Tissue Clearance as a Measure of Nutritive Blood Flow and the Effect of Lumbar Sympathetic Block upon Such Measures in Calf Muscle

By Samuel I. Rapaport, M.D., Albert Saul, B.S., Chester Hyman, Ph.D., and M. E. Morton, Ph.D., M.D.

This paper reports the effect of procedures known to alter local blood flow upon the rate of removal of locally injected Na$^{24}$ and I$^{131}$. An evaluation of this clearance method as a measure of nutritive blood flow is made. A second purpose is to report the lack of effect upon clearance from calf muscle of lumbar sympathetic block, and to discuss its therapeutic implications.

The rate of disappearance of a locally injected radioactive isotope has been proposed as a measure of effective or nutritive blood flow through that part.\textsuperscript{1-3} This paper reports experiments designed to clarify the value and limitations of this method of measurement, by noting the effect upon clearance of technics known to alter local blood flow, namely, reactive hyperemia, increased venous pressure, and the release of sympathetic tone in the distal skin by reflex heating. The method was then used to assess the effect of lumbar sympathetic block upon clearance from resting calf muscle. These latter observations are emphasized because such information about the result of sympathetic nerve interruption upon muscle blood flow helps one to understand what may be expected of lumbar sympathectomy in the treatment of peripheral vascular disease.

The problem of whether or not the blood vessels of resting skeletal muscle are maintained in a state of partial constriction by sympathetic vasmotor impulses has been attacked by many investigators. Evidence from animal investigation suggests the existence of such vasoconstrictor tone.\textsuperscript{4-7} The results of observations in man are less consistent. Friedlander and co-workers\textsuperscript{8} found that deep muscle temperature fell after sympathetic interruption and so concluded that vasoconstrictor tone does not exist. Grant and Pearson\textsuperscript{9} could not demonstrate a significant increase in forearm blood flow after moderate reflex heating. Smith and his co-workers\textsuperscript{10} in an analysis of the effect of spinal anesthetic upon blood pressure, concluded that there is negligible tonic sympathetic activity in skeletal muscle. Measurements, weeks and months after surgery, by various workers\textsuperscript{11,12} have shown that muscle blood flow is not increased by sympathectomy; however, vasodilatation immediately after sympathetic interruption remains a possibility, since denervated vessels soon regain intrinsic tone.

On the other hand, most plethysmographic data support the existence of vasoconstrictor tone in muscle vessels. Wilkins and Eichna\textsuperscript{13} found that warming the body increased forearm blood flow from two- to fourfold. Barcroft and his co-workers\textsuperscript{14,15} reported a similar increase in forearm blood flow after the release of sympathetic tone by nerve block or by reflex heating. They showed this to be due to increased flow through the underlying muscle and not the skin. The case for the existence of vasoconstrictor tone in muscle vessels in man

From the Department of Physiology, School of Medicine, University of Southern California, Los Angeles, and the Radioisotope Unit of the Veterans Administration Hospital, Long Beach, Calif.

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has been convincingly summarized by Barcroft and Edholm.18

There are recent reports in which the clearance technic has been used to evaluate the effect of general vasodilator drugs on calf muscle blood flow. A decrease in the rate of removal of radioactive sodium (Na24) has been described after the administration of Priscoline.14,15 Reflex heating plus tetraethylammonium chloride produced no significant change in the clearance rate.16 These results, however, do not necessarily indicate an absence of vasoconstrictor tone, since some dilatation of the muscle vessels could be masked by a shift of blood to areas more widely dilated by these agents.

We have examined the result of lumbar sympathetic block upon the rate of removal of radioactive iodine (I131) or Na24 from calf muscle in 10 patients. In addition, the effect of the block upon blood flow through the toe tip was determined by skin temperature measurements and venous occlusion plethysmography. This permitted a comparison of the result of the block upon nutritive muscle blood flow estimated by clearance, with its effect upon blood flow through the toe, an area known to be under dominant sympathetic nervous system control.

