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Transitions in skin blood flow fractal scaling: The importance of fluctuation amplitude in microcirculation

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ABSTRACT

Detrended fluctuation analysis (DFA) of laser Doppler flowmetry (LDF) time series from volar skin reveals three scaling regions: cardiac, cardio-respiratory and local. Scaling exponents, slopes (α_C, α_{CR} and α_L) of the straight lines, in these regions indicate correlation properties of LDF signal. Transitions from uncorrelated to positive in cardiac (α_C) and positive to negative correlations in the cardio-respiratory (α_{CR}) exponent have been observed for vasodilatation signals in response to local heating. However, positive correlation in local region (α_L) did not change with vasodilatation. We studied whether the transitions in scaling exponents are correlated with the increase in peak to peak fluctuation amplitude (A_F) of LDF signal. LDF signals were normalized to unity using average values of their pulsatile parts: baseline and saturation signals. If A_F of normalized LDF signal is ≥ 0.5, we observed transitions in α_C and in α_{CR} but not in α_L, in healthy subjects. It is suggested that the transition from positive to negative correlation in α_{CR} with increasing amplitude may be explained by intact arteriolar myogenic activity in healthy young (Y) and middle aged (MA) subjects. In contrast, we did not observe transition in α_{CR} suggesting impaired myogenic activity in patients with essential hypertension (EHT).

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Introduction

Because of the rhythmic pulsation of the heart, the most obvious feature of blood flow in the arterial side of circulation is that it is pulsatile. However, the pressure pulse producing this pulsatile nature of blood flow is the leading hemodynamic risk factor for cardio-vascular system (Nichols and O'Rourke, 2005; Safar and Struijker-Boudier, 2010; Thorin and Thorin-Trescases, 2009). Pressure and flow waves generated during ventricular systole are partially reflected from the vasculature and these reflections can increase pulse pressure and augments mechanical stress on cardiovascular system (Nichols and O'Rourke, 2005; Penny et al., 2008). In addition, increased interaction of macro- and microvascular systems due to wave reflections between them may accelerate the progressive stiffening of the vascular wall that normally occurs with advancing age (Feihl et al., 2009; Thorin and Thorin-Trescases, 2009). Therefore, one of the most important functions of arterial tree is to dampen (cushioning function) the pressure oscillations and to generate continuous blood flow in microvascular beds (Nichols and O'Rourke, 2005).

Although the microcirculation was once considered as a segment of the vascular tree in which pulsations have almost completely disappeared, spectral analysis of cutaneous microvascular blood flow has demonstrated that the cardiac signals, source of pulsatility, exist in these vascular beds (Bračić and Stefanovska, 1998). To calculate the pulsatility of microvascular blood flow, relative contribution of its control mechanisms to power spectral density (PSD) function of laser Doppler flow (LDF) signal from cutaneous vascular beds can be used. Recently, Esen et al. (2013) used a pulsatility ratio (R = central PSD/local PSD) for the assessment of microvascular function and they have been shown that R is useful for diagnostics in patients with essential hypertension (EHT). Although lower pulsatility ratio ($R \leq 1$) has been commonly found from baseline LDF signal in healthy young (Y) subjects, R has been increased to 3 in middle aged (MA) group and to 9 in EHT patients. In addition it has been shown that vasodilatation increases the R in Y and MA subjects but not in patients with EHT. Therefore, Esen et al. (2013) suggested that pulsatility begins to play a role in controlling the baseline blood flow when $R \geq 1$ the local mechanisms lose their control in favor of central mechanisms in microvascular beds. On the other hand, increase in pulsatility due to pathology such as EHT can lower the response of microvascular beds to vasodilator stimuli. However, the level of pulsatility that causes pathology in the microvascular beds is not clearly determined.

Recently, fractal analyses have been used to investigate the nonlinear/nonstationary nature of LDF time series from cutaneous vascular beds (Carolan-Rees et al., 2002; Esen and Esen, 2006; Esen et al., 2009, 2011, 2014; Humeau et al., 2010; Liao et al., 2011). One of the techniques that can cope with nonstationarity of a signal is the detrended fluctuation analysis (DFA). DFA of LDF signals reveals three distinct scaling regions (cardiac, cardio-respiratory and local) indicating individual and/or collective behavior of the microvascular control systems (Esen and Esen, 2006). Scaling exponent (α: slope of

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the straight line in each region) indicates the correlation property of LDF signal for the corresponding time interval. Uncorrelated signals in the cardiac and positively correlated signals in cardio-respiratory and local regions are the common features found in fractal analysis of baseline LDF signals. Transitions from uncorrelated to positive in cardiac and from positive to negative correlation in cardio-respiratory regions are other common features that have been found during vasodilatation (Esen and Esen, 2006; Esen et al., 2009, 2011). This paper is motivated by these previous experimental findings.

The appearance of both transitions with vasodilatation suggests that the increase in pulsatility of blood flow can be the cause of these transitions. In this study, we will focus on finding a potential link between pulsatility (peak to peak fluctuation amplitude, A_F) and scaling exponents of LDF signals. Furthermore, the importance of pulsatility in aging and disease or in understanding a control mechanism may be quantified with finding a threshold for pulse amplitude, above which the scaling exponents change abruptly.

