Separation of Responses of Arteries and Veins to Sympathetic Stimulation

By Ben G. Zimmerman, Ph.D.

The sympathetic innervation of the vascular tree consists of postganglionic fibers derived from the sympathetic ganglion cells in the cervical, thoracic, and lumbar regions of the sympathetic trunks. In most vascular beds the blood vessels receive their innervation from postganglionic nerves which accompany the main arterial vessels supplying the bed. Information is sparse, however, regarding the derivation of the sympathetic innervation of the individual vessels, i.e., the arteries, arterioles, and veins, making up the vascular tree. Kuntz sums up current knowledge regarding innervation of the peripheral vasculature with the statement “The peripheral vessels are supplied by sympathetic fibers that join them through the somatic nerves that lie in closest proximity to them.” One would surmise from this that arteries and veins could be innervated by anatomically separate nerve trunks; however, physiological evidence confirming this is needed.

The perfused hind paw of the dog provided a convenient means of investigating the innervation of the segments of this particular vascular bed. The paw consists mainly of skin and bone and is practically devoid of muscle; therefore, the vasomotor response elicited in this bed is ascribed to cutaneous vessels which can be thought of as responding in a quantitatively similar manner. Application of the technique of Haddy and Gilbert to determine resistance changes of the individual vascular segments arranged in series, i.e., the arteries, small vessels, and veins is considered justifiable since the total segments making up the vascular network in this bed even though arranged in parallel do respond homogeneously.

Methods

Fifteen mongrel dogs weighing from 9 to 20.9 kg were employed in these experiments. The animals were anesthetized with 30 mg/kg of sodium pentobarbital injected intravenously. Supplementary doses of 3 to 6 mg/kg were administered routinely about every hour after the initial dose in order to maintain a deep level of anesthesia. Decamethonium, 0.25 mg/kg, was administered through a cannulated femoral vein and the animals were placed on artificial respiration. Neuromuscular blockade was employed and maintained in order to prevent motor nerve stimulation during the subsequent sectioning and in some cases electrical stimulation of the tibial nerve, and also to prevent voluntary respiratory movements while the animal was on the respirator. Heparin sodium was injected intravenously in a dose of 5 mg/kg to prevent clotting.

The procedure used to perfuse the hind paw and to record segmental vascular blood pressures shown in figure 1 is a modification of that of Haddy and Gilbert and has been described in detail elsewhere. This consisted of exposing the abdominal aorta through a retroperitoneal incision in the left flank, and the right femoral, left cranial tibial, and left saphenous (plantar branch) arteries and a left superficial dorsal metatarsal vein through skin incisions. Great care was taken when separating the saphenous artery from the surrounding tibial nerve, as not to damage the nerve fibers.

Pressures were recorded retrogradely from the small artery (1 mm O.D.) and vein (0.75 mm O.D.) by passing a narrow bore polyethylene catheter (0.6 to 1.0 mm O.D.) as far into the vessel as possible, making sure that the tip of the catheter was not occluded and that a true lateral pressure was recorded. Valid small artery pressure was recorded since the saphenous artery forms many anastomoses with the cranial tibial artery at a site distal to the cannulations. A constant blood flow to the paw was delivered through the cranial tibial artery with a Sigmamotor pump which was supplied with the animal’s own blood from a catheter passed into

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the aorta through the right femoral artery. A tie was made on the aorta around the catheter in order to prevent any collateral blood flow to the paw. All regions of the paw were effectively perfused through the cranial tibial artery because of the anastomoses in the paw. The paw was effectively isolated from the remainder of the leg, since the cranial tibial and saphenous arteries were found to be the main blood supply to the paw and they were tied off. Also, in experiments in which a tight ligature was passed around the paw (with care not to include nerves or veins in the tie), no difference in the vasoconstrictor response to nerve stimulation was noted as compared to experiments in which no ligature was used.

Flow averaged 27 ml/min and this produced a perfusion pressure (large artery pressure) of from 60 to 105 mm Hg in the paw. Perfusion pressure was measured from a T-tube connected to the cannula in the cranial tibial artery. In several experiments a large vein pressure was recorded from the lateral saphenous vein, however, since this pressure did not change significantly during nerve stimulation, its measurement was omitted from most experiments.

The left lumbar sympathetic chain was isolated through the incision made to expose the aorta, and after the perfusion was begun, sympathetic denervation was performed by crushing the chain proximal to the L5 ganglion. A Harvard electrode with its clamp removed, was placed under the nerve distal to L5 and held in place with a small clamp to insure contact of the nerve with the electrode. Stimulation was done by means of a Tektronix pulse wave generator through an isolation transformer. In five experiments pulses of 4 volts, 1 msec duration, and 2 to 10 cycles per second (cycles/sec), were employed, and in the remainder of the experiments 8 to 10 volts which provided a stimulus of supramaximal intensity, were used. The duration of the stimulation period ranged from 30 seconds to 3 minutes, but usually a duration of one minute was employed. In four experiments the tibial nerve was stimulated in order to compare this response to stimulation of the lumbar sympathetic trunk.

