# DISTURBANCE OF CARDIAC CONTRACTILITY IN CHRONIC HEMOLYTIC ANEMIA AND ITS PREVENTION

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KEY WORDS: anemia; myocardium; lipid peroxidation.

Damage to structures of heart muscle is observed in patients with chronic anemias [1, 9, 13] and, after a long period of compensation, signs of heart failure frequently develop [6, 10]. However, the mechanism by which myocardial damage remains compensated for a long time, the pathogenesis of these lesions and, finally, possible ways of preventing them have not hitherto been studied. At the same time, it has been shown that accumulation of lipofuscin, the end-product of lipid peroxidation (LPO), is regularly observed in the myocardium of animals [11] and various organs of human patients [7] with chronic anemia, and these changes are accompanied by a considerable increase in the coronary blood flow [2, 3, 5]. On this basis the writers postulated that activation of LPO plays a role in damage to the structures and disturbance of the function of heart muscle in chronic anemia. An increase in the coronary blood flow may be an important factor in the compensation of these injuries, and one measure which could prevent anemic myocardial damage may be the administration of LPO inhibitors (antioxidants).

The object of this investigation was to test this hypothesis by assessing the contractile function of the isolated heart of animals with chronic hemolytic anemia under conditions of spontaneous (i.e., known to be increased) coronary blood flow, when the coronary blood flow was reduced to the control level (i.e., when this compensatory factor was inactivated), and finally, when in the course of development of anemia, the animals were given the antioxidant ionol.

## EXPERIMENTAL METHOD

Experiments were carried out on 44 male Wistar rats weighing 200-300 g, divided into five groups: 1) control, 2) ionol + control, 3) hemolytic anemia, 4) hemolytic anemia followed by "normalization" of the coronary blood flow, and 5) ionol + hemolytic anemia followed by "normalization" of the coronary flow. Anemia was induced by injection of an aqueous solution of phenylhydrazine hydrochloride subcutaneously in a dose of 70 mg/kg on alternate days. Control animals received the equivalent volume of physiological saline. The animals were killed 1 month after their blood hemoglobin level had been reduced to an average of 7.2 ± 0.2 g% compared with 16.7 ± 0.4 g% in the control. Ionol was given to the control animals and to animals with hemolytic anemia in accordance with the same scheme: daily, intraperitoneally, in a dose of 20 mg/kg for 5 days before the beginning of injections of phenylhydrazine or physiological saline, and simultaneously with those injections for 28 days. Cardiac contractility was studied by the method of Fallen et al. [4].

## EXPERIMENTAL RESULTS

The following basic conclusions can be drawn from the results. In the isolated hearts of animals with chronic hemolytic anemia the coronary flow was increased by 2.5 times compared with the control ($P < 0.001$) with an equal perfusion pressure in the aorta, namely 76 cm water. Under these conditions the pressure developed by the left ventricle in the animals with hemolytic anemia did not differ significantly from the control. The velocity of contraction and relaxation was reduced by one third and the intensity of functioning of struc-

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TABLE 1. Disturbances of Contractility of Isolated Heart of Rats with Hemolytic Anemia and with Spontaneous and Normalized Coronary Blood Flow and Prevention of These Disturbances by the Antioxidant Ionol

