BIOPHYSICS AND BIOCHEMISTRY

Implication of Sympathetic Innervation of the Heart in Antiarrhythmic Action of Intra-Atrial Laser Irradiation

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The role of sympathetic nervous system in the antiarrhythmic effect of intra-atrial laser irradiation (λ=632.8 nm) during myocardial ischemia was studied in acute experiments on Nembutal-anesthetized cats. Laser irradiation applied after bilateral, dextral, or sinistral transection of cardiac branches of stellate ganglia increased the number of ischemic rhythm disturbances that developed after occlusion of the circumflex branch of the left coronary artery. The maximum increase in the number of arrhythmias was observed after dextral transection, the occurrence of ventricular fibrillation being 100%. Bilateral transection provoked a larger number of ischemic rhythm disturbances than the sinistral transection. It is probable that the development of the antiarrhythmic effect of laser irradiation requires sustained sympathetic activity targeted at the nonischemic regions in the myocardium that could play a stabilizing role during local ischemic damage to the heart.

Key Words: *myocardial ischemia; cardiac arrhythmias; ventricular fibrillation; laser irradiation; sympathetic cardiac regulation*

Laser irradiation (LI) has been successfully used in the therapy of myocardial ischemia and prevention of cardiac arrhythmias. The therapeutic effect of LI has been explained by its ability to inhibit lipid peroxidation, to improve blood characteristics, to restore the balance between the coagulant and anticoagulant systems, and to normalize the dynamics of cardiotropic enzymes and basic indices of the acid-base equilibrium [1,3]. However, the role of the nervous system in the antiarrhythmic effect of intra-atrial LI is poorly understood. It is shown that to reveal the protective effect of LI on ischemic cardiac arrhythmia, the integrity of afferent vagal supply to the heart is prerequisite [6]. However, the role of the sympathetic system in this effect remains unclear.

Our aim was to study the role of the sympathetic nervous system in the antiarrhythmic effect of intra-atrial LI on ischemic myocardium.

MATERIALS AND METHODS

Experiments were carried out under Nembutal anesthesia (40 mg/kg intraperitoneally) on 67 cats of both sexes weighing 2-5 kg. Myocardial ischemia was modeled by occluding the circumflex branch of the left coronary artery for 15 min. Arrhythmias were recorded during a 15-min occlusion and subsequent 15-min reperfusion periods. LI of the right atrium was performed using an ILGN-120 He-Ne

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laser (λ=632.8 nm, beam power at the light guide tip 3-5 mW) [6]. The ECG and arterial pressure (AP) in the femoral artery were recorded with a P4CH-02 polygraph 5 min after bilateral or unilateral transection of inferior cardiac nerves and caudal anastomoses at the sites where they emerge from the stellate ganglia. The studied episodes were grouped ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation. The data were statistically analyzed using Student's t test as well as Pierson's and Fisher's tests for 2×2 matrices.

RESULTS

Irradiation of the right atrium with the light of a He-Ne laser significantly decreased the occurrence of ischemic arrhythmias: the idioventricular disturbances in cardiac rhythm were observed in 31% cases, including 23% cases with grouped extrasystoles, while ventricular tachycardia was not observed and the occurrence of ventricular fibrillation was only 7.7% [6]. In the control series (without LI) idioventricular arrhythmias were observed in 72% cases, grouped extrasystoles in 50% cases, tachycardia in 28% cases, and ventricular fibrillation 55% cases [5].

In the first series (12 experiments) we recorded the occurrence of cardiac arrhythmias under the effect of atrium LI performed after bilateral transection of inferior cardiac nerve and caudal anastomoses.

Transection of cardiac nerves from the stellate ganglia led to a decrease in systolic AP (by 13%, $p<0.05$) and in heart rate (HR, by 9.1% $p<0.01$) compared with the initial values (133±3.9 mm Hg and 178±8.9 beat/min, respectively). The subsequent LI did not produce any significant changes in AP and HR. The occlusion of coronary artery caused a 30-sec decrease in AP and HR by 20% ($p<0.01$) against the baseline, which corresponds to changes of these indices during myocardial ischemia in unirradiated animals with intact cardiac innervation [5]. The ischemic idioventricular arrhythmias were observed in 67% experiments, where occurrence of both ventricular tachycardia and fibrillation was 50%. These experiments showed that irradiation of the right atrium with a He-Ne laser has no effect on the occurrence of ischemic arrhythmias in the heart with transected stellate ganglion nerves.

