Effects of Intra-arterial and Intravenous Epinephrine on Disappearance of NaI\textsuperscript{131} from Calf Muscle and on Calf Blood Flow

By Jay D. Coffman, M.D.

It has often been considered that plethysmographic foot or hand, and calf or forearm, measurements are representative of skin or of muscle blood flow, respectively, because of the preponderant amounts of each tissue in these areas. However, Cooper et al.\textsuperscript{1} have demonstrated that 60% of the total forearm flow may be in the skin under certain conditions. It is obvious, therefore, that increases or decreases of blood flow in skeletal muscle, as measured plethysmographically in the calf or forearm, may be hidden or exaggerated by changes in skin flow. In 1949, Kety\textsuperscript{2} introduced the technic of tissue clearance of radioisotopes as an index of blood flow through capillaries near the site of deposition of the isotope.

An important discrepancy between the two technics is said to occur during the intravenous administration of epinephrine; large changes occur in plethysmographic calf or forearm blood flow measurements\textsuperscript{3} while the rate of clearance of radioisotope from skeletal muscle is unaffected.\textsuperscript{4, 6} The explanation given for this finding is that epinephrine probably opens arteriovenous anastomotic channels whose flow would be measured by the plethysmograph but not by a technic indicating capillary blood flow.\textsuperscript{6} The further implication is that this is evidence for the existence of functional arteriovenous shunts in skeletal muscle.

The two principal concerns of this study were validation of tissue clearance as an index of capillary perfusion and the effects of epinephrine on calf blood flow. In assessing the value of the radioisotope technic, the effect of intra-arterial infusion of epinephrine on the rate of radioisotope disappearance has not been studied. This is said to produce only a transient increase in plethysmographic blood flow compared to the sustained response observed with intravenous administration. When it was determined that radioisotope disappearance rates increased with intra-arterial infusions of epinephrine, intravenous administration was reinvestigated. Since intra-arterial epinephrine sometimes produced a sustained increase in the radioisotope disappearance rate, plethysmographic studies were also performed.

**Methods**

The disappearance rate of radioisotope from the lateral calf muscles was used as a measure of capillary blood flow in skeletal muscle. An injection of 0.1 ml of NaI\textsuperscript{131} in saline was made with a 26-gauge 5/8- or 2-inch needle approximately three inches below the head of the fibula; the needle was inserted to its hub in an attempt to control depth of injection. It has been shown by others,\textsuperscript{7, 8} and verified by us, that NaI\textsuperscript{131} disappearance rates are similar to those obtained using Na\textsuperscript{24}. The disappearance rate was monitored by either a shielded scintillation probe, ratemeter\textsuperscript{9} and linear recorder, or a shielded or unshielded scintillation probe and a transistorized scaler\textsuperscript{9} from which counts were recorded every 30 seconds. The scintillation probe contained a 1-inch by 1-inch thick sodium iodide crystal, thallium activated. Disappearance rates determined with the scaler and without a shield were slower. Also, rapid changes in the disappearance rates

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were seen more often with use of the ratemeter than with the scaler. Therefore, the ratemeter and shield were used in the majority of tests involving intravenous epinephrine. Doses of NaI$^{131}$ varied from 0.5 to 10 μc depending on the use of a lead shield. Disappearance rates were plotted on semilogarithmic paper after subtraction of the background counts. As reported previously$^6,10$ such curves may not become linear for several minutes. After the control rate had been determined as linear, experimental stimuli were applied during the same clearance curve. This was necessary because disappearance rates are not always identical even though injections of the same quantity are made in the same area under similar conditions.$^{11,12}$ Occasional disappearance curves demonstrated a continuously increasing clearance rate whether epinephrine was administered or not. These tests, in which the clearance rate continued to increase after discontinuation of the stimulus, were discarded. Disappearance rates are expressed by the clearance constant, $K$, which is the natural logarithm of 2 divided by the half time of the disappearance rate ($K = 0.693/\sqrt{t}$). An increase or decrease in the clearance constant or rate would indicate a rise or fall in capillary blood flow respectively.