**Method**

Clearance is measured by injection into the region to be studied of several microcuries of Na24 or I131 as ions in a small amount of saline. These ions can be used interchangeably, since we have shown that in man they are cleared at the same rate.19 A GM counter is placed next to the skin overlying the site of injection and the external counting rate is continuously recorded. The theoretic basis for the method and the details of the technic have been described by Kety,3 who showed that when blood flow is constant, a constant fraction of the labeled extracellular ion is cleared per unit time. A plot of the log of external counts per minute against time will give a straight line of negative slope, k, which is the clearance rate and may be expressed as per cent of the ion removed per minute. Rates of removal may also be expressed as the half time, t1/2, which is the number of minutes taken for the external counting rate to be halved.

All blood flow measurements were made from the second toe by the use of a Burch-Winsor pneumoplethysmograph20 and the venous occlusion method as described by Goetz.21 Temperatures were measured by a thermocouple and recorded upon a self balancing potentiometer (Micromax).

In the experiments on the effect of lumbar sympathetic block, the patient, lightly clad, rested quietly in the supine position. An attempt was made to have the room cool; most of the experiments were started with a room temperature between 65 and 70 F., in two it was about 75 F., and in one it was 87 F. Room temperature usually increased 2 to 3 F. during the course of the experiment. After about 30 minutes of rest, two or more measurements of toe blood flow were made. Then from 2.5 to 18 microcuries of Na24 or I131 in from 0.05 to 0.80 cc. of isotonic saline were injected into the calf muscle. A gamma-sensitive counter was placed next to the skin overlying the site of injection, and its output was inscribed by a pen activated from the relay of a Tracerlab autoscaler. The external counting rate was recorded for from about 10 to 15 minutes and then toe blood flow was measured again. After this the patient was turned on his side and the lumbar sympathetic ganglions were blocked with procaine. In almost every instance 5 to 15 minutes were required until the beginning rise in toe temperature indicated that a block had been obtained. The patient was then turned onto his back and a second determination of clearance was made over a 10 to 20 minute period. In about half the patients it was necessary to make a second injection at this time because of a low counting rate. Toe blood flow measurements were also made before and after the second clearance determination to establish the persistence of the block.

The experiments on the release of sympathetic tone in the distal skin by reflex heating were done in a similar fashion. The subject rested, almost nude, in a cool room (67 to 73 F.) until toe temperature stabilized at about room temperature. Clearance rates were taken from the subcutaneous tissues at the base of the second toe and blood flow measurements from the tip of the second toe. Na24 measured by a thin-walled beta counter was used in most of these experiments. The body was heated by a “baker” placed over the trunk. After 45 minutes to an hour of heat, when toe temperature had risen and leveled off, the blood flow and clearance determinations were repeated.

**Results and Discussion**

Since any difference between resting muscle clearance and clearance after sympathetic block was to be taken as evidence of an alteration in blood flow produced by the block, it was necessary to establish the fact that clearance did not change spontaneously. On 13 occasions, resting muscle clearance was measured for a 30 minute period. It was found necessary to discard the data of the first two or three minutes after
the injection, since the injected ion frequently did not begin to leave the site during this period. A straight line of constant slope could be fitted to the data obtained throughout the remainder of the period in every instance except one. In the exception, a break in the slope occurred at the end of 12 minutes and a second slope was established which persisted until the end of the determination. Whether this was due to a spontaneous change in muscle blood flow cannot be said. In a large number of clearance determinations made from the subcutaneous tissues of the forearm, for periods of 10 minutes or longer, a straight line could be fitted to the data obtained throughout the experimental period, but rare exceptions, gave straight lines with no change of slope over the experimental period.

