Comparative study of the upper and lower limb skin blood flow control mechanisms in patients with essential hypertension

Ferhan Esen, Necmi Ata, Hamza Esen*

From Departments of Biophysics and *Cardiology, Faculty of Medicine, Eskişehir Osmangazi University; Eskişehir-*Turkey*

Abstract

Objective: To investigate limb specific differences in cutaneous vascular function in patients (n=33) with essential hypertension (EHT).

Methods: In this observational cross-sectional study, baseline skin blood flow and the response to local heating were measured with a laser Doppler flowmeter (LDF) from the volar region of the forearm and the gaiter area of the foot at supine rest. The fractal analysis, detrended fluctuation analysis (DFA), was used to calculate the correlation properties of skin blood flow, LDF signal. The paired t-test and repeated measures ANOVA were used to determine the response to local heating and compare the scaling exponents of different anatomical locations respectively.

Results: We found three linear scaling regions that describe the fractal behavior of LDF signal with their slopes, scaling exponents. For cardiac (α_C) and cardio-respiratory (α_{CR}) scaling exponents, thermal hyperemia (T) induced greater change in the leg (α_C=1.49±0.26; α_{CT}=1.62±0.20 p<0.01 and α_{CR}=0.84±0.29 α_{CRT}=0.42±0.28 p<0.001) than in forearm (α_C=1.28±0.13; α_{CT}=1.33±0.13 p>0.05 and α_{CR}=0.73±0.15; α_{CRT}=0.65±0.018 p<0.05). Local scaling exponents ($\alpha_L \approx \alpha_{LT} \sim 1$) were not significantly different (p>0.05) and, local lines did not shift in parallel with local heating in both extremities.

Conclusion: The results of the present study suggest that skin microvascular function is impaired in both extremities in EHT patients. However, myogenic response is not uniform in both extremities and pronounced response to local thermal hyperemia has been observed in the gaiter area compared with the volar region. Further studies are needed to determine if these limb specific microvascular differences is the result of posture-induced structural and functional adaptation. *(Anadolu Kardiyol Derg 2014; 14: 3-8)*

Key words: skin blood flow, volar region, gaiter area, detrended fluctuation analysis, essential hypertension

Introduction

Essential hypertension (EHT) is a pathology displaying functional and structural changes in the microcirculation. In the last two decade, studies on human cutaneous circulation have provided extensive data to assess microvascular function in a variety of vascular disease states including hypertension (1-6). Although the skin blood flow measured from the volar region of the forearm has been commonly used to assess microvascular function in humans, the gaiter area (proximal to the medial malleolus) in the leg can also be used as an appropriate measurement site in some specific diseases. For example, microvascular dysfunction may occur in the lower extremities of the diabetic (7) and chronic varicose vein (8) patients without significant changes in vessels of the upper extremities. Because the blood flow signals are taken from the most distal part of the vascular system, cutaneous blood flow depend not only on the local control mechanisms of microvascular beds but also cushioning function of the macrovascular system from aorta to the arterioles (1, 2, 9). Therefore, it is possible that the cutaneous circulation at different anatomical locations may reflect the functional impairments in related macrovascular beds. Previous studies have reported less responsive macrovascular beds in the legs than in the arms (10-12). Aging (12, 13) and peripheral arterial disease (14) significantly reduces the reactivity of the lower limbs. The structural and functional alterations of conduit arteries are particularly important in the lower extremities of subjects with cardiovascular disease (15, 16). The attenuated endo-

Address for Correspondence: Dr. Ferhan Esen, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, Biyofizik Anabilim Dalı, 26480 Eskişehir-*Türkiye* Phone: +90 222 239 2979/4601 Fax:+90 222 239 37 72 E-mail: fesen@ogu.edu.tr

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thelium dependent vasodilatation has been found in the upper extremities of subject during acute rise in blood pressure induced by hydrostatic factor (17). Despite the significant work performed on the primary conduit vessels of the arm and leg to assess limb vascular heterogeneity (10-13, 17), only one single work (7) compared upper and lower limb cutaneous vascular function in humans. And, there are currently no data comparing cutaneous blood flow recorded from upper and lower limbs in EHT patients. Therefore, studies on the contribution of EHT to microvascular impairment in different extremities will contribute to the correct selection of skin site in these patients.

In the present study, we analyzed the influence of EHT on skin microvascular function in different anatomical locations: volar region and gaiter area. We applied local heating to induce the control mechanisms of cutaneous blood flow measured with a laser Doppler flowmeter (LDF) and we used a fractal analysis method, detrended fluctuation analysis (DFA), to evaluate LDF signals. Because of the functional adaptation in the legs vasculature to recurrently elevated hydrostatic pressure, we hypothesized that excess blood pressure due to EHT would lead to impairment in vascular function in both limbs but are less pronounced in the legs than in the arms.

