HEMODYNAMIC EFFECTS OF 1-HYDRAZINOPHTHALAZINE (APRESOLINE) IN HUMAN PREGNANCY: RESULTS OF INTRAVENOUS ADMINISTRATION [1]

By N. S. ASSALI, S. KAPLAN, S. OIGHENSTEIN,[2] AND R. SUYEMOTO

(From the Department of Obstetrics and the Cardiac Laboratory, the University of Cincinnati and the Cincinnati General Hospital, Cincinnati, Ohio)

(Submitted for publication October 22, 1952; accepted June 3, 1953)

Gross, Druey and Meier (1) first demonstrated that 1-hydrazinophthalazine (Apresoline) [3] given intravenously or orally to experimental animals, produces a marked and prolonged hypotensive effect, with simultaneous increases in pulse rate, auricular pressure, and renal blood flow.

Further animal experiments showed that this drug is effective against both neurogenic and renal hypertension (2, 3, 4), and that its hemodynamic effects are different from those of typical autonomic or adrenergic blocking agents (1, 5). Marked inhibition and even reversal of the vasopressor effects of epinephrine by Apresoline have been observed by some investigators (1, 2, 6, 7), whereas others, despite the use of large doses of the latter drug, have obtained only slight if any inhibition of such effects (8, 9). Apresoline does not seem to alter the pressor response to hypoxia or to the carotid sinus reflex (6, 9). It has been suggested that it may act through the hypothalamus or that it may counteract the effects of circulating vasopressor substances (1, 3, 4, 10). The drug increases cardiac output and renal blood flow in unanesthetized animals, whereas renal blood flow remains unaltered in anesthetized animals (7).

Patients with hypertension of diverse etiology seem to respond to the vasodepressor action of Apresoline, even when hypertension has persisted or recurred after sympathectomy (3, 4, 10). The induced fall in arterial blood pressure is usually accompanied by an increase in renal plasma flow (11, 12) and a decrease in cerebral vascular resistance (13). In man, inhibition or abolition of vasopressor reflexes by Apresoline, as well as inconsistent effects on the vasopressor action of epinephrine have been reported (2, 14, 15).

In the present study, the hemodynamic effects of Apresoline were investigated in normotensive non-pregnant and pregnant women, in patients with toxemia of pregnancy and with essential hypertension associated with pregnancy. As has been previously reported (16, 17, 18), ganglionic blocking agents induce only a negligible fall in blood pressure in patients with acute toxemia of pregnancy. In contrast, in normal pregnant women and frequently in pregnant patients with essential hypertension these drugs have a marked hypotensive effect, usually associated with a decrease in both cardiac output and renal plasma flow (19, 20). It was considered possible that the variation in response to ganglionic blocking agents of these different groups of patients together with the information gathered from determinations of the responses to Apresoline in comparable groups of subjects might clarify the hemodynamic effects of this drug and perhaps the general problem of toxemia of pregnancy.

CLINICAL MATERIAL

The clinical material for this study consisted of 75 subjects grouped as follows: 12 healthy normotensive non-pregnant women; 12 normotensive pregnant subjects; 33 patients with toxemia of pregnancy (29 with pre-eclampsia and 4 with convulsive eclampsia); and 18 pregnant patients with essential hypertension. The diagnosis of toxemia of pregnancy and of essential hypertension associated with pregnancy was made according to the criteria outlined elsewhere (16). The age of the patients varied from 16 to 39 years and the length of gestation ranged from 22 to 40 weeks.

[1] This investigation was supported (in part) by research grants from the National Heart Institute of the National Institute of Health, Public Health Service, and from Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

[2] Fellow in research, Department of Obstetrics, University of Cincinnati. Present address: Hospital dos Servidores do Estado, Rio de Janeiro, Brazil.

[3] Also known by the code numbers Ba-5968 and C-5968 and furnished through the courtesy of Ciba Pharmaceutical Products, Summit, N. J.

METHOD

With the exception of the four patients with convulsive eclampsia, who were studied upon admission, all the patients were at bed rest on the obstetric wards for at least 24 hours prior to the study. During this period, the spontaneous variations in blood pressure in the toxemic patients and those with essential hypertension were determined by sphygmomanometric readings every one or two hours, the pulse rate also being determined.

On the morning of the study, the patient was moved to a separate room and blood pressure readings, with the patient supine, were taken every one to two minutes for 10 to 50 minutes. The average of all these readings served as the control blood pressure. Apresoline was then given by rapid (20 seconds) single intravenous injection in doses ranging from 20 to 40 mg. Further blood pressure readings were taken every minute for the first half hour and then every five minutes for the next hour, subsequent readings being made at intervals of one-half to one hour until the blood pressure returned to control levels. The three lowest blood pressure readings within the first two hours after the injection were averaged to determine the maximal hypotensive response to the drug. The pulse rate was obtained from the radial or carotid artery. When more than one intravenous dose was given to the same patient, an interval of one to three hours was allowed between subsequent injections. During this time, the blood pressure and pulse rate had usually returned to control levels.

