

RENAL AND HYPOTENSIVE EFFECTS OF ACUTE AND CHRONIC
ORAL TREATMENT WITH 1-HYDRAZINOPHTHALAZINE
(APRESOLINE) IN HYPERTENSION

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AMONG the commonly used antihypertensive drugs, only one, 1-Hydrazinophthalazine (Hydralazine), has been reported by various sources to produce an active dilatation of the renal vessels, when given parenterally to human subjects.¹⁻³ No studies on the effects of administration of single oral doses, acceptable to the patient, have been reported, and with the exception of the report of Dustan and associates,¹ and Moyer⁴ no information is available concerning the effects on the kidneys of long-term therapy with this drug. Since it was hoped that continued renal vasodilatation might reverse the pathologic vasoconstriction of the kidneys in hypertensive disease, it was of particular interest to observe the effect of acute and chronic oral administration of Hydralazine on the resting renal circulation and the basal blood pressure. Such observations form the subject of this paper.

METHODS

1-Hydrazinophthalazine was administered in maximum tolerated oral doses, to seven patients with moderate "essential" hypertension but without azotemia, two of whom (V.G. and W.M.) had undergone a supradiaphragmatic splanchnicectomy, eighth vertebral ganglion to twelfth vertebral ganglion, 15 to 17 months previously. Before and at the end of an 11 to 15-weeks' period of such treatment, the renal blood flow response to a single oral dose of the drug was observed. Renal function was tested by the clearance of para-aminohippurate and inulin, according to conventional techniques. Patients were studied in the fasting state and the blood pressures and renal functions were determined during two 20-minute control periods after which the drug was given orally at the beginning of the third period. The blood and catheterized urine specimens were then collected over six additional intervals of 20 minutes each. The blood pressure for each period was recorded every 3 to 5 minutes throughout the entire procedure, and the mean value for each period was calculated by dividing the average of all systolic and diastolic readings by two. The fluid intake was constant during the test, as the patients each received intravenously 750 c.c. of fluid containing para-aminohippurate and inulin, and routinely were given 120 c.c. of water or fruit juice orally at 45-minute intervals.

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During clinic visits when renal blood flow determinations were not performed, the resting mean blood pressure was calculated by averaging the first two or three recumbent readings taken within 15 to 30 minutes after admission to the clinic. The blood pressure after the test dose was determined by taking the lowest mean recumbent reading during the day in the clinic, the patient remaining ambulatory in the interval between readings. The lowest blood pressure usually occurred about equally after either the first dose at 9 A.M. or the second dose at 12 noon. This system recorded the maximum possible reduction which could be ascribed to the drug.

In addition to this study, the effects of Apresoline on the foot blood flow were studied in selected patients by means of the venous occlusion plethysmographic technique of Abramson.⁵

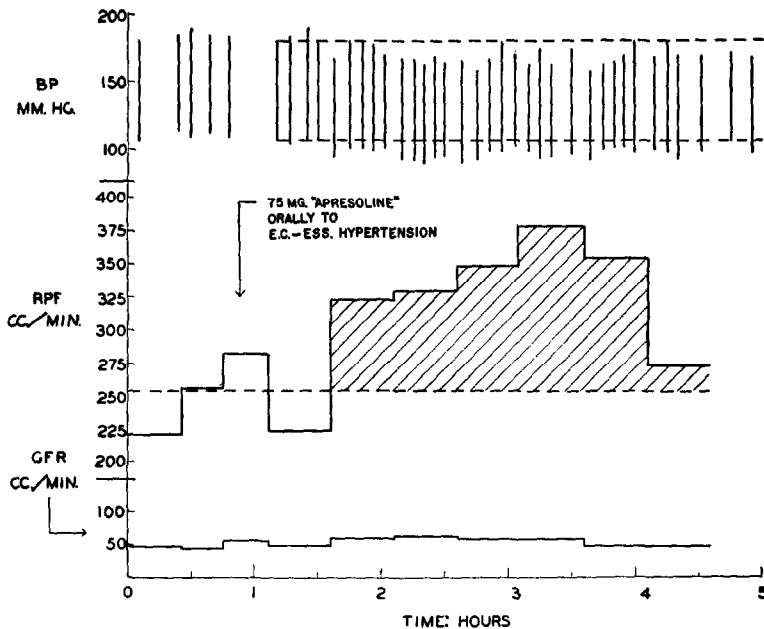


Fig. 1.—Effect of oral Apresoline on blood pressure and renal function.

RESULTS

1. *Effect on Renal Plasma Flow.*—The typical effect of a single oral dose of Hydralazine was to produce a significant increase in renal plasma flow without a significant change in glomerular filtration rate (Fig. 1). The renal vasodilator response was evident approximately 45 minutes after drug administration, was at its maximum in 2 to 2½ hours, and returned to normal levels in 3½ to 4 hours. A moderate reduction in systolic and diastolic blood pressures was also noted.

