CIRCULATORY EFFECTS OF GUANETHIDINE IN HYPERTENSIVE HEART FAILURE

BY

SUJOY B. ROY, M.B., M.R.C.P.Ed.

Professor of Cardiology

V. S. MATHUR, M.D.

Registrar in Cardiology

AND

M. L. BHATIA, M.D.

Assistant Professor in Cardiology

Department of Cardiology and Cardiovascular Laboratory,
All India Institute of Medical Sciences, New Delhi, India

Guanethidine ("ismelin"), a potent hypotensive drug, is being increasingly employed in clinical practice (Page and Dustan, 1959; Dollery *et al.*, 1960), and knowledge of its circulatory effects on the various manifestations of hypertension is essential. In this preliminary report we record the effects of intracardiac guanethidine on the cardiac output and circulatory dynamics in seven patients with hypertensive heart failure. They were studied as a preliminary to the proposed oral treatment with guanethidine. We also report the clinical response to guanethidine of these seven and another four unstudied cases of hypertensive failure treated for two to six months.

Material and Method

The clinical details of seven studied and four unstudied patients are outlined in Table I. Only those patients who had a basal supine diastolic pressure of at least 110 mm. Hg, and who did not receive any hypotensive or anticongestive therapy for the preceding 10 days, were included in this study. To avoid delay in starting guanethidine therapy the seven patients selected for haemodynamic study were catheterized within 24 hours of admission.

The seven patients were studied by right heart catheterization in the resting supine position. The right brachial artery was cannulated for continuous

monitoring of the arterial pressure. The right heart and brachial arterial pressures were recorded through Statham P23Db strain gauge manometers, on a four-channel single-gun photographic system. Baseline for all pressure measurements was taken as half the chest thickness at the second costal cartilage with the patient supine (Roy *et al.*, 1957). Measurements of cardiac output, in duplicate, were made by indicator dilution technique, with a continuous recording densitometer (Colson), and injection of indigo-carmin dye into the main pulmonary artery.

After obtaining the baseline data, 10–20 mg. (0.3–0.5 mg./kg.) of guanethidine was injected as a single bolus into the pulmonary artery. Continuous pulmonary and systemic arterial pressures were recorded for 30 minutes, and then a second set of duplicate cardiac output and pressure measurements was obtained. Patients were too ill to exercise, hence the circulatory effects of guanethidine were studied only in the resting supine position.

Results

Cardiac Output and Heart Rate.—As shown in Table II (columns 9, 3, 10) and Fig. 1, the resting cardiac index was significantly increased in five patients (average 38%, range 16–50%), the heart rate slowed in six patients (average 19%, range 8–28%), and the stroke index increased appreciably in six cases (average 47%, range 14–111%). The above data, compared with the range of our normal values, obtained by studying 65 healthy volunteers (shaded areas in Fig. 1), reveal that cardiac index in three, heart rate in five, and stroke index in four patients only became normal at the end of 30 minutes after intracardiac guanethidine administration. In Case 5 the cardiac index, heart rate, and stroke index were unaffected, and in Case 7, although the cardiac index was unaltered, because of the slowing of the heart, the stroke index increased by 14%.

Systemic Blood-Pressure and Peripheral Arterial Vascular Resistance.—It is apparent from columns 8 and 11 in Table II, and Figs. 1 and 2, that mean arterial pressure in five patients (excepting Cases 5 and 7) fell by an average of 30 mm. Hg (range 19–45 mm. Hg), and that the average reduction in their peripheral arterial vascular resistance was 43% (range 27–56%). The