The control period in the sympathetic stimulation experiments consisted of obtaining responses to stimulation usually at a low frequency (2 cycles/sec) and at a high frequency (10 cycles/sec). In four experiments norepinephrine, 0.5 to 2 μg, was injected intra-arterially to compare the response to direct action of norepinephrine with that of nerve stimulation. The tibial nerve was then tied and cut, and the response to nerve stimulation was repeated. In most experiments the deep fibular nerve was then sectioned and one or both responses to nerve stimulation were repeated. Bretylium tosylate (10 mg/kg) or βTM 10* (10 mg/kg) were given intravenously in several experiments to block the remaining response to sympathetic stimulation. Procaine hydrochloride in 5% solution was injected into the subcutaneous tissue all around the paw in the region below the site where the tibial nerve was exposed, in two experiments. Transection of the subcutaneous tissue completely around the paw and sectioning of the remaining nerve fibers was done in two experiments to abolish the remaining response to stimulation.

The vascular resistance changes occurring in the paw as the result of sympathetic stimulation were calculated as

\[
\frac{\Delta \text{pressure in mm Hg}}{\text{flow in ml/min}}
\]

by means of the following equations:

1. Change in total resistance =

\[
\frac{\text{peak change from control of perfusion pressure}}{\text{flow}}
\]

2. Change in arterial resistance =

\[
\frac{\text{peak change in perfusion pressure} - \text{peak change in small artery pressure}}{\text{flow}}
\]

3. Change in small vessel resistance =

\[
\frac{\text{peak change in small artery pressure} - \text{simultaneous change in small vein pressure}}{\text{flow}}
\]

*Obtained from Smith Kline and French Laboratories.
4. Change in venous resistance =
\[ \frac{\text{peak change in small vein pressure}}{\text{flow}} \]

The main interest in these experiments was how the peak vasoconstrictor effect in the vascular segments was influenced by nerve section, and for this reason the vascular resistances were calculated from the changes of peak pressures. Because the peaks of pressure changes in the small veins were often delayed compared to perfusion and small artery pressures, the small vessel resistance was calculated from peak small artery pressure minus small vein pressure at that time. Because of this and because the peak venous resistance change occurred at a later time, the sum of the arterial, small vessel, and venous resistance changes approximates, but does not necessarily equal, the total resistance change.
by sympathetic stimulation is similar to that reported earlier.3

After sectioning the nerve trunks accompanying the main arterial supply of the paw, the tibial and deep fibular nerves, stimulation of the lumbar sympathetic nerve produced an elevation in total resistance which was accounted for almost entirely by increased resistance of the paw veins. In table 1 and also in figure 2, it can easily be seen that the increments in arterial and small vessel resistance before nerve section were essentially eliminated while the increment in venous pressure was unchanged or increased. The mean reduction in the small vessel resistance increment was -92.8% at 2 cycles/sec and -99.5% at 10 cycles/sec. It appears that the slight residual small vessel constriction which occurred at 2 cycles/sec was masked when stimulation was carried out at 10 cycles/sec. This may result from greater passive distension of the small vessels brought about by the larger increase in small vein pressure at the high frequency. The mean reduction in the arterial resistance increment after nerve section was -94.1% at 2 cycles/sec and -97.4% at 10 cycles/sec.

Venous resistance was increased at 2 cycles/sec after nerve section by amounts similar to those in the control period; however, at 10 cycles/sec the venous resistance increase tended to be greater after nerve section. In most experiments the peak changes in small vein pressures tended to occur later than the peak increases in small artery and perfusion pressures, which usually occurred synchronously. A transient impounding of blood in the larger arteries of the paw caused by the very high resistance of the smaller arteries at the higher frequency, and therefore a transient fall in venous blood flow, may add to the lag in the pressure rise in the veins. Since the pump delivers a constant flow, in a short time the flow in the veins must return to control. In some cases it is possible that the peak rise in venous pressure was not reached in the minute of stimulation before nerve section. However, after nerve section, when no

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Table 1: Changes in Segmental Resistances in Control Period and After Nerve Section

