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Multifractal analysis of nonlinear complexity of sacral skin blood flow oscillations in older adults

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Abstract

The objective of this study was to investigate the relationship between cutaneous vasodilatory function and nonlinear complexity of blood flow oscillations (BFO) in older people. A non-painful fast local heating protocol was applied to the sacral skin in 20 older subjects with various vasodilatory functions. Laser Doppler flowmetry was used to measure skin blood oscillations. The complexity of the characteristic frequencies (i.e., metabolic (0.0095–0.02 Hz), neurogenic (0.02–0.05 Hz), myogenic (0.05–0.15 Hz), respiratory (0.15–0.4 Hz), and cardiac (0.4–2 Hz)) of BFO was quantified using the multifractal detrended fluctuation analysis. Compared with the 65–75 years group, the complexity of metabolic BFO in the 75–85 years group was significantly lower at the baseline ($P < 0.05$) and the second peak ($P < 0.001$). Compared with baseline BFO, subjects in the 65–75 years group had a significant increase in the complexity of metabolic BFO ($P < 0.01$) in response to local heating; while subjects in the 75–85 years group did not. Our findings support the use of multifractal analysis to assess aging-related microvascular dysfunction.

Keywords

Aging; Blood flow oscillations; Complexity; Detrended fluctuation analysis; Laser Doppler; Multifractal analysis

1 Introduction

The natural aging process induces structural and functional changes in the cardiovascular system [26]. These changes may attenuate microvascular reactivity in response to environmental stimuli, thus placing tissue at higher risk for ischemic damage and even pressure ulcers in older people [20, 29, 31]. Local skin temperature is a major causative

factor of pressure ulcers in older people due to the prolonged sitting or bed rest, which may increase skin temperature [9, 32]. Patterson and Fisher studied pressure and temperature patterns under ischial tuberosities in paraplegic subjects and found that skin temperature increased while sitting, and decreased rapidly after removal of external pressure [32]. Fisher et al. investigated the effect of wheelchair cushion on skin temperature in healthy subjects and observed an increase in skin temperature ranged between 2.3 and 2.5°C under ischial tuberosities and between 3.2 and 3.5°C under thighs when sitting on the latex rubber cushion for 30 min [9]. On the contrary, Linder-Ganz and Gefen reported that gracilis muscle of rats under pressure for 2 h shows a decrease in temperature of loaded muscles [24]. They suggested that a decrease in temperature of loaded muscles is related with local ischemia. In the situation of an increase of skin temperature, inability to increase skin blood flow to remove excessive heat and meet the metabolic needs may result in ischemic damage [20]. Thermal stress along with pressure, shear, and moisture are causative factors of pressure ulcers [17]. By assessing microvascular response to local heating, clinicians can assess risk for pressure ulcers in older people.

Wavelet-based spectrum analysis of blood flow oscillations (BFO) has been proposed to develop an in vivo non-invasive assessment of skin microvascular dysfunction [20, 35, 36]. Wavelet analysis reveals five characteristic frequencies embedded in skin BFO, which correspond to metabolic (0.0095–0.02 Hz), neurogenic (0.02–0.05 Hz), myogenic (0.05–0.15 Hz), respiratory (0.15–0.4 Hz), and cardiac (0.4–2.0 Hz) activities. Wavelet analysis can be used to quantify the contribution of each physiological control mechanism to the skin vasodilatory and vasoconstrictive response. Our previous study has demonstrated that older subjects have a lower increase in the amplitude of metabolic, neurogenic, and myogenic frequencies in response to local heating [20]. However, the cardiovascular system is a complex, nonlinear dynamical system consisting of “coupled” subsystems [15, 16, 34, 37]. Wavelet analysis cannot directly account the interactions among the control mechanisms and quantify nonlinear properties of microcirculatory system. Thus, a nonlinear analysis of BFO is needed to fully quantify the dynamics of BFO [18, 20].

