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Short review

The investigation of skin blood flowmotion: a new approach to study the microcirculatory impairment in vascular diseases?

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Abstract

Skin blood flow oscillation, the so called flowmotion, is a consequence of the arteriolar diameter oscillations, i.e. vasomotion, and it is thought to play a critical role in favoring the optimal distribution of blood flow in the skin microvascular bed. Investigation of skin blood flowmotion, using spectral analysis of the skin laser Doppler flowmetry (LDF) signal, showed different flowmotion waves of endothelial, sympathetic or myogenic mediated vasomotion origin. Using this method in peripheral arterial obstructive disease (PAOD) patients an impairment of all the three flowmotion waves was found at level of the diseased leg following ischemia in the II stage of the disease and basally in critical limb ischemia. In patients with essential arterial hypertension (EHT) forearm skin blood flowmotion showed a post-ischemic impairment of myogenic and sympathetic components in newly diagnosed patients, and of endothelial and sympathetic components in long standing patients. In diabetic patients there was a selective impairment of skin flowmotion wave mediated by sympathetic activity in basal conditions. Investigation of skin blood flowmotion in response to different vasoactive substances demonstrated an important role of nitric oxide (NO) in controlling the endothelial component of vasomotion and an insulin action on smooth muscle cells of skin microvessels. All these data suggest that the study of skin blood flowmotion can become a method to early and easily detect skin microvascular impairment in vascular diseases and to investigate the mechanisms of substances active on skin microvascular bed.

Keywords: Skin blood flowmotion; Skin microcirculation; Laser Doppler flowmetry; Arterial hypertension; Peripheral arterial obstructive disease; Diabetes

1. Introduction

Human skin microcirculation can be easily studied in clinical setting by means of laser Doppler flowmetry (LDF), a technique which allows continuous, noninvasive, real-time assessment of skin perfusion in a hemispheral illuminated tissue volume of 1 to 1.5 ml under a measuring probe [22]. It has been suggested that skin microcirculation state mirrors the microcirculation state of other vascular beds [26,38], in this case its study could provide useful clinical data in evaluating the general microcirculatory impairment in different pathological conditions. Recently, the study of skin microcirculation has been implemented by the investigation of skin blood oscillation, the so called flowmotion, which has been demonstrated by Colantuoni et al. [9] to be dependent on arteriolar diameter oscillations, i.e. vasomotion. Some findings suggest a critical role of vasomotion, and the consequent skin blood flowmotion, in favoring the optimal distribution of blood flow in the skin microvascular bed [4,5,23,40]. Therefore, the study of skin blood flowmotion, made possible by the spectral analysis of skin LDF signal, can represent an additional element in the evaluation of the skin microcirculation in clinical setting.

The purposes of this review were to illustrate the role of vasomotion and the consequent blood flowmotion in skin microcirculation, to describe the spectral analysis of LDF signal used for the investigation of skin blood flowmotion, to present and discuss the results obtained using this method in some vascular diseases, as well as in response to vasoactive drugs.

2. Physiology of cutaneous microcirculation: role of vasomotion and flowmotion

The three main functions of skin microcirculation, namely skin tissue nutrition, heat exchange for thermoregulation and blood flow redistribution during stress, are guaranteed by a

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fine control of cutaneous vascular resistance and blood flow distribution [13]. This allows that skin blood flow can span throughout an extremely wide range (in non-acral skin, from 1.0 ml/min per 100 g tissue, needed to meet the relatively low intrinsic tissue metabolic demand, to 8.0 ml/min per 100 g, and in acral regions from 0.2 to 50 ml/min per 100 g,), accounting for up to 50% of total cardiac output during extreme thermal stress [13]. The regulation of skin microcirculation is obtained through the dynamic interaction of sympathetic vasoconstriction, pressure-dependent vasoconstriction, flow-dependent endothelium-mediated vasodilation, metabolic vasodilation, and spontaneous myogenic activity [13].

