Pathogenesis of Hyperadrenergic Orthostatic Hypotension
Evidence of Disordered Venous Innervation Exclusively in the Lower Limbs

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Abstract
The pathogenesis of hyperadrenergic orthostatic hypotension was studied in eight patients. Correction of the abnormal orthostatic changes by an inflated pressure suit (MAST) confirmed previous evidence of excessive gravitational pooling of blood in the leg veins. Intravenous L-norepinephrine infusion raised diastolic blood pressure in the same relationship to the infusion-induced increments in plasma norepinephrine concentrations as in normal subjects, indicating normal arteriolar responses. Contractile responses of the veins to infused L-norepinephrine were measured with a linear variable differential transformer (LVDT). The venous responses of hand veins in the patients fell within the 95% confidence limits of the responses of normal hand veins, as did the responses of foot veins in the seven normal subjects. However, foot veins of the patients with hyperadrenergic orthostatic hypotension, and both hand and foot veins of patients with "diffuse" autonomic failure, were supersensitive to norepinephrine, as reflected by a steeper slope of the regression of log (norepinephrine infusion rate) on percentage reduction in venous distensibility, and a significantly lower ED50 (i.e., norepinephrine infusion rate that induced 50% reduction in venous distensibility). The findings suggest anatomical or functional postganglionic denervation of lower limb veins causing excessive gravitational blood pooling with consequent orthostatic hypotension in these patients. (J. Clin. Invest. 1990. 86:1582–1588.) Key words: orthostatic hypotension • postural hypotension • venous pooling • autonomic dysfunction • venous denervation

Introduction
Orthostatic hypotension occurring in the absence of drug therapy, may result from a variety of disorders, including autonomic failure, adrenocortical insufficiency, hypovolemia, and pheochromocytoma. We have recently shown that orthostatic hypotension of the idiopathic hyperadrenergic type is usually associated with diminished total circulating erythrocyte volume and/or excessive gravitational pooling of blood in the veins of the lower limbs (1, 2). The contractile responses of the arterioles and of the dorsal veins of the hands to logarithmically increasing rates of norepinephrine infusion have been found to be normal in almost all of these patients (3). Normal alpha-2-adrenergic receptor densities and dissociation constants in platelet membranes from a group of these patients indicated that there was no diffuse or generalized defect in these receptors (3). Since external compression of the veins of the lower limbs with an inflated MAST® (military antishock trousers) suit was found consistently to correct this type of orthostatic hypotension, the present study was performed to determine whether the contractile responsiveness of the veins to norepinephrine might be abnormal only in the leg veins despite normal responses in hand veins. In the present studies, supersensitivity of the veins of the lower limbs to infused norepinephrine has been found, suggesting that functional or anatomical denervation of the veins of the lower limbs is the probable mechanism of the orthostatic hypotension in most patients with this disorder.

Methods
Patient selection. Eight patients with orthostatic hypotension were studied, who complained of lightheadedness, palpitations, and (frequently) syncope in the upright posture. In all patients, the blood pressure fell reproducibly by at least 20 mm Hg systolic and/or 10 mm Hg diastolic, and heart rate rose by 28 or to above 108 bpm in the standing posture (2). Preliminary measurements showed that there were normal increases in plasma renin activity and plasma aldosterone concentration after furosemide (40 mg i.v.) and standing or sitting for 2 h, and normal plasma cortisol and aldosterone responses to ACTH infusion (Cosyntropin; Organon, Inc., West Orange, NJ, 0.25 mg i.v. over 8 h). The subjects also had normal or excessive plasma norepinephrine concentrations after standing for 5, 10, and 15 min (Table I).

We also studied four patients with "diffuse" autonomic failure. In these patients orthostatic reductions in systolic (> 20 mm Hg) and diastolic BP (> 10 mm Hg) were associated with absent or subnormal increases in heart rate (to < 100 bpm), low plasma norepinephrine concentrations both recumbent (< 92 pg/ml) and standing (< 140 pg/ml), and, usually, other features of widespread autonomic failure (anhidrosis, impotence, incontinence). The age range of the patients was 22–78 yr and the measurements in the patients were compared with findings in healthy volunteers aged 23–66 yr (Table I). Except for patient 10 who had been quadriplegic since spinal cord trauma following a fall from a roof, all subjects in both groups were ambulatory but unable to stand for prolonged periods.