Our data in all seven cases, studied before and at the end of the period of chronic treatment with the drug, is presented in Fig. 2. The mean renal plasma flow of our patients increased from 385 ± 42.9 c.c./min.* to 523 ± 46.8 c.c./min.* following the initial administration of the drug. This difference was highly significant ($p = 0.011$).

*Mean and standard error of the mean.

At the end of the 11 to 15 weeks of treatment the same dose increased the renal plasma flow from 419 ± 43.9 c.c./min. to 422 ± 66 c.c./min., which is entirely insignificant. Resting renal plasma flow was found to be significantly higher in three of the seven patients (E.V., S.C., E.Z.) at the conclusion of the treatment period. However, the mean change of all cases,* from 385 to 419 c.c./min., was insignificant ($p = 0.35$). Crude renal resistances were found to drop significantly in every case initially, the mean reduction being 40 per cent.

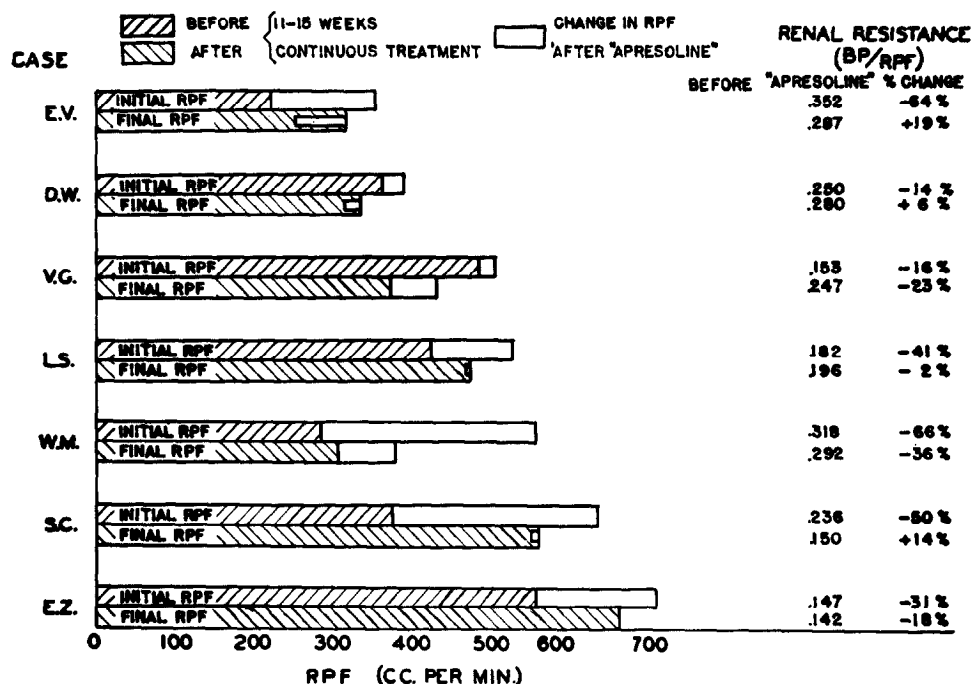


Fig. 2.—Effect of oral Apresoline on renal plasma flow in hypertension. The shaded areas represent the mean resting renal plasma flow (average of two 20-minute periods before and one 20-minute period after oral administration of the effective dose of Apresoline, as indicated in Fig. 3). The open bars indicate the mean change for the fifth to the eighth 20-minute period (third to sixth after oral Apresoline). Renal resistances are calculated by the formula (mean blood pressure divided by renal plasma flow $\times 1/\text{hematocrit}$). It will be seen that substantial increases in renal plasma flow (average = +41 per cent) and decreases in renal resistance produced initially are less conspicuous at the conclusion of the treatment. The resting flows, however, increased slightly in three cases (E.V., S.C., and E.Z.).

In contrast, however, there was an inconstant lowering of resistance of 6 per cent when the same oral dose was given after prolonged treatment. The drug altered the filtration fraction by a mean of -21.6 per cent before and -5 per cent after the treatment interval. The changes were due in large part to the alteration in renal plasma flow. The resting filtration rate and filtration fraction were not significantly affected by the prolonged treatment.

2. *Effect on Blood Pressure.*—The blood pressure changes are individually plotted in Fig. 3 with the magnitude of the solid bars indicating the mean blood pressure reduction to equal doses of the drug given during the two renal blood

*Mean and standard error of the mean.

flow determinations. Open bars represent the acute blood pressure changes to varying doses given during interim visits to the clinic in the treatment period. The size of these doses is recorded on the base line. They were often reduced at these visits because patients complained of side effects from larger amounts. The height of the shaded areas on the base line indicates the daily drug intake between clinic visits. The numerals above the bars indicate the mean blood pressures before each test dose was administered. It can be readily seen that no change in the basal blood pressure occurred as a result of prolonged treatment.

