ADJUSTMENT OF THE CIRCULATION TO HAEMORRHAGE IN DOGS DURING SYMPATHETIC NERVOUS BLOCKADE*

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Phenoxybenzamine-induced sympathetic nervous blockade in dogs was associated with diminished resting cardiac output, increased arterio-venous oxygen difference and smaller bleeding volumes at a given blood pressure. Mean circulatory haematocrit before bleeding was lower in the blocked animals and no significant decrease of the F-cells factor was observed after bleeding. Sympathetic activity is beneficial in the acute stage of rapid haemorrhage.

Loss of blood from the circulation is a major stimulus of sympathetic activity. The sympathetic impulses elicited after haemorrhage serve to minimize the fall in blood pressure and in cardiac output, to increase peripheral resistance and to facilitate venous return. The maintenance of perfusion of vital organs in which vasoconstriction is not prominent at the expense of other organs is an important effect of sympathetic activity in this situation. The maintenance of a critical cardiac output is probably more important in determining survival than is the maintenance of a critical level of arterial pressure. Another significant compensating mechanism connected with blood loss is the restoration of circulating blood volume by means of shift of fluid and protein into the circulation.

There are reports indicating that the elimination or blocking of sympathetic activity increased rather than decreased the tolerance to haemorrhage and subsequent shock. NICKERSON *et al.* (1962) claim that vasoconstriction is a decisive factor in the mechanism of shock by a drastic reduction of blood flow. By pharmacologic sympathetic blockade they could increase survival in shock (NICKERSON 1962). The earlier the blockade was established the better were the results (NICKERSON, personal communication 1963).

Considering that sympathetic hyperactivity seems beneficial in the case of acute blood loss, the present experiments were designed to study the adaptation to haemorrhage in dogs subjected to sympathetic nervous blockade.

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Methods

The experiments were performed on 28 dogs ranging in weight from 13 to 22 kg (average, 16 kg). Under pentobarbital anaesthesia the femoral vessels on both sides and the left jugular vein were exposed. Every small bleeding was controlled with meticulous care by cauterization. Two polyethylene catheters were introduced into the right atrium *via* the femoral veins and two similar catheters into the aorta *via* the femoral arteries. A thin silicon rubber catheter *(Dow Corning Corp.)* was introduced into the pulmonary artery through the left jugular vein. The animals were given 5 mg/kg heparin intravenously. Arterial and central venous pressures were measured by pressure transducers as described previously (NAGY *et al.* 1965). The animals were divided into two groups of 14 each. In one group sympathetic blockade was established by 3 mg/kg phenoxybenzamine. The drug was dissolved in 0.5 ml 96 per cent ethanol and was diluted to twice of its volume with saline. It was injected slowly into the right atrium. The control group received only the ethanol-saline mixture. After the injection one hour was allowed to elapse to let the blockade fully develop. A cuffed endotracheal tube was inserted through which the animals breathed room air spontaneously. The animals were subjected to two haemorrhages and the following determinations were performed before and after bleedings: blood volume determination by the simultaneous application of ^{51}Cr-labelled red cells and T-1824 with 30 minute time-concentration curves. Details of the methods and calculations were published earlier (NAGY *et al.* 1964), with the only difference that radioactivity was determined in saponine-haemolyzed samples, the dye was injected with siliconized glass syringes, and the amount injected was determined gravimetrically (CHIEN and GREGERSEN 1962). Cardiac output was determined by the indicator dilution method, as described (NAGY *et al.* 1965). Plasma proteins were determined according to WEICHSELBAUM and GRADWOHL (1956), blood pH by a *Radiometer* micro electrode in capillary tubes. Blood oxygen content was determined manometrically according to VAN SLYKE and NEILL (1932). Haematocrit values were determined by spinning blood samples in capillary tubes in a *Hawksley* microhaematocrit centrifuge for 10 minutes at 12,000 *g*.

The course of the experiment was as follows. After the control determinations a measured quantity of blood was removed rapidly through the aortic catheter by means of 100 ml siliconized glass syringes until mean arterial pressure had dropped to 80 mm Hg. This pressure was maintained for 15 minutes by withdrawing additional blood volumes when necessary. Then bleeding was stopped and 40 minutes later the determinations were repeated. After an additional 30 minute interval the bleeding was repeated as described above, with the exception that mean arterial pressure was now lowered to 40 mm Hg. Forty minutes after completion of the second bleeding the determinations were performed for the third time.

