Intra-arterial Histamine in the Treatment of Occlusive Peripheral Arterial Disease

By John A. Dixon, M.D., W. J. Merle Scott, M.D., and Marvin A. Epstein, M.D.

Intra-arterial histamine was found to increase significantly the walking tolerance of a small series of cases of obliterative peripheral arterial disease with intermittent claudication. Physiologic determinations during injection show tachycardia, increased cardiac output, increased stroke volume and increased homolateral femoral arteriovenous oxygen difference. The similarity of these results to those caused by arteriovenous fistulas is noted.

One of the most vexing problems with which physicians have to deal is that of intermittent claudication and ischemic changes of the lower extremities in the middle-aged or elderly patient. These individuals are frequently so incapacitated by pains in their legs that they are unable to continue productive activities. Priscoline¹ and occasionally sympathectomy² offer some relief to a certain number of these people, but there still remains a large group that cannot be helped by these measures. Priscoline is not well tolerated in some patients and is ineffective in many others. Sympathectomy is not advisable many times because of the lack of favorable responses to the usual presumptive tests of sympathetic paralysis, or by coexistent cardiac, renal or respiratory diseases. This operation involves a definite risk to these older patients. Some patients have had sympathectomy with no relief or a temporary improvement followed by a return of distress.

A nonoperative treatment which would dilate the collateral circulation and could be repeated according to the patient's needs would be valuable. Mufson³ reported a series of cases with obliterative arterial disease of the lower extremities in which he injected histamine into the femoral artery with favorable results in 84 per cent of the group. It was largely at the insistence of one of our patients who had not been helped by the usual measures that our first intra-arterial histamine injections were tried. The results appeared sufficiently encouraging to be pursued further. This paper is a report of the clinical results obtained in a small series of carefully studied patients with some observations on the physiologic effects of intra-arterial histamine.

Methods and Materials

Eight male patients with intermittent claudication were studied. The average age was 64 years. The patients were selected from a group of more or less chronic clinic visitors who had been refractory to the usual therapeutic measures. They had all been been under observation for a period of several months during which time Buenger's exercises, oral Priscoline, reduction in smoking, moderate doses of alcohol, foot hygiene and reflex heat had been instituted. Unfortunately, treadmill exercise tolerances were not available on these patients during this period of conservative therapy, but it was the opinion of all observers that maximum benefit from these measures had been attained for a period of time prior to the institution of histamine therapy. Prior to injections, the subjects were taken to a constant temperature room and their skin temperature response in the lower extremities to immersing the arms in hot water was measured. If the temperature in the affected leg did not rise significantly, a posterior tibial nerve block was performed with 1 per cent Novocain and the temperatures again measured. On several of the patients a paravertebral block or spinal anesthetic was given as a further check. All of the patients selected for intra-arterial histamine showed very little temperature response with these procedures, and their ischemia was believed to be on the basis solely of arterial occlusion rather than spasm.

It was thought desirable to have an objective controlled method of following the walking tolerance of these patients rather than to depend upon the usual

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statement of the number of blocks walked without pain. A motor-driven continuous belt type treadmill was used which ran at a constant speed of 1.78 miles per hour. The walking surface was inclined to a 10 per cent grade. The grade not only brought out the claudication more sharply, but it also prevented walking with the knee and ankle in a fixed position so that the calf muscles would not become fatigued. It was calculated that walking 10 minutes on this device would be the equivalent of climbing 19 flights of stairs with an eight foot elevation per flight in the same period. Patients were instructed to walk until the appearance of definite claudication of the type usually noted in their ordinary activities. This time was taken as their walking tolerance. The pain end point was surprisingly distinct in most patients.

The histamine injections were given using ordinary intravenous apparatus and a hand bulb to raise the pressure in the bottle, after the method described by Mufson.3 Three mg. of histamine diphosphate in 500 cc. of normal saline were given into the femoral artery over a period of approximately one-half hour.