The next step was to demonstrate the extent of change in muscle clearance produced by changes in muscle blood flow. Kety had shown that reactive hyperemia resulted in a considerable increase in clearance over control levels. We repeated this experiment to obtain additional clearance values to compare with the plethysmographically determined increase in calf muscle blood flow reported by Eichna and Wilkins. They found that, following an arterial occlusion of five minutes, blood flow increased to 14 to 38 cc. per 100 cc. of part per minute (average 23 cc.) which is a ten- to twentyfold increase over resting muscle blood flow. The maximum blood flow is the same after a 5 or 10 minute period of occlusion. The period of marked hyperemia is transient and flow begins to decrease almost immediately after the circulation is reestablished. Grant reports an experiment in which the flow rate may be seen to return almost to the resting level in one minute. Kondo, Winsor and associates describe a return to near control values by the third minute following occlusion of the circulation to the toe for five minutes. Thus it becomes apparent that, if clearance parallels blood flow, a semilogarithmic plot of the counting rate at successive half minute intervals following the release of an arterial tourniquet should not be a straight line but a curve with an initial steep portion followed by a gradual return to the control slope.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Room Temp. °F.</th>
<th>Resting Clearance %/min.</th>
<th>Reactive Hyperemia %/min.</th>
<th>Reactive Clearance %/min.</th>
<th>K′′/K′</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. G.</td>
<td>23</td>
<td>61-68</td>
<td>1.7</td>
<td>24.3</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>A. M. S.</td>
<td>24</td>
<td>64-69</td>
<td>4.1</td>
<td>53.6</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>A. S.</td>
<td>26</td>
<td>59-63</td>
<td>4.9</td>
<td>20.6</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>D. C.</td>
<td>29</td>
<td>62-64</td>
<td>5.8</td>
<td>64.0</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>R. P.</td>
<td>29</td>
<td>—</td>
<td>6.3</td>
<td>21.7</td>
<td>3.4</td>
<td></td>
</tr>
</tbody>
</table>

Average: 4.6 36.8 8

In several normal subjects, rested in a cool room, clearance from calf muscle ranged from 2 to 6 per cent per minute. Reactive hyperemia was produced by a 10 minute arterial occlusion. A plot of the log of the counting rate obtained when the circulation was reestablished against time, was a curve for several minutes. A straight line could be fitted to the initial points of the curve during the first one to two minutes, and the slope of this line was called the "reactive hyperemia clearance rate."

These rates are summarized in table 1 and a representative experiment is shown in figure 1. One sees that the clearance after arterial occlusion is increased from resting values of 2 to 6 per cent (average 4.6 per cent) to 20 to 60 per cent per minute (average 30.9 per cent). In different subjects the increase ranged from three and one-half to fourteenfold (average eightfold). In comparing these values with the magnitude of the blood flow increase as measured plethysmographically, one must keep in
mind that the plethysmographic values are maximum values taken from repeated determinations made during the first 30 seconds after the circulation is released; whereas the clearance rates represent average blood flows estimated from successive counting rates over half-minute intervals. Therefore we feel the data are evidence that clearance reflects blood flow through muscle. It is also obvious, however, that the clearance technic as used in these experiments is not applicable to the measurement of very rapid changes in blood flow, since average counting rates over about one-half minute were used, and several points were necessary to obtain an accurate slope.

In a recent publication Miller and Wilson25 have objected to the use of reactive hyperemia experiments on the grounds that during the period of arterial occlusion radioactive ions are accumulating in the local capillaries, and on return of the circulation an unusually high concentration is swept away. They argue that this, rather than increased blood flow, may be the reason for the increase in clearance. This does not seem valid to us. Blood stagnant in the local capillaries about the injection site would be replaced by fresh blood within about 10 seconds at the most. This may be inferred from the observations of Lewis, Pickering and Rothschild,26 who clearly showed that pain due to the accumulation of local metabolites during ischemic exercise is often relieved within two to four seconds after the circulation is re-established. Thus, our slopes of reactive hyperemia clearance, which are fitted through at least two successive half-minute counting rates after the release of the circulation, could not be due to the removal of blood overly saturated with the radioactive ion.

