Effect of Reserpine in Raynaud's Phenomenon

By Hermes A. Kontos, M.D., Ph.D., and Albert J. Wasserman, M.D.

SUMMARY
The responses of the blood vessels of the hand to intra-arterial infusion of tyramine and to application of ice to the forehead were examined in patients with Raynaud's phenomenon and in normal subjects. The vasoconstrictor responses to tyramine and to ice were not significantly different in the patients and control subjects. Following intra-arterial administration of reserpine the vasoconstrictor response to tyramine was unaffected, while that in response to ice was significantly reduced to a comparable extent in both the patients and the control subjects. Catecholamine concentrations in brachial arterial and hand venous plasma were not significantly different in the patients and in the control subjects. Following oral administration of reserpine (1 mg/day) the vasoconstrictor responses to intra-arterial tyramine and to the application of ice were markedly reduced in patients with Raynaud's phenomenon. In response to this form of treatment eight of the nine patients followed for 1 to 3 years showed improvement characterized by decreased frequency and severity of vasoconstrictor attacks and by healing of ulcerations. In two patients the improvement was temporary despite continued reserpine therapy.

Additional Indexing Words:
Tyramine Vasoconstriction Skin blood flow Vascular effects of cold

SeVERAL INVESTIGATORS1-4 reported good results from the use of reserpine in the treatment of patients with Raynaud's phenomenon. Because of its serotonin-depleting effect, reserpine has been thought to have a beneficial effect, particularly in patients with scleroderma. In addition to controlling Raynaud's phenomenon, reserpine has been reported to inhibit or reverse fibrosis in the skin of such patients.5,6 Peacock5 found increased concentrations of norepinephrine and epinephrine in the venous blood from the hand in patients with Raynaud's disease. He suggested that this may be the result of abnormal catecholamine metabolism. In support of this view he found that monoamine oxidase activity was markedly reduced in digital arteries of one patient with Raynaud's disease. Reserpine, because of its catecholamine-depleting effect, might combat the consequences of such a defect.

The present study was undertaken for two reasons: The available reports of the results of treatment of Raynaud's phenomenon with reserpine covered only the first few weeks of therapy, or the duration of the follow-up was not given. It was considered desirable to study the effects of reserpine in such patients for a longer period. Secondly, physiological studies were undertaken in patients with Raynaud's phenomenon treated with reserpine to identify the mechanism by which this drug exerts its beneficial effect.

Methods
Studies were carried out in 11 patients with Raynaud's phenomenon (six male and five female; mean age, 47 years; range, 33 to 63 years) and in six normal volunteers (three male and three female) who served as controls (mean, age 34 years; range, 30 to 37 years). All patients exhibited typical vasoconstrictor attacks, induced by cold or emotion, involving the digits and characterized by pallor, cyanosis, and pain. Nine patients had primary Raynaud's phenomenon (Raynaud's disease) according to the criteria of

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Allen and Brown. Two patients had secondary Raynaud's phenomenon associated with scleroderma. One of these had, in addition to skin involvement, esophageal and pulmonary involvement, while the other patient had skin and esophageal involvement. Two patients had had a dorsal sympathectomy several months prior to study. Five patients had ulcers of one or more fingers when they were first seen.

All studies were carried out in an air-conditioned laboratory (room temperature, 24-25°C) with the subjects recumbent on a table. Blood flow in the hand was measured by venous occlusion plethysmography by water-filled plethysmographs whose water temperature was maintained at 32°C thermostatically. Arterial blood pressure was measured with a Statham strain gauge connected to a Teflon catheter placed into the right brachial artery at the elbow. Vascular resistance in the hand was calculated as the ratio of mean arterial blood pressure divided by blood flow in the hand. Venous blood was obtained from a catheter placed in a retrograde direction into the cephalic vein at the wrist in such a manner that its tip lay distal to the wrist and within the plethysmograph. Plasma concentrations of norepinephrine and norepinephrine were determined by the method of Weil-Malherbe. Intra-arterial infusions of drugs were given by a constant infusion pump into the right brachial artery. The following pharmacological agents were used: tyramine, 50 μg/min, and reserpine, 0.5 mg given over a period of 5 min. These agents were dissolved in 0.9% NaCl in such a concentration that the rate of infusion was 1 to 2 ml/min.

The experimental procedure was as follows: After the arterial and venous catheters were put in place, the hands were placed in the plethysmographs, and the subject or patient was allowed to rest for approximately 30 min. Simultaneous arterial and venous blood samples were obtained for determination of plasma catecholamine concentrations. Subsequently, hand blood flow determinations were carried out every 15 sec. The response to intra-arterial administration of tyramine was then determined. The response of hand blood vessels to application of ice bag to the forehead was also studied. Then, the subjects received an intra-arterial infusion of reserpine, and the responses to intra-arterial infusion of tyramine and to the application of ice to the forehead were determined again between 40 and 60 min following the end of reserpine infusion. These studies were carried out both in the patients with Raynaud's phenomenon and in the normal subjects. The patients with Raynaud's phenomenon were then given 1 mg/day of reserpine orally for a period of 4 to 6 weeks. The studies described above with the exception of reserpine infusion were then repeated. The results were evaluated statistically by means of a t-test.