The interaction among control mechanisms can be quantified by studying the complexity of the characteristic frequencies of BFO [10, 11, 25]). Goldberger et al. suggested that the complexity of a physiologic system arises from the interaction of structural units and regulatory feedback loops [10, 11]. Lipsitz and Goldberger proposed that a loss of complexity in physiologic function may be due to the impairment of functional components and/or altered coupling between these components [25]. The authors postulated that the aging process can be defined by a progressive loss of complexity in the dynamics of all physiologic systems. The concept has gained its acceptance in various fields recently and has demonstrated usefulness to identify pathological states in patients, including heart rate variability [2, 16] and blood flow oscillations [15].

Complexity of the cardiovascular system is currently assessed by several methods [2]. One method is self-similarity measures such as Hurst exponent and the scaling exponent calculated from the detrended fluctuation analysis (DFA). Several studies of aging showed that the DFA exponents increase with age, indicating that complexity decreases with age [2, 10, 11, 38]. Other methods, including entropy (approximate entropy or sample entropy), correlation dimension (CD), and Lyapunov exponents (LE), describe the complexity of a signal in phase space. The current research results indicate that diseases and aging are associated with a decrease in the complexity of cardiovascular system [23, 34].

Previous studies by our group and others have demonstrated that blood flow signals measured by a laser Doppler flowmetry (LDF) are fractal with several distinct scaling regions that are related to the frequency bands of blood flow control mechanisms [7, 23].

Our results showed that the intermediate-term scaling exponent is associated with myogenic activity and that the coupling between cardiac and respiratory activity is sensitive to thermal stress [23]. The long-term scaling exponent that reflects the overall scaling properties of local mechanisms of blood flow (metabolic, neurogenic, myogenic), however, did not show significant changes. One possible reason is that the metabolic control and neurogenic control are competing factors of blood flow regulation [31, 37], and thus their individual behavior cannot be characterized by an overall scaling exponent. In order to examine this question, we proposed to examine the aging effect on the complexity of the characteristic (metabolic, neurogenic, myogenic, respiratory, and cardiac) components of BFO. For the collected data set, wavelet and several nonlinear analyses of skin BFO have been reported in our previous publications [20, 23]. In this study, a new analysis, multifractal detrended fluctuation analysis (MDFA) [21] was performed to quantify the complexity of characteristic components of BFO in older subjects with various vasodilatory functions. We hypothesized that metabolic BFO exhibits a lower complexity in subjects with advanced age. The rationale for this hypothesis is based on the fact that skin blood flow signals have been shown to be multifractal in young subjects and monofractal in older subjects [15]. However, it is unclear which characteristic frequency of BFO contributes to a decrease in multifractality of BFO in older subjects. Research studies have known that endothelial function declines with age, and aging is associated with a decrease in nitric oxide production and release [29]. Thus, we examined whether the metabolic frequency (0.0095–0.02 Hz) is the main factor causing a loss of complexity of BFO in elderly subjects.

2 Methods

2.1 Research participants

This study was approved by the University Institutional Review Board. Informed consent was obtained from each participant before any testing. A total of 20 subjects were recruited into this study. The degree of vasodilation was quantified by the Biphasic Thermal Index (BTI) [20], defined as ratios of first peak, nadir, and second peak to baseline blood flow during the biphasic vasodilation. The subjects were divided into two groups: 10 subjects (6 males and 4 females) aged 65–75 years with higher degrees of vasodilation (BTI (5.5, 4.5, 10.1)) and 10 subjects (5 males and 5 females) aged 75–85 years with lower degrees of vasodilation (BTI (3.7, 3.2, 6.7)). The exclusion criteria of the two groups included the presence of pressure ulcers, diabetic mellitus, hypertension, cardiopulmonary diseases, or taking of any medications that may affect cardiopulmonary function. One subject in the 65–75 years group took medications for benign prostate enlargement. The demographic data of participants were as follows: the mean (standard deviation, SD) of age, height and weight of the 65–75 years group were 70.3 (3.4) years, 1.74 (0.15) m and 81.3 (9.9) kg, respectively. The means (SD) of age, height and weight of the 75–85 years group were 78.2 (2.0) years, 1.67 (0.10) m, and 70.0 (10.4) kg, respectively.

