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Different responses of the retinal and cutaneous microcirculation to transient dysmetabolic conditions

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Abstract

Objective: This study evaluated the responses of the retinal and cutaneous microcirculation to acute hyperlipidemia and hyperhomocysteinemia.

Methods: Twenty-five clinically healthy men (mean age 24 ± 2 years) were studied four times in a randomized order, with intervals of at least one week between the two dietary interventions always preceded by a day for baseline assessment. The two interventions consisted of either 0.1 g/kg L-methionine to induce hyperhomocysteinemia or of 500 ml whipping cream (30% fat) to induce hyperlipidemia. Microvascular vasodilator responses to flickering-light and to cutaneous acetylcholine iontophoresis were assessed by retinal vessel analysis and laser Doppler flowmetry respectively.

Results: The fat load produced significant increases in triglycerides and total cholesterol which was accompanied by a reduction of the retinal arterial flicker response. Methionine administration induced a threefold increase in homocysteine levels and a concomitant decrease in retinal venous flicker response. Acute hyperlipidemia and hyperhomocysteinemia had no effect on cutaneous microvascular vasodilator responses to acetylcholine. The inter- and intra-subject reproducibility was higher for retinal vessel analysis as compared to laser Doppler flowmetry.

Conclusion: The retinal microcirculation is more sensitive to metabolic changes than the cutaneous microcirculation and can be reliably assessed by retinal vessel analysis. Reproducibility of retinal vessel analysis may be enhanced by multi-vessel assessment.

Keywords: Skin microcirculation; Retinal vessels; Iontophoresis; Reproducibility

1. Introduction

The microcirculation has been recognized as initial site for endothelial damage and vascular remodeling subsequently driving the atherosclerotic process in conduit vessels [1]. The microcirculation therefore constitutes a preferential target to detect and monitor early vascular changes in patients with risk factors [2].

The microcirculation of vital end organs like the kidney, the brain and the heart cannot be easily assessed disqualifying them for risk assessment and monitoring in the general population. As viable alternative laser Doppler flowmetry has been frequently used in science to measure skin microvascular responses to acetylcholine iontophoresis under the assumption that it mirrors endothelial function in other vascular beds [3]. Regulation of the cutaneous microcirculation rather differs from that of vital end organs

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with respect to local, metabolic and neural mechanisms. In the face of life-sustaining functions of vital end organs any vascular damage would be detrimental to the organism so that their microcirculations have evolved a distinct vasomotor plasticity and compensatory capacity [4]. Considering these mechanistic and functional differences between peripheral and central microcirculation it may be questioned that cutaneous microvascular reactivity would be a proper indicator for the microcirculation in vital end organs.

In recent years retinal vessel analysis has been increasingly applied to assess the cerebral microcirculation by measuring retinal blood flow response to flicker-light stimulation [5–7]. As retinal and cerebral vessels have a common embryologic origin the eye is perceived as window into the cerebral circulation [8]. Hence, the retinal microcirculation may be a better indicator of the microcirculatory function of vital end organs than that of the skin. Although depressed vascular responses in both microcirculatory beds have been associated with risk factors and cardiovascular outcome [9–14] retinal vessel analysis and laser Doppler flowmetry have never been compared under the same conditions.

Therefore, the primary goal of this study was to explore whether the retinal and cutaneous microcirculation would react similarly to acute hyperlipidemia and hyperhomocysteinemia. A second objective was to compare retinal vessel analysis and laser Doppler flowmetry regarding their performance (i.e. reproducibility).

2. Subjects and methods

2.1. Study population

Twenty-five young lean men (24 ± 2 years) were investigated to study vascular responses to experimental hypertriglyceridemia and hyperhomocysteinemia. All participants were healthy and free of cardiovascular risk factors. Exclusion criteria were chronic and acute diseases, obesity, intolerance against nitrovasodilators or salbutamol, significant hypotension, migraine, increased ocular pressure (>21 mmHg), current smoking, postoperative conditions, and regular intake of medication and vitamin supplements. All participants received detailed verbal and written information about the study objectives and procedures, and gave written informed consent. The study was approved by the Ethics Committee of the Faculty of Medicine of the Technische Universität Dresden and the study procedure performed with the Declaration of Helsinki.

2.2. Experimental protocol

Each individual was studied four times in a randomized order, with intervals of at least one week between the two interventions always preceded by a day for baseline assessment. The liquid fatty meal consisted of 500 ml whipping cream diluted in 200 ml pineapple juice (100 kcal/200 ml). One hundred milliliters of the cream contained 30 g fat thereof 19.5 g saturated fatty acids. The liquid methionine load consisted of 0.1 g/kg body weight L-methionine powder dissolved in 500 ml apple juice (43 kcal/100 ml). The meals were drunk within 15 min between 6:30 and 7:00 a.m.

Vascular assessments were performed at the days of baseline assessment after a fasting period of 12 h, and at the days of intervention either 2 h after the fat or 4 h after the methionine load, respectively. No other source of energy was provided during the measurements, but water was allowed ad libitum. The participants did not engage in any physical activity during the test, and exercise had been avoided during 24 h preceding the examination.

2.3. Microvascular recordings

2.3.1. Retinal vessel analysis

Following mydriasis of the right pupil by 1% tropicamide eye drops the mean diameter of an arterial and venous segment was continuously measured using the Dynamic Vessel Analyzer (DVA; IMEDOS, Jena, Germany). The DVA consists of a modified retina camera (FF450plus, Carl Zeiss Meditec, Jena, Germany), a charge-coupled video camera for online imaging and computer units for system control, analysis and recording of the obtained data [15]. Video sequences of each retinal vessel examination are digitized, which provides the possibility of off-line reassessment of the data.

For examination of the diameter vessels are measured and recorded in relation to time and position along a vessel segment. Vessel segments of approximately 1 mm in length located between one and two disc diameters from the margin of the optic disc edge were examined in continuous light for 30 s followed by 3 cycles of 20 s flicker light provocation only interrupted by 50 s of steady fundus illumination. Flicker light was generated by an optoelectronic shutter which interrupted the measuring green light with a frequency of 12.5 Hz providing a sequence of one normal illuminated and one single dark frame at a video frequency of 25 Hz. The hyperemic response of retinal vessels to diffuse luminance flicker is most likely a consequence of the increased metabolic demand of stimulated neurons with nitric oxide as putative mediator [16]. An interval of 30 s before each flicker stimulation was considered as baseline to which the subsequent diameter response was normalized. The maximal dilation was the largest vessel diameter at the end of each flicker stimulation averaged across three flicker periods. The maximal constriction was the absolute minimum of the arterial diameter after flicker stimulation. Both parameters were expressed as percent change over baseline values. The peak-to-peak value was calculated as the difference between the maximal and minimal arterial diameters.