### Results

The mean resting blood flow in the hands of patients with Raynaud's phenomenon was $6.6 \pm 0.6$ ml/min/100 ml of hand tissue; the comparable value in the control subjects was $9.8 \pm 2.1$ ml/min/100 ml. These values are not significantly different from each other. The mean values were obtained by averaging the flows in both hands obtained over a period of 5 min; they were therefore based on 40 flow determinations in each subject. The concentrations of norepinephrine and epinephrine in the brachial arterial and the hand venous

<table>
<thead>
<tr>
<th></th>
<th>Arterial</th>
<th>Venous</th>
<th>A-V difference</th>
</tr>
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<tbody>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R (N = 9)</td>
<td>1.10 ± 0.35</td>
<td>1.79 ± 0.72</td>
<td>-0.70 ± 0.48</td>
</tr>
<tr>
<td>C (N = 5)</td>
<td>0.41 ± 0.29</td>
<td>0.70 ± 0.25</td>
<td>-0.29 ± 0.12</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R (N = 9)</td>
<td>0.58 ± 0.20</td>
<td>0.66 ± 0.22</td>
<td>-0.08 ± 0.23</td>
</tr>
<tr>
<td>C (N = 5)</td>
<td>0.22 ± 0.15</td>
<td>0.18 ± 0.08</td>
<td>-0.04 ± 0.07</td>
</tr>
</tbody>
</table>

All values are mean ± standard error of the mean (SE). N = number of subjects; R = patients with Raynaud's phenomenon; C = control subjects. Note that a negative A-V difference indicates that venous concentration is higher than arterial. There is no significant difference between control subjects and patients with respect to any of the values shown.

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plasma in the patients with Raynaud's phenomenon and in the control subjects are shown in table 1. There was no significant difference between the patients and control subjects with respect to the arterial or venous concentration or the arteriovenous differences in the concentration of these catecholamines. Following oral treatment with reserpine for 4 to 6 weeks, norepinephrine was undetectable in arterial and venous plasma in any of the six patients in whom this determination was carried out.

Forty minutes following intra-arterial administration of reserpine, blood flow in the hand increased significantly to $8.8 \pm 0.8$ ml/min/100 ml in the patients with Raynaud's phenomenon and to $18.5 \pm 3.5$ ml/min/100 ml in the control subjects. The increase in flow in the control subjects was significantly greater ($P < 0.01$) than that in the patients with Raynaud's phenomenon.

The responses to intra-arterial tyramine of the patients with Raynaud's phenomenon and of the control subjects are summarized in Table 2 and illustrated in Figure 1. During the control period, tyramine produced a decrease in hand flow which was not significantly different in the control subjects and in the patients with Raynaud's phenomenon. Forty minutes following intra-arterial infusion of reserpine, tyramine produced decreases in hand blood flow in the control subjects and in the patients with Raynaud's phenomenon which were not significantly different from those seen prior to reserpine infusion. Following oral treatment

![Figure 1](image)

**Figure 1**

*Effect of infusion of tyramine into the right brachial artery on the hand blood flow (HBF) of a patient with Raynaud's phenomenon without pretreatment (A), forty minutes after intra-arterial infusion of 0.5 mg of reserpine into the right brachial artery (B), and after 5 weeks of oral administration of reserpine 1 mg/day (C).*

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Table 3

Responses of Hand Blood Flow (HBF), Hand Vascular Resistance (HVR), and Mean Arterial Blood Pressure (MABP) to Application of Ice to the Forehead in Patients with Raynaud's Phenomenon and in Normal Subjects

