Chaos, Solitons and Fractals 91 (2016) 210–213

Contents lists available at ScienceDirect

Chaos, Solitons and Fractals

Nonlinear Science, and Nonequilibrium and Complex Phenomena

journal homepage: www.elsevier.com/locate/chaos

Multifractality in cerebrovascular dynamics: an approach for mechanisms-related analysis

A.N. Pavlov[a,b,*], O.V. Semyachkina-Glushkovskaya[b], O.N. Pavlova[b], A.S. Abdurashitov[b], G.M. Shihalov[b], E.V. Rybalova[b], S.S. Sindeev[b]

[a] Saratov State Technical University, Politehnicheskaya Str. 77, 410054, Saratov, Russia
[b] Saratov State University, Astrakhanskaya Str. 83, 410012, Saratov, Russia

ARTICLE INFO

Article history:
Received 3 April 2016
Revised 2 June 2016
Accepted 5 June 2016

PACS:
05.45.Tp

Keywords:
Cerebrovascular dynamics
Multifractality
Complexity
Blood flow

ABSTRACT

We consider here an approach for multifractal analysis of cerebrovascular dynamics that provides a relation between the occurred changes in the blood flow velocity and the physiological mechanisms of cerebral regulation. We apply this approach to study responses of the cerebral dynamics in rats to variations in the peripheral blood pressure and show that these responses are essentially different for large and small vessels. We conclude that the acute peripheral hypertension is accompanied by changes in the multifractal properties of the microcerebral dynamics associated with the NO-related endothelial function.

© 2016 Elsevier Ltd. All rights reserved.

1. Introduction

During the last decades, complex scaling phenomena are widely studied in the dynamics of many natural systems[1–5]. The recently proposed wavelet-transform modulus maxima method (WTMM) offered possibilities of characterizing multifractal structures in highly inhomogeneous and nonstationary processes[6–8]. It is based on the continuous wavelet-transform that allows ignoring a slow nonstationarity (a trend) by selecting an appropriate wavelet function possessing several vanishing moments. An additional feature of this approach consists in a faster convergence of estimated measures with the amount of data as compared with many other numerical techniques [9]. The latter circumstance is important, e.g., in physiological studies of adaptation processes where analysis of short-term signals provides important diagnostic markers[10–12]. Thus, the WTMM-approach has demonstrated its potential in the study of stress-induced phenomena allowing separation between different responses of the cardiovascular system that are not revealed with the standard spectral or correlation analysis [9,13]. Unlike other tools for multifractal analysis such as, e.g., the structure function method [14], the wavelet-based technique is not restricted by the range of the Hölder exponents and provides more stable analysis of weak singularities (small fluctuations) in data series.

Recent works showed an essential potential of the WTMM-approach in characterizing functional distortions in the cerebrovascular dynamics [15,16]. To assess such distortions noninvasively, changes in the cerebral blood flow (CBF) are typically analyzed with the laser speckle contrast imaging (LSCI) [17,18] or other optical coherent-domain methods that possess a high spatio-temporal resolution. The LSCI-technique provides information about the CBF-velocity in different parts of a selected region that may include cerebral vessels of different size, e.g., arteries or veins and small vessels of the microcirculatory network. Such information is important to reveal early stages of transformation of normal physiological processes into the pathological dynamics that may differ for large and small cerebral vessels. An example of different responses at the macro- and the microscopic levels is discussed in [19] for the case of the development of intracranial hemorrhages in newborn rats.

However, former studies considered the multifractal properties of cerebrovascular dynamics as a whole system. They did not provide any attempt to associate the occurred changes with individual mechanisms of physiological regulation, and the latter resulted in difficulties of an appropriate interpretation of the obtained singularity spectra. Here, we use another ideology of signal processing

* Corresponding author. Tel.: +78452210710.
E-mail address: pavlov.alexeyn@gmail.com (A.N. Pavlov).

http://dx.doi.org/10.1016/j.chaos.2016.06.002
0960-0779/© 2016 Elsevier Ltd. All rights reserved.

that consists in the separate analysis of multifractal properties in distinct frequency ranges related to different physiological control mechanisms. Unlike the traditionally used approaches for multifractal analysis of physiological signals, this ideology provides a way of an appropriate interpretation of the obtained multifractal characteristics and their association with functional distortions in individual mechanisms of the physiological regulation of the CBF-dynamics. Such opportunity occurs due to the fact that distinct regulatory mechanisms are typically related to different frequency ranges [20].

