EFFECT OF LEUKOTRIENE LTC_4 ON THE CORONARY VASCULAR BED AND MYOCARDIAL CONTRACTILITY

A. A. Moibenko*, Yu. N. Kolchin, V. N. Bulakh, and A. E. Sorochinskii

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Administration of exogenous peptide leukotrienes (LT) causes disturbances of the coronary circulation, weakening of the contractile function of the left ventricle, and disturbances of rhythm and conduction [7-9, 12]. However, we have as yet no sufficiently clear ideas on the character of relations between changes in the coronary blood flow induced by LT, and ischemia and contractility of the myocardium. It has to be pointed out that most studies of the effects of LT on the coronary vascular bed have been undertaken on animals under closed chest and artificial respiration conditions.

The aim of this investigation was to study the effect of intracoronary infusion of LTC_4 and transient regional myocardial ischemia on parameters of the cardiodynamics and hemodynamics and on ultrastructural changes in the endothelium of the coronary vessels in anesthetized dogs with a closed chest.

EXPERIMENTAL METHOD

Experiments were carried out on 10 dogs weighing 16-20 kg, anesthetized with chloralose (0.07 g/kg) and urethane (0.2 g/kg). During the experiments the following parameters were recorded: systemic arterial pressure (SBP), pressure in the left ventricle and its first derivative (dp/dt), the coronary blood flow (CBF) using an electromagnetic flowmeter (Nihon Kohden), and the electrocardiogram (ECG) in three standard leads. The coronary vascular resistance (CVR) was determined by calculation. Parameters of the cardiodynamics and hemodynamics were recorded on a Mingograf-82 automatic jet writer. LTC_4 (from "Sigma" and synthesized in the Institute of Bioorganic Chemistry, Academy of Sciences of the Ukrainian SSR by the method in [4]), identified by reverse-phase HPLC [1], was injected for a period of 5 sec in increasing doses directly into the coronary vascular bed. For this purpose, the circumflex branch of the left coronary artery was catheterized through the right carotid artery [2]. Autoperfusion of the coronary vessel was carried out with the animal's own blood from the right brachial artery. The blood flow was recorded in the extracorporeal part of the perfusion system. Transient regional ischemia of the myocardium was produced by stopping the supply of blood from the brachial artery into the coronary catheter for 10-12 sec. For electron-microscopic investigation the coronary arteries were excized, fixed in glutaraldehyde (2.5%), postfixed in 1% osmic acid solution, dehydrated, and embedded in a mixture of Epon and Araldite. Ultrathin sections were examined in the JEM-100 electron microscope. Morphological investigations were carried out according to L. F. Popovich. The significance of changes in the parameters studied was determined by the method of direct differences.

*Corresponding member of the Academy of Sciences of the Ukrainian SSR.

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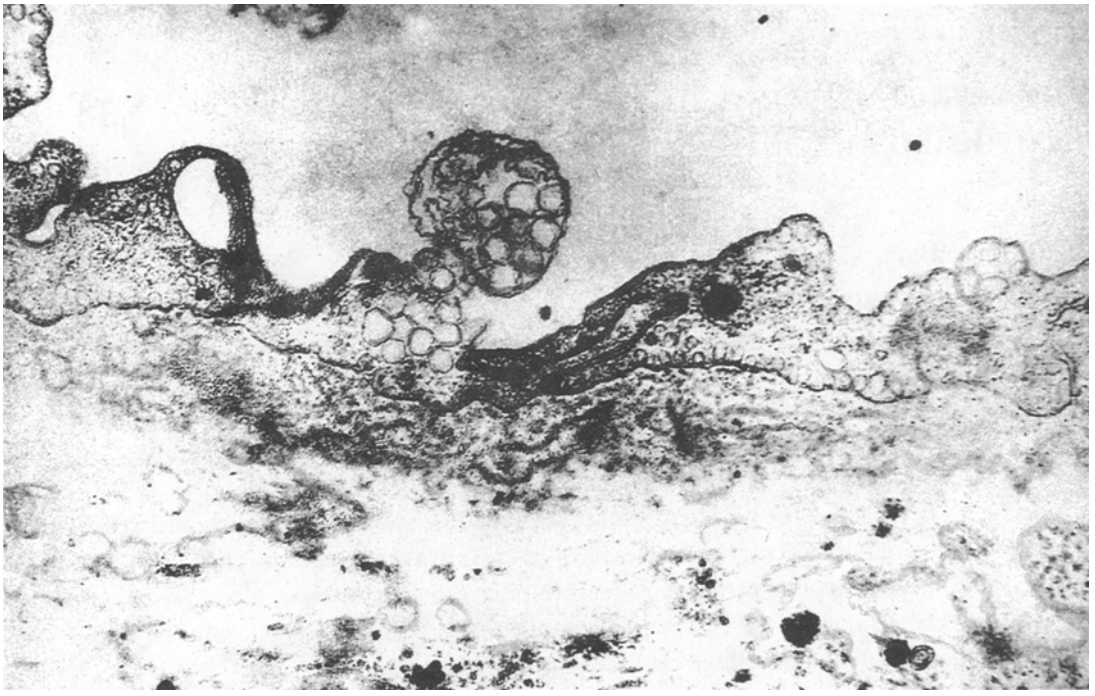

