Effect of Guanethidine Therapy on Total Blood Volume in Patients With Essential Hypertension. (27285)

GERHARD H. MUELHEIMS* AND GORONWY O. BROUN, JR.
(Introduced by D. L. Azarnoff) (With technical assistance of Mrs. Marjorie Records)
Department of Medicine, Cardio-Pulmonary and Radioisotope Laboratories, St. Louis University School of Medicine and University Hospital, St. Louis, Mo.

The maintenance of circulatory homeostasis is intimately connected with the proper relationship between capacity of the vascular bed and blood volume, or, as Gregersen(1) has expressed it, "what there is room for and what happens to be contained in the system." Essential hypertension in which total peripheral resistance is known to be increased, is a disproportion between these 2 parameters, leading to an increased arterial blood pressure.

The purpose of this investigation was to find out whether a change of blood pressure occurring in patients with essential arterial hypertension would be followed by a change in blood volume. Direct information concerning this relationship is not available although data related to this subject have been presented by Rochlin *et al.*(2) who, comparing blood volume in a group of normotensive and hypertensive patients by using the Cr^{51} cell volume-hematocrit method, found a decreased blood volume in hypertensive patients. In the present study total blood volume was calculated in a group of patients with essential arterial hypertension by determining red blood cell volume and plasma volume with Cr^{51} and albumin iodinated with I^{131} respectively.

Methods. Five female patients with essential hypertension who had been followed for several years in the Hypertension Clinic, St. Louis University Hospital (Firmin Desloge Hospital), were selected for this study. The only medication received by the patients was guanethidine [2-octahydro-l-azocinyl)-ethyl]-guanidine sulfate),† which was administered for from 4 to 6 months. Neither diet nor salt intake was restricted. Seasonal variations in blood volume were excluded by conducting this study during the winter months. All patients had passed the menopause. When the investigation was begun the patients selected were taking part in a group study to evaluate the clinical usefulness of guanethidine in treatment of essential hypertension. Therefore when the first total blood volume determination was done the patient's blood pressure had been lowered by administration of the drug. Total blood volume was measured again 61 to 143 days after discontinuation of medication, when the blood pressure had returned to or toward pretreatment level. All blood volume determinations were done with the patient in the recumbent position and after an overnight fast. Total blood volume was calculated as red cell volume plus plasma volume. Red blood cell volume was measured first by using Cr^{51} tagged red blood cells (3), and immediately thereafter albumin iodinated with I^{131} was injected to measure plasma volume(4). After centrifugation plasma was separated from red cells. A 2 by 2 inch well type scintillation counter with a pulse height analyzer‡ was used to determine radioactivity in all samples. No significant radioactivity above background was found when the I^{131} samples were counted in the chromium area.

Results and discussion. The results obtained are summarized in Table I. Following gradual withdrawal of guanethidine, the systemic arterial blood pressure rose in all individuals. The increase in systolic blood pressure in the standing position varied from 8 to 42 mm Hg, and in the recumbent position from 9 to 39 mm Hg, while the rise in diastolic pressure in the standing and recumbent position ranged from 11 to 28 mm Hg and from 8 to 33 mm Hg respectively. The rise in blood pressure was accompanied in all experiments by a consistent and marked fall in

* This investigation was carried out during the tenure of a Special Fellowship from Nat. Heart Inst. U. S. P. H. S. It was supported by a grant-in-aid of research from the Harry Freund Memorial Foundation.

† Kindly supplied by Ciba Pharmaceuticals Inc.

‡ Baird Atomic.

TABLE I. Blood Pressure, Total Blood Volume, Hematocrit and F-Cells Factor in Essential Hypertensives during and after Treatment with Guanethidine.

Patient		D.J.		C.T.		R.L.		C.J.		B.S.	
Age (years)		63		57		54		52		59	
Weight (kg)		61.4		84.6		81.8		85.0		73.2	
Parameters measured		*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
BP	S	136/82	146/109	133/87	175/105	145/95	158/108	125/87	142/115	159/93	175/104
	R	176/132	198/140	146/94	180/110	152/93	161/102	152/96	163/107	183/103	222/136
TBV		4517	3864 (−14.5%)	5300	4835 (−8.8%)	4629	4114 (−11.1%)	4493	4229 (−5.9%)	4330	3921 (− 9.4%
RCV		1527	1424 (− 6.7%)	1899	1771 (−6.7%)	1861	1757 (− 5.6%)	1842	1771 (−3.9%)	1521	1407 (− 7.5%
PV		2990	2440 (−18.4%)	3401	3064 (−9.9%)	2768	2357 (−14.8%)	2651	2458 (−7.3%)	2809	2514 (−10.5%
Het		41.8	44.0	43.5	44.1	43.9	45.1	45.0	47.5	37.0	39.8
TBHct		33.8	36.8	35.8	36.6	40.2	42.7	40.9	41.8	35.1	35.9
F-cells		.81	.84	.82	.83	.92	.95	.91	.88	.95	.90

