Norepinephrine and Phenoxybenzamine Redistribution of Dog Forelimb Blood Flow and Volume[1] (35969)

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Increased adrenergic stimulation is reported to cause increases in pre- and postcapillary resistance (1) and mobilization of significant amounts of blood (2). Redistribution of blood flow and blood volume within the parallel circuits would also occur (3). Alpha adrenergic blockade should release the vessels from the stimulation and could return the distribution of blood flow and volume to the control state. However, if all pre- and postcapillary vessels are not affected in the same manner the distribution of blood flow and volume would be affected accordingly.

In the study of this problem, isolated, but innervated, dog forelimbs were perfused under conditions of controlled blood flow. Blood flow resistance, net capillary transfer of fluids, vascular volume, tissue volume change, and relative capillary surface areas were followed throughout the experiment.

Methods. Eleven dogs averaging 17 kg in weight were pretreated with 10 mg/kg of morphine sulfate and anesthetized with 20 mg/kg of pentobarbital. The left forelimb was isolated by ligating the muscle groups above the elbow, leaving the brachial artery vein, and cephalic vein, and the brachial nerve trunks outside the ligatures. The skin flap produced by the exposure of the muscle groups was used as a seal for a plethysmograph connected to a Statham transducer. The animals were heparinized and the two veins were cannulated and blood from both was channeled into a single tube passing through a scintillation detector connected to a rate meter. The blood was collected in a graduated cylinder. The brachial artery was cannulated and perfused from the right femoral artery by a Harvard pressure independent pump. The inflow tubing had sidearms for measurement of pressure and injection of indicators and drugs. The forelimbs were perfused with blood at 37°. The venous outflow pressure was set so the limb was nearly isovolumetric and averaged 5 mm Hg.

Determinations were made in the following order: (i) during the control state with blood flow set so that the perfusion pressure approximated the dog's mean arterial pressure; (ii) During ia infusion of norepinephrine (0.5–1.0 μg/min); (iii) during the norepinephrine infusion, but following stabilization of the preparation subsequent to a slow injection of 1.0 mg of phenoxybenzamine.[2]

Total vascular volume change and the net capillary transfer were determined from the plethysmograph record. They were calculated as previously reported (4).

Active vascular volume was calculated by the mean transit time technique (5) utilizing venous time concentration curves resulting from intra-arterial injections of red cells-^{51}Cr and albumin-^{131}I. There was no recirculation of indicator since all of it was collected in the graduated cylinder. Active vascular volume of the limb was the calculated volume minus the volume of the inflow and outflow tubing. The recovery of ^{86}RbCl in the venous outflow was used as an index of capillary surface area available for exchange. The three indicators were injected successively, each one after the venous time concentration curve resulting from the previously injected indicator had returned to the base line.

A timed collection of the effluent blood during each curve was used to measure blood

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[2] Phenoxybenzamine (Dibenzyline) was generously supplied by Smith, Kline and French Laboratories.

