# The Physics of Biomedical Effect of Blood Oxyhemoglobin Photodissociation

M. M. Asimov[1], R. M. Asimov[2], A. N. Rubinov[1], A. I. Gisbrecht[3]

[1] Institute of Physics National Academy of Sciences of Belarus, 68 Nezavisimosti Ave, 220072 Minsk, Belarus

[2] Sensotronic Ltd., Belarus High Technologies Park, 11 Kulman Str, 220100 Minsk, Belarus

[3] Institute of Electronics Bulgarian Academy of Sciences, Tsaregradsko Blvd, 1784 Sofia, Bulgaria

[1] m.asimov@dragon.bas-net.by; [2]asimov@anitex.by; [3]aig@abv.bg

***Abstract*-The results in vivo investigation biophotonics of laser-induced photodissociation of oxyhemoglobin in cutaneous blood vessels and its role in biomedical processes are presented. New method for determination of an individual response to the effect of laser radiation is presented. It is shown that, in order to make the methods of phototherapy as well as laser therapy really efficient, one has to control the oxygen concentration in tissue to keep it at the necessary level. A novel method of optical "dosimetry" based on the use of changes in oxygen concentration in tissue as a feedback signal for optimization of the therapeutic effect of low intensity laser radiation has been developed.**

***Keywords-Hemoglobin; Oxyhemoglobin; Tissue Oxygenation; Hypoxia; Phototherapy; Photodissociation***

## I. INTRODUCTION

Biophotonics of "laser-tissue" interaction and the effect of laser radiation on oxyhemoglobin in cutaneous blood vessels and capillaries are considered to be interesting aspects of modern photomedicine and photobiology. Application of low intensity laser radiation in treatment of a variety of diseases has being extensively developed during the last five decades.

Biostimulation and therapeutic effect of laser radiation is a well-established fact, which is currently widely used in clinical practice. At the same time, the mechanism of therapeutic effect of laser radiation is not yet clearly understood and considered to be very complex and accompanied by anti-inflammatory, analgesic and anti-inflammatory effect on tissue [1-4]. The most exciting effect of laser therapy could be seen in wound healing where a process of fast epithelization clearly demonstrated its efficiency.

The mechanism of therapeutic effect of laser radiation still remains unclear, which makes it difficult to develop a correct method for controlling the efficiency of laser therapy – the correct "dose" of average energy of laser radiation delivered.

At present the efficiency of therapeutic effect is controlled by using an empirical unit based on average power density of the output laser radiation. Experimental study dedicated to the therapeutic effect of He-Ne and Argon laser radiation on the open skin wound healing [5] was carried out at power density of 45mW/cm$^2$. Maximal therapeutic effect due to the significant increase of collagen synthesis at the total energy density of 4J/cm$^2$ has been reached. Similar experimental study [6] with He-Ne laser radiation at power density of 4,0mW/cm$^2$ demonstrated the therapeutic dose (complete heeling of wound) at lower average energy ~1,22J/cm$^2$.

Big differences in experimental results between two healing cases of identical open wounds where therapeutic effect is reached at different output power of He-Ne laser radiation are remains not clear.

Nevertheless the power density of 4J/cm$^2$ is accepted as extreme level ("dose") for reaching maximal therapeutic effect. Accepted empirical criterion for controlling the efficiency of the therapeutic effect of low intensity laser radiation (optical "dosimetry") is not correct and reliable.

In this paper a new method of optical "dosimetry" based on the use of changes in oxygen concentration as a feedback signal for optimization of the therapeutic effect of laser radiation is presented. It is shown that photodissociation of oxyhemoglobin, the main biological function of the transportation of molecular oxygen, gives a unique possibility of additional oxygen supply and allows developing a laser-optical method of tissue hypoxia elimination for restoring normal cell metabolism.

## II. THE PHENOMENON OF LASER-INDUCED BLOOD OXYHEMOGLOBIN PHOTODISSOCIATION

Since 1998 a new technology of laser-induced photodissociation of oxyhemoglobin ($HbO_2$) in cutaneous blood vessels and its biomedical applications has been developed. The efficiency of the interaction of laser radiation in different wavelengths on $HbO_2$ in cutaneous blood vessels has been studied. Mathematical model for calculating optimal parameters of laser radiation to induce an effective photodissociation of hemoglobin (Hb) complexes in cutaneous blood vessels has been developed [7-10].