Fig. 1. Changes in cardiodynamics and hemodynamics in anesthetized dogs after intracoronary injection of LTC_4 (μg) and after 10-12 sec of ischemia. Abscissa, dose of LTC_4 injected into the coronary vessel (in μg); ordinate, changes in parameters studied (in per cent of initial values after injection of LTC_4 and ischemia for 10-12 sec). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with original data.

EXPERIMENTAL RESULTS

The blood flow in the circumflex branch of the left coronary artery in the initial stage of these experiments averaged 51.9 ± 7.0 ml/min or 115.3 ± 15.5 ml/min/100 g myocardial tissue, significantly higher than in the corresponding experiments on dogs with an open chest [5, 10]. This could have a definite bearing on the analysis of the results, considering that the intensity of the response of the coronary vessels to LT depends on the magnitude of the initial blood flow [6].

In all experiments, intracoronary injection of LTC_4 was accompanied by a decrease in CBF against a background of a virtually unchanged heart rate. The threshold dose of LTC_4 in these experiments was 0.1-0.3 μg, in agreement with results obtained by other workers [8, 9, 14]. LTC_4 caused a dose-dependent decrease in CBF and an increase in CVR (Fig. 1). Meanwhile SBP, the systolic pressure in the left ventricle (SPLV), and velocity parameters characterizing myocardial contractility, the maximal rate of rise and fall of pressure in the left ventricle (dp/dt max and dp/dt min) fell significantly. An increase in the end-diastolic pressure in the left ventricle (EDPLV) was observed only with doses of 20-40 μg. Reduction of the coronary blood flow began 9-13 sec after the time of injection, reached a maximum 7-10 sec after the beginning of the response, and continued for 1 to 4 min depending on the dose.

After injection of 0.5-1 μg LTC_4 a significant reduction of CBF (by 13.2-22%) was observed, although no signs of myocardial ischemia were present on the ECG. Meanwhile there was a small but significant decrease in the values of the myocardial contractility parameters.

Clearly marked signs of focal myocardial ischemia were discovered in 37% of cases after injection of 2 μg and in 88% of cases after injection of 5 μg LTC_4 by the intracoronary route, as shown by elevation of the ST segment by 0.1-0.15 mV. With these doses the coronary vascular resistance was increased by 49-87% and the coronary blood flow fell by 31-44%.

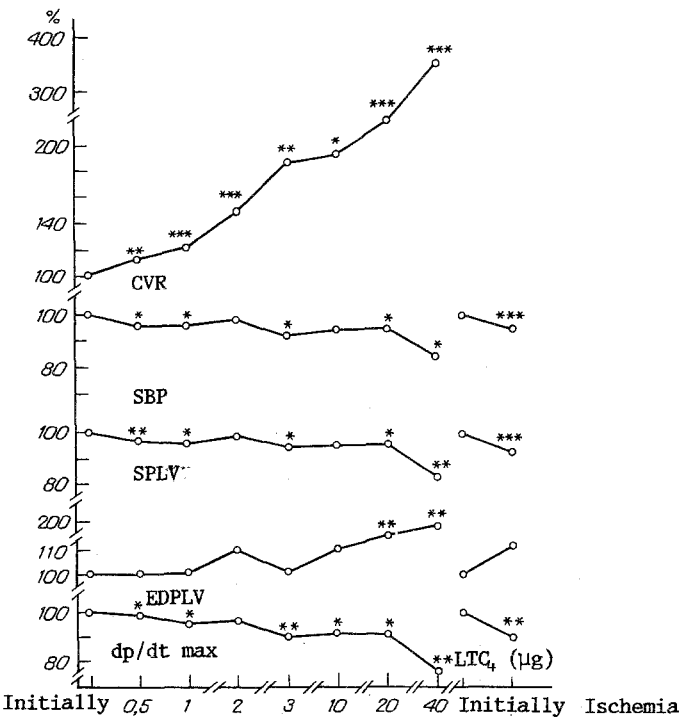

Fig. 2. Ultrastructure of coronary arterial endothelium of dog's heart after injection of LTC_4. Active microvesicular transport on luminal and abdominal surface of endothelium, widening of interendothelial spaces. "Racemose" evagination in region of interendothelial junction, consisting of microvesicles surrounded by a membrane. 10,000×.