TABLE I.—Clinical Details

Case No.	Sex and Age	Duration of Known Hypertension in Years	Duration of Cardiac Decom-pensation in Months	Range of B.P. (mm.Hg)	Fundus Changes (Grade)	Circulatory Congestion				Blood Urea (mg./100 ml.)	E.C.G. Left Ventricular Hypertrophy	Radiography		Therapy
						Liver Below Costal Margin	Neck Veins at 45°	Oedema	Lungs			Cardio-megaly	Pulmonary Congestion	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	55 M	2	2	200–180/ 140–120	III	3 cm.	4 cm.	Mild	Moderate	50	Mild	Moderate	Moderate	G.
2	56 M	1	2	180–160/ 120–110	I	5 "	6 "	Moderate	Mild with pleural effusion	25	"	"	Moderate with effusion	G. + M.
3	50 M	2	3	250–220/ 170–140	III	2 "	3 "	Mild	Severe	65	Moderate	Severe	Severe	G.
4	30 F	1	6	240–220/ 145–135	II	4 "	7 "	"	Moderate	50	Severe	Moderate	Mild	G.
5	52 F	8	6	200–180/ 130–110	III	8 "	6 "	Severe	Severe	60	Moderate	Severe	Severe	G. + M.
6	56 M	5	6	200–170/ 145–125	III	7 "	7 "	Moderate	Moderate	75	Severe	"	Moderate	Died
7	29 M	1	6	220–200/ 140–115	II	2 "	3 "	Mild	Mild	45	Moderate	Moderate	Mild	G.
8	22 F	6	1	245–210/ 160–150	III	3 "	4 "	Moderate	Moderate	70	Severe	"	"	G.
9	51 M	4	6	220–180/ 130–110	II	6 "	3 "	Mild	Mild	90	Moderate	"	Moderate	G. + M.
10	60 M	5	2	250–220/ 150–135	II	3 "	5 "	"	"	34	"	Mild	Mild	G. + M. + D.
11	50 M	3	1	230–200/ 170–150	III	3 "	3 "	"	Severe	74	Severe	Moderate	Severe	G.

G. = Guanethidine. M. = Mercurial. D. = Divita's.

Note.—Haemodynamic studies were performed in Cases 1–7 only. Cases 8–11 are included for study of clinical response.

reduction of blood-pressure and vascular resistance in Case 7 was insignificant, whereas in Case 5 the blood-pressure fell by a little, but vascular resistance slightly increased.

Pulmonary Arterial Pressures and Resistance.—There was a significant fall in the pulmonary arterial pressures in all the seven patients, the average reduction in the mean pressure being 13 mm. Hg (range 6–24 mm. Hg). However, effects on the pulmonary arterial wedge (reflected left atrial) pressure varied. In Case 5 there was no change, in Cases 1, 2, and 6 the mean pressure fell by 10 mm. Hg, and in Cases 3, 4, and 7 by 5 mm. Hg (see columns 6 and 7, Table II). It is also to be noted that in spite of the fall (Fig. 2) the reflected left atrial pressure was normal in only one case, slightly elevated (15–19 mm. Hg) in three, and moderately elevated (+20 mm. Hg) in three.

Because of the fall in pulmonary arterial pressure the total pulmonary vascular resistance was reduced in every case, but pulmonary arterial vascular resistance (gradient resistance) showed slight difference. As seen in column 12, Table II, in all except Case 2 the resistance

decreased by an average of 55% (range 21–83%). It is also of interest to observe that the pulmonary arterial resistance was normal (less than 2 mm. Hg/l./min./m.²) in only two cases, slightly elevated (2–5) in two, moderately elevated (5–10) in one, and severely elevated (+10) in two (Fig. 1).

Right Heart Filling Pressures.—Guanethidine was effective in lowering the high filling pressures of the failing right heart in five patients, as evidenced by normal mean right atrial (3–7 mm. Hg) and right ventricular end diastolic pressures (5–8 mm. Hg). No significant changes were observed in Cases 2 and 5 (Table II, columns 4 and 5, and Fig. 2).

