AD NUMBER

AD135240

LIMITATION CHANGES

TO:

Approved for public release; distribution is unlimited.

FROM:

**Distribution authorized to U.S. Gov't. agencies and their contractors;
Administrative/Operational Use; 13 JUN 1957.
Other requests shall be referred to Army Medical Research Lab., Fort Knox, KY.**

AUTHORITY

USAMRL ltr 27 Feb 1970

U.S. ARMY MEDICAL RESEARCH LABORATORY

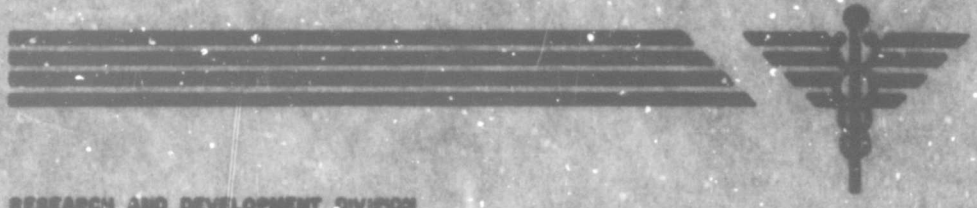
FORT KNOX, KENTUCKY

REPORT NO. 287
13 June 1957

THE EFFECT OF EPINEPHRINE, NOREPINEPHRINE AND SEROTONIN UPON SYSTEMIC SMALL AND LARGE VESSEL RESISTANCES*

FC

*Subtask under Environmental Physiology, USAMRL Project No. 6-64-12-028, Subtask, Cold Injury Studies.



RESEARCH AND DEVELOPMENT DIVISION
OFFICE OF THE SURGEON GENERAL
DEPARTMENT OF THE ARMY

REPORT NO. 287

THE EFFECT OF EPINEPHRINE, NOREPINEPHRINE AND SEROTONIN UPON SYSTEMIC SMALL AND LARGE VESSEL RESISTANCES*

by

F. J. Haddy, M. Fleishman, D. A. Emanuel
and J. Scott

from

Circulation Section
Department of Environmental Medicine
US ARMY MEDICAL RESEARCH LABORATORY
FORT KNOX, KENTUCKY

*Subtask under Environmental Physiology, USAMRL Project No. 6-64-12-028. Subtask, Cold Injury Studies.

Report No. 287
Project No. 6-64-12-028
Subtask USAMRL S-8
MEDEA

ABSTRACT

THE EFFECT OF EPINEPHRINE, NOREPINEPHRINE AND SEROTONIN UPON SYSTEMIC SMALL AND LARGE VESSEL RESISTANCES

OBJECT

To determine separately the arterial, small vessel and venous geometry changes caused by epinephrine, norepinephrine and serotonin.

RESULTS

The above compounds were infused into the brachial artery of 11 dogs at the rate of 2.1, 2.5 and 4.6 γ/min, respectively. Foreleg blood flow rate was maintained constant while pressures were measured in the brachial artery, foot pad small artery, paw small vein and cephalic vein. Epinephrine and norepinephrine greatly elevated calculated small vessel resistance. Serotonin decreased small vessel resistance but elevated artery and vein resistances.

CONCLUSIONS

Locally injected epinephrine and norepinephrine elevate dog foreleg vascular resistance primarily through small vessel constriction. Serotonin does not significantly change total resistance, constricts large arteries and veins, and dilates small vessels.

RECOMMENDATIONS

Extend the study to include observations in denervated limbs.