The temperature dependence of the quantum yield of photodissociation of $HbO_2$ observed earlier in vitro has been proved experimentally in vivo [10]. A unique possibility in selective and local increase of free molecular oxygen ($O_2$) concentration in tissue has been demonstrated.

It's a well-known fact that the concentration of oxygen is critical in enhancing a wide variety of biochemical reactions in vivo, including cell metabolism. Aerobic cell metabolism is a primary mechanism of energy production in tissue. Controlling this mechanism gives a unique possibility of biological stimulation to reach therapeutic effect. This goal could be reached by the means of laser-induced photodissociation of oxyhemoglobin in cutaneous blood vessels.

Absorption of light by blood Hb and $HbO_2$ allows considering and discussing the following photophysical and photochemical processes. Photophysical process is connected with nonradiative dissipation by Hb and $HbO_2$ electronic excitation energy. The heat generated in this process is transferred to the blood capillaries, which has the characteristic time of thermal relaxation ~ 0.05-1.2 msec.

The mechanism of laser-tissue interaction is very much dependent on the output laser energy. The effect of high-energy lasers action is quite clear and is based on photothermal processes such as selective photothermolysis.

The following basic mechanisms of “Laser-Tissue” interaction are currently accepted: photochemical, photothermal, and photomechanical (see Table Ⅰ).

TABLE Ⅰ MECHANISM OF “LASER-TISSUE” INTERACTION

**PHOTOCHEMICAL**
- PHOTODINAMIC THERAPY
- BIOSTIMULATION

**PHOTOTHERMAL**
- COAGU-LATION
- RESECTION
- VAPORI-SATION

**PHOTOMECHANICAL**
- ABLATION
- BREAKING

The effect of high output laser interaction with tissue is based on photothermal and photomechanical transformation of absorbed energy. Depending on the value of local temperature, the following thermal processes may be realized:

| TEMPERATURE | PROCESS |
|---|---|
| 37-60 $^{O}$C → | HEATING |
| 60-80 $^{O}$C → | DENATURATION OF PROTEIN |
| 100 $^{O}$C → | DEHYDRATION |
| >150 $^{O}$C → | CARBONIZATION |
| 300 $^{O}$C > → | EVAPORATION; COMBASTION |

This mechanism is used in clinical practice, for example, in laser surgery, cosmetology, laser correction of vision, etc. It is clear that the effect of heating due to absorption of low energy laser radiation in a tissue is negligible. Estimations show that in a typical case the local increase of temperature only by 0.1 - 0.5 $^{0}$C may be expected. Such a small rise of a local temperature may promote only some improvement in capillary microcirculation of blood and hardly could stimulate the metabolism of cells.

We suppose that in case of low energy lasers, the most important process is the photodissociation of $HbO_2$, the main biological function of which is molecular oxygen transport. The quantum efficiency of the photodissociation [11] of oxyhemoglobin is amazingly high and reaches 10 % in a wide visible spectral range. The molecular oxygen is generated due to laser-induced photodissociation of $HbO_2$ in blood vessels, which allows controlling the local increase of oxygen concentration at irradiating region (Fig. 1).

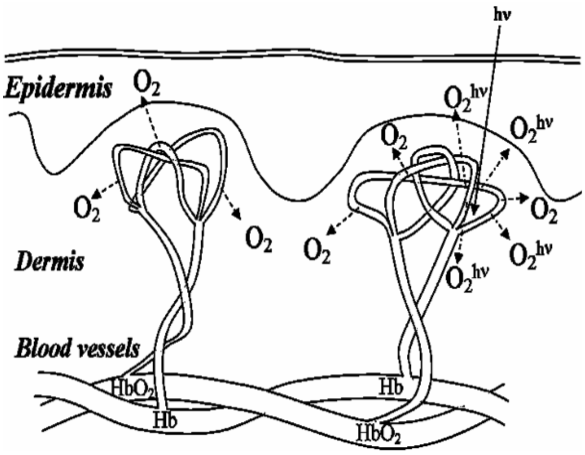


Fig. 1 Illustration of laser-induced tissue oxygenation caused by photodissociation of arterial blood $HbO_2$

The possibility of additional oxygen supply allows developing a new method of tissue hypoxia elimination that restores normal cell metabolism. Investigation of photodissociation of hemoglobin complexes in vivo could be carried out using arterial blood saturation parameter.