### Table 2—The Effect of Increased Venous Pressure upon Clearance

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Site</th>
<th>Control K', %/min.</th>
<th>Venous Pressure K', %/min.</th>
<th>Post-Venous Pressure K'', %/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. F.</td>
<td>61</td>
<td>Cerebral arteriosclerosis</td>
<td>I. M.</td>
<td>50</td>
<td>10.4</td>
<td>4.3</td>
</tr>
<tr>
<td>W. B.</td>
<td>54</td>
<td>Bronchogenic carcinoma</td>
<td>I. M.</td>
<td>50</td>
<td>5.4</td>
<td>1.7</td>
</tr>
<tr>
<td>J. P.</td>
<td>59</td>
<td>Arteriosclerosis obliterans</td>
<td>I. M.</td>
<td>50</td>
<td>3.2</td>
<td>1.4</td>
</tr>
<tr>
<td>S. E.</td>
<td>59</td>
<td>Arteriosclerosis obliterans</td>
<td>Subcut.</td>
<td>35</td>
<td>3.7</td>
<td>0.5</td>
</tr>
<tr>
<td>R. M.</td>
<td>55</td>
<td>Arteriosclerosis obliterans</td>
<td>Subcut.</td>
<td>35</td>
<td>5.6</td>
<td>2.0</td>
</tr>
<tr>
<td>H. F.</td>
<td>29</td>
<td>No known disease</td>
<td>Subcut.</td>
<td>50</td>
<td>6.3</td>
<td>5.9</td>
</tr>
</tbody>
</table>

![Figure 2](image.png)

**FIG. 2.** Effect of increased venous pressure upon muscle clearance of Na$^{24}$.

Data were also obtained which illustrate the effect of a decrease in blood flow upon resting clearance rates. In several subjects clearance was measured before, during and after a period of elevated venous pressure produced by a proximal pressure cuff at 35 or 50 mm. Hg. These values are collected in table 2 and a single experiment is graphed in figure 2. In all subjects except H. F., the measured muscle or subcutaneous clearances were definitely decreased by raising venous pressure. These results could be explained either by the assumption that the transcapillary diffusion rate is
decreased by an elevated capillary hydrostatic pressure, or, alternatively, by the assumption that blood flow is decreased. Landis\(^{27}\) has stressed the fact that the diffusion rate of a small ion is independent of "filtration" across the capillary wall. We have shown this for ourselves by a comparison of the clearance rate of Na\(^{2+}\) or I\(^{131}\) when injected in hypertonic albumin and, simultaneously, in a comparable contralateral site, in isotonic saline. The hypertonic albumin produces an outpouring of fluid from the capillaries and a noticeable swelling of the injection site, yet no statistically significant difference was found in the clearance from the two sites. Therefore, if diffusion rates are not significantly altered by filtration, the decrease in clearance produced by a raised venous pressure reflects a decrease in blood flow. That blood flow is significantly reduced by an elevation of venous pressure has been shown by gasometric and plethysmographic measurements.\(^{26, 29}\)

We studied next the effect of reflex heating upon clearance from the distal skin. This procedure, when performed on a previously cooled subject, will result in a large rise in blood flow. This will be due to both an increased capillary blood flow, and the opening of arteriovenous shunts in the toes. The increased capillary flow increased the rate of removal of a labeled ion, but blood shunted through arteriovenous channels would not be expected to increase clearance.

Figure 3 is a record of such an experiment. The upper portion of the figure is a plot of clearance measured from the subcutaneous tis-sues of the dorsum of the foot at the base of the second toe before and after reflex heating. The lower portion shows typical venous occlusion plethysmographic tracings obtained from the tip of the toe during these periods. Before heating there was no measurable flow through the toe and no movement of the isotope. Heating resulted in an increase in blood flow to 27 cc. per 100 cc. of part per minute, and of clearance to 5.1 per cent per minute.

Data from eight experiments are given in table 3, which lists the temperature of the tip of the first toe, blood flow from the second toe, and subcutaneous clearance from the base of

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**Fig. 3.** The effect of reflex heating upon subcutaneous clearance from the dorsum of the foot and blood flow through the toe.
the second toe expressed as per cent per minute. The values for blood flow in this table are averages of at least three determinations. These results clearly demonstrate that an increased blood flow produced by the release of sympathetic tone is accompanied by a large increase in clearance rate. The magnitude of the increase in blood flow is greater than that for clearance. This is to be expected, since after heating total flow through the toe tip includes a large quantity of blood which passes through arteriovenous shunts.

