Effect of Denervation on Diameter and Reactivity of Arteries in the Bat Wing

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Responsiveness of the arterial vessels to intravenous and topically applied epinephrine was determined before and after denervation. Responsiveness to injected epinephrine increased 14 days after denervation; responsiveness to topically applied epinephrine was unaffected by denervation; arterial vessels remained dilated in excess of three weeks following denervation.

It has been suggested that increased permeability of the effector cell following denervation might be responsible for the sensitivity to circulating excitor agents that is seen to develop. A recent investigation showed that an increase in responsiveness to epinephrine could be demonstrated in the minute vessels of the bat wing, after section and degeneration of nerves to the area, if epinephrine was injected intravenously. No increased responsiveness was demonstrated if epinephrine was topically applied to the denervated vessels. It was concluded from these studies that increased permeability of the denervated effector cell was not a factor in producing increased responsiveness.

The observation that denervation produced changes in the physical character of vascular supplies to the bat wing suggested that modification of blood flow and internal pressure might contribute to the changed responsiveness of the vessels to injected epinephrine. The present investigation was carried out to determine if there was a correlation between the marked relaxation of the vessels following denervation and their altered responsiveness to epinephrine.

**Method**

Common brown bats (myotis) and eptesicus were prepared for observation as described by Nicoll and Webb.

Vessel diameters were measured in the following manner: a diagram was made of the vessels pattern of both wings and the inside diameters of the major artery and its successive branches were recorded. Measurements were made at a magnification of 400X using an eyepiece micrometer (fig. 1).

**Results**

**Diameter Changes Immediately After Denervation.** In 21 animals, measurements were made on vessels of both wings before and immediately after section of the nerve accompanying the major artery. Only one of these bats failed to show an increase in the diameter of the major vessel of the denervated side within 10 minutes. The greatest increase in diameter was 60 per cent, the smallest increase was 12. The average increase in diameter of the major vessels was 29 per cent. The contralateral intact wing which served as a control showed a diameter change in only 5 animals, the greatest increase being 20 per cent, the smallest, 4 and the average increase for the group was 2.9 per cent.

The changes in a branch of the major vessel were similar. Of 21 animals, 18 showed an increase in diameter, the greatest increase being 50, the smallest was 15 and the average, 27 per cent. Similar vessels in the contralateral control wing showed a diameter increase in only six animals. Here the increase ranged between 25 and 11 with the average value of 5 per cent.

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Measurements of diameters of arterioles and terminal arterioles were also made. They showed no visible increase in diameter. Because of the rapid relaxation and the magnitude of diameter change in vessels 1 and 2, all
further tests were conducted, using these vessels only. A statistical evaluation of their diameter changes immediately after denervation appears in Table 1.

**Diameter Changes During a 25 Day Period After Denervation.** In order to determine how long relaxation of the arterial vessels persisted, readings were made on groups of animals at 7 to 9 days, 13 to 14 days, 18 days and 21 to 25 days after denervation. The results are presented in figure 2.

On the seventh and ninth days after denervation, the average diameter of the main artery was 39 per cent greater than the contra-

| Diameter Changes During a 25 Day Period After Denervation. |
|-------------------|-------------------|
| **Mean Change**    | 20.1              |
| **Std. Deviation** | 12.9              |
| **Std. Error**     | 2.88              |
| **t**              | 6.98              |
| **p**              | 0.001             |

**Table 1.—Statistical Evaluation of Diameter Changes in Major Vessels Shown in Figure 1**

![Diagram of major artery and its branches in the bat wing.](image)

On the 18th day, the main vessel on the sectioned side averaged a 32 per cent increase over the other wing, the first branch averaged a 45 per cent increase. Twenty-one to 25 days after denervation the denervated wing showed an increase of 26 per cent over the control; the major branch was 31 per cent. It seems conclusive that no decrease in diameter occurs in the major vessels of the denervated wing through the twenty-fifth day after section of the nerve.