A further mechanism which makes possible the high skin microcirculatory reserve is the functional recruitment of previously inactive microvascular units, a phenomena suggested to be dependent on vasomotion and the consequent skin blood flowmotion [4,5,23,40]. Theoretical analysis of complex oscillations in multibranched microvascular networks suggested that stimulated vasomotion can increase of 40–60% the mean blood flow, compared with that under steady-state condition [40]. Moreover, as shown by Parthimos et al. [23], vasomotion may modify local blood flow distribution. In particular, it can reduce resistance in microvascular network and ensure an intermittent but adequate flow to the tissue in presence of a decreased blood flow supply [4]. This was confirmed by the results of studies in which skin blood flowmotion was investigated during the recovery following skin ischemia in healthy subjects. Ischemia elicited an amplification of skin blood flowmotion besides an increment of skin perfusion [2,27,28,42]. An amplification of skin blood flowmotion was also observed in response to acute exercise in healthy subjects [16,30]. This physiological response can favor a further reduction of resistance in skin microvascular bed during exercise, with increased capacity to transport and eliminate heat [16,30].

Vasomotion, which varies in frequency according to the vessel diameter [8], does not appear to be dependent on systemic factors, since it is readily observed in isolated vessels [10]. An important factor causing vasomotion is the myogenic response in terminal arterioles [20,39,40]. A further mechanism of vasomotion depends on endothelial activity, as suggested by the role of endothelium in the regulation of vascular tone [19]. Experimental findings obtained in hamster cutaneous muscle microcirculation confirm this hypothesis [41]. In this animal model the endothelium-dependent vasodilator acethylcholine (ACh) increased vasomotion amplitude and arteriolar effective diameter, whereas N^G-monomethyl-L-arginine (L-NMMA), an inhibitor of nitric oxide (NO) synthase from endothelium, caused a slight increase in vasomotion frequency and decrease in arteriolar effective diameter [41].

3. Spectral analysis of the LDF signal in the study of skin blood flowmotion

LDF signal, being generated by the movement of blood cells in both subpapillary thermoregulatory bed and nutritive capillaries, provides information about nutritional and non nutritional skin blood perfusion [22]. The continuous registration of the LDF signal by an interfaced computer equipped with an acquisition dedicated software allows the investigation of skin blood flowmotion in clinical setting.

Skin blood flowmotion waves with a frequency of 60–100 cycles per min can be directly observed on the cutaneous LDF signal. The amplitude of these flowmotion waves can be measured in conventional perfusion units (PU; 1 PU = 10 mV). Its frequency can also be easily measurable.

More recently, spectral analysis of skin laser Doppler signal was used in the study of skin blood flowmotion [27,33,36,37]. Two methods were used: the classical method of spectral analysis based on Fast Fourier Transform (FFT) algorithm or the generalized wavelet analysis. The first method measures the power spectral density of flowmotion waves in PU^2/Hz, using a short-time Fourier transform with a different window length for each frequency interval considered [33,27]. Generalized wavelet analysis, introduced by Stefanovska et al. [36,37], is a scale-independent method, with adjustable time and frequency resolution. This method breaks down the steady fluctuating time series into its frequency elements and computes the power of signal components in predetermined frequency bands, allowing to measure the amplitude of different flowmotion waves in PU/Hz [36,37].

Both methods used for the spectral analysis of skin laser Doppler tracing allowed to identify different skin blood flowmotion waves in the total spectrum of 0.009–1.6 Hz considered [27,33,37]. Two flowmotion components are the frequency interval of 0.6–1.6 Hz and of 0.2–0.6 Hz, due to the transmission to the skin microcirculation of the hemodynamic modifications synchronous with heart activity and respiration, respectively [7,36,37].

The findings that ACh iontophoresis increased amplitude of the oscillation around 0.009–0.02 Hz to a greater extent than sodium nitroprusside iontophoresis [15,17,37] or than ischemia [27] suggested a role of the endothelium in the control of this flowmotion component. This role was confirmed by the observation that L-NMMA abolished this difference [15].

Other findings suggested that the flowmotion waves around 0.02–0.06 Hz and 0.06–0.2 Hz are referred to local sympathetic activity [14,34,35], and to myogenic activity of the microvessel wall [37], respectively.