It would, of course, have been desirable to have run a control series of placebo intra-arterial injections. With this in mind, several intra-arterial injections of normal saline were given. No alteration in claudication distance was noted following such injections. After receiving a histamine injection, with its attendant warmth and erythema, the patients readily detected subsequent saline injections, thus negating the value of this form of investigation. Further placebo injections were not carried out for lack of an adequately impressive safe substitute injectant.

The usual therapeutic schedule was two injections per week for the first three weeks, then one injection per week until the walking tolerance appeared to have stabilized. Injections were discontinued then and the patient’s walking tolerance checked at monthly intervals. If regression was noted, injections weekly were then reinstated. Patients were all followed for a minimum of five months.

RESULTS

The immediate effects of intra-arterial histamine are usually rather striking. There is first an erythema which appears rapidly and roughly corresponds to the distribution of the main unobstructed arteries. Following this there is an intense pilomotor reaction with the hair on the leg “standing on end.” Shortly following this, scattered areas showing wheal formation appear. In patients with occlusion of a major vessel, such as the popliteal, the changes described appear rapidly in the thigh and knee in the region of the genicular anastomoses, then slowly extend down over the calf and foot. The veins uniformly become distended and very prominent, accompanying the erythema.

The thigh skin temperature increases early, but it was found that the temperature of the toes would usually increase very little or might even decrease initially. In several patients the circulation in the foot during the early part of the injection appeared to be somewhat further impaired. This was evidenced by mild cyanosis, mottling and a concomitant fall in skin temperature. This would suggest that initially the capillary flow was actually decreased. However, this phase was always transitory and followed immediately by the typical erythema and increase in skin temperature. Even after a good erythema had appeared in the foot, the skin temperature frequently did not rise significantly in the recumbent position. A typical response to injection in the recumbent position is seen in figure 1. The marked effects of posture on the skin temperatures of the toes during injection is seen in figure 2. Along with the elevation in temperature, the color of the skin of the toes changed to a much brighter pink on standing.

The results of the walking tolerance tests appear in figure 3. Unfortunately, in two of our patients the treadmill was not available to take walking tolerance prior to injection. The initial time which appears on the graph is calculated from their history and is indicated in both cases. All of the patients except one (F.B.) showed a definite increase in their walking tolerance.

Of the seven patients given a course of hista-
mine injections, five were considered to have a "good" result, one a "fair" result and one a "poor" result, or almost no change in walking tolerance. It is very difficult to classify results in patients with intermittent claudication as to whether their response to therapy has been good, fair or poor on the basis of changes in walking tolerance alone because of the wide difference in demands of the individual. For instance, one patient (J.W.) is classified as a good result even though his tolerance increased by only two minutes. He is a moderately severe cardiac and his activities are limited. The small increment in walking tolerance which occurred during treatment was sufficient to practically eliminate symptoms referable to his legs. By the same token, one patient (A.W.) is classified as a fair result even though he nearly doubled his walking tolerance because he is younger, more active, and his legs still cause him some distress in his regular activities. One patient who does not appear in the clinical table of results is worthy of mention. He is a 68 year old white male who had had a mid-thigh amputation on the left for gangrene, and at the time we saw him had several small gangrenous areas on the toes of his right foot. He was in constant pain and was unable to tolerate even the slightest pressure on his toes. The nailbeds were infected and necrotic. Amputation appeared imminent, but a trial of intra-arterial histamine was instituted. Though some increased pain was noted in the leg during the period of the first injection, later that same day he had almost complete and permanent relief from the severe pain in the foot. Following subsequent injections the gangrenous area disappeared and his nails have shown definite evidence of new growth. In the first injection there was no erythema noted below the knee. With subsequent injections his foot still became blue initially, but a good erythema developed in the lower leg and spread to the foot.

Though it is difficult to be certain in so small a series of cases, it appears that those individuals who are going to be appreciably helped by histamine injections show definite evidence of increased walking tolerance by approximately the sixth injection. The appearance of good erythema below the knee during the first injection is a good prognostic sign.

