Plasma Volume Expansion Resulting from Interference with Adrenergic Function in Normal Man

By John V. Weil, M.D., and Charles A. Chidsey, M.D.

SUMMARY
Guanethidine was administered to 10 normal subjects in order to examine the effects of reduced adrenergic function on plasma volume. An increase in the plasma volume was observed averaging 21.4% after 1 week, and 12.1% and 13.1% after 2 and 3 weeks of drug administration. A similar change in plasma volume resulted when alpha-adrenergic blockade was produced with phenoxybenzamine. These changes occurred in the absence of sodium retention and were associated with attenuation of forearm venous sympathetic reflexes and a rise in forearm venous compliance. The increase in venous compliance which was observed was proportional to the changes in plasma volume in these subjects. Thus, the sympathetic nervous system through its control of venous resistance may provide a means whereby the blood volume can be regulated.

IN ADDITION to its well recognized effects on the heart and blood vessels, the adrenergic nervous system may be an important determinant of the total blood volume and thereby may provide an additional mechanism wherein it may influence cardiovascular function. This concept has been suggested by observations indicating that administration of epinephrine or norepinephrine reduces plasma volume acutely, and that chronically diminished plasma volume is present in patients with elevated circulating catecholamines due to pheochromocytoma. However, there is little information regarding the effects of reduced sympathetic activity. Although plasma volume has been found to increase in hypertensive patients treated with guanethidine, it is recognized that this drug can produce congestive heart failure in patients with underlying heart disease. Indeed, the reported plasma volume changes in hypertensive patients occurred in association with sodium retention and diminished glomerular filtration. Thus, previously it has not been possible to determine whether there is a direct effect of diminished sympathetic function on the blood volume. In contrast to its effects on patients with cardiovascular disease, guanethidine does not produce sodium retention, diminished glomerular filtration, or congestive heart failure in normal man. Accordingly, the present study was undertaken to examine the effects of inhibition of adrenergic activity in normal control subjects. Measurements of plasma volume, sodium balance, and venous compliance were performed before and during the administration of either guanethidine, a peripheral adrenergic neuronopelgic, or phenoxybenzamine, an alpha-adrenergic blocking drug.

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From the Department of Medicine, University of Colorado Medical Center, Denver, Colorado.

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Methods

These studies were carried out on 18 male subjects, 21 to 40 years of age. Ten of these subjects who were not hospitalized were school teachers and physicians. Eight subjects, hospitalized during the study, were selected from a group of prisoners in the Denver County Jail who had volunteered for this research project and these were paroled to the Clinical Research Unit of the Colorado General Hospital for the period of the study. Informed consent was obtained from all subjects. Clinical evaluation, consisting of history and physical examination, chest x-rays, and electrocardiogram indicated that the cardiovascular system was normal in all subjects.

The 10 subjects who were not hospitalized received guanethidine in a dose of 0.25 to 0.71 mg/kg daily. Lying and standing blood pressures were recorded twice daily, and the drug resulted in minimal reduction in the standing arterial blood pressure, from an average of 117/85 to 110/75 mm Hg. Plasma volume measurements were performed during an initial control period and at weekly intervals during drug administration. Eight subjects were hospitalized for sodium balance studies. Four received guanethidine, 0.63 to 0.85 mg/kg/day for 1 week and were placed on a 120-mEq sodium diet with caloric level adjusted to their estimated previous intake level. Four received phenoxybenzamine, 0.27 to 0.30 mg/kg/day for 1 week and were placed on a 150 mEq sodium diet with similar adjustment of caloric intake. During an initial control week sodium balance, plasma volume, and on 3 separate days in each subject, forearm venous tone and cold pressor response were measured. During drug administration the venous tone and the cold pressor response were determined daily and the plasma volume determination was repeated at the end of 1 week. The guanethidine-treated group manifested a fall in standing arterial blood pressure from an average control value of 114/85 to 95/69 with no change in heart rate. The phenoxybenzamine treated group also demonstrated a reduction in standing pressure from an average control value of 113/86 to 104/73 with an increase of standing heart rate from an average control value of 91 to 118 during drug administration.

