Current Methods for the Assessment of Oxygen Status and Biotissue Microcirculation Condition: Diffuse Optical Spectroscopy (Review)

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The problem of studying the oxygen status and biotissue microcirculation is of special interest for many directions in medical science since one of the causes of hypoxia development as a typical pathophysiological process is a microcirculatory "failure" associated with the impairment of normal anatomy of the capillary wall, changes in the rheological blood properties, acceleration or slowdown of the blood flow. Current imaging techniques enable the researchers to study the processes of biosystem vital activity at various levels: from organs and tissues to the substance molecular composition. Methods of functional bioimaging implemented into clinical practice provide the opportunity of watching online the processes of substance movement in the body, monitoring blood flow parameters, assessing hypoxia level, characterizing metabolism in greater detail, and, at the same time, correcting timely pathological conditions.

The main advantages and disadvantages of bioimaging examination methods such as BOLD functional magnetic resonance tomography, positron emission tomography, optical imaging, laser Doppler flowmetry, and transcutaneous oximetry are considered in the present review. Special attention is paid to diffuse optical spectroscopy as a noninvasive method of lifetime study of substance content in biotissues.

The principle of diffuse optical spectroscopy is based on the ability of tissue chromophores (oxyhemoglobin, deoxyhemoglobin, fatty acids, collagen) to absorb diffusely scattered light of a definite wavelength. Their concentrations are calculated with the allowance for the absorption coefficients of chromophores. Diffuse optical spectroscopy is being introduced in clinical practice to diagnose the degree of tumor malignization, evaluate vascularization in reconstructive operations, diagnose hypoxic tissue conditions, monitor intraoperatively blood flow parameters, measure hypoxia levels in diabetes mellitus. It provides the possibility to define and make clear indications to skin plastic surgery and, conceivably, to develop new methods of skin plasty.

Key words: functional bioimaging; tissue oxygen status; microcirculation; hypoxia; diffuse optical spectroscopy; reconstructive operations; diabetes mellitus.

Introduction

Currently, the diagnosis of pathological conditions, prophylactic examinations, and research works are impossible without the application of imaging techniques. The traditional thinking paradigm relied on the methods allowing the assessment of anatomical changes in the human body (structural visualization). A fundamentally new opportunity appeared with technical advances: presently, methods providing the assessment of the tissue functional state have come into existence. This opportunity could not until recently be realized due to a multicomponent chemical composition and complex arrangement of tissue structure and, therefore, the danger to impair the finely adjusted biological system which may respond to the action done [1–4]. With

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the advent of the methods based on the computer processing of data on propagation and interaction of radiation of different nature with biological media, it became possible to form a new direction in the diagnosis of tissue and organ state: functional imaging, which enables the evaluation of the metabolism level, hemodynamics, changes of its biochemical composition.

Functional imaging teczhniques

Positron emission tomography (PET), functional magnetic resonance tomography (fMRT), and optical bioimaging techniques (optical coherence tomography, OCT, and diffuse optical spectrometry, DOS) are referred to the functional imaging techniques.

The diagnostic potential of PET is high and allows the study of quite different processes such as metabolism, substance transport, ligand-receptor interactions, gene expression, etc., however this method is technically complicated, bears a large radiation load, and its diagnostic power is largely determined by the range of available labeled chemical compounds — radiopharmaceuticals [5].

fMRT is a variant of magnetic resonance tomography. It is an actively developing method of neurovisualization which is used for measurements of hemodynamic reactions caused by the activity of the brain or spinal marrow. It is based on the association between the brain blood flow and neuron activity [5–8].

Optical bioimaging implies a set of methods using different effects of light interaction (scattering, absorption, fluorescence, optoacoustic and acousto-optic effects) with biological tissues [9–11]. These effects may be multiply enhanced by the introduction of additional contrast agents [12]. A distinctive feature of the biotissue optical imaging is a high molecular sensitivity which is realized owing to the differences in the absorption spectra of tissue chromophores. Besides, some chromophores fluoresce rather intensively increasing essentially the contrast and, consequently, molecular sensitivity.

It should be kept in mind that cellular and subcellular resolution in optical microscopy is possible only at small depths [12] (Figure 1).

A fundamental research task facing optical bioimaging is a real-time visualization of functional activity of the living biological systems at the tissue, cellular, and subcellular levels and its applied purpose is creation of new methods of diagnosis and control of physiological and pathological processes.

