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Selected applications of near infrared optical methods in medical diagnosis

R. MANIEWSKI*, A. LIEBERT, M. KACPRZAK, and A. ZBIEĆ

Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences,
4 Trojdena Str., 02-109 Warsaw, Poland

Optical methods from the near infrared range, in particular the laser-Doppler flowmetry and the near infrared spectroscopy offer a new non-invasive, real-time technique for monitoring of the blood perfusion and oxygenation in a living tissue. In spite of some instrumental problems, e.g., relative calibration and unknown sampling measurement depth, these methods have been already used in clinical studies. In this paper, the principle of the methods and instrumentation have been described. The advantages and limitations of these techniques are also discussed and new trends in technical development of the laser-Doppler flowmetry and the near infrared spectroscopy, especially contactless perfusion scanning and photons time of flight measurement, have been shown. Finally, selected clinical applications of all presented methods have been described.

Keywords: laser-Doppler flowmetry, near infrared spectroscopy, blood perfusion, tissue oxygenation, clinical applications.

1. Introduction

Optical methods offer a new non-invasive, real-time technique for measurement of some physiological variables important in medical diagnostics. When light travels through the tissue, reflection, absorption and scattering occur. The intensity of these effects depends on the optical properties of the tissue and the wavelength of the light applied. In particular, in the so-called "therapeutic window" of the wavelength range from 600–1200 nm, the penetration of light is deep because the scattering of light in the living tissue is much more pronounced than the absorption [1–3]. Thus, in recent years, the research has been focused on the development of non-invasive optical methods based on the near infrared light application, in particular the laser-Doppler (LD) flowmetry and the near infrared spectroscopy (NIRS). The both techniques have rapidly developed from the scientific experiment to the monitoring technique that is becoming frequently applied in clinical research [3–9]. They allow for a non-invasive, real-time and continuous monitoring of the tissue microperfusion and oxygenation. The laser-Doppler method is applied mainly for measurement of the skin microperfusion in the extremities, especially fingers [2–5], while the near infrared spectroscopy is usually used for monitoring of the cerebral oxygenation [7–10], but other applications, e.g., in optical mammography, are also in progress [11]. In this paper, the authors present their own clinical studies curried out at the medical centres collaborating with the Institute of Biocybernetics and Biomedical Engineering (IBBE) in Warsaw.

Several types of commercial laser-Doppler instruments and near infrared spectroscopes are presently available. However, there is still a number of unsolved technical problems, e.g., absolute calibration, sampling measurement depth, instruments standardisation, limiting the routine use of these methods in clinical practice. The authors studied calibration and standardisation methods of LD instruments [12,13] as well as influence of the LD probe geometry on the results obtained with this technique [14,15]. In particular, it was shown that the standard LD technique may be improved significantly by the use of the multidistance measurement of light intensity fluctuations caused by the Doppler effect [13,16]. Such a measurement allows for estimation of the sampling volume and may lead to the absolute calibration of LD instruments. The technical progress concerns also development of the contactless laser-Doppler blood perfusion imaging.

Classical near infrared spectroscopy based on the intensity changes is limited to applications were the short-time oxygenation changes are clinically relevant information. More complete information about the tissue under investigation provides the time-resolved near infrared spectroscopy (TRNIRS). This modern optical technique is based on the analysis of temporal broadening of short (picosecond) laser light pulses during their travel between the point of emission and detection [10,17,18]. The technique remains expensive and its use is connected with some technical problems but has already shown many advantages. In par-

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[*] e-mail: Roman.Maniewski@ibib.waw.pl

ticular, the TRNIRS can be used to measure mean pathlength of the photons which allows for quantitative determination of oxygenation of the tissue. This technique may be also used for the depth-resolved analysis of changes of the absorption coefficient in the tissue which, in the case of the multiwavelength measurement, leads to evaluation of the changes of concentrations of oxy- and deoxyhemoglobin at different depths [18]. This capability is especially important for measurements on the head of adult subject because of significant influence of oxygenation of the extracerebral tissues (skin, skull) on the measured signals.