**Physiologic Studies**

When it became evident early in the course of this study that some beneficial results were being obtained, a number of procedures were carried out to determine some of the physiologic effects of intra-arterial histamine and gain information concerning its possible mode of action in peripheral arterial disease. The effects of intravenous and subcutaneous histamine in man have been extensively studied and an excellent review of the subject was recently published.4 In general, intravenous

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**Fig. 2.** Composite graph (eight patients) of skin temperature difference of injected leg compared with uninjected leg showing marked rise in temperature on standing.

**Fig. 3.** Walking tolerance time on treadmill and number of injections given. Early and marked increase in tolerance is shown.
histamine causes an increase in heart rate, a decrease in stroke volume, a moderate increase in minute volume, and a slight fall in systolic and diastolic blood pressure. The arteriovenous oxygen difference is increased.\textsuperscript{3} Peripherally it produces arteriolar dilatation, dilatation of the capillary bed and venules, and mild constriction of larger veins and arteries.\textsuperscript{6,7} There are no reports on the corresponding effects of intra-arterial histamine.

Methods and Materials

The subjects were five of the patients with peripheral vascular disease, and one young man convalescing from a minor surgical procedure. Seven experiments in all were done to determine the effects of intra-arterial histamine on the heart rate, stroke volume and arterial pressure. The subjects were allowed to recline on a high frequency undamped ballistocardiograph (BCG) table, as has been described elsewhere.\textsuperscript{8} A chest pneumograph and electrocardiographic (ECG) electrodes were applied. The subject was then rested for 15 to 20 minutes, during which time the control ballistocardiogram, electrocardiogram, and respiratory curve were recorded. The ballistocardiogram was picked up with either a variable capacitance transducer\textsuperscript{9} or a piston type strain gage.\textsuperscript{10} No amplification was required with the latter method. The records were made with Sanborn & Hathaway mirror galvanometers on direct positive recording paper.

At the end of the rest period the arterial puncture was made, and in three patients a control direct arterial pressure was recorded before beginning the histamine injection. In others the histamine was begun as soon as the puncture was completed. For the pressure records a Statham fluid pressure gage was attached to the intra-arterial needle by a 10 cm. piece of polythene tubing. The system was flushed with heparinized saline, a record taken and the histamine started.

Records were then taken about every eight minutes until the histamine was finished. The same amount, concentration, and speed of injection were used as in the purely therapeutic infusions. In four of the subjects tracings were taken before, during and after a pneumatic cuff was inflated, first on the injected, and then on the other leg. This cuff was placed just below the inguinal region and inflated to 100 mm. Hg. The histamine infusion usually lasted about 25 minutes. In the subjects in whom femoral pressure was recorded, the needle was kept open with heparinized saline after the histamine was stopped, and an arterial pressure record taken 5 to 10 minutes after the infusion was over. In the others the needle was withdrawn as soon as the infusion was finished. After removing the needle the patient remained on the table for 10 to 15 minutes more for recovery records of the ballistocardiogram, electrocardiogram and respirations. The experiment was concluded when these were taken. Blood pressures were determined by the auscultatory method in the right arm at about 10-minute intervals during six of the experiments.

The stroke volume and cardiac output (minute volume) were calculated from the ballistocardiographic record using the area formula of Tanner.\textsuperscript{11} This is: Stroke volume in cubic centimeters = 100 \sqrt{(2I area + J area) \over C}. Representative inspiratory and expiratory complexes, usually the largest and smallest, respectively, were measured for each period of the experiment. Where there was marked variation in complex amplitude from one respiration to the next, several additional complexes were measured and averaged. In each record the amplitudes were corrected back to a 1 cm. weight standardization (baseline deflection of 1 cm. when 280 Gm. is allowed to pull on the end of the table). This was done by dividing the complex amplitude by the number of centimeters the baseline actually moved with the weight. Both pickups are sufficiently linear to make this correction permissible. The fluid pressure gage, which is also linear in its deflection, was standardized with three different pressures after each experiment. The standardization factor was used to calculate the femoral pressure.

Femoral arterial blood samples were obtained through the needle used for the injection. A specimen was taken before and immediately following the completion of the infusion. Venous blood specimens were taken from the femoral vein and venous pressures recorded directly by a saline manometer. All samples were then analyzed for oxygen and carbon dioxide by the VanSlyke method.