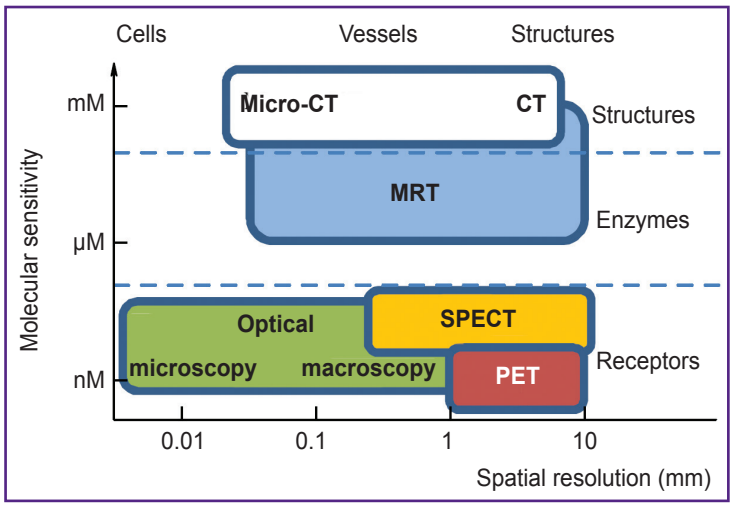

Figure 1. Comparison of molecular sensitivity of different imaging techniques:
CT — computer tomography; MRT — magnetic resonance tomography; SPECT — single-photon emission computed tomography; PET — positron emission tomography [12]

Methods of blood flow assessment

Among the typical pathological states, hypoxia is of special interest since the impairment of delivery and utilization of oxygen by the tissues determines the course of a great number of diseases such as tumorous processes, diabetes mellitus complications, trophic ulcers. Hypoxia is a state of oxygen deficit in the body, separate organ, or tissue either due to its insufficient supply from the outside or impairment of biological oxidation process at the cellular level [13].

A key value for the evaluation of the oxygen supply to the biological tissues is the information about the state of the vascular and microcirculatory bed.

Digital systolic pressure measurement, determination of the ankle-brachial pressure index, computer capillaroscopy, X-ray contrast angiography, magnetic resonance angiography, multispiral computer tomography are widely used for blood flow and microcirculation assessment in clinical settings which give an idea about the condition of the circulatory bed up to the digital artery level. Ultrasound examination of the vascular bed (Doppler ultrasound and segmental Doppler ultrasound, ultrasound angioscanning) also evaluates only macrovascular component of tissue blood supply.

Functional magnetic resonance tomography, PET and single-photon emission CT with contrast agents are not available for a wide application because of their high cost. PET and fMRT are capable of identifying the zones of necrotized and viable tissues, however their resolution does not permit capillary visualization, the equipment does not meet the requirement of portability, low cost, and could not be used for repeatable procedures [14, 15].

X-ray contrast angiography, the most informative noninvasive examination method in the current clinical practice requires the introduction of foreign substances into the circulatory bed. Modern angiography is not capable to visualize the human and animal capillary bed, and during large vessel

investigations it is not capable of long-term monitoring of their state [16–19]. Investigations of endothelium-dependent vasodilatation (venous occlusion plethysmography with the injections of acetylcholine and nitroglycerin), rheolymphovasography, impedansometry, thermovision examination give only indirect information about the adequacy of tissue blood supply.

Microscopy methods based on sidestream dark field imaging (SDF) used for lifetime microcirculation visualization are being developed and technologically improved [20–23]. However, they do not provide depth resolution, create only "full-face" images like in ordinary microscopy, and are limited by a low visualization depth (less than 1 mm).

A perspective direction of lifetime diagnosis is an application of exogenous fluorophores and photosensitizers. In particular, fluorescein and indocyanine green are used for intravital microcirculation assessment [24–28]. However, fluorescent visualization of the vascular bed is not a label-free method. The fluorescein emits in the visible range, therefore, it is impossible to explore the deep-sited pathological foci, and the indocyanine green interacts with the blood proteins and has a low fluorescence yield [29–32].

Methods of measuring tissue oxygen status

Polarography with the introduced microelectrodes for oxygen partial pressure measurements is an invasive technique which is quite unsuitable for patients with compromised microcirculation, e.g. in people with diabetes mellitus. Histomorphometric investigations being a golden standard in verification of necrotic changes and other disorders of tissue morphological structure do not imply in principle examination of the native tissue *in vivo*, besides repeated investigations are also not possible.