Venous cardiac catheterization was performed on three patients with toxemia of pregnancy according to the method of Cournand and Ranges (21). Cardiac outputs were determined on these patients by direct Fick principle, and pressures were recorded by means of a five channel optical oscillograph (Hathaway). Pulmonary "capillary" pressures were measured according to the method of Hellems, Haynes, and Dexter (22) and pulmonary arteriolar resistance calculated by the formula described by Fowler, Westcott, and Scott (23). Cardiac output determinations were also made on a series of patients with a high frequency ballistocardiograph (24). Although the validity of this method has been questioned, it is still believed by some authors (25) that relative values may be obtained from studies made on the same patient, particularly when the ballistic form is not abnormal. Mean arterial pressure was obtained either directly from the brachial artery or by adding one-third of the pulse pressure to the diastolic pressure. Blood volume studies (T-1824) were carried out according to Chinard's (26) modification of the single injection technique of Gregersen. Skin temperature was recorded in a constant temperature room with a Rauh electric pyrometer. Vasopressor reaction to cold and to the Valsalva

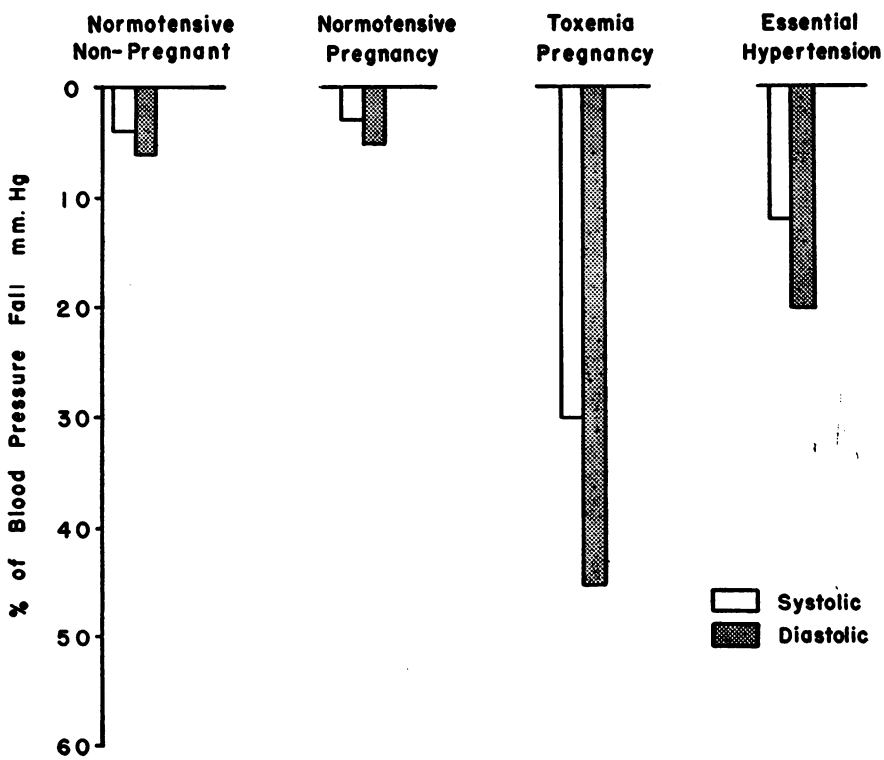

FIG. 1. BLOOD PRESSURE RESPONSES IN 75 PATIENTS WHO WERE GIVEN 163 INJECTIONS OF APRESOLINE

The figures represent per cent of change from the control blood pressure.

maneuver were determined once before and several times during the response to the drug. For the study of the Valsalva "overshoot," the blood pressure was recorded directly from the brachial artery. The effects of the drug on the vasopressor action of epinephrine were studied by giving single intravenous injections of varying doses of commercial epinephrine during the control period and again during maximal hypotensive response to Apresoline. After epinephrine injection, the blood pressure was recorded every one half minute; the pulse rate was obtained from electrocardiographic recordings.

RESULTS

1) *Blood pressure and pulse rate:* Blood pressure and pulse rate were determined in the 75 individuals given a total of 163 single injections. Three normotensive pregnant subjects and three toxemic patients were given 20 mg. doses. The remaining patients received doses of either 30 or 40 mg.

(a) *Normotensive nonpregnant and normotensive pregnant subjects:* Both groups of subjects responded in a similar manner. The average diastolic fall was 5 and 6 per cent, respectively; the change in systolic pressure was slight (Figure 1). Within this narrow range, the blood pressure response varied among the individual subjects even though the dosage was usually the same. In some patients the hypotensive effect lasted only for 30 minutes, whereas in others it persisted for approximately 2 hours. The pulse rate increased by 20 to 30 beats per minute without relationship to blood pressure response.