For $HbO_2$ the value of saturation $SaO_2$ in arterial blood vessels is defined by the concentration of $HbO_2$, taking into account contribution of Hb, methemoglobin (MetHb) and carboxyhemoglobin (HbCO).

$$SaO_2 = \{[HbO_2] / ([HbO_2]+[Hb]+[MetHb]+[HbCO])\}100$$

At normal conditions of gas exchange, the concentrations of MetHb and HbCO are extremely low (0.2 - 0.6 % and 0.8 % correspondingly) so the contribution of these components can be neglected. Thus in practice the value of $SaO_2$ could be determined as

$$SaO_2 = \{[HbO_2] /([HbO_2]+[Hb])\}100$$

Photodissociation of $HbO_2$ induced by laser radiation releases free molecular oxygen. Meanwhile, the proportion between $[HbO_2]$ and [Hb] concentrations is changed which decreases the value of $SaO_2$.

$$SaO_2 = SaO_2 - SaO_2^{h}$$

where $SaO_2$ is saturation without and $SaO_2^{h}$, with laser irradiation.

Amount of oxygen available for cell metabolism delivered by microcirculation is the function of:

$$O_2\,(TcPO_2) = f(F(HbO_2)*[O_2])$$

where $HbO_2$ is the value of oxyhemoglobin arterial blood and $[O_2]$ - is the concentration of oxygen released into plasma.

In case of deterioration of the blood microcirculation extra oxygen supply is critical to provide the demands of cell for normal metabolism. This could be reached by in vivo laser-induced photodissociation of $HbO_2$ directly to the zone where it is necessary to increase local concentration of free molecular oxygen.

As a result we obtain average concentration of oxygen releasing in a conventional way and due to photodissociation.

$$\Sigma[O_2] = [O_2] + [O_2^{hv}]$$

Thus the phenomenon of laser-induced in vivo photodissociation of oxyhemoglobin in cutaneous blood vessels and capillaries gives a unique possibility of optical increase in local tissue oxygen concentration.

## III. REGISTRATION OF IN VIVO OXYHEMOGLOBIN PHOTODISSOCIATION

Experimental study of the arterial blood saturation change due to laser-induced photodissociation of oxyhemoglobin is based on the registration of its value variations on the background natural oscillations of saturation. Specialized pulse oximeter spectrophotometer for recording photoplethysmogram with high accuracy and detailed numerical signal processing has been applied. Despite of traditional pulse oximeter with two channels for signal registration in red and infrared spectral ranges four channels that provides parallel eight independent signal processing has been used [12,13]. As a result, the registration of small changes of arterial blood saturation for one heart pulse is reached with accuracy less than 0.5 %.

The measurements of $SaO_2$ value were taken by the highly sensitive pulse oximeter sensors transmitting light with accuracy better than 0.5 %. The sensor was placed on the first of the two phalanxes of the finger; the measuring elements were in the region of the first phalanx (Fig. 2).

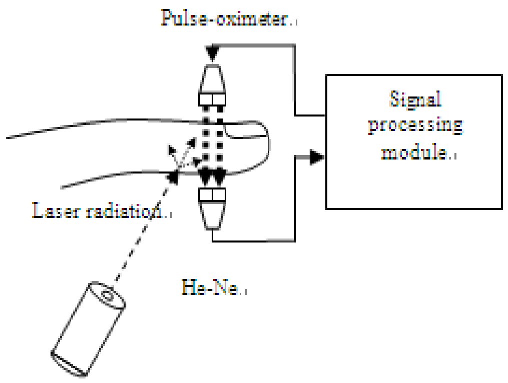


Fig. 2 Experimental setup for investigation of the effect of laser radiation on the value of arterial blood saturation

The effect of laser radiation on arterial blood oxygen saturation has been observed through using He-Ne laser with wavelength of 632 nm, which is mostly applied in medical practice. Lasers spot on a skin was about 7-8 mm with power density of 20 $MW/cm^2$. The laser radiation was guided to the interior of the third phalanx of the finger.

The concept of laser-induced tissue oxygenation allows understanding the mechanism of biological response and therapeutic effect of laser radiation. It’s also suggests a unique method of selective local tissue oxygenation, which could be used in a wide range of biomedical applications.

The method of transcutaneous oximeter (Fig. 3) that is based on the principle of measuring oxygen tension $PO_2$ in arterial blood is a direct method of registration of gases that dissolved in blood plasma.