Results

The changes in heart rate and minute volume after intra-arterial histamine are summarized in table 1. It can be seen that 10 to 20 minutes after the infusion was started the heart rate had increased significantly in three of the patients, and only slightly in three. The cardiac output increased by 20 per cent or more in five of the patients within the first 20 minutes after the histamine was begun, and by only 13.8 per cent in the other subject. The changes after the infusion was stopped are shown. In general, the values returned rather rapidly toward normal. Figure 4 shows the changes in cardiac index (liters per minute per square meter of body surface) in six experiments (five patients) during the course of the intra-arterial histamine injection. The peak cardiac output
is reached between 10 and 20 minutes after the injection is begun. The return of the cardiac index to normal is relatively rapid; sometimes the fall occurs before the histamine is finished. Sample records from one patient (H.F.) during the second experiment for which he was the subject are shown in figure 5. The marked reciprocal changes in ballistocardiogram amplitude and femoral arterial pressure can be seen easily.

![Figure 4](http://circ.ahajournals.org/)

**Fig. 4.** Increase in cardiac index during intraarterial histamine injection.

The femoral blood pressure changes are summarized in table 2. Both the systolic and diastolic pressures dropped in these three patients, but had risen somewhat again within 10 minutes after the infusion was stopped. The systolic pressure decreased more than the diastolic. Changes in the indirect brachial pressure were relatively slight but in the same direction as the direct femoral pressures.

![Figure 5](http://circ.ahajournals.org/)

**Fig. 5.** Patient H. F. A. Control records with saline prior to histamine injection. The scale at the left is arterial pressure in mm. Hg. B. Marked fall in blood pressure, increase in amplitude of IJ stroke and heart rate with histamine. Note that the IJ strokes are much greater during inspiration than expiration. C. The record again resembles the control taken 10 minutes following cessation of histamine injection.

<table>
<thead>
<tr>
<th>Subject</th>
<th>% Change in Heart Rate</th>
<th>% Change in Cardiac Output (cc./min.)</th>
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<tbody>
<tr>
<td></td>
<td>Minutes after Histamine Began</td>
<td>Minutes after Histamine Begun</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>H. F. I</td>
<td>+8.9</td>
<td>+6.4</td>
</tr>
<tr>
<td>H. F. II</td>
<td>+25</td>
<td>+27.8</td>
</tr>
<tr>
<td>F. L.</td>
<td>+20</td>
<td>+18.8</td>
</tr>
<tr>
<td>A. W.</td>
<td>+22.6</td>
<td>+17.1</td>
</tr>
<tr>
<td>G. B.</td>
<td>+12.6</td>
<td>+7.4</td>
</tr>
<tr>
<td>C. A.</td>
<td>+1.2</td>
<td>+3.5</td>
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The stroke volume usually increased during the injection period. Four of the six patients showed a definite rise in stroke volume 15 to 20 minutes after the histamine was started. One showed only a slight increase, and the sixth patient showed no change. These data are shown in figure 6.

The effects of venous occlusion of the injected and the un.injected leg were somewhat variable. This is difficult to evaluate because the changes produced by intra-arterial histamine may be evanescent and a fall in the cardiac index apparently produced by the cuff may be the naturally occurring fall in output due to inactivation of the histamine. Table 3 summarizes the findings with venous occlusion. There is a tendency for the heart rate and cardiac output to decrease when the cuff is applied to the injected leg. This occurred in two of the patients, and, in the third, the minute volume was probably rising when the cuff was applied to the uninjected leg, since the output rose even higher after the last value recorded here. In only one patient did the output fall when the cuff was placed on the uninjected leg. Since the effects of histamine vary from one injection to the next in the same subject (table 1, H.F.) it will require further carefully planned experiments to be certain about the relationship of venous occlusion to the minute volume and heart rate. However, it does appear that these determinations rapidly revert toward normal when the cuff is applied to the injected leg.

