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Impact of Nd:YAG laser radiation (λ = 1.44 μm) on myocardial tissue in the treatment of coronary heart disease by transmyocardial laser revascularisation

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Abstract. **We have studied the impact of Nd:YAG laser radiation with a wavelength of λ = 1.44 μm on the myocardial tissue for the formation of channels in the treatment of coronary heart disease by transmyocardial laser revascularisation (TMLR). The mechanism of perforation of the myocardial tissue by a laser pulse is presented and an experimental setup for TMLR is developed. In experiments on biological objects, the optimal parameters of radiation energy and duration necessary for the formation of channels of a given size in a single laser pulse are determined. The exposure regime ensures the adequate character of myocardial tissue destruction, assessed by such criteria as the perforation force, exposure energy, size of the coagulation zone, and level of carbonisation.**

Keywords: *laser radiation, ischemia, laser revascularisation, angiogenesis.*

1. Introduction

Despite the successes of modern cardiology, the coronary heart disease remains the main cause of adult mortality in leading countries of the world. A highly effective method of surgical treatment of coronary artery disease is coronary artery bypass grafting (CABG), which is currently the most frequently performed heart surgery [1, 2]. However, for 25%–30% of patients with angina pectoris, CABG is impossible due to diffuse lesions of the coronary arteries, recurrent forms of angina pectoris after coronary angioplasty, as well as a number of other reasons [2, 3]. In such cases, cardiac blood flow can be restored using transmyocardial laser revascularisation (TMLR) [3–9]. The idea of using a laser for myocardial revascularisation in patients with coronary arteries that cannot be bypassed belongs to M. Mirhoseini [5]. Evidence-based medicine confirms the presence of active angiogenesis after TMLR in patients with coronary artery disease with a diffuse form of coronary artery lesion [6, 7, 10]. During this operation, channels are formed in the thickness of the heart muscle of the left ventricle using laser radiation that open into the cavity of the heart. Typically, TMLR surgery involves the formation of several tens of channels with a diameter of 0.3 to 1.5 mm in the myocardium. Channels are produced in the cardiac muscle from the outside when radiation is supplied using a terminal device connected to a laser by a fibre-optic radiation delivery system.

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The experience of using a CO_2 laser in the Bakulev Scientific Centre of Cardiovascular Surgery of the Russian Academy of Medical Sciences and in the Sechenov First Moscow State Medical University, as well as the results of experimental studies of the erbium laser effectiveness [2, 11], allow us to formulate the basic principles of channel formation in myocardial tissues during TMLR [8, 10, 11].

1. The channel is formed in a single laser pulse of millisecond duration on a working heart. In this case, the onset of laser exposure is synchronised with the R-wave of the patient's electrocardiogram and can last until the T-wave, which is about 150 ms, i.e., the time of interaction of radiation with myocardial tissues is limited by the interval between two contractions of the working heart. At this time, the left ventricle of the heart is completely filled with blood, which absorbs part of the radiation transmitted through the channel, thus protecting the internal structures of the heart from damage. In addition, the risk of induced arrhythmia due to the acousto-optical effect of laser radiation is minimised.

2. The channel is formed by a series of radiation pulses, which is transmitted via an optical fibre, without synchronisation with the rhythm of the working heart.

3. The channel is formed on the idle heart in the process of independent intervention or in addition to coronary artery bypass grafting.

Nevertheless, it should be noted that the best results are achieved using a single laser pulse of millisecond duration, synchronised with the patient's ECG [8, 10, 12]. Below we summarise the comparative characteristics of existing laser medical systems (LMS's) (Table 1) and lasers (Table 2) for TMLR.

Analysis of Tables 1 and 2 allows us to draw conclusions about the efficiency of using different types of lasers. In particular, a functional drawback of CO_2 lasers is the high probability of the shock wave occurrence during perforation of myocardial tissue in one pulse. In addition, the high cost of high-power CO_2 lasers, high energy consumption (10–16 kW), and the complexity of operation impede the widespread use of TMLR in medical institutions. Practice shows that the implementation of TMLR using CO_2 lasers requires specially equipped operating rooms and the presence of specialists from the supplying company for maintenance.