Submitted 3 January 1957 by:
F. J. Haddy, Major, MC
M. Fleishman, Capt, MC
D. A. Emanuel, Capt, MC
J. Scott, Biologist

APPROVED: Thomas R.A Davis
THOMAS R. A. DAVIS
Head, Environmental
Medicine Department

APPROVED: Floyd A. Odell
FLOYD A. ODELL
Director of Research

APPROVED: Joseph R. Blair
JOSEPH R. BLAIR
Lt Colonel, MC
Commanding

THE EFFECT OF EPINEPHRINE, NOREPINEPHRINE AND SEROTONIN UPON SYSTEMIC SMALL AND LARGE VESSEL RESISTANCES

I. INTRODUCTION

In 1952, Haddy, Richards and Visscher (1) noted that instantaneous brachial artery injections of commercial epinephrine, l-epinephrine bitartrate and l-norepinephrine bitartrate monohydrate in 0.5-5.0 γ doses elevated dog foreleg blood flow rate and did not change foreleg large vessel pressures. Serotonin creatinine sulfate in the same amounts decreased small artery pressure, increased small vein pressure and did not greatly change large vessel pressures or blood flow rate. The methods employed, however, did not permit a precise analysis of changes in vascular geometry. These data were only reported in part in abstract form.

The present report concerns a reinvestigation of the above problem utilizing improved methods. Studies have separately been made of changes in the geometric component of resistance of the dog foreleg arteries, veins and small vessels and these changes have been compared between epinephrine, norepinephrine and serotonin.

II. METHODS

Mongrel dogs weighing approximately 30 to 40 pounds were anesthetized with sodium pentobarbital and placed on their sides. The brachial and femoral arteries were exposed high in the dependent fore and hind legs respectively. A foreleg dorsal foot vein and a ventral foot artery, each about 1 mm in diameter, were dissected free. After completely heparinizing the animal, the proximal end of the femoral artery was connected to the distal end of the brachial artery by a length of polyethylene tubing. The tubing coursed through a blood pump*. Utilizing glass tubes (0.5 mm O.D.), retrograde catherterization of a subcutaneous small paw vein and foot pad small artery (both 0.5 mm) was carried out according to methods previously described (2). A 20 gage needle was inserted into the cephalic vein at the level of the elbow. Utilizing a multiple stopcock arrangement, pressures were rapidly and consecutively measured in the brachial artery, small artery, small vein and cephalic vein with the same 0-75 cm Hg resistance wire pressure transducer.

*Sigmamotor Pump Model T-6, Sigmamotor Inc., Middleport, N.Y.

The blood pump was adjusted so as to produce a mean brachial artery pressure approximating 120 mm Hg. At this pressure, blood flow rate varied from 50 to 96 ml/min in individual animals but was maintained constant in a given animal throughout an experiment. The various vessel pressures were measured during the first, third and fifth minute of a five minute control period. Using a constant infusion pump*, 2.1 γ/min of the base of epinephrine hydrochloride was infused into the brachial artery. Pressures were measured at the first, third and fifth minute of a five minute infusion period. The infusion was stopped and pressures were again measured three times during a five minute post-infusion period. The sequence was repeated in the same animal using 2.5 γ/min of the base of l-norepinephrine bitartrate monohydrate and 4.6 γ/min of the base of serotonin creatinine sulfate**.

The pressure gradients from brachial artery to cephalic vein, brachial artery to small artery, small artery to small vein and from small vein to cephalic vein were divided by the blood flow rate. The resulting values in mm Hg/ml/min were taken to be the resistance for the total, arterial, small vessel and venous segments respectively.

The above methods provide several advantages over those previously used in which blood flow rate was monitored with a flowmeter following instantaneous drug injections. A constant blood flow rate obviated errors involved in estimating flow with a flowmeter, minimized the possibility of changes in small vessel and venous geometry dependent upon changing metabolite (O_2, CO_2, H^+) concentrations and eliminated anomalous viscosity as an initating casual factor in observed changes in calculated resistance. Further, infusion of the drugs at a constant rate eliminated confusing transients associated with the instantaneous injection technique.

III. RESULTS

Figure 1 shows that epinephrine and norepinephrine greatly elevated brachial and small artery pressures. Epinephrine elevated small artery pressure more than brachial artery pressure. This relationship was reversed during infusion of norepinephrine. Serotonin caused irregular changes in brachial artery pressure but greatly decreased small artery pressure. At the dose levels tested, only norepinephrine and serotonin

*Constant Infusion Machine, Model ES-4B. Engineering Specialties, Maderia, Ohio.