Total blood flow in the calf was measured by venous occlusion plethysmography on lightly covered subjects lying in the supine position. The subject's calf was slightly elevated and enclosed in a plethysmograph filled with water at a temperature of 34°C. This position maintained the posterior aspect of the lower leg approximately at heart level. The technic for enclosing the limb in the water plethysmograph has been previously described in detail.$^{13}$

The subjects were medical students or hospitalized convalescent patients without peripheral vascular disease; their average age was 36 years (range 21 to 57 years). Several of the medical students had received intravenous catecholamines during previous studies and were aware of the expected symptoms. A rest period of 45 to 60 minutes at a constant room temperature of 78 to 83°F preceded each experiment. Three groups of subjects were tested. Group A was given epinephrine into the femoral artery via a Cournand needle while NaI$^{131}$ disappearance rates were being determined from the calf muscles of the same extremity. In group B, epinephrine was infused into the femoral artery while plethysmographic calf blood flows were being measured. The third group, C, received intravenous epinephrine while plethysmographic blood flows were determined on one calf and simultaneous NaI$^{131}$ disappearance rates were measured in the opposite calf. When the plethysmograph was used, five control blood flows were recorded every five minutes over a 15-minute period, and the control rate of NaI$^{131}$ disappearance was always determined for at least five minutes before infusions. Intravenous and intra-arterial solutions of epinephrine hydrochloride$^{9}$ were diluted with saline and were administered by a constant infusion pump usually at 1 ml per minute. The concentrations of epinephrine solutions are expressed in terms of the salt. Intravenous infusions were made via the tubing of a saline intravenous drip which ran throughout the experiment. Local anesthesia by procaine infiltration preceded insertion of the femoral artery needles.

Radial pulse rates and sphygmomanometric blood pressure determinations were followed every five minutes during control periods and more frequently during the infusions. Calf and toe skin temperatures were measured with a thermocouple in most tests.

**Results**

Intra-arterial and intravenous epinephrine infusions produced an early, but transient, large increase in calf blood flow usually followed by a decrease below control levels. After the brief vasoconstrictor phase, a second, lesser elevation of blood flow usually occurred. In the following analysis of data, "initial" increase refers to the peak blood flow value obtained during the early vasodilator phase and "sustained" flow denotes the average of the flows during the second vasodilatation following the vasoconstrictor period. An absent initial increase does not indicate that a change in blood flow or disappearance rate did not occur during this period but only that it was not different from the sustained response.

**GROUP A. INTRA-ARTERIAL EPINEPHRINE AND NaI$^{131}$ DISAPPEARANCE RATES**

Femoral arterial infusions of epinephrine, 0.1 μg/min in seven tests on six subjects, produced an average initial increase in the clearance constant from 0.032 to 0.065 which lasted an average of 1.8 minutes ($P < 0.05$, SE 0.0122). Two of the seven disappearance rates were unaffected by this dose. Three of the five initial responses were followed by sustained increase disappearance rates for the

$^9$Obtained from Parke, Davis and Co., Detroit, Michigan.
INTRA-ARTERIAL EPINEPHRINE:
NaI\(^{131}\) DISAPPEARANCE RATES FROM SKELETAL MUSCLE

The effect of intra-arterial infusions of epinephrine on NaI\(^{131}\) disappearance rates from calf skeletal muscle.

duration of the infusion. The sustained increases (average \(K = 0.044\)) were not significant statistically \((P < 0.1, \text{SE } 0.0067)\), probably because of the small number of cases. Only one of five experiments with an intra-arterial dose of 0.05 \(\mu\)g/min demonstrated a transient increase in the disappearance rate; no sustained responses occurred.

One \(\mu\)g/min of epinephrine infused intra-arterially led to an initial increase from an average control clearance constant of 0.032 to 0.081 for an average time of 1.4 minutes in 16 tests on 12 subjects. This was a significant increase \((P < 0.001, \text{SE } 0.0064)\). Since only eight trials produced a sustained increase and four tests caused an initial increase followed by a decrease, the average sustained rate \((K = 0.032)\) was not different from the control. Only one disappearance curve was unaffected by this dose.

At an intra-arterial infusion rate of 10 \(\mu\)g/min of epinephrine, there was an average initial increase in clearance constant from 0.035 to 0.077 which lasted an average time of one minute in seven tests on seven subjects \((P < 0.02, \text{SE } 0.0108)\). In all subjects, the disappearance then either slowed or stopped before the end of the infusion period. In two subjects, intra-arterial infusions of normal saline did not affect the NaI\(^{131}\) disappearance rates.

Figure 1 illustrates the effects of intra-arterial epinephrine on the NaI\(^{131}\) disappearance rates in two subjects. One test demonstrates a transient 2-minute increase with 1 \(\mu\)g/min of epinephrine while the other subject had a small increase in clearance rate for the duration of a 1 \(\mu\)g/min infusion of epinephrine and a more rapid disappearance rate followed by a cessation of clearance during the 10 \(\mu\)g/min infusion.