Plasma volumes were measured with T 1824 dye (Evans blue).

All determinations were done in the early morning on fasting subjects who were recumbent for 50 minutes prior to dye injection. Heparinized blood samples were drawn at 10, 20, and 30 minutes through an indwelling needle without stasis, and plasma dye concentrations were extrapolated to give concentration at zero time. With this method in nine other ambulatory subjects, the experimental error estimatated from duplicate determinations of plasma volume was 0.098 L. In nine subjects plasma volumes were also measured with autologous 51Cr-tagged red cells using a slight modification of the standard procedure. The subjects' cells were tagged during a 3-minute incubation with 60 µc of sodium chromate (51Cr) at room temperature and washed twice with normal saline. Cells containing 30 µc of 51Cr were then injected and a single blood sample, which was taken without stasis, was drawn at 15 minutes. All measurements of radioactivity were made in a semiautomatic, flat field counting apparatus. Plasma volume was calculated from total blood volume and hematocrit determined by the micro method. The hematocrit was not corrected for trapped plasma or for body to venous ratio (F cells).

As a measure of interference with sympathetic neurohumoral secretion, measurements of 24-hour urinary excretion of norepinephrine, epinephrine, and vanilmandelic acid were performed. Catecholamines were determined fluorometrically by the trihydroxyindole method and vanilmandelic acid by the periodate method.

Forearm venous compliance measurements were made with a water-filled plethysmograph in which volume changes were measured as pressure changes in the air space of the closed plethysmograph with a low displacement Statham PM5d transducer. The pressures determined in the air space during venous occlusion were less than 5 mm Hg. The cold pressor response was assessed by measuring the change in venous tone produced by a 30-sec application of an ice pack to the subject's neck.

The plasma volume and catecholamine excretion data in the initial ambulatory study were statistically analyzed with the Student's t test. Subsequent data on plasma volume in the hospitalized patients were tested specifically for an increase with this test. Analysis of the data on venous tone and cold pressor response, for which multiple control and experimental values were available on each subject, were performed by calculation of individual probabilities for each subject from paired control and experimental values using the Student's t test. The significance levels for the groups of subjects were then determined from the chi-square value derived from the combined individual probabilities as described by Fisher.

Results

The plasma volume measured with T 1824 dye in 10 nonhospitalized subjects averaged

Volemetron, Ames Atomium Co., Bellerica, Massachusetts.
Table 1

Effects of One Week of Guanethidine on Ten Normal Nonhospitalized Subjects

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Dose (mg/day)</th>
<th>Body weight (kg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Plasma volume (L)</th>
<th>Hematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Drug</td>
<td>Control</td>
<td>Drug</td>
<td>Control</td>
</tr>
<tr>
<td>J.R.</td>
<td>20.0</td>
<td>71.9</td>
<td>71.0</td>
<td>127/93</td>
<td>120/83</td>
</tr>
<tr>
<td>W.W.</td>
<td>20.0</td>
<td>80.3</td>
<td>80.8</td>
<td>103/83</td>
<td>106/82</td>
</tr>
<tr>
<td>R.P.</td>
<td>20.0</td>
<td>61.5</td>
<td>61.8</td>
<td>116/77</td>
<td>103/65</td>
</tr>
<tr>
<td>H.O.</td>
<td>40.0</td>
<td>58.6</td>
<td>58.6</td>
<td>110/78</td>
<td>120/80</td>
</tr>
<tr>
<td>C.C.</td>
<td>40.0</td>
<td>70.0</td>
<td>70.7</td>
<td>100/70</td>
<td>110/72</td>
</tr>
<tr>
<td>J.W.</td>
<td>40.0</td>
<td>82.7</td>
<td>82.3</td>
<td>116/72</td>
<td>120/88</td>
</tr>
<tr>
<td>W.S.</td>
<td>40.0</td>
<td>78.2</td>
<td>79.1</td>
<td>117/82</td>
<td>115/75</td>
</tr>
<tr>
<td>R.G.</td>
<td>50.0</td>
<td>104.8</td>
<td>107.0</td>
<td>112/78</td>
<td>115/72</td>
</tr>
<tr>
<td>J.T.</td>
<td>50.0</td>
<td>85.5</td>
<td>86.2</td>
<td>123/91</td>
<td>115/65</td>
</tr>
<tr>
<td>L.G.</td>
<td>50.0</td>
<td>69.8</td>
<td>69.5</td>
<td>117/83</td>
<td>99/70</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>76.3</td>
<td>76.7</td>
<td>114/81</td>
<td>112/75</td>
</tr>
<tr>
<td>SEM*</td>
<td></td>
<td>4.2</td>
<td>4.4</td>
<td>2.5/2.3</td>
<td>2.4/2.5</td>
</tr>
</tbody>
</table>

