Diagnostic value of skin vasomotion investigation in vascular diseases

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Abstract: - Skin vasomotion is the rhythmic variation of the skin microvessel diameter, responsible for the skin microcirculatory blood flow oscillation, the so called skin blood flowmotion. Experimental and clinical findings suggest that vasomotion depends on several mechanisms, such as the endothelial activity, the spontaneous myogenic activity of the microvascular wall and the sympathetic activity. Skin vasomotion can be indirectly investigated in humans by means of the spectral analysis of skin laser Doppler flowmetry tracing. A high number of studies have recently investigated skin vasomotion in patients with various vascular diseases, using this method. Findings obtained in these studies have contributed to the understanding of the pathophysiology of the microcirculatory impairment in the pathological conditions investigated. The aim of the present review is to describe the method that can be used to analyze skin vasomotion and the diagnostic value of skin vasomotion investigation in vascular diseases.

Key-words: - skin microcirculation, vasomotion, vascular diseases, laser-Doppler flowmetry, spectral analysis.

1 Introduction

In recent years, the investigation of microcirculation has received a lot of attention from researchers and clinicians interested in the study of the pathophysiology of human cardiovascular diseases. Such attention is due to the crucial role that microcirculation plays as the final target of the cardiovascular system, where trans-capillary exchanges occur, supporting the necessary homeostasis of tissues. The impairment of this function is a critical event, which allows a given cardiovascular disease to become clinically evident. Given the facility with which microcirculation can be investigated in humans at the level of the skin by means of laser Doppler flowmetry (LDF), skin microcirculation has been the object of many clinical studies in several cardiovascular diseases. Since it has been demonstrated that functional impairments of skin microcirculation mirror impairments of the microcirculatory function of other districts, including the myocardium (1-4), this approach can be useful in those pathological conditions in which other districts rather than skin can be involved.

Human skin microcirculation can be easily investigated by LDF, a technique that allows continuous, noninvasive, real-time assessment of skin blood perfusion in an illuminated hemispheric tissue volume of 1 to 1.5 ml under a measuring probe [5]. The LDF signal, being generated by the movement of blood cells in both sub-papillary thermoregulatory bed and nutritive capillaries, provides information about nutritional and non nutritional skin blood perfusion [5]. Using LDF, skin blood perfusion can be assessed under baseline conditions and in response to different stimuli, such as ischemia [6], heat stimulation [7] or pharmacological substances [8]. These functional tests are useful for investigating adaptive reserves of skin microcirculation and to estimate the state of mechanisms regulating skin blood flow. By analyzing changes in the skin blood perfusion of the examined area, clinicians can obtain information on changes of skin microvascular function, and such information can be used as a criterion for diagnosing a more general microcirculatory impairment in the studied subjects. Recently, the study of skin microcirculation has been implemented by the investigation of skin vasomotion, that is to say, the rhythmic oscillations of skin microvessel diameter [9, 10].
2 Mechanisms and functional role of vasomotion

Vasomotion, which has been observed in various tissues and species for many years, is responsible for rhythmic fluctuations of blood flow in microvessels, the so called flowmotion [10]. Vasomotion and the consequent blood flowmotion have been suggested to be beneficial for tissue oxygenation, especially in situations where perfusion is critically limited [9]. This hypothesis comes from the theoretical model proposed by Tsai and Intaglietta [12], according to which periods of high flow at low frequency, such as during the slow-wave vasomotion, permit long-distance diffusion of oxygen to capillaries. Further studies, based on the theoretical analysis of complex oscillations in multi-branched microvascular networks [13, 14], showed that stimulated vasomotion can increase the mean blood flow by 40-60 %, compared with that under steady-state conditions. The experimental observation that vasomotion increased under tissue hypoxia, acidosis or hypotension [15] gave a further argument in favour of the beneficial effect of vasomotion on microcirculatory blood perfusion. More recently, an “in vivo” study on rabbit ear skin clearly demonstrated that skin vasomotion enhances blood perfusion in skin microvascular bed and promotes material exchange between tissues and blood [16].