For this purpose one usually uses Clark-type polarographic sensor (“$TcPO_2$ electrode”, see Fig. 3) that consist of a silver anode, electrolyte, and an oxygen permeable membrane; heating section and electronic system for measuring and controlling the sensor temperature.

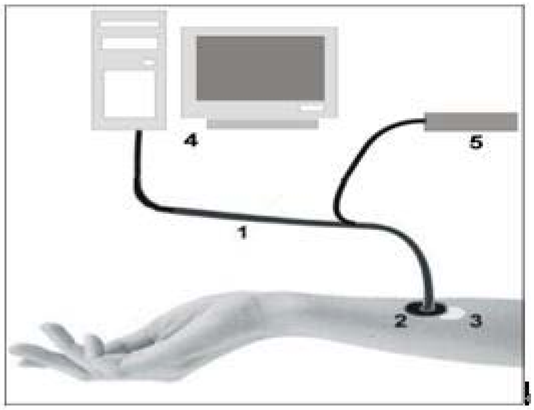


Fig. 3 Measurement of tissue oxygen tensions due to photodissociation of blood $HbO_2$: 1 - Clark sensor, 2 - electrolytic cell, 3 - irradiating zone, 4 - monitor TCM - 4, 5 - He- Ne laser

The initial oxygen tension in tissue was measured by placing $TcPO_2$ electrode on human skin in shoulder area. Then He-Ne laser radiation at the power of 1mW was applied. Kinetics of tissue oxygen tension was experimentally investigated [14]. The results obtained were normalized to the initial oxygen tension value.

These methods mentioned above allow to measure and control the process of releasing extra oxygen from $HbO_2$ under laser irradiation directly to arterial blood plasma and further it diffusion into tissue.

## IV. NEW METHOD OF OPTICAL “DOSIMETRY” BASED ON CONTROLLING LOCAL TISSUE OXYGENATION

Laser-induced photodissociation of $HbO_2$ gives a novel and unique method to optically increase the local concentration of free molecular oxygen in tissue which significantly enhances cell metabolism. Taking into account the fact that blood delivers $O_2$ to all cell tissues and that cell metabolism requires consumption of oxygen, we suggest establishing the therapeutic effect of laser radiation based on controlling summary tissue oxygen concentration.

The proposed method aimed at optimization of therapeutic efficiency laser radiation effect is based on using the change in oxygen concentration as a feedback signal.

-Oxygen released into tissue is proportional to the energy of aerobic cell metabolism.

-Photodissociation of $HbO_2$ increases the level of tissue oxygenation.

-Oxygen release rate could be directly measured in vivo through the value of saturation - $SaO_2$.

-The capacity of circulatory system to carry oxygen is defined by hemoglobin concentration [Hb] and also serves as a function to determine how much blood per minute is pumped from the heart.

Controlling parameters are:

- Aerobic metabolism (energy production);
- Extra oxygen release into tissue due to photodissociation of $HbO_2$;
- Ability of blood circulation system to transport oxygen.

Measuring parameters:

-Amount of oxygen released into tissue;

-Changes in arterial blood saturation $DSaO_2$;

-Hemoglobin concentration and heart pulse rate.

In this case we can refer to the pulse volume of heart VH which is equal to the volume of blood in litres that pump the heart at one bit. Then oxygen flux $F(O_2)$ through the irradiating zone of tissue can be described in the following way

$$F(O_2) = 4[O_2]/ ([Hb] + 4[O_2]) * C * V_H * [Hb]* ( SaO_2 / 100),$$

where C is a coefficient of blood delivery to tissue indicating tension in capillary blood vessels and [Hb] is the concentration of hemoglobin in gm/l. $SaO_2$ is the degree of hemoglobin oxygen saturation in percents, and $[O_2]$ molar concentration of oxygen.

Then we introduce the notion of "standard flux of oxygen through the tissue"

$$S(F.O_2) = 4 [O_2] / ([Hb] + 4 [O_2]) * [Hb]_n* C * V_H$$

"Standard flux of oxygen through the tissue" indicates a flux of oxygen that is necessary for supplying tissue at normal conditions.

Normal conditions are related to the concentration of hemoglobin in blood that corresponds to the given age and complete saturation with oxygen.