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Total</th>
<th>Arterial</th>
<th>Small vessel</th>
<th>Venous</th>
<th>Stimulation at 2 cycles/sec</th>
<th>Total</th>
<th>Arterial</th>
<th>Small vessel</th>
<th>Venous</th>
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<td>7.27</td>
<td>2.87</td>
<td>3.80</td>
<td>0.56</td>
<td>1.17</td>
<td>0.37</td>
<td>1.13</td>
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<tr>
<td>93</td>
<td>4.00</td>
<td>1.83</td>
<td>1.30</td>
<td>1.23</td>
<td>1.07</td>
<td>0.13</td>
<td>0.27</td>
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<tr>
<td>94</td>
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<td>0.67</td>
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<td>1.10</td>
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<td>103</td>
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<td>0.20</td>
<td>0.28</td>
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<tr>
<td>116†</td>
<td>5.87</td>
<td>4.56</td>
<td>0.35</td>
<td>0.96</td>
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<td>0.13</td>
<td>0.96</td>
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<tr>
<td>Mean</td>
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<td>2.22</td>
<td>0.80</td>
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<tr>
<td>sd</td>
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Stimulation at 10 cycles/sec

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<th>Exp. no.</th>
<th>Total</th>
<th>Arterial</th>
<th>Small vessel</th>
<th>Venous</th>
<th>Stimulation at 10 cycles/sec</th>
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<th>Venous</th>
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<td>1.00</td>
<td>3.80</td>
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<td>0.83</td>
<td>0.07</td>
<td>-0.20</td>
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<td>7.23</td>
<td>4.57</td>
<td>0.63</td>
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<td>0.13</td>
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<tr>
<td>103</td>
<td>7.60</td>
<td>2.72</td>
<td>2.72</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
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<td>2.14</td>
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<tr>
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<tr>
<td>Mean</td>
<td>6.69</td>
<td>2.97</td>
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<tr>
<td>sd</td>
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<td>1.55</td>
<td>0.58</td>
<td>0.51</td>
<td>0.17</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*imm Hg/ml per min.
†Stimulation: 5 cycles/sec in this experiment.
‡Stimulation: 20 cycles/sec in this experiment.
such impounding of blood occurs due to absence of arterial constriction, venous pressure rises faster and a higher peak is thus attained at the end of one minute. Such a result is found in figures 2 and 3; it should be noted also that after nerve section, the increases in perfusion, small artery, and venous pressures occur synchronously, which would be expected if the increase in venous resistance accounts for the increase in small artery and perfusion pressure.

The venous constrictor response after nerve section was blocked completely or reduced markedly after administration of the adrenergic neuronal blocking agents, bretylium and βTM 10 (table 2). This indicates that stimulation of sympathetic nerves was responsible for the rise in small vein pressure. Sectioning the nerves accompanying the veins on the anterior surface of the paw in two experiments reduced (−35 and −23%), but did not abolish, the venous constrictor response remaining after arterial nerve section. However, transection of all tissue around the paw, except the large veins, eliminated essentially the remaining venous response to sympathetic nerve stimulation (table 2). Similarly, infiltration of procaine into this same region also blocked the remaining response to sympathetic nerve stimulation (table 2).

Responses to intra-arterially administered norepinephrine were neither altered significantly by nerve section in four of these experiments, nor was the response to norepinephrine reduced by the infiltration of procaine (fig. 3). The latter result indicates that blockade of venous constriction by procaine was not due to a direct depressant effect on the venous smooth muscle, but was due to nerve blockade.

Stimulation of the peripheral end of the cut tibial nerve elicited the segmental vascular resistance changes shown in table 3. A large increase in total resistance was produced which consisted predominantly of an increase in arterial resistance and to a lesser extent in small vessel resistance. In two of the four experiments no change in venous resistance was obtained and in two experiments only a small increase was elicited; these changes in venous resistance were far less than those brought about by lumbar sympathetic nerve stimulation.

**Discussion**

This investigation has provided evidence for the partial segmentalization of the sympathetic innervation of the blood vessels in the dog’s paw. The sympathetic postganglionic fibers included in the somatic nerve bundles accompanying the main arterial vessels in the paw distribute mainly to specific sections of the vascular tree. The evidence that the innervations of the arteries and small vessels are derived from these arterial nerves is provided by the finding that their responses to lumbar sympathetic stimulation are nearly abolished by sectioning the tibial and deep fibular nerves. The veins, on the other hand, receive

<table>
<thead>
<tr>
<th>Exp. no.</th>
<th>Agent</th>
<th>Change in venous resistance*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before blockade</td>
</tr>
<tr>
<td>90</td>
<td>Bretylium</td>
<td>1.00</td>
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<tr>
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<td>Bretylium</td>
<td>1.03</td>
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<td>Bretylium</td>
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<tr>
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<td>βTM 10</td>
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<tr>
<td>113</td>
<td>Procaine</td>
<td>2.08</td>
</tr>
<tr>
<td>116</td>
<td>Procaine</td>
<td>0.96</td>
</tr>
<tr>
<td>162</td>
<td>Transection</td>
<td>3.03</td>
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<tr>
<td>172</td>
<td>Transection</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*Δmm Hg/ml per min.
most of their sympathetic supply from nerves separate from those which accompany the arteries, because the venous response remained after arterial nerve section and only a small venous constrictor effect was obtained on subsequent tibial nerve stimulation. A small proportion of the fibers innervating vessels included in the segment defined as the small vessels segment, accompanies the nerves which supply the veins, since at low frequency of stimulation a small degree (about 7% of control) of small vessel constriction persisted after arterial nerve section.