Using a Ho:YAG laser, part of the Solargen 2100s system, does not provide through-hole perforation of the myocardium in a single pulse or in a series of pulses within one contraction of the heart muscle. The radiation pulses generated by it have a short (0.2 ms) duration, which can lead to the

Table 1.

LMS parameters	The described Nd:YAG-based LMS	Perfokor CO_2-based LMS (IPLIT RAS, Russia)	HeartLaser CO_2-based LMS (PLC Medical System, USA)	Solargen 2100s Ho:YAG-based LMS (Cardiogenesism, USA)
Radiation wavelength/μm	1.44	10.6	10.6	2.08
Operating regime	Pulsed	Pulsed	Pulsed	Repetitively pulsed (up to 5 Hz)
Radiation pulse duration/ms	2–20	10–200	1–99	0.2
Maximum radiation pulse power/W	200	400	1000	Up to 20000
Energy of laser pulse with 20 ms duration/J	4	8	20	Up to 4 at 0.2 ms
Probability of a shock wave occurrence	Low	High	High	Low
ECG synchronisation	Present	Present	Present	Absent
Diameter of silica fibre/mm	0.4–9830.6	Absent	Absent	No data
Fibre perforator movement/mm	20	Absent	Absent	Absent
Dimensions/mm	660 × 235 × 650	800 × 800 × 2080	900 × 800 × 2030	910 × 360 × 530
Weight/kg	45	240	230	58

Table 2.

Laser parameters	Erbium fibre laser (IPG Photonics Corporation, IRE-Polus, Fryazino, Moscow region)	Thulium fibre laser (IPG Photonics Corporation, IRE-Polus, Fryazino, Moscow region)	Diode laser (IPG Photonics Corporation, IRE-Polus, Fryazino, Moscow region)
Radiation wavelength/μm	1.55	1.94	0.97
Operation regime	Continuous, repetitively pulsed	Continuous, pulsed, repetitively pulsed	Continuous, pulsed, repetitively pulsed
Radiation pulse duration/ms	1–1000	0.2–1000	1–1000
Maximum mean radiation power/W	15	120	60
Energy of a laser pulse with a duration of 20 ms/J	0.3	~25	~1.2
Probability of shock wave occurrence	Low	Low	Low
ECG synchronisation	Absent	Absent	Absent
Diameter of silica optical fibre/mm	0.4–0.6	0.4–0.6	0.2–0.6
Fibre perforator movement/mm	Absent	Absent	Absent
Dimensions/mm	286 × 460 × 545	86 × 460 × 545	253 × 310 × 419
Weight/kg	38	38	6

formation of shock waves that can provoke cardiac arrhythmias. Erbium fibre lasers also do not provide end-to-end myocardial perforation per pulse or per series of pulses within one contraction of the heart muscle [12, 13]. Thulium fibre lasers can provide single-pulse perforation, but they are very expensive.

The use of a solid-state neodymium-doped yttrium aluminium garnet laser is of interest for TMLR, since the radiation generated by it (λ = 1.44 μm) falls into the local maximum of the biological tissue absorption band, which is about 4.5 mm^{-1}. The energy and time parameters of laser radiation make it possible to obtain a through channel in the myocardial tissue with a depth of up to 20 mm and a diameter of ~1 mm per pulse with the pulse energy up to 4 J and the duration up to 20 ms. In this case, the impact of radiation can be implemented on a working heart in the absence of the shock wave effect.