**Response of Normal Wing Vessels to Topically Applied Epinephrine.** Threshold responses were determined on right and left wings in a group of 18 animals. A small area was denuded in each wing to expose a branch from the main artery and various concentrations of epinephrine were applied until the vessel responded by constricting. The threshold was considered to be reached when the vessel's average diameter was reduced 50 per cent. Often complete occlusion occurred in a limited area as if a few spiral muscle cells were affected. The concentrations needed to elicit a response ranged from $1.0 \times 10^{-6}$ Gm./ml. to $5.0 \times 10^{-7}$ Gm./ml. These concentrations were considerably higher than those needed to cause complete constriction of the arterioles and precapillaries. In five animals a different concentration was needed to produce a constriction in the right wing as compared to the left. This was felt to be within the range of normal variation.

**Responses of Vessels in Acute and Chronically Denervated Wings to Topically Applied Epinephrine.** In eight animals threshold determinations were made in the right and left wings, immediately following section of the nerve to the right wing. In three of these animals, a stronger concentration of epinephrine was needed to cause a response in the denervated wing than in the contralateral control. All of the denervated wing vessels were at least 16 per cent larger in diameter than the control wing vessels. There was no correlation between the per cent increase of the diameter of the vessel and its responsiveness to topically applied epinephrine.
The changes in responsiveness of the denervated wing vessels, whether compared to the responsiveness before denervation or to the contralateral normal, did not appear significant. It is believed, therefore, that dilation of the muscular arteries following denervation did not affect the responsiveness of the artery to topically applied epinephrine. If there was a trend, the acutely denervated vessels were perhaps less responsive than the intact wing vessels in the earlier intervals after denervation.

Topical applications were made to determine thresholds of branches from the main vessel in a group of eight animals after the right wing had been denervated for two weeks. No difference existed in the responsiveness of the denervated right and the intact left wing. This is in accord with tests done on minute vessels in the bat wing in earlier work. The caliber of the denervated vessels exceeded that of the contralateral normal vessels by 12 per cent. However, the concentration of epinephrine needed to produce constriction was the same in both wings regardless of whether the diameter of the denervated wing vessels was larger than the control or not.

Response to Intravenous Epinephrine in Normal and Denervated Wings. It has previously been established that by 14 days after nerve section, the arteriolar vessels in a denervated wing would respond to concentrations of epinephrine injected in the tail vein that had no effect on the contralateral normal wings. These studies were repeated with the larger artery under observation.

In control studies on 12 intact animals, both wings responded to the same concentration of epinephrine. Tests made on five animals one week after section of the nerve to the right wing revealed that both wings in three animals responded to the same concentration of epinephrine. In two animals the intact wing responded to a concentration that caused no constriction in the denervated wing. In four animals tested 14 days after denervation of one wing, all of the denervated wings responded to a concentration of epinephrine that had no effect on the control wing. These same results
were found in five animals tested between 22 and 25 days following denervation.

Thus it is shown that increased responsiveness to intravenous epinephrine occurs in the muscular arteries at some time between the first and second week after denervation and continues in excess of 3 weeks. Because at this time the arterial vessels are still dilated from the denervation procedure, it seems evident that the increased responsiveness to injected epinephrine is not affected by the resting diameter of the vessel.

**DISCUSSION**

The observation that relaxation of a large magnitude following section of the major nerve persists for a time in excess of 3 weeks concurs with that of Adson and Brown.4 Also, Lee5 reported that conjunctival vessels in man remained relaxed 3½ to 5 weeks following removal of the superior cervical ganglion. However, Barcroft and others,6 using decreased blood flow as a criterion, believe that regain of tone occurs within a few days following sympathectomy. It must be assumed that decreased blood flow is accounted for by a decrease in the caliber of denervated vessels. This was not found to be the case for arteries in the subcutaneous areas in the bat wing. A reduction in blood flow may be the result of increased constriction of the terminal arteriolar vessels. Webb and Nicoll7 have demonstrated that terminal arterioles show a progressive tendency to remain in a contracted state in denervated areas.