(b) *Toxemia of pregnancy:* The response of the patients with toxemia of pregnancy differed from that of normotensive subjects. Four to 15 minutes after the injection, the blood pressure began to fall gradually, the diastolic pressure before and more markedly than the systolic, and within 10 to 25 minutes after the injection, normal pressure levels were achieved and were maintained for several hours. The average fall in blood pressure was 30 per cent for systolic and 45 per cent for diastolic pressure (Figure 1). The average duration of the hypotensive effect of a single dose was 5 hours, although in three toxemic patients who received 20 mg., 30 mg., and 30 mg., respectively, the blood pressure remained low for 22, 24 and 25 hours, respectively, and then began to return gradually to control levels. The pulse rate invariably increased by 20 to 40 beats per minute after the injection but without relationship to the magnitude of fall in blood pressure.

(c) *Essential hypertension associated with pregnancy:* In this group, the average blood pressure fall was 11 per cent for systolic and 19 per cent for diastolic pressure (Figure 1). Here, again, the blood pressure did not begin to fall

TABLE I

Effect of Apresoline on cardio-pulmonary dynamics

Patient		(1) B.A.	(2) Mean B.A.	(3) C.O.	(4) C.I.	(5) P.C.	(6) P.A.	(7) Mean P.A.	(8) P.A.R.	(9) R.V.	(10) Mean R.A.	(11) R.V. Work	(12) T.P.R.
R. M. F.	Rest	178/102	130	7.82	4.77	8	32/15	20	123			0.75	1324
	After Apres.	162/78	105	12.67	7.73	13	33/15	23	63	33/2	9	1.55	664
G. T.	Rest	164/100	128	9.25	6.42	8	30/17	24	138			1.84	1102
	After Apres.	102/48	62	10.56	7.33	9	30/17	23	87	32/5	4	1.79	468
M. L.	Rest	203/127	158	4.47	2.81								2815
	After Apres.	125/52	80	7.63	4.80						4		834

(1) B.A.—brachial artery pressure mm. Hg.
(2) Mean B.A.—mean brachial artery pressure—mm. Hg.
(3) C.O.—cardiac output—litres per minute.
(4) C.I.—cardiac index—litres per minute per square meter.
(5) P.C.—mean pulmonary "capillary" pressure mm. Hg.
(6) P.A.—pulmonary artery pressure mm. Hg.
(7) Mean P.A.—mean pulmonary artery pressure mm. Hg.
(8) P.A.R.—pulmonary arteriolar resistance dynes. sec. cms^{-5}.
(9) R.V.—right ventricular pressure mm. Hg.
(10) Mean R.A.—mean right auricular pressure mm. Hg.
(11) R.V. work—mean right ventricular work kilogram meters per minute per square meter.
(12) T.P.R.—total peripheral resistance—dynes. sec. cm^{-5}.

TABLE II

The effect of Apresoline on skin temperature

Patient	Diagnosis	Skin temperature (° F.) before Apresoline			Skin temperature (° F.) after Apresoline*		
		B.P. *mm. Hg*	Toes	Fingers	B.P. *mm. Hg*	Toes	Fingers
F. D.	Toxemia	158/106	82	88	139/79	83	92
H. O.	Toxemia	140/98	84	90	119/69	84	96
B. C.	Toxemia	150/90	81	89	118/73	82	94
V. S.	Toxemia	153/101	83	87	140/87	83	97
B. M.	Toxemia	174/115	84	88	130/82	86	96
R. K.	Toxemia	180/110	82	89	140/80	84	95
J. T.	Ess. hypert.	204/106	82	88	170/92	83	92
R. B.	Ess. hypert.	184/110	82	86	140/98	83	95
O. W.	Ess. hypert.	160/105	82	87	130/90	82	93
S. D.	Normotensive	123/83	85	89	127/71	85	92
B. B.	Normotensive	120/84	84	90	124/68	86	93
N. G.	Normotensive	110/70	84	88	105/60	84	92

* The figures on skin temperature represent the average readings before and during the maximal Apresoline response.

until 5 to 20 minutes after the injection, and the maximal fall occurred 20 to 30 minutes after the administration of the drug. In all patients tachycardia of the same magnitude as in the preceding group was observed.

2) *Cardiac output, peripheral and pulmonary resistance:* The effects of Apresoline on the cardiopulmonary dynamics of three patients with toxemia are listed in Table I. Although the "resting" cardiac output and index were elevated in two patients (R. M. F. and G. T.), there was a further increase after injection of the drug. In the patient in whom the cardiac output was normal at rest, it was markedly increased after Apresoline. The pulmonary artery and pulmonary "capillary" pressures were normal at rest and did not vary consistently after the injection of the drug. The fall of the pulmonary arteriolar resistance was comparable to the marked fall of the total peripheral resistance.