2. Methods and instrumentation

The laser-Doppler method is used for point measurements and imaging of the tissue perfusion in microcirculation. The method is based on the differences in scattering of the laser light by moving and non-moving structures within the tissue. The laser light back-scattered from moving particles, such as blood cells (mainly red blood cells), is shifted in frequency according to the Doppler principle, while the radiation back-scattered from static (non-moving) structural components of the tissue remains at the initial frequency. This Doppler shift of the laser light frequency is the carrier of the information about the velocity and concentration of the red blood cells [19,20]. Finally, application of the appropriate signal processing [21,22] provides the output signal directly proportional to the perfusion as the product of speed and concentration of the red blood cells averaged in the probed tissue volume. The block diagram showing the idea of LD instrument is presented in Fig. 1.

In practical measurements, the LD perfusion index is given only in relative values. Thus, accurate and reproducible results can be obtained using controlled stimulation tests [4,5]. In our clinical experiments, the large vessels occlusion and thermal test were applied [5].

The microvascular perfusion was measured with the multichannel laser-Doppler instrument Oxford Array (Oxford Optronix, Ltd.) operating at the 780-nm wavelength and the double channel MBF-3D blood flow monitor (Moor Instruments, Ltd.) working at the 810-nm wavelength. In both instruments, right angle LD probes were used with the emitter-detector fibre separation of 0.2 and 0.3 for Oxford Optronics and Moor Instruments, respectively. In some studies, also the modern technique of blood perfusion imaging was applied. In this solution, as shown in Fig. 2, the laser beam is directed on the tissue from some distance (20–100 cm), without the use of optic fibres and scans the tissue by application of the movable mirror [23,24]. A fraction of the backscatter light is detected by a sensitive photodetector. After the whole scanning has been completed, the colour image of the blood perfusion is processed and displayed. In clinical measurements, the laser-Doppler imager LDI (Moor Instruments, Ltd) [23] working at the 633-nm wavelength was used.

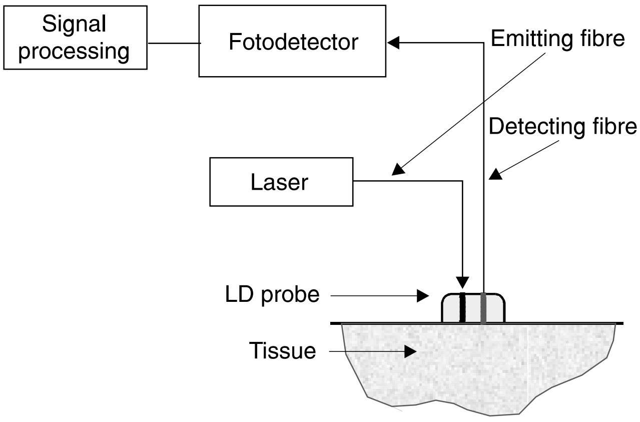

Fig. 1. Idea of laser-Doppler instrument for blood perfusion measurement in a single spot.

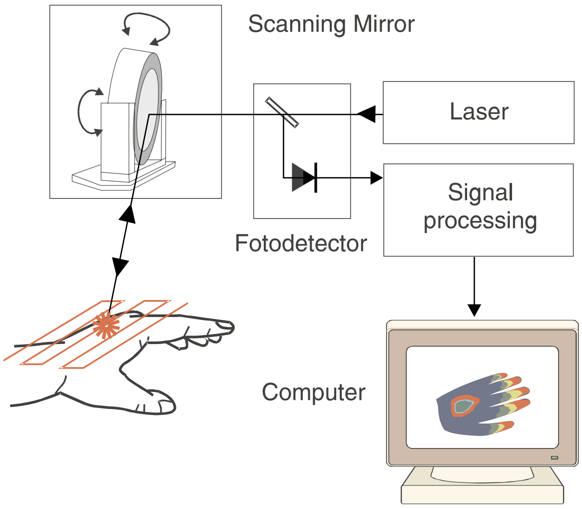

Fig. 2. Principle of laser-Doppler scanner for blood perfusion imaging.

The near infrared spectroscopy was used for the tissue oxygenation monitoring. The method is based on the specific chromophores absorption of the near infrared light for various wavelengths [2,6–9]. The main tissue chromophores are: haemoglobin, myoglobin (in muscles) and oxidised cytochrome. The changes of concentrations of these chromophores depend on the tissue oxygen supply.