The mechanisms controlling microvascular vasomotion have been the object of many investigations. In experimental models, spontaneous repetitive oscillation in calcium cytosolic concentration of rat microvascular smooth muscle cells was associated with membrane potential oscillations and vasomotion [17], suggesting the central role of calcium ion in the genesis of vasomotion. In other experimental studies [18] mechanical or chemical removal of the endothelium from isolated arterioles abolished vasomotion, suggesting a contemporary crucial role of the endothelium itself in the genesis of vasomotion. This role was confirmed by findings showing that vasomotion was reduced or abolished by the exposure of isolated intact arteries to N\(^{G}\)-monomethyl-\(L\)-arginine (L-NMMA), an inhibitor of nitric oxide (NO) synthesis from the endothelium, as well as by the observation that vasomotion was restored in pre-contracted endothelium-denuded vessels by sodium nitroprusside (SNP), a donor of NO [19]. Taken together, these data suggest that NO release from the endothelium represents the main contribution of the endothelium to vasomotion. Other experimental studies from rat mesenteric arteries showed that vasomotion was critically dependent on \(\text{Ca}^{2+}\)-activated K\(^+\) channels in endothelial cells [20], suggesting that the release of the endothelium-derived hyperpolarizing factor (EDHF) from the endothelium is a further mechanism involved in the genesis of vasomotion. On the other hand, the observation that vasomotion occurred in isolated arterioles in the absence of the endothelium [18] suggests that vasomotion is also dependent from other extra-endothelial mechanisms. Experimental data showed that one of these mechanisms is the spontaneous activity of microvascular smooth muscle cells, depending on the spontaneous repetitive oscillation in calcium cytosolic concentration [21]. Other data obtained from human skin suggested that the local sympathetic nerve activity too is involved in the control of skin vasomotion [22].

3 Investigation of skin vasomotion in humans

Different methods can be used for investigating skin vasomotion. Skin vasomotion has been directly investigated in experimental setting using an “in vivo” hamster window skin preparation [9]. The method that can be used in clinical setting is based on the assessment of the blood cell movements at the level of a single capillary or at the level of the skin microvascular bed. The first one uses a capillaroscopy apparatus equipped with a single photon laser Doppler apparatus, the second one uses a conventional laser Doppler apparatus. Both these methods are based on the assumption that the blood flow oscillations that are detectable at the level of skin microvessels are dependent, at least in some of their components, on skin vasomotion. The blood flow oscillations detectable a the level of a single or multiple microvessels can be examined in the frequency domain by means of the spectral analysis of the LDF signal. The second one of these two methods, based on a conventional LDF apparatus, has been definitively validated and, at present, it is generally considered an easy and reliable approach in this field of clinical investigation.

Two methods can be used for the spectral analysis of skin LDF signal: the classical method of spectral Fourier analysis, which has been slightly modified for this specific approach, and the generalized wavelet analysis (GWA). The first one uses a Fast Fourier
Transform algorithm in which different window lengths are adopted, depending on the frequency interval considered [23, 24]. Using this method, the spectral power of a given flowmotion component can be measured in PU²/Hz (perfusion units²/Hz). The GWA, firstly used in this approach by Aneta Stefanovska [25-27], is a scale-independent method, with adjustable time and frequency resolution. Using the GWA, the steady fluctuating time series are broken down into their frequency elements and computed in their spectral power into predetermined frequency bands. The GWA allows the spectral power of a given flowmotion component to be measured in PU/Hz [26, 27]. Both these methods allow us to measure the spectral power of a given skin blood flowmotion component that can be identified in the skin LDF signal previously recorded by an interfaced computer, equipped with a dedicated software.