Four patients with toxemia, four with essential hypertension associated with pregnancy, and three normotensive pregnant subjects were studied with the ballistocardiograph. None of the patients had abnormal ballistic forms either before or after the administration of the drug. The average control "cardiac output" in the toxemic and hypertensive group was 5.2 L. per min. increasing to 6.8 L. per min. after Apresoline; the total peripheral resistance was reduced 40 per cent. In the normotensive group, there was an average increase in the cardiac output of 600 cc. per min. and an average reduction of 18 per cent in the total peripheral resistance. The patients who were studied with the ballistocardiograph showed less individual variations than those studied with the Fick method in the values for cardiac output both before and after Apresoline.

3) *Skin temperature:* Skin temperature measurements were made in six patients with toxemia of pregnancy, three patients with essential hypertension associated with pregnancy, and three normotensive pregnant subjects. Before measurements were made, the patient was kept supine uncovered at a temperature close to 78° F. Readings were then taken from the fingers, hand, face, chest and abdominal walls, feet and toes.

The intravenous injection of Apresoline was followed by a significant rise in the temperature of the upper extremities, little change being observed in the temperature of the lower extremities (Table II and Figure 2). Significant rises also occurred in the temperature of the face and anterior wall of the chest. The changes in skin temperature showed no obvious relationship to the changes in blood pressure.

4) *Blood volume:* "Blood volume" changes were studied in four patients with toxemia of pregnancy and two normotensive pregnant subjects. Samples of venous blood for the dye determinations and hematocrit were obtained without stasis during the control periods and at the time of maximal hypotensive response to Apresoline. No significant changes in the blood volume were observed either in normotensive pregnant subjects or patients with toxemia of pregnancy.

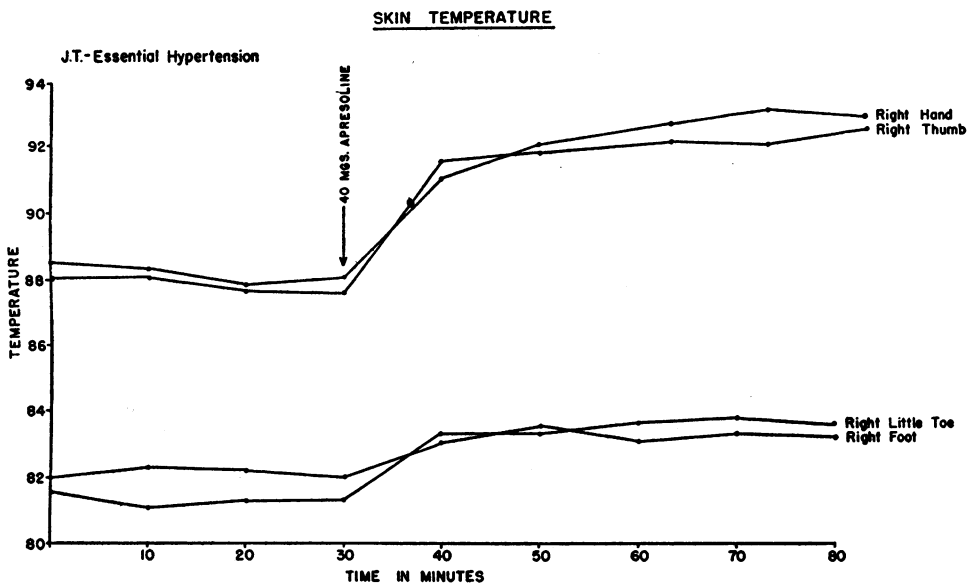

FIG. 2. PATTERN OF SKIN TEMPERATURE CHANGES AFTER INTRAVENOUS APRESOLINE

5) *Vasopressor reflexes:* Cold pressor tests were performed on five patients with toxemia of pregnancy, three pregnant patients with essential hypertension and two normotensive pregnant subjects by immersing the hand up to the wrist for one minute in ice water. Blood pressure readings were then taken every half minute. During the control period, a vasopressor reaction of varying magnitude was observed in all individuals tested. Following the injection of Apresoline, the pressor response to cold was unchanged (Table III). In five patients, the pressor response to the Valsalva maneuver was determined before and after the injection of the drug with direct blood pressure measurement. No significant changes in the Valsalva "overshoot" were observed.

