# EFFECT OF GANGLIOLYTICS AND ETHIRONE ON THE CIRCULATION IN EXPERIMENTAL OLIGEMIC SHOCK

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Experiments on dogs showed that in oligemic shock if the reinfusion of blood is accompanied by procedures with the opposite action on vascular tone, by administration of gangliolytics (azamethonium bromide) and ethirone, the vascular resistance is reduced, the minute blood volume is increased, and the cardiovascular system is more easily brought out of its hypodynamic state, thereby ensuring a more complete elimination of the sequelae of shock.

In severe oligemic shock transfusion therapy does not always restore the normal systemic blood flow, and its combination with both vascoconstrictor and vasodilator agents is ineffective [8-11].

It was decided to supplement blood transfusion in the treatment of shock by simultaneous and opposite pharmacological action on vascular tone in order to increase the venous return to the heart, as reflected in the minute volume of the circulation [6]. Tests were made of the vasodilator action of gangliolytics [2] and the vasoconstrictor effect of isothiuronium compounds (ethirone), which raise the arterial pressure after ganglionic block and do not excite the adrenergic systems [1].

## EXPERIMENTAL METHOD

Experiments were carried out on 28 dogs weighing from 12 to 23 kg. In 9 experiments the simultaneous effect of gangliolytics (hexamethonium or azamethonium bromide) and ethirone on the hemodynamics of the intact organism was studied. In 19 other dogs, which were in a state of uncompensated oligemic shock through loss of about 40% of the original blood volume, the effectiveness of resuscitation measures was investigated. In 10 animals with a mean body weight of 13.4±1.6 kg (body surface area 0.62±0.06 $m^2$) and a blood loss of 36.5±2.5 ml/kg (780±33.6 ml/$m^2$) shock treatment consisted of reinfusion of the blood. In 9 dogs with a mean body weight of 16±2 kg (body surface area 0.7±0.07 $m^2$) and a blood loss of 39.2±2.7 ml/kg (890±18.2 ml/$m^2$), besides reinfusion of the blood, resuscitation also included the simultaneous administration of azamethonium bromide and ethirone (1 mg/kg). The principal parameters of the circulation were determined by the dye dilution (T-1824) method [6, 7] and by catheterization of the great vessels and heart [5]. The dilution curve of the dye, which was injected into the right atrium or pulmonary artery, was recorded by means of a type 0-36 oxyhemograph and a transparent cell joining the femoral vessels. In some experiments the principal parameters of water and mineral metabolism [3] and acid-base balance [4] were studied.

## EXPERIMENTAL RESULTS AND DISCUSSION

Investigation of the combined effect of gangliolytics and isothiuronium compounds in intact dogs showed that minimal changes in arterial and central venous pressures took place after administration of various doses of azamethonium and ethirone starting from 1 to 5 mg/kg. When hexamethionium was used,

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TABLE 1. Changes in Hemodynamics during Treatment of Oligemic Shock by Reinfusion of Blood Combined with Administration of Azamethonium Bromide and Ethirone