Methods

Study design

This is an observational cross-sectional study.

Subjects

Thirty four 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 were excluded from participation if they were suffering from diabetes, hypercholesterolemia, hyperhomocysteinemia, chronic renal failure, peripheral vascular disease, coronary artery disease and heart failure. 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 (PR-10-03-19-38) and conducted according to the principles of the Declaration of Helsinki 2008. Subject characteristics are summarized in Table 1.

Table 1. Patient demographics

Data are presented as mean±SD	
Age, years	44±4
Sex, male/female	25/8
Body mass index, kg/m^2	25.4±3.6
Sistolic blood pressure, mmHg	128±12
Diastolic blood pressure, mmHg	80±10
Heart rate, beats/min	72±4
Respiratory rate, cycles/min	14±2
Data are presented as mean±SD and ratio	

Instrumentation

A data acquisition system (Biopac Systems, Inc. Santa Barbara, CA, USA) equipped with a laser Doppler flowmeter (780 nm, 1 mW) was used to record the forearm cutaneous blood flow (measured in relative blood perfusion units BPU). The data sampled at 1 kHz.

The local vasodilator mechanisms of volar/gaiter skin were induced by thermal hyperemia (18). To record the blood perfusion in the center of a locally heated area of skin, the fibers of the LDF probe (480 µm diameter) were placed in the center of a heating probe. This combined probe was fixed to the volar/gaiter region with double sided adhesive tape. The heating unit (Moor Instruments Ltd. UK) was able to control the temperature of the probe with ±0.3°C accuracy.

Measurement of basal and evoked skin blood flow

Cutaneous blood flow of the subjects lying in supine position studied on two regions: volar site of the forearm and the gaiter area of the leg. 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 30 min rest before the test. After a 15 min baseline skin blood flow recording, a constant local heat (42°C) was applied for at least 30 min. The recording of LDF signal was continued during the increased blood flow in response to local heating.

Detrended fluctuation analysis

Cutaneous blood flow measured with a laser Doppler flowmeter (LDF) is a nonstationary biological signal (19-22). One of the techniques that can cope with nonstationarity of a signal is the detrended fluctuation analysis (DFA). Detrended fluctuation analysis is a method, for determining the scaling behavior of data in the presence of possible trends. Complete details of the methodology are published elsewhere (23). In brief, the LDF time series x_i, where i=1,2,3,…,N and N the length of the series is first integrated:

$$y(k) = \sum_{i=1}^{k} (x_i - \bar{x})$$

where

$$\bar{x} = \frac{1}{N} \sum_{i=1}^{N} x_i$$

Next, the integrated series is divided into boxes of equal length, n. In each box a least-squares line is fit to the data, representing the local trend in that box. The y-coordinate of the straight line segments is denoted by $y_n(k)$. Then we detrend the integrated series, $y(k)$, by subtracting the local trend, $y_n(k)$, in

each box. The root-mean square fluctuation of this integrated and detrended series is calculated by.

$$F(n) = \sqrt{\frac{1}{N}\sum_{k=1}^{N}[y(k) - y_n(k)]^2}$$

Repeating this calculation over all box sizes, we obtain a relationship between $F(n)$ and the box size n. If $F(n)$ behaves as a power-law function of n, data obey a scaling: $F(n) \sim n^{\alpha}$. Thus the fluctuations in LDF signal can be described by the scaling exponent α, representing the slope of the line fitting *Ln F(n)* to *Ln n*. For a white noise process α=0.5. $0.5<\alpha\leq1$ indicates the presence of positive long range correlations. On the other hand $0<\alpha<0.5$ indicates the presence of negative long range correlations. For a flicker noise type of fluctuation in a dynamical system of self-organized critical state α=1. Brownian motion like dynamics is characterized by a scaling exponent α=1.5. And α>1.5 describes deterministic long-range correlations (24, 25).

Data analysis

The DFA analyses were performed on the responses to local heating and on the baseline LDF signals by using tools written within Labview (National Instruments Corp. Austin, TX, USA). The baseline period of ~11 min before the local heating and the last 11 min of the response to local heating (saturation level) were used for DFA to find the baseline and evoked scaling exponents respectively. The data, which was originally sampled at 1 kHz, were resampled at 200 Hz and the signal length of $N=2^{17}$ data points were used for the fractal analysis performed in this study. The length of data and the sampling rate were adequate to reliable calculation of the fractal scaling exponent (25).