6) *Vasopressor action of epinephrine:* The effect of Apresoline on the vasopressor action of epinephrine was studied in four normotensive pregnant subjects and four patients with toxemia of pregnancy. Epinephrine was given by single rapid intravenous injections in doses varying from 0.05 to 0.25 mg. before, and 20 to 30 minutes following, the administration of the drug (Table IV). The highest blood pressure reading within the first three minutes after the injection of epi-

TABLE III

Name	Diagnosis	Before Apresoline		After Apresoline	
		B.P. mm. Hg.	Response to Cold*	B.P. mm. Hg.	Response to Cold*
C.H.	Toxemia	130/100	19/8	120/70	20/7
A.C.	"	160/100	22/4	132/80	20/4
O.O.	"	200/120	8/3	140/90	9/4
V.S.	"	150/110	16/6	110/68	14/6
B.S.	"	130/92	10/4	105/70	11/3
I.F.	Ess. hypert.	160/100	21/5	150/98	19/5
H.O.	"	170/98	16/7	162/86	14/4
F.D.	"	150/102	17/6	140/92	16/6
S.O.	Normotensive	120/80	10/2	114/76	8/2
B.B.	"	122/78	6/3	118/74	7/2

*The response to cold was taken from the highest blood pressure reading recorded during the one minute test and the figures represent percent of rise from the control blood pressure and from the blood pressure level after Apresoline injection.

TABLE IV.

Effects of Apresoline on Vasopressor Action of Epinephrine.

Name	Diagnosis	Epinephrine Dose mg.	Before Apresoline				After Apresoline		
			B.P. mm. Hg.	Pulse	% of Change B.P.	% of Change Pulse	B.P. mm. Hg.	% of Change B.P.	% of Change Pulse
O.O	Toxemia	0.25	136/86	98	+105/63	+14	104/54	+140/141	+20
M.B.	"	0.25	140/97	88	+100/50	+ 9	115/79	+143/65	+21
M.S.	Normotensive	0.10	130/85	65	+ 92/41	+23	112/59	+123/116	+11
M.M.	"	0.10	110/66	76	+ 91/67	+10	107/60	+ 90/62	+15
R.S.	Toxemia	0.05	135/90	103	+ 56/27	0	129/76	+ 40/18	+ 2
E.J.	"	0.05	130/80	99	+ 55/25	+ 1	128/68	+ 48/18	+15
I.L.H.	Normotensive	0.05	101/67	81	+108/49	+19	80/48	+132/88	+10
F.A.	"	0.05	119/79	77	+ 85/47	+ 3	116/75	+ 55/33	+ 3

The percent of changes in B.P. and pulse rate before Apresoline represents the percent of the control blood pressure; that after Apresoline represents the percent of blood pressure level after the administration of the drug.

nephrine was taken as the maximal pressor response. Before Apresoline, the intravenous injection of epinephrine evoked a rise varying from 55 to 108 per cent in systolic pressure and from 25 to 67 per cent in diastolic pressure. After Apresoline, the epinephrine response was increased in five cases and slightly decreased in three. A decrease occurred in two individuals receiving doses of 0.05 cc. of epinephrine, although in one case, receiving this dosage, the epinephrine response was increased (Table IV). In no instance was the epinephrine response significantly inhibited or reversed.

The pulse rate showed variable changes after the first epinephrine injection, increasing in some subjects and decreasing in others. The tachycardia usually following administration of Apresoline was not significantly changed by the second epinephrine injection. Figure 3 illustrates epinephrine responses in a toxemic subject who received 0.25 mg. doses of epinephrine.

Tolerance: Tolerance to the drug was studied in 20 patients with toxemia who were given repeated intravenous injections of the same dosage of Apresoline. The blood pressure was allowed to return to control levels before a successive dose was administered. Table V shows the degree of fall in both systolic and diastolic blood pressure after successive injections. One fifth of the patients developed some tolerance after the second injection. However, with succeeding doses, the degree of tolerance became more marked as evidenced by the progressive increase in the number of patients who showed diminished response to the drug.

Side effects: Palpitation and a sensation of warmth were the most frequent complaints. Headache, "throbbing of the head," and dizziness were complained of by approximately 50 per cent of the entire group. Nausea and vomiting occurred in nine cases (two normotensive subjects, three patients with toxemia of pregnancy, and four pregnant patients with essential hypertension). These side effects were not related to the magnitude of response to the drug. In a few instances,

TABLE V

*Tolerance to Apresoline in toxemic patients**

Dose	No. patients	Patients with tolerance	Per cent fall systolic	Per cent fall diastolic
1st	20	0	30	42
2nd	20	4	20	36
3rd	20	11	17	25
4th	20	13	12	22
5th	15	11	10	13

* The blood pressure response is given as per cent of the average control blood pressure obtained before the administration of each dose. The degree of blood pressure fall listed after the first injection refers to those patients who developed tolerance.