The origin of flowmotion components which are detectable within the total spectrum of 0.005-1.6 Hz in the LDF signal has been the object of many investigations. The skin blood flowmotion component with frequency interval within 0.009-0.02 Hz was shown to be related to the endothelial-dependent vasomotion. This was suggested by the observation that endothelial-dependent vasodilator acetylcholine (ACh) increased the relative contribution of this flowmotion component to a greater extent than endothelial-independent vasodilator SNP [27, 28]. This difference disappeared when the production of NO from the endothelium was inhibited by L-NMMA, and reappeared after the substrate for NO synthesis, l-arginine, was administered [29]. These data confirm that the 0.009-0.02 Hz skin blood flowmotion component is due to endothelial-dependent vasomotion and, in particular, to the NO release from the endothelium. Similarly, another skin blood flowmotion component, with frequency interval within 0.005-0.0095 Hz, has been shown to be dependent on endothelial function, since ACh increased its relative contribution to a greater extent than SNP [29]. On the other hand, either the inhibition of NO by L-NMMA, or the inhibition of prostaglandins synthesis by Aspirin did not abolish this difference [29], suggesting that other endothelium-dependent mechanisms, such as the release of the EDHF from the endothelium, can be involved in the control of this flowmotion component. The skin blood flowmotion component with a frequency interval within 0.02-0.06 Hz has been shown to be related to the sympathetic-dependent vasomotion [30, 31], since its spectral power was lower at the level of human microvascular flaps deprived of sympathetic nerve activity, compared to adjacent intact skin [30] and decreased in human skin after ganglion nerve block or sympathectomy [31]. The skin blood flowmotion component with a frequency interval within 0.06-0.2 Hz has been demonstrated to be related to spontaneous myogenic-dependent vasomotion, since its spectral power did not change either in response to ACh [26, 32] or after sympathectomy [31]. Among the several blood flowmotion components that can be identified in the total spectrum of 0.009-1.6 Hz, two of them, with frequency intervals of 0.6-1.6 Hz and of 0.2-0.6 Hz, are not related to vasomotion. They represent the blood fluctuations due to the transmission to skin microcirculation of the haemodynamic modifications synchronous with heart activity and with respiration, respectively [26]. It has been assumed that the spectral power of a given skin blood flowmotion component reflects the efficiency of the vasomotion mechanism responsible for that specific blood flow oscillation [26, 27]. On the basis of this assumption, the spectral analysis of skin LDF signal allows the mechanisms controlling vasomotion (namely the endothelial, sympathetic and spontaneous myogenic activity) to be evaluated in their efficiency.

4 Clinical studies on skin vasomotion

In recent years, skin vasomotion has been investigated in patients with several pathological conditions such as peripheral arterial obstructive diseases (PAOD) [33, 34], arterial hypertension [35], hypercholesterolemia [36], chronic kidney disease [37, 38], systemic sclerosis [39], diabetes [11] and obesity [40], as well as in chronic smokers [41]. In these studies, skin vasomotion was investigated both under basal conditions and in response to different stimuli, such as ACh iontophoresis or skin ischemia. These stimuli have been shown to induce a significant increase of skin vasomotion in healthy subjects [32]. A severely blunted post-ischemic increase in endothelium-, sympathetic- and myogenic-dependent skin vasomotion was found in the diseased leg of II stage PAOD patients [34], consistently with a microvascular endothelial, sympathetic and myogenic dysfunction. A preserved skin vasomotion was observed under basal conditions in the diseased leg of II stage PAOD patients in the same study [34]. A
reduced endothelium-, sympathetic and myogenic-dependent skin vasomotion was observed at the level of the skin of the diseased leg of PAOD patients with critical limb ischemia, under basal conditions in another study [33]. Taken together, these data suggest that skin vasomotion is impaired in the diseased leg of PAOD patients, with a greater impairment according to the severity of PAOD.

A severely blunted post-ischemic increase in endothelium-, sympathetic- and myogenic-dependent vasomotion was observed in chronic smokers without clinically known vascular diseases [41]. This finding suggests that the chronic exposition to smoke impairs all the mechanisms controlling skin vasomotion. In the same study [41], a preserved skin vasodilator response to ischemia was observed in smokers. Taken together, these findings suggest that in smokers, skin vasomotion investigation in response to ischemia is a more sensitive test than the simple study of skin blood flow response to ischemia.

