Microvascular Research 113 (2017) 50–55

Contents lists available at ScienceDirect

Microvascular Research

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

Temporal and spatiotemporal variability in comprehensive forearm skin microcirculation assessment during occlusion protocols

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ARTICLE INFO

Article history:
Received 6 December 2016
Revised 21 April 2017
Accepted 24 April 2017
Available online 26 April 2017

Keywords:
Laser Doppler flowmetry
Diffuse reflectance spectroscopy
Tissue oxygenation
Perfusion
Vascular occlusion

ABSTRACT

Forearm skin hyperemia during release after brachial occlusion has been proposed for evaluating peripheral arterial disease and endothelial dysfunction. We used a novel fiberoptic system integrating Laser Doppler Flowmetry and Diffuse Reflectance Spectroscopy for a comprehensive pointwise model based microcirculation characterization. The aim was to evaluate and compare the temporal and the spatiotemporal variabilities in forearm skin microcirculation parameters (speed resolved perfusion; low speed <1 mm/s, $Perf_{SR,<1}$; mid-speed 1–10 mm/s, high speed >10 mm/s, and total perfusion ($Perf_{SR,tot}$); the concentration and oxygenation of red blood cells, C_{RBC} and S_{O2}). Ten healthy subjects underwent arterial and venous forearm occlusions (AO, VO), repeated within one week. The repeatability was calculated as the coefficient of variation (CV) and the agreement as the intra-class correlation coefficient (ICC). The temporal CVs for conventional perfusion, $Perf_{conv}$, $Perf_{SR,tot}$, C_{RBC} and S_{O2} were 14%, 12%, 9% and 9%, respectively, while the ICC were >0.75 (excellent). The perfusion measures generally had a higher spatiotemporal than temporal variability, which was not the case for S_{O2} and C_{RBC}. The corresponding spatiotemporal CVs were 33%, 32%, 18% and 15%, respectively. During VO, C_{RBC} had a CV<35% and ICC>0.40 (fair-good), and after release this was the case for C_{RBC} (AO and VO), S_{O2} (VO) and $Perf_{SR,<1}$ (VO).

In conclusion, the skin microcirculation parameters showed excellent temporal repeatability, while the spatiotemporal repeatability especially for perfusion was poorer. The parameters with acceptable repeatability and fair-good agreement were: C_{RBC} during and after release of VO, the $Perf_{SR,<1}$ after release of VO, the S_{O2} and the C_{RBC} after release of AO. However, the value of these parameters in discriminating endothelial function remains to be studied.
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1. Introduction

The cutaneous microvascular function in terms of vascular reactivity can be noninvasively examined using various provocation protocols such as hyperemic responses to iontophoresis of acetylcholine and sodium nitroprusside, local heating and vascular occlusion (Roustit and Cracowski, 2013). The methods for evaluation of vascular reactivity are normally pointwise measurements of microvascular perfusion using laser Doppler flowmetry (LDF) (Roustit et al., 2014). This is challenging due to large biological variability, such as local spatial and temporal variations in blood flow, and technical variability in terms of uncertainty in optical properties of the tissue and measurement volume (Roustit and Cracowski, 2012). Thus, the perfusion is measured in arbitrary units, not allowing calibration in physiological perfusion units (Larsson et al., 2002). While the spatiotemporal variability can be high, the temporal variability when the probe is kept in place has been shown to have good reproducibility (Huang et al., 2012).

Development of the conventional laser Doppler technique towards assessment of speed resolved blood flow utilizes the laser Doppler power density spectra for analysis in different ways (Fredriksson et al., 2010b; Larsson and Strömberg, 2006; Liebert et al., 2006). These measures separate the effect in low speed vessels (preferentially capillaries) from those in high speed microvascular vessels. With speed resolved perfusion, a reduced high speed perfusion was observed for the first time in type 2 diabetes mellitus during heat provocation, presumably due to inability to dilate shunt vessels (Fredriksson et al., 2010a). By integrating LDF and diffuse reflectance spectroscopy (DRS), that utilize different absorption spectra of oxygenized and deoxygenized hemoglobin in an adaptive skin model, it is possible to determine red blood cell (RBC) oxygen saturation, tissue concentration of RBCs and speed resolved perfusion simultaneously (Stromberg et al., 2014) and also in absolute units (Fredriksson et al., 2013; Jonasson et al., 2015) as shown in