Thus, the disturbances in sympathetic traffic to the heart abolishes the protective effect of LI evaluated by the occurrence of ischemic cardiac arrhythmias.

There is evidence that cardiac sympathectomy produces pronounced antiarrhythmic effect during myocardial ischemia [14]. Therefore, in the second series (10 experiments) we made bilateral transection of cardiac branches of the stellate ganglia with subsequent coronary occlusion without LI. The stellectomy led to a decrease in AP and HR by 15.7% ($p<0.05$) compared with the initial values (128±7.9 mm Hg and 165±9.4 beat/min, respectively). On the 30th sec of ischemia, systolic pressure decreased by 21% ($p<0.01$) and HR by 13% ($p<0.01$). In 30% experiments there were severe idioventricular arrhythmias, which was about half the control value. These severe idioventricular disturbances included the following arrhythmic manifestations (Fig. 1, *a*): grouped extrasystoles (10%), ventricular tachycardia (10%), and ventricular fibrillation (20%). Comparison of these data with those obtained in the experiments with intact cardiac innervation points to a profound antiarrhythmic affect of bilateral sympathetic denervation: it decreases the total occurrence of severe idioventricular arrhythmias, including grouped extrasystoles (5-fold, $p<0.05$), ventricular tachycardia (3-fold, $p<0.05$), and ventricular fibrillation (3-fold, $p<0.05$).

Thus, LI of the right atrium after bilateral transection of the stellate ganglion cardiac nerve branches not only abolished the protective effect of stellectomy (as observed under vagal cold block [6]), but also increased the occurrence of arrhythmic episodes in comparison with experiments on unirradiated heart under the same conditions. The increase in the number of ischemic arrhythmias by LI may be caused by an increase in blood catecholamine content [2,4]. Taking into consideration that the majority of LI effects are mediated by opioid peptides which are stored in sympathetic nerves and are capable of inhibiting the activity of catecholamines [11,13,15], one can suggest that this mechanism does not operate in the sympathectomized heart, which makes it possible to observe the arrhythmogenic effect of catecholamines.

The sympathetic influences on the heart are characterized by functional asymmetry: the right stellate ganglion affects predominantly the right half of the heart and the anterior surface of the right atrium, while the left ganglion innervates mostly the left half of the heart, including the basin of the circumflex branch of the left coronary artery [8]. Based on these data, we studied individual effects of the left and right sympathetic nerves on ischemic arrhythmias, as well as their contribution to the protective effect of LI.

First, we studied the occurrence of ischemic arrhythmias without LI after unilateral transection of the cardiac nerve branches running to the heart from the right and left stellate ganglia.

The dextral transection (n=13) decreased AP and HR by, respectively, 5.1% and 10.8% from the baseline values of 147.0±5.1 mm Hg and 171.2±17.0 beat/min (p<0.01). On the 30th sec after occlusion of the left circumflex branch of coronary artery, AP and HR dropped by 20.7% and 20.9% of the initial level (p<0.01). The idioventricular arrhythmias were observed in 85% cats in this series. Ventricular tachycardia and ventricular fibrillation developed in 38% cats (Fig. 1, *b*). In spite of the increase in the occurrence of idioventricular arrhythmias (ventricular tachycardia included) in the cats with dextral transection, there was a 1.5-fold decrease in the occurrence of ventricular fibrillation in comparison with experiments where cardiac innervation was intact.

The sinister transection (n=10) decreased AP by 8.1% of the baseline 133.0±7.4 mm Hg and did not affect HR, which remained at the level of 182.3± 13.0 beat/min. On the 30th sec after occlusion of the left circumflex branch of coronary artery, AP and HR dropped by 19.0% and 2.5% of the initial level (p<0.05). The idioventricular arrhythmias were observed in 50% cats in this series, in which 10% developed ventricular tachycardia and ventricular fibrillation (Fig. 1, *c*).