Barcroft states "the rate of regain of tone is so remarkably similar to the rate of development of adrenaline supersensitivity... it is difficult to escape the conclusion that the events they represent must be very closely related." The experiments reported here have demonstrated that increased responsiveness to injected epinephrine was found and this developed regardless of the resting diameter of the wing vessels which remained dilated. Increased sensitivity to topically applied epinephrine could not be demonstrated, which is a potent argument against a change in the responsive character of the muscle cell itself.

A recent theory to explain increased responsiveness of denervated vessels has been advanced by Armin and associates.8 They provide evidence to show that normally a sympathetic cholinergic nerve mechanism releases acetylcholine and this tends to keep the artery in a state of dilatation. The authors suggest that the disappearance of acetylcholine from the artery, after sympathetic nerve section, may be partly responsible for the heightened reactivity of the vessel to constrictor stimuli.

It is also possible that the increased responsiveness to injected epinephrine can be explained on a physical basis. A denervated vascular area may be more sensitive to intravenously injected epinephrine than a similar intact area in the same animal because of some change in the vessel wall which allows a larger amount of the chemical excitor to reach the effector cell. Such a condition might be brought about by prolonged distention of the vessel wall and the increased amount of blood flowing through the vessel. Experiments are now in progress to investigate this possibility.

**SUMMARY AND CONCLUSIONS**

Section of the nerve entering the bat wing with the major artery causes relaxation of major blood vessels that persists for at least 25 days.

The increased diameter of the arteries does not cause a change in responsiveness to topical applications of epinephrine immediately after denervation or 14 days thereafter.

Increased responsiveness to injected epinephrine develops in 14 days and continues for at least 25 days regardless of the resting diameter.

It is suggested that the increased responsiveness of denervated vascular areas to injected epinephrine may be explained on the basis of physical changes. The change in diameter and flow in denervated vessels may produce an increased permeability in the vessel walls that allows greater quantities of circulating chemical excitor agents per unit time to reach the smooth muscle cells and produce constriction. This is not related to any change in intrinsic responsiveness of the smooth muscle cell.
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Relation of Pulsatile Pressure to Flow in the Femoral Artery

The correlation of phasic changes in arterial pressure and flow has been interpreted differently by investigators who used phasic flowmeters designed on different principles. McDonald has recently recorded the movement of injected oxygen bubbles in a femoral artery by high speed cinematography. Femoral flow during a cardiac cycle is described as having four phases: (1) A fast forward flow reaching a peak of about 100 cm/sec slightly in advance of the peak of the pressure pulse. This is followed by a rapid decline in flow velocity to zero shortly after the summit of the pressure curve. (2) A back flow reaching a negative velocity of 30 cm/sec. (3) A forward flow starting at 210 and ending at 330 degrees of the cycle which reaches a maximum velocity of 20 cm/sec. (4) A short and small back flow immediately preceding the next systole.

The flow curves so recorded were compared with those derived from differential pressure curves recorded simultaneously at two close points of a femoral artery and with pressure gradients obtained by electrical differentiations of the output of a capacitance manometer. Flow curves were calculated using equations derived by Womersley (J. Physiol. 127: 553, 1955). Good agreement between directly recorded and derived curves was found as regards phase relations of flow patterns and dimensions of systolic forward flow. But there were discrepancies as to magnitude of back flow and diastolic forward flow. Possible reasons are discussed.

The magnitude of the positive and negative phases of femoral flow are not entirely a function of the oscillation pressure gradients; they are also affected by distortions of the wave form and the fall in mean pressure. The latter should enhance the positive and reduce the negative phases as the pulse wave passes into small arteries.

For other interesting details see D. A. McDonald, J. Physiol. 127: 533, 1955.
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