2. Materials and method

2.1. Mechanism of myocardial tissue perforation with a laser pulse with λ = 1.44 μm

The mechanism of perforation of the myocardial tissue under the action of a laser pulse can be represented as follows. A perforating device (a piece of optical silica fibre) is inserted into the myocardial tissue and a laser pulse is simultaneously applied. The absorption of laser radiation leads to the rapid heating of a thin layer of biological tissue adjacent to the distal end of the fibre, which causes boiling of water and coagulation of biological tissue. Channel formation primarily depends on the optimal choice of radiation energy and pulse duration, which determine the generation of heat. In this case, the criterion of optimality is an increase in temperature to 250 °C under conditions of adiabatic heating of a thin layer of biological tissue, since at higher temperatures there is a threat of carbonation during exposure to a laser pulse. In the latter case, carbon is released, which leads to the formation of polyenes (chains of carbon atoms with many double bonds), crosslinks, and groups of carbon atoms [14]. The formation of polyenes and carbon complexes leads to an increase in the effective absorption coefficient and is visually manifested in the darkening of irradiated areas of biological tissues, which is a manifestation of their carbonisation. The kinetics of photo- and thermal degradation of biopolymers under laser irradiation is limited by diffusion processes of migration of released gases and coagulation of biological tissue. Tissue carbonisation during channel formation is unacceptable since it impedes the process of revascularisation.

Active absorption of laser radiation also leads to the evaporation of water molecules inside a thin layer of tissue and to laser-induced boiling at the surface of the fibre end. One should distinguish between heterogeneous boiling (on the surface to which heat is supplied from outside) and homogeneous boiling (in the volume of superheated liquid). Intense convective heat fluxes and latent heat consumption for vaporisation make boiling an effective way of heat transfer [15]. In this case, when the laser radiation is efficiently absorbed by the biological tissue near the end of the fibre, heterogeneous boiling of water occurs, leading to the appearance of two-phase flows in the tissue fluid [12]. The resulting vapour–gas mixture with an average temperature of about 150 °C consists of vapour–gas bubbles. Due to the high vapour pressure inside the bubble ($\sim 8 \times 10^5$ Pa) and intense evaporation, the bubble size rapidly increases [16]. As a result of evaporation processes, the temperature of the mixture at atmospheric pressure drops to equilibrium temperature ($\sim$100 °C), and no overheating of the adjacent surrounding tissues is observed. Thus, the volume of vapour increases sharply, which, in turn, leads to an increase in pressure in the tissue and causes local mechanical destruction of its fragments at the end of the fibre. In this case, structural modification and local destruction of biological tissue occur not by direct laser heating, but as a result of the rapid heat delivery by two-phase flows of tissue fluid that form when it boils [17]. In this case, both overheating leading to carbonisation and overheating of nearby tissues are eliminated, and the resulting gas fraction is removed through the lumen of the perforated channel. In addition, rapid heating of the myocardial tissue adjacent to the end surface of the fibre causes its thermal ablation. As a result of these processes, the force needed to introduce the silica fibre into the tissue of the heart muscle becomes almost imperceptible.

2.2. Setup for Nd:YAG laser-based TMLR

The TMLR setup was developed using a solid-state laser based on yttrium aluminium garnet doped with neodymium ($Y_3Al_5O_{12}:Nd^{3+}$), generating radiation with a wavelength of 1.44 μm and an output energy of up to 5 J. The pulse duration is adjustable in the range of 2–20 ms, the pulse shape is close to rectangular, and the pulse repetition rate reaches 3 Hz; all this allows perforation of the myocardium during one cardiac cycle with the possibility of ECG synchronisation and with the simultaneous injection of a drug. The fact that in the process of perforation the radiating end face of the fibre touches the tissues of the heart muscle allows, despite the relatively small pulse energy, the formation of a through channel 20–25 mm long and about a millimetre in diameter in the myocardium using a single pulse with a duration of up to 20 ms. The effectiveness of radiation over the entire pulse is ensured by the continuous mechanical supply of the optical fibre in the direction of the radiation. The best results are achieved using a single laser pulse of millisecond duration, synchronised with the patient's ECG.

The setup layout and the scheme of communication between the setup units are shown in Fig. 1. The unit of laser radiation sources consists of a working and aiming lasers. The working laser provides the generation of laser radiation in single-pulse and pulse-repetition regimes; the aiming laser operates in the continuous-wave regime in the visible wavelength range. The active element of the working Nd:YAG laser is a cylindrical rod with a diameter of 6.3 mm and a length of 100 mm (active element GP6.3Kh100); the pumping lamp is a gas discharge lamp filled with xenon (INP 6×90).

