

CARDIAC OUTPUT AND OXYGEN UPTAKE AFTER HAEMORRHAGE IN CONSCIOUS DOGS UNDER SYMPATHETIC ALPHA-RECEPTOR BLOCKADE

By

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In conscious dogs arterial pressure was lowered to 30 mm Hg by bleeding. This pressure was maintained for 60 min and thereafter all the blood was reinfused. Cardiac output, blood pressure, oxygen content of arterial and mixed venous blood were determined before and after the bleeding at intervals of one hour, altogether six times. One mg/kg of phenoxybenzamine given together with the reinfusion decreased blood pressure when compared to the control (untreated) group. There was usually no difference in cardiac output, peripheral resistance, arterio-venous oxygen difference and oxygen consumption between the treated and control groups. The mortality within 48 hours was 8/12 in the control group and 12/12 in the treated group.

In previous experiments (NAGY *et al.* 1965b) the influence of sympathetic alpha-receptor blockade by phenoxybenzamine on the adjustment of the circulation to acute blood loss was examined. In these experiments resting cardiac output diminished, arterio-venous oxygen difference increased, bleeding volume at a given blood pressure decreased. In the present experiments alpha-receptor blockade was established only after the bleeding, simultaneously with the reinfusion of blood and the effects on cardiac output, oxygen transport and survival have been examined. The experiments were done in conscious dogs to eliminate the eventual disturbing effect of general anaesthesia.

Methods

The experiments were performed on 24 dogs (mean body weight, 17.6 kg). The animals lying on their back were loosely bound to the operating table. While diverting their attention by petting, the femoral vessels on both sides were exposed under sterile conditions from small incisions after local procaine infiltration. Two catheters were introduced into the aorta, one into the right atrium and one into the pulmonary artery. For the latter purpose a special catheter (Silastic 373 .040" X .085" Dow Corning Corp.) was used, which has the advantage that owing to its light weight and flexibility it is guided by the blood stream itself into the proper direction and thus obviating the necessity of lengthy manipulation or X-ray control for the catheterization of the pulmonary artery. The position of the catheter was checked by connecting it to a pressure transducer and manometer and observing the pulmonary artery pressure curves. The catheters were used for pressure measurements (for details see NAGY *et al.* 1965a), bleeding, blood sampling and indicator injection. After introducing the catheters the animals were given 5 mg/kg heparin i. v. For the determination of cardiac output, 0.3 per cent solution of Evans blue was used. The dye (approximately 3 ml) was filled into the right atrial catheter; the syringe containing the dye was weighed together with the dye and also after filling the catheter. The dye was injected by a sudden flush with saline after which 0.2 ml arterial blood samples were taken every second in cadence with a metronome, for 24 sec. The concentration of the dye

in the samples after dilution with saline and centrifugation was determined with a spectrophotometer (NAGY *et al.* 1964b). The descending limb of the dilution curve was extrapolated exponentially and cardiac output was calculated from the standard *Hamilton* equation.

Together with each cardiac output determination the oxygen content of arterial and mixed venous (pulmonary artery) blood was determined by the manometric method of VAN SLYKE and NELL (1924). Oxygen consumption was computed by multiplying the value for arterio-venous oxygen difference with that for cardiac output.

The experimental protocol was as follows. After the control cardiac output and oxygen determinations the animals were bled into a reservoir (for details see NAGY *et al.* 1964a) until mean arterial blood pressure had lowered to 30 mm Hg. This pressure was maintained with the reservoir for 60 min after which all blood in the reservoir was returned to the animal by intravenous infusion. Twelve animals were given 1 mg/kg of phenoxybenzamine together with the reinfusion. Twelve animals received only the solvent of the drug (for details of phenoxybenzamine administration see NAGY *et al.* 1965b). Thirty minutes after the reinfusion, cardiac output and blood oxygen content were again determined and these determinations were repeated at intervals of one hour four times (*i.e.* six times during the experiment).

After the experiment the catheters were removed, the wounds sutured and the animals observed for 48 hours. Food and water were offered without restriction. The results were analysed statistically by the methods of WILCOXON *et al.* (1963).

Results

The small surgery was tolerated well by the animals. In a few cases there was some excitement but it could be effectively dealt with by fondling. After the bleeding had begun the animals showed no excitement till the end of the experiment.