For the estimation of current oxygen delivery through the tissue, we normalize the local flux to the standard one:

$$F(O_2) = F(O_2) / SF(O_2)$$

Then we obtain

$$F(O_{2)} = [Hb]/[Hb]_n* ( SaO_2 / 100)$$

This parameter allows us to estimate current efficiency of oxygen delivery depending on the concentration of hemoglobin and degree of its saturation with oxygen. Now we can determine the quantity of oxygen that releases into tissue during elimination with low intensity laser radiation.

$$\Delta FO_2 =F(O_2) - F(O_2 )^{h\nu}$$

where $FO_2$ - is normalized flux of oxygen without laser irradiation and $FO_2^{h\nu}$ - is normalized flux of oxygen during laser irradiation.

The dose of oxygen that releases into tissue during the elimination with low energy laser radiation can be determined from following expression:

$$[O_2] = \{F(O_2) - F(O_2 )^{h\nu}\} * T * Pr$$

where T – is the time of irradiation and Pr - is pulse rate.

Substituting expressions for $FO_2$ and $FO_2^{h\nu}$ we obtain:

$$[O_2] = ([Hb]/[Hb]_n* ( SaO_2 / 100) - [Hb]/[Hb]_n* ( SaO_2^{h\nu} / 100)) *T * Pr =$$

$$= T * Pr * [Hb]/[Hb]_n *( SaO_2 - SaO_2^{h\nu}) / 100 = T * Pr * [Hb]/[Hb]_n *(\Delta SaO_2 / 100)$$

Thus the "dose" of oxygen that that releases into tissue during irradiation with low intensity laser radiation can be determined from following expression:

$$[O_2] = T * P_r * [Hb]/[Hb]_n *(\Delta SaO_2 / 100),$$

The suggested method of laser radiation therapeutic dose determination correlating with tissue local oxygenation could be applied in clinical practice. The developed highly sensitive pulse oximeter provides complete determination of all parameters required for establishing the therapeutic dose for treating a huge variety of diseases using laser phototherapy.

Laser induced photodissociation of $HbO_2$ allows to extract additional amount of oxygen locally at irradiating zone. This phenomenon provides a unique possibility to use optical methods for regulation of local tissue $O_2$ concentration. Additional oxygen release rate is directly measured through the value of oxyhemoglobin arterial blood saturation ($SaO_2$). The amount of oxygen released into tissue depends also on the capacity of circulatory system to carry oxygen.

This capacity is mainly defined by the contribution of the following two parameters: concentration of blood hemoglobin [Hb] and its circulation speed. The impact of actual hemoglobin concentration is described by the ratio of [Hb]/[Hb]n.

Here [Hb]n is standard concentration that is normal for particular sex and age. The impact of blood circulation speed is taken into account through the heart pulse rate Pr.

Finally, the therapeutic "dose" can be determined through the value of $\Delta SaO_2 = SaO_2 - SaO_2^{h\nu}$, where $SaO_2$ is saturation without and $SaO_2^{h\nu}$ with laser irradiation, heart pulse rate Pr, time of exposure T, ratio of actual and standard hemoglobin concentrations [Hb]/[Hb] n.

$$D(O_2) = \frac{[Hb]}{[Hb]_n} \cdot \left( \frac{\Delta SaO_2}{100} \right) \cdot P_r \cdot T$$

It should be noted that the involved parameters are objective and could be measured in the course of a well-known clinical routine. The new suggested method of optical "dosimetry" based on key biological parameters measurement and connected with aerobic cell metabolism provides possibility of precise determination of therapeutic effect of laser radiation.

## V. EXPERIMENT

Experimental investigation of laser-induced tissue oxygenation phenomenon has been carried out using transcutaneous oxygen monitor (TCOM) - "Radiometer" TCM-4 (Fig. 4). Direct in vivo measurements of tissue oxygen tension $TcPO_2$ under irradiation by He-Ne laser with the power of 1mW has been taken [14].

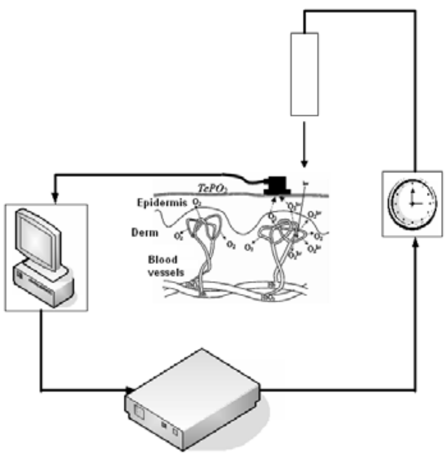


Fig. 4 Experimental setup for controlling local tissue oxygen concentration directly at the zone of laser irradiation

Using a simple diffusion model we calculated what amount of oxygen should be released into blood plasma in order to reach experimentally observed tissue $O_2$ concentration (Fig. 5). The target criteria were kinetics of tissue oxygenation in response to laser irradiation. The variable parameters were diffusion coefficient of oxygen in tissue and oxygen release rate.

