# CHANGES IN THE MICROCIRCULATION DURING POISONING BY ORGANOPHOSPHOROUS CHOLINESTERASE INHIBITORS

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A quantitative study of the microcirculation based on certain indices of the gas exchange and acid–base balance of the blood was carried out in rats and rabbits during poisoning by compound GA-70, an organophosphorus cholinesterase inhibitor with peripheral action. Comparison of the findings shows that a disturbance of the microcirculation plays the leading role in the development of hypoxia during GA-70 poisoning.

KEY WORDS: microcirculation; gas exchange; acid–base balance; organophosphorus cholinesterase inhibitors.

Severe hypoxia develops in acute poisoning with organophosphorus cholinesterase inhibitors (OPI). This has been attributed mainly to respiratory disturbances [3, 4], although other workers ascribe greater importance to circulatory disorders [5, 6].

To determine the role of circulatory hypoxia in the pathogenesis of OPI poisoning the velocity of the capillary blood flow was studied and compared with some indices of the oxygen supply to the body.

## EXPERIMENTAL METHOD

Experiments were carried out on rabbits (2.5-3 kg) and albino rats (180-200 g). The degree of hypoxia was estimated from the $O_2$ consumption, the $CO_2$ excretion, and data for the acid–base balance (ABB) of the blood. The gas exchange was investigated with the "Spirolite" instrument. ABB and the partial oxygen pressure ($pO_2$) in the venous blood (from the femoral vein) of the rabbits was investigated by the micro-Astrup apparatus (model ABC-1). Values of the partial $CO_2$ pressure ($pCO_2$), standard bicarbonate (SB), buffer bases (BB), and buffer base shift (BBS) were calculated from the Sigaard–Andersen nomogram. The oxygen saturation of the arterial blood ($HbO_2$) was determined on the oxyhemometer included in the outfit of the instrument. The velocity of the blood flow was measured and the capillaries photographed with the MFN-12 camera mounted on the base of the MBR-1A microscope, using a 10× ocular and 9× objective. The velocity of the blood flow was determined by a method based on the stroboscopic effect, i.e., the illusory stopping of the blood flow when the rate of movement of the blood cells in the vessel was equal to the frequency of the flashes [5]. To obtain a smooth change in flash frequency, the ST-5 strobotachometer was used. The mesoappendix part of the mesentery, exteriorized under pentobarbital anesthesia, was placed on the light guide of a special Plexiglas chamber, irrigated with a mixture of Ringer–Locke solution and 3% dextran solution, warmed to 37°C. During irrigation with fluid (pH 7.2-7.8) the capillary circulation of the intact animals was unchanged for 3 h or more. The capillaries of the mesentery were photographed by the "Praktika" camera using the IFK-120 flash lamp.

GA-70 ($C_3H_7O(CH_3)P(O)SC_2H_4SC_2H_5 \times CH_3SO_4$), a charged OPI with peripheral action, was injected into the animals. The synthesis and anticholinesterase properties of this compound were described previously [2, 9].

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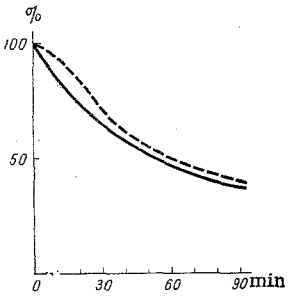


Fig. 1

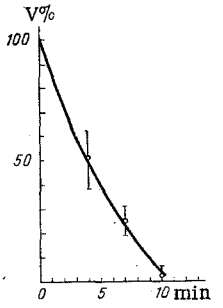


Fig. 2

Fig. 1. Changes in oxygen uptake and $CO_2$ excretion (in % of initial levels) in experimental rabbit during poisoning with GA-70 in a dose of 0.1 mg/kg ($1 \cdot 10^{-4}$ M) intramuscularly. Continuous line) $CO_2$ excretion; broken line) $O_2$ uptake.

Fig. 2. Change in velocity of blood flow (in % of normal) in rats poisoned with GA-70 in a dose of 0.1 ml/100 g ($2 \cdot 10^{-5}$ M).

TABLE 1. Changes in Partial Pressure of Oxygen ($pO_2$) in Venous Blood, Oxygen Saturation of Arterial Blood ($HbO_2$), and ABB Values in Experimental Rabbit 10-90 min after Intramuscular Injection of GA-70 in a Dose of 0.1 mg/kg ($1 \cdot 10^{-4}$ M)

| Index | Initial level | Times after injection of GA-70 | | | | |
|---|---|---|---|---|---|---|
| | | 10 min | 20 min | 30 min | 60 min | 90 min |
| $PO_2$ (in mm Hg) | 48 | 45 | 40 | 35 | 37 | 35 |
| $HbO_2$ (in %) | 96 | 95 | 97 | 95 | 94 | 92 |
| pH | 7,4 | 7,3 | 7,22 | 7,1 | 6,98 | 6,72 |
| $PCO_2$ | 32 | 38 | 41 | 48 | 48 | — |
| SB | 21 | 18,5 | 16 | 13 | 10 | <6 |
| BB | 45 | 41 | 37 | 33 | 26 | — |
| BBS | —4 | —75 | —11 | —16 | —20 | >>—22 |

## EXPERIMENTAL RESULTS AND DISCUSSION

Cholinesterase activity of the blood was inhibited by 100% 10-12 min after intramuscular injection of GA-70 in a dose of $LD_{90}$. The character of the change in gas exchange in the rats and rabbits during GA-70 poisoning was identical. Typical curves of the change in gas exchange in one of the experimental rabbits are given in Fig. 1: The decrease in $CO_2$ elimination took place parallel to the decrease in $O_2$ consumption. $CO_2$ excretion during the development of poisoning changed in the same way as in animals lifted to an altitude of 8-10 km. Changes in pH of the venous blood, $pO_2$ in the arterial blood, and the ABB values (Table 1) pointed to the development of marked oxygen insufficiency in the poisoned rabbits. However, the oxygen saturation of the arterial blood was practically unchanged during the development of poisoning. This fact can be understood on the assumption that the developing hypoxia was mainly circulatory in character, for the decrease in $O_2$ consumption because of bronchospasm ought to have led to arterial hypoxemia.