**The creatinine sulfate salt of serotonin used in these experiments was donated by Abbott Laboratories, North Chicago, Ill.

elevated small vein pressure and the maximal levels reached during individual experiments were 30 and 32 mm Hg respectively.

Figure 2 and Table 1 describe these data in terms of resistance, the former presenting absolute values and the latter direction, magnitude and variability of resistance changes. Epinephrine and norepinephrine greatly increased total resistance in each of 11 experiments. Total resistance during serotonin infusion increased in 6 experiments, decreased in 4 experiments and did not change in the remaining experiment.

Artery resistance decreased during epinephrine infusion in 10 of 11 experiments. Norepinephrine increased artery resistance in 7 of 10 animals. Resistance decreased in two and remained unchanged in the remaining animals. The average result was a moderate increase in resistance. Serotonin caused a pronounced rise in artery resistance in each instance.

The small vessel segment constricted greatly in each experiment during infusion of epinephrine and norepinephrine. A pronounced dilatation was observed in each animal during infusion of serotonin. The serotonin effect persisted slightly longer than those due to epinephrine and norepinephrine.

Venous resistance increased in 8 of 10 experiments during norepinephrine infusion. In 4 of the 8, the resistance increases ranged from 260 to 384% of the control values. Serotonin elevated venous resistance in 6 of 11 experiments. In 4 of the 6, the resistance increases ranged from 312 to 771% of the control values. At the dose level used, epinephrine did not change venous resistance.

IV. DISCUSSION

The results presented appear to demonstrate that whereas epinephrine and norepinephrine primarily constrict dog foreleg small vessels, serotonin dilates these vessels concomitant with large artery and sometimes large vein constriction. The directionally opposite changes in segmental resistances account for the failure of serotonin to greatly affect total resistance. These observations provide additional evidence that dog foreleg arteries, small vessels and veins constitute independent resistances whose magnitudes may vary in the same or opposite directions through both active or passive mechanisms. The validity of the preceding statement is predicated upon the following summary and analysis of the above and previously reported observations.

Almost every possible combination of active and passive change in segmental resistances has been observed during one or another experimental arrangement. The epinephrine response illustrates active small vessel constriction concomitant with passive artery dilatation. The artery segment likely was subjected to both the passive vasodilatory effect of a rising intraluminal pressure and the active constrictor effect of epinephrine, with the former predonimating. This statement is based upon the finding of an earlier study (3) which showed that a 30 mm Hg rise in average artery segment intraluminal pressure (the mean between brachial and small artery pressures) was associated with a passive artery resistance decrease of about 20%. In the present experiment, artery resistance decreased only 20% even though average artery intraluminal pressure increased 75 mm Hg. A similar combination of directionally opposite active and passive segmental changes has been observed following venous obstruction. This mancuver was associated with active small vessel constriction and passive artery and vein dilatation (3).

The changes during norepinephrine infusion illustrate active constriction in all segments. The rise in artery resistance might have been even greater had conditions been arranged to provide constant brachial artery pressure and variable blood flow rate, thereby partially avoiding passive dilatation dependent upon rising intraluminal pressures. Active constriction in all segments was previously observed during cold exposure (4). Active small vessel and vein constriction occur during faradic sympathetic nerve stimulation (5). Passive dilatation and passive constriction of all segments follows elevation and decrease respectively of brachial artery perfusion pressure (3). That examples of the above categories of responses would be observed might have been accurately predicted.

However, current concepts of hemodynamics appeared to make unlikely the possibility of finding examples of directionally opposite active changes in segmental resistances. Yet several combinations in this category have appeared. Active vein constriction and small vessel dilatation occur during the rewarming period following cold exposure (4). Kelly and Visscher (5) have described changes which likely represent the same event following the release from faradic sympathetic nerve stimulation. Active artery constriction and small vessel dilatation occasionally occur in the rewarming period following cold exposure (4). This response also occurs in the nerve intact foreleg during elevation of blood hydrogen ion concentration. The reverse occurs during decrease of hydrogen ion concentration. However, the most striking example of directionally opposite active changes in segmental resistances yet observed are those accociated with local serotonin infusion.