The small values for clearance from the subcutaneous tissues of the foot when the subject was cool are of interest. These ranged in the four well subjects from no movement at all up to 1.5 per cent per minute. They may be compared with the values in table 1 for clearance in resting calf muscle, which averaged 4.6 per cent in five normal subjects. If this average value for clearance from resting muscle reflects a nutritive flow of 1 to 2 cc. per 100 cc. of part per minute, one may readily appreciate the very small blood flow needed to maintain the nutrition of the subcutaneous tissues in a cool environment. None of the subjects noticed any discomfort in their feet; each could have remained indefinitely in the cool environment. The average value in the four normal subjects after reflex heating was 5.4 per cent per minute.

We have attempted to produce maximum clearance from the subcutaneous tissues of the hand in resting supine subjects by a combination of reflex heating for one hour, the consumption of 60 cc. of 45 per cent alcohol and direct heating of the hands by a bank of lights for 15 minutes. In 20 measurements, a clearance rate over 10 per cent per minute was obtained five times. The maximum obtained was 13.2 per cent. Values above this in normal subjects have been reached only by applying enough heat to the hands to produce an erythema of the skin for several hours.

Once assured that the release of sympathetic tone in the skin of the foot increased clearance from that site, it was possible to interpret the data obtained from calf muscle before and after lumbar block. These data are summarized in table 4. This table lists the temperature of the big toe before and after the block; the average blood flow through the tip of the second toe

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Room Temp. °F.</th>
<th>Toe Temperature °F.</th>
<th>Blood Flow cc./100cc./min.</th>
<th>Clearance Before Heating K, %/min.</th>
<th>After Heating K, %/min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. P.</td>
<td>No known vascular disease</td>
<td>70-74</td>
<td>72-73</td>
<td>90-92</td>
<td>3.0</td>
<td>26</td>
</tr>
<tr>
<td>F. S.</td>
<td>No known vascular disease</td>
<td>69-70</td>
<td>71-72</td>
<td>90-93</td>
<td>4.5</td>
<td>28</td>
</tr>
<tr>
<td>F. S.</td>
<td>No known vascular disease</td>
<td>67-69</td>
<td>66-67</td>
<td>82-83</td>
<td>5.5</td>
<td>32</td>
</tr>
<tr>
<td>T. V.</td>
<td>No known vascular disease</td>
<td>68-69</td>
<td>69-71</td>
<td>91-92</td>
<td>&lt;1</td>
<td>36</td>
</tr>
<tr>
<td>L. P.</td>
<td>Vasospasm, after frostbite</td>
<td>73-74</td>
<td>73-74</td>
<td>94-95</td>
<td>&lt;1</td>
<td>44</td>
</tr>
<tr>
<td>J. S.</td>
<td>Vasospasm, after frostbite</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4.5</td>
<td>29</td>
</tr>
<tr>
<td>C. D.</td>
<td>Arteriosclerosis obliterans</td>
<td>70-74</td>
<td>78-82</td>
<td>90-91</td>
<td>5.0</td>
<td>16</td>
</tr>
<tr>
<td>R. C.</td>
<td>Diabetes mellitus</td>
<td>75-76</td>
<td>75-76</td>
<td>85-88</td>
<td>4.0</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 3.—The Effect of Reflex Heating upon Blood Flow through and Clearance from the Dialtal Skin

before and after each clearance determination; and the clearance from calf muscle, expressed as per cent per minute, determined both before and after the block. Fifteen experiments are given. In the first 10 a definite block was obtained as indicated by a rise in skin temperature and blood flow through the toe. In the last five listed, either the block was missed or arterial occlusion was so severe that the release of sympathetic tone did not significantly increase blood flow through the toe. These experiments may be considered controls, if one assumes that blood flow through the calf could not be altered by sympathetic block without a simultaneous change in blood flow through the toe.