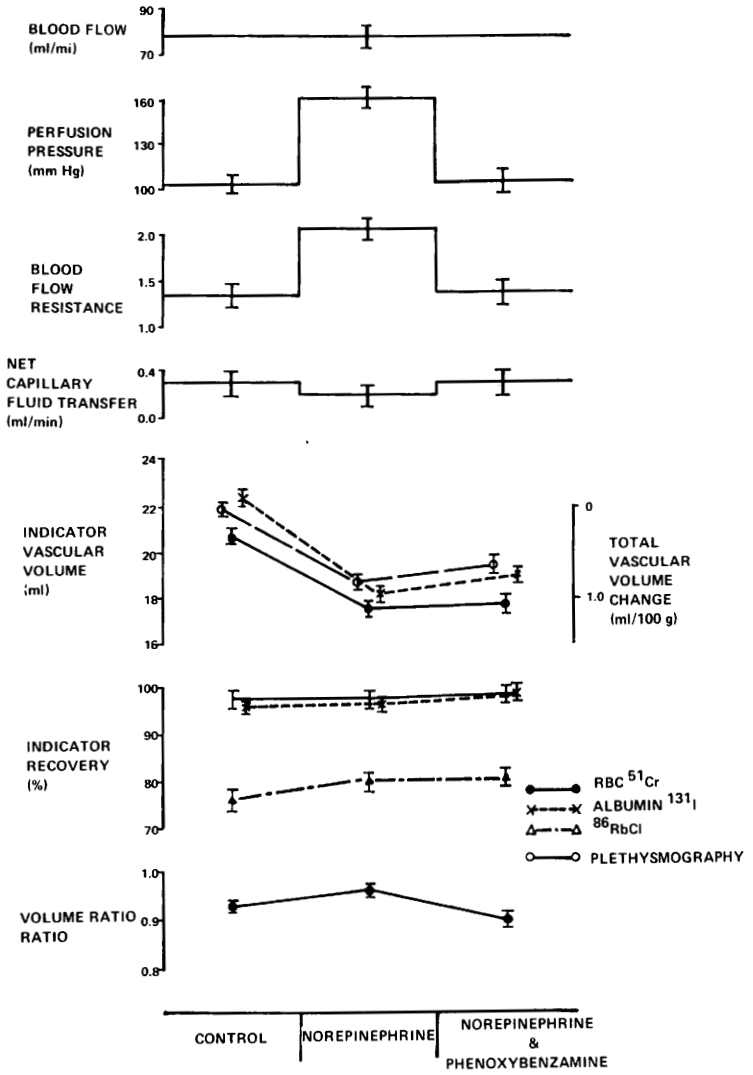

FIG. 1. Responses of the circulation of isolated dog forelimbs to norepinephrine infusion and phenoxybenzamine: brackets indicate ± SEM.

flow. Since the collected blood also contained the isotope, a mixed sample was counted to determine the recovery of each isotope.

A continuous infusion of homologous blood was made into the dog at approximately the same rate as it was being collected from the venous outflow of the limb.

All parameters were recorded on an Electronics for Medicine recorder. Related values were compared, using analysis of variance and the Newman-Kuels range test. In appropriate cases a paired t test was used.

Results. Resistance changes (Fig. 1). In the control period, the forelimb blood flow averaged 78 ± 5 ml/min and the perfusion pressure averaged 104 ± 6.0 mm Hg with a calculated resistance of 1.39 ± 0.12 mm Hg min/ml. Norepinephrine infusion with the blood flow unchanged increased the calculated resistance to 2.11 ± 0.12 mm Hg min/ml ($p<.01$). Following the injection of 1.0 mg of phenoxybenzamine with the same flow rate, the resistance decreased to 1.37 ± 0.12 mm Hg min/ml ($p<.01$).

Net capillary transfer of fluid (Fig. 1). In

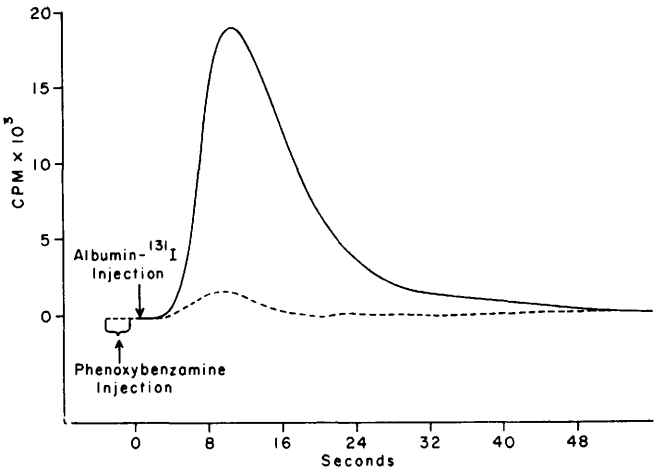

FIG. 2. Time-concentration curves recorded from the venous outflow of isolated dog forelimbs: (—)albumin-^{131}I slug injection just prior to administration of phenoxybenzamine; (- - -) washout of sequestered indicators subsequent to ia injection of 1.0 mg of phenoxybenzamine. The beginning of the upslope of each curve has been superimposed.

the control period the net capillary transfer of fluid averaged 0.31 ± 0.12 ml/min and decreased slightly, but not significantly during the norepinephrine infusion. Six of the limbs showed a decrease; three, an increase; and one, no change in filtration. Phenoxybenzamine returned the filtration rate to control.

Vascular volume changes (Fig. 1). In the control period the vascular volume as determined by the red cells-^{51}Cr and albumin-^{131}I averaged 20.8 ± 0.5 and 22.5 ± 0.5 ml, respectively, and decreased during the norepinephrine infusion to 17.5 ± 0.5 and 18.3 ± 0.4 ml, respectively ($p<.01$). The plethysmograph recording indicated a significant volume reduction of 3.3 ± 0.37 ml. The changes in volume, as determined by the three methods, were not significantly different from each other. Phenoxybenzamine blockade during the norepinephrine infusion did not change the red cell-^{51}Cr space but did significantly increase the albumin-^{131}I space to 19.3 ± 0.4 ml. Total vascular volume was unchanged.

Indicator recovery (Fig. 1). The recovery of the red cells-^{51}Cr averaged 98 ± 2, 98 ± 2, and 99 ± 2% for the three parts of the experiment. The recovery of albumin-^{131}I averaged 97 ± 2, 97 ± 2, and 99 ± 2% for the three steps of the experiment.

