Effect of Beta-Adrenergic Blockade on Plasma Volume in Human Subjects[1] (36594)

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Variations in the sympathetic tone are known to induce changes in plasma volume. Infusion of catecholamines decreases the plasma volume (1, 2). Some patients with pheochromocytoma show subnormal values of plasma volume (3). Increased sympathetic activity after hypoxia is associated with a reduction of plasma volume (4).

During the course of an investigation on plasma volume in borderline hypertension (5) we encountered data related to the role of the sympathetic nervous system in the regulation of plasma volume. Plasma volume was measured before and after beta-adrenergic blockade with propranolol. In order to better understand observed changes in plasma volume an attempt is made to separate the effect of beta blockade on cardiac output, peripheral resistance and central venous pressure from its other hemodynamic effects.

Materials and Methods. Twenty-seven males from 18 to 26 years of age were studied. Fourteen subjects had borderline hypertension, *i.e.*, at least one diastolic above and one below 90 out of a minimum of three readings taken in the last year. A full description of these patients can be found elsewhere (5).

A set of resting recumbent measurements of intraarterial blood pressure, cardiac output, hematocrit, and plasma volume were taken 10 min after all the catheters were introduced. After an additional 20 min at rest, 0.2 mg/kg of body weight of propranolol was injected intravenously. Seven minutes later, cardiac output and plasma volume were determined. This was followed in 2 min by an intravenous injection of 0.04 mg/kg of atropine with repeat measurements 7 min after this injection.

Cardiac output was determined by dye dilution with indocyanine green. Details of the procedure are described in a previous paper (6).

The plasma volume was determined by the dye T-1824 (Evans blue, Warner Chilcot) reading optical density of 10, 15, 20 min samples in a Coleman junior spectrophotomer and extrapolating the slope to zero time. Changes in plasma volume after propranolol and atropine were determined by reading the optical density of duplicate samples 7 min after each injection and calculating the difference from the projected down-slope of the initial curve of optical density (Fig. 1). Changes in plasma volume were also determined by changes in arterial hematocrit corrected by F_{cells} factor of 0.91 (7) read in Wintrobe tubes in a fixed angle centrifuge using the formula PV after $=$ PV before [HCT bef. (1 - HCT aft.)/HCT aft. (1 - HCT bef.)]. In six cases determination of changes of plasma volume by optical density was supplemented by simultaneous measurements of plasma protein cencentration (8). Changes of plasma volume by plasma protein concentration were calculated using the forumula PV after $=$ PV before (plasma protein before/plasma protein after).

Results. The results of patients and normotensive controls were analyzed separately (Table I). As previously reported (5), resting plasma volume in patients with borderline hypertension was similar to normotensive controls. This was not altered when plasma

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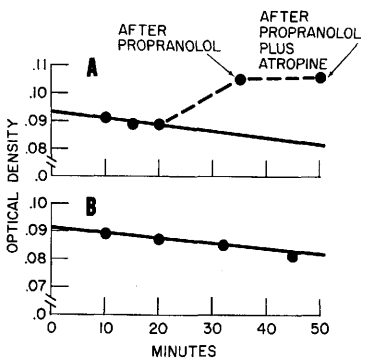

FIG. 1. Optical density of two separate plasma volume determinations in the same subject. (A) measurements during the experimental procedure; (B) 5 weeks later a new determination was performed. Note the linearity of the downslope at 32 and 45 min and the close resemblance of this curve to the projected portion of the curve in Expt. A.

volume was corrected for height but became significantly lower among patients when adjusted for body weight ($p < .001$). As there was no difference between the two groups in regards to plasma volume changes after propranolol and atropine, results of all 27 subjects are presented as a single group.

Table II gives the resting plasma volume and the observed changes after injection of propranolol and later atropine. Plasma volume after these drugs was determined by changes of optical density and by changes of hematocrit. A substantial reduction of plasma volume occurred after propranolol. Plasma volume remained decreased after addition of atropine. The decrease in plasma volume when determined by hematocrit, though highly significant, was substantially smaller than when it was calculated from optical density. To further examine this discrepancy, change of plasma volume was also calculated from observed concentration of plasma protein in six experimental subjects. The results are given in Table III. It is evident that changes calculated by plasma protein concentration and optical density are of the same order of magnitude.

The question whether observed changes of plasma volume are secondary to the action of propranolol on cardiac output, central venous pressure and peripheral resistance or stem from its action upon some other circulatory parameters is explored in Table IV.

It is evident that cardiac output decreased after propranolol and returned close to normal values after atropine. Plasma volume, however, remained decreased regardless of the levels in cardiac output. Table IV also shows similar independence of the change in plasma volume from trends in peripheral resistance and central venous pressure.

Discussion. This study presents three main findings; (a) that substantial decrease of plasma volume occurs shortly after extensive beta-adrenergic blockade with propranolol, (b) that the change in plasma volume does not seem to be dependent upon the influence of propranolol on cardiac output, peripheral resistance and central venous pressure, and (c) that changes in the hematocrit after beta-adrenergic blockade are lesser than expected for the observed decrease of plasma volume.