These data show that interruption of the sympathetic supply to the blood vessels of resting calf muscle does not increase nutritive blood flow as measured by clearance. Rather,
in all except one of the definite blocks, there was some decrease in postblock clearance; in several patients this was of considerable magnitude; for example, in L. P. it was from 9.5 to 4.1 per cent per minute, in J. S. from 5.8 to 1.5 per cent per minute, and in R. B. from 4.3 to 2.4 per cent per minute. One of the experiments is illustrated in figure 4. One measurement of toe blood flow before block is seen to be 3 cc. per 100 cc. of part per minute. Muscle clearance before block was 3.5 per cent per minute. After the block, toe blood flow increased to 32 cc. but muscle clearance fell to 2.7 per cent. In two of the experiments in which there was no definite evidence of a block, the second clearance was also decreased; in subject R. B. from 3.2 to 2.3 per cent per minute, and in subject J. B. from 3.3 to 2.2 per cent per minute. Therefore, we cannot be sure that the reduced clearance measured after most of the proved blocks was due to the effect of the block, although this would seem likely in the three instances cited in which the decrease after block was large. In any event,

Table 4.—The Effect of Lumbar Sympathetic Block upon Clearance from Calf Muscle

<table>
<thead>
<tr>
<th>Subject</th>
<th>Diagnosis</th>
<th>Room Temperature °F</th>
<th>Toe Temperature °F</th>
<th>Blood Flow cc./100cc./min</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before Block</td>
<td>After Block</td>
<td>Before K</td>
<td>After K</td>
</tr>
<tr>
<td>I. T.</td>
<td>Vasospasm, idiopathic</td>
<td>69-71</td>
<td>74-75</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
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<td>65</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.8</td>
</tr>
<tr>
<td>L. P.</td>
<td>Vasospasm, after cold exposure</td>
<td>76-79</td>
<td>75-76</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>9.5</td>
</tr>
<tr>
<td>A. A.</td>
<td>Thrombophlebitis</td>
<td>68-70</td>
<td>78-79</td>
<td>&lt;1</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>28</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.7</td>
</tr>
<tr>
<td>W. F.</td>
<td>Thrombophlebitis</td>
<td>87-88</td>
<td>92-93</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td></td>
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<td>&gt;100</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. M.</td>
<td>Persistent pain in feet, etiology unknown</td>
<td>67-70</td>
<td>69-70</td>
<td>3.0</td>
<td>3.0</td>
</tr>
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<td></td>
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<td>3.5</td>
</tr>
<tr>
<td>J. S.</td>
<td>Thromboangiitis obliterans</td>
<td>67-73</td>
<td>69-70</td>
<td>90-92</td>
<td>4.0</td>
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<td>J. W.</td>
<td>Arteriosclerosis obliterans</td>
<td>70-74</td>
<td>70-71</td>
<td>89-91</td>
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<td>4.1</td>
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<tr>
<td>J. S.</td>
<td>Arteriosclerosis obliterans</td>
<td>70-82</td>
<td>86-88</td>
<td>90-91</td>
<td>6.5</td>
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<td>5.5</td>
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There is clear evidence that sympathetic nerve interruption does not increase clearance from resting skeletal muscle.

These results are similar to the observations of others that vasodilator drugs and reflex heating do not increase clearance from skeletal muscle. However, they do not agree with the plethysmographic measurements of Barcroft and his co-workers, who reported more than a twofold increase in forearm muscle blood flow.
flow after peripheral nerve block. Such a doubling of flow really represents an increase of only about 2 to 3 cc. per 100 cc. of part per minute, yet this rise should produce a corresponding increase in clearance rate.