Using the LSCI-method for noninvasive measurements of the blood flow velocity in cerebral vessels in rats and the WTMM-approach for data analysis, we quantify responses of the cerebrovascular dynamics to variations in the peripheral blood pressure. According to the traditional physiological assumptions, the CBF-dynamics remains nearly unchanged at such variations (a model for static cerebral autoregulation [21]). Nevertheless, recent studies established a relation between the hypertension and the increased risk for the stroke associated with the distortions in the CBF-dynamics [22,23]. Due to this, analysis of the increased CBF-sensitivity to variations of the peripheral blood pressure is important for a clearer understanding of reasons preceding the development of intracranial hemorrhages.

The paper is organized as follows. Section 2 briefly discusses experimental procedures and tools for data processing. A study of responses of the cerebrovascular dynamics caused by the acute peripheral hypertension is described in Section 3. Main concluding remarks are given in Section 4.

2. Experiments and methods

2.1. Experimental procedure

Experiments were performed in mongrel normotensive male rats (n=11) weighing from 200 to 250 g in accordance with the Guide for the Care and Use of Laboratory Animals. Rats were housed at 25 ± 2 °C, 55% humidity, and 12:12 h light/dark cycle.

One day before the experiment, anesthetized animals were instrumented with polyethylene catheters for the continuous recording of the mean arterial pressure (MAP). In the course of this procedure, the catheter PE-50 with the PE-10 tip (Scientific Commodities INC., Lake Havasu City, Arizona) was inserted into the femoral artery. The femoral vein was also catheterized for phenylephrine infusions that provide a pharmacologically induced acute peripheral hypertension.

MAP was monitored with the PowerLab system (ADInstruments, Australia). Recordings were acquired for three states: (i) the base-line measurements, (ii) the first dose of phenylephrine (0.125 μg/kg, iv), and (iii) the second dose of phenylephrine (0.25 μg/kg, iv). The phenylephrine-related responses in MAP were controlled in each rat. After each phenylephrine infusion, MAP increased by about 10%. Segments of experimental data associated with the strongest responses were selected for the further analysis.

A study of how the acute peripheral hypertension is reflected in the cerebrovascular dynamics was performed using a home-made system for LSCI. Speckle images were recording by illuminating the exposed rat cortex with the HeNe laser (Thorlabs HNL210L, 632.8 nm). The monochromatic CMOS camera Basler acA2500-14 g and Computar M1614-MP2 lens were used to acquire raw laser speckle images with the rate of 40 frames/second. An additional averaging procedure was provided for noise reduction. Averaging was performed within a moving window (55 × 55 pixels) over 50 consequent images. A conversion of raw laser speckle images into the flow velocity data was based on the Gaussian approach. Two time series reflecting the CBF-velocity in the macroscopic vessels (the sagittal sinus) and the microscopic vessels (small vessels of microcirculatory network) were selected at each stage of the experiments. All measurements were performed when CBF becomes stable.

2.2. Data preprocessing

The recorded CBF-data were band-pass filtered to separate between rhythmic contributions associated with distinct mechanisms of the physiological regulation. Three frequency ranges were selected for the further thorough analysis:

Range I: 0.05–0.1 Hz. Typically, two assumptions about the origin of the corresponding rhythmic activity are considered. It is associated with the metabolic processes or with the NO-related endothelial function. The latter mechanism can be responsible for the impairments of CBF [24].

Range II: 0.1–0.25 Hz. This rhythmic activity is related to the neurogenic regulatory mechanism [25]. The CBF-dynamics in the given frequency range can also be associated with the metabolic activity [26], however, the latter mechanism is less expressed.

Range III: 0.25-0.75 Hz. The given activity is caused by the myogenic response of smooth muscle cells in the vessel's walls [27,28].

