

Principles and Practice of Clinical Research

A Global Journal in Clinical Research



PPCR

ISSN: 2378-1890

A review of endothelial reactivity test and skin conditions

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Received September 14, 2015; accepted October 19, 2015; published December 4, 2015.

Abstract:

Background: Skin microcirculation is routinely used to assess systemic endothelial function. The advantages of this exam are; low cost, a noninvasive good predictor for cardiovascular diseases, and a valuable intermediate endpoint to assess cardiovascular therapies. Because some skin particularities such as age, dermatological diseases, it is desirable to review these points to understand better some exam variations.

Aim: This review aimed to discuss skin anatomical characteristics, and skin conditions that can influence endothelial function interpretation.

Key-Words: skin, endothelium, aging, connective tissue, vascular resistance.

DOI: <http://dx.doi.org/10.21801/ppcrj.2015.13.2>

INTRODUCTION

The skin microcirculation is organized in two plexuses: dermal (1-1.5mm below epidermis) and subdermal (dermic - subdermal junction) (1-3). Subdermal plexus are originated by perforator vessels from muscle and adipose tissue. Consequently, arterioles from subdermal plexus (communicant vessels) will penetrate the dermis and will create dermal plexus (1-4). Both plexuses are connected by ascending arterioles and descending venules (2, 3, 5). From the dermal plexus, terminals ascending to arterioles forms dermal papillary loops enhancing the vascular skin area (6, 7).

The bloodstream regulation in the skin microcirculation is determined by: the arteriolar myogenic response, the flow-induced vasodilation, and the neural and metabolic control. The first factor promotes interaction with the smooth muscle cells and the endothelium secretors (nitrous oxide, prostacyclin), and releases vasodilators and vasoconstrictor substances (4). The second factor, the flow-induced vasodilation reflects the interaction between elements of the blood (red cells), and the stress-shear with the internal arteriolar layer (8, 9). The last one is influenced by sympathetic substances, such as norepinephrine, the P-substance (8-10).

Because of these characteristics, the skin microcirculation allows many pieces of equipment to analyze systemic endothelium. This test studies the ischemia-reperfusion phenomenon and depends on the endothelial function this reactivity test will amplify the cardiovascular alteration signals. Moreover, the low cost and noninvasive nature are some advantages of its use in clinical practice. However, several physiologic and pathologic aspects of the skin itself can interfere with the outcome. Because of this, it is desirable to discuss how dermic alterations can modify the reactivity test outcome. The aim of this review was to discuss the endothelial function test outcome in different skin condition.

METHODS

We searched the following electronic databases: MEDLINE via Pubmed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) from 1984 to 2015. The search strategy is presented on Table 1.

RESULTS AND DISCUSSION

In order to understand how skin conditions interfere in the endothelial function test we described the most common reactivity tests. The reactivity is studied by the

Test	Advantage	Limitation
Arterial occlusion	Simple, low cost	Oral contraceptives, statins interfere on the outcome
Pressure Stimuli	Simple	Aging and interfered by diabetes
Thermal challenge	Not standardized	Age, statins and contraceptive use interfere on results
Pharmacological challenge	Expensive, pharmacological control	Topical anesthetic interfere on results
Electrical challenge	Non-invasive	Iontophoresis is affected by topical anesthetics. Saline solution can interfere on results

Table 1. Research Strategy

ischemia/reperfusion effect according to different stimuli (4, 11).

Videocapillaroscopy is one of the methods to evaluate endothelium. Basically, this method uses a magnification lens to measure arteriolar density. It is interesting in systemic sclerosis (12, 13).

Another technique is the Laser Doppler that provides an index of skin perfusion by measuring the Doppler shift induced by coherent monochromatic light scattering by moving red blood cells (4). These equipment measure limited signals, which increase information from reactivity tests that are associated to this method (14). Reactivity tests can be performed by arterial occlusion, pressure – induced vasodilation (16), pharmacological stimuli (15, 18), thermal challenge (17), and electrical stimuli (4, 14). The most frequent reactivity test is arterial occlusion. All these techniques present advantages and limitations. Table 2.

#1 Endotelium	#7 Aging
#2 Endotelium function	#8 Skin disease
#3 Skin microvasculature	#9 1 AND 3
#4 Cutaneous vessels	#10 1 AND 7
#5 Microcirculation	#11 2 AND 6
#6 Reactivity test	#12 2 AND 8

Table 2. Advantages and limitations of endothelial function tests

Based on this information we will show how different skin conditions interfere in the reactivity test outcome.

Aging

Aging causes functional and anatomical modifications in endothelium reactivity (19). Age leads to structural

vascular changes, such as luminal enlargement, intimal and medial thickening, increased vascular stiffness, migration of smooth muscle cells (SMCs) from the tunica media and accumulation of SMCs in the tunica intima. Functional alterations are arteriosclerosis, dermal papillary planning, and decrease of angiogenesis. Anatomic variations are decrease of extra cellular matrix and decrease of the circulation area. Smooth muscle cells respond differently in apoptosis and proliferative behavior. The decrease of alpha subunits of calcium and Na-K channels results in an imbalance in vasoconstriction and dilation mechanism. Additionally, endothelium function (nitric oxide excretion) decreases and selective permeability is altered. Arterial distention decreases while arterial stiffness increases leading to a slow vasodilation-contraction response in the pressure stimuli reactivity test (20).

Connective tissue disease and endothelial function

Auto-immune diseases are related to vascular alteration. A nail videocapillaroscopy showed some alterations in microvasculature, but until now, there is no relation between these immunological conditions as a predictor for cardiovascular disease. We have more data related to Doppler flow and vascular alterations.

Recent studies, pointed out that immunological conditions cause endothelial dysfunction. The physiologic hypothesis is that protein deposition in arteriolar layers by endothelial inflammation increases vascular resistance (21).

Systemic sclerosis is initiated by genetic predisposition, but it is exacerbated by the ischemic process; the presence of cytotoxic autoantibodies in the blood; infectious agents; and environmental factors. All these factors trigger free radicals that decrease vasodilation/vasoconstriction substances (22).

In systemic sclerosis and Raynaud Phenomenon, the vascular dysfunction is related to immunological and autonomic relationship. Reactivity challenge shows these autonomic interaction, peripheral arterial disease, and peripheral tissue perfusion. In a pilot study conducted by McKay et al., systemic sclerosis impaired endothelial function, but there was no alteration in Raynaud Phenomenon (23).

CONCLUSION

In conclusion, skin is one of the vascular windows to study endothelial function. There are several techniques to assess microvasculature. The clinical relevance is the possibility to assess in a low cost and noninvasive way the

systemic vasculature. The clinician must be advised that some skin conditions, such as aging and connective tissue disease interfere in the reactivity test outcome. It is desirable to have some knowledge to interpret the results.

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Conflict of interest and financial disclosure

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest.

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