The results of measurements are shown in figures. *Fig. 1* shows that blood pressure after the reinfusion was lower in the treated group than in the control group.

Cardiac output measurements are shown in *Fig. 2*. Except for the third determination cardiac output was not significantly different statistically in

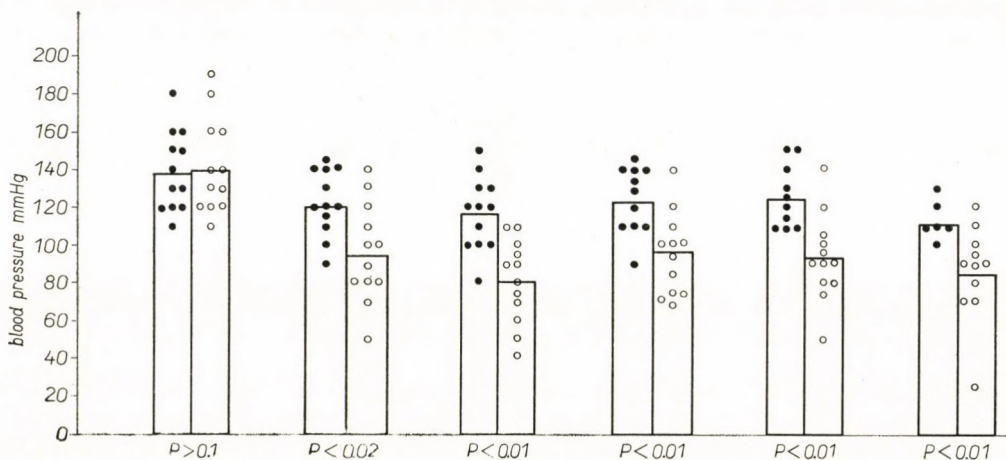


Fig. 1. Blood pressure, mm Hg. Filled circles show values for the control group, empty circles those for the treated group. The height of the bars shows mean values. Bleeding and reinfusion took place between the first and second pairs of bars from the left