The same physiological mechanisms are observed in humans, however, they are associated with lower frequencies, namely, 0.0095–0.02 Hz (range I), 0.02–0.06 Hz (range II), and 0.06–0.15 Hz (range III).

Time series related to the indicated frequency ranges in rats were analyzed separately to reveal possible changes in the CBF-dynamics at the macro- and the microscopic levels induced by the acute peripheral hypertension.

2.3. Data analysis

Data analysis was performed using the wavelet-based multifractal formalism that represents a powerful approach for statistical analysis of inhomogeneous processes and short signals. For this purpose, the wavelet-transform modulus maxima method (WTMM) was applied [6,7]. Its thorough description is given in the review paper [8]. This technique provides estimations of the singularity spectrum and the Hölder exponents of a signal $x(t)$ based on its continuous wavelet-transform

$$T(s,z)=\frac{1}{s}\int_{-\infty}^{\infty}x(t)\psi\left(\frac{t-z}{s}\right)dt, \tag{1}$$

where the parameters s and z characterize the time scale and the position of the wavelet-function $\psi(t)$ along the time axis. Irregular behavior of the signal $x(t)$ is typically analyzed using real-valued wavelets representing different derivatives of the Gaussian function, with the MHAT-wavelet being the widely used function

$$\psi=(1-t^2)\exp\left(-\frac{t^2}{2}\right). \tag{2}$$

Main information about singularities of the function $x(t)$ is extracted from the lines $L(s)$ of the local maxima of modulus of the wavelet-coefficients $T(s, z)$, i.e., from the skeleton. For this purpose, the partition functions $Z(q, a)$ are constructed as

$$Z(q,s)=\sum_{l\in L(s)}|T(s,z_l(s))|^q\sim s^{\tau(q)} \tag{3}$$

with $z_l(s)$ defining the maximum associated with the line l, and the parameter q characterizing the strength of irregular behavior, from weak ($q<0$) to strong ($q>0$) singularities. In order to avoid incorrect definitions of $Z(q, s)$ when $T(s, z)$ approaches to zero value, a modification of Eq. (3) is mainly considered (see [8] for details).

The power-law dependence of the partition functions (3) is used to estimate scaling exponents $\tau(q)$. Based on $\tau(q)$, the spectrum of Hölder exponents $h(q)$ and the singularity spectrum $D(h)$

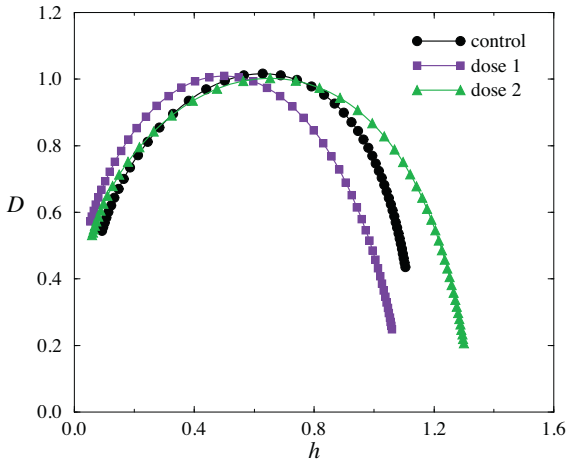

Fig. 1. Singularity spectra characterizing multiscale macrocerebral dynamics of blood flow associated with the frequency range I. The complexity measure Δ_h takes the values 1.02 (control), 1.01 (dose 1) and 1.22 (dose 2).