2.2 Instrumentation

The laser Doppler flowmetry (LDF) (BPM2 main unit and P-435 probe, Vasamedics, Eden Prairie, MN) was used to measure sacral skin blood flow oscillations. The LDF used in this study utilizes a 780 nm laser light with a separation of 0.25 mm between emitting and receiving probes. This configuration leads to a measurement depth on the order of 0.5–1 mm for the human skin [14]. The output value is defined as the number of red blood cells in the floodlighted volume times their velocity, and is reported as perfusion units, which are arbitrary [14]. The laser Doppler flowmetry is a well accepted tool to assess microcirculation [30]. A comparison of skin perfusion measured between LDF and radioisotopic clearance techniques (the most accurate measurement of skin perfusion) yields a linear relationship with correlation coefficients up to 0.98 [30]. Skin blood flow was

recorded on a computer via an analog-to-digital converter with a sample frequency of 20 Hz. The temperature of the heater probe (TCO, Vasamedics, Eden Prairie, MN) was set to 42°C to heat the sacral skin. This heating protocol was designed to differentiate between axon reflex mediated vasodilation and nitric oxide mediated vasodilation [28].

2.3 Multifractal detrended fluctuation analysis

Skin blood flow signals have been shown not to be monofractal signals [15]. A monofractal signal is homogeneous, in the sense that it has the same scaling properties throughout the entire signal. A multifractal signal, on the contrary, is composed of many subsets that have different scaling properties. The multifractality may exhibit in several ways[21]: a type of correlations on small (time-) scales and another type of correlation or uncorrelated behavior on larger scales, different scaling behavior in different parts of the time series, and different scaling behaviors in interwoven fractal subsets of the series.

The multifractal characterization of nonstationary time series can be reliably detected by means of multifractal detrended fluctuation analysis (MDFA) [21], which is based on a generalization of the standard DFA. Its procedure can be briefly sketched as follows. First, for a time series $x(k)$ of length N on a compact support, one determines the integrated signal profile

$$Y(i) = \sum_{k=1}^i (x(k) - \langle x \rangle), \quad i=1, \dots, N. \quad (1)$$

where $\langle x \rangle$ is the mean of the time series. Then the profile is divided into N_s nonoverlapping segments of length s and the same procedure is repeated starting from the opposite end ($2N_s$ segments total). The local trend for each segment v is estimated by fitting a m th-order polynomial $P_v^{(m)}$ and subtracted from the segment. Next, one determines the variance

$$F^2(v, s) = \frac{1}{s} \sum_{i=1}^s \{Y[(v-1)s+i] - P_v^{(m)}(i)\}^2 \quad (2)$$

For each segment v , $v = 1, \dots, N$, and

$$F^2(v, s) = \frac{1}{s} \sum_{i=1}^s \{Y[N - (v - N_s)s + i] - P_v^{(m)}(i)\}^2 \quad (3)$$

For $v = N_s + 1, \dots, 2N_s$. Finally, a q th order fluctuation function is defined as

$$F_q(s) = \left\{ \frac{1}{2N_s} \sum_{v=1}^{2N_s} [F^2(v, s)]^{q/2} \right\}^{1/q} \quad (4)$$

For $q \neq 0$ and $F_0(s)$ is defined as

$$F_0(s) = \exp \left\{ \frac{1}{4N_s} \sum_{v=1}^{2N_s} \ln [F^2(v, s)] \right\} \quad (5)$$

If the series $x(k)$ are long range power-law correlated, $F_q(s)$ increases for s values in a certain range, as a power-law

$$F_q(s) \sim s^{h(q)} \quad (6)$$

For $q = 2$, the standard DFA procedure is retrieved.

The q th order fluctuations $F_q(s)$ plotted versus various observation window sizes (scales) s form a family of lines. The slopes of these lines indicate the exponents $h(q)$. It has been found the MDFA method performs well if the 2th order polynomial trend is extracted. Therefore, unless mentioned otherwise, a quadratic polynomial was used in the fitting procedure.