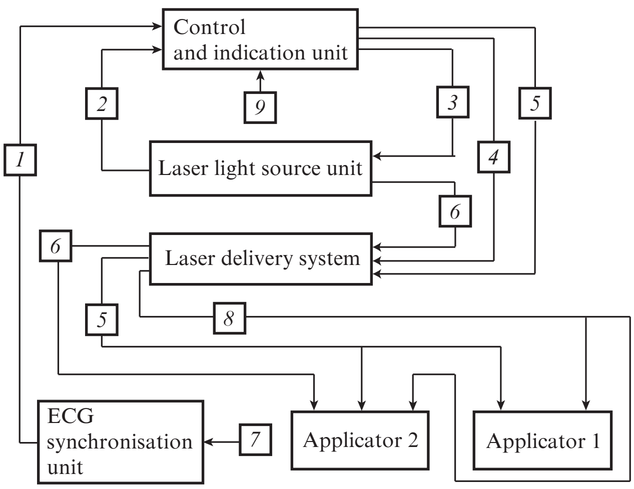


Figure 1. Schematic of the setup for TMLR. Communication between the units:
(*1*) ECG clock signal; (*2*) laser ready clock signal; (*3*) laser generation clock signal; (*4*) signal of injection control; (*5*) signal of perforation control; (*6*) perforating laser pulse; (*7*) biological signals from the patient's heart; (*8*) executive signal; (*9*) signal of the control pedal.

In order to suppress the laser lines with a wavelength of 1.064 μm and stimulate the lasing at a wavelength of 1.44 μm, the radiating cavity is designed according to a three-mirror scheme. The dependences of the laser pulse energy E_{las} on the discharge current of the pump lamp for various pump pulse durations are shown in Fig. 2. Energy measurements were carried out using an IMO2N laser power and energy meter installed at the optical fibre exit with a diameter of 0.6 mm. The pump energy E_{pump} was controlled by changing the discharge current through the pump lamp at a fixed pump pulse duration τ_{pump}.

Oscillograms of laser pulses at various durations of the pump lamp pulse are shown in Fig. 3. It is seen that within 5–20 ms the pulse has a rectangular shape; this ensures, within the energy range of 1–4 J, the constancy of the laser action on the biological tissue during the pulse.

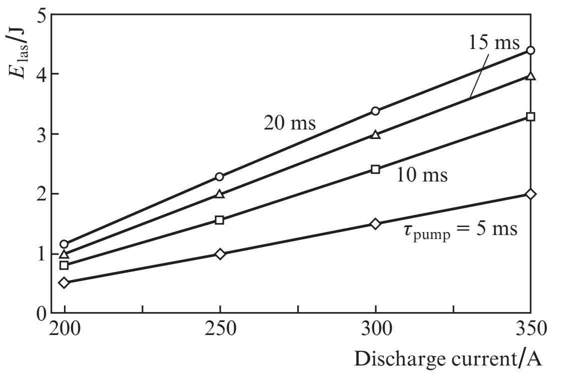


Figure 2. Dependences of the pulse energy E_{las} on the discharge current of the pump lamp for various pulse durations τ_{pump} of pump radiation.

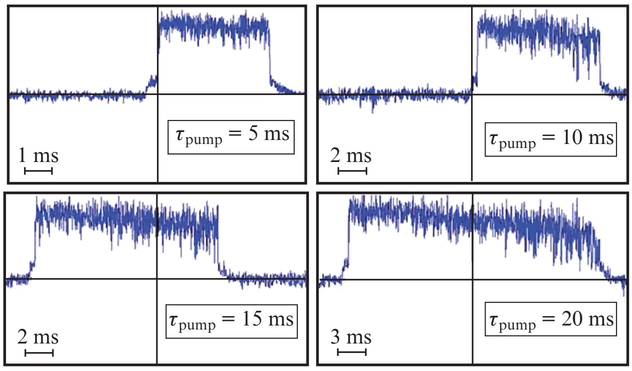


Figure 3. Shapes and durations of the laser pulse for various pump pulse durations τ_{pump}.