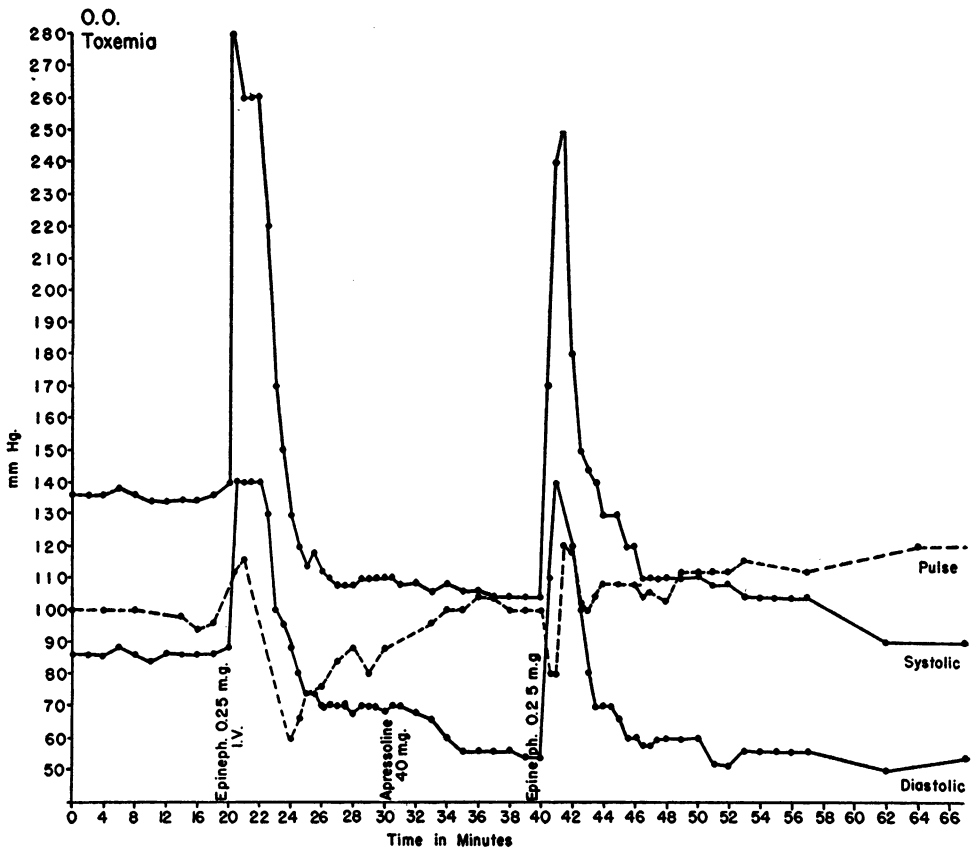

FIG. 3. PATTERN OF RESPONSE TO INTRAVENOUS EPINEPHRINE BEFORE AND AFTER APRESOLINE

anxiety, restlessness and epigastric pain were additional complaints.

DISCUSSION

Adequate explanation of the mechanism of action of Apresoline is not as yet available. The original observations of Gross, Druey, and Meier (1) showed that in animals the drug produces a significant decrease in the pressor effect of splanchnic stimulation and a partial to complete inhibition of the vasopressor action of epinephrine. These observations were supplemented by those of Freis and Finnerty (14) and Grimson, Chittum, and Metcalf (2) who observed some inhibition of vasopressor reflexes and concluded that the drug has certain "sympatholytic" properties. On the other hand, Britton, Taylor, and Ahlquist (6) and Walker and his co-workers (9), observed no significant action of Apresoline on the carotid sinus reflex or the pressor effect of hypoxia. Similarly, Craver, Barrett, Cameron, and Yonkman (5) found no evidence of sympatholytic activity of the drug in the cat.

The present data obtained from studies on pregnant subjects show that Apresoline failed to block the vasopressor reaction to cold and to Valsalva maneuver, even though the dosage employed was similar or higher than that used by Freis and his associates. The discrepancy between our results and those reported by these authors is not apparent.

Evidence has been presented (27, 28) that the vasopressor reactions to cold and to the Valsalva maneuver is mediated through the autonomic nervous system, and that this reaction can be inhibited by ganglionic blocking agents (17, 27, 28). The fact that Apresoline did not inhibit this reaction in pregnant women indicates that probably it does not act as a ganglionic blocker. This fact is further substantiated by Schroeder's observations that the drug remains effective after extensive sympathectomy. Also, the marked hypotensive effects

and increase in the cardiac output produced by Apresoline in toxemic patients in contrast to the slight effects observed in normal pregnancy, make this drug altogether different from the known ganglionic and adrenergic blocking agents. These observations, however, do not preclude the possibility that Apresoline might act through the autonomic nervous system by some as yet unknown mechanism.

Reports of the effects of Apresoline on the vasopressor action of epinephrine are inconsistent. Freis and his co-workers (14, 15) found no constant changes in the pressor response to epinephrine, whereas Walker and his co-workers (9) noted some depression after large doses of the drug. Moyer, Handley, and Huggins (7), on the other hand, have obtained in dogs complete abolition and even reversal of epinephrine pressor effects by Apresoline. Our observations are in agreement with those of Freis and would seem to indicate that Apresoline, in the dosage used, either has no effect on the vasopressor action of epinephrine, or may actually enhance its action. In fact, in the majority of instances, the vasopressor reaction to epinephrine and the associated subjective complaints were more marked after the administration of Apresoline than before.