For a monofractal signal, $h(q)$ is independent of q , whereas for a multifractal signal, there is a significant dependence of $h(q)$ on q . The reason is that, for positive values of q , $h(q)$ describes the scaling behavior of the segments with large fluctuations, whereas for negative values of q , $h(q)$ describes the scaling behavior of the segments with small fluctuations. Figure 1 compares the dependence of $h(q)$ on q between a typical monofractal signal (fractional Brownian motion $fBm_{0.25}$, 0.25 is the Hurst exponent) and a multifractal signal (binomial multifractal series).

The multifractality is traditionally characterized by the dimension of the fractal subsets, $f(\alpha)$, as a function of the Hölder exponent of the subsets, α . The scaling exponent $h(q)$ is directly related to the traditional multifractal formalism by [21]

$$\alpha = h(q) + qh'(q) \text{ and } f(\alpha) = q[\alpha - h(q)] + 1 \quad (7)$$

It has been demonstrated that DFA is closely related to power spectral density analysis [12, 39]. Let the power spectral density (PSD) of the integrated data, Y (Eq. 1), be $P_Y(f)$. If the integrated series, Y , is divided into non-overlapping boxes with a length of s seconds and detrended, it can be numerically verified that the PSD of the detrended series, Y_d , obeys the following relation

$$P_{Y_d}(f) \approx \begin{cases} 0, & 0 \leq f \leq 1/s \\ P_Y(f), & \text{otherwise} \end{cases} \quad (8)$$

As illustrated in Figs. 2, detrending in boxes with a length of s seconds is equivalent to applying a high-pass filter to the integrated series with a cut-off frequency $1/s$ Hz. This means that scales, s , are related to frequencies, f , by $s = 1/f$. Thus, the scaling regions related to metabolic, neurogenic, myogenic, respiratory, and cardiac BFO are $1/0.02$ – $1/0.0095$, $1/0.05$ – $1/0.02$, $1/0.15$ – $1/0.05$, $1/0.4$ – $1/0.15$, $1/2$ – $1/0.4$ (s), respectively.

Previous studies have used the width of multifractal spectrum $\alpha_{\max} - \alpha_{\min}$ (α is the Hölder exponent) or $h(q_{\min}) - h(q_{\max})$ to quantify the multifractality degree of time series. However, estimates of the width of multifractal spectrum often encounter a problem of numerical instability, e.g., enormously large wings of the multifractal spectrum. On the other hand, simulation tests performed on fractional Brownian motion showed that the measure $h(q_{\min}) - h(q_{\max})$ may give a negative value due to numerical errors. We thus used the range of the exponents $h_{\max}(q) - h_{\min}(q)$ to measure the complexity degree. As shown in Fig. 1, a monofractal signal has a very narrow range of $h(q)$, whereas a multifractal signal has a broad

range of $h(q)$. In Fig. 1e, the spread $h_{\max} - h_{\min}$ characterizes the error of calculation, since for real multifractal objects, $h(q)$ is a monotonically decreasing function (as seen in Fig. 1f).

To further test whether $h_{\max}(q) - h_{\min}(q)$ can reflect the complexity degree of blood flow signals, we performed two tests with surrogate time series. First, we generated surrogate time series by shuffling the blood flow signal shown in Fig. 2a (51–60 min). The surrogate time series preserve the distribution of the original signal but destroy all correlations. Second, we generated surrogate time series by preserving the amplitudes of the Fourier transform of the original data but randomizing the phases. These two procedures are known to lead to a loss of multifractal complexity of the original signal [16, 21]. As shown in Fig. 3, values of $h_{\max}(q) - h_{\min}(q)$ of surrogate data in both the scale intervals corresponding to metabolic and neurogenic frequencies are significantly smaller than that of the original signal. We repeated these two tests on all records and observed the similar results. The results indicate that $h_{\max}(q) - h_{\min}(q)$ can reflect the complexity degree of blood flow signals.