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
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<th>Ice</th>
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</thead>
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<tr>
<td></td>
<td>HBF</td>
<td>HVR</td>
<td>MABP</td>
<td>HBF</td>
<td>HVR</td>
<td>MABP</td>
</tr>
<tr>
<td>No pretreatment</td>
<td>R(N = 8)</td>
<td>6.7 ± 0.6</td>
<td>14.7 ± 1.2</td>
<td>91.8 ± 3.0</td>
<td>4.6 ± 0.6</td>
<td>24.7 ± 2.3</td>
</tr>
<tr>
<td></td>
<td>C(N = 6)</td>
<td>10.5 ± 2.3</td>
<td>11.1 ± 2.5</td>
<td>91.5 ± 2.4</td>
<td>6.6 ± 1.6</td>
<td>24.2 ± 7.1</td>
</tr>
<tr>
<td>After intra-arterial reserpine</td>
<td>R(N = 8)</td>
<td>8.8 ± 0.6</td>
<td>10.9 ± 0.7</td>
<td>90.9 ± 2.0</td>
<td>8.3 ± 0.5</td>
<td>13.6 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>C(N = 6)</td>
<td>18.3 ± 3.5</td>
<td>6.0 ± 1.3</td>
<td>89.8 ± 3.7</td>
<td>15.7 ± 3.1</td>
<td>8.9 ± 2.3</td>
</tr>
<tr>
<td>After oral reserpine</td>
<td>R(N = 6)</td>
<td>7.3 ± 1.1</td>
<td>14.5 ± 3.3</td>
<td>90.7 ± 6.8</td>
<td>6.4 ± 0.9</td>
<td>18.7 ± 4.1</td>
</tr>
</tbody>
</table>

All values are mean ± se. HBF = hand blood flow in ml/min/100 ml; HVR = hand vascular resistance in mm Hg/ml/min/100 ml; MABP = mean arterial blood pressure in mm Hg; R = patients with Raynaud's phenomenon; C = control subjects; N = number of subjects.

with reserpine for 4 to 6 weeks in the patients with Raynaud's phenomenon, there was still a small but significant reduction in hand blood flow in response to intra-arterial tyramine (P < 0.05); this decrease, however, was less pronounced than that prior to oral reserpine therapy (P < 0.001).

The responses to application of ice to the forehead in the patients with Raynaud's phenomenon and in the control subjects are summarized in table 3 and illustrated in figure 2. In response to the cold stimulus, the mean arterial blood pressure increased, the hand blood flow decreased, and the hand vascular resistance increased in both the control subjects and the patients with Raynaud's phenomenon. The increase in hand vascular resistance was not significantly different in the two groups studied. Following intra-arterial administration of reserpine, the increase in vascular resistance produced by application of ice to the forehead was much less in both the control subjects and in the patients with Raynaud's phenomenon than it was before this treatment. After oral reserpine therapy, application of ice to the forehead still produced a significant increase in hand vascular resistance in the patients with Raynaud's phenomenon; this increase was of comparable magnitude to that seen following intra-arterial reserpine, but it was significantly less pronounced than that seen in the control period prior to administration of intra-arterial or oral reserpine.

Of the 11 patients included in this study, two (one with scleroderma) did not return for a follow-up study, and a third did not improve after oral reserpine therapy. The patient who failed to improve had Raynaud's phenomenon secondary to scleroderma. The remaining eight patients showed clear-cut improvement characterized by decrease in the frequency and severity of vasospastic attacks. The patients noted that the attacks were less severe, were not accompanied by pain, were of shorter duration, and were less easily provoked. There was healing of ulcerations in the five patients who had finger tip ulcers prior to reserpine therapy. Healing began within a week from the onset of reserpine therapy. In three patients the ulcerations did not recur during the follow-up period which extended from 1 to 3 years. In two patients the initial improvement after the initiation of reserpine therapy was followed by deterioration which was characterized by increasing severity and frequency of vasospastic attacks and by recurrence of ulcerations.

Of considerable interest is a sequence of events which occurred in the last-mentioned two patients on repeated investigation in relationship to their clinical course. This is illustrated in figure 3 in the case of patient N.T.
RESERPINE IN RAYNAUD'S PHENOMENON

Figure 2

Effect of application of ice to the forehead (indicated by the shaded bar above the time scale) on mean arterial blood pressure (MABP) and on hand blood flow (HBF) in a patient with Raynaud's phenomenon before pretreatment (A), 40 min after infusion of reserpine into the right brachial artery (B), and after 5 weeks of oral administration of reserpine (C). Same patient as in figure 1.

This patient, when first seen in August 1965, had ulcerations on all fingers. In response to intra-arterial administration of tyramine he showed pronounced vasoconstriction as indicated by the decrease in hand blood flow. Following oral reserpine therapy the vasoconstriction was essentially abolished. By the end of September 1965, his ulcers had healed almost completely. In October 1965, he noted increasing severity and frequency of vasospastic attacks, and in the middle of this month new ulcerations began to develop on his fingers, while he was still receiving 1 mg/day of reserpine orally. On October 28, 1965, he showed vasoconstriction in response to intra-arterially administered tyramine. Following this study the oral dose of reserpine was increased to 2 mg/day. He again improved, the ulcerations healed, and on a repeat study 3 weeks later he showed no vasoconstriction in response to tyramine. Deterioration again recurred in February 1966, and on February 21, 1966, he showed pronounced decrease in hand blood flow in response to tyramine given intra-arterially. The dose of reserpine was increased to 3 mg/day and he again improved with complete healing of ulcerations. He remained on this dose until the summer of 1967 when he moved to Florida and subsequently discontinued the drug. When he was last seen in March 1968, he remained free of symptoms.