At this point it is necessary to call attention to two reports which challenge the validity of the clearance technic as a measure of muscle blood flow. Semple and associates30 doubt the sufficient occlusive disease to prevent a normal resting flow of 1 to 2 cc. per 100 cc. of part per minute. Resting clearance was measured by these workers for 10 minutes. The clearance after exercise was begun within 40 seconds after completion of exercise, but the duration of the measurement which determined the post-exercise clearance value is not given. This would seem important because, just as in the instance

![Diagram](http://circ.ahajournals.org/)

**Fig. 4.** The effect of lumbar sympathetic block upon clearance from calf muscle and blood flow through the toe.

method because they were unable to find consistent differences between normal subjects and patients with intermittent claudication due to occlusive vascular disease. This was true both for resting values and for the ratio of the rate of removal after exercise to the resting values. There is, in our opinion, very little reason to expect to find a consistent difference in the resting values for the two groups if the criterion for selection of the second group was only the presence of intermittent claudication. The fact that the circulation is insufficient to prevent pain after exercise does not mean that there is of reactive hyperemia, blood flow after exercise does not remain constant but rapidly diminishes. This is seen in Grant’s23 and Shepherd’s31 figures. It is only within the first two to three minutes that there is a large difference between the normal and the patient with intermittent claudication. Except for very strenuous exercise, one would expect that after this time interval, blood flow in the normal subjects would fall within the range obtained in the claudicators. It seems unlikely that averages for plethysmographic values which were begun after two to three minutes would clearly deline-
ate the two groups. Therefore, unless the post-
exercise clearances were determined from the
rate of removal in the first two to three minutes
only, the data of these workers need not dis-
credit the clearance method.

Miller and Wilson\textsuperscript{25} have questioned the
clearance technic because they were unable to
detect an increased clearance from the sub-
cutaneous tissues of the hand or finger after
reflex heating sufficient to increase the heat
elimination from the hand. It is to be noted,
in two of the four experiments they reported,
that subcutaneous clearance before reflex heat-
ing was greater than 5 per cent per minute.
With such an initial clearance rate one suspects
that, although the A-V shunts might still be
closed, there was little reflex sympathetic con-
striction of the nutritive supply to the tissues
before the heating. In our eight experiments on
the effect of reflex heating on the subcutaneous
clearance from the dorsum of the foot, particu-
lar care was taken to cool the subject
thoroughly. Clearance before heating was below
2 per cent in six subjects and below 5 per cent
in the other two. A significant rise with heating
was obtained without exception.

The second objection of Miller and Wilson,
that intravenous adrenaline failed to increase
muscle clearance, must be recognized, since
Allen and co-workers\textsuperscript{22} have shown that a two-
fold increase in flow through skeletal muscle
will persist during the period of infusion. There-
fore, despite the evidence,\textsuperscript{1, 2, 23} which our own
experiments support, that clearance does
parallel blood flow, it remains to be proved
specifically that small increases of about 2 to 3
c. per 100 cc. of part per minute in total
muscle blood flow will increase muscle clear-
ance. This is the order of magnitude of the
increase Barcroft reported after nerve block.
The answer must await simultaneous plethys-
mographic measurements of muscle blood flow
and clearance determinations.

Whether or not the clearance method proved
as sensitive as plethysmography, one should
remember that a measurement of the rate of
removal of a rapidly diffusible ion such as
sodium or iodide ion has clinical meaning. For,
if some of the materials of muscle metabolism
have about the same rates of diffusion, the result
of a therapeutic procedure upon clearance is a
useful measure of the value of that procedure
in improving the nutrition of the muscle. There-
fore, our observations on the lack of effect of
lumbar sympathetic block upon resting muscle
clearance suggest that acute sympathetic in-
terruption is without value as a therapeutic
procedure to increase nutritional blood flow to
resting skeletal muscle. However, this is rarely
the clinical problem, since the patient usually
presents an associated arterial insufficiency of
the distal skin which may be improved by
sympathetic interruption, or else his complaint
is of muscle pain on exercise.