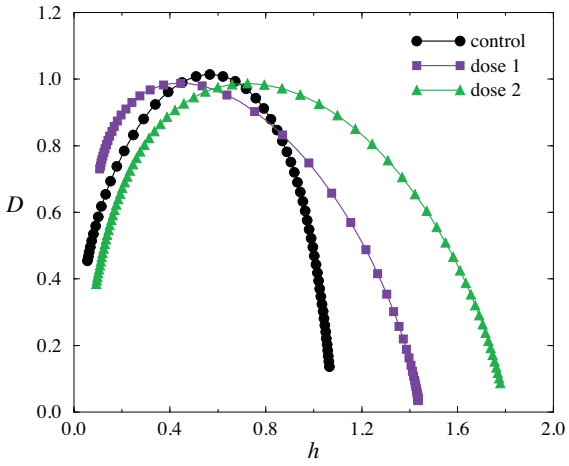

Fig. 2. Singularity spectra characterizing multiscale microcerebral dynamics of blood flow associated with the frequency range I. The complexity measure Δ_h takes the values 1.01 (control), 1.34 (dose 1) and 1.68 (dose 2).

are estimated as follows

$$h(q) = \frac{d\tau(q)}{dq}, \quad D(h) = qh - \tau(q). \tag{4}$$

The values $D(h)$ are related to the Hausdorff dimension D of subsets of data satisfying to the condition $h(x) = h$. The width of the function $D(h)$, namely, $\Delta_h = h_{max} - h_{min}$, is considered as a complexity measure quantifying the inhomogeneity of the signal $x(t)$. Higher inhomogeneity characterized by a wider singularity spectrum denotes an increased complexity of the analyzed processes. Taking into account that experimental data are short, we used here the range $q \in [-3.0, 3.0]$.

Results of the statistical analysis are reported as mean ± standard error. Distinctions in the CBF-dynamics between different physiological states are evaluated using the Mann-Whitney test. Significance level was set at $p < 0.05$.

3. Results and discussion

Unlike previous studies [15,16], here we quantify complexity of the CBF-dynamics associated with individual regulatory mechanics and analyze how the pharmacologically induced acute peripheral hypertension influences the blood flow velocity in cerebral vessels of different size. In order to do this, three complexity measures are estimated for each rat describing the macroscopic CBF-dynamics in the sagittal sinus related to the frequency ranges I, II, and III. Besides, three analogous complexity measures are introduced to characterize the microscopic CBF-dynamics in small vessels surrounding the sagittal sinus. Because the absolute values of the considered measures may essentially vary between the animals, we are mainly concentrated on the relative changes of complexity of CBF-dynamics after the phenylephrine infusions.

The considered approach for analysis of the CBF-dynamics in several distinct frequency areas provides additional abilities for unraveling mechanisms responsible for changes in the complexity measures. Fig. 1 shows an example of typical variations of the singularity spectrum reflecting the macroscopic CBF-dynamics in the sagittal sinus in the frequency range I. For all three considered states, the singularity spectrum confirms the presence of an inhomogeneous (the multifractal) structure of experimental recordings. The phenylephrine-related acute peripheral hypertension generally provides non-essential changes in numerical measures of multifractality characterizing the macroscopic dynamics of cerebral vessels (Fig. 1). Non-significant changes of the multifractality degree are comparable with those related to variations of algorithmic parameters. Thus, analysis of the macroscopic CBF-dynamics in the frequency range I does not reveal clear phenylephrine-related responses in the blood flow velocity in the sagittal sinus.

An essentially different response is observed at the level of small vessels of the microcirculatory network. CBF-dynamics in the frequency range I that is associated with the NO-related endothelial function shows a clearly expressed growth of the multiscality degree (Fig. 2) thus reflecting a higher inhomogeneity (complexity) of the velocity of blood flow caused by the acute peripheral hypertension. Fig. 2 demonstrates the strongest response of the microcerebral dynamics. When considering other frequency ranges, distinctions between the singularity spectra related to three considered physiological states are significantly less pronounced. Thus, we can conclude that the microcerebral dynamics in the frequency ranges II and III demonstrates subtle signs of the phenylephrine-related responses. Analogous results are obtained for the macroscopic cerebral dynamics associated with the discussed frequency ranges where no clear responses are revealed.