In these tests, the counts were recorded...
TABLE 1

Effect of Intravenous Epinephrine (8 µg/min) on Plethysmographic Calf Blood Flow and Skeletal Muscle NaI\(^{131}\) Clearance Constants

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>Initial increase</th>
<th>Sustained</th>
<th>NaI(^{131}) clearance constants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ml/100 ml/min</td>
<td></td>
<td>Control K</td>
</tr>
<tr>
<td>6</td>
<td>2.8</td>
<td>26.0</td>
<td>7.5</td>
<td>0.069</td>
</tr>
<tr>
<td>7</td>
<td>3.9</td>
<td>7.8</td>
<td>5.2</td>
<td>0.069</td>
</tr>
<tr>
<td>8</td>
<td>3.1</td>
<td>12.8</td>
<td>4.6</td>
<td>0.055</td>
</tr>
<tr>
<td>9</td>
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<td>8.6</td>
<td>6.0</td>
<td>0.022</td>
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</tr>
<tr>
<td>13</td>
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<td>8.2</td>
<td>7.0</td>
<td>0.051</td>
</tr>
<tr>
<td>10</td>
<td>4.8</td>
<td>10.6</td>
<td>6.6</td>
<td>$0.100$</td>
</tr>
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<td>14</td>
<td>4.4</td>
<td>15.5</td>
<td>6.0</td>
<td>$0.116$</td>
</tr>
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<td>6.4</td>
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<td><em>0.045</em></td>
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<td>2.9</td>
<td><em>0.071</em></td>
</tr>
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<td>2.7</td>
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</tr>
<tr>
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<tr>
<td>15</td>
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<td>6.6</td>
<td>3.7</td>
<td><em>0.054</em></td>
</tr>
<tr>
<td>Average</td>
<td>2.9</td>
<td>10.2</td>
<td>4.8</td>
<td>0.065</td>
</tr>
<tr>
<td>SE</td>
<td>0.1281</td>
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<td></td>
<td>$0.01050$</td>
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<tr>
<td>P</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*These experiments were performed using a scaler; all others were done with a ratemeter and recorder.

†The "initial increase" columns are compared statistically with the "sustained" columns. The "control" columns are compared to the "sustained" columns.

§NaI\(^{131}\) injected in deep muscle with 2-inch long needle.

from a transistorized scaler, usually with an unshielded probe. This may account for the lower average clearance constants compared with those reported in the literature\(^2,4,5,9,10\) and found in our intravenous experiments using a shielded probe and ratemeter.

GROUP B. INTRA-ARTERIAL EPINEPHRINE AND PLETHYSMOGRAPHIC CALF BLOOD FLOWS

These studies were performed in order to confirm the sustained increases observed in some of the disappearance rates with intra-arterial epinephrine. In 15 tests on 13 subjects, intra-arterial infusions of 0.1 µg/min of epinephrine produced an initial increase in the plethysmographic blood flow from 3.0 to 9.8 ml/100 ml of calf/min for an average time of 1.2 minutes (SE = 0.931, P = <0.001). In four trials, the blood flow returned to control values despite continuation of the infusion, but in ten tests, a sustained increase in blood flow occurred, usually after a small decline below control levels. The average sustained blood flow following the initial increase was 4.1 ml/100 ml of calf/min. This was a significant change from the control value (SE = 0.298, P = <0.01). One subject demonstrated no response to this dose.

GROUP C. INTRAVENOUS EPINEPHRINE, PLETHYSMOGRAPHY, AND NaI\(^{131}\) DISAPPEARANCE RATES

With an intravenous continuous infusion of 8 µg/min of epinephrine (table 1), 13 subjects had an average initial increase of plethysmographic blood flow from 2.9 to 10.2 ml/100 ml of calf/min, and a sustained flow which averaged 4.8 ml/100 ml of calf/min. Simultaneous NaI\(^{131}\) disappearance rates from the opposite calf increased initially from a clearance constant of 0.065 to 0.127 and showed a sustained clearance constant of 0.096.

With an intravenous dose of 20 µg/min (table 2), the blood flow rose from 3.3 ml to an initial peak of 12.4 ml followed by a sustained response of 4.9 ml/100 ml of calf/min in 15 tests on 14 subjects. The disappearance rates from the opposite calf increased initially
from a clearance constant of 0.059 to 0.123 and showed a sustained elevation at an average K of 0.079.