In another study [35], the endothelium- and sympathetic-dependent skin vasomotion responses to ischemia resulted to be reduced in long standing essential arterial hypertensive (EHT) patients. In the same study [35], newly diagnosed EHT patients showed a reduced post-ischemic increase in sympathetic- and myogenic-dependent vasomotion, together with a normal post-ischemic response of the endothelial-dependent vasomotion. Moreover, both groups of EHT patients showed a normal skin vasodilator response to ischemia [35]. Taken together, these findings suggest that the arterial hypertension selectively impairs mechanisms of vasomotion, according to the length of the disease: the myogenic-dependent vasomotion being impaired in the early stages of this disease and the endothelial-dependent vasomotion in the later stages. Moreover, the same findings suggest a greater sensitivity of skin vasomotion investigation than the measurement of post-ischemic skin blood flow response in detecting microvascular dysfunction in EHT patients.

A blunted post-ischemic increase in endothelial-dependent skin vasomotion was observed in patients with chronic kidney diseases (CKD) on conservative treatment [38], consistently with a microvascular endothelial dysfunction. CKD patients exhibited a preserved skin blood flow response to ischemia in the same study [38]. The endothelium-dependent skin vasomotion was found basally reduced in uremic CKD patients on dialytic treatment in another study [37]. Taken together, these results suggest that the severity of the impairment in endothelial-dependent skin vasomotion in CKD patients depends on the severity of the CKD.

The endothelium-dependent skin vasomotion resulted to be reduced in response to ACh iontophoresis in hypercholesterolemic patients without clinically manifest arterial diseases, consistently with a microvascular endothelial dysfunction in the studied patients [36]. The endothelial-dependent skin vasomotion response to ACh was impaired in II type diabetes patients compared to control subjects in another study [11]. Similar findings were observed at the level of finger skin in patients with systemic sclerosis [39]. In the same study [39], systemic sclerosis patients also exhibited a blunted vasomotion response to ACh or SNP in the frequency intervals related to sympathetic and spontaneous myogenic activity. Finally, in a recent study [40], a decreased endothelial- and sympathetic-dependent skin vasomotion was observed in obese women under basal conditions.

5 Discussion and conclusions

A number of studies showed that the spectral analysis of LDF signal is a useful method for the evaluation of skin microvascular vasomotion in clinical setting. Impairments of skin vasomotion were observed under basal conditions or following different stimuli in all the primary or secondary vascular diseases investigated. Findings obtained in these studies have contributed to understand the patho-physiology of the microcirculatory impairment in the investigated pathological conditions. Some of these studies also showed that skin vasomotion investigation in response to ischemia or ACh iontophoresis is a more sensitive diagnostic approach in the evaluation of microvascular dysfunction than tests based on the simple measurement of skin blood flow response to the same stimuli.

Taking into account all the published studies on skin vasomotion investigation in humans, we can notice that the spectral power of skin vasomotion has been defined in several ways: as the highest absolute or normalized spectral value found in a given frequency interval [24, 42], as the area under the spectral frequency curve [11] or as frequency distribution in the total spectral power of LDF signal [37]. This prevents us from directly comparing results obtained in different studies and casts a certain shadow over the very reliability of vasomotion investigation. In order to overcome these problems, methodological standardization of the way
to define the spectral power of a given frequency interval will have to be achieved by researchers interested in this specific field.

In conclusion the study of skin vasomotion by means of the spectral analysis of skin LDF signal has been demonstrated to be an easy and sensitive method in detecting skin microvascular impairment in vascular diseases. If the standardization of some methodological aspects of spectral analysis of skin LDF signal will be achieved, the reliability of this method will further increase and results obtained from studies will be more easily compared with a greater contribution in understanding the patho-physiology of the investigated vascular diseases. Further studies will be also needed in order to evaluate whether the results of vasomotion investigation can predict clinical and therapeutic outcomes in patients with various primary or secondary vascular diseases.

References:


