* **36**, 4771 (2003).
[14] A.V. Zimin, B.R. Hunt, E. Ott, *Phys. Rev.* **E67**, 016204 (2003).
[15] N. Platt, E.A. Spiegel, C. Tresser, *Phys. Rev. Lett.* **70**, 279 (1993).
[16] Y.Li, C. Meneveau, *Phys. Rev. Lett.* **95**, 164502 (2005).
[17] Z.R. Struzik *et al.*, *Europhys. Lett.* **82**, 28005 (2008).

[18] K. Kiyono *et al.*, *Heart Rhythm* **5**, 261 (2008).
[19] J.P. Crutchfield, K. Young, *Phys. Rev. Lett.* **63**, 105 (1989).
[20] Z.R. Struzik *et al.*, *IEEE Trans. Biomed. Eng.* **53**, 89 (2006).
[21] B. Castaing, Y. Gagne, E.J. Hopfinger, *Physica D* **46**, 177 (1990).
[22] K. Kiyono, Z.R. Struzik, Y. Yamamoto, *Phys. Rev.* **E76**, 041113 (2007).