We performed MDFA to the blood flow data at baseline (1–10 min) and during the second peak (51–60 min). We used quadratic polynomials in the fitting procedure and the parameters $q \in [-5, 5]$, $\Delta q = 0.1$ (see Sect. “4”). The range of the scaling exponents, $h_{\max}(q) - h_{\min}(q)$, was used as a measure of the complexity of metabolic (neurogenic) component.

2.4 Statistical analysis

The Wilcoxon signed rank test was used to compare the complexity at baseline and during the second peak in the same subject. The Wilcoxon rank sum test was used to compare the complexity in the groups of 65–75 years and 75–85 years. The level of significance was set at 0.05. Matlab Statistics Toolbox (R2008b, MathWorks, Natick, MA) was used to implement statistical analyses.

3 Results

Figure 4 shows that in the 65–75 years group, the complexity of the metabolic component significantly increased in response to local heating ($P < 0.01$) (Fig. 4a), and the complexity of the neurogenic component moderately decreased ($P = 0.06$) (Fig. 4b); whereas in the 75–85 years group, the complexity of the metabolic component did not significantly increase ($P > 0.05$). Figure 4 also shows that compared with the 65–75 years group, the metabolic component in the 75–85 years group were significantly less complex at baseline ($P < 0.05$) and during the second peak ($P < 0.001$) (Fig. 4a), while there was no significant difference in the complexity of the neurogenic component between the 65–75 years group and 75–85 years group ($P > 0.05$) (Fig. 4b). Additionally, in response to local heating, the complexity of myogenic component did not significantly change ($P > 0.05$) (Fig. 4c), the complexity of respiratory component significantly decreased ($P < 0.05$) (Fig. 4d), whereas the complexity of cardiac component significantly increased in both groups ($P < 0.05$) (Fig. 4e).

Figure 5 demonstrates an inverse relationship between age and vasodilatory function ($R = -0.31$, Fig. 5a). Figure 5 also shows the correlations between age and the complexity of metabolic and neurogenic components. The complexity of the metabolic component at baseline ($R = -0.52$, Fig. 5b) and during the second peak ($R = -0.54$, Fig. 5c) declined with age, and the complexity of the neurogenic component at baseline ($R = -0.44$, Fig. 5d) declined with age.

4 Discussion

We have demonstrated for the first time that the metabolic and neurogenic BFO have less complexity in older subjects. This finding supports the use of nonlinear analysis of BFO for assessing skin microvascular dysfunction. Such tools may help clinicians to identify people at risk for pressure ulcers and to evaluate specific interventions for compensating the impaired function. Changes in BFO are traditionally analyzed using Fourier or wavelet spectrum-based approaches. Wavelet analysis of BFO has revealed that aging leads to a decrease of endothelial-related metabolic activity [20, 34]. In previous studies, nonlinear methods such as fractal dimension, approximate entropy (or sample entropy), correlation dimension, Lyapunov exponents, detrended fluctuation analysis (DFA), and multifractal analysis have been used to measure the complexity of BFO [5, 7, 8, 15]. However, these studies did not aim to address the complexity of the characteristic components of BFO. In this study, we demonstrated that the MDFA method can be used to quantify the complexity of the characteristic components of BFO, and showed that metabolic and neurogenic BFO have less complexity in older subjects.

In this study, we identified the scaling regions that can be used to quantify the complexity of metabolic and neurogenic controls of cutaneous microcirculation. Laser Doppler blood perfusion signals are generally fractal with several distinct scaling regions [7, 23]. As illustrated in Fig. 2, the metabolic and neurogenic components are related to a specific scaling region, respectively. The scaling exponent in this region reflects the scaling behavior of metabolic activity. For a set of values of q , the range of the scaling exponents serves as a measure of the complexity of metabolic oscillations. A wider range of scaling exponents indicates richer structures, i.e., more complex variability.