A comparison of the occurrence of ischemic arrhythmias in the cats with dextral and sinister transection of the cardiac branches of the stellate ganglia shows that the development of severe ischemic arrhythmia is strongly influenced by the sympathetic nerves of the left stellate ganglion that innervates predominantly the ischemic regions. This finding is consistent with published data [9,10,14]. Having revealed the role of left and right stellate ganglia in the genesis of ischemic arrhythmias, we investigated their role in the protective antiarrhythmic effect of LI.

The dextral transection (n=10) decreased AP and HR by, respectively, 3.0% and 12.6% of the baseline values of 146.0±6.2 mm Hg and 188.3±17.0 beat/min (p<0.01). Subsequent LI of the right atrium increased AP by 10% (p<0.05), which surpassed the baseline level, although it did not significantly affect HR. On the 30th sec after occlusion of the left circumflex branch of coronary artery AP exceeded the initial level, while HR was lower by 20% (p<0.05). The idioventricular arrhythmias were observed in all the cats in this series. Ventricular tachycardia and ventricular fibrillation were observed in 50% and 100% cats, respectively (Fig. 1, *b*).

The high level of AP in the cats of this group observed both before ischemia and at the early stages of its development was probably caused by the LI-induced increase in myocardial contractility [1]. Change in the activity of mechanoreceptors in the right atrium is accompanied by changes in sympathetic inflow to the heart and modification of contractility of the left ventricle [7]. Taking into consideration the fact that irradiation of the right atrium in this experimental series was performed with intact left sympathetic nerves, enhancement of ventricular contractility may be related to increased sympathetic activity in these nerves, which innervate the ischemic region and are known to control predominantly the myocardial contractility [8]. Therefore, if LI is performed in the heart with intact sympathetic innervation of ischemic region and with essential sympathectomy of the intact region of the myocardium, it leads to aggravation of myocardial ischemia and to fatal outcome due to irreversible ventricular fibrillation.

In the next series (n=12) we studied the occurrence of ischemic arrhythmias under the effect of LI of the right atrium after transection of the cardiac nerves running from the left stellate ganglion, i.e., after sympathectomy of predominantly ischemic area. The sinister transection decreased AP by 5.8% and did not affect HR relative the baseline levels of 127.0±7.3 mm Hg and 185.5±17.0 beat/mean, respectively. Subsequent LI of the right atrium restored AP to the initial level. At the same time, in

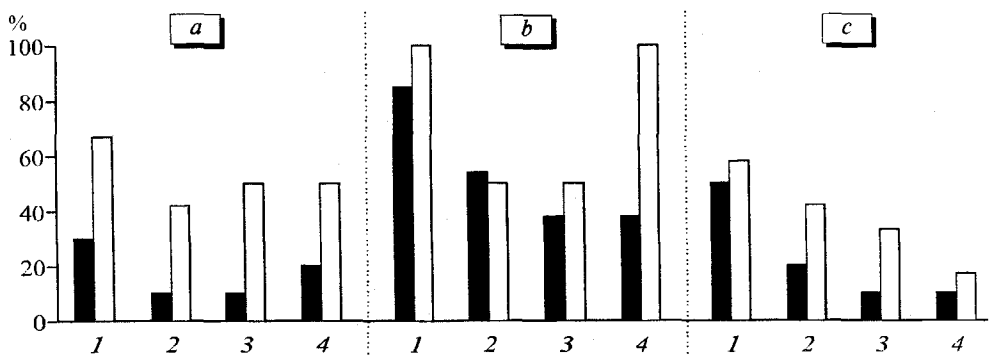

Fig. 1. Development of ischemic arrhythmias against the background of laser irradiation of the right atrium (white bars) and without irradiation (solid bars) under (*a*) bilateral, (*b*) right, and (*c*) left stellectomy (transection of cardiac branches of stellate ganglia). *1*) total number of severe idioventricular arrhythmias; *2*) grouped extrasystoles, *3*) ventricular tachycardia, and *4*) ventricular fibrillation.

contrast to dextral transection experiments, a 30-sec occlusion of the left circumflex branch of the coronary artery decreased AP and HR by, respectively, 19 and 12% from the initial level ($p<0.05$). The idioventricular arrhythmias, including ventricular tachycardia (33%) and ventricular fibrillation (17%) were observed in 58% cats.