Using spectral analysis of skin LDF signal, skin blood flowmotion can be investigated in basal condition and in response to different stimulus such as ischemia (Fig. 1). Different mechanisms are involved in the skin microcirculatory response to ischemia. Accumulation of vasodilator metabolite adenosine in the ischemic skin [25], and the vascular smooth muscle relaxation due to the reduced transmural pressure in the resistance vessels, distal to the site of circulatory arrest [24], are considered the main mechanisms responsible for post-ischemic skin hyperemia. Recent findings also showed that post-ischemic skin hyperemia is partly mediated by vasodilator prostaglandins produced by endothelial cells in response to shear-stress [6]. However, the quantitative measurement of

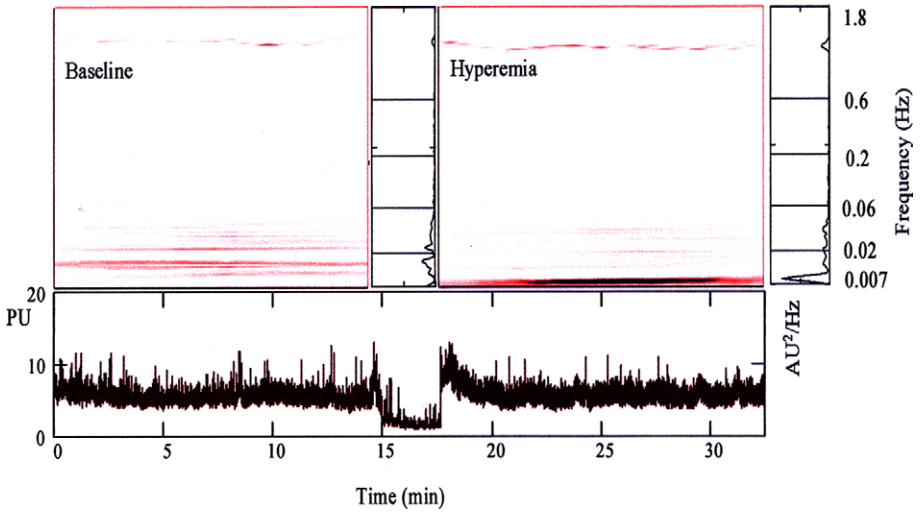

Fig. 1. A typical leg skin LDF tracing during baseline and post-ischemic hyperemia from an healthy subject. The power spectra of skin blood flowmotion obtained by the wavelet analysis with the averaged spectra (the right panel) in the two conditions are shown. PU = laser Doppler perfusion unit.

post-ischemic skin hyperemia does not inform either about the mechanisms by which it occurs or, above all, about its efficiency in favoring the optimal blood flow distribution in the skin microvascular bed. Differently, the study of the different components of the skin blood flowmotion following ischemia can give information about the mechanisms involved in post-ischemic skin hyperemia and about its efficiency in ensuring an adequate blood flow supply to the tissue [2,27,28].

4. The study of skin blood flowmotion in vascular diseases

Considering that the spectral intensity of the skin blood flowmotion components related to the endothelial, myogenic and sympathetic activity reflects the efficiency of each of these different mechanisms in the control of skin vasomotion [3,16,37], the investigation of skin blood flowmotion by means of LDF signal spectral analysis was performed in different vascular pathological conditions with the aim of obtaining information about the microcirculatory mechanisms implicated. Interesting findings have been recently obtained from the study of skin blood flowmotion in peripheral arterial obstructive disease (PAOD), in essential arterial hypertension (EHT) and in diabetes. Table 1 summarizes the principal findings.

4.1. PAOD

Initial studies of skin blood flowmotion in PAOD patients did not use spectral analysis of the skin LDF signal. These studies found two distinct frequency ranges of the skin flowmotion waves in the diseased leg of stage II PAOD patients: the so-called alpha, or fast waves, with a frequency of 10–20 cycles per min, and the so-called beta, or slow waves, with a frequency band of 1–3 cycles per min [12,32]. The same studies showed that the fast flowmotion waves increased according with the severity of PAOD and that leg skin flowmotion was abolished in the leg skin with more severe ischemia [12,32].

More recently, skin blood flowmotion was studied in PAOD patients by means of spectral analysis of LDF signal [28]. In basal conditions, the leg skin blood flowmotion waves related to the endothelial, sympathetic and myogenic activity, showed an increased amplitude in stage II PAOD patients, compared to control healthy subjects [28], while, contrarily to control subjects, they did not increase at all following ischemia in the PAOD patients (Fig. 2) [28]. A normal basal leg skin perfusion and a delayed leg skin post-ischemic hyperemia were also observed in PAOD patients [28]. These findings suggested that in II stage PAOD patients leg skin blood perfusion was not basally impaired because of a compensatory mechanism due to increased endothelial, myogenic and sympathetic vasomotion activities. The same findings were consistent with the exhaustion of these compensatory mechanisms in the diseased leg skin of PAOD patients during the recovery from ischemia, in accordance with a delayed leg skin post-ischemic reactive hyperemia observed in these patients.