In this kind of a continuous wave near infrared spectroscope, the laser light with a constant intensity at selected wavelengths is introduced into the tissue examined, and the intensity of the remitted (or transmitted) light detected by the receiver is measured (Fig. 3). Concentrations of the chromophores are calculated using the Lambert-Beer law and at least a number of light wavelengths equal to the number of the measured chromophores needs to be applied. The NIRO500 spectroscope (Hamamatsu Photonics, Japan) [7] used in our clinical studies operates at four wavelengths: 775, 825, 850, and 905 nm and allows for monitoring oxyhaemoglobin (HbO_2), deoxyhaemoglobin (Hb) and

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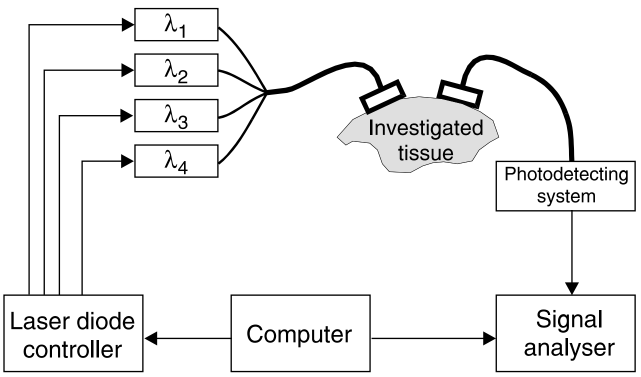

Fig. 3. Block diagram of near infrared spectroscope.

cytochrome oxidise (Cyt O_2) concentration. Besides, the total haemoglobin, as the sum of the oxy- and deoxy-components, corresponds to the tissue blood flow, assuming that hematocrite remains unchanged. The optodes for the light transmission are fixed usually on the forehead of the subject with the interoptode distance of about 4 cm.

Time-resolved near infrared spectroscopy (TRNIRS) is based on the analysis of temporal broadening of the ultra-short laser light pulses during their travel between the points of emission and detection. The TRNIRS system constructed in the IBBE consists, as shown in Fig. 4, of four diode semiconductor picosecond lasers and four detection channels which allow for recording of distributions of times of photons flight at four detection points on the surface of the examined tissue [25]. The laser pulses are delivered to the tissue with the use of optical fibres. The diffusely reflected photons are collected by high numerical aperture fibre bundles at the distance of 1.5–6 cm from the position of an emission fibre. Four photomultiplier tubes were used for the reemited light detection and independent time-correlated single photon counting electronics were applied for acquisition of photons times of flight distributions. By fitting theoretical distributions to the experimentally obtained data, the absorption coefficient and the reduced scattering coefficient of the tissue was determined. It allows finally for evaluating the tissue chromophore, e.g. oxyhaemoglobine, concentration.

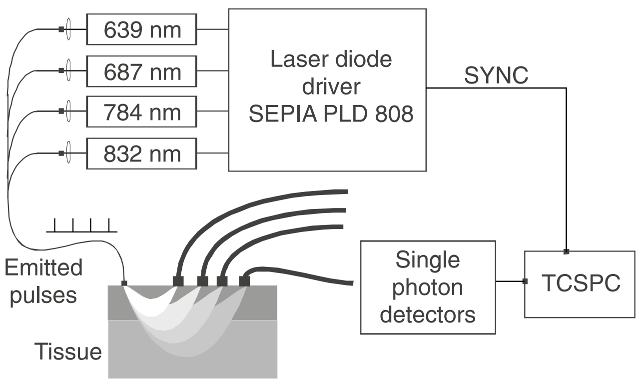

Fig. 4. Experimental set-up for photons time of flight measurement.

3. Results of clinical examination

A thorough study of the microvascular perfusion in insuline-dependent diabetic mellitus (IDDM) and normal controls was carried out in collaboration with the Clinic of Gastroenterology and Metabolic Diseases, the Medical University of Warsaw [5,26]. The study involved 65 subjects divided into four subgroups: male and female controls, and male and female IDDM patients without overt complications. The measurements were performed with a multichannel laser Doppler perfusion system, Oxford Array, using 6 surface probes located in the distal part of the lower limbs. The 3-minute occlusion test was performed using a cuff located on the limb over the knee.

