# EFFECT OF CYCLO-OXYGENASE AND LIPOXYGENASE BLOCKADE ON THE DEVELOPMENT OF IMMUNOGENIC SHOCK

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The writer showed previously that, besides reduction of myocardian contractility [1], a decisive role in the development of the shock reaction following immune attack on the heart is played by reduction of the pumping function of the heart due to deposition of blood at the periphery of the vascular bed and subsequent limitation of the venous return of blood to the heart, which are humoral in nature [2, 3]. In recent years, an important role among the humoral mediators of allergic reactions has been ascribed to prostaglandins and leukotrienes, derivatives of the cyclo-oxygenase (CO) and lipoxygenase (LO) pathways of arachidonic acid metabolism [12]. Prostaglandins have been shown to play an essential role in the development of shock states of varied origin, and CO blockade considerably reduces the severity of the observed circulatory disturbances [10]. During immunogenic shock the initial part of the response of blood deposition has been shown to be due to the action of derivatives of the CO pathway [5], whereas the delayed part of the response is due to the action of derivatives of the LO pathway of arachidon in acid metabolism [4].

The aim of the present investigation was to study the role of these metabolites in the development of immunogenic shock by comparing changes in the cardio- and hemodynamics after exposure of dogs to immune factors with and without simultaneous CO and LO blockade, i.e., blockade of prostaglandin and leukotriene synthesis.

## EXPERIMENTAL METHOD

Two series of acute experiments were carried out on 21 mongrel dogs weighing 17-23 kg, anesthetized with chloralose (0.07 g/kg) and urethane (0.03 g/kg). In the experiments of (control) series I, intact dogs were subjected to immune attack, in those of series II (experimental), the dogs were similarly exposed after preliminary CO and LO blockade, by intravenous injection of indomethacin (3 mg/kg) and quercetin (10 mg/kg) [13].

Immune damage to the heart was induced 10-15 min after injection of the blocking agents and changes were observed in the parameters of the cardio- and hemodynamics for 1 h. The immune challenge consisted of injection of 1 ml of a solution of anticardial immune γ-globulin (1 mg/kg) into one branch of the left coronary artery, through a special metal catheter, without opening the chest. The γ-globulin was obtained from anticardial serum taken from rabbits immunized with canine heart tissue and containing anticardial antibodies in a titer of 1:320-1:640 in the complement fixation test. The systemic arterial pressure, central venous pressure, perfusion pressure in the system of the coronary and femoral arteries, the response of the venous bed of the hind limb (by means of an extracorporeal reservoir [6]), the pressure in the left ventricle, its end-diastolic component and first derivatives, the cardiac output and volumes of the left ventricle (by the thermodilution method), and the ECG were recorded. Several parameters (indices of contractility and relaxation, ejection fraction, total peripheral resistance, etc.) were calculated. The results were subjected to statistical analysis.

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TABLE 1. Changes in Parameters of Hemodynamics after Immune Challenge on Dogs without Blockade (control) and after Blockade of CO and LO (experiment)

| Parameter | Series of experiments | Initial data | Time after injection of anticardial antibodies, min | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 15 | 30 | 45 | 60 |
| Systemic arterial pressure, mm Hg | Control | 132±7,9 | 75±5,2* | 69,8±5* | 80±6,7* | 88±6,9* | 76,4±5,7* |
| | Experimental | 157±8 | 157±12** | 158±13** | 155±14** | 161±12** | 162±12** |
| Central venous pressure, mm Hg | Control | 14,7±4 | 5,3±6* | 6,5±5,2* | 7,7±4,7* | 8,7±5,4 | 9,2±6,2 |
| | Experimental | 23±5 | 20±4 | 24±3** | 24±5** | 26±4** | 24±4 |
| Cardiac index, ml/min/m² | Control | 2186±198 | 1241±98* | 1190±101* | 1256±100* | 1353±132* | 1134±168* |
| | Experimental | 2162±253 | 2039±266** | 1714±212*,** | 1690±208* | 1764±196* | 1613±211* |
| Total peripheral resistance, dynes·sec·cm$^{-5}$ | Control | 7121±474 | 6315±691 | 6416±506 | 6509±488 | 6965±631 | 7168±722 |
| | Experimental | 7188±1022 | 7837±1198 | 9204±1407 | 9085±1579 | 8836±1231* | 9077±1217* |
| Perfusion pressure in coronary artery, mm Hg | Control | 153±4,8 | 140±7,8 | 149±8,9 | 156±9,7 | 164±6,7 | 151±6,3 |
| | Experimental | 139±12 | 140±10 | 143±13 | 150±13 | 146±10 | 144±10 |
| Perfusion pressure in femoral artery, mm Hg | Control | 138±4,4 | 114±6,6* | 128±6,6 | 141±6,3 | 136±6,7 | 139±9,7 |
| | Experimental | 126±12 | 135±16 | 131±16 | 134±16 | 145±16* | 153±14* |
| Volume of blood deposited in system of femoral vessels, ml | Control | | 6,6±1,3* | 18,7±3,7* | 17±5,5* | 14,6±5* | 12,2±7,2 |
| | Experimental | | 0,2±0,6** | 0,1±0,9** | 0,2±0,9** | 0,03±0,6** | −1,4±2 |

Legend. Here and in Table 2: *) significance of differences compared with initial data (difference method), **) significance of differences between series.