With doses of 10-40 μg the pathological changes in the heart were most marked. Besides reduction of the coronary blood flow by 50-78%, in all cases signs of focal myocardial ischemia (elevation of the ST segment by 0.15-0.2 mV), and a marked reduction of myocardial contractility were observed. Complex arhythmias were observed in all experiments, and in two cases they ended with ventricular fibrillation and death of the animals.

The effects of cessation of the blood flow in the circumflex branch of the left coronary artery for 10-12 sec and the maximal effect of LTC_4, occurring between 7 and 10 sec after the beginning of the response, were compared in nine experiments. As Fig. 1 shows, complete cessation of the coronary blood flow was comparable in its consequences with the effect of 5 μg of LTC_4, but the coronary blood flow was reduced by only 41.7%. It can be tentatively suggested that besides reduction of the coronary blood flow and the development of myocardial ischemia, following injection of LTC_4, certain additional factors may also have affected cardiac function.

This hypothesis is supported by the results of electron-microscopic investigations. As will be clear from Fig. 2, after injection of LTC_4 in increasing doses significant changes were observed in the endothelium of the coronary vessels, comparable in character with those in the early stage of immunocytotoxic action on the heart [3]. Besides widening of the interendothelial junctions and activation of microvesicular transport, loosening of the structure of the subendothelial layer was observed with the formation of microvesicles measuring 20-100 nm in diameter, in the form of "racemes," surrounded by a single membrane and projecting into the lumen of the coronary vessel. Ultrastructural changes of this type were not characteristic of myocardial ischemia.

The results are evidence that myocardial ischemia is not a necessary condition for the development of the negative inotropic effects of leukotrienes. It must be assumed that LT may have a direct inhibitory action on cardiac activity, although results obtained by different workers on this question are contradictory [8, 12, 14]. Nevertheless, the possibility of an inhibitory action of leukotrienes on the contractile function of isolated myocardial cells [11, 13], in our opinion is an important argument in support of such a suggestion.

LITERATURE CITED

1. S. V. Galushko, M. Yu. Belik, A. E. Sorochinskii, et al., Bioorg. Khim., No. 7, 252 (1989).
2. A. A. Moibenko, M. M. Povzhitkov, L. A. Grabovskii, and N. P. Kuz'minskii, Kardiologiya, No. 2, 131 (1976).
3. L. F. Popovich, Abstracts of Proceedings of the Second All-Union Symposium on Physiology and Pathophysiology of the Heart and Coronary Circulation [in Russian], Kiev (1987), pp. 132-133.
4. I. Ernest, A. J. Main, and R. Menasse, Tetrahedron Lett., **23**, No. 2, 167 (1982).
5. G. Ertl, V. Fiedler, B. Bauer, et al., J. Cardiovasc. Pharmacol., **8**, No. 5, 1078 (1986).
6. G. Ertl, Eur. Heart J., **8**, 457 (1987).
7. D. Ezra, L. Boyd, G. Feuerstein, et al., Am. J. Cardiol., **51**, No. 8, 1451 (1983).
8. V. Fiedler, J. Cardiovasc. Pharmacol., **3**, 588 (1986).
9. V. Fiedler and T. Abram, Cardiology, **74**, 89 (1987).
10. G. A. Kopia, R. E. Valocik, T. J. Torphy, et al., J. Pharmacol. Exp. Ther., **241**, No. 1, 87 (1987).
11. J. Hattory and R. Levi, Fed. Proc., **43**, No. 4, 992 (1984).
12. F. Michellassi, L. Landa, R. Hill, et al., Science, **217**, 841 (1982).
13. M. Tones, L. Letts, G. Fleetwood, et al., Adv. Myocardiol., **6**, 395 (1985).
14. O. Woodman and G. Dusting, Eur. J. Pharmacol., **86**, No. 1, 125 (1982).