In general, DFA of LDF signal yields three scaling regions with two crossovers. Based on the DFA of original and high-pass filtered LDF signals, three scaling regions/frequency intervals corresponding to the "linear" parts of the each DFA curve were defined (20). For convenience, these scaling regions are called with the name of contributing physiological systems: cardiac, cardio-respiratory and local (20). For each region of every DFA graph, linear regression analysis was used to find the best fit line. Squared correlation coefficient, r^2, and the p value for the best fit line were used to quantify the degree of linear association between Ln F_n and Ln n. The slopes, scaling exponents, of these best fit lines can be used to evaluate the vascular/microvascular functions (1, 20, 26) and thus will be the focus of this study. The intercepts of best fit lines have no specific meaning for the cardiac and cardio-respiratory regions and we paid no attention to these parameters. In the local region, however, intercept causing a statistically significant parallel shift on best fit line that have a slope of ~1 represents the response of healthy vascular beds to vasodilator stimuli. Therefore, we studied slope and intercept in the local region.

Statistical analysis

Statistical analyses were performed with Instat 2.00 (GraphPad Software, Inc. La Jolla, CA USA). Basal (B) scaling exponents of cardiac, cardio-respiratory and local regions and their values in stimulated state induced by local heating (T) were expressed as mean±SD. The Kolmogorov-Smirnov test was employed to determine whether or not the distribution of scores in a scaling exponent conforms to a normal distribution. All scaling exponents were passed this normality test. Then, the paired t-test was used to identify significant changes in each of the 3 scaling exponents with local heating within same anatomical location, volar region or gaiter area. The repeated measures analysis of variance (ANOVA) followed by a post test, Tukey-Kramer multiple comparison test, was used to compare the mean values of the basal and induced scaling exponents between two anatomical locations. Differences were considered as statistically significant when a p value <0.05.

Results

The representative scaling curves, *Ln F(n)* vs. *Ln n graphs*, obtained by DFA of LDF signals displayed three distinct scaling regions as shown in Figure 1. Linear regression analysis of the data in each region revealed significant correlation, and we found at least r^2~0.915 and p<0.001 for the best fit lines calculated in these regions. The results of statistical analyses were summarized in Figure 2.

Cardiac region (α_C)

Basal (B) value of the cardiac scaling exponent was greater (p<0.001) in the gaiter area than in volar region. Local heating (T) significantly changed (p<0.01) the α_c in gaiter area but not in the volar region (Fig. 2).

Cardio-respiratory region (α_{CR})

For basal condition, the scaling exponent of cardio-respiratory region was not significantly different between the gaiter area and volar region. Thermal hyperemia significantly changed scaling exponents in these two anatomical locations but the change was higher in gaiter area than in volar region (Fig. 2).

Local region (α_L)

There were no differences between thermal hyperemic and basal local scaling exponents in volar region. The same result was obtained in gaiter area (Fig. 2). The intercept of local line with 95% confidence intervals in response to thermal hyperemia was not significantly different from the intercept of basal local line in both locations: volar region and gaiter area.

Discussion

In the present study, we evaluated differences in fractal scaling of skin blood flow between upper and lower extremities in patients with EHT. We used a fractal analysis method, DFA, indi-

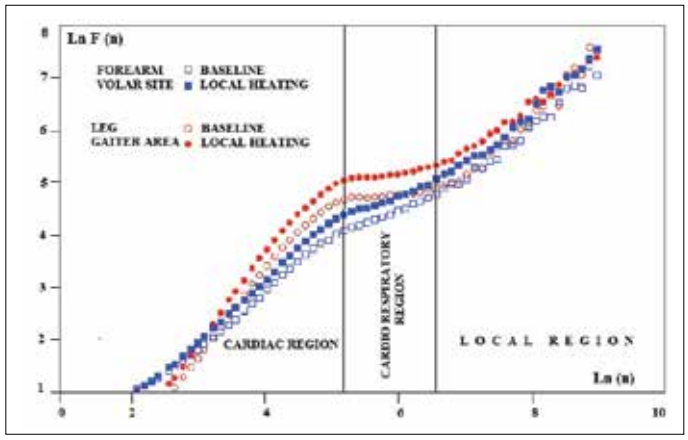

Figure 1. Scaling behavior of LDF signals. Under the same resting conditions slopes (scaling exponents) in cardiac region are higher in the gaiter area than in volar region. The slope of cardio-respiratory line is smaller than the 0.5 in gaiter area but not in volar region. Local lines have similar characteristics in both anatomical locations: gaiter area and volar region

