Pharmacological Reports 67 (2015) 803–810

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Skin microvascular endothelial function as a biomarker in cardiovascular diseases?

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ARTICLE INFO

Article history:
Received 19 February 2015
Received in revised form 13 May 2015
Accepted 13 May 2015
Available online 28 May 2015

Keywords:
Endothelium
Skin microcirculation
Reactivity tests
Laser Doppler
Laser speckle contrast imaging

ABSTRACT

Skin microvascular endothelial function is impaired in many cardiovascular diseases, and could be therefore considered as a representative vascular bed. However, today, available evidence allows considering skin microvascular endothelial function neither as a diagnostic biomarker nor as a prognostic biomarker in cardiovascular diseases. Large follow-up studies using standardized methods should now be conducted to assess the potential predictive value of skin microvascular function in cardiovascular diseases.

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Introduction

Cardiovascular diseases are the leading cause of death in industrialized countries. Great emphasis has recently been placed on the involvement of endothelial dysfunction in the pathogenesis of a wide spectrum of cardiovascular diseases such as atherosclerosis and hypertension [1]. Indeed, endothelium plays a crucial role in the inhibition of platelet aggregation, coagulation, fibrinolysis and the regulation of vascular tone by releasing vasoactive substances, including nitric oxide (NO), prostacyclin and endothelium-derived hyperpolarizing factors (EDHF). Endothelial dysfunction of conductance arteries has been extensively studied as a surrogate endpoint of coronary artery disease, especially by using flow-mediated dilatation (FMD) [2]. Although less studied, microvascular dysfunction may precede endothelial impairment in large arteries and the subsequent clinical manifestations. For example, some microvascular beds such as the retina and kidney are specifically altered in cardiovascular diseases. The cutaneous circulation is an accessible vascular bed that has been proposed to be used as a model of generalized microvascular function [3].

After a brief section about the different methods that are used for non-invasive assessment of skin endothelial function, we

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http://dx.doi.org/10.1016/j.pharep.2015.05.008
1734-1140/

aimed at summarizing available evidence that explore the relationship between cardiovascular disease and skin microvascular reactivity, with a focus on endothelium-dependent pathways.

Assessment of skin microvascular endothelial function

Different methods enable to study peripheral microcirculation. Isolated subcutaneous microvessels can be mounted on isometric myographs, but such an approach remains invasive and presents many limitations of *in vitro* studies. Although interesting, such experiments take place outside the tissue in a controlled and artificial milieu without influences of neural and mechanical stimuli as well as circulating hormones and metabolites. Indeed, it is very difficult to apply the results in clinical conditions [4]. Several noninvasive techniques have been designed to explore *in vivo* the peripheral microcirculation. Among them, videocapillaroscopy is routinely used to assess capillary morphology. Although of great diagnostic value, this method does not allow convenient mechanistic studies of microvascular function. In contrast, laser Doppler techniques or the more recent laser speckle contrast imaging (LSCI) provide a real-time quantification of relative changes in skin perfusion. Thus, the conventional approach is to couple these techniques with various endothelium-dependent reactivity tests [5].

Laser Doppler is based on the reflection of a beam of laser light. The light undergoes changes in wavelength (Doppler shift) when it hits moving blood cells. The magnitude and frequency distribution of these changes in wavelength are related to the number and velocity of blood cells [6]. The first developed technique is called laser Doppler flowmetry (LDF). Single point LDF assesses blood flow over a small volume (1 mm^3) and is accurate at detecting and quantifying rapid changes in skin blood flux in response to a given stimulus [7]. However, the regional heterogeneity of skin perfusion leads to spatial variability, which contributes to the relatively poor reproducibility of the technique [8]. Integrating probes made of several collecting optical fibers improve the reproducibility of the technique. In order to overcome these disadvantages, laser Doppler imaging (LDI) is a non-contact tool that measures blood flow over larger area providing 2D perfusion maps. Although, LDI has a lower spatial variability compared with LDF, it takes often few minutes of scanning to obtain one image. Therefore, LDI is relatively poor in terms of temporal resolution.

