POSTOCCLUSIVE REACTIVE HYPEREMIA IN HEALTHY VOLUNTEERS AND PATIENTS WITH PERIPHERAL VASCULAR DISEASE MEASURED BY THREE NONINVASIVE METHODS

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Abstract: Postocclusive reactive hyperemia (PORH) was evaluated in three healthy volunteers and in three patients with different etiologies and suffering from peripheral arterial occlusive disease (PAOD). Three noninvasive methods were used: transcutaneous oximetry ($TcPO_2$), near-infrared spectroscopy (NIRS), and laser Doppler flowmetry (LDF). Changes in perfusion and oxygenation of tissue were measured on foot before, during, and after arterial occlusion on thigh. Numerical parameters were derived from measured signals for quantification of the PORH response. Results of all three methods provided distinction between healthy volunteers and patients. The experimental optical techniques of NIRS and LDF demonstrated more clearly than the well-established $TcPO_2$ method the difference between healthy volunteers and patients. The dynamics of the PORH response proved to be a better indicator of peripheral vascular disorder than the amplitude of responses.

Key words: Human subjects; Laser Doppler flowmetry; Near-infrared spectroscopy; Noninvasive measurement methods; Oxygenation of tissue; Peripheral arterial occlusive disease.

Abbreviations: HbO_2: concentration of oxygenated hemoglobin; LDF: laser Doppler flowmetry; NIRS: near-infrared spectroscopy; PAOD: peripheral arterial occlusive disease; PORH: postocclusive reactive hyperemia; $TcPO_2$: transcutaneous oximetry

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1. INTRODUCTION

Different invasive and noninvasive methods based on different physical principles have been developed for assessment of tissue oxygenation and blood perfusion. In recent years much effort has been put in development of optical techniques, which enable noninvasive monitoring of tissue oxygenation and perfusion [1,2].

Near-infrared spectroscopy (NIRS) is a relatively new optical technique for noninvasive monitoring of tissue oxygenation and hemodynamics. The technique is based on relative transparency of human tissue for the near-infrared light (wavelengths roughly between 700 and 1000 nm) and on the oxygenation- or oxidation-dependent absorption of light by certain compounds (chromophores) involved in transport and consumption of oxygen in tissue, such as hemoglobin, myoglobin and cytochrome-c-oxidase. In its most fundamental implementation NIRS can be used to quantify the changes in concentration of these chromophores. This is accomplished by applying the modified Beer-Lambert law to the measured changes in absorption of near-infrared light at different wavelengths [1,3,4].

Laser Doppler flowmetry technique (LDF) is a noninvasive optical method for monitoring of skin blood flow [2,5,6]. It is based on the principle of changes of the frequency of light (the Doppler shift) when scattered by moving structures in cutaneous and subcutaneous layers of tissue. Since the predominant moving particles at this level are erythrocytes in capillaries and small vessels the detected frequency shift is a carrier of information about the skin blood flow. The recorded signal is related to perfusion, which is defined as the product of the concentration of blood cells and their speed averaged over the measured volume. The method yields relative perfusion data in arbitrary units. As is the case with the basic implementation of the NIRS method, the LDF method requires a provocation to induce changes in perfusion (or blood oxygenation in case of NIRS), which can be measured and then used for assessment of tissue oxygenation and perfusion status.

In contrast to experimental methods of NIRS and LDF the transcutaneous oximetry ($TcPO_2$) has already been established in clinical environment as a tool for assessment of tissue oxygenation [1]. It measures the diffusion of dissolved oxygen from the extracellular space through heated skin to a sensor, which is attached to the surface of the skin. In principle it is a polarographic method. The electric current generated by the diffusion of oxygen to the negatively polarized sensor is in theory proportional to the partial pressure of oxygen in the local area under the sensor. Absolute values of pO_2 can thus be measured. But many conditions have to be met for the measurements to be truly representative of tissue oxygenation.

In the presented preliminary study we measured changes in tissue oxygenation and perfusion in foot of three healthy volunteers and three patients with peripheral arterial occlusive disease (PAOD). The arterial occlusion on thigh and the subsequent postocclusive reactive hyperemia (PORH) were used as a provocation. PORH is a reproducible transient increase in blood flow after the release of arterial occlusion [6]. It is also one of the well-known tests in clinical practice for evaluation of the functional aspects of arterial blood flow in extremities.

