COMPARISON BETWEEN LASER DOPPLER FLOWMETRY SIGNALS RECORDED IN GLABROUS AND NON GLABROUS SKIN

Time and Frequency Analyses

Edite Figueiras
Instrumentation Center (GEI-CI), Physics Department, Faculty of Sciences and Technology of Coimbra University
Rua Larga, P-3004-516 Coimbra, Portugal

Pierre Abraham
Laboratoire de Physiologie et d'Explorations Vasculaires, UMR CNRS 6214-INSERM 771
Centre Hospitalier Universitaire d'Angers, 49033 Angers Cedex 01, France

Luis F. Requicha Ferreira
Instrumentaiton Center (GEI-CI), Physics Department, Faculty of Sciences and Technology of Coimbra University
Rua Larga, P-3004-516 Coimbra, Portugal

Anne Humeau
Groupe Esaip, 18 rue du 8 mai 1945, BP 80022, 49180 Saint Barthélémy d'Anjou cedex, France
Laboratoire d'Ingénierie des Systèmes Automatisés (LISA), Université d'Angers
62 Avenue Notre Dame du Lac, 49000 Angers, France

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Abstract: Skin microvascular properties vary with anatomical zones. Thus, glabrous skin found in fingers, toes, nail beds, hand palms and feet soles has a high density of arteriovenous anastomoses (AVAs). In contrast, skin found in sites such as ventral face of the forearms do not possess AVAs and therefore microvascular blood flow in this non glabrous skin is different. We herein propose to analyse laser Doppler flowmetry (LDF) signals that reflect skin microvascular perfusion, in two different sites of healthy subjects: hand (glabrous skin) and ventral face of the forearm (non glabrous skin). The signal analysis is performed both in the time and in the frequency domains. Our results show that the mean amplitude of LDF signals recorded in the hand is generally higher than in the forearm. Moreover, the signal fluctuations observed in the hand are much higher than the ones observed in the forearm. Our work also shows that the power spectrum of LDF signals recorded in hand and forearm can be different. They both may possess characteristics of fractal processes but these characteristics may be different for the two anatomical sites.

1 INTRODUCTION

The human skin anatomy and function vary with age and region of the body. Human skin consists of three main layers: the epidermis, the dermis, and the hypodermis. The dermis has a microvascular network, i.e. it has blood flow passing through vessels smaller than 100 µm (Morales, 2005), organized in two horizontal plexuses: the upper horizontal plexus and the lower horizontal plexus. Some parts of the skin also possess arteriovenous anastomoses (AVAs) or shunts that allow blood flow to bypass superficial skin layers, thus providing efficient thermal regulation (Berardesca *et al.*,

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2002). Therefore, different types of skin are found. Thus, glabrous skin is found in regions such as hand palms (where there are AVAs), whereas non glabrous skin is found in zones such as forearms (where there are no AVAs). Glabrous skin is mediated by a vasoconstrictor system, whereas non glabrous skin is mediated by both adrenergic vasoconstrictor nerves and an active vasodilator system.

Disorders of the blood microcirculation system are known to play a significant role in the development of various diseases, such as diabetes, peripheral vascular disease or Raynaud's phenomenon. Because the skin is so accessible, there are many new ways of studying it, based mainly on the quantification of its optical and thermal properties which are modified by the amount of blood perfusion (Berardesca *et al.*, 2002). These techniques are being improved constantly. In the last few years, attention has been drawn to the laser Doppler flowmetry (LDF).

LDF is a non invasive technique enabling the monitoring of microvascular blood flow. With this technique it is possible to monitor blood flow at a single point (laser Doppler perfusion monitoring - LDPM) or map tissue blood perfusion (laser Doppler perfusion imaging - LDPI) (Nilsson *et al.*, 2003).

LDF can be used in dermatology to assess the degree of skin irritability in patch test procedures, in pharmacology to study the microvascular effects of vasoactive substances and drugs, in plastic surgery... The technique also allows the study of the changes in microvascular blood flux in diabetic patients, in people with peripheral vascular diseases or Raynaud's phenomenon.

