Blood Flow and Volume Distribution Following Alpha Adrenergic Blockade[1] (34671)

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There have been numerous attempts to define the effects of the sympathetic neural outflow and the circulating catecholomines (*e.g.* 1–3) on the various segments of the vascular bed. It has been reported (4–6) that there are differential neural and humoral effects on (a) certain precapillary sphincters, (b) certain postcapillary vessels including the venules and small veins, or (c) on certain parallel circuits.

The question can then be asked if the use of an alpha adrenergic blocking agent such as phentolamine mesylate (Regitine) prevents these differential effects on the vascular elements and circuits.

In order to study these questions, isolated 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 and vein, the 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 dogs' mean arterial pressure. (ii) A slug injection of phentolamine mesylate (5 mg) (Ciba) into the arterial inflow was followed by a constant infusion of phentolamine (2 mg/min). Determinations were made after the hemodynamic parameters had stabilized and the pressure response to 1 μg of norepinephrine was blocked. (iii) Determinations were made following denervation of the forelimb, and (iv) following 33% elevation of the blood flow. The phentolamine infusion was continued through steps three and four.

The total vascular volume change and the net capillary transfer were determined from the plethysmograph record. They were calculated as previously reported (7).

Active vascular volume was calculated by the mean transit time technique (8) utilizing venous time concentration curves resulting from intra-arterial slug 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

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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 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-Keuls range test. In appropriate cases a paired t test was used.

Results. Resistance changes (Fig. 1). In the control period blood flow was set at an average of 86 ± 4 ml/min and the perfusion pressure averaged 129 ± 6 mm Hg with a calculated resistance of 1.55 ± 0.10 mm Hg min/ml. Following phentolamine blockade with blood flow unchanged the calculated resistanced decreased to 1.20 ± 0.05 mm Hg min/ml ($p < 0.01$). Following denervation the resistance was unchanged at 1.15 ± 0.04 and was still not significantly changed when the blood flow was increased to 114 ± 6 mm Hg min/ml.

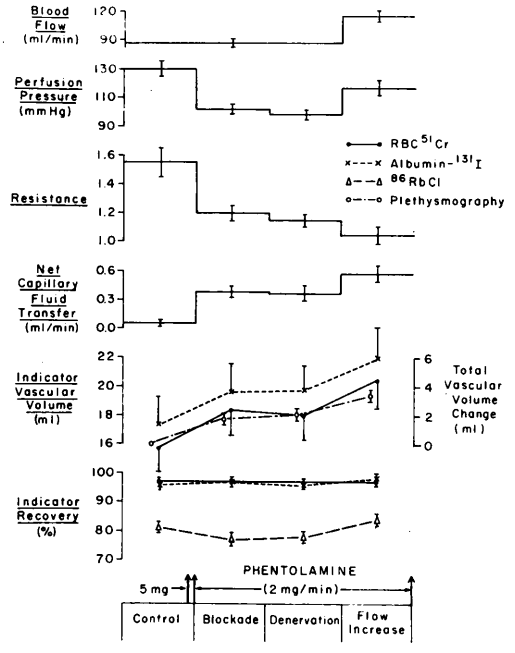

FIG. 1. Responses of the circulation of isolated but innervated dog forelimbs to alpha adrenergic blockade; brackets indicate ± SEM.

Net capillary transfer (Fig. 1). In the control period the net capillary transfer of fluid averaged 0.06 ± 0.03 ml/min and increased significantly ($p < 0.01$) to 0.39 ± 0.06 ml/min following phentolamine blockade. After denervation the transfer rate was unchanged at 0.37 ± 0.07 ml/min. With elevated blood flow fluid transfer increased to 0.57 ± 0.08 ml/min ($p < 0.01$).