NIRS and LDF methods were used in the study simultaneously with $TcPO_2$ method, which is a standard method for evaluation of tissue oxygenation. The aims of the study were: a) to examine the applicability of near-infrared spectroscopy and laser Doppler flowmetry for quantification of PORH, (b) to determine parameters which could be used to evaluate the level of PAOD or other vascular disorders in lower extremities and (c) to compare the three methods from the point of applicability for detecting differences between healthy and diseased subjects.

2. MATERIALS AND METHODS

2.1 Subjects

Three healthy volunteers and three patients suffering from PAOD in lower extremity were included in this preliminary study. Both groups were age-matched. The basic patient data is presented in Table 1. The study was approved by the ethical committee of the host institution (Institute of the Republic of Slovenia for Rehabilitation).

2.2 Near-infrared spectroscopy

The $NIRO_2X$-2 instrument (Keele University, U.K.) was used. The device measures light attenuation changes at the nominal wavelengths 775, 800, 845, and 904 nm which enables measurement of concentration changes of oxygenated and deoxygenated hemoglobin by application of the modified Beer-Lambert law. The emitting and the receiving optode were attached to the top and to the bottom of foot respectively (Figure 1) using a custom-made silicone strap. The geometrical interoptode distance was within the 3.5--4.0 cm range as measured by a caliper gauge individually on all subjects after the measurement.

Table 1. Basic subject data. Description of healthy volunteers (H1--H3) and patients with PAOD (P1--P3)

subject	age (years)	blood pressure* (mmHg)			PAOD†	comments‡			
		arm	thigh	ankle		Smok.	Diab.	Alco.	Hyp.
H1	59	120/80	140	130	-	no	no	no	no
H2	75	120/70	130	110	-	no	no	no	no
H3	65	135/70	140	125	-	no	no	no	no
P1§	74	130/80	150	95	IIa	no	yes	no	yes
P2§	62	135/75	200	50	IIb	yes	no	yes	yes
P3§	68	135/70	185	95	IIa	yes	no	yes	no

* The pressures given are systolic/diastolic for arm and systolic for thigh and ankle.
† Clinical stage of peripheral arterial occlusive disease according to the Fontaine classification (IIa = claudication distance > 200 m; IIb = claudication distance < 200 m).
‡ Smok = smoker; Diab = diabetic; Alco = alcoholic; Hyp = hypertension.
§ All patients had one leg amputated (below knee in P1 and above knee in P2 and P3) as a result of PAOD and the measurements were performed on the foot of the remaining leg.

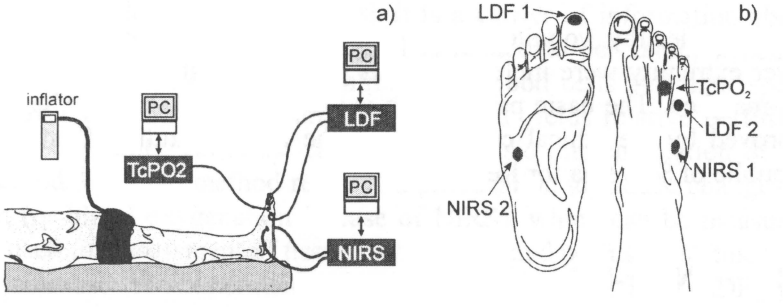

Figure 1. Experimental setup (a) and placement of probes on foot for NIRS, LDF, and $TcPO_2$ instruments (b). LDF 1 and LDF 2 belong to two channels of the laser Doppler instrument and NIRS 1 and NIRS 2 correspond to placement of the emitting and the receiving optode, respectively, for the one-channel NIRS instrument.

2.3 Laser Doppler flowmetry

The two-channel instrument MBF3/D (Moor Instruments, U.K.) was used. The standard probe (distance between fibers 0.5 mm, fiber diameter 0.2 mm) was attached to the lower surface of the big toe and the other probe

was placed on the top of the foot as shown in Figure 1. Wavelength of the light used in this instrument is 810 nm.

2.4 Transcutaneous oximetry

The TCM3 instrument (Radiometer, Denmark) was used. The probe was attached to the upper surface of the foot between the third and the fourth digit (Figure 1). Skin under the sensor was heated to 43 degrees Celsius. Stabilization of the pO_2 readings took between 15 and 30 minutes.