Differences in vascular anatomy and physiological control, and differences in scattering and absorbency properties, have mainly been studied with LDPM signals in different tissues, such as muscle, liver, and skin in general. However, no deep studies have been conducted in order to know how glabrous and non glabrous skin properties influence LDF recordings. Moreover, to the best of our knowledge, no spectral domain comparison of LDF signals recorded in hand palm (glabrous skin) and forearm (non glabrous skin) has been performed. However, the physiology and skin thickness of these two regions of interest are very different. How do these differences impact LDF recordings? In order to answer this question, we herein propose to compare LDF signals recorded simultaneously in glabrous and non glabrous zones of healthy subjects. This comparison is performed through both temporal and spectral analyses.

2 LASER DOPPLER FLOWMETRY

As mentioned previously, in the last years, LDF has drawn much attention for the monitoring of skin perfusion. In LDF technique, a coherent light beam is directed toward the tissue under study. There, it is scattered by moving objects and by static tissue structures. When light is scattered by a moving particle, like a red blood cell, it is frequency shifted. This shift depends on the velocity of the particle, the direction of the incoming light and the direction of the scattered light. On the contrary, light scattered by static structures remains unshifted in frequency (see for example Fredriksson *et al.*, 2007). Thus, when a photon encounters a particle moving with a velocity $\vec{v}$ (m/s), and if $\vec{k}_i$ (rad/m) describes the propagation vector of the incoming photon, the propagation vector of the photon after being scattered, $\vec{k}_s$, comes out as represented in Figure 1. The angular Doppler frequency shift w (rad/s) is:

$$w = -\vec{q}\cdot\vec{v} = -\vec{v}\cdot(\vec{k}_i - \vec{k}_s) = -\frac{4\pi}{\lambda_t}|v|\sin\left(\frac{\alpha}{2}\right)\cos\theta \quad (1)$$

where λ_t represents the wavelength (m) of the photon in the surrounding medium, α is the scattering angle between $\vec{k}_i$ and $\vec{k}_s$, and θ is the angle between the projection of $\vec{v}$ in the plane of scattering and $(\vec{k}_i - \vec{k}_s)$ vector. The difference between $\vec{k}_i$ and $\vec{k}_s$ is often denoted by the scattering vector $\vec{q}$.

If the reflected mixed light (frequency shifted and unshifted) by the skin is detected by a photodetector, optical mixing of light shifted and unshifted

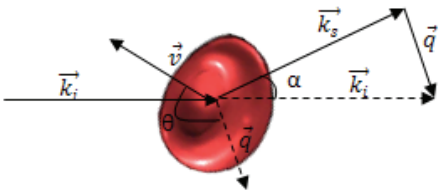

Figure 1: Single scattering event between a photon and a moving scatterer, in this case a red blood cell. $\vec{k}_i$ and $\vec{k}_s$ denote the incoming and scattered wave vectors, and α is the angle between the two. $\vec{v}$ is the velocity vector of the red blood cell. $\vec{q}$ is the difference between $\vec{k}_i$ and $\vec{k}_s$. θ is the angle between $\vec{q}$ and $\vec{v}$.

in frequency will result in a stochastic photocurrent. The photocurrent consists of a static part and a fluctuating part. The total signal can be described with the autocorrelation function (ACF), which is directly related to the power spectral density of the signal. The autocorrelation obtained can be divided into different terms of the origin of the current: stationary (currents produced by the unshifted light), heterodyne-mixing (produced by mixing of the unshifted light and the shifted light) and homodyne-mixing (produced by mixing of the shifted light by red blood cells (RBCs) with different velocities). Usually the homodyne part is disregarded, because the measurements are made in low to moderate blood volumes, where the heterodyne part dominates over the homodyne part. The ACF of the heterodyne part can be expressed as (see for example Fredriksson *et al.*, 2007):

$$ACF = CMBC * I^2 \left(\left\langle e^{iqvt} \right\rangle + \left\langle e^{-iqvt} \right\rangle \right) \quad (2)$$

where I is the average of the current produced by the unshifted light – DC current, CMBC is the concentration of moving blood cells, q is the scattering vector and v is the velocity. According to the Wiener-Khintchine theorem, the Fourier transform of the ACF is equal to the power spectral density $P(w)$ of the input. Therefore, for the heterodyne part we have (see for example Fredriksson *et al.*, 2007):