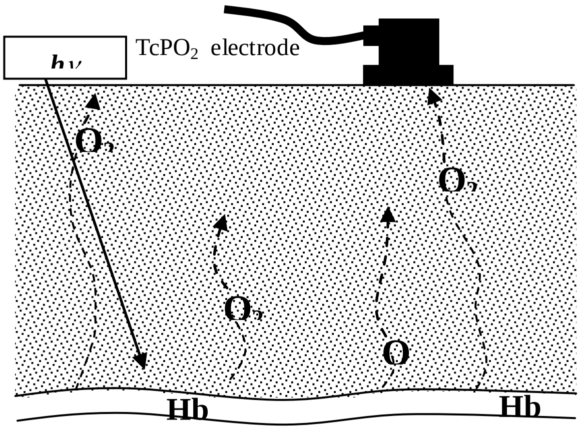


Fig. 5 Simple model of oxygen diffusion in tissue

As it was shown experimentally [10], the response of oxygen release on laser irradiation is relatively fast and remains constant during the irradiation. To simulate this effect in the model, the oxygen release rate was increased instantly and remained constant during the time of irradiation.

The main aim of the calculation was to reach the closest fit of the data produced by the model to the experimentally measured one. The target criteria were kinetics of tissue oxygenation in response to laser irradiation. The variable parameters were diffusion coefficient of oxygen in tissue and oxygen release rate.

## VI. RESULTS AND DISCUSSION

The kinetics of oxygen tension in tissue in two cases including normal blood circulation and artificially induced ischemia was investigated. The obtained results were normalized to initial oxygen tension value.

In Fig. 6 the experimental results of in vivo laser induced tissue oxygenation for volunteer in normal condition and in case of artificially induced ischemia are presented. As it can be seen, we still can extract extra oxygen from arterial blood and optically satisfy the cell metabolism demand for the required period of time.

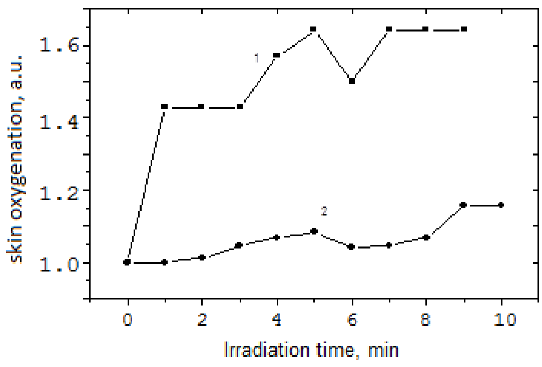


Fig. 6 The kinetics of laser-induced tissue oxygenation during laser irradiation in norm blood microcirculation - 1, and in artificially induced ischemia - 2

As it can be seen from Fig. 6 during laser irradiation, the value of tissue oxygenation increases and exceeds its initial level by 1.6 times (Curve 1) after ten minutes of illumination. In case of induced ischemia, additional extraction of oxygen is also observed. This result clearly demonstrates that laser-induced tissue oxygenation could be applied to clinical practice for restoration of normal cell metabolism in tissue with damaged microcirculation.

The results of calculations demonstrate that, in order to reach the experimentally observed rise of $TcPO_2$ by approximately 1.6 times on the tissue surface, the calculation indicating the increase of oxygen release rate from arterial $HbO_2$ into blood plasma should increase by approximately 4.3 times.

Photodissociation of $HbO_2$ induced by laser radiation and release rate of free molecular oxygen into blood plasma has been measured experimentally in vivo using highly sensitive pulse oximeter. The oxygen released from $HbO_2$ primarily increases the $PO_2$ of blood plasma and then $O_2$ diffuses into the tissue.

It is exciting that the value of $PO_2$ in blood plasma reached by laser-induced photodissociation of $HbO_2$ is comparable to that one typically reached by the method of HBO. The distribution of $TcPO_2$ in the volume at the irradiation zone depends on the time of exposure and the tissue properties.