Clinical Response.—The clinical response to guanethidine of 11 patients with hypertensive heart failure has been followed for a period of two to six months (average four months). As shown in the last column of Table I, one patient (Case 6) died of myocardial infarction shortly after starting treatment. Of the remaining 10 patients, six came out of failure with guanethidine alone, three needed one or two mercurial injections, and only one patient needed mercurials and

FIG. 1.—Immediate effect of intracardiac guanethidine on systemic and pulmonary flows and resistance in seven hypertensive subjects in congestive failure. Solid and open circles represent resting values before and 30 minutes after administration of guanethidine respectively. The shaded area in each panel is the range of normal values obtained by studying 65 healthy volunteers in this laboratory.

FIG. 2.—Immediate effect of intracardiac guanethidine on the intracardiac and systemic pressures in seven hypertensive subjects in failure. Solid and open circles represent resting values before and 30 minutes after the administration of guanethidine respectively. The shaded area in each panel is the range of normal values obtained by studying 65 healthy volunteers in this laboratory.

TABLE II.—Effect of Guanethidine on Cardiac Output and Circulatory Dynamics

Case No.	Amount of Drug Injected	Heart Rate per min.		Right Atrial Mean		Right Ventricle (End Diastolic)		Pulmonary Artery		Mean Pulmonary Artery Wedge		Brachial Artery		Cardiac Index l./min./m. ²		Stroke Index ml./beat/m. ²		Systemic Resistance		Pulmonary Resistance	
		3		4		5		6		7		8		9		10		11		12	
		B	A	B	A	B	A	Syst./Diast. Mean	B	A	Syst./Diast. Mean	B	A	B	A	B	A	B	A	B	A
1	20 mg.	84	60	8.0	4.0	10.0	7.0	68/21 (34)	51/20 (28)	17	8	187/116 (139)	160/90 (119)	1.2	1.8	14.3	30.0	109	64	14.0	11.0
2	10 "	125	116	22.0	18.0	24.0	19.0	45/26 (33)	38/14 (27)	28	17	162/110 (129)	138/95 (110)	1.8	2.1	14.4	18.1	59	44	3.0	4.7
3	20 "	130	100	13.0	7.0	16.0	8.0	76/22 (47)	34/14 (23)	24	18	222/142 (170)	174/110 (138)	3.9	5.2	30.0	52.0	40	25	5.9	1.0
4	20 "	96	75	9.0	5.0	10.5	8.0	65/28 (44)	42/19 (27)	25	20	225/120 (145)	187/94 (112)	2.5	3.6	26.0	48.0	54	30	7.6	2.0
5	15 "	140	140	11.0	9.0	13.0	13.0	70/42 (52)	56/27 (37)	20	20	195/110 (135)	190/102 (130)	1.2	1.1	8.6	7.8	103	110	26.5	15.5
6	20 "	84	68	18.0	7.0	16.5	7.0	60/34 (42)	40/24 (30)	27	15	188/130 (152)	152/80 (107)	1.1	1.8	13.1	26.5	122	54	13.6	8.3
7	20 "	80	70	9.0	5.0	9.5	7.0	62/30 (40)	45/25 (31)	28	24	205/116 (146)	180/106 (135)	2.6	2.6	32.5	37.1	53	50	4.6	2.7

Note.—B is before and A is after intracardiac administration of guanethidine.

digitalis. At the time of this report all the 10 were clinically well compensated.

One patient (Case 1) was re-studied after six weeks of guanethidine therapy, when he was completely out of failure. Re-study values were: right ventricular end diastolic pressure 4 mm. Hg, indirect left atrial mean pressure 6 mm. Hg, and cardiac index 2.6 l./min./m.². With 15 minutes of moderate exercise (cardiac rate rose 78 to 120 beats a minute) the ventricular filling pressures were unaffected but the cardiac index had increased to 4.3 l./min./m.².

Discussion

From the data presented it would appear that the immediate circulatory effect of guanethidine in five of the seven hypertensive subjects in heart failure was lowering of the peripheral arterial, ventricular filling, pulmonary arterial, and reflected left atrial pressures, increasing the cardiac output, slowing of the heart with increase in the stroke volume, and reduction in the systemic and pulmonary vascular resistance. As the other two patients (Cases 5 and 7) subsequently came out of failure with oral guanethidine therapy, it is possible that the dose or the period of observation was inadequate, and they might have responded differently with a larger dose or if observed for a longer period of time.