Results of the statistical analysis performed for the whole group of animals (Fig. 3) confirm that the neugenic regulation and the myogenic response of smooth muscle cells are nearly insensitive to the peripheral dynamics. To avoid effects of intra-groups distinctions between the used complexity measures, the values Δ_h estimated after the phenylephrine infusions are normalized to the value of Δ_h related to the base-line measurements for each rat. Although some distinctions between the macro- and the microcerebral circulation are revealed, e.g., the complexity measure Δ_h describing the CBF-dynamics in the range II slightly decreases for the velocity of blood flow in the sagittal sinus ($\Delta_h = 0.85 \pm 0.12$, dose 1) and slightly increases for the CBF-velocity in small vessels of the microcirculatory network ($\Delta_h = 1.14 \pm 0.13$, dose 1), these changes are non-significant.

According to Fig. 3b, only the CBF-dynamics associated with the microcerebral circulation in the frequency range I shows clear phenylephrine-related responses ($\Delta_h = 1.54 \pm 0.19$, dose 1; $\Delta_h = 1.63 \pm 0.22$, dose 2, $p < 0.05$). In other words, the pharmacologically induced acute peripheral hypertension influences the microscopic dynamics of small cerebral vessels, and the latter influence is associated with the NO-related endothelial mechanism of CBF-regulation. The corresponding responses at the macroscopic level are less pronounced ($\Delta_h = 0.97 \pm 0.09$, dose 1; $\Delta_h = 1.16 \pm 0.18$, dose 2, $p > 0.05$). Similar results are obtained for other wavelet functions such as, e.g., WAVE-wavelet.

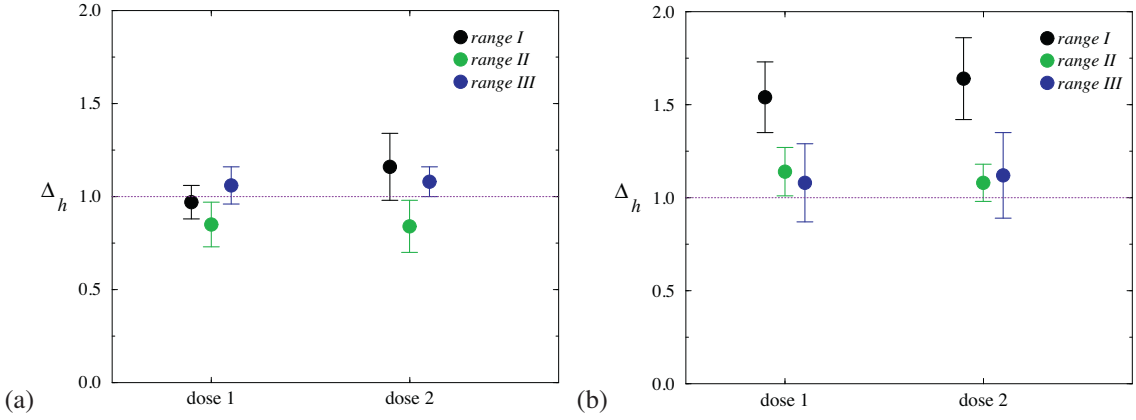

Fig. 3. Statistical analysis of complexity of macro- (a) and microcerebral dynamics (b) related to different mechanisms of physiological regulation.

4. Conclusions

Multifractal analysis is related to the most effective approaches that provide statistical analysis of time-varying processes. This tool has shown its strength in diagnostics of functional distortions of vessels dynamics. Its advantage consists in the ability of quantifying complex scaling phenomena using nonstationary, short and noisy signals. However, this tool is usually applied to complex processes generated by physiological systems that include many regulatory mechanisms. Pathological changes associated with an individual mechanism are reflected in the whole structure of the measured time series and can be quantified with the singularity spectrum. A disadvantage is that variations of the dependence $D(h)$ are difficult to associate with any mechanism of the physiological regulation. This is one of the reasons, why the multifractal analysis has few applications in physiological studies.