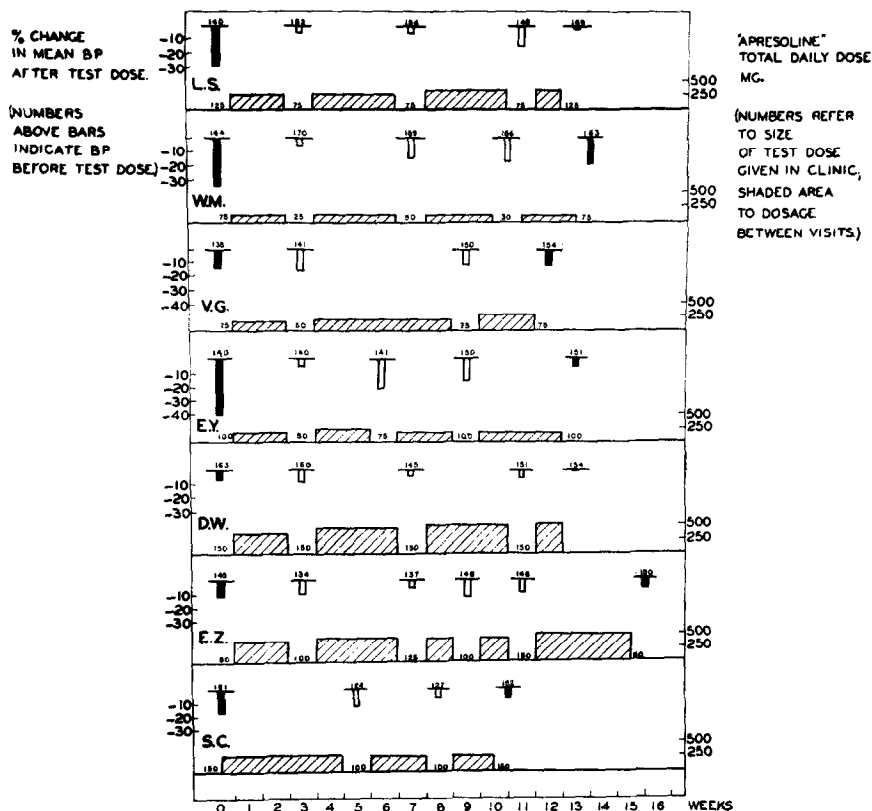


Fig. 3.—Response of recumbent blood pressure to oral Apresoline therapy. Shows changes in mean blood pressure after acute and chronic administration of Apresoline to seven hypertensive patients. Method of calculation of the resting blood pressure and the change in blood pressure after the test doses is described in the section under "Methods" and the interpretation of the figure is as described in the text in the section under "Results."

Further inspection of Fig. 3 shows that the initial test dose during the renal function test reduced the blood pressure significantly in six of the seven patients, the mean change being a -22 per cent. In contrast, the mean decrease in blood pressure during the final renal blood flow determination with the same oral dose was less prominent, representing a -8 per cent change and only two patients (W.M. and V.G.) showed a significant (i.e., greater than 10 per cent) response. This tolerance also extended to side effects, such as headache, dizziness, palpitation, nervousness and insomnia, which were much decreased on the second

administration at the end of the treatment period. Because of the development of tolerance, attempts were made to elevate the dosage taken at home, but headaches and palpitation prevented us from making substantial increases.

3. *Effect on Foot Blood Flow.*—Foot blood flow studies were done on seven patients, three of whom were also followed for their renal response to Hydralazine. In all cases a definite increase in flow was observed, occurring about 45 to 60 minutes after the ingestion of the drug and disappearing in 2 to 2½ hours (Fig. 4).