In fact, direct measurement showed a sharp decrease in the velocity of the blood flow in the capillaries of the mesoappendix of the poisoned rats practically immediately after the beginning of poisoning (during the first 2-3 min after intramuscular injection of the OPI (Fig. 2). The linear velocity of the blood flow in the capillaries and venules (in the intact animals) was 400-800 $\mu$/sec, falling 10 min after poisoning began to 10-20 $\mu$/sec; in some animals the blood flow stopped completely at times and often a to-and-fro movement of the blood was observed.* This pattern remained until the animals died, which was 25-30 min after injection of the poison.

*The linear velocity of the blood flow was obtained by multiplying the mean distance between the centers of neighboring erythrocytes in the capillary (about 10 $\mu$) by the frequency of flashes coinciding with the velocity of displacement of the blood cells.

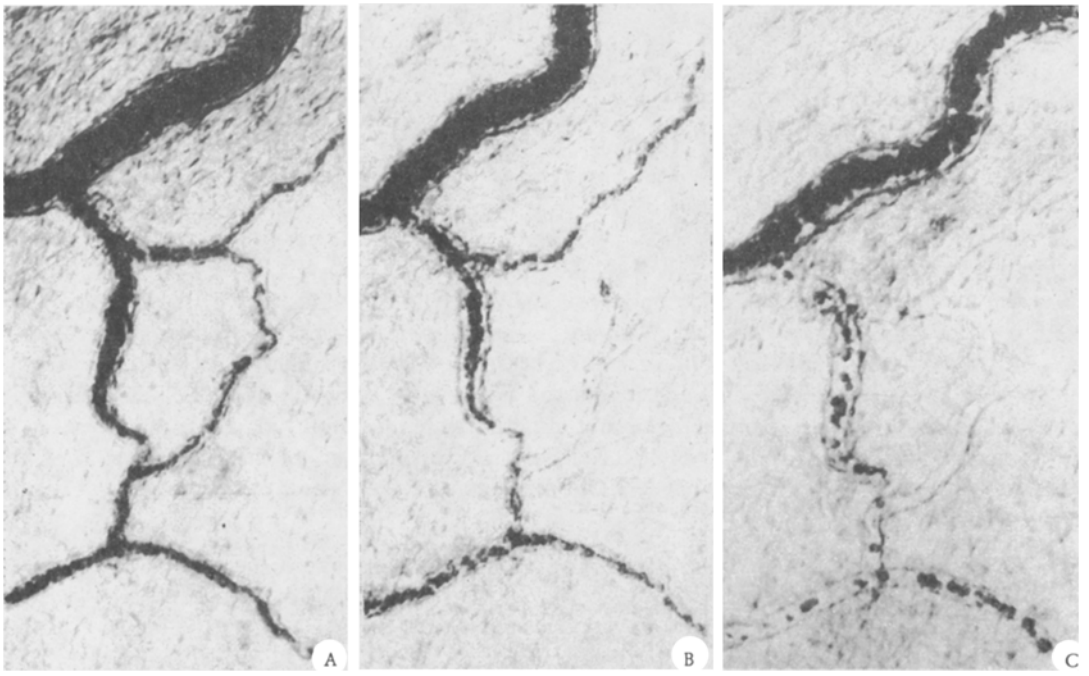


Fig. 3. Changes in microcirculation in vessels of mesoappendix of a rat poisoned with GA-70: a) before poisoning, b) 5 min after poisoning, c) 10 min after poisoning.

Part of the vascular network of the rat mesentery before poisoning is shown in Fig. 3a. The blood flow in all vessels was linear and axial, and the blood cells were distributed uniformly in the blood stream. However, 5 min after injection of the poison, the laminar blood flow disappeared, and aggregates of erythrocytes and capillaries containing only plasma and no erythrocytes were observed (Fig. 3b). During the development of poisoning these changes increased in severity (Fig. 3c), and they evidently led to impairment of tissue oxygenation. Since the microcirculation in the mesentery adequately reflects the state of the peripheral blood flow in other organs [8], the results can be extrapolated to the body as a whole.

Comparison of the results of an investigation of the microcirculation, the gas exchange, and the acid base balance thus shows that disturbance of the microcirculation in fact plays a leading role in the development of hypoxia in GA-70 poisoning. The velocity of the blood in the capillaries is known to depend on various parameters, many of which cannot yet be directly measured [10]. Since the disturbance of the microcirculation in these experiments took place at times when the arterial blood pressure and the diameter of the vessels were both virtually unchanged, it can be concluded that this disturbance was mainly due to a change in the properties of the circulating blood. The rapid inhibition of the blood cholinesterase after injection of the poison suggests that the OPI is bound with certain components of the blood, and possibly modifies their physicochemical properties. On the other hand, the ability of some OPI to undergo selective adsorption on the surface of the capillary endothelium [1] means that the direct effect of the poison on the structure of the capillary wall cannot be ruled out.

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