Clinical studies. On separate days, the following studies were performed: (a) Previous evidence of orthostatic hypotension (by sphygmomanometer) and abnormal heart rate changes was confirmed with a Dinamap Vital Signs Monitor (Critikon Co., Tampa, FL) and the effects on BP and heart rate of inflating a pressure suit (MAST; Clark Co., Worcester, MA) including the abdominal compression component, worn by the patients, to 45 mm Hg for 5–10 min in the standing posture, were measured.

(b) The effects of L-norepinephrine infusion on BP and heart rate were measured every minute with a Dinamap. Measurements were made in recumbency for 30 min before and for successive 20–30-min

1. Abbreviations used in this paper: A-II, angiotensin II; LVDT, linear variable differential transformer; MAST, military antishock trousers.
The distensibility was hand determined for distensibility at 23.7 min, through light maintained hypotension. The rate of norepinephrine was described as venous inch, compared to the arm abducted or reversed posture. The rate of norepinephrine concentration was determined whether increasing plasma norepinephrine concentrations would correct the orthostatic hypotension.

(c) Venous contractile responses to infused l-norepinephrine were measured with a linear variable differential transformer (LVDT), as described elsewhere (4), in a dorsal hand vein and a vein on the anterior surface of the foot or ankle. Essentially, by measuring the upward displacement of the light, central core of the equipment which had been positioned on the skin covering the vein, the increase in the diameter of the selected vein was determined after the vein had been emptied by resting the forearm or leg on an upward-sloping support, and then distended until fully dilated with a sphygmomanometer cuff inflated to 45 mmHg. The magnitude of the change in venous diameter which is described here as venous distensibility, was measured in this way, while l-norepinephrine in 5% dextrose—0.9% saline solution was infused through a No. 25 “butterfly” needle inserted into the same vein ~ 2.5 cm from the LVDT, at rates of 0, 1, 4, 16, 64, and 250 ng (5.9, 23.7, 94.7, 378.7, and 1,479 pmol) norepinephrine/min and at a constant rate of 0.1 ml/min. The effect of each rate of norepinephrine infusion was measured at least twice in each subject. The room temperature was maintained at 22–23.5°C. The mean percentage reduction in venous distensibility induced by the infusion of norepinephrine at each rate for 10–15 min, compared with the distensibility when vehicle alone was infused, was used to compute dose-response curves for the hand and foot veins of each subject.

In five of the patients the effect of angiotensin II (A-II) on venous distensibility was measured at A-II infusion rates of 6.6, 33, and 330 ng/min in both a hand and a foot vein.

Laboratory measurements. Plasma norepinephrine concentrations were measured on heparinized blood samples, with an electrometric assay after separation by HPLC (5). Coefficients of variation of these measurements were 7.7% (interassay), and 3.0% (intraassay).

Statistical analyses employed in these studies included Student’s t tests, determinations of correlation coefficients by the method of least squares, and computation of the 95% confidence limits of the dose-response curves, using standard procedures (6).

These studies were approved, in advance, by the Institutional Review Board for the Protection of Human Subjects of the SUNY Health Science Center at Syracuse.

Results

Effects of posture. The effects of the standing posture on the blood pressure, heart rate, and plasma norepinephrine concentration are depicted in Fig. 1. This figure shows that the patients experienced reductions in mean systolic and diastolic BP, and increases in mean heart rate and plasma norepinephrine concentration when they assumed the standing posture. Inflation of a MAST suit which the subjects were wearing, to 45 mmHg, reduced or reversed these orthostatic changes in blood pressure and heart rate. The differences observed in all parameters between the recumbent and the standing postures and between standing posture with the MAST suit inflated and deflated were significant by the t test for paired variables (P < 0.01).