Results

The results have been tabulated. In *Table I* blood volume data are shown. It can be seen that in the phenoxybenzamine treated animals a smaller blood loss was sufficient to lower blood pressure to the same level. In *Table II* the results of plasma volume determinations are presented. After the first bleeding when blood pressure was lowered to 80 mm Hg only very small amounts of fluid were mobilized from the extravascular space. After the second bleeding an average of 8.2 ml/kg of fluid entered the circulation in the control dogs whereas only 2.0 ml/kg in the animals under sympathetic blockade. When expressed as a percentage of lost plasma it was found that control animals replaced 88 per cent of the plasma lost with the haemorrhage (and samples), while blocked animals only 24 per cent. However, when the data for the two groups were analysed by the Wilcoxon rank sum test (WILCOXON *et al.* 1963) it was found that there was no sufficient evidence at the 5 per cent probability level to reject the hypothesis that the samples had come from the same population.

Table I

Group	Blood volume ml/kg				
	Before bleeding	Lost with first bleeding	After first bleeding	Lost with second bleeding	After second bleeding
Control	89.0 (14) ± 2.7	22.1 (14) ± 2.1	67.4 (13) ± 4.6	18.2 (13) ± 0.7	56.1 (10) ± 3.7
Phenoxybenzamine	88.0 (12) ± 4.7	7.7 (14) ± 1.2	81.1 (9) ± 2.5	13.9 (14) ± 2.7	68.7 (10) ± 5.8

Figures following ± are standard errors of the mean
Figures in parenthesis denote the number of determinations

Table II

Group	Plasma volume ml/kg						
	Before bleeding	Lost with first bleeding	After first bleeding	Volume of fluid entering the circulation after the first bleeding	Lost with second bleeding	After second bleeding	Volume of fluid entering the circulation after the second bleeding
Control	48.8 (14) ± 1.7	11.8 (14) ± 1.1	37.2 (14) ± 3.0	0.25 (14) ± 3.6	9.3 (11) ± 0.4	36.8 (10) ± 2.5	8.2 (10 ± 3.8
Phenoxy-benzamine	51.3 (14) ± 1.6	4.7 (14) ± 0.7	47.0 (13) ± 1.8	0.90 (13) ± 2.3	8.4 (14) ± 0.5	40.8 (12) ± 0.4	2.0 (12) ± 4.5

Identical results were obtained when the method was applied to the data for protein mobilization (protein mobilization after the second bleeding: 0.411 ± 0.27 (S. E.) g/kg in the control group; −0.005 ± 0.24 (S. E.) g/kg in the treated group). When the WILCOXON signed rank test was applied to the data of each group it was found that fluid mobilization in the control group was significant at the 5 per cent level, while that of the treatment group was not.

In *Table III* are presented the volumes of the circulating red cell mass together with the volume of lost and mobilized red cell masses. After the first haemorrhage an insignificant red cell mobilization occurred but red cell disappearance was seen in both groups after the second bleeding.

Table III

Group	Red cell volume ml/kg						
	Before bleeding	Lost with first bleeding	After first bleeding	Entering the circulation after the first bleeding	Lost with second bleeding	After second bleeding	Entering the circulation after the second bleeding
Control	40.1 (14) ± 1.3	10.3 (14) ± 1.0	29.8 (13) ± 2.0	0.5 (13) ± 1.9	7.6 (11) ± 0.5	20.0 (10) ± 2.0	−3.2 (9) ± 1.3
Phenoxy-benzamine	36.2 (12) ±2.5	3.0 (14) ± 0.5	35.9 (10) ± 2.4	2.3 (9) ± 1.3	5.5 (14) ± 0.3	27.2 (11) ± 2.4	−4.0 (9) ± 0.8

In *Table IV* can be seen the values of mean circulatory ("total body") haematocrit and F-cells factor (ratio of large vessel haematocrit to mean circulatory haematocrit). The mean circulatory haematocrit and F-cells factor decreased after the second haemorrhage in both groups, but because of the scattering the decrease was not statistically significant in the treated group.