The blood perfusion signals recorded during the lower limb occlusion in a normal subject and in an IDDM patient are shown in Fig. 5. The postocclusive hyperemic response

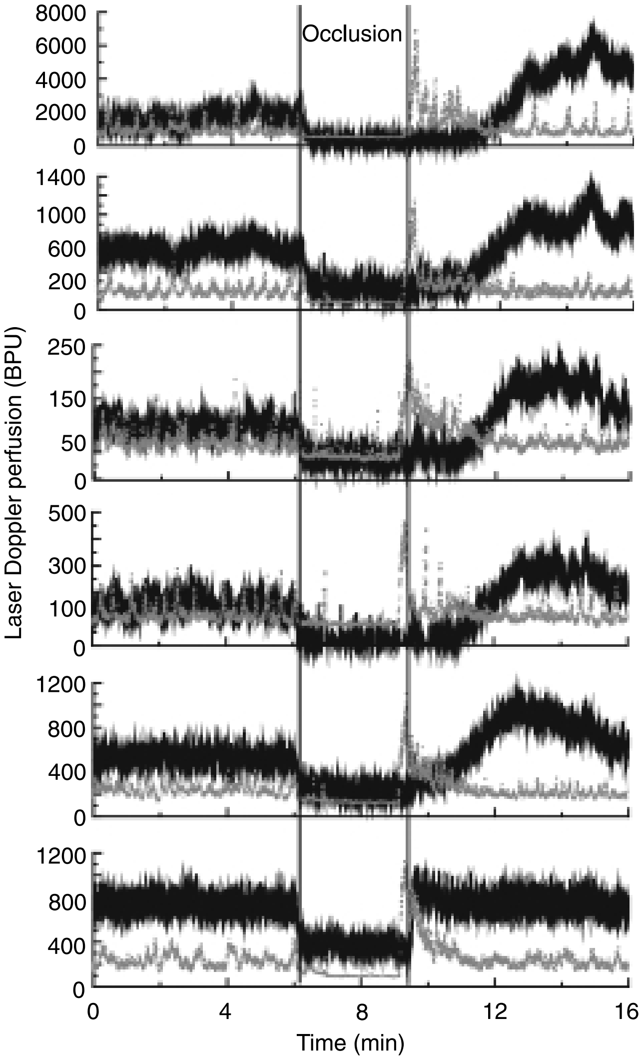

Fig. 5. Laser-Doppler perfusion signals recorded during the lower limb occlusion in normal subjects (grey line) and IDDM patients (black line). Location of the LD probes were as follows: 1 – tip of the big toe, 2 – nailfold of the big toe, 3 – the base of the second toe, 4 – the base of the little toe, 5 – dorsum of the foot, and 6 – tibial bone below the knee. BPU – blood perfusion unit.

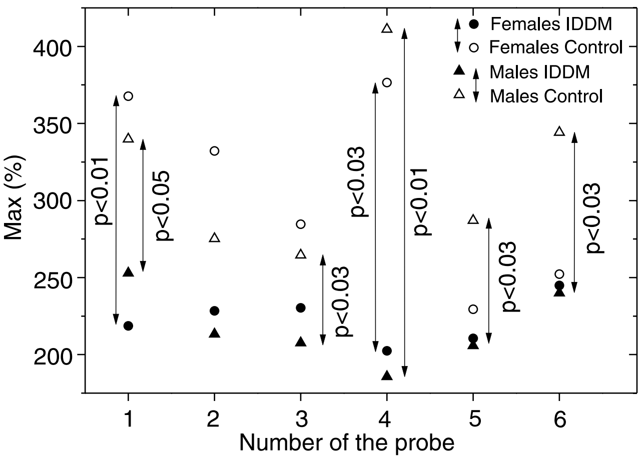

Fig. 6. Mean values of the maximum hyperaemic response (MAX) for the diabetic patients and control groups. In cases of statistically significant differences *p* values are marked (after Ref. 19).