It has not been determined in the present study whether all veins, or only veins of a certain size making up the venous segment, or only localized sites in the veins are responsible for the increase in venous resistance elicited by nerve stimulation. The evidence does indicate, however, that the increase in small vein pressure is brought about by constriction somewhere along the venous segment beginning at the collateral vessels from which the small vein pressure is derived (veins of about 0.1 to 0.5 mm O.D.) and ending at the large vein (about 3 to 4 mm O.D.) which is at the level of nerve section. Constriction of larger veins upstream to this site does not contribute significantly to the venous response for the following reasons. Transection of the subcutaneous tissue, at the level at which the tibial nerve was cut, abolished for the most part the venous response to sympathetic nerve stimulation. The nerve fibers that innervate the veins contributing mainly to the response run with the somatic nerves accompanying the veins themselves and through the subcutaneous tissue in the absence of somatic nerves. This conclusion was reached because sectioning the somatic nerves accompanying the veins reduced the venous response to some extent but did not abolish it in two experiments and because transection of the remaining small nerves visible in the subcutaneous tissue abolished the response in two other experiments. Apparently relatively few fibers innervating the veins also accompany the tibial nerve because in two of four animals tibial nerve stimulation did cause slight venous constriction. The nerve distribution to the arterial side of the vascular bed does not appear to be as diffuse as that to the venous side, since arterial and small vessel constriction can be largely eliminated by cutting two nerve bundles, the tibial and deep fibular nerves. It appears that the majority of the sympathetic fibers supplying the arteries and small vessels run in the tibial nerve, because a large increment in arterial and total resistance was obtained upon stimulation of this trunk. However, some fibers accompany the deep fibular nerve as
well, because section of this nerve is necessary to eliminate the arterial and small vessel constriction during sympathetic stimulation.

It can be argued that if maximal constriction of the veins occurs at a lower frequency of stimulation than that required for the arteries and small vessels, it would be possible to eliminate most of the arterial and small vessel constriction elicited by sympathetic stimulation by only a partial denervation and not affect the venous response as much. In this study it was found that the arterial and small vessel responses were abolished or greatly reduced, and the venous response was left intact, by stimulation at 2 cycles/sec as well as at 10 cycles/sec even though the venous response was not maximal at 2 cycles/sec. Furthermore, in previous work no difference was found in the frequency response curves for the arteries and veins of the dog's paw, whereas maximal constriction of the small vessels did seem to occur at lower frequencies of stimulation. These results would rule out the possibility that the separation of the arterial and venous responses by arterial nerve section is dependent on frequency of stimulation.

Besides providing physiological evidence for the separate innervation of arteries and veins in the paw, this study has verified further the validity of the procedure for the measurement of segmental vascular resistances in the cutaneous vessels in the paw. Calculations of segmental resistances assume that the vascular bed is a continuous system and, when flow is constant, that resistance changes in veins, small vessels, and arteries will be reflected back and raise pressure in that portion of the vascular bed proximal to the site of constriction. Under the conditions of these experiments, the resistance increase in the veins produced by sympathetic nerve stimulation after arterial nerve section was reflected back into the small vessels and arteries, raising their respective pressures and accounting for the increase in calculated total resistance. The apparent complete closure of the small veins and the lack of communication with the circulation in the proximal vessels in the paw during sympathetic nerve stimulation obtained by Davis and Hamilton may be attributed to a difference in techniques. In their preparation blood flow was not maintained constant. When changes of segmental vascular resistances during sympathetic stimulation are to be determined, as in the present study, it appears essential to maintain constant blood flow.

**Summary**

Lumbar sympathetic nerve stimulation produced an increase in arterial, small vessel and venous segmental resistances in the perfused hind paw of the dog. Repeating the stimulation, after having sectioned the somatic nerve bundles accompanying the main arterial supply of the paw, brought about an increase only in venous resistance which was equal to or greater than that obtained in the control period. This venous constrictor response was reduced greatly by the intravenous administration of adrenergic neuronal blocking drugs, by local infiltration of procaine around the paw, or by transection of the subcutaneous tissue around the paw and the nerves accompanying the veins. These results indicated that sympathetic postganglionic fibers supplying the arteries and small vessels were derived from nerve bundles accompanying the arteries (tibial and deep fibular nerves). The fibers supplying the veins are distributed more diffusely in that they are found in somatic nerve bundles accompanying the veins themselves, in the tibial nerve, and in the subcutaneous tissue of the paw.

**References**


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