Table IV

Group	Mean circulatory haematocrit			F-cells factor		
	Before bleeding	After first bleeding	After second bleeding	Before bleeding	After first bleeding	After second bleeding
Control	45.1 (14) ± 2.0	44.6 (13) ± 2.1	34.2 (10) ± 1.5	0.99 (14) ± 0.01	1.01 (13) ± 0.01	0.81 (10) ± 0.02
Phenoxy-benz-amine	40.7 (12) ± 0.7	42.3 (9) ± 2.7	37.9 (9) ± 4.3	1.03 (12) ±0.04	1.04 (9) ±0.06	0.92 (9) ± 0.09

Values for cardiac output and peripheral resistance are presented in *Table V*. In the control group cardiac output decreased considerably and resistance increased after bleeding. Under sympathetic blockade cardiac output decreased even before the bleeding when compared to the controls (to 72 per cent of the control group's value) and resistance did not rise significantly after haemorrhage. If the initial cardiac output of the control group is considered to represent the normal value for both groups then after the second haemorrhage a decrease of 37 per cent in the circulating blood volume was accompanied

Table V

Group	Cardiac output *L*/min			Peripheral resistance dyn. sec.cm^{-5}		
	Before bleeding	After first bleeding	After second bleeding	Before bleeding	After first bleeding	After second bleeding
Control	2.91 (13) ± 0.23	1.23 (13) ± 0.09	1.25 (10) ± 0.24	3689 (13) ± 135	6471 (13) ± 601	6258 (10) ± 1020
Phenoxy-benz-amine	2.09 (13) ± 0.08	1.61 (13) ± 0.11	1.47 (11) ± 0.15	3570 (13) ± 382	4094 (13) ± 336	3983 (11) ± 620

Table VI

Group	Arterio-venous O_2 difference ml/100 ml			O_2 consumption ml/kg		
	Before bleeding	After first bleeding	After second bleeding	Before bleeding	After first bleeding	After second bleeding
Control	4.62 (14) ± 0.41	8.15 (13) ± 0.67	11.65 (10) ± 1.06	7.76 (13) ± 0.62	6.33 (13) ± 0.70	8.26 (10) ± 1.44
Penoxy-benz-amine	6.55 (11) ± 0.39	7.79 (13) ± 0.41	9.51 (10) ± 0.48	8.10 (11) ± 0.48	7.63 (12) ± 0.44	8.67 (10) ± 0.59

by a 57 per cent reduction of cardiac output in the control group. In the treated group a decrease of only 22 per cent in blood volume was accompanied by a 51 per cent reduction in cardiac output.

In *Table VI* are shown the values for arterio-venous oxygen difference and oxygen consumption. Oxygen content was determined in samples taken from the aorta and pulmonary artery. Arterio-venous oxygen difference increased progressively after haemorrhage in both groups and compensated the effect on tissue oxygen uptake of diminished oxygen transport due to the low cardiac output. The increase in the oxygen difference was due to a decrease in oxygen content of mixed venous blood; arterial oxygen content did not change significantly. The coefficient of oxygen utilization before bleeding was 0.25 in the control group and 0.37 in the treated group.

Discussion

Phenoxybenzamine was shown to have a protective action against different types of shock (NICKERSON 1962). The mechanism of this effect is not completely understood. The most widely accepted explanation is that it acts

by abolishing the severe vasoconstriction which develops in the course of shock. This vasoconstriction is due mainly to sympathetic activity. It is known since CANNON's basic experiments (1929) that sympathetic hyperactivity is favourable on survival in emergency situations such as haemorrhage. These data can be reconciled if we presume that vasoconstriction which is beneficial in acute haemorrhage becomes harmful in the subsequent subacute shock. Contrary to this hypothesis is the experience of the majority of investigators who found that the shock-protecting effect of sympatholytic agents is the most pronounced if they are given before the development of shock. According to the data of NICKERSON (1962), animals which show signs of sympathetic hyperactivity (increased blood pressure and heart rate) in the resting state are less likely to survive a standardized haemorrhagic shock.

The bleeding method employed in our experiments produced only haemorrhagic hypotension and not haemorrhagic shock in the time interval studied. To reach the same level of arterial pressure much less blood was sufficient in the blocked animals, therefore their sensitivity to blood loss increased. GOURZIS, ROQUE and NICKERSON (1963) have shown that phenoxybenzamine blockade did not affect maximal bleeding volumes in haemorrhagic shock. The difference against our results may be explained by time and dose differences.

NICKERSON and GOURZIS (1962) observed an increase in the volume of circulating plasma in dogs one hour after the administration of 1 mg/kg of phenoxybenzamine. In our experiments no such increase was observed one hour after 3 mg/kg of the drug. Also, ROZEK, LOGIC and STEKIEL (1964) failed to find an increase in plasma volume 18 hours after 2 mg/kg of phenoxybenzamine.