for the IDDM patient was longer and had different (smoother) shape then for the normal subject. The amplitude and time relations of postocclusive hyperemia were evaluated in all the recorded LD signals. The mean values of the maximum hyperemic response calculated for the IDDM patients and the control group are presented, as an example, in Fig. 6 for all measurement locations [26]. The maximum hyperemic response for both sex subgroups was significantly lower in the diabetic patients as compared to the control group. The most valuable data were obtained from the laser-Doppler probes located on the big toe (probe 1) and the base of the little toe (probe 4). The females showed smaller changes in the foot perfusion than the males, probably due to the protection by estrogens.

The laser-Doppler method has been also successfully used to investigate vasoconstriction disorders in the Raynaud's phenomenon. In these studies, the thermal stimulation test has been applied. The test used in the past in our studies performed in collaboration with Rangueil University Hospital in Toulouse consisted of four temperature phases: the resting phase (22°C), the warm phase (40°C), the cool phase (5°C), and the warm phase (40°C). Microperfusion was measured on the pulp of the third finger of the left hand of 69 patients with the Raynaud's syndrome and 25 normal subjects [27]. Clinically oriented algorithm for spectral analysis applied to these data, allows distinguishing the Raynaud patients from the control group [28]. However, it was difficult to obtain a statistically significant differentiation of the patients with Raynaud's syndrome type I and type II.

Lately, the mentioned thermal test was supplemented with the additional intermediate temperature phase of 13°C. This allows obtaining the distinct and valuable laser-Doppler signals during the examinations, painless for the patients comparing to the measurements at the temperature 5°C. Exemplary results obtained during the thermal test are shown in Fig. 7. An interesting cold-induced vasolidation, called the hunting response or the Lewis wave [29], which is the subject of our recent investigation, can be seen.

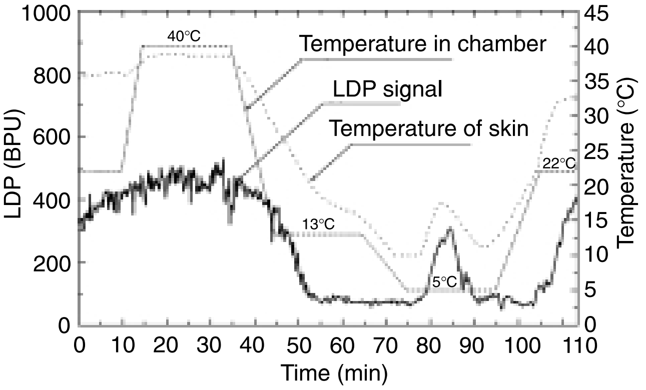

Fig. 7. Blood perfusion and skin temperature changes during thermal test as measured with laser-Doppler monitor on the third finger of the Raynaud's patient.

In some studies of the Raynaud's phenomenon, the laser-Doppler imager (Moor Instrument Ltd.) was also used. In this case, the effect of hand cooling at 10°C-water was observed [30]. In Fig. 8, changes of the blood perfusion images of the right hand of a patient with the Raynaud's syndrome are shown. This technique allows for contactless monitoring of the blood perfusion along the entire distal part of the hand almost simultaneously.

Monitoring of the microvascular perfusion may provide interesting information about the renal malfunction and hemodialysis process. The preliminary study conducted in collaboration with the Institute of Transplantology of the Medical University of Warsaw showed a good reproducibility of the laser-Doppler measurements during all the dialysis sessions [31]. Changes in the microvascular perfusion depend on the ultimate fluid status before and after the dialysis (hipervolemia, normovolemia and hipovolemia). During the hemodialysis of normovolemic patients, an increase in the red blood cells velocity was observed. It could be explained by more even or regular distribution of blood in the peripheral circulation. Increase in erythrrocide concentration could be also expected, but this was not the case, most probably because of the refilling effect (outflow of water from the tissue into the blood vessels).

In the past, we also used the laser-Doppler method for monitoring the microvascular dysfunction due to acute lower extremities ischemia, e.g. clamping of the abdominal aorta during the aortic aneurysm surgery [32], as well as for evaluation of effects of anaesthetic drugs on microcirculation in the regional anaesthesia during urinary tract surgery [33].