Our results on the effects of Apresoline on the cardiac output, pulmonary dynamics and total peripheral resistance are in agreement with those observed by Wilkinson, Heikki, and Hecht (29). The fact that Apresoline increases markedly the cardiac output and at the same time reduces significantly the blood pressure and peripheral resistance suggests that its action may be limited to dilatation of the arteriolar system probably in the splanchnic bed and that the venous side of the circulation is not significantly affected.

Of interest is the rise in the skin temperature of the upper extremities as contrasted with the slight changes in that of the lower extremities. These findings differ from those seen after ganglionic blockade, which produces a more pronounced rise in the skin temperature of the lower extremities (30). These dissimilarities point to differences in mechanisms controlling blood flow to various segments of the body.

Several investigators (3, 10) have suggested that Apresoline may counteract the effects of circulating humoral agents. The fact that the drug is effective in reducing the hypertension of toxemia of pregnancy and that associated with acute nephritis (4, 31) lend support to this hypothesis, since available evidence suggests that the hypertension in these two disorders is not maintained by neurogenic mechanisms (16, 17, 32).

The delay in onset of the fall in blood pressure after intravenous administration of Apresoline has been observed by all investigators. It has been attributed by some (14) to a conversion of the drug to an active principle, but this possibility needs further investigation.

SUMMARY AND CONCLUSIONS

1) Hemodynamic effects of intravenous injection of Apresoline were studied in 12 normotensive non-pregnant, 12 normotensive pregnant, 33 toxemic and 18 pregnant subjects with essential hypertension.

2) Marked and prolonged blood pressure fall was observed in the toxemic group in contrast to a slight fall in the normotensive groups. Moderate blood pressure fall occurred in the essential hypertensive group.

3) Significant increase in cardiac output and reduction in the total peripheral and pulmonary arteriolar resistances occurred at the height of hypotension without any change in the blood volume. The temperature of the upper extremities rose more markedly than that of the lower extremities.

4) The drug failed to block the vasopressor reaction to cold and to the Valsalva maneuver in pregnant subjects.

5) The hemodynamic properties of Apresoline indicate that it may serve as a valuable adjunct in the treatment of toxemia of pregnancy.

ACKNOWLEDGMENT

The authors are indebted to Drs. John Braunstein, Ralph Scott and R. Helm and to Miss Mary Jane Tompkins for their assistance.

REFERENCES

1. Gross, F., Druey, J., and Meier, R., Eine neue Gruppe blutdrucksenkender Substanzen von besonderem Wirkungscharakter. Experientia, 1950, **6**, 19.
2. Grimson, K. S., Chittum, J. R., and Metcalf, B. H., Actions of 1-hydrazinophthalazine (C-5968) on vasomotor reflexes and hypertension in dogs and man. Federation Proc., 1950, **9**, 279.