^{86}Rb recovery averaged 76 ± 2% in the control period and increased to 80 ± 2% ($p<.05$) during the norepinephrine infusion and remained at this level following phenoxybenzamine blockade.

Subsequent to and as a result of the injection of phenoxybenzamine there was a small but significant washout of indicator (Fig. 2). The effluent blood was analyzed by pulse height analysis indicating the presence of all three indicators. This recovered indicator averaged approximately 0.4% of the total activity injected during the control and norepinephrine determinations. This loss should not significantly affect the calculations made from the MTT of the indicators.

Volume ratio (Fig. 1). The volume ratio (RBC-^{51}Cr volume:albumin-^{131}I volume) averaged 0.92 ± 0.01 in the control period and increased significantly to 0.96 ± 0.01 during norepinephrine infusion ($p<.05$). Phenoxybenzamine decreased the ratio to 0.93 ± 0.92.

Discussion. It has been reported that shifts of blood flow from the cephalic vein to the brachial vein occurs with norepinephrine or epinephrine infusion (1, 6) in the dog forelimb. This seems to indicate a greater increase in skin than muscle resistance. It has also been shown that redistribution of flow on the microvascular level is possible with nerve stimulation (3).

We have shown previously that shifts of blood flow and volume can also be accomplished at the microvascular level between the capillary and noncapillary circulations with changes in neural tone (7–9), perfusion pressure (4), acetylcholine dilation (10) and epinephrine constriction (11).

It is evident, from the present data, that microvascular flow and volume alterations from the control can occur as a result of norepinephrine infusion and during norepinephrine infusion with alpha adrenergic blockade.

Intra-arterial infusion of norepinephrine produced a marked increase in blood flow resistance and decrease in vascular volume. The active vascular volume reduction as measured by the red cells-^{51}Cr was less than that measured by the albumin-^{131}I. A similar reduction in total vascular volume occurred. An area of the circulation was therefore closed off that had limited availability to red cells but had been available to albumin. This was further pointed out by a significant increase in the volume ratio. There was a small reduction in net capillary filtration along with increased recovery of ^{86}RbCl. This would indicate that in this controlled flow preparation many precapillary sphincters were not closed by the norepinephrine infusion and that not all of the blood flow was redistributed through the nonexchange vessels. The sphincters were apparently held open by the elevated perfusion pressure. However, it would seem that a larger proportion of the total flow to the forelimb was not passing through nonexchange vessels as evidenced by the increased ^{86}Rb recovery.

Following alpha adrenergic blockage by phenoxybenzamine during the norepinephrine infusion, there was a marked reduction in peripheral resistance, with a significant washout of indicator (Fig. 2), a small increase in capillary filtration and differential effects on vascular volume. The red cells-^{51}Cr space was unchanged from the preblockade value. However, there was an increase in the albumin-^{131}I space so that it once again was significantly larger than the red cells-^{51}Cr space. There was a significant reduction in the volume ratio as well. The increase in albumin space was only about 1/3 of the original reduction in volume caused by the norepinephrine infusion. It would appear from these data that alpha adrenergic blockade caused a reduction in precapillary resistance, which results in the opening of areas of the circulation, which are constructed, at least in part, of nonexchange vessels. The postphenoxybenzamine washout of indicator suggests that the opened vessels contained a significant pool of blood. These newly opened vessels are in turn apparently not available to red cells. These conclusions can be reached since there is no increase in red cell space while the albumin space is increased. This is an unusual response since a procedure that reduces the resistance normally opens exchange vessels (8, 10). This may be best considered from the view that nonexchange vessels may be of two kinds. (i) true A-V shunts; and (ii) capillaries with a high linear flow velocity, thus limiting exchange. The latter may be the best explanation as it has been shown microscopically that many capillaries do not contain red cells. It would appear that, since both the active and total vascular volumes remained low, the capacitance vessels were constricted by the norepinephrine even after phenoxybenzamine administration. This is true even though the blood flow resistance is apparently at or near the control levels. Since a high percentage of the resistance is precapillary it would follow that this is the site of resistance reduction.

Summary. Dog forelimbs were perfused under constant blood flow conditions. Norepinephrine significantly increased blood flow resistance and decreased total and active vascular volumes. ^{86}Rb recovery was increased. Phenoxybenzamine returned the resistance to control without changing total vascular volume or red cells-^{51}Cr volume. However, albumin-^{131}I space was increased with no change in ^{86}Rb recovery. Norepinephrine caused a reduction in capillary flow with redistribution of flow to shunt vessels. Alpha blockade allowed opening of circulatory areas constructed at least in part of nonexchange vessels.

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