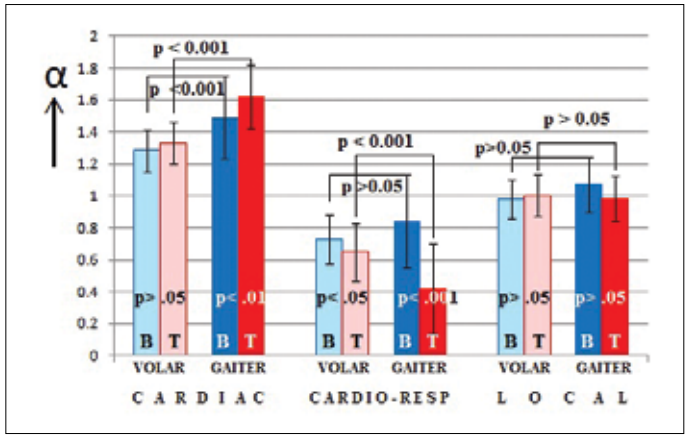

Figure 2. Scaling exponents (B- baseline and T- responses to local heating) calculated from the fractal analysis of skin blood flow (LDF) signals that were measured in two anatomical locations: volar region of the forearm and gaiter area of the foot. Note the similar exponents in local scaling region, whereas cardiac and cardio-respiratory scaling exponents and their change with thermal hyperemia are significantly different in gaiter area compared with volar region. Values (α's) are means±SD. The repeated measures analysis of variance (ANOVA) was used to compare the mean values of scaling exponents between two anatomical locations (F=109.81 and p<0.0001)

cating long range correlation in skin blood flow signal and a local heating test reflecting microvascular function. The major finding was that, a greater cardiac scaling exponent in basal condition and a larger response to local heating has been observed in the gaiter area compared with the volar region. Our data also suggest that the local regulatory mechanisms in the volar region as well as in the gaiter area were impaired in EHT patients.

Cardiac region

There is evidence suggesting close connection between cardiac scaling exponent and the pulsatility of blood flow in cutaneous microcirculation (1, 20, 26).

Microvasculatures adjust their resistance, *i.e.*, viscous force, to flow using their intrinsic local mechanisms; myogenic, neurogenic and endothelial (20, 27, 28). This viscous force opposes the blood flow, so that to maintain constant flow there must be an equal magnitude of driving force; arterial pressure difference generated by the heart and the pressure difference generated by the lungs for the venous return. Although the measurements of viscous and driving forces are not easy it would be fair to say that the central and local signals in microcirculation and their spectral powers represent these forces to some degree (2). Therefore, the ratio, R=central power/local power, is thought to reflect the pulsatile character of skin blood flow. In healthy young subject, this ratio is found equal to 1 in supine rest suggesting that the driving and viscous forces are in equilibrium and, blood flow is laminar not pulsatile (2). Fractal analysis of such a signal confirms this suggestion. The basal value of volar cardiac scaling exponent is α_c ~1.5 when R ≤1 in a healthy young subject and, indicates that the signal is random walk (20, 24, 25). However, we found α_c~1.3 that describes different blood flow characteristics from random walk in the volar region at basal condition in EHT. This result is in consistent with the finding of a previous study (2) that found R ~ 3 and, suggests blood flow is pulsatile in the volar region even in supine rest in EHT.

The pulsatility parameter approximates to 9 during vasodilatation in healthy young subjects in supine rest and indicates that the cardiac driving force become a dominant control mechanism in microvascular beds in volar region (2). In agreement with this increase in pulsatility, the value of cardiac scaling exponent increases in the range of 2>α>1.5 and corresponds to a correlations that can reflect deterministic correlations controlled by cardiac pump not a stochastic process (25). It is interesting to compare the changes in cardiac scaling exponents of two regions in response to vasodilatation. We found increased cardiac scaling exponent, α_{cT}=1.62>1.5, for the gaiter area. However, cardiac scaling exponent, α_{cT} ~1.3<1.5 did not change significantly with vasodilatation in the volar region. The reasons for these conflicting results are unclear. One possibility is that the leg is chronically exposed to higher hydrostatic pressure and may have developed adaptations to deal with high pressure. If pressure remains elevated over longer times, as in the case of hydrostatic factor on lower limbs, arterioles remodel (29), and thickening the vascular wall to maintain a constant value for tension and diameter according to Laplace law (30). Thus, remodeling of vascular wall from childhood to adulthood normalize vascular function, so that myogenic activity, after being initially enhanced, returns towards its pre-hydrostatic factor level and, operates at a higher level of perfusion pressure at the end of adaptation. Interestingly, upper extremities do not displays similar alterations of structure of the lower extremities and, intima thickness to lumen diameter ratio is largest in the arteries of the foot (31). These results support limb specific vascular characteristics that may be related to the functional adaptation of vasculatures to the hydrostatic factor. Thus the adapta-