TABLE 2. Changes in Cardiodynamics after Immune Challenge on Dogs without Blockade (control) and after Blockade of Prostaglandin and Leukotriene Synthesis (experiment)

| Parameter | Series of experiments | Initial data | Time after injection of anticardial antibodies, min | | | | |
|---|---|---|---|---|---|---|---|
| | | | 5 | 15 | 30 | 45 | 60 |
| Pressure in left ventricle, mm Hg | Control | 139±5,1 | 79±5,4* | 82±4,6* | 90±6,9* | 91±6,2* | 88±5,6* |
| | Experimental | 166±7** | 164±12** | 157±12** | 157±15** | 161±11** | 168±12** |
| End-diastolic pressure of left ventricle, mm Hg | Control | 3,3±0,5 | 2,1±0,4* | 2,2±0,5* | 2,6±0,4* | 2,8±0,4 | 3,0±0,3 |
| | Experimental | 2,1±0,5 | 1,8±0,4 | 2,2±0,5 | 2,3±0,7 | 2,0±0,7 | 2,0±0,7 |
| End-diastolic volume of left ventricle, ml | Control | 41,8±4,5 | 37,2±6,6 | 33,1±4,5* | 33,1±3,4* | 39,2±4,4 | 36,8±3,9 |
| | Experimental | 39,2±6,3 | 44,3±5,8* | 39,8±6,3 | 38,4±6,5 | 36,2±5,6 | 36,6±7,8 |
| End-systolic volume of left ventricle, ml | Control | 28,7±3,7 | 27,4±5,5 | 25±3,5 | 24±2,5 | 30,2±3,4 | 27,9±3,0 |
| | Experimental | 28,8±5,8 | 34,2±5,1* | 31±5,7 | 29,6±5,9 | 27±5,0 | 28,6±7,4 |
| Ejection fraction of left ventricle, % | Control | 34,2±1,8 | 30,1±1,7 | 28±1,8* | 29,9±1,7 | 24,2±1,8* | 26,2±1,6* |
| | Experimental | 28,8±3,1 | 23,8±2,8* | 23,9±3,1 | 25,1±3,2 | 26,8±2,9 | 25,8±3,4 |
| $dp/dt_{max}$ of left ventricle, mm Hg/sec | Control | 3217±552 | 1488±267* | 1207±147* | 1676±230* | 1896±287* | 2008±557 |
| | Experimental | 3988±240 | 3849±266** | 3769±253**,* | 3957±331** | 3895±312** | 4085±286** |
| $dp/dt_{min}$ of left ventricle, mm Hg/sec | Control | 3380±418 | 1799±233* | 1773±212* | 1856±256* | 1946±298* | 1780±267* |
| | Experimental | 3458±225 | 3508±284** | 3242±315** | 3354±357** | 3394±208** | 3512±278** |
| Index of contractility, sec$^{-1}$ | Control | 44,9±4,5 | 37,8±3,5* | 39,5±4,1* | 37,1±3,6* | 37,6±4,5* | 36,8±4,7* |
| | Experimental | 39±3,3 | 37±2,6 | 37±3 | 38±2,9* | 37±3,3* | 37±2,3 |
| Heart rate, beats/min | Control | 179±10,2 | 167±10,2 | 166±8,2 | 174±8,5 | 176±9,5 | 183±9,6 |
| | Experimental | 185±11 | 180±12 | 175±9 | 175±9 | 175±11 | 180±11 |

## EXPERIMENTAL RESULTS

Blockage of biosynthesis of arachidonic acid derivatives (prostaglandins and leukotrienes) significantly reduced the changes in several parameters of the hemodynamics after immune challenge (Table 1). Several other parameters, however, were virtually unchanged. For instance, the arterial blood pressure of the animals of group II was virtually unchanged whereas in the control series its level in the first minutes after injection of anticardial antibodies reached shock values. Differences between the groups for changes in arterial pressure were highly significant ($p<0.001$).

This significant difference was due to the fact that in animals of the experimental series the response of blood deposition was virtually absent (Table 1), whereas in the control animals, the volume of blood deposited in the skin and muscles after 15 min reached 18.7 ± 3.7 ml/kg. The absence of this response of blood deposition in animals of the experimental series did not lead to any changes indicating restriction of the venous return of blood to the heart, such as were observed in dogs of the control series. After blockade, no significant change in the venous pressure and the end-diastolic pressure in the left ventricle could be observed, but the end-diastolic volume of the left ventricle actually increased significantly during the first minutes of the response (Table 2).