3. Schroeder, H. A., Effects on hypertension of sulfhydryl and hydrazine compounds. J. Clin. Invest., 1951, **30**, 672.
4. Schroeder, H. A., The effect of 1-hydrazinophthalazine in hypertension. Circulation, 1952, **5**, 28.
5. Craver, B. N., Barrett, W., Cameron, A. and Yonkman, F. F., The activities of 1-hydrazinophthalazine (Ba-5968), a hypotensive agent. J. Am. Pharm. A. (Scient. Ed.), 1951, **40**, 559.
6. Britton, J. B., Taylor, J. P., and Ahlquist, R. P., Cardiovascular actions of 2,3-benzodiazine-4-hydrazine (C-5968). Federation Proc., 1951, **10**, 282.
7. Moyer, J. H., Handley, C. A., and Huggins, R. A., Some pharmacodynamic effects of 1-hydrazinophthalazine (C-5968) with particular reference to renal function and cardiovascular response. J. Pharmacol. & Exper. Therap., 1951, **103**, 368.
8. Craver, B. N., and Yonkman, F. F., Some pharmacological properties of 1-hydrazinophthalazine, a hypotensive agent. Federation Proc., 1950, **9**, 265.
9. Walker, H., Wilson, S., Atkins, E. C., Garrett, H. E., and Richardson, A. P., The effect of 1-hydrazinophthalazine (C-5968) and related compounds on the cardiovascular system of dogs. J. Pharmacol. & Exper. Therap., 1951, **101**, 368.
10. Taylor, R. D., Page, I. H., and Corcoran, A. C., A hormonal neurogenic vasopressor mechanism. Arch. Int. Med., 1951, **88**, 1.
11. Reubi, F., Renal hyperemia induced in man by a new phthalazine derivative. Proc. Soc. Exper. Biol. & Med., 1950, **73**, 102.
12. Schmid, A., and Reubi, F., Hamodynamische eigenschaften zweier neuer phthalazinderivate. Helvet. med. acta., 1950, **17**, 543.
13. Hafkenschiel, J. H., Friedland, C. K., Yobaggy, J., and Crumpton, C. W., Effects of 1-hydrazinophthalazine on cerebral hemodynamics and oxygen metabolism in hypertensive subjects. J. Pharmacol. & Exper. Therap., 1951, **103**, 345 (abstract).
14. Freis, E. D., and Finnerty, F. A., Jr., Suppression of vasomotor reflexes in man following 1-hydrazinophthalazine (C-5968). Proc. Soc. Exper. Biol. & Med., 1950, **75**, 23.
15. Freis, E. D., Mackay, J. C., and Oliver, W. F., The effect of "sympatholytic" drugs on the cardiovascular responses to epinephrine and norepinephrine in man. Circulation, 1951, **3**, 254.
16. Brust, A. A., Assali, N. S., and Ferris, E. B., Evaluation of neurogenic and humoral factors in blood pressure maintenance in normal and toxemic pregnancy using tetraethylammonium chloride. J. Clin. Invest., 1948, **27**, 717.
17. Assali, N. S., and Prystowsky, H., Studies on autonomic blockade. I. Comparison between the effects of tetraethylammonium chloride (TEAC) and high selective spinal anesthesia on blood pressure of normal and toxemic pregnancy. J. Clin. Invest., 1950, **29**, 1354.
18. Assali, N. S., Vergon, J. M., Tada, Y., and Garber, S. T., Studies on autonomic blockade. VI. The mechanisms regulating the hemodynamic changes in the pregnant woman and their relation to the hypertension of toxemia of pregnancy. Am. J. Obst. & Gynec., 1952, **63**, 978.
19. Assali, N. S., and Prystowsky, H., Studies on autonomic blockade. II. Observations on the nature of blood pressure fall with high selective spinal anesthesia in pregnant women. J. Clin. Invest., 1950, **29**, 1367.
20. Assali, N. S., Kaplan, S. A., Fomon, S. J., Douglass, R. A., and Tada, Y., The effect of high spinal anesthesia on the renal hemodynamics and the excretion of electrolytes during osmotic diuresis in the hydropenic normal pregnant woman. J. Clin. Invest., 1951, **30**, 916.
21. Cournand, A., and Ranges, H. M., Catheterization of the right auricle in man. Proc. Soc. Exper. Biol. & Med., 1941, **46**, 462.
22. Hellems, H. K., Haynes, F. W., and Dexter, L., Pulmonary "capillary" pressure in man. J. Applied Physiol., 1949, **2**, 24.
23. Fowler, N. O., Westcott, R. N., and Scott, R. C., Pulmonary artery diastolic pressure: its relationship to pulmonary arteriolar resistance and pulmonary "capillary" pressure. J. Clin. Invest., 1952, **31**, 72.
24. Braunstein, J. R., Oelker, C. E., and Gowdy, R. C., Design of a two-dimensional ballistocardiograph. J. Clin. Invest., 1950, **29**, 1219.
25. Scarborough, W. R., Davis, F. W., Jr., Baker, B. M., Jr., Mason, R. E., and Singewald, M. L., A review of ballistocardiography. Am. Heart J., 1952, **44**, 910.
26. Chinard, Francis P., Estimation of plasma volume by dye dilution method. Methods in Medical Research. Volume 4, page 38, Year Book Publishers, Chicago, 1951.
27. Reiser, M. F., and Ferris, E. B., Jr., The nature of the cold pressor test and its significance in relation to neurogenic and humoral mechanisms in hypertension. J. Clin. Invest., 1948, **27**, 156.
28. Sarnoff, S. J., Hardenbergh, E., and Whittenberger J. L., Mechanism of the arterial pressure response to the Valsalva test. The basis for its use as an indicator of the intactness of the sympathetic outflow. Am. J. Physiol., 1948, **154**, 316.
29. Wilkinson, E. L., Heikki, B., and Hecht, H. H., Cardiovascular and renal adjustments to a hypotensive agent (1-Hydrazinophthalazine: ciba BA-5968: Apresoline). J. Clin. Invest., 1952, **31**, 872.
30. Assali, N. S., et al., Hemodynamic effects of a thiophanium derivative (RO 2-2222) in human subjects. Circulation, in press.
31. Assali, N. S., et al., unpublished observations.
32. Ferris, E. B., Reiser, M. F., Stead, W. W., and Brust A. A., Jr., Clinical and physiological observations of interrelated mechanisms in arterial hypertension. Tr. A. Am. Physicians, 1948, **61**, 97.