*SEM = standard error of mean.

The effect of guanethidine on plasma volume in normal, nonhospitalized subjects. The average values are plotted with their standard errors. Circulation, Volume XXXVII, January 1968

Figure 1

Plasma Volume (ml/kg)

Time (Weeks)

0.5

2

3

50

Control

30

40

45

50

The effect of guanethidine on plasma volume in normal, nonhospitalized subjects. The average values are plotted with their standard errors. Circulation, Volume XXXVII, January 1968

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The effect of guanethidine administration for 2 to 3 weeks on the urinary excretion of catecholamines and vanilmandelic acid (VMA) in 10 normal subjects.

ethidine. In nine subjects studied after receiving guanethidine for 3 weeks, the plasma volume, determined by the $^{51}$Cr method, rose from $34.9 \pm 0.9$ ml/kg to $38.8 \pm 1.2$ ml/kg ($P < 0.01$). The T 1824 plasma volumes in this group by comparison averaged $38.5 \pm 1.4$ ml/kg and $42.1 \pm 1.5$ ml/kg ($P < 0.05$), respectively, during the control and treatment periods. Thus, the increments in plasma volume in these subjects were almost identical by the two methods, $3.9 \pm 1.0$ ($^{51}$Cr) and $3.6 \pm 2.3$ (T 1824). These results support the validity of the T 1824 method under these circumstances and suggest that the observed plasma volume increases were not due to an alteration of the F-cells factor or other artifact introduced by the administration of guanethidine.

The effect of guanethidine administration on the excretion of catecholamines and their major metabolite, vanilmandelic acid, was studied in 10 patients (fig. 2). The norepinephrine excretion averaged $30.3 \pm 2.1$ $\mu$g/24 hr during the control period and was not significantly altered after 1 to 3 weeks of drug administration, $27.1 \pm 2.2$ $\mu$g/24 hr ($P > 0.05$). Epinephrine excretion on the other hand increased from $6.1 \pm 1.4$ $\mu$g/24 hr to $9.9 \pm 2.1$ $\mu$g/24 hr, a small but significant increase ($P < 0.01$). Vanilmandelic acid excretion was significantly reduced by guanethidine from $3.7 \pm 0.3$ to $2.6 \pm 0.2$ mg/24 hr ($P < 0.01$).