Comparison of these data with that obtained in the experiments on unirradiated heart with left stellectomy shows that LI slightly increases the occurrence of ischemic arrhythmias (Fig. 1, *c*). At the same time, similar comparison with the data on dextral transection and subsequent LI indicates that LI performed in the heart with sympathectomized ischemic region decreases the occurrence of arrhythmias (ventricular tachycardia 1.5-fold, ventricular fibrillation 5.9-fold, $p<0.05$) than in the heart with sympathectomized intact region and intact sympathetic innervation of the ischemic area.

In conclusion, the protective effect of LI depends on the activity in sympathetic fibers that innervate predominantly intact (nonischemic) parts of the myocardium. Elimination of their influence by right stellectomy leads to irreversible ventricular fibrillation under preserved sympathetic activity in the left sympathetic nerve, which innervates the ischemic regions of the myocardium. The fact that left stellectomy decreases the occurrence of irreversible fibrillation 2-fold attests to a damaging effect of transmitters to ischemic myocardium. The leading role in this effect belongs to sympathetic activity in the fibers innervating the ischemic regions of the myocardium, since elimination of this influence by sympathectomy significantly decreases the occurrence of irreversible ventricular fibrillation during LI. This finding indicates that the protective effect of LI is possible only in the heart with intact sympathetic traffic to the nonischemic regions in the myocardium, which probably plays a stabilizing role under local ischemic damage to the heart. Our data suggest that endogenous opioid peptides not only participate in the analgesic effect of LI [15], but also mediate its antiarrhythmic action.

REFERENCES

1. E. B. Gel'fgat, R. I. Samedov, Z. N. Kurbanova, *et al.*, *Kardiologiya*, **33**, No. 2, 22-23 (1993).
2. T. N. Zyryanova, V. M. Lavrova, A. T. Pikulev, and I. P. Khrinchenko, *Radiobiologya*, **27**, No. 1, 94-97 (1987).
3. I. M. Korochkin and E. V. Babenko, *Sov. Med.*, No. 3, 3-8 (1990).
4. V. N. Koshelev (Ed.), *Laser in Treatment of Injuries* [in Russian], Saratov (1980).
5. S. D. Mikhailova, T. M. Semushkina, and N. A. Bebyakova, *Kardiologiya*, **31**, No. 1, 13-15 (1991).
6. S. D. Mikhailova, G. I. Storozhakov, S. Yu. Gukova, *et al.*, *Byull. Eksp. Biol. Med.*, **113**, No. 5, 460-461 (1992).
7. B. I. Tkachenko, S. A. Polenov, and A. K. Agnaev, *Cardiovascular Reflexes* [in Russian], Leningrad (1975).
8. V. N. Shvalev, A. A. Sosunov, and G. Guski, *Morphological Principles of Cardiac Innervation* [in Russian], Moscow (1992).
9. M. S. Gardner, S. Kimber, D. E. Johnstone, *et al.*, J. *Cardiovasc. Electrophysiol*, **4**, No. 1, 2-8 (1993).
10. J. Han, P. Garciade Jalon, and G. K. Moe, *Circ. Res.*, **14**, 516-524 (1964).
11. K. Kinouchi, S. Maeda, K. Saito, *et al.*, *Eur. J. Pharmacol.*, **164**, No. 1, 63-68 (1989).
12. M. Manoach, D. Varon, and M. Erez, *Mol. Cell. Biochem.*, **147**, No. 1-2, 181-185 (1995).
13. A. H. Mulder, G. Wardeh, F. Hogenboom, and A. L. Frankhuyzen, *Neuropeptides*, **14**, No. 2, 99-104 (1989).
14. P. J. Schwartz, N. G. Snebold, and A. M. Brown, *Am. J. Cardiol.*, **37**, No. 7, 1034-1040 (1976).
15. D. M. Wedlock and R. A. Shephard, *Psychol. Rep.*, **78**, No. 3, Pt. 1, 727-731 (1996).