Effect of Epinephrine, Norepinephrine and Serotonin
Upon Systemic Small and Large Vessel Resistance

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

In 1952, Haddy, Richards and Visscher noted that instantaneous brachial artery injections of commercial epinephrine, 1-epinephrine bitartrate and 1-norepinephrine bitartrate monohydrate in 0.5-5.0 γ doses elevated dog forepaw small artery and vein pressures, decreased 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.

Methods

Caliber changes in various segments of the dog foreleg vascular system during exposure to epinephrine, norepinephrine and serotonin were inferred from calculated resistance changes in corresponding segments. Foreleg blood flow rate was maintained constant with a blood pump while pressures were measured at four sites along the length of the system. 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 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 300 cm. length of 3 mm. O. D. polyethylene tubing which coursed through a blood pump. The pump was immediately set in motion thereby supplying the foreleg with arterial blood from the femoral artery. The pump had been previously calibrated to deliver blood at rates of 50, 75 and 90 ml./min. When set at any of the above flow rates, the pump output did not change measurably even though the pressure against which it pumped varied from 0 to 250 mm. Hg. The 1 mm. small artery and vein were catheterized in a distal direction with 5 cm. lengths of 0.5 mm. O. D. glass tubing according to methods previously described. The catheter tips were finally positioned in a 0.5 mm. vein and artery in the toe web and foot pad respectively. 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.

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 5 min. 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 5 min. infusion period. The infusion was stopped and pressures were again measured three times during a 5 min. postinfusion period. The sequence was repeated in the same animal using

* Sigmamotor Pump Model T-6, Sigmamotor Inc., Middleport, N. Y.
† Constant Infusion Machine, Model KS-4B, Engineering Specialties, Madeira, Ohio.
2.5 γ/min. of the base of 1-noradrenaline 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 (O₂, CO₂, H⁺) concentrations and eliminated anomalous viscosity as an initiating causal 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.

**Results**

Figure 1 Top 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 elevated small vein pressure and the maximal levels reached during individual experiments were 30 and 32 mm. Hg respectively.

Figure 1 Bottom 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 these experiments was donated by Abbott Laboratories, North Chicago, Ill.

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* The creatinine sulfate salt of serotonin used in these experiments was donated by Abbott Laboratories.
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TABLE 1.—Average Change, in Total and Segmental Foreleg Vascular Resistance (mm. Hg/ml./min. ± S.D.)

<table>
<thead>
<tr>
<th>Segment</th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>Serotonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>+1.12</td>
<td>+1.56</td>
<td>+0.10</td>
</tr>
<tr>
<td></td>
<td>±0.54</td>
<td>±0.56</td>
<td>±0.41</td>
</tr>
<tr>
<td>Arterial</td>
<td>-0.14</td>
<td>+0.16</td>
<td>+0.77</td>
</tr>
<tr>
<td></td>
<td>±0.20</td>
<td>±0.23</td>
<td>±0.37</td>
</tr>
<tr>
<td>Small vessel</td>
<td>+1.25</td>
<td>+1.33</td>
<td>-0.71</td>
</tr>
<tr>
<td></td>
<td>±0.56</td>
<td>±0.41</td>
<td>±0.33</td>
</tr>
<tr>
<td>Venous</td>
<td>-0.024</td>
<td>+0.074</td>
<td>+0.067</td>
</tr>
<tr>
<td></td>
<td>±0.046</td>
<td>±0.100</td>
<td>±0.153</td>
</tr>
</tbody>
</table>

7 of 10 animals. Resistance decreased in 2 and remained unchanged in the remaining animal. 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 200 to 384 per cent 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 per cent of the control values. At the dose level used, epinephrine and norepinephrine.

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 effect 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 predominating. This statement is based upon the finding of an earlier study2 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 per cent. In the present experiment, artery resistance decreased only 20 per cent 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 maneuver 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.6 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. Kelly and Visscher 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. 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 associated 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 passively 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. As mentioned, a previous study showed that a 30 mm Hg decrease in average artery transmural pressure was associated with a 20 per cent rise in artery resistance. Serotonin decreased the average artery transmural pressure by 16 mm Hg but resistance increased to 230 per cent of the control value.

These observations and calculations establish the active nature of the resistance changes associated with local infusion of serotonin. From these observations and analyses 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 artificially induced heart disease. Since large blood flow rate changes cause only minimal small vein pressure variations, 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 important implications regarding water and salt transport across capillary membranes, blood volume distribution and cardiac filling.

The results presented may explain how serotonin produces peculiar 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.

Noradrenaline 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 g 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.

SUMMARY

The effects 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, but 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.

SUMMARIO IN INTERLINGUA

Le effecto de epinephrina, norepinephrina, e serotonin super le resistencia de minor e major vasos esseva studiate in le gamba anterior de canes sub anesthesia per pontobarbital.

Al nivellos de dosage investigate, epinephrina e norepinephrina augmentava grandemente le resistencia total, primarimente per constringer le vasos minor. Norepinephrina etiam constrin-geva arterias e venas major. Serotonin non alterava le resistencia total a grados significative, sed illo augmentava le resistencia del arterias e a vices del venas major e reduceva le resistenza del vasos minor. Iste datos corroborava additionalmente que le arterias, vasos minor, e venas del gamba anterior de canes constitue areas de resistencia independente in que le magnitudes pote variar in le mesme direction o in directiones contrari sub le effecto de active e etiam de passive mechanismos.

REFERENCES

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