| Parameter | Series of experiments | Spontaneous coronary blood flow | Normalized coronary blood flow | Hypoxia, 20 min | Reoxygenation, 5 min |
|---|---|---|---|---|---|
| Coronary blood flow, ml/min | 1. Control (14) | 9,0±0,4 | 8,9±0,5 | 6,4±0,3 | 8,6±1,2 |
| | 2. Ionol + control (7) | 10,1±0,5 | 10,3±0,3 | 8,8±0,2 | 9,5±0,7 |
| | 3. Anemia (7) | 23,1±1,1 | 23,0±0,8 | 21,4±2,2 | 23,3±2,0 |
| | 4. Anemia followed by normalization of coronary blood flow (8) | 24,3±1,2 | 8,8±0,4 | 6,2±0,2 | 8,3±1,2 |
| | 5. Ionol + anemia followed by normalization of coronary blood flow (8) | 16,2±1,5<br>$P_{1-3}<0,001$<br>$P_{1-2}$ n.d.<br>$P_{1-5}<0,05$ | 8,6±0,3 | 8,1±0,3<br>$P_{1-3}<0,001$ | 9,2±0,6 |
| Pressure developed, mm Hg | 1. Control | 104,3±8,7 | 102,3±0,5 | 28,4±2,8 | 81,4±2,6 |
| | 2. Ionol + control | 105,4±4,2 | 106,4±0,3 | 34,8±4,1 | 87,1±3,3 |
| | 3. Anemia | 96,8±7,0 | 95,6±6,0 | 46,0±4,5 | 79,0±6,5 |
| | 4. Anemia followed by normalization of coronary blood flow | 102,5±5,0 | 66,4±2,1 | 23,0±4,1 | 62,8±3,1 |
| | 5. Ionol + anemia followed by normalization of coronary blood flow | 98,5±6,3<br>$P_{1-3}$ n.d.<br>$P_{1-2}$ n.d.<br>$P_{4-5}$ n.d. | 93,6±5,3<br>$P_{3-5}$ n.d. | 32,0±3,2<br>$P_{1-3}<0,05$<br>$P_{1-4}>0,3$ | 80,1±4,7 |
| IFS, mm Hg | 1. Control | 19,6±1,5 | 19,5±0,9 | 5,4±0,8 | 14,9±1,8 |
| | 2. Ionol + control | 19,2±0,9 | 19,1±0,7 | 6,1±0,5 | 15,4±0,9 |
| | 3. Anemia | 13,5±1,2 | 13,6±0,9 | 6,4±1,0 | 11,8±2,0 |
| | 4. Anemia followed by normalization of coronary blood flow | 15,2±1,1 | 9,8±0,8 | 3,4±0,4 | 9,3±0,8 |
| | 5. Ionol + anemia followed by normalization of coronary blood flow | 15,4±1,6<br>$P_{1-3}<0,05$<br>$P_{1-2}$ n.d.<br>$P_{4-5}$ n.d. | 14,3±0,9<br>$P_{3-5}$ n.d. | 4,9±0,6<br>$P_{1-3}$ n.d.<br>$P_{1-4}<0,05$ | 12,9±1,2 |
| Rate of contraction, mm Hg | 1. Control | 2250±147 | 2245±123 | 575±47 | 1548±172 |
| | 2. Ionol + control | 2541±151 | 2640±140 | 680±58 | 1910±181 |
| | 3. Anemia | 1525±100 | 1574±95 | 837±81 | 1775±250 |
| | 4. Anemia followed by normalization of coronary blood flow | 1640±132 | 970±86 | 311±41 | 920±78 |
| | 5. Ionol + anemia followed by normalization of coronary blood flow | 1810±151<br>$P_{1-3}<0,05$<br>$P_{1-2}$ n.d.<br>$P_{4-5}$ n.d. | 1776±141<br>$P_{3-5}>0,2$ | 553±70<br>$P_{1-3}<0,01$<br>$P_{1-4}<0,05$ | 1890±62 |
| Rate of relaxation, mm Hg | 1. Control | 1557±98 | 1552±75 | 311±30 | 768±80 |
| | 2. Ionol + control | 1748±109 | 1762±100 | 390±25 | 870±74 |
| | 3. Anemia | 1125±50 | 1136±50 | 500±62 | 775±85 |
| | 4. Anemia followed by normalization of coronary blood flow | 1040±82 | 540±38 | 201±24 | 495±51 |
| | 5. Ionol + anemia followed by normalization of coronary blood flow | 1240±101<br>$P_{1-3}<0,005$<br>$P_{1-2}$ n.d.<br>$P_{4-5}$ 0,1 | 1133±75<br>$P_{3-5}$ n.d. | 303±49<br>$P_{1-3}<0,05$<br>$P_{1-4}<0,05$ | 890±68 |

Legend. n.d.) Not determined.

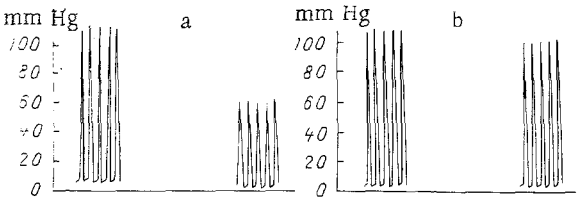


Fig. 1. Effect of "normalization" of coronary blood flow on pressure developed by left ventricle in animals with hemolytic anemia not receiving (a) and receiving (b) a course of antioxidant therapy. a: Left — spontaneous coronary flow 22.5 ml/min; right — coronary flow reduced to 8.6 ml/min; b: left — spontaneous coronary flow 15.2 ml/min; right — coronary flow reduced to 8.8 ml/min.

tures (IFS) by 25%. The last change was due to hypertrophy of the left ventricle, the increase in the dry weight of which was about the same as the decrease in IFS. Since hypertrophy of the heart and an increase in the coronary blood flow are quite familiar in anemia [2, 3, 5], the principal finding in this case is that, when the coronary blood flow was increased, disturbances of cardiac contractility in the anemic animals were significant ($P < 0.05$) but comparatively small. That is why in these experiments on animals stable compensation could be preserved and heart failure was not observed.