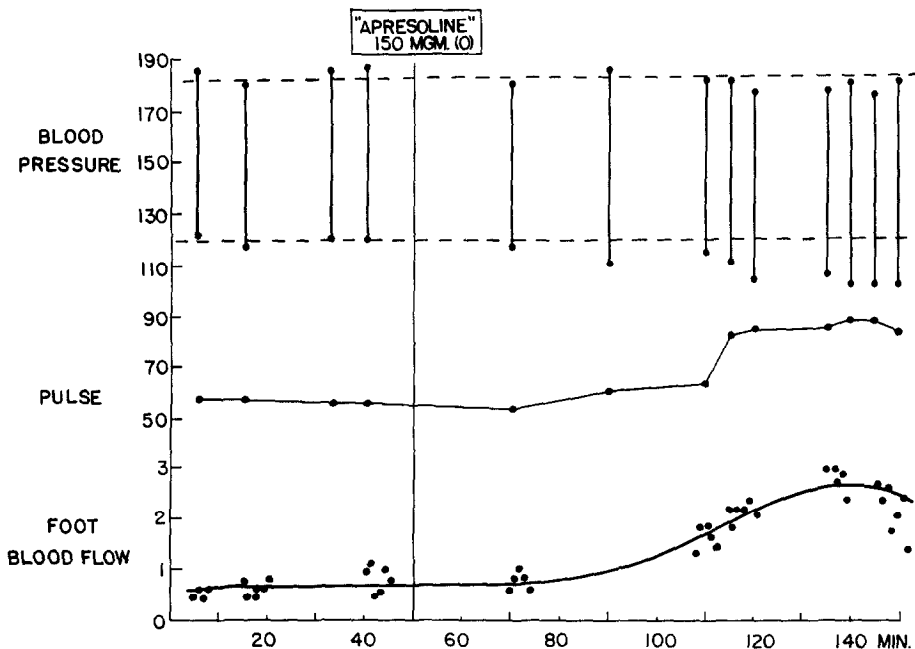


Fig. 4.—The effect of oral Apresoline on the foot blood flow as measured in the venous occlusion plethysmograph together with the changes in blood pressure and pulse rate. The definite vasodilator response to oral administration of the drug together with the widening of pulse pressure and increase of pulse rate suggests that a generalized vasodilatation is produced.

The heart rate increased considerably and there was a decrease in blood pressure, especially diastolic. The mean flow in all our patients increased from 2.72 c.c./100 c.c. of foot volume per minute to 4.4 c.c./100 c.c. of foot volume per minute. This represented a 43 per cent drop in regional resistance in this vascular bed, i.e., almost identical to that found in the renal area, in spite of the fact that the two areas are under quite unequal sympathetic tone.

DISCUSSION

The observations described above agree with those of Moyer⁴ that Hydralazine is a potent renal vasodilator, but that tolerance to its renal effects is soon established. Dustan and associates¹ also noted a failure of renal vasodilatation to occur after prolonged oral treatment with the drug, but stated that in certain cases an increase in the resting renal blood flow was observed after chronic treatment. We also observed slight increases in resting renal plasma flow in three of our patients after prolonged treatment.

Observations of tolerance to the depressor effects of acute administration of Hydralazine after chronic treatment have also been reported by Moyer.⁴ The report of Taylor and associates⁵ does not include repeated careful studies of the acute response to oral administration of the drug before and after prolonged treatment, but it is reported that the blood pressure fell after treatment and rose when placebos were administered. Since the drug was given four times daily, it is probable that the blood pressure they recorded, particularly in the clinic, followed at least one dose of the drug and therefore does not represent changes in the "basal" level of the blood pressure. It should be emphasized that Hydralazine has a relatively transient effect and that the time since last administration of the drug is important in evaluating the blood pressure response. For the same reason it is not likely that drug administration during the day will affect blood pressure during the night unless the "basal" blood pressure level of the patient is reduced. This we have shown does not occur with the relatively small doses tolerated by our patients.

That the drug is an active generalized dilator at least in hypertensive individuals is demonstrated by our observation that peripheral blood flow in the foot is regularly increased, which parallels the observations of Wilkinson and associates,³ and Schmid,⁷ who noted increased digital temperatures following parenteral administration. Increases in splanchnic blood flow reported by Freis⁸ also favor the concept that this drug is a generalized vasodilator.

The mode of action is not clearly defined, but the following bits of evidence suggest that a peripheral or central sympathetic inhibition is not involved: (a) vasodilatation in the kidney is not blocked by pretreatment with hexamethonium⁴ and (b) sympathetic inhibition with tetraethylammonium results in no increases in renal blood flow and greater increases in foot blood flow than here observed.^{9,10} That the drug may have a direct action on the blood vessels themselves is suggested by (a) the widespread character of the vasodilatation, (b) the effect of intra-arterial administration in increasing local blood flow in animals¹¹ and local skin temperatures in man,³ and (c) absence of the hypotensive property of the drug in the spinal animals with a mean blood pressure of 60 and its reappearance if the blood pressure is raised with ephedrine.¹¹ It may be concluded that Hydralazine (Apresoline) is an effective generalized vasodilator in hypertension but that tolerance to its effects is soon established and that the renal hyperemia initially produced by the drug does not lead to reduction of the basal blood pressure in established hypertension.

CONCLUSIONS

1. Well-tolerated oral doses of Hydralazine produce a definite and prolonged renal vasodilatation associated with a moderate decrease in blood pressure and increase in heart rate. However, prolonged treatment diminishes these responses.
2. In three of seven patients examined after two months or more of chronic treatment, there was a slight but definite increase in resting renal plasma flow, but no change in the basal blood pressure was noted in any of the patients studied.
3. The extremital circulation shares in the vasodilator response to the drug, based on observations of foot blood flow in hypertensive patients.

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