Here, we consider a way for mechanisms-related analysis of the cerebrovascular dynamics with the wavelet-based multifractal formalism. A preliminary band-pass filtering of experimental data provides an opportunity for separation of rhythmic contributions related to the NO-related endothelial regulation, the neurogenic regulatory mechanism and the myogenic response of smooth muscle cells in the vessel's walls. Based on experiments with the phenylephrine-related acute peripheral hypertension, we studied responses of the CBF-dynamics in the sagittal sinus being one of the major sinuses collecting blood from veins of the brain, and in small vessels of the microcirculatory bed nearby the sagittal sinus. The obtained results confirm essentially different responses: while the macrocirculation is nearly insensitive to variations in the peripheral blood pressure, the microcirculation is characterized by increased complexity (inhomogeneity) of the CBF-dynamics. Moreover, this effect is caused by changes in the endothelial mechanism of the CBF-regulation. Thus, the used approach provides both, numerical characteristics of functional changes in the microcerebral dynamics caused by the acute peripheral hypertension and their possible physiological interpretation that offers a way for a deeper understanding of the observed phenomena. In particular, these results show that the traditional assumption about a static cerebral dynamics should be corrected for the microcerebral dynamics. The considered approach can be applied in humans, however, abilities of LSCI-technique are restricted in depth of the performed analysis. A promising area is the study of cerebrovascular dynamics in newborns where recordings of the CBF-velocity can be non-invasively provided through the fontanel.

Acknowledgments

A.P. acknowledges support from the Ministry of Education and Science of Russian Federation in the framework of the implementation of state assignment 3.23.2014/K (project SSTU-157) and within the basic part (project SSTU-141), and from the Russian Foundation for Basic Research (grant 14-52-12002). O.P. acknowledges support from the Russian Foundation for Basic Research (grant 16-32-00188). O.S.-G. acknowledges support from the Russian Foundation for Basic Research (grant 14-02-00526a).

References

[1] Mandelbrot BB. Multifractals anf 1/F Noise: wild self-affinity in physics. New York: Springer-Verlag; 1999.
[2] Bunde A, Havlin S. Fractals in science. Berlin: Springer; 1994.
[3] Benzi R, et al. Phys Rev Lett 1991;67:2299.
[4] Strait BJ, Dewey TG. Phys Rev E 1995;52:6588.
[5] Arrault J, et al. Phys Rev Lett 1997;79:75.
[6] Muzy JF, Bacry E, Arneodo A. Phys Rev Lett 1991;67:3515.
[7] Muzy JF, Bacry E, Arneodo A. Phys Rev E 1993;47:875.
[8] Muzy JF, Bacry E, Arneodo A. Int J Bifurcat Chaos 1994;4:245.
[9] Pavlov AN, Anishchenko VS. Physics-Uspekhi 2007;50:819.
[10] Ivanov P, et al. Nature 1999;399:461.
[11] Stanley HE, et al. Physica A 1999;270:309.
[12] Ivanov P, et al. Chaos 2001;11:641.
[13] Pavlov AN, Ziganshin AR, Klimova OA. Chaos, Solit Fractals 2005;24:57.
[14] Frish U, Parisi G, Ghil M, Benzi R, Parisi G. editors. Turbulence and predictability in geophysical fluid dynamics and climate dynamics. Amsterdam: North-Holland; 1985. p. 71.
[15] Semyachkina-Glushkovskaya OV, et al. Biomed Opt Exp 2015;6:4088.
[16] Pavlov AN, et al. J Innov Opt Health Sci 2015;8:1550041.
[17] Briers JD, Webster S. J Biomed Opt 1996;1:174.
[18] Liu S, Li P, Luo Q. Opt Exp 2008;16:14321.
[19] Pavlov AN, et al. Chaos, Solit Fractals 2015;77:6.
[20] Shoigai Y, Stefanovska A, McClintock PVE. Phys Rep 2010;488:51.
[21] Lassen NA. Physiol Rev 1959;39:183.
[22] Gianaros PJ, Greer PJ, Ryan CM. Neuroimage 2006;31:754.
[23] Beason-Held LL, et al. Stroke 2007;39:1766.
[24] Stefanovska A, Bračič M, Kvernmo HD. IEEE Trans Biomed Eng 1999;46:1230.
[25] Zhang R, et al. Circulation 2002;106:1814.
[26] Kitney RI, et al. J Biomed Eng 1985;7:217.
[27] Rowley AB, et al. Physiol Meas 2007;28:161.
[28] Sosnovtseva OV, et al. Am J Physiol Renal Physiol 2007;293:F1545.