2.5 Measurement protocol

Subjects were in supine position and were lying comfortably on a cushioned bed during the experiment. The room temperature was 23 degrees Celsius. A large contoured thigh cuff (Hokanson, U.S.A.) was placed on the leg above the knee. Probes of the three instruments were attached to the foot at locations shown in Figure 1. After this initial manipulation the subjects were left to rest for 20 to 30 minutes before the experiment. During this period stable baseline values for all three methods were established. Following this rest period the cuff was inflated to a pressure of 30 mmHg above the individual systolic pressure using the standard TD312 cuff inflator (Hokanson Inc., USA). Inflation of the cuff to the final pressure took approximately 45 seconds. After the maximum pressure had been reached the arterial occlusion thus obtained was maintained for five minutes and was then followed by a rapid release of the cuff. The measurement continued for about 10 minutes until the preocclusion conditions were restored as demonstrated by a return of all measured signals to vicinity of their initial preocclusion values.

3. RESULTS

Different parameters were calculated from NIRS, LDF, and $TcPO_2$ signals in order to evaluate changes in perfusion and oxygenation during PORH. Their definition is presented in Figure 2 and given as follows.

NIRS signal (change in oxygenated hemoglobin concentration HbO_2) and LDF signal (perfusion):

t_R (seconds): time of recovery; the time interval between release of the cuff and the moment when HbO_2 (or LDF) signal reaches the initial preocclusion level for the first time.

t_M (seconds): time to maximum; the time interval between release of the cuff and the moment of the maximum hyperemic response for HbO_2 and LDF signals.

MR (%): maximum hyperemic response; the amplitude difference for HbO_2 and LDF signals between the lowest level reached at the end of arterial occlusion and the maximum level reached during hyperemia after release of the cuff. This difference is expressed as a percentage of the total decrease of HbO_2 and LDF signals during arterial occlusion.

$TcPO_2$ signal (partial pressure of oxygen):

pO_2 (mmHg): the absolute value of pO_2 at rest immediately prior to inflation of the cuff.

t_H (seconds): half time; the time interval between release of the cuff and the moment when 50% of the rest pO_2 value is restored

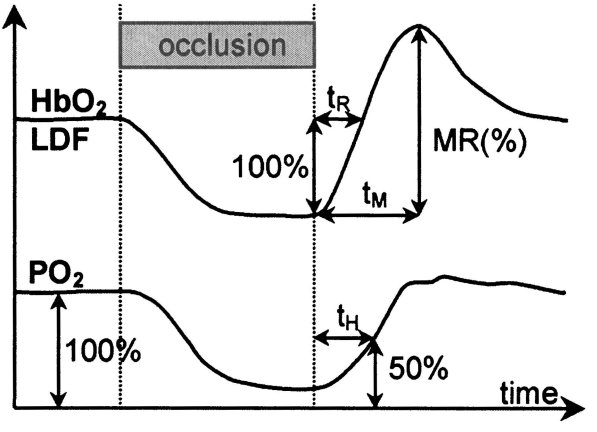

Figure 2. Parameters derived from the HbO_2, the LDF perfusion, and the pO_2 signals. The same type of parameters were calculated for the HbO_2 and the LDF signals.

Values of evaluated parameters for all subjects are given in Table 2 and presented in Figures 3 and 4. The results clearly show that the hyperemic response was significantly slower in patients with PAOD than in healthy subjects as demonstrated by larger t_R and t_M values for both HbO_2 and LDF with the LDF method. Hyperemia after release of the cuff could not be observed by the $TcPO_2$ method since there was no significant increase of the pO_2 value above the initial pre-occlusion level in either healthy subjects or patients. The rest pO_2 value however was higher and the recovery after occlusion demonstrated by parameter t_H was faster in healthy subjects than in patients (Figure 4a,b).