To determine the factors which might be involved in the observed plasma volume expansion, eight patients were hospitalized for daily measurement of sodium balance and forearm venous compliance. Interference with sympathetic function was induced in four with guanethidine and in four with phenoxybenzamine. Plasma volume in the guanethidine-treated group averaged 3.01 L during the control period and increased $0.19 \pm 0.09$ L during drug administration ($P < 0.05$). In the phenoxybenzamine-treated group, plasma volume rose from an average control value of 2.77 L by $0.23 \pm 0.05$ L ($P < 0.01$). The integrity of the sympathetic venomotor reflexes, as evaluated by the response of forearm venous compliance to cold stimulation, was markedly attenuated by the administration of both of these sympathetic inhibitory drugs (fig. 3). Cold stimulation produced
venomotor constriction in the control state manifest as an 11.0% decrease in basal venous compliance while this response was 3.5% during guanethidine and 2.1% during phenoxybenzamine ($P < 0.01$). The basal resting level of forearm venous compliance, determined as venous volume at a congesting pressure of 30 mm Hg (VV$_{30}$), averaged 3.43 ml/100 forearm volume in the control state in these subjects. This basal level of venous compliance was less consistently changed by drug administration. In the guanethidine group, the changes in basal venous compliance were variable and on the average a significant increase was not observed, whereas in the phenoxybenzamine group, the mean venous compliance was increased, $0.49 \pm 0.11$ ml/100 ml ($P < 0.05$). When the changes in venous compliance in all eight of the subjects were considered in relation to the degree of augmentation of plasma volume, it appeared that a correlation between these two variables was present (fig. 4). The coefficient of regression between the change in plasma volume and the change in venous compliance was significant, $r = +0.755$ ($P < 0.025$). One of the eight subjects had no change in plasma volume and a rather large reduction in venous compliance. These findings suggest that drug administration did not significantly alter vascular tone in this subject.

Administration of guanethidine and phenoxybenzamine in these eight subjects did not result in a consistent change in the sodium balance during the drug period. The mean cumulative sodium balance in these subjects during the 1 week of drug administration was $-5$ mEq with guanethidine and $+7$ mEq with phenoxybenzamine; these values

![Figure 4](image)

Relationship between increase in plasma volume ($\Delta$PV) and increase in forearm venous compliance ($\Delta$VV$_{30}$) following 1 week of guanethidine (■) or phenoxybenzamine (●) administration.

![Figure 5](image)

The effect of guanethidine on forearm venous compliance (VV$_{30}$), hematocrit (Hct), plasma volume (PV), and sodium excretion in one hospitalized subject. This patient received a constant sodium intake of 120 mEq/day throughout the study period.
ranged from −58 to +65 mEq. Body weight remained essentially constant during the balance studies, falling only slightly during guanethidine, 0.55 kg, and rising slightly during phenoxybenzamine, 0.83 kg. The sodium balance data from the subject in whom the largest plasma volume increase occurred are shown in conjunction with serial observations of venous compliance and large vessel hematocrit (fig. 5). Although sodium balance indicated that a calculated accumulation of 65 mEq of sodium occurred in this particular subject, this amount of sodium retention could not account for the increase observed in plasma volume. Increasing venous compliance was measured concomitantly with falling hematocrit values. The final measurement of plasma volume showed this value to be augmented by 13%.

Discussion

Although previous experimental studies have shown that plasma volume was decreased during administration of norepinephrine and epinephrine,1–2 these observations did not indicate the extent to which sympathetic activity influences plasma volume in normal man under basal conditions. The present observations in which plasma volume increased during interruption of basal sympathetic function suggest that, indeed, in normal man the sympathetic nervous system is an important factor in regulation of blood volume. The importance of this regulation is emphasized by the magnitude of the plasma volume increase, 21.4%. This increase was greatest after 1 week of guanethidine in the nonhospitalized subjects. The reason for the smaller increment after 2 and 3 weeks is not readily apparent. However, this may relate to the recognized increase in sensitivity of the adrenergic receptor to catecholamines which occurs after 2 weeks of guanethidine administration.15 It was notable that plasma volume changes were smaller in the hospitalized subjects than those not in hospital. It is not clear whether this finding can be attributed to a difference in sodium intake, level of activity, or to some other unknown factor.