To apply MDFA to quantify the complexity of a cardiovascular signal, one needs to decide the range of q (Eq. 4). A wider range of q is beneficial for detection of subtle multifractality of a signal. However, a too large $|q|$ may lead to statistically meaningless results based on short data series in terms of the width of observation windows. For most of our data sets, when $|q| = 5$, the $\log(F_q(s)) - \log(s)$ plot still exhibits a clear scaling region related to the frequency band of metabolic (neurogenic) component. Therefore, we restricted our calculations to $q \in [-5, 5]$ with a step $\Delta q = 0.1$.

Our long-term goal is to develop non-invasive tools for detecting risk for pressure ulcers in various pathological populations. In our previous studies, we have confirmed that wavelet analysis of BFO can be used to study blood flow regulatory mechanisms [18–20], and that nonlinear properties of skin BFO are associated with vasodilatory function [23]. In this study, we further demonstrated that the complexity of the characteristic components, e.g., the metabolic component and neurogenic component, of BFO is associated with vasodilatory function. The complexity of metabolic (neurogenic) component was estimated by the range of the scaling exponents, which measures the structural inhomogeneity of a signal. Capturing such structural information by linear methods such as Fourier spectral analysis, wavelet analysis might be difficult. The results of surrogate tests (Fig. 3) indicated that the range of scaling exponents can reflect the nonlinear correlations of the characteristic frequencies of BFO, which are cancelled by the randomization of the Fourier phases. The observed complexity degree of the characteristic frequencies of BFO is independent of their amplitude or power. For example, in our previous study we observed an increase in both the power of metabolic component and the power of neurogenic component in response to local heating [20], while in this study we observed an increase in the complexity of metabolic component but a decrease in the complexity of neurogenic component in the 65–75 years group.

According to the previous study by Goldberger et al. [10, 11] and by Lipsitz et al. [25], it is reasonable to assume that the complexity of a characteristic component of BFO reflects the richness of its sub-components (if existent), the coupling between the corresponding sub-systems, and the interactions between the control mechanism underlying this characteristic component and other control mechanisms of skin perfusion. There are evidences demonstrating the existence of interactions among blood flow control mechanisms. For example, metabolic activity depends on the respiratory activity which provides for oxygen in the blood [37]. Holowatz and Kenney assessed the contribution of nitric oxide to the axon reflex mediated vasodilation and concluded that attenuated reflex cutaneous vasodilation was due to a reduced nitric oxide-dependent vasodilation [13]. Ping et al. found the myogenic response could be enhanced by sympathetic tone [33]. Stefanovska et al. proposed a model of the cardiovascular system, in which neurogenic activity was assumed to positively couple with myogenic activity and negatively couple with metabolic activity [37]. Therefore, complexity is an important property of the characteristic components to be considered in understanding blood flow control mechanisms and assessing vasodilatory function.

Complexity analysis of the metabolic component of BFO may be a promising tool for assessing endothelial function. Endothelial function is clinically assessed by examining changes in blood flow or diameter of blood vessels in response to endothelial stimulation [3], which are usually taken as estimates of vascular nitric oxide bio-availability. However, such testing outcomes depend not only on endothelial function but also on other factors. An increase in skin blood flow in response to local heating is an overall result of activations of all control mechanisms [20]. Clinical studies have shown that endothelial dependent vasodilation progressively declines with age, which is associated with attenuated endothelial nitric oxide synthase expression [3]. Wavelet-based spectrum analysis revealed that older subjects had a lower increase in the power of metabolic component in response to local heating [20]. In this study we observed a decline in the complexity of metabolic oscillations with age both at baseline and during the second peak (Figs. 4 and 5b, c). On the other hand, older subjects had a lower increase in the complexity of metabolic oscillations due to local heating. These findings are consistent with current consensus that nonlinear complexity breaks down with aging and disease, reducing the adaptive capabilities of the individual.