Table 2. The results -- values of evaluated parameters as defined in Figure 2 for healthy volunteers (H1--H3) and patients with PAOD (P1--P3)

subject	NIRS (HbO_2)			LDF (perfusion)			$TcPO_2$ (pO_2)	
	t_R (s)	t_M (s)	MR (%)	t_R (s)	t_M (s)	MR (%)	rest pO_2 (mmHg)	t_H (s)
H1	6	23	420	1	11	530	52	90
H2	11	45	127	1	25	210	48	105
H3	11	56	200	2	33	280	37	95
P1	105	150	83	111	111	97	37	150
P2	92	216	177	144	174	123	32	170
P3	36	78	88	48	110	150	34	105

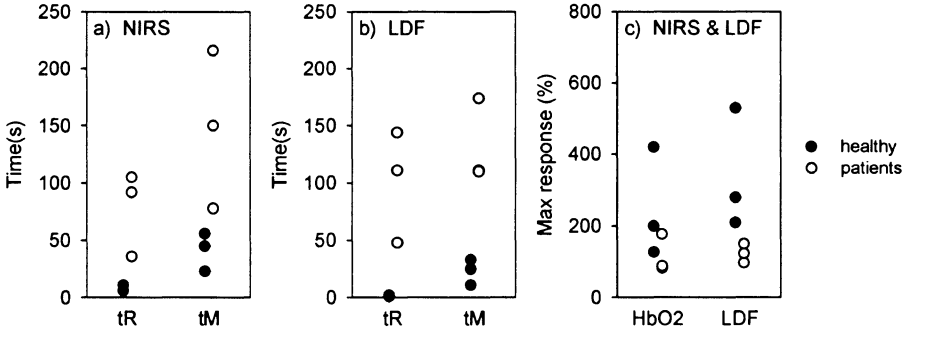

Figure 3. Values of evaluated parameters for NIRS and LDF measurements for healthy volunteers (solid circles) and patients (open circles): a) time of recovery t_R and time to maximum response t_M for the HbO_2 signal; b) time of recovery t_R and time to maximum response t_M for the LDF perfusion signal; c) the amplitude of the maximum response (MR) for the HbO_2 and LDF perfusion signals. See Figure 2 for definitions of the parameters.

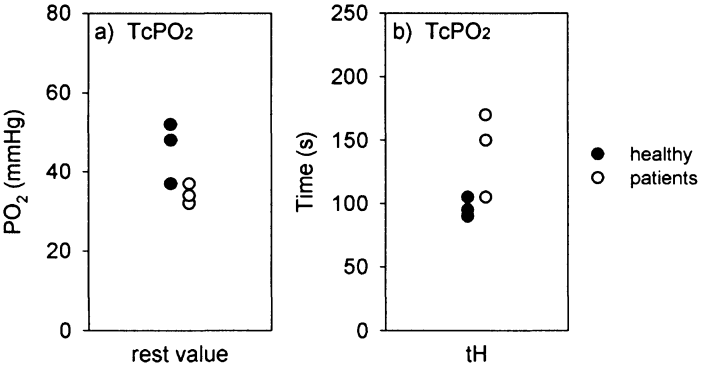

Figure 4. Values of evaluated parameters for $TcPO_2$ measurements for healthy volunteers (solid circles) and patients (open circles): a) absolute pO_2 values at rest before the occlusion; b) half time t_H. See Figure 2 for definitions of the parameters.

4. DISCUSSION AND CONCLUSIONS

The difference in hyperemic response between healthy volunteers and patients with PAOD was demonstrated with all applied measurement methods. However, NIRS and LDF methods provided a better distinction between the two groups of subjects. The dynamics of response expressed by parameters t_R, t_M, and t_H are by far better indicators of these differences than the amplitude of hyperemic response measured by NIRS and LDF (parameter MR) or the rest pO_2 value measured by $TcPO_2$. This is clearly observable in Table 2 and in Figures 3 and 4. It is important to note that patient P2 (see Tables 1 and 2) who was diagnosed with the severest PAOD (clinical stage IIb according to the Fontaine classification) also turned out to have the lowest pO_2 value at rest and the slowest response after occlusion as demonstrated by values of parameters t_R (LDF), t_M (NIRS and LDF) and t_H ($TcPO_2$). The amplitude of response MR did not provide this distinction of patient P2.

The three different methods used in the study measure different variables, which reflect oxygenation of tissue under observation. These variables are related to each other even though the anatomical sites at which measurements are made as well as the sampling volumes of tissue are different for each method. This preliminary study included only a small number of subjects but in general it appears that both experimental optical methods could be suitable for evaluation of the level of peripheral arterial occlusive disease and that they could supplement the more established $TcPO_2$ method. This is also supported by another study in which we have

shown that the repeatability of measurements is better with NIRS than with $TcPO_2$ method (unpublished observations). In any case the provocation protocol and signal analysis will have to be improved and more patients with various diagnosed stages of PAOD will have to be included in the study in order to support our preliminary findings.

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