Transcutaneous oximetry provides data on oxygen tension in the tissues, but the question whether oxygen bound to hemoglobin is shunted or utilized remains unanswered [33–35]. Laser Doppler flowmetry does not provide visualization presenting the results of vessel examination in the digital form [36–39]. The following methods which can visualize the saturation of the tissues with oxygen are BOLD fMRT, PET with $^{15}O_2$ isotopes and hypoxia-selective markers (such as ^{18}F-fluorothymidine) [40], phosphorescence imaging with oxygen-sensitive stains [41].

Diffuse optical spectroscopy

Diffuse optical spectroscopy is one of the variants of optical bioimaging techniques. It is a promising method which meets the current criteria of reliability, continuity, and noninvasiveness [42–44], and allows tissue oxygenation measurements at the depth of 8 cm. The idea that lies behind this method consists in probing the tissues with optical radiation and registration of the diffusely scattered light to calculate absorption and transport scattering indices (Figure 2 (a)) [45–47].

The value of the transport index describes specific tissue cellular structure, while the value of the coefficient of absorption enables the evaluation of biological chromophore concentration (oxyhemoglobin, deoxyhemoglobin, water, fats, collagen, etc.) [48–51]. The total hemoglobin concentration reflects blood filling of the tissue, shows oxygen supply, deoxyhemoglobin reflects its consumption.

The main difficulty of DOS is in calculation of tissue optical properties by the parameters of diffusely scattered light. This calculation is based on the mathematical model binding the values of spectral intensity of the probing radiation inside the examined object with the indices of absorption and light transport scattering [52–54].

The simplest and commercially available way of using DOS consists in measuring spectral intensity of diffusely scattered light at various distances from the probe radiation source (Figure 2 (b)) [55]. But this approach demands constant device calibration and correct consideration of the external factors (background illumination, the gain of the receiving path,

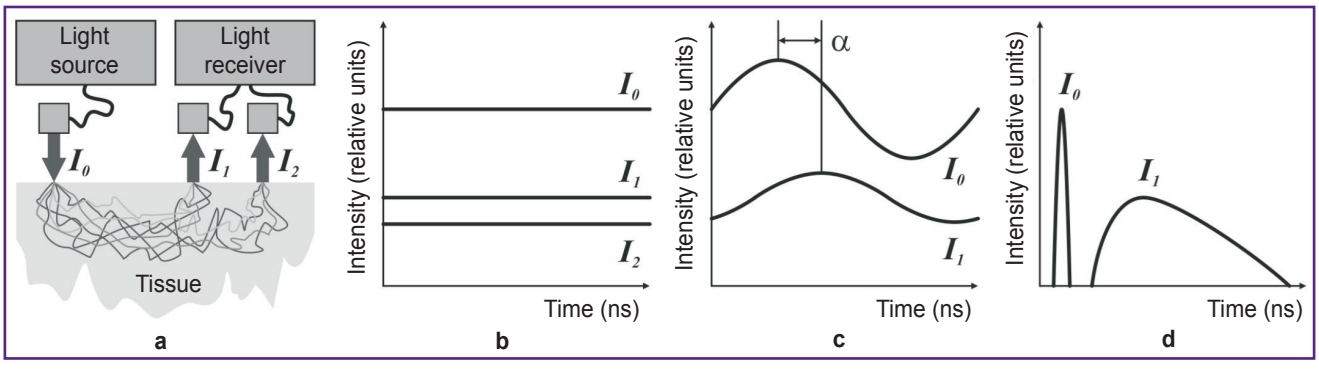

Figure 2. Diffuse optical spectroscopy:
the scheme of measurements in diffuse optical spectroscopy (a), and also the characteristic time dependencies of spectral intensity of probe radiation (I_0) and diffusely scattered light (I_1 and I_2) for continuous (b), amplitude modulated (c) and pulsed (d) light sources

the quality of the optical contact with the tissue, etc.). The application of amplitude-modulated (Figure 2 (c)) [56] or pulsed (Figure 2 (d)) [57] probe radiation makes it possible to restore indices of absorption and light transport scattering in the tissue according to the time characteristics of the registered radiation (the form of the diffusely scattered impulse or the phase shift of the measured signal) at the fixed distance between the source and light receiver, and simplifies the calibration requirements. However DOS systems with time resolution are more complicated and expensive since they need application of special sources and radiation receivers.