Vascular volume changes (Fig. 1). In the control period, the active vascular volume, as determined by red cells-^{51}Cr and albumin-^{131}I, averaged 15.8 ± 1.8 and 17.4 ± 1.9 ml, respectively, and increased to 18.4 ± 1.8 and 19.7 ± 1.9 ml ($p < 0.01$) following phentolamine blockade. The total vascular volume as measured by plethysmography increased 1.8 ± 0.4 ml ($p < 0.01$). Following denervation the active vascular volume as measured by the red cells-^{51}Cr and albumin-^{131}I were unchanged at 18.1 ± 1.8 ml and 19.8 ± 1.7 ml. The total vascular volume also did not change significantly at 2.0 ± 0.4 ml above the control. Consequent to elevating the blood flow rate the red cell-^{51}Cr space increased to 205 ± 1.8 ml and the albumin-^{131}I space increased to 22.0 ± 2.1 ml ($p < 0.05$). There was an increase in total vascular volume to 3.4 ± 0.3 ml above the control level.

Indicator recovery (Fig. 1). The recovery of red cells-^{51}Cr averaged (%): 97 ± 1, 97 ± 1, 97 ± 1, and 97 ± 1 and the recovery of albumin-^{131}I averaged (%): 96 ± 1, 97± 2, 96 ± 1, 98 ± 1 for the four parts of the experiment. None of these values were significantly different. The recovery of ^{86}Rb averaged 81 ± 2% during the control and

decreased ($p < 0.01$) to 77 ± 2% with phentolamine blockade. Following denervation the recovery remained unchanged at 78 ± 2% but increased to 84 ± 2% following elevation of blood flow ($p < 0.01$).

Discussion. Removal of the tonic activity of the sympathetic nervous system by denervation results in reduced resistance, opening of precapillary sphincters and/or changing capillary flow patterns, thus making a larger capillary surface area available (4). However, the question arises as to how much influence circulating catecholamines have on the vascular bed in such a situation. Blockade by the alpha adrenergic blocking agent phentolamine should prevent the effects on the vasculature of both circulating catecholamines and neural influences.

In this report we have shown that blockade by phentolamine resulted in a reduction of blood flow resistance, an increase in net capillary transfer of fluid and a decrease in recovery of ^{86}RbCl. These changes were associated with increases in vascular volumes as determined by both of the indicators and by the plethysmograph indicating that both the active and total vascular volumes increased by comparable amounts. Alpha adrenergic blockade, therefore, caused the precapillary sphincters to relax, thus bringing about an increase in capillary surface area. The capacity change seems to be due mostly to increased venous volume with smaller changes due to precapillary vessels and capillaries increasing in radius and number.

Denervation of the forelimb following blockade by phentolamine resulted in no significant changes in any of the parameters measured. Thus, along with the fact that a test dose of norepinephrine produced no effect, it would seem that this dosage of phentolamine was sufficient to block both the neural and circulating catecholamine effects. If these experiments can be regarded as comparable to those previously published (4), it would suggest that circulating catecholamines have little effect on the vasculature in these preparations with one possible exception. In our earlier report on denervation without blockade there was a greater increase in albumin than red cell space, indicating redistribution of plasma following denervation. The absence of such an effect in these alpha adrenergically blockaded and denervated preparations suggest that circulating catecholamines in our earlier experiments may have been active in restricting red cells to certain vessels. That is, denervation allowed structures such as the precapillary sphincters to only partially open and, therefore, allowing only plasma to flow through these circuits.

When the blood flow was elevated through the phentolamine blocked, denervated forelimb, there were significant and equal increases in vascular volume determined by all three methods. This was associated with a marked increase in net capillary transfer of fluid, presumably due to increased capillary pressure. The greater recovery of ^{86}RbCl would seem to indicate that a portion of the increase in blood flow is passing through nonexchange vessels. These vessels (A–V shunts) are found in the skin of the foreleg in large numbers in parallel with the capillaries.

Summary. It would seem that both phentolamine blockade and denervation affected the series-coupled circuits by lowering precapillary resistance and opening precapillary sphincters, thus making a larger capillary surface area available. Capillary hydrostatic pressure probably was also increased. The parallel-coupled circuits were affected by making A–V shunts available to elevated flow. These shunts are apparently in the skin and one could, therefore, expect blood flow to pass through the skin at an increasingly greater percentage of the total limb flow as the flow rate is increased.

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