In analyzing the potential mechanisms which may be responsible for plasma volume expansion, consideration first must be given to the possibility that primary sodium retention has been induced by an interference with sympathetic function. It is recognized that sympatholytic agents may produce or worsen congestive heart failure in patients with cardiovascular disease.6 When this question was investigated in patients with valvular heart disease, guanethidine on occasion was observed to produce sodium retention associated with elevated venous pressure and weight gain.6 In contrast, the administration of this drug to normal subjects was found to facilitate sodium excretion. This effect was observed both during sodium restriction and loading and during administration of sodium-retaining steroids.7,8 Thus, the previously reported findings that guanethidine produced plasma volume expansion in hypertensive patients in association with sodium retention must be interpreted in the light of these observations.1 Such patients may well have an underlying defect in myocardial function which was aggravated by interruption of cardiac sympathetic innervation resulting in sodium retention and consequent plasma volume expansion. Because the present study was carried out in normal man, it is unlikely that primary sodium retention can explain the augmentation of plasma volume observed. Furthermore, consistent increases in body weight were not found nor was a substantially positive sodium balance measured in four of these subjects. The comparable changes in plasma volume occurring in subjects treated with phenoxybenzamine gives additional support to this contention because this drug does not interfere with cardiac sympathetic innervation.

Another mechanism potentially responsible for the expansion in plasma volume occurring during the administration of sympatholytic agents is a redistribution of extracellular volume between the intravascular and extravascular compartments. This redistribution could result from an alteration in the intracapillary pressure as a consequence of modification of
vascular resistance. It has been emphasized that venular resistance is an important determinant of capillary pressure, and it has been shown that a close relationship exists between increases in venular resistance and estimated capillary pressure and decreases in plasma volume in response to administration of pressor drugs. Conversely, a diminution in venular resistance could be anticipated to result in a decrease in capillary pressure causing a net shift of extravascular fluid into the vascular space.

Direct serial measurements of venular resistance would have been desirable in order to calculate capillary pressure, but these determinations were not judged to be feasible under the conditions of the present study. However, reproducible measurement of forearm venous tone and venomotor reflexes could be carried out repeatedly. It has in fact been demonstrated previously that, after several weeks of guanethidine therapy in man, increase in venous compliance and attenuation of venous reflexes occur. The present study has established that changes similar to these were evident at the time when the plasma volume expansion was observed and furthermore that the measured changes were related in magnitude to the increments in plasma volume. While observations of forearm venous tone and venomotor reflexes do not provide direct information regarding the venular resistance or capillary pressure, they do demonstrate effective interference with sympathetic innervation of the venous circulation by the administered drugs. It is presumed that similar alterations in the venular resistance vessels also occurred and that these were responsible for the increase in plasma volume observed with inhibition of sympathetic function. Thus, the present findings suggest that adrenergic activity may contribute to the control of cardiovascular function through its effects on total blood volume, as well as through its established effects on the circulation. This relationship between adrenergic activity and blood volume may serve to buffer the changes in cardiac filling pressure which occur in the presence of altered distensibility of the capacitance vasculature.

References


Fifty Years Ago
Some Effects of Coronary Artery Ligation

... The ligation of the first descending branch of this artery (ramus circumflexus sinister) generally resulted in fibrosis of the anterior papillary muscle; the ligation of the posterior descending portion of the ramus circumflexus sinister resulted in fibrosis of the posterior papillary muscle. So constant were these results that we could produce lesions of either one of these papillary muscles.

... If confirmed, these observations may be of considerable value from a diagnostic point of view, at least as concerns the left coronary artery. The early exaggeration of the T-wave, its marked negative drop below the line within twenty-four hours and its more gradual return to its positive position and its final iso-electric or negative location were so characteristic in dogs watched for several days, that similar changes in the wave in man might reasonably be supposed to be due to similar lesions. In fact, one case in man, which will be reported later, was observed in which a clinical diagnosis of coronary thrombosis was made by Dr. James B. Herrick which was verified later at necropsy. The T-wave of the electrocardiogram of the patient ran a course similar to that of the dogs previously described.—FRED M. SMITH: Ligation of Coronary Arteries with Electrocardiographic Study. Arch Intern Med 22: 21, 1918.
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