The near infrared spectroscopy was introduced in the Vascular Surgery Clinic Centre for Postgraduate Medical Studies in Warsaw for monitoring of the cerebral tissue oxygenation and brain ischaemia during carotid artery surgery [34,35]. The long-term recordings of HbO_2, Hb and Hb_{total} were carried out during the whole time of carotid endarterectomy in 220 patients with carotid stenosis. Particular attention was paid to the relation between the neurological state of the patients and the chromophores level,

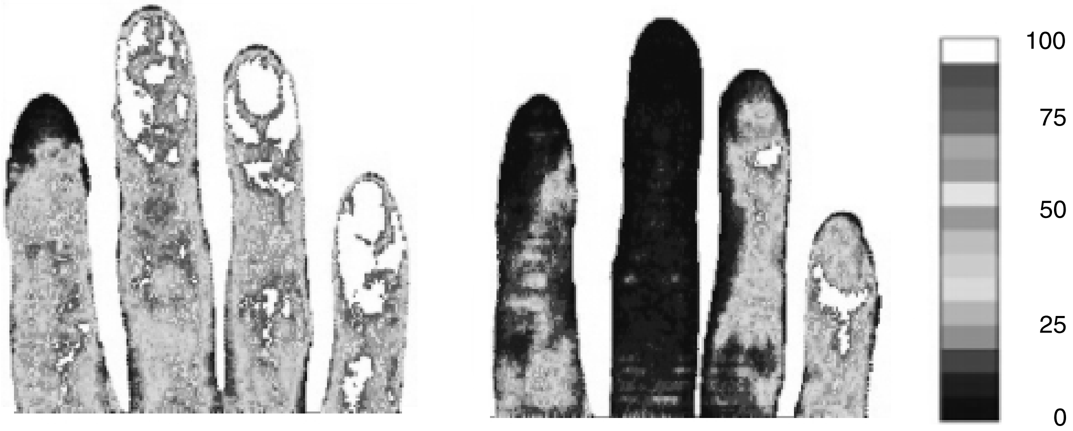

Fig. 8. Change of the blood perfusion image during cooling of the hand of Raynaud's syndrome patient: (a) reference image at 22°C and (b) image after cooling to 10°C.

during the test of cross-clamping the carotid artery. During the test clamping period (Fig. 9), a distinct decrease of HbO_2 and the reciprocal increase in Hb were usually observed. In about 70% patients, the rapid changes of chromophores were followed by their stabilisation on almost a constant level after about 1 minute [Fig. 9(a)]. This was indicative of sufficient collateral circulation and the carotid surgery was performed on these patients without intraluminal shunt insertion. In the remaining patients, the carotid cross-clamping had either no distinct effect [Fig. 9(c)] or resulted in an immediate, rapid decrease in HbO_2 and increase in Hb signals with no stabilisation during the test clamping [Fig. 9(b)]. The last group of patients showed insufficient collateral circulation and needed a shunt to prevent cerebral ischaemia. Thus, this study suggests that the near infrared spectroscopy may be very helpful in intraopretative cerebral monitoring, especially when the necessity of the shunt insertion is considered.

The near infrared spectroscopy and laser-Doppler flowmetry were used in the same Vascular Surgery Clinic for evaluation of the effectiveness of the sympathectomy [36]. The results obtained from 15 operations showed strong correlation of the clinical effects of sympatectomy with the changes in the tissue perfusion and oxygenation measured by the LD and NIRS methods in 75% cases studied. The optoelectronic methods proposed may allow for an