The last finding parallels other observations under conditions of sympathetic stimulation. Thus Cohn (1) observed a discrepancy between changes in concentration of dye and of hematocrit after intensive sympathetic

TABLE I. Comparison of Resting Values and Changes of Plasma Volume in Patients and Control Subjects.[a]

		Change	
	Resting	Rest to propranolol	Rest to atropine
Control subjects	3452 ± 173	−501 ± 87	−636 ± 117
Borderline hypertensives	3245 ± 129	−394 ± 48	−451 ± 52
Significance: control vs borderline	NS	NS	NS

[a] Plasma volume is in milliliters; ± = standard error of the mean; NS = not significant ($p > .1$).

TABLE II. Resting Plasma Volume and Changes Determined Simultaneously from Changes of the Dye Concentration and of Hematocrit.[a]

Resting		After propranolol			After atropine		
		New value	%	p	New value	%	p
3344 ± 106	By optical density	2898 ± 98	—13.4	<.00001	2804 ± 98	—16.2	<.00001
	By hematocrit	3190 ± 98	—4.6	<.0004	3205 ± 93	—4.1	<.0005

[a] Plasma volume in milliliters; ± = standard error of the mean; % = percentage change from the resting value; p = significance of the change from the resting value, by paired t test.

stimulation with norepinephrine and epinephrine. After beta blockade, under conditions of prevailing alpha sympathetic tone, as in our experiment, a similar discrepancy is observed. The difference in plasma volume change from hematocrit and from other methods may reflect a change in the distribution of cells in the circulation. Thus a change in F_{cells} after medication may account for the difference observed.

However, an alternative explanation of the discrepancies between changes in hematocrit and plasma volume after beta-adrenergic blockade can be offered. This explanation is contingent on acceptance of mounting evidence that while the predominant sympathetic influence on the venous tone is alpha adrenergic, beta-adrenergic venodilatory receptors may also be demonstrated (9–13). Within the framework of such a hypothesis, after beta-adrenergic blockade venodilating influences are removed and an alpha-adrenergic venoconstriction ensues, resulting in trapping of the red blood cells in constricted small veins. Predominance of postcapillary venoconstriction after the removal of beta-adrenergic influences on the veins also provides a reasonable hypothesis for interpretation of other observations in this paper. Thus, we feel that the decrease of the plasma volume after beta blockade does not stem from cardiac actions of propranolol, neither from its influence on peripheral resistance. Depression of cardiac output and increased central venous pressure after injection of propranolol were reversed with atropine but the plasma volume remained decreased. Therefore, increased venous hydrostatic pressure due to decreased cardiac output is not a likely explanation for the changes in plasma volume. Similarly, no constant relationship of the changes in plasma volume and peripheral resistance was observed. Mechanisms unrelated to cardiac output and peripheral resistance must be invoked to explain the decrease of plasma volume after propranolol. The most attractive one is in keeping with the hypothesis that after propranolol there is a predominance of alpha tone in the postcapillary venous bed leading to increased transcapillary filtration of fluid. That such increased capillary fluid filtration indeed does occur after sympathetic stimulation has been shown by Cohn (1). He found that changes in the capillary pressure index in human subjects after infusion of sympathomimetic amines were inversely related to plasma volume. Similarly, Weil *et al.* (14)

TABLE III. Resting Plasma Volume and Changes in Six Subjects Determined Simultaneously from Changes of the Concentration of Dye and of Plasma Proteins.[a]

Resting values		After propranolol	%	After atropine	%
3102 ± 214	By optical density	2778 ± 195	—10.4	2658 ± 193	—14.3
	By plasma protein	2729 ± 153	—12	2748 ± 269	—12

[a] Plasma volume is in milliliters; ± standard error of the mean; % = percentage change from the resting value.

TABLE IV. Hemodynamic Measurements and Plasma Volume at Rest, After Propranolol and After Atropine.[a]

	Plasma vol[b] (ml)	Cardiac index liters/m²/min	Mean blood pressure (mm Hg)	Resistance index[c]	Central venous pressure (mm H_2O)
Rest	3344 ± 106	3.59 ± 0.19	85.5 ± 1.7	25.1 ± 1.1	1.3 ± 0.8
After propranolol	2898 ± 98	2.77 ± 0.10	85.4 ± 2.3	31.8 ± 1.3	4.3 ± 0.8
After atropine	2804 ± 98	3.42 ± 0.14	90.6 ± 2.2	27.5 ± 1.3	−1.5 ± 0.7

[a] ± = standard error.
[b] By optical density.
[c] In arbitrary units (cardiac index/mean BP).

found that hypoxia, a stress in which there is increased activity of the sympathetic nervous system, produces a decrease in plasma volume, in association with an increase in forearm venous tone.

To our knowledge the basic observation that plasma volume in human subjects decreases after an intravenous injection of propranolol has not been previously reported. Our interpretation of the possible mechanisms is clearly hypothetical, and calls for further experimental verification. These findings are reported to alert other investigators to a hitherto unrecognized effect of propranolol. Investigative efforts in our laboratory are not related to physiology of the fluid distribution, and the reported finding will not receive further scrutiny by us. However, many interesting physiologic implications of this phenomenon are worth exploring.

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