$$P(w) = CMBC * I^2 \int_{-\infty}^{\infty} \left(\left\langle e^{iqvt} \right\rangle + \left\langle e^{-iqvt} \right\rangle \right) \cdot e^{-jwk} dt \quad (3)$$

where w is the angular frequency, k is the wave number, v is the velocity of the RBC and q is the scattering vector. The photocurrent power spectrum is related to the properties of the blood cells in the illuminated volume. By further derivation of this expression it can be shown that the CMBC and the perfusion (PERF) can be estimated from the power spectrum. The CMBC is proportional to the integral of the Doppler power spectrum density (see for example Fredriksson *et al.*, 2007):

$$CMBC = \int_0^{\infty} P(w) dw \quad (4)$$

and the perfusion, in arbitrary units (a.u.) is proportional to the integral of the frequency-weighted Doppler power spectrum (see for example Fredriksson *et al.*, 2007):

$$PERF = CMBC * \langle v \rangle \propto \int_0^{\infty} wP(w) dw \quad (5)$$

where $\langle v \rangle$ is the mean speed of the blood cells (see for example Fredriksson *et al.*, 2007).

Currently, LDF does not give any absolute measure of blood perfusion. In the clinical setting this is a limiting factor and the reason why LDF instruments are not routinely used in health care. However, LDF has found its use in research.

The dynamics of the microcirculatory flow, measured by LDF, consists of rhythmic oscillations. The latter can be analysed using spectral techniques. Thus, the spectral analysis of LDF signals revealed six peaks within the range frequency from 0.005 Hz to 2.0 Hz (see among others Stefanovska *et al.*, 1999). The peak in the interval from 0.6 Hz to 2.0 Hz is due to heart beats; the one between 0.145 Hz and 0.6 Hz is due to respiratory activity; the one between 0.052 Hz and 0.145 Hz is the intrinsic myogenic activity. The one from 0.021 Hz to 0.052 Hz is due to the neurogenic activity caused by the sympathetic system, whereas the one from 0.0095 Hz to 0.021 Hz is due to NO-dependent endothelial activities. Finally, the one between 0.005 Hz and 0.0095 Hz is due to non NO-dependent endothelial activities.

3 PHYSIOLOGICAL DIFFERENCES BETWEEN ARM (NON GLA-BROUS) AND HAND (GLABROUS) SKIN

There are large differences between the microcirculatory system in hands (glabrous skin) and in arms (non glabrous skin). The main difference is the high density of AVAs or shunts in the glabrous skin (like fingers and toes, the nail beds, the palm of the hands, the sole of the feet, and the earlobe) that is not present in skin elsewhere (Roustit *et al.*, 2008). However, portion of cardiac output passing through skin AVAs in humans is not well known. Regarding the reflex control of the skin blood flow, there are differences when glabrous and non glabrous skin are compared: non glabrous skin is mediated by both adrenergic vasoconstrictor nerves and an active vasodilator system, whereas glabrous skin is mediated by a vasoconstrictor system only - the classic adrenergic nervous system (Wilson *et al.*, 2005).

Very few studies have compared LDF signals from fingers and arms. A characteristic pattern of large, spontaneous fluctuations in blood flow has been described in human glabrous skin by several authors (see for example Thoresen and Walloe, 1980). Some authors assumed that the fluctuations are caused by synchronous opening and closing of skin AVAs (Lossius *et al.*, 1992). Skin AVAs are densely innervated with sympathetic vasoconstrictor fibres. There is also a connection between the fluctuations in glabrous skin blood flow and the spontaneous heart rate and blood pressure variability (Lossius *et al.*, 1992).