Abbreviations: AO, arterial occlusion; VO, venous occlusion; CV, coefficient of variation; ICC, intra-class correlation coefficient; RBC, red blood cell; PU, perfusion units; LDF, laser Doppler flowmetry; DRS, diffuse reflectance spectroscopy; $Perf_{SR,<1}$, speed resolved perfusion for RBC speeds <1 mm/s; $Perf_{SR,1-10}$, speed resolved perfusion for RBC speeds 1–10 mm/s; $Perf_{SR,>10}$, speed resolved perfusion for RBC speeds >10 mm/s; $Perf_{SR,tot}$, total speed resolved perfusion; $Perf_{conv}$, conventional perfusion; C_{RBC}, concentration of RBC; S_{O2}, oxygenation of RBC.

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http://dx.doi.org/10.1016/j.mvr.2017.04.005
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a healthy population (Jonasson et al., 2015). Simultaneously measured blood flow and blood oxygen saturation enables a more comprehensive understanding of microvascular pathophysiology. These two methods have been used in an integrated probe but with separate signal analysis schemes (Kuliga et al., 2014).

The aim of this study was to assess the temporal and the spatiotemporal variability in the model based microcirculation parameters blood flow distribution in different speed regions, RBC tissue concentration, and RBC oxygen saturation during occlusion protocols in healthy subjects.

2. Materials and methods

2.1. Subjects

Ten healthy Caucasian subjects (5 F/5 M) with mean age 26.1 (standard deviation SD = 5.1) years, mean height 1.77 (SD = 0.10) m, mean weight 67.1 (SD = 9.9) kg, mean BMI 21.3 (SD = 1.7) kg/m^2, mean systolic blood pressure 116.8 (SD = 9.4) mm Hg, were included in the study after they had given written informed consent. The subjects were asked not to drink anything that contained caffeine or tea on the day of the experiment. Reasons for exclusion were cardiovascular disease, diabetes, skin diseases, regular use of nicotine or medication (except oral contraceptives), pregnancy and a systolic blood pressure of >150 mm Hg or a diastolic of >90 mm Hg. Blood pressure was measured before and after the experiment. The study was conformed with the Declaration of Helsinki and was approved by the regional ethics review board at Linköping University, Sweden (Dnr 2010/120-32).

2.2. Diffuse reflectance spectroscopy and laser Doppler flowmetry

The microcirculation was measured using a PeriFlux 6000 EPOS system (Enhanced Perfusion and Oxygen Saturation; Perimed AB, Järfälla, Stockholm, Sweden), integrating diffuse reflectance spectroscopy (DRS) and laser Doppler Flowmetry (LDF) in a fiber-optic probe. The system consisted of a PF 6010 laser Doppler unit, a PF 6060 spectroscopy unit, a broadband white light source (Avalight-HAL-S, Avantes BV, The Netherlands) and a fiber-optic thermostatic heating probe. The PF 6010 unit contained a laser light source at 785 nm and a thermostatic heating controller. The PF 6060 unit had two spectrometers (AvaSpec-ULS2048L, Avantes BV) and an optical notch filter behind the slit in the spectrometers in order to suppress wavelengths 790 ± 20 nm to ensure minimal influence from the PF 6010 laser light source on the DRS spectra. The fiber-optic probe (Fig. 1), consisted of two central emitting fibers and three detecting fibers. The fiber for the LDF laser light source and the LDF detecting fiber at a distance of 0.8 mm had a core diameter of 125 μm. Two detecting fibers were placed at a distance of 0.4 and 1.2 mm from the fiber connected to the white light source and were connected to one spectrometer each. Those fibers had a core diameter of 200 μm and all fibers had a numerical aperture of 0.37 and were made of fused silica. During the measurements, the probe was fixated to the skin using rings of double-sided adhesive tape (PF 105-1, Perimed AB), not covering the fiber ends.