The results in the 23 year old man with no evidence of cardiovascular disease are summarized in figure 7. This experiment was done mainly to determine if saline injection intraarterially would cause the changes we had observed. This single experiment showed some decrease in cardiac index, stroke volume, and pulse rate with saline, a change that could be due to prolonged rest in the supine position. Marked increments in cardiac index, pulse rate and a brief fall in stroke volume occurred after the histamine was begun. This subject also showed definite decrease in minute volume.

![Figure 6](image-url)  
Fig. 6. This shows the changes in stroke volume during intra-arterial histamine injection in six subjects.
one venous sample (G.B.) which did not show these changes was drawn 15 minutes after the histamine was stopped and probably reflects the rapid return to normal of the cardiovascular adjustments.

The femoral venous pressure rose an average of 25 mm. of saline in three of the patients and was unchanged in two.

**DISCUSSION**

During an arterial infusion of 3 mg. of histamine diphosphate in 500 cc. of saline given over a one-half hour period into one of the femoral arteries of patients with occlusive peripheral arterial disease, the following changes have been observed in most of the subjects: (1) an increase in heart rate; (2) an increase in stroke volume; (3) a marked increase in cardiac output; (4) a fall in systolic and diastolic blood pressures as recorded directly from the femoral artery; (5) a rise in skin temperature; (6) a variable rise in femoral venous pressure; (7) an increase in oxygen saturation and a decreased carbon dioxide content of femoral venous blood; and (8) a constantly occurring fall of varying magnitude in femoral arterial oxygen saturation with slight change in carbon dioxide content.

Although this series of experiments is small, we feel that these observations are worth reporting and should add to the understanding of the effects of intra-arterial histamine. The number of observations is insufficient to submit to statistical analysis; however, according to recent work establishing normal standards for cardiac output, using Tanner's formula,11, 12 our cardiac indexes are within the proper range and the changes observed are probably

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**TABLE 4.—Effect of Injection on Femoral Arterial and Venous Oxygen and Carbon Dioxide Saturation**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Preinjection artery</th>
<th>Postinjection artery</th>
<th>Preinjection vein</th>
<th>Postinjection vein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% O₂ saturation</td>
<td>CO₂ vol. %</td>
<td>% O₂ saturation</td>
<td>CO₂ vol. %</td>
</tr>
<tr>
<td>C. A.</td>
<td>93</td>
<td>53</td>
<td>91.8</td>
<td>51</td>
</tr>
<tr>
<td>G. B.</td>
<td>90.7</td>
<td>47.5</td>
<td>83.1</td>
<td>49.09</td>
</tr>
<tr>
<td>F. L.</td>
<td>88.9</td>
<td>48.5</td>
<td>83.4</td>
<td>48.7</td>
</tr>
<tr>
<td>S. B.</td>
<td>91.3</td>
<td>48.8</td>
<td>89.46</td>
<td>48.7</td>
</tr>
<tr>
<td>H. F.</td>
<td>94.6</td>
<td>42.25</td>
<td>91.7</td>
<td>43.3</td>
</tr>
</tbody>
</table>

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**Fig. 7.** Results of studies on a normal young man showing a slight decrease in pulse rate, stroke volume and cardiac index with intra-arterial saline; marked increase in pulse rate, stroke volume and cardiac index with histamine intra-arterially.

when the venous return from the injected leg was occluded, and a much smaller change when the cuff was on the other leg (table 3, C.W.).

It should be mentioned that the ballistocardiogram showed qualitative as well as quantitative changes. The pattern usually became slightly irregular with histamine, even without marked tachycardia. The respiratory variation usually increased after histamine. This is to be expected, since the respiratory variation usually increases when the cardiac output rises.

The results of the femoral arterial and venous oxygen determinations appear in table 4. The venous blood showed a definite and uniform rise in oxygen saturation and a fall in carbon dioxide. The arterial blood showed a variable fall in oxygen saturation, with the carbon dioxide changing relatively less. The
significant. The results were confirmable and relatively uniform from one subject to the next.