The second patient (R.B.) who showed a similar sequence of events noted side effects when the dose of reserpine was increased, and for this reason guanethidine in a daily dose of 25 to 50 mg was substituted for reserpine. To date, he has been followed for 33 months and has had no recurrence of ulcerations, although he has had occasional mild vasospastic attacks on prolonged exposure to cold.
lar to those on reserpine. Side effects from reserpine were generally minor and included nasal stuffiness, weakness, loss of energy, and sleepiness. Potentially serious side effects were noted only in patient R.B. described above, who developed depressive behavior when placed on 2 mg of reserpine daily.

Discussion

Definitive conclusions concerning the efficacy of any form of therapy in a disorder, such as Raynaud's phenomenon, characterized by considerable variation in response to uncontrolled factors must be based on long-term, well-controlled, and preferably double-blind studies. We consider the good results obtained in the present investigation and those obtained by others who used reserpine in the treatment of Raynaud's phenomenon as sufficiently encouraging to warrant initiation of such a study. The mechanism of the return of the vasoconstrictor response to tyramine and of the clinical deterioration in two of our patients while on reserpine therapy is not clear. It is uncertain whether or not this may be a serious limiting factor in the treatment of patients with Raynaud's phenomenon with reserpine.

In our study there was no difference between control subjects and patients with Raynaud's phenomenon with respect to the concentrations of epinephrine and norepinephrine in the brachial arterial and hand venous plasma or in the arteriovenous difference in the concentrations of these catecholamines across the hand. These findings contrast with the results of Peacock who found much higher venous plasma concentrations of epinephrine and norepinephrine in patients with Raynaud's disease than in normal control subjects and suggested that this might be the result of a local defect in catecholamine metabolism.

Several reasons, however, cast doubt on the validity of Peacock's conclusions. In his study, only venous plasma catecholamine concentrations were measured; consequently, the possibility that the high venous values reflected increased arterial concentrations could not be
evaluated. This possibility is supported by the fact that the concentrations of both epinephrine and norepinephrine in venous blood were high. A local defect in catecholamine metabolism would not be expected to affect materially the concentration of epinephrine. In addition, the mean blood flow in his patients with Raynaud's disease was half of that found in normal subjects. Obviously, if catecholamines were released from the tissues of the hand, venous blood concentration in the patients would be considerably higher as a result of the lower blood flow and would not necessarily reflect increased release. If, as a result of faulty metabolism, there were increased release of norepinephrine in response to a given stimulus, or decreased destruction of released norepinephrine, one might reasonably have expected enhanced vasoconstrictor responses to tyramine or to application of cold. This was not the case in our experiments. The fact that the vasodilatation in response to intra-arterial reserpine was of lesser magnitude in our patients than in the control subjects would be consistent with increased stores of tissue norepinephrine. It would also, however, be consistent with the possibility that the diminished response in the patients might be due to structural changes in the blood vessels of the hand which are known to occur in patients with this disorder, especially when they have ulcerations. We conclude on the basis of these considerations that there is no evidence supporting the existence of a defect in catecholamine metabolism in Raynaud's phenomenon that leads to increased release of catecholamines from the tissues of the hand.

Our results suggest that the beneficial effect of reserpine in patients with Raynaud's phenomenon is related to its catecholamine-depleting effect and the consequent diminution of adrenergic vasoconstriction. This is based on the fact that equally good results could be obtained with reserpine and guanethidine and on the good correlation between clinical improvement and sympathetic blockade. Although our results have no bearing on the possible existence of a local defect in the blood vessels of the skin in patients with Raynaud's phenomenon that makes them more responsive to cold, they show that blockade of neurogenic vasoconstriction is of benefit in these patients. They, therefore, suggest that an element of neurogenic vasoconstriction might be of importance in the pathogenesis of Raynaud's phenomenon and of its consequences. Reserpine therapy, by diminishing neurogenic vasoconstriction, decreases the frequency, severity, and duration of vasospastic attacks which are in turn less likely to result in permanent damage to the tissues.

It is of interest that none of the tests used in this investigation, including measurement of resting hand blood flow, the response to intra-arterial infusion of tyramine, and the response to application of ice to the forehead, could reliably distinguish between the patients with Raynaud's phenomenon and normal subjects. It is, therefore, clear that these measurements cannot be used in the diagnosis of Raynaud's phenomenon.

It is of interest that, following intra-arterial administration of reserpine, reflex vasoconstriction was significantly decreased, while the vasoconstrictor response to tyramine was unaffected. This finding is consistent with the view that tyramine is capable of releasing norepinephrine from an extragranular reserpine-resistant portion of the neurotransmitter pool, while nerve stimulation is not.

Acknowledgment

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References

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