tion of lower limbs to hydrostatic pressure may protect their microvasculature against an excess pressure such as in EHT. Our findings confirming this suggestion are also supported by the studies investigating increased blood pressure on conduit artery function. In a study, Padilla et al. (17) have shown that the brachial artery endothelial vasodilatation was impaired following increase in blood pressure but poplietal artery endothelial function was unaltered. Similar result is found in a study that used the leg press exercise to increase the blood pressure (32).

Cardio-respiratory region

Studies (1, 20) have shown that the value of cardio-respiratory scaling exponent is in the range of $1 \geq \alpha_{CR} > 0.5$ for baseline LDF signal during supine rest in healthy young subjects and, vasodilatation decreases its value in the range of negative correlation, $0.5 > \alpha_{CRT} > 0$. Because of the increased myogenic response due to increased pulsatility during vasodilatation, α_{CR} is thought to reflect the coupling between central (cardiac and respiratory) and local mechanisms via a myogenic system. Thus, the basal value of cardio-respiratory scaling exponent and its change in response to vasodilatation have been used to investigate the myogenic mechanism (1, 26).

The basal value of cardio-respiratory scaling exponent was not significantly different in volar region compared with the gaiter area (Fig. 2). Although vasodilatation induced minute change in volar cardio-respiratory scaling exponent it was not as big as in the gaiter area (Fig. 2). Contrary to the findings of the earlier works (20, 26) in healthy young subjects, α_{CR} is always greater than 0.5 in volar region and did not change this character with vasodilation in EHT. However, vasodilation cause to change of α_{CRT} in the range of $0.5 > \alpha_{CRT} > 0$, at the group level, for gaiter area. Although both extremities experience similar high blood pressure due to EHT, myogenic response to vasodilatation was higher in the lower extremities. This finding suggests that the arm is more susceptible to increase in blood pressure and is a suitable extremity to identify the vascular impairment compared with leg. Thus, the greater myogenic response to vasodilator stimulus in the gaiter area is open to speculation whether it is a consequence of less affected vascular function than in volar region due to functional adaptation to high blood pressure, hydrostatic factor.

Local region

The vasodilatory response to local heat test has been shown to be mediated by two local mechanisms; axon reflex and endothelial nitric oxide (NO) dependent mechanisms (22). Besides, DFA analysis of LDF signals have shown that all local mechanisms lie on the same straight line; the slope of this line is approximately equal to 1 in healthy young subjects during supine rest and, this line shifts with vasodilatation in parallel to itself (19). Thus, the parallel shift of local line and its slope has been used to evaluate the local mechanisms of skin blood flow (1, 26). Although we found local lines with slopes equal to 1, these lines did not shift in parallel in both anatomical locations; volar region and gaiter area. These findings suggest that the local vascular functions are impaired in volar region and in gaiter area in EHT patients and are in agreement with the finding of existing literature (1-6). Under pathological condition such as EHT, remodeling can eventually compromise vessel elasticity. Therefore, EHT is characterized by impaired myogenic response; reduced vasodilatation (5) and structural remodeling of arteries/arterioles (29, 30) with augmented response to vasoconstrictors (33).

Study limitations

Because neural and endothelium-independent dilation was not evaluated, blood flow changes observed in the present study are also depend on these local mechanisms and do not reflect the smooth muscle response without contribution of others. Therefore, further studies administering a nitric oxide donor and/or inhibiting neural and endothelial mechanisms may provide valuable information about the functional adaptation attributed to the myogenic system. The absence of the healthy control group may be regarded another limitation of the present study, although fractal analysis provides invariant parameters, scaling exponents, for healthy vascular beds (1, 20, 26). Of course, similar comparisons within age matched healthy control and, between control and EHT groups will improve our understanding of vascular pathology that is uneven between leg and arm. Multifractal analysis (21, 22) and wavelet analysis (28), in combination with pharmacological/physiological stimuli can also be used to find the functioning of individual local mechanisms.

Conclusion

In conclusion fractal analysis of LDF signals revealed that the myogenic response to local heating is more pronounced in the gaiter area suggesting adaptation of lower extremities to hydrostatic pressure. In contrast, this does not appear to be the case in volar region. There were no limb specific differences in local mechanisms and they were impaired in both extremities. The signal analysis used in the present study provides an alternative way to the existing methods to discriminate myogenic mechanism from others.

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