To calculate tissue optical properties, spatially structured illumination of the examined object can be employed and the distribution of the diffuse scattering over the area of interest may be registered [58, 59]. This approach provides contact-free diagnosis but limits the examination depth to 5–10 mm while for contact methods the diagnostic depth may reach 60–80 mm. It is important to note that physical parameters of diffusely scattered light may be more conveniently measured in the reflective geometry when the radiation source and receiver are situated from the same side of the biotissue [60], but investigations of large specimens or at a depth exceeding 40–50 mm require projection geometry of measurements when the light source and receiver are located on different sides of the object [61].

To calculate the component composition of the tissue by the light absorption index, the known table values of the coefficients of absorption of the main chromophores: oxyhemoglobin, deoxyhemoglobin, water, fats, collagen (Figure 3) [62] are used. And for the correct isolation of each chromophore, the spectral intensity of the diffusely scattered light should be measured at different

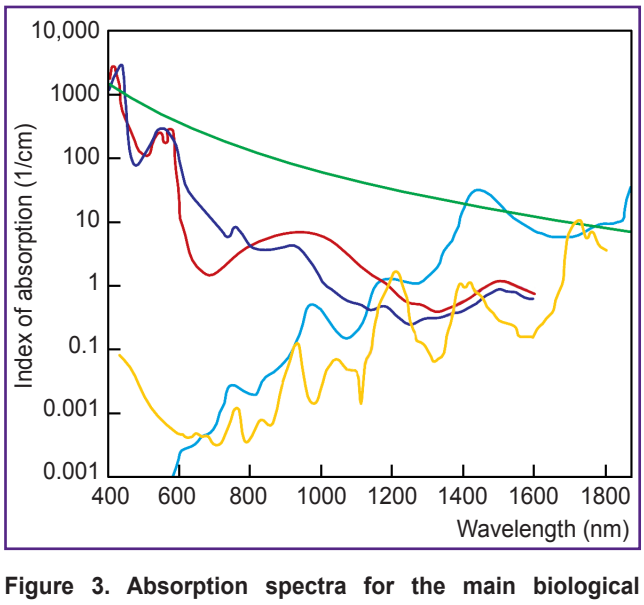

Figure 3. Absorption spectra for the main biological chromophores:
green — melanin; *red* — oxyhemoglobin; *dark blue* — deoxyhemoglobin; *blue* — water; *yellow* — lipids [12]

wavelengths of the probe radiation. Spectral resolution of the measurements may be obtained using a set of narrowband light sources at different wavelengths [63, 64] or one broadband radiation source and a spectrometer as a receiver of the diffusely scattered light [65]. The most effective approach is the combination of several methods. For example, a broadband source of the probe radiation may be used together with several narrowband amplitude-modulated or pulsed light sources of different wavelengths and register diffusely scattered radiation with several receivers [66].

Due to its specificity (a large distance between the source and light receiver), DOS techniques have low spatial resolution (1–10 mm), however this drawback may be overcome by using hybrid approaches combining optical molecular sensitivity and high spatial resolution of other imaging techniques: US [67], CT or MRT [68]. Presently, first commercial optoacoustic devices have already appeared providing visualization of 3D distribution of tissue chromophores (iThera Medical, Germany; TomoWave Laboratories, USA; VisualSonics, Canada, and others) with the disadvantage of being too sophisticated and expensive.

Areas of clinical applications of diffuse optical spectroscopy. The analysis of the literature data shows that DOS becomes a powerful tool in biomedical investigations of pathological states such as malignant neoplasms, circulatory bed pathology, and skin plastic reconstructions. The majority of publications describe its application for breast tumor detection and monitoring of their treatment, for brain activity studies, functional imaging of the skin and muscular tissue condition in various pathologies.

Vascularization assessment during of organ and tissue reconstruction. DOS can visualize arteries in angiosurgical and plastic operations [69, 70]. In the recent literature, a great number of reports describe successful results of DOS monitoring of superficially located skin fascial flaps used in breast reconstruction with tissue oxygenation assessment to the depth of 5–12 mm [71–74]. This method has been shown to detect abnormal blood supply to the flap and feeding pedicle prior to the first clinical manifestations [75]. In some works, it is underlined that application of DOS for tissue oximetry may give variable values therefore it is important to evaluate the dynamics of the indices rather than the absolute figures [76, 77]. In the work by Malykhina et al. [78] where this method was used to assess the viability of the skin flap in a free plastic surgery on microvascular anastomoses, the conclusion has been drawn that the oxygenation indices of the microsurgically transplanted flaps below 70% must be interpreted only in comparison with the indices in the control area and not in the compromised one which is topographically most similar to the recipient zone. Based on the conducted studies the authors believe that DOS enables the differentiation of arterial and venous character of perfusion impairments though the