The control and indication unit provides a choice of commands for loading the parameters of the regime, system status, switching on/off the aiming laser, exposure regimes and characteristics of laser radiation, namely, the output radiation energy of the working laser and the number of emitted pulses during the procedure, as well as alphanumeric indication of the setup operating regimes.

The ECG synchronisation unit is aimed to form a sync pulse, to which the phases of the TMLR procedure are locked. The total duration of one or more pulses is synchronised with the R-wave of the patient's electrocardiogram and can last up to the T-wave. Thus, the time of interaction of radiation with myocardial tissues, limited by the interval between two contractions of the working heart, is about 150 ms.

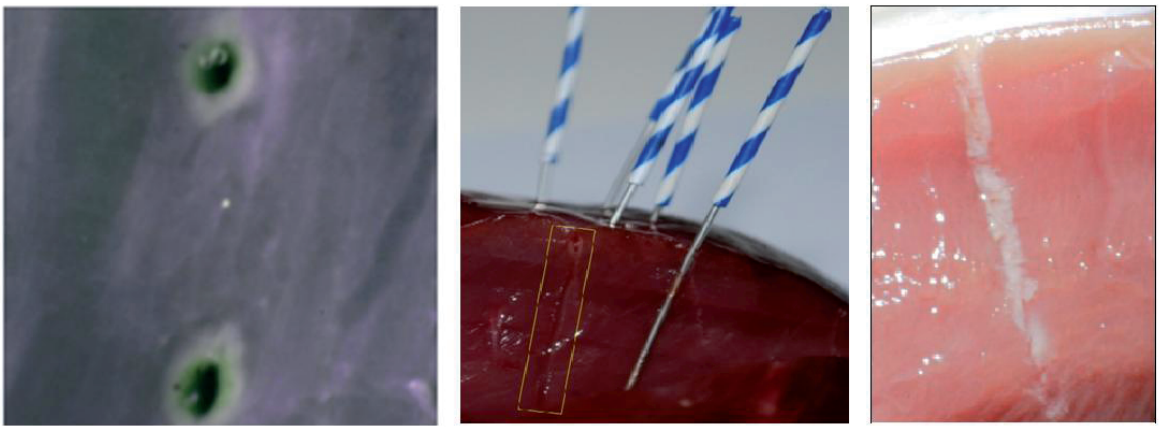
The laser delivery system includes a fibre optic cable based on Q/Q 600/660 WF silica fibre with a diameter of 600 μm and a system for holding the applicator in the position necessary for the surgeon. Applicators are devices designed to perforate the myocardium. They provide the movement of the optical fibre to a distance of 20 mm in a time of not more than 20 ms with subsequent return to its initial position.

3. Results and discussion

3.1. Experimental studies on tissue samples (*in vitro*)

Using the developed setup, experimental studies were conducted on biological objects *in vitro*. As the biological material, the front wall of the left ventricle of the heart of a pig was used. The objective of the experiment was to evaluate the efficiency of channel formation by a single laser pulse as a function of the energy and duration of the laser exposure. During the study, channels that opened into the cavity of the heart were produced in the thickness of the heart muscle of the left ventricle using laser radiation. The channels were made in the heart muscle (from the outside) by a silica fibre with a diameter of 600 μm during a single laser pulse. About ten channels were formed by the action of laser radiation with the pulse energy of 3.5 J and pulse duration of τ_{las} = 15 ms. Fragments of perforation of channels with a diameter of 0.6 mm and a depth of 17–18 mm in the myocardial tissue are shown in Fig. 4.