The intravenous infusion of norepinephrine at rates of 1–16 μg/min (5.9–94.7 nmol/min), raised diastolic BP progressively in the patients with hyperadrenergic orthostatic hypotension. The increases in blood pressure showed a correlation with the infusion-induced increments in plasma norepinephrine concentration that fell consistently within the 95% confidence limits of the same relationships in 15 previously
Figure 1. Effects of posture and MAST suit inflation on BP, heart rate, and plasma norepinephrine concentrations (mean±SEM) in eight patients with orthostatic hypotension of the hyperadrenergic type. Inflation of the MAST suit corrected the abnormal orthostatic fall in BP and reduced the excessive rise in heart rate. Recumbent measurements all differed significantly (P < 0.01) from orthostatic measurements and the latter were significantly improved (P < 0.01) by the inflated MAST suit, when analyzed by Student’s t test for paired variables.

Figure 2. Correlation of infusion-induced increments in plasma norepinephrine concentrations, during step-wise increasing rates of i.v. norepinephrine infusion, with increases in diastolic BP in six patients with hyperadrenergic orthostatic hypotension (lower curves) and four patients with diffuse autonomic failure (upper curves). The data for the hyperadrenergic patients fell entirely within the 95% confidence limits of these relationships in 15 normal subjects (shaded areas) while the autonomic insufficiency patients showed a supersensitive diastolic BP response to norepinephrine.

Figure 3. Relationship between increasing rates of norepinephrine infusion (log plot) and reduction in venous distensibility of (a) dorsal hand veins and (b) dorsal foot veins of seven normal subjects. In Figs. 3, 4, and 6 the shaded areas enclose the 95% confidence limits of the regressions of these relationships in normal hand veins. It is evident that the data obtained in normal foot veins (b) fell almost invariably within the 95% confidence limits of the results in normal hand veins.
normal subjects. The corresponding measurements on the veins of the patients with hyperadrenergic orthostatic hypotension are shown in relation with the 95% confidence limits of the findings in the normal hand veins, in Fig. 4. It is evident that the findings in the hand veins of these patients, with the exception of two data points, all fell within the 95% confidence limits of the relationships in the hand veins of the normal subjects (Fig. 4 a). However, 11 of the 25 observations on the foot veins of the patients with orthostatic hypotension, made in six of the eight patients, fell outside the 95% confidence limits of the relationships in the normal hand veins (Fig. 4 b).

Actual measurements of venous distensibility in a hand vein and a foot vein of a patient with hyperadrenergic orthostatic hypotension, are reproduced in Fig. 5, a and b, respectively. It is evident that the venous distensibility of the hand vein (5 a) was changed from a mean control value of $46 \times 10^{-2}$ mm to $46.5, 47, 41, 27$, and $21.5 \times 10^{-2}$ mm when norepinephrine was infused at $1, 4, 16, 64$, and $250$ ng/min ($5.9, 23.7, 94.7, 378.7$, and $1.479$ pmol/min), respectively. The distensibility of the foot vein was much more strikingly reduced from a control value of $22.5$ to $8, 4.5$, and $3.5 \times 10^{-2}$ mm when norepinephrine was infused at $0.5, 1$, and $4$ ng/min ($3.0, 5.9$, and $23.7$ pmol/min) (Fig. 5 b). It should be mentioned that the term distensibility is used here to connote a linear (not a volume) change in response to the application of a constant increase in pressure (to $45$ mmHg).

Fig. 6 shows the effects of norepinephrine on the venous distensibility of a hand vein of four and a foot vein of two of the patients with autonomic insufficiency. It is evident that these data both for the hand and for the foot veins all fall far above the 95% confidence limits of the relationships found in the hand veins of the normal subjects.