In order to be of lasting benefit in occlusive peripheral arterial disease, a therapeutic agent must be capable of producing an augmentation of collateral circulation to the involved extremity. In this series the majority of patients treated with intra-arterial histamine showed a definite increase in walking tolerance. The difference in physiologic effects obtained with intravenous and intra-arterial histamine is evident. This suggests that the local intensive effect of intra-arterial administration on the vascular bed of the extremity injected produces an alteration in circulatory dynamics which is quite distinct from that noted with the intravenously administered drug. One is impressed by the resemblance between the physiologic effects of intra-arterial histamine and the alterations noted in experimental and clinical arteriovenous fistulas. The tachycardia, increased cardiac output and stroke volume, fall in local arterial blood pressure, increase in local venous pressure, increase in local venous oxygen saturation and fall in local venous carbon dioxide content all suggest a shunting of blood in considerable quantity from the femoral arterial to the femoral venous circuit. Starr has previously reported a high cardiac output in a case of arteriovenous fistula as measured by the ballistocardiogram and showed a 17 per cent drop in cardiac output when a cuff was placed on the leg and inflated. It was with this in mind that the occlusion cuff experiments were done. Though not conclusive, due to the factors previously discussed, the result in two of three cases showed a distinct fall in cardiac output and a slowing of the pulse rate when the blood flow to the injected leg was occluded. It is known that arteriovenous shunts stimulate the development of extensive collateral circulation, and the mechanisms of this effect have recently been reviewed. In general, the larger the shunt and the longer the duration of its action, the greater is the development of the collateral circulation. However, changes of a lesser nature undoubtedly occur very early following the establishment of the fistula.

Anatomic arteriovenous shunts have been demonstrated in many parts of the body. The skin, muscle, liver, omentum and lungs all have been shown to possess such vessels in great numbers. Those in the lungs are of considerable size, being reported as large as 150 to 300 microns in diameter. Under ordinary circumstances these vessels remain relatively contracted and of constant diameter. In response to heat, trauma or histamine marked dilatation has been reported. The possibility exists that the actions of intra-arterial histamine noted might be due to the dilatation of arteriovenous shunts in the leg and that the increase in walking tolerance noted is a reflection of increased collateral circulation stimulated by repeated periods of shunting. The fall in arterial oxygen saturation noted was an entirely unexpected finding and might possibly indicate shunting of blood in the pulmonary circuit. Both of these possibilities will certainly require further investigation.

Clinically, the arteriosclerotic patient with early claudication who showed a diffuse pink erythema on injection seemed to gain the most benefit from this form of injection. In considerably over 200 injections no serious complication incident to arterial puncture was encountered. No untoward systemic reactions have been noted, although our patients include one with asthma, a man with severe angina, and several individuals with borderline cardiac reserve. The transitory initial ischemia produced during the injection was not felt to be harmful and the beneficial effects obtained were thought to be due to stimulus to collateral circulation during periods of arteriovenous shunting rather than to the opening of the arteriovenous shunts per se.

Certainly no definite conclusions can be reached regarding the efficacy of this method of treatment on the basis of such a small series of cases followed over a relatively short period of time. This preliminary investigation does seem to indicate that intra-arterial histamine may have a limited field of therapeutic usefulness in selected cases of occlusive arterial disease in a class of patient that has been regarded as refractory to treatment.
SUMMARY

1. Seven men with obliterative peripheral arterial disease were given a course of arterial infusions of histamine diphosphate. Five of the seven had good results from the course of treatment, one a fair result and one a poor result.

2. The results were measured by subjective change and objective increment in tolerance to walking on a treadmill. Those who were helped generally showed improvement by the sixth injection.

3. During the arterial infusion of histamine the following changes occurred in most of the subjects: increase in heart rate, stroke volume, cardiac output, skin temperature, oxygen saturation in the femoral vein, decrease in the blood pressure and oxygen saturation in the injected artery and arteriovenous oxygen difference, with less change in the brachial indirect blood pressure.

4. The similarity of the observed physiologic changes to those seen in arteriovenous shunts is noted.

5. It is speculated that the beneficial effects of intra-arterial histamine may be due to development of acute arteriovenous shunting and subsequent improvement in the collateral arterial circulation to the involved extremity.

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