The experimental data made it possible to establish some dependences that allow optimisation of the laser exposure parameters for the formation of channels in the myocardial wall. Figure 5 shows the dependence of the perforation force P on the laser radiation energy E_{las} for different pulse durations τ_{las}. The dependence of the perforation depth L on τ_{las} for different energy values E_{las} is shown in Fig. 6.



Fibre inlets in myocardial tissue — Introduction of applicators into the myocardium — Perforated channel on a tissue section

Figure 4. Fragments of channel perforation in the myocardium.

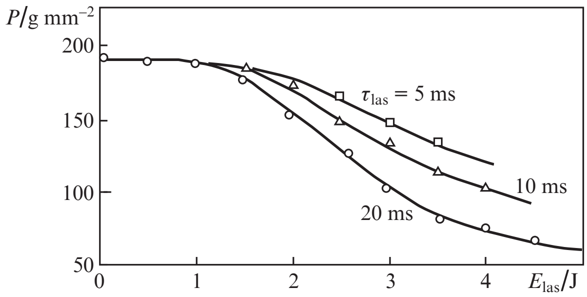


Figure 5. Dependences of the perforation force on the laser radiation energy for various pulse durations τ_{las}.

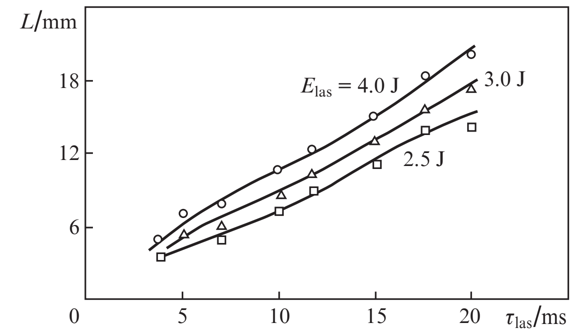


Figure 6. Dependences of the perforation depth on the laser pulse duration for various E_{las}.

The initial perforation pressure in the experiment was P = 175.0 ± 5.0 g mm^{-2}.

Data on the depth of perforation as a function of the energy and duration of the laser pulse are summarised in Table 3.

Analysis of the results showed that the optimal values of the duration and energy of the laser pulse are in the range of 10–20 ms and 2–4 J, which allows producing a channel with a depth of 10–20 mm and a diameter of 0.6–0.9 mm. The coagulation zone was 50–300 μm in the absence of carbonisation traces.

3.2. Experimental animal studies (*in vivo*)

In vivo studies were conducted on experimental animals (mini pigs). The objective of the experiment was to evaluate the effectiveness of the TMLR procedure. Under intubation anaesthesia, intercostal opening of the chest of the pig was performed and a tenfold perforating impact on the working heart was executed. After the operation, the animals were placed in an aviary. On the 30th day after the TMLR procedure, the animals were sacrificed and myocardial sections were subjected to histological studies, the results of which are shown in Fig. 7.

Table 3.

Perforation depth/mm	Laser pulse energy/J	Laser pulse duration/ms
10 ± 1	2.0	10
12 ± 1	2.4	12
14 ± 1	2.8	14
16 ± 2	3.2	16
18 ± 2	3.6	18
20 ± 2	4.0	20

The histograms show through channels of the pig myocardium (from the epicardium to the endocardium) in the form of light eosinophilic staining. In the centre of the oxyphilic zone, along the entire length, there is a longitudinal slit-like lumen of the laser channel. The central sections of the slit-like structure are filled with elements of the costitutive granulation tissue – macrophage cell elements, neutrophils, and blood cells (Figs 7a and 7b). The same site of laser exposure in the form of a zone of necrobiotic changes in cardiomyocytes with granulation tissue already formed in the lumen of the gap and newly formed capillaries is shown in Fig. 7c. The results of histological studies show that the formation of capillaries of granulation tissue occurs, which subsequently integrate with the capillary network of the myocardium, leading to a decrease in the level of ischemia. Thus, the activation of oxygen transport to the ischemic heart region is achieved.