There are several clinical reports of large
groups of patients\textsuperscript{81, 39} which discuss the effect of
lumbar sympathectomy upon intermittent
claudication. These vary in their enthusiasm
for the result of the procedure. In general,
surgeons have reported that the walking dis-
tance of many patients is moderately pro-
longed, that is, about one-half to three or four
blocks. There are some patients who are not
helped at all, while an occasional patient is
strikingly benefited and may be completely
relieved of muscle cramp on ordinary activity.
It is difficult to understand how sympathetic
interruption can improve intermittent claudi-
cation. We have shown that its effect upon
muscle blood flow at rest is insufficient to
increase the removal rate of a rapidly diffusible
small ion. The metabolites which accumulate
during exercise or circulatory occlusion are the
most profound dilators of muscle vessels. Their
action is independent of the sympathetic sys-
tem. Thus, reactive hyperemia has been shown
to be the same before and after preganglionic
sympathectomy.\textsuperscript{22}

However, it has been suggested that the
pain of exercise may be due to circulatory
insufficiency which results not so much from
the presence of occlusive vascular disease as
from added vascular spasm. This has been in-
ferred from the study of an occasional patient
in whom, after exercise, the foot may get white
and cold and a previously palpable pulse may
disappear. Pear\textsuperscript{40} distinguished such patients
as having angiospastic claudication and felt it
was this group that benefited from sympathetic
interruption. Freeman and Montgomery\textsuperscript{41} felt
that improvement in claudication time after lumbar sympathetic block indicated the presence of abnormal vasospasm.

There is no evidence that pain produced in well subjects by ischemic exercise is associated with vascular spasm. Rather, the vessels are fully dilated. Furthermore, it has been shown that reactive hyperemia muscle flow is not decreased by sympathetic stimulation which produces vasoconstriction in the distal skin. However, there are two reports which disclose that, in contrast to the normal subject, some patients with occlusive vascular disease may exhibit a decreased blood flow during or immediately after exercise. Lindquist described several patients who showed a marked decrease in oscillometric readings with the onset of muscular cramps. Shepherd who measured calf muscle blood flow plethysmographically after exercise, found a group of patients with arteriosclerosis and claudication in which blood flow after exercise failed to reach a maximum until 1 to 14 minutes after the exercise was stopped. Yet these observations cannot be taken as evidence of sympathetic spasm, since they occur after sympathetic interruption.

Therefore, from the data available at present, it would appear that sympathetic interruption will not increase the effective resting blood flow through skeletal muscle, nor is there evidence that it will improve blood flow after exercise. Rather, the observations of Lindquist and Shepherd indicate that it will not prevent the decreased blood flow after exercise seen in some patients with intermittent claudication. Furthermore, in a careful study, Shepherd could find no increase in blood flow after exercise as a result of sympathetic block. The reason why an occasional patient obtains marked relief of intermittent claudication after lumbar block or lumbar sympathectomy remains obscure.

**Summary**

This paper is in part a report of the effect of procedures known to alter local blood flow upon clearance of locally injected Na or I. The increase with reactive hyperemia has been shown to approach that measured plethysmographically by others. The effect of increased venous pressure is to decrease the rate of removal because it decreases blood flow. The release of sympathetic tone in the distal skin by reflex heating results in a large rise in subcutaneous clearance rate. When these results were established, the clearance method was then used to assess the effect of lumbar sympathetic block upon clearance from calf muscle. No increase in resting muscle clearance was found after lumbar sympathetic block. The relation between the result of lumbar sympathetic block upon muscle blood flow and its clinical effect has been discussed.

**Acknowledgments**

We take this opportunity to record our indebtedness to Dr. E. V. Edwards, Manager of the Veterans Administration Hospital, Long Beach for his cooperation and interest. Drs. Hugh Frank and Edward W. Hayes kindly performed the required lumbar sympathetic blocks. Mr. Frank Grossman executed the figures.

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Tissue Clearance as a Measure of Nutritive Blood Flow and the Effect of Lumbar Sympathetic Block upon Such Measures in Calf Muscle

SAMUEL I. RAPAPORT, ALBERT SAUL, CHESTER HYMAN and M. E. MORTON

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