Materials and methods

Subjects

Fifty nine normotensive healthy subjects (25 Y, 34 MA) and 34 EHT patients participated voluntarily in this study. EHT patients had a history of blood pressure without any apparent underlying cause. Their blood pressure was controlled (below 140/90 mm Hg) with the antihypertensive agents. EHT subjects with diabetes, hypercholesterolemia, hyperhomocysteinemia, chronic renal failure, peripheral vascular disease, coronary artery disease and heart failure were excluded from the study. All subjects were non-obese (body mass index <30 kg/m^2), non-smokers and physically active but none of them were involved in a regular exercise program. The study protocol was approved by the ethics committee of the university hospital and conducted according to the principles of the Declaration of Helsinki 2008. Subject characteristics are summarized in Table 1.

Instrumentation

A data acquisition system (Biopac Systems, Inc. USA) equipped with a laser Doppler flowmeter (780 nm, 1 mW) was used to record the forearm cutaneous blood flow. Analog signal of the LDF instrument was sampled at 1 kHz. To record the blood perfusion in the center of a locally heated area of the skin, the fibers of the LDF probe (480 μm diameter) were placed in the center of a heating probe. The heating unit (Moor Instruments Ltd. UK) was able to control the temperature of the probe with ±0.3 °C accuracy. This combined probe was fixed to the volar region of the forearm with a double sided adhesive tape.

Measurement of basal and evoked skin blood flow

Cutaneous blood flow of the subjects lying in supine position was studied on the volar site of the forearm. The studies were performed in a quiet room at 23 ± 2 °C. All subjects were asked to refrain from consuming alcohol and caffeine containing drinks a day before the measurements. Each subject had a 30 min rest before the test. After a 15 min baseline skin blood flow recording, a constant local heat (42 °C) was applied (Minson et al., 2001). The temperature of the local heating unit was increased at a rate of 0.1 °C per second to a temperature of 42 °C and was held constant at 42 °C for at least 35 min. The recording of LDF signal was continued to observe the plateau region in response to local heating.

Table 1
Characteristics of the subjects.

Characteristic	Control groups		
	Y	MA	EHT
n	25	34	34
Age (years)	21 ± 3	50 ± 7	44 ± 4
Systolic BP (mm Hg)	115 ± 5	120 ± 5	135 ± 5
Diastolic BP (mm Hg)	75 ± 5	70 ± 10	75 ± 15
Heart rate (beats/min)	78 ± 4	75 ± 8	71 ± 6

Normalization of LDF signals

The values of baseline and vasodilatation LDF signals are not absolute and even in the same subject may have substantial variability due to varying orientation and distribution of the arterioles beneath the probe. Therefore, appropriate data normalization is required prior to subsequent statistical analysis. Several different approaches are commonly used based on assumptions about the characteristics of the data. Since LDF signals have a baseline (minimum) and a plateau region of the vasodilatation (maximum), min–max normalization was used by scaling their average values so that they fall within a range 0 to 1. In general, local heating evokes an initial dilator response that peaks in a few minutes, falls a little and then followed by a secondary dilatation that has a plateau after ~25 min of heat application. The LDF signal in this plateau region (saturation level of the response to local heating) was used for our analyses. The following equation was used to implement a unity-based normalization;

$$\mathrm{LDF} = \frac{(\mathrm{LDF})_i - (\mathrm{LDF})_B}{(\mathrm{LDF})_S - (\mathrm{LDF})_B}$$

where: $(\mathrm{LDF})_i$ is the each data point i, $(\mathrm{LDF})_B$ is the average value of baseline signal, $(\mathrm{LDF})_S$ is the average value of saturation signal during vasodilatation and LDF is the normalized data point between 0 and 1.

Fluctuation amplitude (A_F)

Since there is a constant DC component that is equal to the mean value of a normalized signal, deviations were measured from these average reference signals. The fluctuation amplitude of a LDF signal is defined as the difference between its maximum and minimum values. Two LDF signals, baseline and vasodilatation (plateau region), were used for these measurements and we calculated two amplitude values for each subject.

Detrended fluctuation analysis (DFA)

The fractal nature of the irregular and nonstationary LDF signal can be obtained by DFA, a method for determining the scaling behavior of data in the presence of possible trends. Complete details of the methodology are published elsewhere (Peng et al., 1994). In brief, the original LDF time series is integrated and then divided into boxes of equal length, n. To find the local trend in each box of length n, a least-squares line is fitted to the data. The root mean square deviation between integrated series and its trend in each box is then calculated and denoted by $F(n)$. This computation is repeated over all box sizes (time scales). A linear relationship between $Ln[F(n)]$ and $Ln(n)$ indicates the presence of scaling (self similarity): $F(n) \sim n^{\alpha}$. In other words, fluctuations in small boxes are related to the fluctuations in larger boxes in a power-law fashion. The slope of the line relating $Ln[F(n)]$ to $Ln(n)$ determines the fractal scaling exponent, α.

To test whether LDF time series exhibit fractal behavior and to determine their correlation properties, we can apply the DFA algorithm to LDF signal. $\alpha = 0.5$ for a white noise process. Scaling exponent in the range of $0.5 < \alpha \leq 1$ indicates the presence of positive long range correlations. On the other hand $0 < \alpha < 0.5$ indicates the presence of negative long range correlations. $\alpha = 1$ for a flicker noise type of fluctuation in a dynamical system of self organized critical state.

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