BP — Blood pressure (mm Hg)
TBV — Total blood vol (ml)
RCV — Red cell vol (ml)
PV — Plasma vol (ml)
Het — Hematocrit (%)
TBHct— Total body hematocrit (%)
F-cells — (total body hematocrit) / (venous hematocrit)

A—Guanethidine
B—No guanethidine

S—Standing
R—Recumbent

total blood volume, mainly due to a decrease in the plasma volume compartment; red blood cell volume underwent a lesser though constant reduction. Total blood volume, plasma volume and red blood cell volume fell by a mean of 9.9, 12.2, and 6.1% respectively. In all patients the venous hematocrit and total body hematocrit increased, while the F-cells factor(5) remained essentially unchanged.

Changes in blood volume after administration of drugs, which presumably modify the capacity of the vascular bed since they are vasopressor or vasodilator drugs, have been studied in acute experiments by several investigators. Kaltreider *et al.*(6) estimated blood volume by the azo-blue dye (T-1824)-hematocrit method in normal individuals and found that administration of epinephrine produced a prompt and definite decrease in plasma volume and in the majority of subjects a slight increase in red cell volume. A similar fall in plasma volume was reported by Finnerty *et al.*(7), when levarterenol was given to normal individuals. These investigators, however, found no change in the red cell mass when total blood volume was measured by the dye (T-1824) and Cr^{51} tagging procedure. In dogs in which a pump of controlled constant output was substituted for the left ventricle, levarterenol decreased the capacity of the vascular bed by 12% and hexamethonium increased it by 15%(8). Recently Brunjes *et al.*(9) showed that a chronic hypovolemic state and a decreased red cell mass may be present in individuals with pheochromocytoma. Shu Chen(10) found a rise in total blood volume due to an increase in the plasma volume compartment and no change in red cell volume in sympathectomized dogs.

It has been postulated that the reduction in blood pressure following administration of guanethidine is primarily due to relaxation of sympathetic venoconstriction, leading to pooling of blood in the venous system and a fall in cardiac output, since the peripheral resistance decreased only slightly(11). By comparing the experimental results in the present study before and after discontinuation of guanethidine, it is evident that blood pressure was lowered and total blood volume was increased while the drug was being administered. When guanethidine was withdrawn blood pressure rose and total blood volume decreased. One wonders whether the abrupt discontinuation of vasodilators in patients with essential hypertension may not lead to the coexistence of a high arterial blood pressure with a reduction of the vascular capacity in the presence of an increased blood volume if the vasodilating effect of the drug disappears before the circulation has adjusted to the decreased vascular capacity by a decrease in blood volume. Such a set of circumstances would seem to increase the risk of pulmonary congestion and pulmonary edema. Therefore gradual reduction of any drug with vasodilating properties would seem indicated, until information is available about its duration of action and the time necessary to reestablish circulatory homeostasis by a decrease in blood volume. Such caution would seem especially valid in patients with essential hypertension where cardiac hypertrophy and dilatation are frequently present and the cardiac reserve may be compromised.

Summary. Total blood volume was determined in 5 female patients with essential arterial hypertension during and after treatment with guanethidine. Administration of the drug resulted in a decrease of arterial blood pressure and an increase in total blood volume. The increase in total blood volume was mainly due to an increase in plasma volume.

1. Gregersen, M. I., *Medical Physiol.*, 1956, Edition 249, C. V. Mosby Co.

2. Rochlin, D. B., Shohl, T. E., Cary, A. L., *Fed. Proc.*, 1959, v18, 129.

3. Gray, S. J., Sterling, K., *J. Clin. Invest.*, 1950, v29, 818.

4. Crispell, K. R., Porter, B., Nieset, R. T., *ibid.*, 1950, v29, 513.

5. Reeve, E. B., Gregersen, M. I., Allen, T. H., Sear, H., *Am. J. Physiol.*, 1953, v175, 195.

6. Kaltreider, N. L., Meneely, G. R., Allen, J. R., *J. Clin. Invest.*, 1942, v21, 339.

7. Finnerty, F. A., Jr., Buchholz, J. H., Guillaudeau, R. L., *ibid.*, 1958, v37, 425.

8. Rose, J. C., Freis, E. D., *Am. J. Physiol.*, 1957, v191, 283.

9. Brunjes, S., Johns, V. J., Jr., Crane, M. G., *N. Engl. J. Med.*, 1960, v262, 393.

10. Shu Chen, *Am. J. Physiol.*, 1958, v193, 605.

11. Richardson, D. W., Magee, J. H., Ciba Symposium on Guanethidine, 1960, 37.

Received November 29, 1961. P.S.E.B.M., 1962, v109.