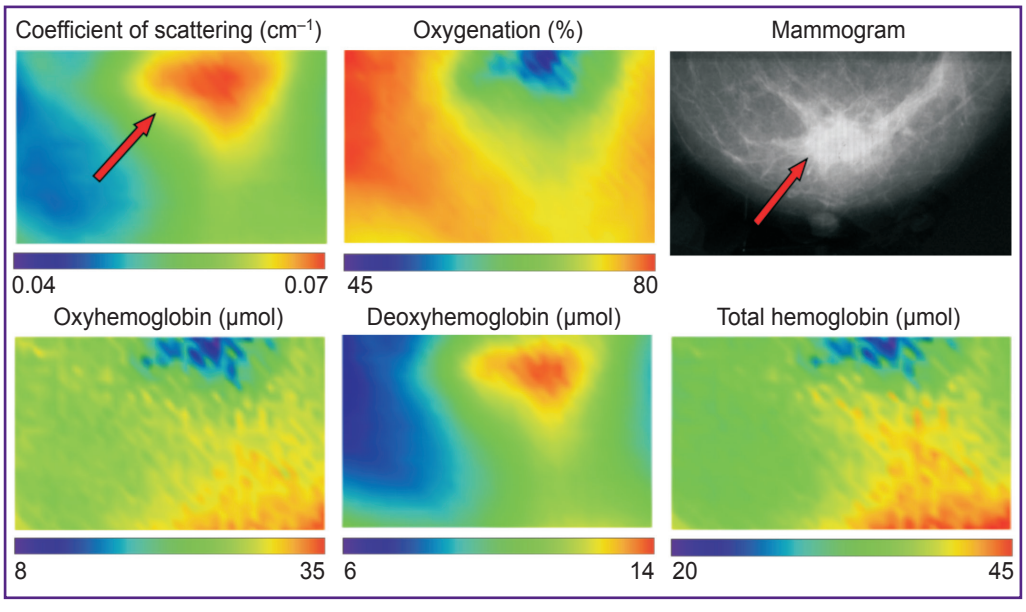

Figure 4. Results of mammography and DOS breast examination in a patient with the diagnosis of breast cancer
DOS image dimension — 50×40 mm; the arrow points to the tumor zone

capabilities of this method are limited by hematoma formation and excessive flap edema. Of special importance is the conclusion of the authors about the necessity of interpreting these measurements on the basis of the dynamics of their changes in comparison with the contralateral side and absolute values. Besides, image reconstruction of the diffuse optical spectroscopy is a complicated mathematical nonlinear reverse problem the solution of which needs exclusion of background noise, consideration of light scattering and various measurement errors [79–81].

Assessment of breast neoplasms. DOS has the most significant clinical value for screening, diagnosis, and treatment monitoring of breast neoplasms. This method gives valuable functional information about pathophysiological characteristics of the tumor (metabolic activity, angiogenesis, blood flow condition) [82]. Malignant neoplasms are more vascularized relative to the surrounding normal tissues which changes their optical properties [83]. Hypoxia is a characteristic feature of malignant tumors determining tumor response to the treatment and influencing the prognosis [84].

Maslennikova et al. [85] show in their study the possibility of using DOS for differentiation between the tumor tissue and surrounding normal tissues by the level of blood oxygenation and by the content of oxy- and deoxyhemoglobin. In the tumor zone, the concentration of oxy- and deoxyhemoglobin appeared to be higher than in the surrounding normal tissues while the level of blood oxygenation was lower relative to them. Besides, in the projection of the tumor center, the reduction of the oxyhemoglobin was observed while its level grew along the periphery. The authors have noted that the distribution of the examined compound concentrations significantly differed in each clinical case. In the other research [86] in which the value of DOS in the diagnosis of breast pathology was compared with MRT, the results were comparable.

Examples of images characterizing the distribution of scattering coefficients, content of oxy-, deoxy-, and total hemoglobin, and the level of blood oxygenation in the tumor and normal breast tissue obtained by DOS technique are presented in Figure 4.