| Index | Control group | | | Experimental group | | | P for groups with shock | P for groups after treatment |
|---|---|---|---|---|---|---|---|---|
| | number of observations | shock | treatment | number of observations | shock | treatment | | |
| Heart rate, beats/min | 10 | 165±5,4 | 139±9,5 | 9 | 160±4 | 135±3 | 0,7 | 0,9 |
| Mean pressure in femoral artery (in mm Hg) | 10 | 45±5,3 | 96±6,3 | 9 | 46±6,9 | 117±10 | 0,9 | 0,2 |
| Central venous pressure (in mm water) | 10 | 21±5,8 | 34±9,8 | 9 | 22±6,3 | 48±8 | 0,9 | 0,3 |
| Mean pressure in pulmonary artery (in mm Hg) | 6 | 11±1,1 | 12,5±1,7 | 4 | 9,5±1 | 11±0,5 | 0,5 | 0,8 |
| Plasma volume (in ml/kg) | 10 | 36,6±2,1 | 38,6±2,3 | 9 | 27±2,9 | 50±3,7 | 0,05 | 0,05 |
| Erythrocyte volume (in ml/kg) | 10 | 33±5,1 | 36,3±6,6 | 9 | 26±2,7 | 49±5,5 | 0,5 | 0,2 |
| Blood volume (in ml/kg) | 10 | 68,3±6,8 | 76,3±10,7 | 9 | 53±4,9 | 91±8,9 | 0,4 | 0,5 |
| Minute volume of heart (in liters/min) | 10 | 0,9±0,16 | 1,1±0,11 | 9 | 0,48±0,06 | 1,75±0,13 | 0,001 | 0,05 |
| Cardiac index (in liters/min/mm$^2$) | 10 | 1,5±0,25 | 1,8±0,2 | 9 | 0,78±0,15 | 2,5±0,25 | 0,001 | 0,05 |
| Stroke volume of heart (in ml/contraction) | 10 | 5,6±1,1 | 8,2±0,8 | 9 | 3±0,25 | 13,2±2 | 0,4 | 0,05 |
| Stroke index (in ml/contraction/m$^2$) | 10 | 9,1±1,5 | 13,5±1,5 | 9 | 4,9±0,6 | 18,4±1,5 | 0,01 | 0,05 |
| Circulation time in pulmonary system (in sec) | 10 | 12,6±1,2 | 8,6±0,8 | 7 | 13±1,2 | 8,8±0,9 | 0,9 | 0,9 |
| Intrathoracic blood volume (in ml/kg) | 9 | 23,7±4,1 | 22,8±2,7 | 7 | 17,3±3,1 | 29±5,1 | 0,4 | 0,4 |
| Ratio between intrathoracic total blood volumes (in %) | 9 | 35,4±4,1 | 32,6±3,1 | 7 | 34±5,8 | 31±5,4 | 0,9 | 0,9 |
| Circulation time of blood (in sec) | 10 | 68±11,8 | 45,4±7,6 | 9 | 124±24 | 53±4,6 | 0,1 | 0,5 |
| Peripheral vascular resistance (in dyn·sec·cm$^{-5}$) | 10 | 4760±90 | 7160±110 | 9 | 7100±150 | 5600±142 | 0,001 | 0,001 |
| Resistance of pulmonary circulation (in dyn·sec·cm$^{-5}$) | 6 | 960±15,3 | 980±18,3 | 4 | 1500±45 | 640±50 | 0,001 | 0,001 |
| Work of the left ventricle (in kg-m/min) | 10 | 0,68±0,26 | 1,5±0,3 | 9 | 0,31±0,04 | 2,3±0,22 | 0,3 | 0,001 |
| Work of the right ventricle (in kg-m/min) | 6 | 0,17±0,03 | 0,22±0,03 | 4 | 0,07±0,02 | 0,22±0,04 | 0,1 | 0,9 |

the arterial and venous pressures were virtually unchanged, provided that ethirone was given in doses exceeding the dose of hexamethonium by 1.5-2 times. If the dose of hexamethonium was raised above 5 mg/kg, 3 or 4 times more ethirone had to be injected in order to maintain the arterial and venous pressures at the previous level. These experiments showed that ethirone induces tachyphylaxis. Its hypertensive effect was reduced after each successive injection. The state of the hemodynamic system in the intact dogs after administration of azamethonium in a dose of 1 mg/kg body weight (a dose capable of inducing total ganglioplegia and arterial hypotension), and of the same dose of ethirone was studied in 5 experiments. No significant changes were found in the principal indices of the hemodynamics. Only the circulating blood volume was increased by a statistically significant degree (on the average by 25.3%) after 30 min, mainly on account of plasma.

The parameters of the hemodynamics studied during the treatment of oligemic shock are given in Table 1.

The blood volume of the experimental animals 1 h after the beginning of the resuscitation measures was higher than in the controls, mainly on account of plasma. The intensity of the systemic blood flow exceeded that found after treatment by ordinary blood transfusion. The minute volume of the heart was increased on the average by 60%, and the cardiac index by 38% ($P < 0.05$). An increase in the stroke volume of the heart (on the average by 60%) and in the stroke index (by 38%; $P < 0.05$) was observed. The work of the heart increased mainly on account of the left ventricle. Favorable changes in the hemodynamics took place as the result of the regulatory effect of azamethonium bromide and ethirone on vascular tone. They were expressed ultimately as a decrease in the peripheral vascular resistance, on the average by 21% ($P < 0.001$) and of the pulmonary resistance by 34% ($P < 0.001$) compared with the control group. The absence of statistically significant differences in arterial pressure and the simultaneous increase in the minute volume of the circulation can be explained by an increase in the venous return of the blood as the result of a decrease in the tone of the resistance vessels and an increase in the resistance of the capacitance vessels [6]. The increase in cell volume indicated that the phenomenon of aggregation and sequestration of the blood cells had been overcome. The improvement in the macrocirculation and microcirculation was accompanied by a tendency toward correction of the severe metabolic acidosis through an increase in the concentration of buffer bases, mainly bicarbonate, and through correction of the base deficit. In the experimental animals this index was 30% smaller than in the control group ($P < 0.01$). All the dogs resuscitated with the aid of gangliolytic drugs and ethirone survived. In the control group only 2 dogs survived longer than 24 h.

Administration of gangliolytics and ethirone during blood transfusion therapy in experimental oligemic shock thus provides a reliable method of bringing the cardiovascular system out of its hypodynamic state, evidently by reducing the vascular resistance and intensifying the venous return of blood to the heart.

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