Table 1
Principal skin blood flowmotion abnormalities in different vascular diseases

Vascular disease	Main SBF abnormality	Place of finding	Study condition
Recent onset EHT	Myogenic and sympathetic components impaired	Forearm	Following ischemia
Long standing EHT	Endothelial and sympathetic components impaired	Forearm	Following ischemia
II stage PAOD	All components impaired	Leg	Following ischemia
Critical Limb ischemia	All components impaired	Leg	Basal
Diabetes	Sympathetic component impaired	Leg	Basal

EHT = essential arterial hypertension; SBF = skin blood flowmotion.

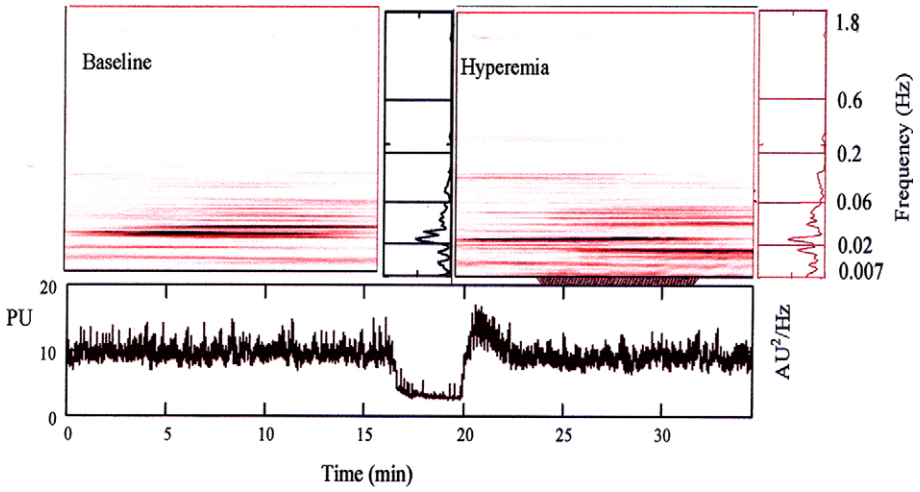

Fig. 2. A typical leg skin LDF tracing during baseline and post-ischemic reactive hyperemia from a patient affected by II stage PAOD. The power spectra of skin blood flowmotion obtained by the spectral analysis and the averaged spectra (the right panel) in the two conditions are shown. PU = laser Doppler perfusion unit.

A severely altered pattern of toe skin blood flowmotion was found in basal conditions in PAOD patients with critical limb ischemia [1]. This pattern consisted in a decreased amplitude of flowmotion spectrum of 0.016–0.6 Hz [1], which includes sympathetic and myogenic flowmotion components, as well as part of the endothelial flowmotion component. This finding suggested that exhaustion of the skin vasomotion mechanisms occurred in basal conditions during critical limb ischemia.

4.2. EHT

Forearm skin blood flowmotion during baseline and following ischemia was recently investigated in newly diagnosed and long standing well treated EHT patients, using spectral analysis of forearm skin LDF signal [31]. In basal condition, a normal amplitude of different skin blood flowmotion components was observed both in newly diagnosed and long standing EHT patients. Both groups of EHT patients did not differ from normotensive control subjects as to post-ischemic forearm skin reactive hyperemia. However, an abnormal different skin blood flowmotion response following ischemia was observed in the two groups of EHT patients [31]. Newly diagnosed EHT patient showed a normal increase in amplitude of endothelial mediated flowmotion component as well an absent increase in amplitude of myogenic and sympathetic mediated flowmotion components. Long standing EHT patient showed a preserved increase in amplitude of myogenic component, as well an absent increase in amplitude of endothelial and sympathetic flowmotion components. These findings suggested that an impairment of the endothelial mechanism involved in skin blood flowmotion occurs by the time in the course of human EHT [31], and that an impairment of the myogenic and sympathetic mechanisms of skin blood flowmotion occurs early in the course of this disease. Moreover, the normal post-ischemic increase in amplitude of myogenic skin flowmotion component observed only in long standing EHT patients was interpreted by the hypothesis that an adequate antihypertensive treatment can favor the recovery of myogenic flowmotion mechanism. The same study showed also that the study of skin blood flowmotion is more sensitive than the quantitative measurement of skin reactive hyperemia in evaluating the skin microcirculatory impairment in human EHT.