Moreover, measurements were made both on the fingertip and in dorsal forearm skin by Freccero *et al.* (2003) and it was concluded that local heating increases superficial blood flow in fingertip and forearm skin by different adjustment of blood cell concentration and velocity (differences are of a rather minor character). Roustit *et al.* (2008) studied the lidocaine/prilocaine effect, a pharmacological tool to inhibit the axon reflex, on finger pads and forearms when they are submitted to a local heating. They found that there is a smaller effect of lidocaine/prilocaine cream on the finger pad. This is due to a decreased anesthetic effect of topical lidocaine/prilocaine on the finger pads. In another study, conducted by Roustit *et al.* (2009), the sodium nitroprusside (SNP) iontophoresis test, used to assess the non endothelium-dependent microvascular function of the finger pad, was compared with SNP iontophoresis test on the forearm, because most data available on SNP iontophoresis concerns the skin of the forearm. In the forearm there was an increase in cutaneous vascular conductance but, on the finger pad, such hyperemia was not consistent. They concluded that standard protocols used for SNP iontophoresis cannot be used on the finger pad as tools to assess non-endothelium-dependent skin microvascular dilation. Also, the thicker epidermis of the finger pulp may present a barrier to the diffusion.

Furthermore, the effect of nerve blockade on forearm and finger skin blood flow during body heating and cooling was studied by Saumet *et al.* (1992). They concluded that the active vasodilator system plays an important role, as far as the timing and the amplitude of the cutaneous vasodilator response to whole body heating in the forearm, but not in the finger. The vasoconstrictor response to cooling occurred only in the finger. Moreover, there were found differences in vasodilator response in the two types of skin (Tucker *et al.*, 1998). The authors attributed these differences to the higher baseline flow in the finger circulation.

Wilson *et al.* (2005) tested the hypothesis that, independent of neural control, glabrous and non glabrous cutaneous vasculature is capable of autoregulating blood flow. In addition to neural control, a number of local factors are capable of modulating skin blood, for example, local alterations in temperature and venous congestion or increased transmural pressure. They found that glabrous skin of the hand palm has the capability to autoregulate blood flow in response to dynamic changes in blood pressure. However, they noted less intrinsic autoregulatory capabilities in non glabrous skin of the forearm. Glabrous skin is capable of both static and dynamic autoregulation while non glabrous skin retains static with no dynamic autoregulatory capabilities.

4 COMPARISON BETWEEN LDF SIGNALS RECORDED IN GLABROUS AND NON GLABROUS SKIN

4.1 Measurement Procedure

In order to compare LDF signals from glabrous and non glabrous skin, thirteen healthy subjects (between 21 and 44 years old) were studied. All were informed of the measurement procedure and gave their written informed consent. After at least 10 min of acclimatization in the supine position, the acquisitions started in a room at ambient temperature. The flowmeter used was a Periflux 5000 (Perimed, Sweden) for which the time constant was chosen equal to 0.2 s and the wavelength was 780 nm. Two signals were recorded simultaneously in a.u.: one probe of the flowmeter was positioned in the ventral face of the right forearm of the subject (non glabrous skin), while the other probe was positioned in the right hand palm (glabrous skin). The two signals were recorded for at least 5 min with a sampling frequency of 20 Hz. In what follows, 6000 samples of signals (5 min) are processed. Two signals recorded simultaneously in the forearm and in the hand are shown in Figure 2.

4.2 Signal Processing Analysis

In what follows, temporal and spectral analyses of LDF signals recorded simultaneously in glabrous and non glabrous skins are performed. For the spectral study, the power spectrum is computed and possible power-law properties are analyzed.

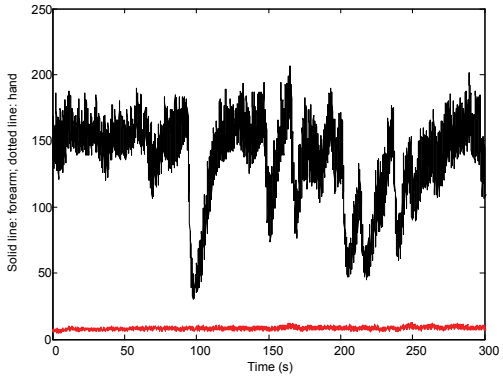

Figure 2: LDF signals recorded simultaneously in a healthy subject. The red solid line (lower curve) corresponds to the data recorded in the ventral face of the forearm; the black line (upper curve) corresponds to the data recorded in the hand palm.