Our results showed that the complexity of neurogenic component at baseline decreased with age (Figs. 4 and 5d). This might be due to attenuated sympathetic nervous system activity in older subjects [31]. The neurogenic component of BFO has been found to be associated with sympathetic nerve activity [22, 35]. So"derstro"m et al. observed significant lower amplitudes in the frequency interval 0.02–0.05 Hz on flaps of transplanted skin as compared with those for intact skin [35]. The authors concluded that sympathetic nerve activity influences skin blood flow in the frequency band of 0.02–0.05 Hz. A recent study of the effects of local anesthesia by Landsverk et al. confirmed the connection between sympathetic activity and the spectral peak in this frequency interval [22]. Ogrin et al. observed an increase in basal blood flow with age and suggested that sympathetic nervous system activity is decreased in older subjects [31].

The second peak of biphasic vasodilation has been shown to be primarily mediated by local generation of NO [28]. Minson et al. did not observe differences in blood flow in response to local heating between two protocols, with antebrachial cutaneous nerve block and without block [28]. They suggested that sympathetic cutaneous nerves do not contribute to the plateau-phase dilation. A later study by this group suggested that an unknown vasodilator is present and mediates a portion of the plateau-phase dilation [29]. In our previous study, we observed an increase in the power of neurogenic component response to local heating [20]. In this study, we observed a decrease in the complexity of neurogenic component in the 65–

75 years group. These findings imply that the neurogenic control mechanism is also involved in the plateau-phase vasodilation. However, studies are needed to further explore the connection between sympathovagal control and the power of BFO within the 0.02–0.05 Hz frequency band.

To use the proposed MDFA to quantify complexity of BFO, a minimum of 10 min length of skin blood flow signal is recommended. Theoretically, a minimum number of cycles of the lowest frequency should be larger than 4 [21]. Kantelhardt et al. proposed to exclude scales $s > N/4$, where N is the length of the time series, because when scale $s > N/4$, the fluctuation function, $F_q(s)$, becomes statistically unreliable [21]. In a previous study conducted by Esen et al. [7], skin blood flow signals with lengths of $N > 2^{15} = 32768$ data points, sampled at 200 Hz, were used to calculate DFA coefficients. The largest scale was around 40 s.

Therefore, the signals contained about 4 cycles of the lowest frequency. In a later study of this group [8], blood flow signals with a length of $2^{17} = 131072$ points, sampled at 200 Hz, were used. The largest scale was around 110 s. Thus, the signals contained about 6 cycles of the lowest frequency. In the present study, all data series have the same length of 10 min.

The largest scale of metabolic oscillations (0.0095–0.02 Hz) is $1/0.0095 = 105$ s, for which the integrated data series is divided into $\text{int}(600/105) = 5$ non-overlapping segments starting from one end and the same procedure is repeated starting from the opposite end. Thus, $F_q(s)$ is calculated from 10 different segments of the data series (see Eq. 2–Eq. 4). As for fractal dimension, an approach has been shown to be suitable for short time series [1]. This approach involves the calculation of the slope of the log-log regression, $\log(SD(m)) \sim \log(m)$, where m is the number of points grouped to calculate the standard deviation (SD). Carolan-Rees et al. applied this approach to laser Doppler series of 10 min (the sampling frequency was 10 Hz) [5]. The largest value of m around 110 s was used. The authors concluded that this approach is more robust than Hurst analysis, particularly in showing less bias [1]. Therefore, when data series contains the order of 10 cycles of the lowest frequency, application of multifractal DFA and correlation dimension is reasonable.

The complexity of the characteristic components may be useful for identifying risk for pressure ulcers. Future study may need to investigate whether the complexity of the characteristic components of BFO is associated with changes of skin perfusion response to other causative factors of pressure ulcers (e.g. pressure, shear and moisture), to establish the normal ranges of this index, and to investigate how this index changes with the development of pressure ulcers.

4.1 Study limitations

There were limitations in this study. The complexity of the characteristic components of BFO was assessed during maximal vasodilatory response. Whether our findings can be applied to pressure induced vasodilation or reactive hyperemia remains unknown. However, we have demonstrated the feasibility of using the complexity of characteristic components of baseline BFO to predict thermally induced vasodilatory function. In this study, we only recruited 20 older subjects with various degrees of vasodilatory functions into the study. We excluded subjects with diagnosed cardiovascular diseases. Further studies may need to investigate whether our methods can be applied in older subjects with existing cardiovascular diseases. Studies suggested that both estrogen and progesterone affect skin blood flow response in both young women [6] and postmenopausal women [4]. Although gender may have an influence on skin blood flow response to local heating [4, 6, 27], we did not observe a significant difference in skin blood flow between males and females in either the preheating period or the maximal vasodilation period in this study. Future studies need to consider the gender effect on complexity of BFO in elderly people.