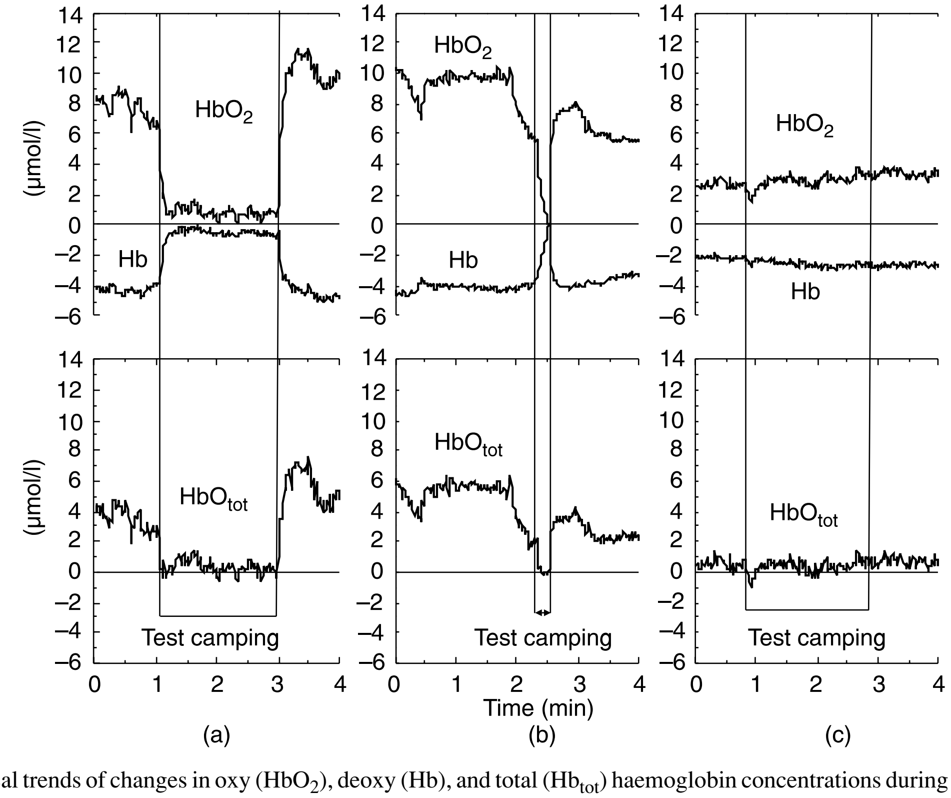

Fig. 9. Three typical trends of changes in oxy (HbO_2), deoxy (Hb), and total (Hb_{tot}) haemoglobin concentrations during the test clamping of the carotid artery.

early and non-invasive prediction of the long-time effects of the lumbar sympathectomy.

Measurement of oxy- and deoxygenated haemoglobin levels in brain by NIRS might be a useful technique for studies of the mechanism of vasovagal syncope. Preliminary results of the examination during the tilt test performed in collaboration with the National Institute of Cardiology have showed that the changes in the cerebral oxygenation measured by the NIRS technique are clearly visible (see Fig. 10) [37,38]. Gradual decrease in HbO_2 followed by a sudden drop was observed in all 42 patients with the provoked vasovagal syncope. A simultaneous increase in Hb was usually noted. The shape of the hemoglobine change curves depends in some extend on the syncope type: cardiodepressive, vasodepresive or mixed. It has been noticed that the characteristic changes in the brain oxygenation monitored by NIRS precede the changes in the blood pressure, hart rate, EEG and the early clinical symptoms of syncope [38].

Example of application of time-resolved NIRS in neurophysiological investigation is shown in Fig. 11. The distributions of times of photons flight is presented in this case for the wavelength of 803 nm. The optode was positioned above the motor cortex of the right hemishere of the brain in healthy subjects. The volunteer was sitting comfortably and was instructed to squeeze a toy positioned in the contalateral (left) hand. Twenty cycles of 20 s squeezing and 20 s rest was performed and the signals of the moments of measured distributions of times of flight of photons were averaged from these 20 cycles. The analysis of changes in absorption coefficient was performed with the use of the sensitivity factors calculated by Monte Carlo simulations [18]. The intra- and extracerebral compartments were differentiated from the measured signals. The measurement was performed at a wavelength close to isosbastic point which allows calculating the depth-resolved changes of the total hemoglobin concentration during the experiment. As it can be seen in Fig. 11, stimulation of the motor cortex results in inflow of blood to the intracerebral compartment of the tissue, which is a phenomenon known from the functional MRI studies. The observed changes of the hemoglobin concentration in the extracerebral tissues is rather small and may result from properties of the used reconstruction algorithm.