Few observations on the circulatory effect of guanethidine in hypertensive patients without failure are reported (Richardson *et al.*, 1960; Taylor and Donald, 1960), but data on its immediate effect in hypertensive subjects with congestive heart failure are not available. However, ganglion-blocking agents appear to exert similar circulatory effects in patients with hypertensive failure. Thus our observations are in agreement with those of Freis *et al.* (1953), who reported a similar response of hypertensive congestive failure to hexamethonium. They suggested the increase in the cardiac output of heart-failure subjects was due to arteriolar vasodilatation and peripheral pooling of blood, reduction of the loading pressure of right heart facilitating the work of the heart, and lowered aortic pressure allowing more complete emptying of the failing left ventricle. Eichna (1960) also reported a similar effect of vasodilatation, produced by trimetaphan camphor-sulphonate ("arfonad"), on the cardiac output and circulatory dynamics in hypertensive congestive failure. On the other hand, by giving sodium nitrite orally, Eichna was able to increase the cardiac output of subjects with hypertensive congestive failure by lowering the right heart filling pressure and without reducing the arterial pressure.

In this study cardiac output increased only in those five subjects who had a significant fall in peripheral arterial pressure. The right ventricular filling pressure fell concomitantly in four patients, but in Case 2, though the filling pressure of the right ventricle was reduced by 20%, it was still very high. Furthermore, the right ventricular filling pressure in Case 7 became normal without significant fall in the peripheral arterial pressure, but the cardiac output remained unchanged. Our observations do not support the view of Richardson *et al.* (1960) that the reduction of the peripheral blood-pressure in hypertensives when treated with guanethidine was due to decreased cardiac output rather than to the relaxation of the arterioles.

Guanethidine and bretylium tosylate have similar hypotensive effects on peripheral arterial pressure

(Evanson and Sears, 1960), but their effect on pulmonary arterial pressure is quite dissimilar. Taylor and Donald (1960) recorded that bretylium increased the pulmonary arterial pressure in both normotensive and hypertensive subjects, and Halmagyi and Colebatch (1961) observed a similar increase in the pulmonary arterial pressure in experimental sheep. In the present study the pulmonary arterial pressure was significantly lowered in every patient. In another study conducted in this laboratory to observe the circulatory effect of guanethidine in hypertensive patients without failure (to be reported), guanethidine lowered the pulmonary arterial pressure in 13 out of 16 patients. In the remaining three the pulmonary arterial pressure remained unchanged. In no instance was an increase of the pulmonary arterial pressure observed in this laboratory when hypertensive patients with or without failure were given guanethidine.

Patients with hypertensive heart failure have been successfully treated with hexamethonium alone (Smirk *et al.*, 1958), but a similar response with guanethidine therapy has not been reported so far. Our findings in a limited number of patients with hypertensive failure treated with guanethidine would suggest that this drug has similar potentialities as hexamethonium in the immediate or long-term management of hypertensive heart failure. Furthermore, as guanethidine is relatively free from side-effects it may be the drug of choice in the management of hypertension and its complications. It is of interest to note that in one patient (Case 1) who was re-studied when compensated the cardiac output increased significantly with exercise.

Summary

Data on the immediate effect of intracardiac guanethidine on the cardiac output and circulatory dynamics in seven hypertensive subjects in failure are given.

The immediate haemodynamic response of five of the seven patients was an increase in cardiac output, a decrease in ventricular filling pressure, and a reduction in systemic and pulmonary arterial pressures and resistance.

Unlike bretylium tosylate, guanethidine had the uniform effect of lowering the pulmonary arterial pressure in hypertensive patients with or without failure.

Clinical response to oral guanethidine of 11 patients with hypertensive heart failure followed for an average of four months is presented.

Clinical and haemodynamic data suggest that guanethidine is a useful drug in the immediate and long-term management of hypertensive heart failure.

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