Power-law relationship is observed when the general shape of the power spectrum is a power-law decreasing curve without eminent peak. In that case, the power versus frequency relationship is:

$$PS(f) \sim f^{-\beta} \qquad (6)$$

where PS is the power spectrum and f is the frequency. In a log-log plot, Eq. 6 gives a straight line with slope β. For such signals, data may be regarded as a fractal: the corresponding time series reveals self-similarity or scale-independence. Self-similarity means that a feature has the same characteristic value independent of the scale at which the signal is explored. When the time scale is changed by a factor m, the statistical distribution remains unchanged by the factor m^H, where H is called the Hurst scaling exponent. The latter scale-independence represents the irregularity of the time series. Fractal methods are amongst those used to show long-range correlations.

In what follows, in order to focus on the oscillations of the data, the mean of each signal was subtracted and the result was divided by the standard deviation of the original signal before the computation of the power spectrum.

4.3 Results

From our recordings and results, we first note that the mean amplitude of LDF signals recorded in the hand palms is generally higher than the one observed when the recordings are performed in the ventral face of the forearms. The latter conclusion has already been mentioned by other authors (see for example Freccero *et al.*, 2003). Furthermore, from the temporal domain analysis, we observe that the

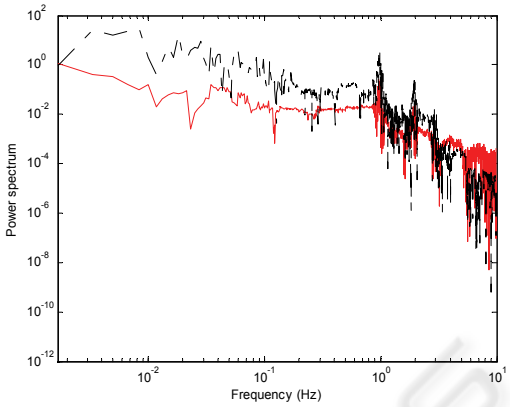

Figure 3: Power spectra of LDF signals recorded in a healthy subject. The red solid curve corresponds to the power spectrum of the LDF signal recorded in the ventral face of the forearm; the black dotted line corresponds to the power spectrum of the LDF signal recorded in the hand palm.

amplitude variations of LDF signals recorded in the hands are much higher than in the forearms. Thus, in average, for the 13 subjects, the amplitude variations for the hand were 69.5 a.u., whereas they were 13.5 a.u. for the forearm.

An example of power spectrum versus frequency in logarithmic scales is shown in Figure 3. From all our power spectrum plots, we observe a clear peak around 1 Hz for both the hand and the forearm. This peak is at exactly the same frequency for the signals recorded simultaneously. This peak is therefore probably of central origin and probably corresponds to the heart beat. Furthermore, another peak is visible around 0.3 Hz, at exactly the same frequency for the two signals recorded simultaneously. This peak may be due to the respiration of the subject.

The power spectrum plots also show three regions, with different slopes. The changes in slopes occur around 1 Hz and 5 Hz. This is in accordance with the work of Popivanov *et al.* (1999). Our results show that cutaneous LDF signals may exhibit scale-independence. This has already been predicted by other authors (see for example Popivanov *et al.*, 1999). However, the slopes for these three regions are different for hands and forearms (see an example in Figure 3). From our knowledge, no comparison between glabrous and non glabrous skin has already been published.

Such power spectrum studies have already been performed on central cardiovascular data (heart rate variability) and they led to the same conclusion (see for example Ivanov *et al.*, 2001 and its references).

5 CONCLUSIONS

This study shows that the fluctuations of cutaneous blood flow (cutaneous LDF signals) recorded in healthy human subjects are different in hand (glabrous skin) and forearm (non glabrous skin). These differences are observed in both the temporal and the spectral domains. Thus, the mean amplitude of LDF signals recorded in the hand is generally higher than in the forearm, and the fluctuations observed in the hand are much higher than the ones in the forearm. Furthermore, our work shows that the power spectrum of LDF signals recorded in hand and forearm of healthy subjects may be different. They both may possess characteristics of fractal processes, but these characteristics are different for the two analyzed anatomical sites.

In this paper, a monofractal study has been performed through the power spectral density analysis. A multifractal analysis could also be carried out. Multifractal time series are heterogeneous, self-similar only in local ranges of the structure and their fractal measure does vary in time; hence, they can be characterized by a set of local fractal measures. Some papers have recently been published on this field of interest for LDF data (see for example Humeau *et al.*, 2009; Humeau *et al.*, 2008).

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