The comparison of calculated results with experimental data demonstrates that kinetics of $TcPO_2$ considered in relation to time of elimination by laser radiation gives possibility to determine $O_2$ diffusion coefficient in tissue. This means that one could calculate and determine how to reach desirable level of $TcPO_2$ in zones with disturbed blood microcirculation such as solid tumour, burn or wounds. So it's possible to determine optimal parameters of irradiation taking into account the volume that has to be oxygenated and the time of elimination.

Thus our suggested novel method can eliminate the deficit of oxygen until the new vascular net in tissue is restored. This result could be applied for those pathologies where elimination of tissue hypoxia is critical.

Supplemental oxygen can lead to the increased rate of collagen deposition, epithelization and improved healing of split thickness grafts. Increased subcutaneous $TcPO_2$ has also been shown to improve bacterial defences. Thus a unique possibility in selective and local increase of the concentration of free molecular oxygen in tissue which enhances metabolism of cells has been developed. Laser-induced enrichment of tissue oxygenation stimulates cell metabolism and allows developing new effective methods of laser therapy as well as phototherapy of pathologies where elimination of local tissue hypoxia is critical.

Laser-induced photodissociation of $HbO_2$ may serve as a unique method in laser therapy for optical increase of free molecular oxygen local concentration in tissue which significantly enhances cell metabolism.

It is valuable that even in regard ischemia cases we still can extract extra oxygen from arterial blood and optically satisfy the cell metabolism demand for the required period of time. Thus laser-induced tissue oxygenation allows to optically eliminating the deficit of oxygen until the new vascular net in tissue is restored.

The obtained results provide experimental argumentation for considering the primary mechanism of biostimulation and therapeutic effect of low energy laser radiation that could be based on increasing tissue local oxygen concentration directly in the zone of irradiation.

This phenomenon allows developing an objective method of controlling the efficiency of treatment by laser phototherapy. Now in clinical application the parameters of laser radiation can be tuned to optimal wavelength, power and exposition time in depends on optical characteristics of the patient skin tissue.

The obtained results also show the way of increasing the efficiency of biostimulation and the therapeutic effect of low energy laser radiation based on its combination with the method of oxygen hyperventilation therapy.

An important conclusion can also be drawn from the obtained results. To interpret the bio-stimulating and healing effects of laser radiation, the phenomenon of induced photodissociation of blood $HbO_2$ should be taken into account.

## VII. CONCLUSIONS

The new optical method of local tissue hypoxia elimination has been developed. The value of tissue $O_2$ concentration increases significantly during the laser irradiation.

It is shown that establishing the therapeutic dose of laser radiation could be based on adjusting the local concentration of free oxygen in tissue by laser-induced photodissociation of blood $HbO_2$.

To make the phototherapy as well as laser therapy methods really efficient, one has to control the $O_2$ concentration in tissue to keep it at necessary level. This goal could be reached by the use of laser-induced photodissociation of $HbO_2$ in tissue blood vessels.

The method of determination of oxygen diffusion coefficient on kinetics of tissue $O_2$ under the laser irradiation has been developed.

It has been shown that the efficiency of laser-induced oxygenation is comparable to the method of hyperbaric oxygenation (HBO) which gains advantages at the same time in local action.

Novel method of optical “dosimetry” based on using the changes in tissue oxygen concentration as a feedback signal for the optimization of low intensity laser radiation therapeutic effect has been developed.

Photodissociation of oxyhemoglobin, the main biological function by which molecular oxygen transport, gives a unique possibility of additional oxygen supply and allows developing laser-optical method of tissue hypoxia elimination that can restore normal cell metabolism.

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**Mustafo M. Asimov** is a head research scientist at the Institute of Physics of National Academy of Sciences of Belarus. He specializes in Laser Physics and Spectroscopy. In 1979 his Candidate thesis (PhD): "Investigation of the excited state absorption in laser media at flash lamp excitation" was defended. In 1994 he received a Doctor of Sciences degree (professor) for the work: "New active media for flash lamp-pumped dye lasers".

The basic filed of scientific activity is connected with laser physics and spectroscopy. In 1997 he proposed and developed a new scientific direction connected with laser-induced photodissociation of hemoglobin ligands with gases and suggested its biomedical applications. New approach in detection of local tissue hypoxia based on noninvasive optical method and its elimination by novel technology of laser-induced tissue oxygenation was proposed. Different biomedical applications on the basis of the proposed method are currently being developed.