4.3. Diabetic vascular disease

Study of skin blood flowmotion in diabetic patients has been focused on the investigation of the sympathetically mediated flowmotion component, with the aim of elucidating the role of the sympathetic nervous system in the development of diabetes-associated microcirculatory alterations. Bernardi et al. [3] firstly demonstrated that diabetic patients showed a selective decrease in spectral intensity of skin blood flowmotion component, related to the sympathetic activity. This abnormality was significantly more frequent and precocious than abnormalities in parasympathetic autonomic tests. Since sympathetic denervation has been proposed as the main cause of the increased skin capillary blood flow in the lower limbs of diabetic patients when standing, this may explain the intractable ankle edema which might occur in diabetics.

More recently, Lefrandt et al. [18] demonstrated that a selective decrease in amplitude of sympathetically mediated skin flowmotion component in diabetic patients with peripheral neuropaty was associated with an increased capillary leakage. In the same study, multiple regression analysis disclosed that the abnormality of sympathetically mediated skin flowmotion component independently contributed for 30% to the variance in capillary leakage. These findings suggested that loss of sympathetic tone, apart from sensory-motor nerve dysfunction, seemed to be a major determinant of an increased capillary permeability in diabetic patients with neuropathy.

5. The study of skin blood flowmotion in response to vasoactive drugs

The mechanisms of a given skin vasoactive substance has been evaluated by measuring the variation in spectral intensity

of the different skin blood flowmotion components induced by the substance [15,17,29].

Kvandal et al. [15] demonstrated that the normalized spectral amplitude of the skin endothelial mediated flowmotion component with a frequency around 0.01 Hz, was increased to a greater extent by ACh than by sodium nitroprusside. Moreover in the same study, L-NMMA abolished this difference, whereas it reappeared after infusion of L-arginine. Aspirin did not affect this difference [15]. These findings suggested that endothelial mediated skin vasomotion is mainly dependent on NO and not on endogenous prostaglandins produced by the endothelium.

Skin blood flowmotion response to insulin iontophoresis has been recently investigated in order to explore the microvascular mechanisms involved in the vasodilatory activity of this hormone [29]. The use of iontophoresis [11] for delivering insulin to the skin in this study was preferred because this method allowed to study insulin cutaneous vasoactive effect without confounding influences related to the systemic effect of this hormone [21,27]. Using this method, the absolute and the normalized spectral amplitude of the skin blood flowmotion component with a frequency around 0.1 Hz, due to the myogenic vasomotion mechanism, was increased to a greater extent by insulin iontophoresis than by saline iontophoresis, used as control procedure [29]. This finding suggested that the cutaneous vasodilatory activity of insulin is, almost in part, due to an important action of this hormone on skin microvascular smooth muscle cells.

6. Conclusions

A number of studies demonstrated that spectral analysis of LDF signal is useful and accurate for the evaluation of skin blood flowmotion, a critical factor in favoring the optimal blood flow distribution in skin microvascular bed. Important abnormalities of skin blood flowmotion have been observed in PAOD, EHT and diabetic patients. In PAOD patients all flowmotion components were impaired in the diseased leg skin both in II stage of the disease and in stage of critical limb ischemia. Different skin flowmotion patterns were observed according to the time course of EHT. Myogenic and sympathetic flowmotion components were impaired in EHT of recent onset, while endothelial and sympathetic flowmotion components were impaired in long standing EHT. In diabetic patients there was a selective impairment of skin flowmotion component mediated by sympathetic activity. The ischemic stimulus was essential in detecting the above mentioned skin flowmotion abnormalities in II stage PAOD patients and in long standing EHT patients. In diabetic patients and in PAOD patient with critical limb ischemia the above mentioned skin flowmotion abnormalities were detected in basal conditions. Investigation of skin blood flowmotion in response to different vasoactive substances demonstrated an important role of NO in controlling endothelial component of vasomotion and the insulin action on smooth muscle cells of skin microvessels. All these data suggest that the study of skin blood flowmotion can be used to early and easily detect skin microvascular impairment in vascular pathological conditions as well as to investigate the mechanisms of vasoactive substances on skin microvascular bed.

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