2.3. Protocol

The subjects rested semisupine in a room with a controlled temperature of 22 (0.5) °C. Lighting was kept low by closing blinds and turning off lights, but there was usually enough light for reading. A pressure cuff was attached around the right upper arm. The forearm was kept at heart level with the volar surface upward and supported by a pillow. The white light spectroscopy probe was placed on the volar forearm. Subjects were asked to keep still during the experiments. A 15 min acclimatization period was allowed before the measurements.

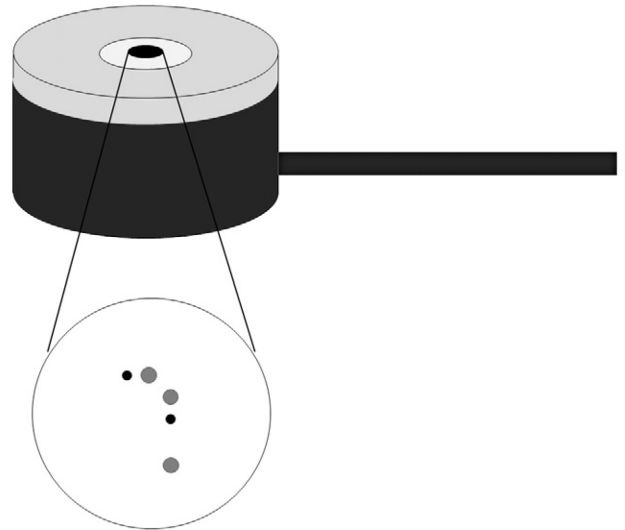

Fig. 1. Fiber optic probe with fiber configuration. The probe (D = 23 mm), included a thermostatic heater, a central black part with fibers (D = 3 mm), a central white ring where adhesive tape is not attached to and the outer light grey ring where the double adhesive tape is applied. The fibers are two LDF fibers (black; D = 125 μm) and three DRS fibers (grey; D = 200 μm). The upper two fibers are the LDF and DRS source fibers. DRS detector fibers are at distances 0.4 mm and 1.2 mm from the source, while the LDF detector fiber is at 0.8 mm from the source.

2.4. Experimental procedures

After the acclimatization period, blood pressure was measured in the other arm using an automatic sphygmomanometer (M6 Comfort, Omron Healthcare, Hoofddorp, The Netherlands). The optical probe was placed on the volar side of one forearm (randomly selected in balance order). The prope position and rotation was marked with ink including the orientation of the fiber bundle (rotation), assuring a repeatable position during the second recording occasion. The subject was instructed to fill in the markers until the second recording occasion that was done after seven days. After a 10 min baseline period, the first occlusion was done (randomly selected either arterial or venous occlusion in balance order). The blood pressure cuff was inflated to a pressure of either 250 mm Hg (arterial occlusion) or to a pressure of 30 mm Hg above the diastolic pressure (venous occlusion). This pressure was kept for 5 min. It was then released and a 30 min recovery and baseline of the next occlusion period occurred. The next occlusion (arterial if first occlusion was venous and vv) lasted 5 min. After release, data were recorded for a further 10 min recovery period. Total data recording time was 60 min. After the recovery period, a second blood pressure measurement was done.

2.5. Data preprocessing

A three layer skin model for DRS and LDF was used to calculate the tissue concentration of RBC (C_{RBC} [g RBC/100 g tissue] = [%]), RBC oxygen saturation (S_{O2} [%]) and model based total perfusion ($Perf_{SR, tot}$ [%RBC mm/s]), and perfusion divided in three speed regions (0–1 mm/s, 1–10 mm/s and above 10 mm/s; $Perf_{SR, <1}$ [%RBC mm/s], $Perf_{SR, 1–10}$ [%RBC mm/s]; $Perf_{SR, >10}$ [%RBC mm/s]). The model is described in Fredriksson et al. (Fredriksson et al., 2013), with a modified 200 μm thickness of the second layer. DRS and LDF spectra were calculated from the skin model and compared to measured spectra in an optimization routine to find the skin model with the best fit to measured spectra. When the best fit model was found, the microcirculatory parameters were calculated directly from the model. Conventional perfusion ($Perf_{conv}$ [PU], PU = perfusions units, calibrated to 250 PU in the Perimed motility standard), was calculated as a reference to data in many previous studies.

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