4. Conclusions

This paper is devoted to the development of an experimental setup for TMLR based on a Nd:YAG laser (λ = 1.44 μm) and the evaluation of the efficiency of perforation of the myocardial tissue with an optical fibre simultaneously with the action of a single laser pulse synchronised with the heart rhythm. Efficiency assessment was carried out according to criteria such as perforation pressure, exposure energy, size of coagulation necrosis zone, level of carbonisation. Such esti-

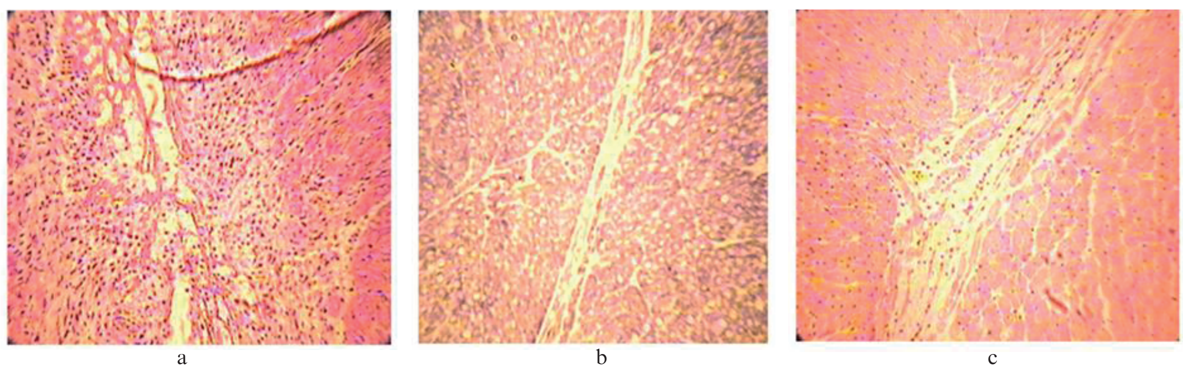


Figure 7. Histograms of sections of a porcine myocardium on the 30th day after TMLR.

mates of the effectiveness of the Nd : YAG laser (λ = 1.44 μm) for use in TMLR have not been carried out earlier.

As a result of experiments on tissue samples *in vitro*, the dependence of the perforation pressure on the laser radiation energy and the dependence of the perforation depth on the pulse duration were found. In the course of testing the operating modes of the installation, a relationship was obtained between the energy and the duration of the laser pulse, one the one hand, and the depth of perforation, on the other hand. The velocity of moving of the perforating part of the fibre at various energies and durations of the laser pulse was maintained constant and amounted to approximately 1 m s^{-1}, which was due to the need to complete the TMLR cycle in no more than 150 ms.

The results of *in vivo* animal experiments showed that the experimental setup based on the Nd : YAG laser (λ = 1.44 μm) provides effective revascularisation of the myocardial tissue in the zone of laser exposure. Histograms of sections of biological tissues indicate active angiogenesis, proliferation of connective tissue elements and intercellular substance during the rehabilitation period.

From the analysis of the results, it follows that the use of a Nd : YAG laser (λ = 1.44 μm) allows the formation of laser radiation pulses that produce a vapour phase leading to restructuring of the myocardial tissue in the heating zone, which ensures free insertion of the optical fibre to a depth of 20 mm. The presence of a vapour phase during laser-induced tissue heating limits the temperature increase to about 150 °C and causes its decrease to an equilibrium temperature at atmospheric pressure. Such heating forms an adequate coagulation zone of the channel walls of 50 – 300 μm in the absence of carbonisation. Perforation of myocardial tissue with an optical fibre simultaneously with the action of a single laser pulse with optimal values of energy and duration leads to a significant decrease in the required laser pulse energy (up to 4 W) compared with the case of using a CO_2 laser. At the same time, the channel perforation process meets the main criteria of effectiveness (perforation force, exposure energy, size of coagulation necrosis zone, carbonisation level). Thus, the use of a Nd : YAG laser (λ = 1.44 μm) in the treatment of coronary heart disease using transmyocardial laser revascularisation is efficient and has several advantages.

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