There can be little doubt that the serotonin induced segmental resistance changes occur through active mechanisms. Venous resistance increased in the presence of elevated venous transmural pressures. The small vessel segment dilated while small vessel intraluminal pressures were falling. This was especially apparent in those experiments in which small vein pressure failed to rise. Since small artery pressure decreased greatly, the small vessel segment most certainly was subjected to falling transmural pressures which would tend to passibely constrict that segment. Yet small vessel resistance decreased markedly. On the average, artery resistance increased markedly in the presence of a small rise in brachial artery pressure and a large decrease in small artery pressure. Hence, the average transmural pressure over the arterial segment likely decreased, tending to passively increase artery resistance. However, in several experiments, artery resistance increased with transmural pressure. In one such experiment, serotonin elevated brachial artery pressure 45 mm Hg without changing small artery pressure. Therefore, resistance increased in the presence of a rising transmural pressure. Further, as pointed out above, a previous study (3) showed that a 30 mm Hg decrease in average artery transmural pressure was associated with a 20% rise in artery resistance. Serotonin decreased the average artery transmural pressure by 16 mm Hg but resistance increased to 230% of the control value. These observations and calculations establish the active nature of the resistance changes associated with local infusion of serotonin.

From the above observations and analysis of observations, there can be little doubt that arteries, small vessels and veins can function as independent resistances under experimental conditions. There also can be little doubt that some of these events occur spontaneously in the intact animal. We have previously reported that small vein pressure is spontaneously variable over wide ranges in resting wakened dogs, especially following artifically induced heart disease (2). Since large blood flow rate changes cause only minimal small vein pressure variations (3), these small vein pressure fluctuations were interpreted as being due to active changes in venous caliber. This ability of various vascular segments to function as independent resistances has obvious inportant implications regarding water and salt transport across capillary membranes, blood volume distribution and cardiac filling.

The results presented may explain how serotonin preduces perculiar skin color changes without predictable blood pressure variations when injected into intact animals or man. They also indicate that serotonin may influence volume distribution of blood within various segments of

the circulatory system. That serotonin may influence water and salt distribution between intravascular and extravascular compartments is suggested by its ability to greatly elevate small vein pressure in some instances. Since capillary pressure in open beds cannot be lower than small vein pressure, net fluid transport was likely out of the capillary in those experiments.

Norepinephrine also constricted the venous segment. At the dose level tested, epinephrine did not. In the earlier study utilizing the instantaneous injection technique, both substances appeared to equally constrict veins. This difference in results between the two studies may be related to differences in dose levels employed. In the first study 0.5 to 5.0 γ were injected instantaneously into the brachial artery. Undoubtedly the foreleg vessels were exposed to peak drug concentrations which were considerably higher than in the present study where the drugs were infused into the brachial artery at a constant rate of 2.1 and 2.5 γ/min.

V. CONCLUSIONS

The effect of epinephrine, norepinephrine and serotonin upon small and large vessel resistances have been studied in the foreleg of the pentobarbital anesthetized dog.

At the dose levels tested, epinephrine and norepinephrine greatly increased total resistance primarily through small vessel constriction. Norepinephrine also constricted large arteries and veins. Serotonin did not significantly change total resistance, increased large artery and sometimes vein resistance and decreased small vessel resistance. These data provide additional evidence that dog foreleg arteries, small vessels and veins constitute independent resistances whose magnitudes may vary in the same or opposite directions through both active or passive mechanisms.

VI. RECOMMENDATIONS

Extend the study to include observations in low resistance (denervated) and high resistance (stimulated cephalic end of sectioned vagi) limbs.

VII. BIBLIOGRAPHY

I. Haddy, F. J., A. G. Richards and M. B. Visscher. Pressures in small and large veins and arteries. Am. J. Physiol. 171: 731, 1952.

2. Haddy, F. J., A. G. Richards, J. L. Alden and M. B. Visscher. Small vein and artery pressures in normal and edematous extremities of dogs under local and general anesthesia. Am. J. Physiol. 176: 355, 1954.