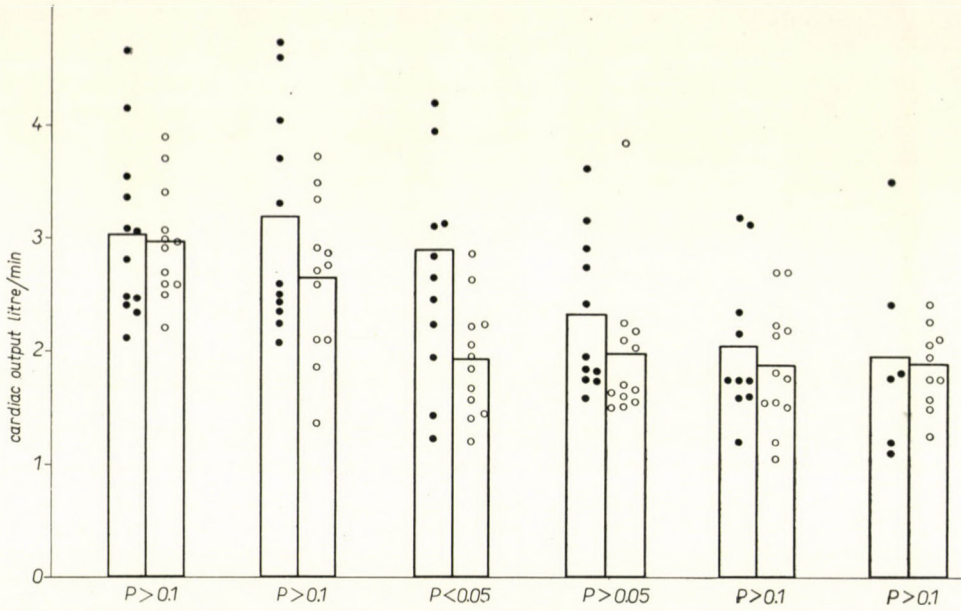


Fig. 2. Cardiac output, 1000 ml/min. For further explanation see Fig. 1

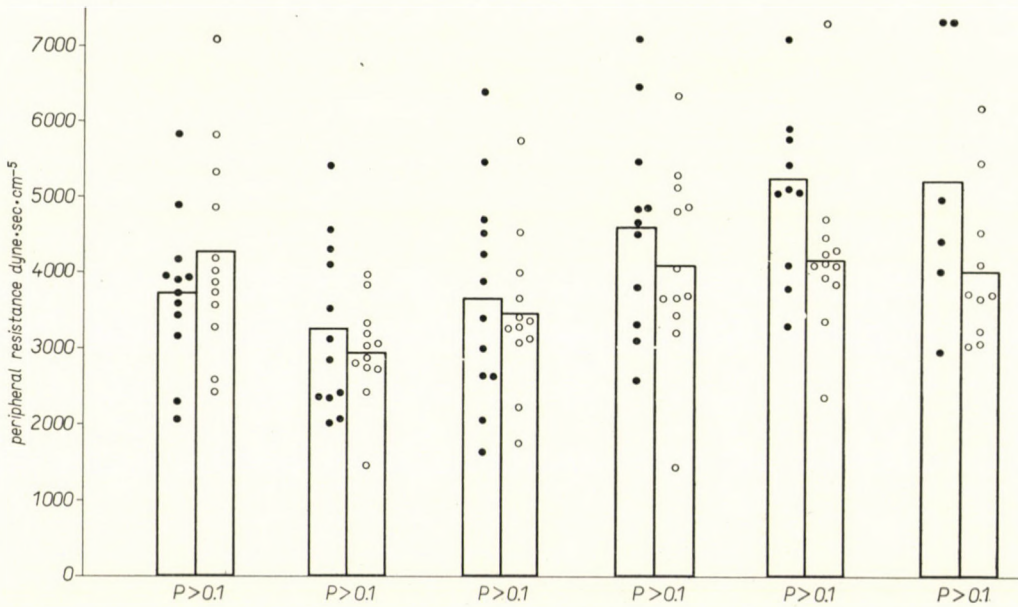


Fig. 3. Peripheral resistance, $\text{dyne} \cdot \text{sec} \cdot \text{cm}^{-5}$. For further explanation see Fig. 1

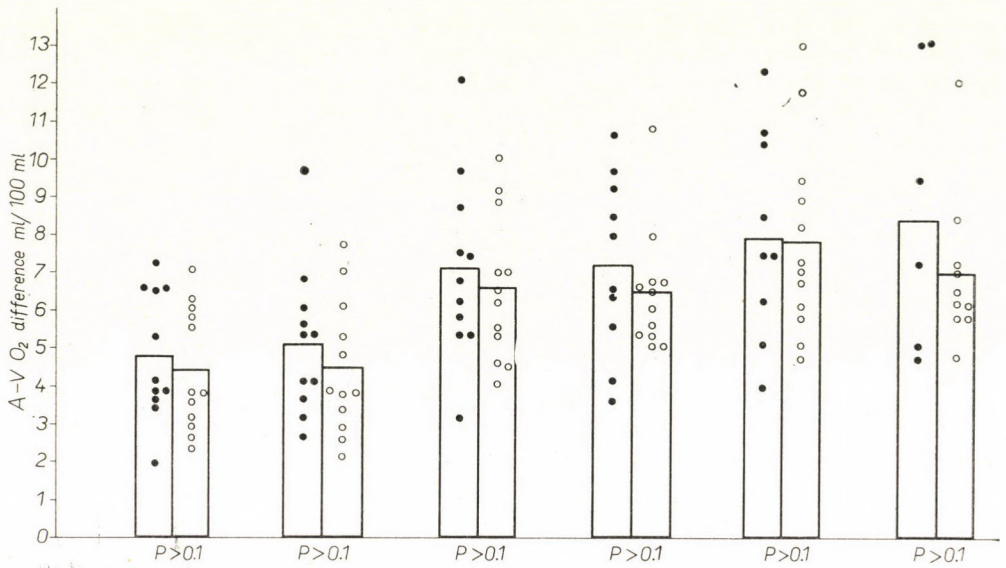


Fig. 4. Arterio-venous oxygen difference, ml/100 ml. For further explanation see Fig. 1