In Table II are shown the computed regression data relating log rates of norepinephrine infusion to observed changes in venous distensibility in the hand and foot veins of the normal subjects and the patients with hyperadrenergic orthostatic hypotension. It is evident that (a) the means of the correlation coefficients of the four groups of data were all between 0.96 and 0.98; (b) there were no significant differences between the intercepts of the regression lines for normal hand and foot veins, or for normal subjects vs. hyperadrenergic orthostatic hypotension patients; (c) the slopes of the computed regression lines did not differ significantly between hand and foot veins in the normal subjects. However, the mean slope of the regressions for the foot veins in the patients with hyperadrenergic orthostatic hypotension (80.2) was significantly greater than the (mean) slope of the regressions in the hand veins of the same subjects (46.4, $P < 0.05$) and greater than the mean slope of the regressions in the foot veins of the normal subjects (80.2 vs. 30.5, $P < 0.02$); (d) the mean rate of norepinephrine infusion which reduced venous distensibility by 50% ($E_{D50}$) provided a characteristic of the regressions that reflected both the slope and the intercept of each regression. The table shows that 50% reduction of venous distensibility resulted from a norepinephrine infusion rate of $19.0$ ng/min (112 pmol/min) in the normal foot veins, and $5.29$ ng/min (31.2 pmol/min) in the foot veins of the patients ($P < 0.05$).

The $E_{D50}$ differences between hand and foot veins were significant ($P < 0.05$) for the patients with hyperadrenergic orthostatic hypotension but were not significant for the normal subjects.

Thus, both the slopes of the computed regressions and the $E_{D50}$ values show that the foot veins of the patients were significantly more sensitive to the contractile action of infused norepinephrine than the hand veins of the same patients and than the foot (and hand) veins of the normal subjects.

In five patients the effects of A-II on venous distensibility of hand and foot veins were compared. There were no significant differences between the reductions in venous distensibility when A-II was infused at $6.6$ ng/min. (hand vein $-34.2\pm8.4$% foot vein $-13.7\pm6.9$%), or at $33$ ng/min (hand vein $45.5\pm10.4$%, foot vein $36.8\pm12.6$%), or at $330$ ng/min (hand vein $54.8\pm9.0$, foot vein $58.1\pm6.1$%).

**Discussion**

The magnitude of orthostatic pooling of blood in the legs has been measured in previous studies by scintillation-probe counting over the calves of human subjects in the recumbent and standing postures, after labeling the subjects' erythrocytes with $^{99}$mTc-pertechnetate ($1, 2, 7$). These past experiments have shown that gravitational pooling of blood in the dependent legs is significantly excessive in patients with orthostatic hypotension of the hyperadrenergic type, as a group, and in most individual patients with this disorder (1). The gravitational blood pooling would be expected to occur predominantly in the capacitance vessels, i.e., the veins, and strong support for this expectation is provided by the observation that inflation to $45$ mmHg of a pressure suit (MAST) worn by the patients consistently restored the excessive BP and pulse-rate changes into the normal range, as shown previously (1) and confirmed in the present studies (Fig. 1). It is unlikely that bed rest, per se, was responsible for the orthostatic disorder seen in these patients since all of them spent most of the day seated and varying periods of time walking about. The mechanism of the beneficial effect resulting from inflation of the MAST suit
probably involved prevention of excessive orthostatic blood pooling. It is not likely to have been mediated through a local venous arteriolar reflex since such a local reflex causing arteriolar constriction has been described following venous distension and increased transmural pressures in veins and not following external compression of veins (8–11).

There is conflicting evidence in the literature on the occurrence and significance of venous constriction in response to orthostasis in human subjects (12). Page et al. (13), Wood and Eckstein (14), and Sharpey-Schafer (15) all documented forearm vein constriction immediately after assumption of the upright posture. This phenomenon was confirmed both in hand and in foot veins during head-up tilting to 70° by Samueloff et al. (16), who showed that the orthostatic rise in venous pressure lasted no longer than 4 min in normal subjects, before venous pressure returned to normal, recumbent levels (see their Figs. 1, 2, 3, and 5). In contrast with these findings, the venous pressure rise with head-up tilting was shown to last only 75 s, and to be followed by a fall of about 10 mmHg in a patient with orthostatic hypotension (see their Fig. 8). Thus, although orthostatic venoconstriction may not be persistent in normal subjects, an abnormal orthostatic venodilatation appeared to occur in this patient and this might well have contributed to his fall in blood pressure in the upright posture. Moreover, an abundance of more recent evidence in patients with excessive gravitational pooling in the leg veins indicates that orthostatic venous contractility is important in maintaining normal venous return, cardiac filling, and cardiac output (1, 2). It is difficult to explain the dramatic and reproducible correction of orthostatic hypotension by an inflated MAST suit in our patients except by the effect of the external pressure in preventing venous pooling and promoting normal venous return.