3. Haddy, F. J. and R. P. Gilbert. The relation of a venous-arteriolar reflex to transmural pressure and resistance in small and large systemic vessels. Circ. Res. 4: 25, 1956.

4. Haddy, F. J., M. Fleishman and J. Scott. The effect of change in air temperature upon systemic small and large vessel resistance. AMRL Report No. 252, Ft. Knox, Ky., 1956. Circ. Res. 5: 58, 1957.

5. Kelly, W. D. and M. B. Visscher. Effect of sympathetic nerve stimulation on cutaneous small vein and small artery pressure, blood flow and hind paw volume in the dog. Am. J. Physiol. 185: 453, 1956.

TABLE 1

AVERAGE CHANGE IN TOTAL AND SEGMENTAL FORELEG VASCULAR RESISTANCE (mm Hg/ml/min ± S.D.)

Segment	Epinephrine	Norepinephrine	Serotonin
Total	+1.12 ± 0.54	+1.56 ± 0.56	+0.10 ± 0.41
Arterial	-0.14 ± 0.20	+0.16 ± 0.23	+0.77 ± 0.37
Small Vessel	+1.25 ± 0.56	+1.33 ± 0.41	-0.71 ± 0.33
Venous	-0.024 ± 0.046	+0.074 ± 0.100	+0.067 ± 0.153