5 Conclusion

Our results demonstrated that complexity analysis of the characteristic components of BFO may provide a new way to gain insight into the interactions among blood flow control mechanisms. Nonlinear complexity analysis (MDFA) can complement linear spectral analysis (wavelet) of BFO to quantify microvascular dysfunction.

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Fig. 1.

A comparison between a monofractal signal (*left panels*) and a multifractal signal (*right panels*). To match these time series with the real signals, we assumed that the sampling frequency is 20 Hz. **a** A monofractal signal, a fractional Brownian motion $fBm_{0.25}$ (0.25 is the Hurst exponent). **b** A multifractal signal, a binomial multifractal series defined by $x_k = \alpha^{n(k-1)} (1 - \alpha)^{n_{\max} - n(k-1)}$ where $\alpha = 0.75$, $n_{\max} = 13$, and $n(k)$ is the number of digits equal to 1 in the binary representation of the index $k = 1, 2, \dots, 2^{n_{\max}}$. **(c, d)** Log(fluctuation)-log(scale) plots of **(a, b)**. **e** Scaling exponents $h(q)$, $q \in [-5, 5]$ with a step 0.1, of $fBm_{0.25}$. **f** Theoretical scaling exponents of the binomial multifractal series and numerical results obtained by using MDFA

Fig. 2.

Relationship between scales (box size) and frequencies in the MDFA method. **a** Sacral skin blood flow response to a rapid local heating. **b–f** Comparisons of the power spectral density between the integrated data series, Y , and the detrended series, Y_d . The original data is the blood flow signal shown in **(a)** during 51–60 min. Detrending in boxes of length s (scale in seconds) is equivalent to applying a high-pass filter to the integrated series with a cut-off frequency $1/s$ Hz. In the fitting procedure, quadratic polynomials were used

Fig. 3.

Surrogate tests of the measure $h_{\max}(q) - h_{\min}(q)$. For the blood flow signal shown in Fig. 2a (51–60 min), 50 randomly shuffled series and 50 phase-randomized series were generated. Values of $h(q)$ of surrogate data are means ± 0.5 SD (SD is the standard deviation represented by the lengths of error bars). In the shuffling procedure, all correlations are destroyed but the distribution is preserved. In the phase-randomizing procedure, the Fourier phases are randomized (nonlinearities are eliminated). Both of these two procedures lead to a significant decrease in $h_{\max}(q) - h_{\min}(q)$ of metabolic and neurogenic components. **a, c** $h(q)$ in the scale interval corresponding to the metabolic frequency band 0.0095–0.02 Hz. **b, d** $h(q)$ in the scale interval corresponding to the neurogenic frequency band 0.02–0.045 Hz.

Range of scaling exponents of the characteristic components

Fig. 4. Range of scaling exponents, $h_{\max}(q) - h_{\min}(q)$, of the metabolic (a), neurogenic (b), myogenic (c), respiratory (d), and cardiac (e) characteristic components of skin blood flow oscillations at baseline and during the maximal vasodilation. Significant differences between the 65–75 years and 75–85 years group are observed in the metabolic frequency during baseline and second peak blood flow. Values are means $\pm$ SE. * indicates $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Fig. 5. Correlation between age and the complexity of metabolic and neurogenic components of BFO. **a** An inverse relationship is observed between vasodilatory function and age. **b–d** The complexity of metabolic component at baseline (**b**) and during the second peak (**c**) declined with age, while only at baseline the complexity of neurogenic component declined with age (**d**). The stars represent the 65–75 years group, and the filled circles represent the 75–85 years group