The hearts of animals with hemolytic anemia were much more resistant to hypoxia than the hearts of the control rats. As Table 1 shows, at the 20th minute of hypoxia the developed pressure and the rates of contraction and relaxation of the isolated hearts of the anemic animals with the spontaneous coronary blood flow were about 1.5 times greater than in the hearts of the control rats. Thus, under conditions of the spontaneous (definitely increased) coronary blood flow the hearts of animals with hemolytic anemia exhibit comparatively mild depression of contractility under aerobic conditions and their resistance to hypoxia is increased.

If the increased coronary blood flow in the hearts of animals with hemolytic anemia was reduced by lowering the perfusion pressure in the aorta to the level observed in the hearts of control animals, i.e., from 24.3 to 8.8 ml/min, a catastrophic depression of cardiac contractility developed. This was shown by the fact that the developed pressure was reduced by one third, IFS and the rate of contraction were reduced by 40% and, finally, the rate of relaxation suffered the greatest decrease, namely by about half. Moreover, normalization of the coronary blood flow in the hearts of the anemic rats caused their resistance to hypoxia to be, not increased but, on the contrary, reduced compared with the control. In fact, under hypoxic conditions the value of IFS, the rate of contraction, and the rate of relaxation were about one third less than in the control rats. There is thus no doubt that maintenance of a considerably increased coronary blood flow in the intact animal with anemia [2, 9] and, correspondingly, the increase in coronary blood flow demonstrated in the present experiments in isolated hearts, is a factor which compensates for injuries to the heart muscle arising in anemia [1, 8, 12], and which prevents depression of the contractile function and leads to a considerable increase in resistance to hypoxia.

Injection of ionol had no effect on contractility or the coronary blood flow in the control animals and had no significant effect on the contractile function of the heart muscle of animals with hemolytic anemia, with the spontaneous (i.e., compensatorily increased) coronary blood flow. Meanwhile the LPO inhibitor led to the appearance of three important shifts in the hearts of the anemic animals. First, maintenance of near-normal contractility of the hearts of the anemic animals was possible without a 2.5-fold increase in the coronary blood flow; the actual increase in the coronary blood flow was only 80% ($P < 0.05$). It is thus very probable that anemic injuries to the myocardium, which this shift compensated, were less marked under the influence of ionol. Second, depression of contractility in the hearts of the anemic animals receiving ionol, which usually develops in response to a decrease in the coronary blood flow to the control level, did not take place and, consequently, the antioxidant prevented disturbance of the contractile function of the heart under condi-

tions of a "normalized" coronary blood flow. These situations can be observed if the data in Fig. 1 are compared. Third and last, preliminary injection of ionol abolished the decrease in resistance to hypoxia compared with the control described above, and which was observed in the myocardium of animals with hemolytic anemia on normalization of their coronary blood flow. This can most likely be explained on the grounds that ionol prevented injuries to the myocardium which caused the fall in its resistance to hypoxia in hemolytic anemia. This protective effect of the LPO inhibitor is evidence in support of the important role of hyperactivation of LPO in the pathogenesis of myocardial damage in hemolytic anemias and it opens up prospects for the use of antioxidants in the combined treatment of disturbances of cardiac function in patients with anemias.

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# MECHANISMS OF DISTURBANCE OF RHEOLOGIC PROPERTIES OF THE BLOOD AFTER PROLONGED CLINICAL DEATH FROM ACUTE BLOOD LOSS


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The "increased viscosity syndrome" or "syndrome of hemorheologic disturbances" [1, 5-7, 9], observed in various pathological states, is based on increased viscosity of the blood which may be connected with changes in the hematocrit index and concentrations of protein and fibrinogen in the plasma, disturbance of hemostasis and of the acid–base balance of the blood, and also with changes in the morphological and functional state of the erythrocyte membranes. An increase in blood viscosity has also been observed in postresuscitation states [2, 4, 5], but the leading causes of this change in the early postresuscitation period are not yet sufficiently clear.

The object of this investigation was a comprehensive study of several factors affecting blood viscosity in the early period after resuscitation from prolonged clinical death from acute blood loss.

## EXPERIMENTAL METHOD

Acute and chronic experiments were carried out on 22 anesthetized (trimeperidine 6-8 mg/kg, pentobarbital 10-15 mg/kg) mongrel dogs weighing 10-17 kg. Clinical death from acute


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