LSCI is a more recently developed technique based on speckle contrast analysis that provides an index of blood flow [9]. LSCI allows noninvasive real-time monitoring of peripheral microcirculatory perfusion on a wide area of tissue with a very good spatial resolution and an excellent reproducibility [10]. It should be noted that the skin penetration depth of LSCI is about 300 μm, whereas it is deeper (about 1–1.5 mm) with laser Doppler techniques [11]. Both techniques do not provide an exact measure of flow (mL/min). Measurements are therefore expressed as arbitrary perfusion units (PU) or as cutaneous vascular conductance (CVC), which is flux divided by mean arterial pressure. Such an approach is more physiological as it takes into account differences and variations in blood pressure.

Among reactivity tests, post-occlusive reactive hyperemia (PORH) is the sudden increase in skin blood flow observed immediately after the release of an arterial occlusion. This test is performed by placing a cuff on the upper arm and increasing the pressure above the systolic blood pressure. The commonly used ischemic period is 3–5 min. The flux is then measured commonly on the ventral face of the forearm. Insights into the mechanism of cutaneous post-occlusive hyperemia have shown that the inhibition of cyclooxygenase (COX) and NO do not alter skin PORH. Recently, EDHF has been suggested as the major endothelial contributor to PORH [12].

Local thermal hyperemia (LTH) consists in a temperature-dependent, sustained increase in skin blood flow and achieves a maximal vasodilatation between 43 °C and 44 °C. Rapid heating protocols induce a biphasic vasodilatation mediated by two independent mechanisms. A rapid initial peak in blood flow, during the first 2–3 min, relies predominantly on local sensory nerves [13]. By contrast, a prolonged plateau, observed within 20–30-min, mostly depends on endothelial factors, among which NO accounts for approximately two-thirds of this response, whereas EDHF are involved in the remaining response [14].

Finally, iontophoresis of acetylcholine has been used extensively. Iontophoresis is based on the principle that a charged drug in solution will migrate across the skin under the influence of a direct low-intensity electric current [15]. Acetylcholine and sodium nitroprusside (SNP) are commonly used to access microvascular endothelium-dependent and independent vasodilatation, respectively. Iontophoresis of acetylcholine results in an early peak that is followed by a late prolonged vasodilatation. The precise mechanisms by which acetylcholine induces vasodilation of the human skin microvessels remain unknown. A COX-dependent pathway seems to play an important role, although data are conflicting. In contrast, NO is not likely to be extensively involved in this vascular response [16,17].

Another approach to study endothelial function is using a strain-gauge venous plethysmography to quantify forearm blood flow. Although reproducible, this technique is challenging for nonspecialists and requires a brachial artery catheterization, which limits its routine use. Moreover, venous occlusion plethysmography measures blood flow in peripheral muscular arteries [18]. In contrast, laser Doppler and laser speckle imaging quantify skin microcirculation perfusion. Laser Doppler flowmetry signal correlates well with forearm blood flow and appear to produce the same response pattern during reflex cutaneous vasodilatation [19].

Peripheral arterial tonometry enables to measure endothelial function in the finger using beat-to-beat plethysmographic recordings of the finger arterial pulse wave amplitude [2]. Peripheral finger endothelial function measured with peripheral arterial tonometry is correlated with coronary microvascular function in patients with early atherosclerosis [20]. However, to the best of our knowledge, there is no study which explored a relation between laser Doppler and peripheral arterial tonometry.

Is skin microvascular endothelial function altered in cardiovascular diseases?

Given that skin is easily accessible, an ongoing issue is to determine whether skin microvascular function is abnormal in patients with atherosclerosis and related disorders. Table 1 summarizes the methods and results of the reviewed studies.

Using LDI, it has been shown that PORH time to peak response was roughly doubled in patients with coronary artery disease (CAD) compared with control subjects, while the hyperemic response was decreased when reactive hyperemia was expressed as a percentage of baseline, but not AUC [21]. Similarly, in another study with LDF, a prolonged PORH time to peak was observed in CAD patients, while the peak response was not different after correction for cardiovascular risk factors [22]. In contrast, using LDI, another group showed significantly reduced PORH AUC and amplitude in CAD patients [23]. Similarly, with LDI, acetylcholine iontophoresis and local thermal hyperemia induced lower responses in CAD patients, acetylcholine induced hyperemia being similarly altered in another study [24]. ROC curve analysis demonstrated that LTH was a better discriminator of CAD patients than acetylcholine iontophoresis and PORH [22]. Using LDF, an increased risk for CAD was associated with a decreased acetylcholine iontophoresis-induced vasodilatation. However, this was not