Excessive pooling of blood in the leg veins could be due to a circulating or locally released venodilator such as bradykinin (17), acetylcholine (18), or histamine (19), or to a subnormal venous contractile response to the erect posture. The veins might fail to contract or to maintain their tone normally because of an intrinsic disorder of their smooth muscle. It is also possible that there might be a defect in the autonomic release of norepinephrine or in the action of the norepinephrine at the adrenergic receptor or postreceptor level in the veins. Diffuse or widespread autonomic failure causes profound orthostatic hypotension, which is characterized by a lack of the normal orthostatic rise in heart rate, because of cardiac denervation. In these patients orthostatic hypotension is presumably due, to a large extent, to failure of the arterioles to contract in the upright posture. However, venous pooling due to failure of the normal venous contractile response to orthostasis is probably an important contributing factor, perhaps the most important factor, even in these patients, since an inflated MAST suit will greatly reduce the orthostatic hypotension in about 50% of patients with autonomic insufficiency (2).

Patients with diffuse autonomic insufficiency of the post-ganglionic type, show supersensitivity of the contractile responses of the arterioles (as reflected by increases in recumbent diastolic BP (20, and Fig. 2), and of the veins to infused norepinephrine (see Fig. 6), presumably because of upregulation of alpha adrenergic receptors (21, 22). The present data show that in the patients with hyperadrenergic orthostatic hypotension the arteriolar responses to norepinephrine, as reflected by changes in diastolic BP, and the responses of the hand veins to norepinephrine were consistently normal, whereas the contractile action of infused norepinephrine on the veins of the feet was significantly excessive. Since such an excessive response of the veins to norepinephrine is typical of denervated veins (Fig. 6), it seems likely that anatomical or functional denervation, confined to the veins of the lower limbs, is the cause of the excessive venous pooling and the orthostatic hypotension in these patients. An attempt to confirm these conclusions by microscopic study of biopsied veins has been initiated.

It is unlikely that the differences in norepinephrine sensi-
tivity between the hand and foot veins were due to disparities in the diameters of the veins since during distension at 45 mmHg in the absence of norepinephrine infusion, the protraction of the veins above the skin ("diameter" of the veins) was not significantly different in the upper and lower limbs, as is evident in Table I.

The specificity of the differences in distensibility between the hand and foot veins during norepinephrine infusion was supported by the absence of any significant differences in the responses of hand and foot veins to A-II.

Hoeldtke et al. (23) have recently reported four patients with hyperadrenergic orthostatic hypotension whose autonomic surface potentials were measured with an Evomatic system (DISA/DANTEC Electronics, Inc., Franklin Lakes, NJ). Their measurements showed slightly decreased amplitudes and slightly prolonged latencies of the autonomic surface potential in the soles of the feet compared with the palms of the hands in these patients. They conclude that hyperadrenergic orthostatic hypotension "may result from localized autonomic neuropathy that primarily affects lower thoracic or lumbar sympathetic nerves."

The data presented here support the evidence of Hoeldtke et al. that the autonomic insufficiency in these patients is restricted to the sympathetic innervation of the lower limbs. Furthermore, the sympathetic defect clearly involves the veins but probably not the arterioles of the lower limbs.

Acknowledgments

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References


13. Page, E. B., J. B. Hickam, H. O. Sieker, H. D. McIntosh, and

Table II. Summary of Correlations between Log (Norepinephrine Infusion Rate) and Percentage Reduction in Venous Distensibility

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