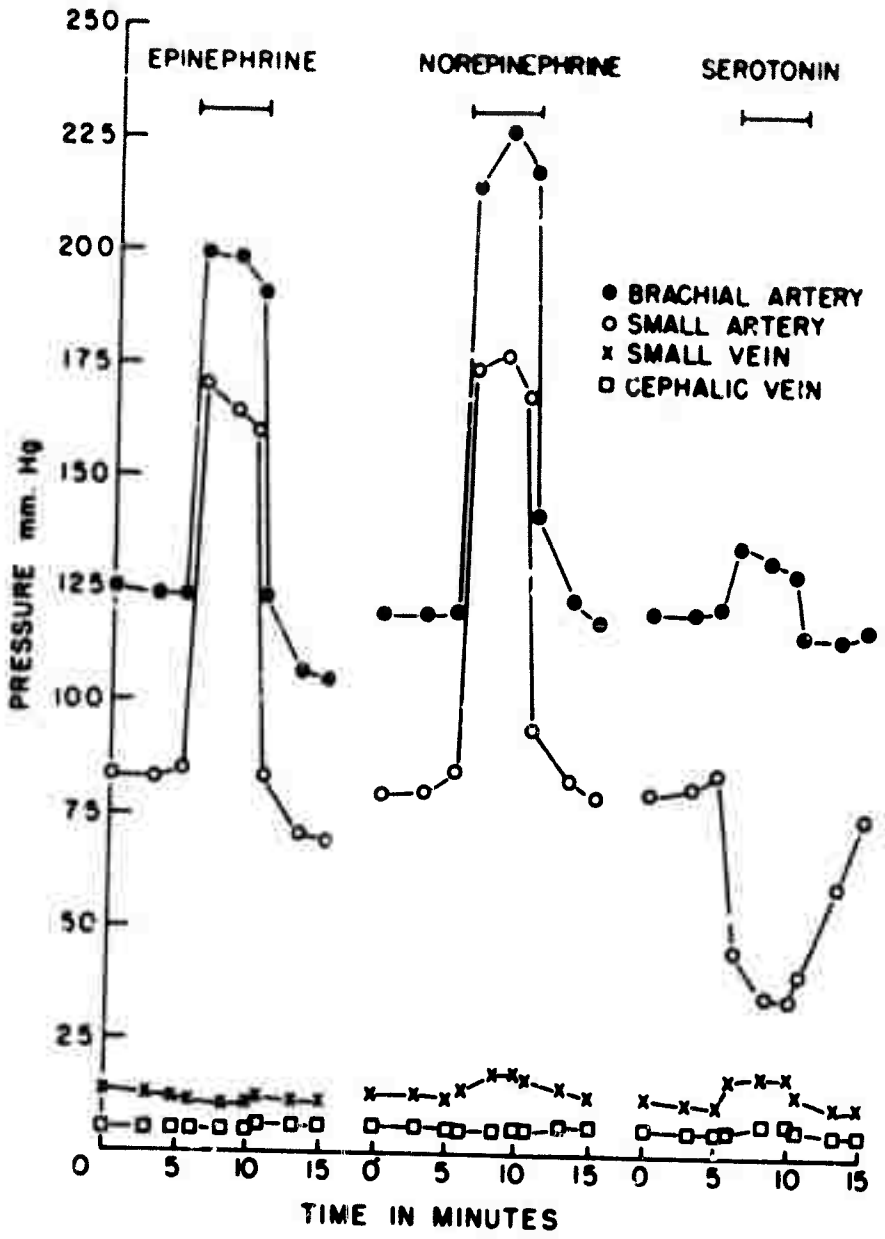


Fig. 1. Average effect of epinephrine, norepinephrine and serotonin upon vascular pressures in 11 dog forelegs. Foreleg blood flow rates were maintained constant at average values of 69, 69 and 75 ml/min, respectively.

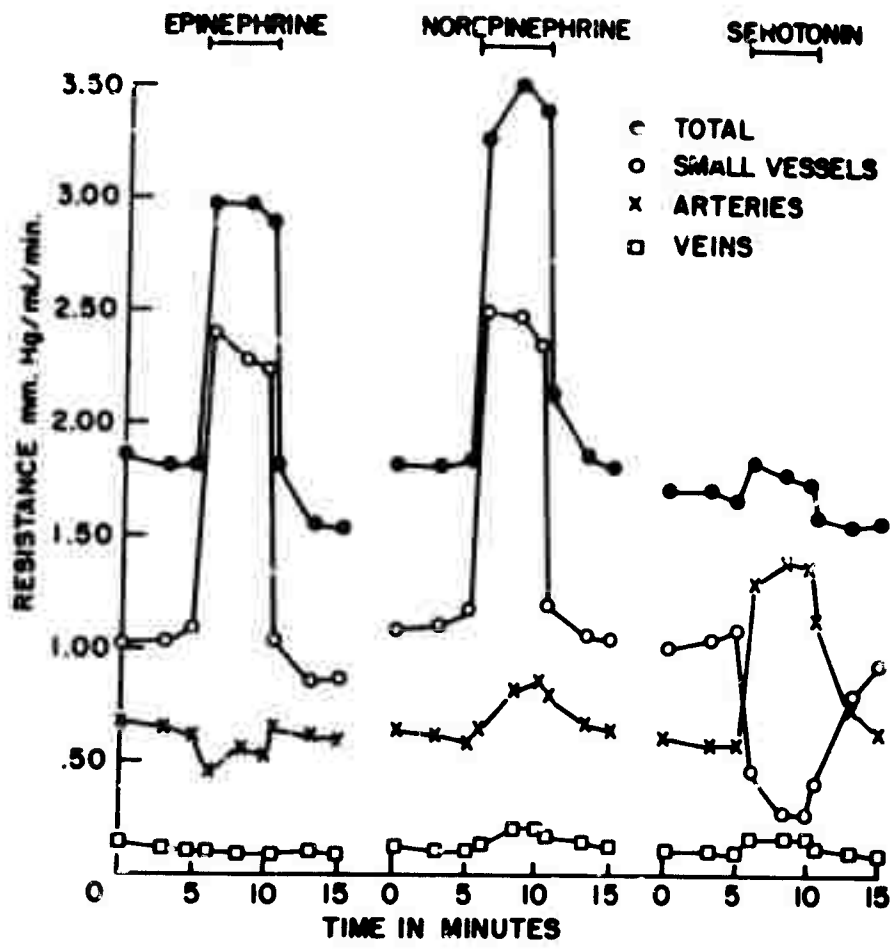


Fig. 2. Average effects of epinephrine, norepinephrine and serotonin upon total and segmental vascular resistances in 11 dog forelegs.

AFP-2756-O-Army-Knox-Jun 57-3C