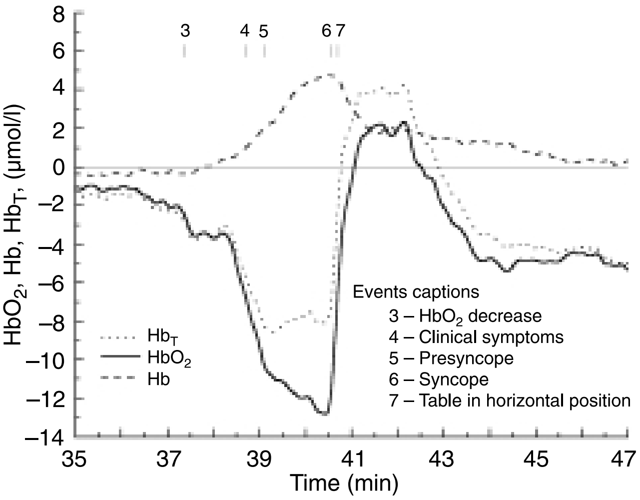

Fig. 10. Hemoglobine changes measured by NIRS during vasovagal syncope induced by the tilt table test.

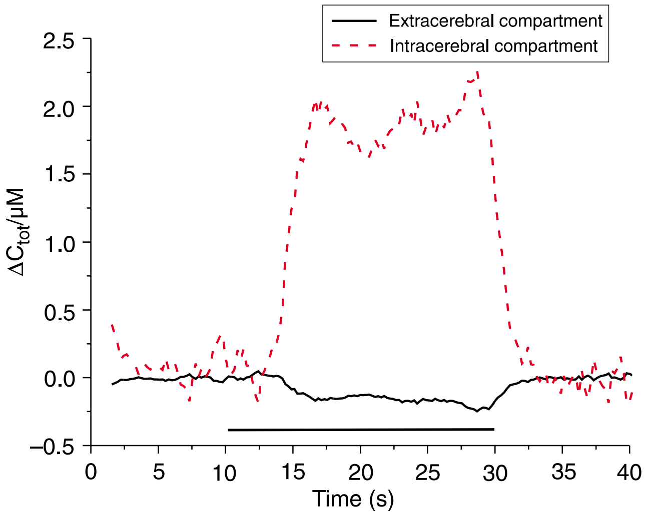

Fig. 11. Time course of changes in concentration of total hemoglobin in extra and intracerebral tissue compartments observed during the motor stimulation of the cortex. Time period of finger is tapping marked by a horizontal line.

4. Discussion and conclusions

The laser-Doppler flowmetry and near infrared spectroscopy offer a new non-invasive, real-time technique for monitoring of blood perfusion and oxygenation in a tissue. The both techniques have rapidly developed from the scientific experiment to the monitoring technique that is becoming frequently applied in the clinical research. The laser-Doppler method allows for clinically important microvascular examination in various diseases, e.g., diabetes mellitus, Raynaud's syndrome, renal malfunction, and lower extremity ischemia. However, there is still a number of unsolved technical problems concerning absolute calibration, measurement depth, instruments standardisation, limiting the routine use of these methods in clinical practice. The method may be improved significantly by further development of contactless scanner for blood perfusion imaging and multichannel probes for perfusion measurements with depth discrimination.

The continuous wave near infrared spectroscopy seems to be a sensitive and reproducible method for the cerebral oxygenation monitoring. In spite of some individual variances among the patients, this method is very helpful in the cerebral monitoring during the carotid surgery, especially when the necessity of the shunt insertion is considered as well as during the tilt test examination of vasovagal syncopes. The signals measured by continuous wave NIRS represent, however, a mixture of components originating from intra- and extracerebral tissue compartments. Additionally,

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the assumption on the photon pathlength in the tissue under investigation does not allow calculating properly absolute values of oxy- and deoxyhemoglobine concentration. Also oxygenation index defined as a relation between oxyhemoglobin and total hemoglobine concentration cannot be determined. The use of time-resolved NIRS technique allows for depth resolved analysis of changes of chromophores which solves one of the most critical problems and limitation of the clinical routine application of the continues wave near infrared spectroscopy.

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