Intravenous epinephrine, 40 μg/min, was infused into eight subjects. Of these infusions seven followed previous doses immediately so that both technics of blood flow measurement had already shown increases. In these last trials, only two disappearance rates demonstrated a large transient increase while plethysmographic calf blood flows increased in four. The average control clearance constant of 0.050 showed a sustained elevation to 0.073 for all eight tests (P < 0.02); one disappearance rate slowed and one returned to control levels. Plethysmographic calf flows increased from 3.1 ml to a sustained response of 4.9 ml/100 ml of calf/min (P < 0.2); one trial showed a decrease in flow.

Figure 2 illustrates the radioisotope curve and calf plethysmographic flows from one experiment with intravenous epinephrine infusion. The initial large increases in plethysmographic flows and clearance constants correlated closely in time of onset and duration in this example and in the other tests, indicating that the two methods paralleled each other at least qualitatively.

**BLOOD PRESSURE, PULSE RATE, AND SKIN TEMPERATURE**

With intra-arterial infusions of the epinephrine, blood pressure and radial pulse rates were unaffected while skin temperatures of the infused limb decreased from an average of 88.8 to 88.3 (calf) and from 85.0 to 83.4°F (toe). Intravenous epinephrine in doses of 8 and 40 μg/min produced an average change in systolic blood pressure of +22 and +68 mm Hg, in diastolic blood pressure of −1.6 and + 8.5 mm Hg, in pulse rate of

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**TABLE 2**

*Effect of Intravenous Epinephrine (20 μg/min) on Plethysmographic Calf Blood Flow and Skeletal Muscle NaI<sup>131</sup> Clearance Constants*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>Initial Increase</th>
<th>Sustained Flow</th>
<th>Control K</th>
<th>Initial K</th>
<th>Sustained K</th>
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<td>6</td>
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<td>8</td>
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<td>0.084</td>
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<td>5.7</td>
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<td>0.141</td>
<td>0.058</td>
</tr>
<tr>
<td>12</td>
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<td>9.1</td>
<td>7.6</td>
<td>0.053</td>
<td>0.123</td>
<td>0.069</td>
</tr>
<tr>
<td>13</td>
<td>12.6</td>
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<td>7.4</td>
<td>0.053</td>
<td>0.069</td>
<td>0.069</td>
</tr>
<tr>
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<td>12.7</td>
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<td>0.058</td>
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<td>0.084</td>
</tr>
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<td>11.6</td>
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<td>*0.045</td>
<td>0.075</td>
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</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>7.5</td>
<td>2.3</td>
<td>*0.071</td>
<td>0.071</td>
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</tr>
<tr>
<td>3</td>
<td>11.5</td>
<td>3.7</td>
<td>3.1</td>
<td>*0.065</td>
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</tr>
<tr>
<td>4</td>
<td>3.9</td>
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<td>*0.028</td>
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<tr>
<td>5</td>
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<td>4.9</td>
<td>*0.083</td>
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<td>Average</td>
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<td>0.059</td>
<td>0.123</td>
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<td>&lt;0.01</td>
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</tbody>
</table>

*These experiments were performed using a scaler; all others were done with a ratemeter and recorder.
†The 'initial increase' columns are compared statistically with the 'sustained' columns.
The 'control' columns are compared to the 'sustained' columns.
§Na<sup>131</sup> injected in deep muscle with 2-inch long needle.

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+12 and +14 beats per minute, in toe temperature from 78.7 to 78.1 and 81.3 to 79.1°F, and in calf skin temperature from 88.7 to 88.1 and 81.3 to 87.6°F, respectively. All subjects receiving intravenous epinephrine became aware of their heart beats and many expressed a feeling of anxiety; such subjective symptoms usually decreased after the first two minutes of the infusion. Skin pallor of the face and extremities was usually present and an increase in the respiratory rate was often noticed.

Discussion

In these studies, intra-arterial and intravenous epinephrine affected the NaI\textsuperscript{131} disappearance rates from human calf skeletal muscle in a manner which could be predicted from the present and previously reported plethysmographic blood flow studies.\textsuperscript{3, 11-16} Contrary to previous reports,\textsuperscript{4, 5} the intravenous infusion of epinephrine was found to affect the NaI\textsuperscript{131} disappearance rates. The time of onset and duration of the initial and sustained changes usually corresponded with simultaneous increases in plethysmographic calf flow measurements on the opposite limb. However, the NaI\textsuperscript{131} curves frequently failed to demonstrate a further increase in rate when plethysmographic flows transiently rose with increasing concentrations of epinephrine. In this regard, Walder\textsuperscript{17} has shown that the clearance rate from cat skeletal muscle reaches a maximum beyond which increases in blood flow do not affect it. However, such high levels of blood flow were considered to be outside the physiological range in these animals. Theoretically, the radioisotope clearance should increase less rapidly than blood flow and should become independent at high flows.\textsuperscript{18} The present demonstration that intra-arterial and intravenous epinephrine affect radioisotope disappearance rates and plethysmographic measurements similarly in skeletal muscle adds strong evidence favoring inclusion of the radioisotope disappearance rate among the valid technics for measuring muscle blood flow.