Fluid mobilization into the circulation was not significant in our blocked animals. This is in agreement with the results of CHIEN (1958) who has shown in sympathectomized splenectomized dogs that sympathetic activity promoted fluid mobilization after haemorrhage.

The distribution of red cells within the cardiovascular system showed differences between our two experimental groups. Mean circulatory haematocrit decreased considerably after the second haemorrhage in the control group. In the phenoxybenzamine treated group it was significantly lower before the haemorrhage than in the control group. Its decrease after the second haemorrhage was not significant because of the wide scattering. The value of the F-cells factor showed a significant decrease after the second haemorrhage in the control group. In the treated group, however, the smaller decrease was masked by the scattering. It seems interesting that the same phenomenon was observed by us (NAGY *et al.* 1964) in noradrenaline treated bled dogs.

A significant difference was observed in prehaemorrhage cardiac output of the two groups; cardiac output in the group subjected to sympathetic blockade

decreased when compared to the untreated group. There was no significant difference in oxygen consumption but the treated group could achieve this only by an increased oxygen extraction from the blood; this was reflected by the increased arterio-venous oxygen difference. WILLENKIN and GREEN's (1963) experiments may be mentioned here: they observed a decrease in skeletal muscle oxygen tension and the appearance of "excess lactate" in dogs after the administration of the ganglionic blocking agent hexamethonium.

Sympathetic blockade did not influence resting peripheral resistance but abolished its considerable rise after haemorrhage seen in the control group. CHIEN and BILLIG (1961) found in sympathectomized dogs that within the range of 10—25 per cent reduction of blood volume fluid mobilization and sympathetic activity are about equally important in maintaining arterial pressure. In haemorrhage larger than 25 per cent sympathetic activity becomes the most important compensating mechanism. They also observed that the posthaemorrhage cardiac output expressed as a percentage of control showed a linear relationship with the percentage reduction of blood volume in sympathectomized dogs. Our present data are insufficient for calculating such a relationship in phenoxybenzamine blockade. It may, however, be stated that in sympathetic blockade cardiac output falls after haemorrhage out of proportion to blood loss.

The fall in cardiac output due to sympathetic blockade observed in our experiments might be explained by a decrease in venous return to the heart. KAISER *et al.* (1964) have shown that the systemic venous bed contains alpha and beta adrenergic receptors. The blockade of alpha receptors by phenoxybenzamine causes vasodilatation in the capacitance vessels with consequent decreased venous return. According to GUYTON (1963, p. 300) complete loss of sympathetic activity probably reduces cardiac output to about half the normal, while maximal sympathetic activity increases the output to about twice the normal. The results of DAVIS *et al.* (1964) somewhat contradict this. They observed an increase of cardiac output in phenoxybenzamine-induced adrenergic blockade. Their results may, however, probably be explained by the fact that they have administered blood whenever it was necessary to maintain blood pressure, and thus they raised "mean circulatory pressure" (GUYTON 1963, p. 193) while inducing dilatation of resistance vessels.

Concerning the mechanism of the protective action of phenoxybenzamine in shock our experiments have furnished only indirect evidence. It seems possible that the protective action cannot be explained entirely on the basis of haemodynamic alterations under blockade. We agree with KOVÁCH *et al.* (1961) who did not find a favourable effect on cardiac output in tourniquet shock during dibenamine blockade although they observed an improvement of survival (KOVÁCH *et al.* 1958) and certain other parameters. The antishock properties of phenoxybenzamine according to GOURZIS *et al.* (1963) are correlat-

ed with its adrenolytic effects because structurally related compounds without adrenergic blocking effects are without antishock effect. It remains to be seen which of the many effects of sympathetic activity are concerned here.

STEKIEL *et al.* (1964) suggest that the protective action of phenoxybenzamine may involve inhibition of catecholamine induced alterations of normal tissue perfusion. In interpreting the data obtained with the use of sympathetic blocking agents one must also bear in mind that these agents do not cause absolute and uniform sympathetic blockade, and the improvement in survival might be due to a redistribution or preferential blockade of sympathetic activities, *e.g.* by blocking the vasoconstrictor effects but sparing the cardiac influences (CHIEN 1964). Although the present experiments indicate that sympathetic activity is beneficial in the acute stage of rapid haemorrhage, the exact role played by the sympathetic nervous system in the late stages of haemorrhagic shock deserves further investigation.

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