The differential diagnosis between malignant and benign breast tumors (content of water, oxy- and deoxyhemoglobin) became one of the main directions of using DOS in oncology [87, 88]. In recent years, it was suggested to use variants of DOS to predict individual reaction of neoplasms to therapy and prognosticate treatment efficacy [89–91].

Tissue hypoxia diagnosis. DOS is an indirect method of assessing the tumor oxygen status. Findings of the investigations comparing the application of DOS and standard methods of oxygenation measurement (polarography, immunohistochemical assay with a hypoxia marker) showed that the DOS technique allows the correct determination of the oxygenation level in the biological tissues and revealing tissue mechanisms of the emerging changes [92–94].

The work [95] was devoted to the study of the possible interconnection between the data acquired with the help of US-controlled DOS and the concentration level of hypoxia-induced factor (HIF-1α) and CD34 in confirmed breast cancer. Immunohistochemical examination of HIF-1α and CD34 revealed differences in the total hemoglobin concentration and microvessel density

between the HIF-1α positive and negative groups. The conclusion was drawn that HIF-1α may promote tumor angiogenesis and, in that way, increase blood supply and hemoglobin concentration, and DOS can indirectly reflect the angiogenic activity of breast cancer.

In the work [96], the authors investigated the possibility of using DOS for tumor deoxyhemoglobin and oxyhemoglobin mapping in patients *in vivo*. Since these chromophores react differently at various wavelengths, four laser diodes with 740, 780, 808, and 830 nm wavelengths were used. To verify the accuracy of the oxygenation assessment, foci of different sizes located at various depths were chosen as the diagnostic targets. The absolute deviations between the indices of tissue saturation with hemoglobin obtained from the chromophore absorption maps and oxygen measurements performed by means of pO_2 electrode were below 8% over the measured range of oxygen saturation. The authors consider proven the possibility of using DOS for determination of tissue saturation with deoxyhemoglobin and oxyhemoglobin in breast cancer.

Intraoperative monitoring of blood flow parameters. Application of DOS during minimally invasive surgical interventions to prevent damage to the important anatomical structures is suggested in the work [97]. In the experiments on pigs, the authors have demonstrated the possibility to assess blood flow indices for intraoperative identification of the retroperitoneal space vessels during laparoscopic maneuvers in the abdominal cavity and retroperitoneal space.

Blood supply in diabetes. Of real interest is the investigation in which the authors studied the capabilities of DOS for the assessment of blood supply disorders in the lower extremities in diabetic patients [98]. Perfusion activity was compared in healthy volunteers, patients with atherosclerosis of lower extremity vessels, and with diabetic angiopathy. Significant differences connected with the concentration of oxy- and deoxyhemoglobin in the tissue was found in all three groups. In the research [99], it has also been proved that the total hemoglobin content decreases and oxygenation level increases in the limb tissues of the diabetic patients compared to the healthy tissues.

To monitor the processes of reparative regeneration of diabetic ulcers in the experiments on animals (rats), the methodology of DOS application in the near infrared range (680–830 nm) has been developed [100]. Differences in skin defect healing in the control (healthy animals) and the main diabetic group have been noted.

Interesting data are presented in the work by Zhao et al. [101]. The authors acquired *in vivo* images of human lower extremities and forearms during DOS in the infrared spectrum to assess their anatomical and functional indices. They managed to visualize some blood vessels during the investigation. Besides, based on the analysis of the concentration of oxyhemoglobin, deoxyhemoglobin, and total hemoglobin in the forearm, information was obtained about the changes in the volumetric blood flow, oxyhemoglobin concentration in the arteries, and, what is of great interest for us, the hypoxia condition in the appropriate muscles was diagnosed concurrently.

Conclusion

Diffuse optical spectroscopy favorably differs from other methods of vascular bed visualization in that it allows the diagnosis of hemodynamics state and also the assessment of the efficiency of oxygen utilization by the tissues. The capability of diffuse optical spectroscopy to evaluate the tissue hypoxic status, which is a crucially important pathogenical link of the pathological states such as tumor processes and diabetes mellitus, opens new opportunities for the application of this method. In oncology, DOS is a promising method for differential diagnosis of tumor processes. Making angioplastic operations in patients with obliterating diseases of lower extremity vessels, diffuse optical spectroscopy will enable precise definition of indications, the volume, and efficacy of operative intervention. DOS is also perspective in defining and specifying indications to skin plastic surgery and, conceivably, in developing new methods of skin plasty.

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Conflicts of interest. The authors have no conflicts of interest.

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