The hypothesis that epinephrine increases blood flow only by its action on arteriovenous shunts in skeletal muscle, in order to explain its lack of effect on radioisotope disappearance rate, is made untenable by the present experiments. These studies do not provide information concerning the question of whether or not functional arteriovenous shunts are present in human skeletal muscle. Zweifach\textsuperscript{19} has demonstrated the presence of vessels capable of acting as functional arteriovenous shunts in rat skeletal muscle. However, evidence is at present lacking for the existence of "functional" arteriovenous shunts in human skeletal muscle.

A satisfactory explanation as to why our results with intravenous epinephrine differ from previous reports is not apparent. Similar concentrations of the agent were used. In the present experiments, a scintillation probe was used to detect radioactivity while both

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Intravenous Epinephrine: Skeletal Muscle & Total Calf Blood Flow

The effect of intravenous epinephrine on simultaneous calf plethysmographic blood flow and skeletal muscle NaI\textsuperscript{131} disappearance rate.
previous studies used a Geiger-Muller counter. Also, initial increases were seen more often with the ratemeter and recorder than with the scaler. The detection of a greater amount of radioactivity may allow more exact counting rates at short intervals, thereby facilitating the recognition of rapid or transient changes in capillary muscle blood flow. In the two previous reports at least one of six and two of seven subjects had an increased clearance rate with intravenous epinephrine. A recent report by Barlow et al. asserts that superficial muscular injections, in the cat hind limb, of Na\textsuperscript{24}—as compared to those in deep muscle—were more often affected by intravenous epinephrine. In many of the present tests, injections might be considered "superficial" since a \(\frac{5}{8}\)-inch needle was used. Therefore, two trials with a "deep" injection of the radioisotope using a 2-inch needle were performed; in both, the disappearance rates were definitely affected by intravenous epinephrine (tables 1 and 2).

Previous workers have found that continuous infusions of intravenous epinephrine induced a transient large increase, in calf or forearm blood flow as measured by plethysmography, followed by a lesser sustained response while intra-arterial administration produced only a transient elevation of blood flow followed by a return to control levels. The initial vasodilatation seen with both intra-arterial and intravenous epinephrine was attributed to a direct local action but the secondary increase in blood flow, which occurred only with intravenous injection, was considered to be a possible effect of a humoral substance released by epinephrine. In the present studies, a secondary sustained increase in plethysmographic blood flow and in Na\textsuperscript{19} disappearance rates was often demonstrated for the duration of the infusion of intra-arterial epinephrine. This result was usually obtained with the smaller doses. Andres et al. and Golenhofen also have recently reported a secondary substantial increase in blood flow after the initial vasodilatation with intra-arterial epinephrine; two different techniques of measuring blood flow, plethysmography and a thermoelectric needle, were used in their studies. Thus the initial and sustained effects are presumably local actions of epinephrine and a second "vasoactive intermediate phase" need no longer be postulated. Despite the fact that intravenous epinephrine has many effects, i.e., on blood pressure, heart rate, etc., the magnitude of the responses was very similar with both intravenous and intra-arterial administration.

**Summary**

The effects of intra-arterial and intravenous infusions of epinephrine on total blood flow in the calf and on capillary blood flow in calf muscle were determined in human subjects using venous occlusion plethysmography and radioisotope disappearance rates respectively. The two techniques usually demonstrated similar changes with both intravenous and intra-arterial routes of administration. Since intravenous epinephrine affected the radioisotope disappearance rates, the hypothesis that epinephrine acts on arteriovenous shunts alone does not appear to apply in these experiments. Intra-arterial epinephrine often produced a sustained increase in blood flow similar to that produced by intravenous epinephrine, indicating that the initial and sustained actions could be explained by local effects of the agent. These studies also add further support for using the radioisotope disappearance rate as a qualitative measure of skeletal muscle blood flow.

**Acknowledgment**

The author is grateful to Drs. Belton A. Burrows and Melvin H. Farmelant for valuable assistance and suggestions concerning the use of the radioisotope detection instruments.

**References**

EPINEPHRINE AND MUSCLE BLOOD FLOW


Effects of Intra-arterial and Intravenous Epinephrine on Disappearance of Nal 131 from Calf Muscle and on Calf Blood Flow

JAY D. COFFMAN

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