The response of blood deposition and subsequent limitation of the venous return and lowering of the cardiac output and arterial pressure, characteristic of the response to immune challenge, were evidently largely due to the action of endogenously formed prostaglandins and leukotrienes on the venous parts of the peripheral vascular bed.

However, prevention of the blood deposition response and subsequent limitations of the venous return to the heart, did not completely prevent the decrease in cardiac output. The sharp reduction of cardiac ejection during the first minutes of the reaction, characteristic of animals of the control series, was absent after premedication with indomethacin and quercetin. Starting with the 15th minute of the response, however, a gradual decrease of the cardiac index was observed, and after 60 min it was 25% below the initial value. This decrease in cardiac ejection in the animals of this group was evidently due to a decrease in contractility of the myocardium due to the damaging effect of the immune factors. This is shown by ECG changes, evidence of the development of focal myocardial damage, and also the significant decrease in the parameters of myocardial contractility at certain times of observation. In the first minutes of the response the ejection fraction of the left ventricle was significantly reduced, after 15 min the maximal rate of rise of the intraventricular pressure was significantly reduced, and after 45 min, the index of myocardial contractility was similarly reduced (Table 2). However, reduction of the cardiac output in animals of the experimental series was compensated by an increase in vascular resistance, and for that reason it did not cause the systemic arterial pressure to fall. Evidence of the increase in vascular resistance was given by a significant increase of the perfusion pressure of the femoral artery and of the total peripheral resistance after 45-60 min.

The protective action of blockade of arachidonic acid metabolizm is thus evidently due mainly to prevention of blood deposition induced by arachidonic acid metabolites, namely prostaglandins and leukotrienes. Immune challenge may be accompanied by removal of arachidonic acid from the cell membranes by the last components of the activated complement system [7], by activation of the LO pathway of its metabolism by anaphylatoxin [8], and by secretion of prostaglandins and leukotrienes into the circulatory system.

Some prostaglandins can cause venous dilatation in dogs [9, 11]. The development of systemic hypotension after injection of leukotriene also is accompanied by changes indicating limitation of the venous return of blood to the heart [14]. It must also be recalled that prostaglandins and leukotrienes can significantly disturb vascular permeability, and that the extravasation of blood which develops under those circumstances can cause the venous outflow to fall. Our own results agree with data in the literature, indicating that arachidonic acid derivatives can induce blood deposition, followed by limitation of the venous return of blood to the heart and the development of a shock response.

Preliminary blockade of biosynthesis of arachidonic acid derivatives thus prevents the development of immunogenic shock. This effect is due to complete inhibition of the retention of blood at the periphery of the vascular bed, subsequent limitation of the venous return of the blood to the heart and a sudden decrease in cardiac ejection. Arachidonic acid metabolites, which dilate the venous compartment of the vascular bed, play the decisive role in the develop-

ment of immunogenic shock. The use of blockers of prostaglandin and leukotriene synthesis may be an effective means of preventing the development of immunogenic shock.

## LITERATURE CITED


1. N. N. Gorev, V. F. Sagach, A. P. Zaichenko, et al., Kardiologiya, No. 2, 11 (1973).
2. A. A. Moibenko and V. F. Sagach, Fiziol. Zh. SSSR, No. 1, 73 (1981).
3. V. F. Sagach, Byull. Éksp. Biol. Med., No. 6, 533 (1979).
4. V. F. Sagach, Byull. Éksp. Biol. Med., No. 2, 151 (1986).
5. V. F. Sagach, Farmakol. Toksikol., No. 3, 104 (1987).
6. V. I. Tkachenko, The Venous Circulation [in Russian], Leningrad (1979).
7. M. Betz and G. M. Hänsch, Immunobiology, 166, 473 (1984).
8. R. M. Claney, C. A. Dahinden, and T. E. Hugli, Folia Allergol., 32, 311 (1985).
9. T. G. Fulghum, I. P. DiMarco, E. W. Supple, et al., J. Clin. Invest., 76, 999 (1985).
10. A. M. Lefer, Fed. Proc., 44, 275 (1985).
11. P. M. Vanhoutte and W. I. Janssens, Microvasc. Res., 16, 196 (1978).
12. S. G. Wasserman, J. Allergy, 72, 101 (1983).
12. T. Yoshimoto, M. Furukawa, S. Yamamoto, et al., Biochim. Biophys. Res. Commun., 116, 612 (1983).
14. Z. Zukowska-Grojec, M. A. Bayorh, et al., Circulation, 68, Suppl. 111, 332 (1983).