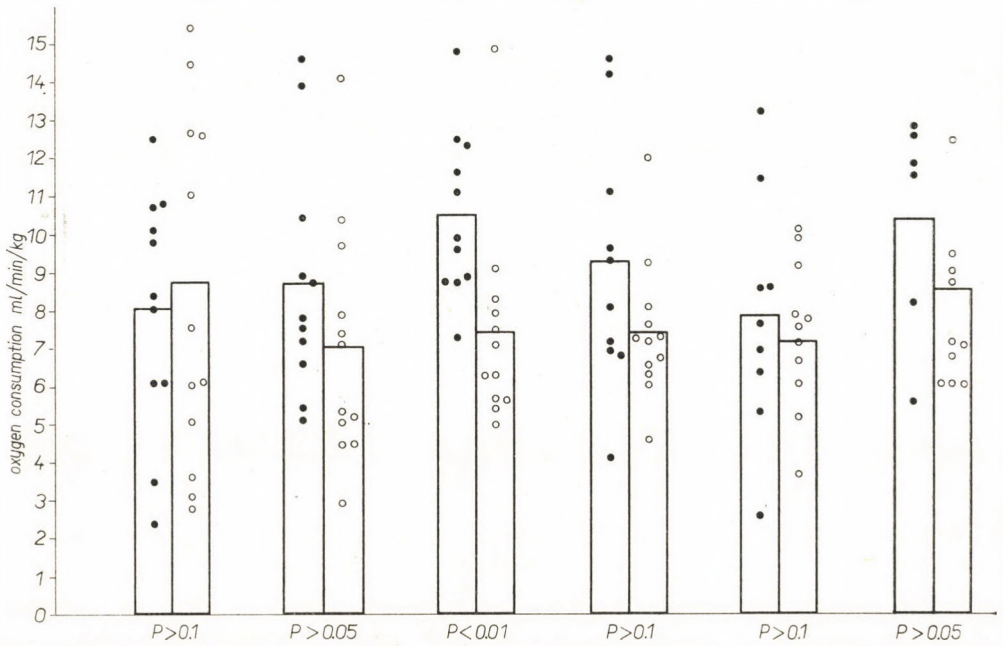


Fig. 5. Oxygen consumption, ml/min/kg. For further explanation see Fig. 1

the two groups, although mean values were lower in the treated group. The difference in the case of the third determination was significant only at the 5 per cent level.

There was no significant difference in peripheral resistance between the two groups at any time (*Fig. 3*). Similarly, arterio-venous oxygen difference was not different in the two groups (*Fig. 4*).

Oxygen consumption in the treated group was significantly lower at the third determination but no significant difference between the two groups was found at the other determinations (*Fig. 5*).

In the control group 4 out of 12 animals were alive after 48 hours. In the treated group none of the 12 animals were alive at that time.

Discussion

Several investigators have found that alpha-receptor blockade by phenoxybenzamine is protective against different types of shock. (For a review of the literature see NICKERSON and GOURZIS 1962.) The mechanism of the effect is not entirely clarified but the predominant view is that it is in some way related to the inhibition of vasoconstriction which develops in the course of shock. This vasoconstriction is a compensatory mechanism in the case of acute blood loss or trauma which precedes shock. Its inhibition at this time is harmful rather than beneficial (LEVY *et al.* 1954; NICKERSON and CARTER 1959; NAGY *et al.* 1965b). In the present experiments therefore the blockade was established only after bleeding and reinfusion had been terminated, essentially under normovolaemic conditions. It was remarkable that while in our previous experiments alpha-receptor blockade caused the cardiac output of normal, unbled dogs to decrease, in the present experiments cardiac output did not decrease significantly. A possible explanation may be, in addition to the lack of general anaesthesia, that some compensatory mechanisms operate in post-haemorrhagic, normovolaemic shock to maintain cardiac output, counteracting thus the cardiac output decreasing effect of phenoxybenzamine. This latter effect of phenoxybenzamine may probably be explained by the blockade of alpha-receptors in the venous system (KAISER *et al.* 1964).

From the observed difference in survival between our two groups of animals we do not wish to draw any far-reaching conclusions as to the protective value of phenoxybenzamine-induced sympathetic blockade in shock. However, the blockade did not increase survival under our experimental conditions. We think it probable that in addition to replacement of the lost blood and the application of the blockade in the proper time, other factors are necessary to achieve a favourable effect on survival.

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