

Pathogenesis of Hyperadrenergic Orthostatic Hypotension

Evidence of Disordered Venous Innervation Exclusively in the Lower Limbs

David H. P. Streeten

Department of Medicine, State University of New York Health Science Center, Syracuse, New York 13210

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 MAST¹ (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 mmHg systolic and/or 10 mmHg 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 mmHg) and diastolic BP (> 10 mmHg) 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 mmHg 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

Address reprint requests to Dr. David Streeten, Dept. of Medicine, SUNY Health Science Center, 750 East Adams Street, Syracuse, NY 13210.

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1. Abbreviations used in this paper: A-II, angiotensin II; LVDT, linear variable differential transformer; MAST, military antishock trousers.

Table I. Patient Data

No.	Sex/age	Other disorders	Medications	Heart rate		Plasma norepinephrine		Max. venous distension	
				Lying	Standing	Lying	Standing	Hand v.	Foot v.
				bpm		pg/ml		mm × 10 ⁻²	
A. Hyperadrenergic orthostatic hypotensives									
1	F/49	None	None	70	99	778	1490	79	42
2	F/51	Orthostatic edema	None	100	120	217	397	21	36
3	F/37	None	None	86	109	160	603	48	29
4	M/25	None	None	76	120	163	295	88	92
5	F/51	Diabetes mellitus	Insulin	82	101	167	294	21	123
6	F/32	None	None	71	147	135	532	27	33
7	M/20	None	None	74	110	156	216	66	20
8	M/23	None	None	65	98	198	384	58	95
Mean	—	—	—	78	113	247	526	51	59
B. Diffuse autonomic insufficiency									
9	F/53	Diabetes mellitus, anhidrosis, colitis	Insulin	61	61	0	0	67	—
10	M/24	Impotence, lower limb muscle atrophy	None	79	93	0	0 (60° tilt)	24	49
11	F/68	Angina, anhidrosis	None	69	77	58	71	23	—
12	M/78	Angina, impotence, anhidrosis	None	69	75	0	117	53	27
Mean	—	—	—	70	77	15	47	42	38

periods during norepinephrine infusion by Harvard pump (Harvard Apparatus Co., Inc., Millis, MA) at 1, 2, 4, 8, and 16 $\mu\text{g}/\text{min}$ or until systolic and diastolic BP had been raised by ~ 20 –30 and 10–20 mmHg, respectively. Blood was drawn from a forearm vein for plasma norepinephrine measurements after the 30-min control period and at the end of each rate of norepinephrine infusion. While the highest rate of norepinephrine infusion continued, the patients were asked to stand for 5–10 min for further BP and heart rate measurements made with the arm abducted and resting on a stand at approximately the level of the second rib anteriorly. These measurements were made in order to determine 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 overlying 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 $\mu\text{g}/\text{min}$ (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

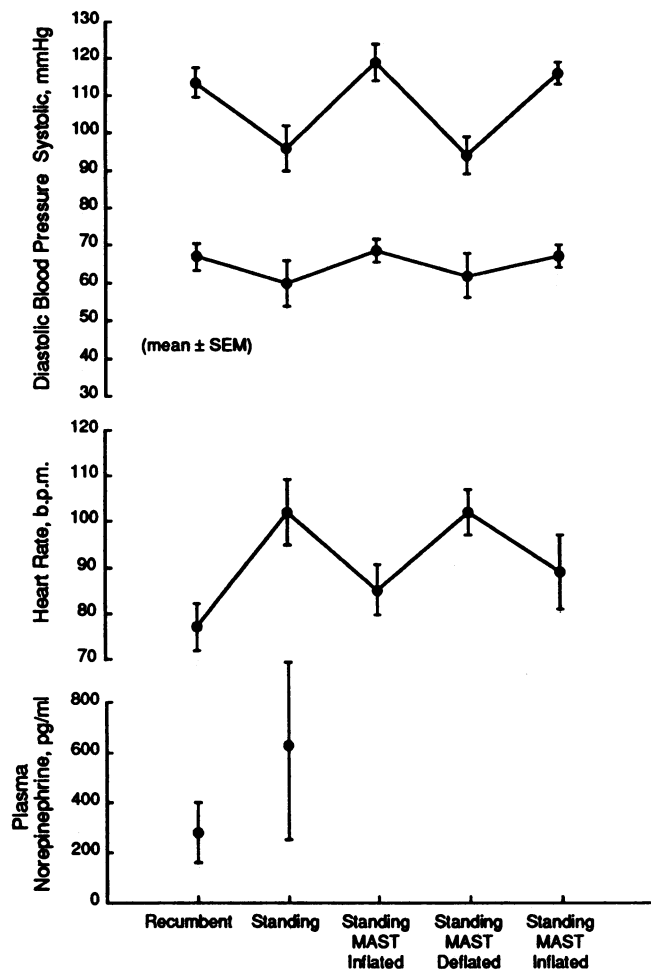


Figure 1. Effects of posture and MAST suit inflation on BP, heart rate, and plasma norepinephrine concentrations (mean±SEM) in eight patients with orthostatic hypotension of the hyperadrenergic type. Inflation of the MAST suit corrected the abnormal orthostatic fall in BP and reduced the excessive rise 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.

studied normal subjects (Fig. 2). In contrast with these findings, the diastolic BP increased at a steeper slope and with curves which rose out of the normal 95% confidence limits in the four patients with diffuse autonomic insufficiency (Fig. 2).

The norepinephrine clearance rate was calculated from the standard formula, clearance rate = infusion rate/induced rise in plasma norepinephrine concentration. There was no significant difference between the mean plasma norepinephrine clearance rate in the healthy subjects ($7,264 \pm 1,154$ ml/min) and in the patients with hyperadrenergic orthostatic hypotension ($6,209 \pm 1,468$ ml/min).

The effects of intravenous norepinephrine infusion on venous distensibility were closely related to the prevailing rates of norepinephrine infusion, with correlation coefficients between 0.91 and 0.99 in every study on each individual. Fig. 3 shows the relationships between the increasing rates of norepinephrine infusion (plotted logarithmically) and the observed

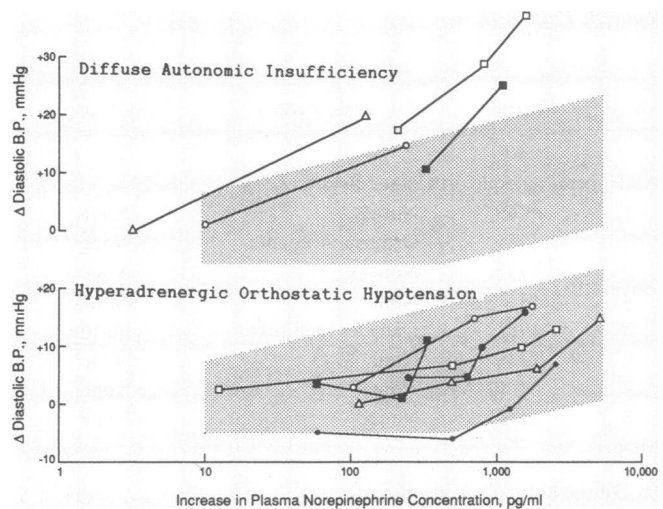


Figure 2. Correlation of infusion-induced increments in plasma norepinephrine concentrations, during step-wise increasing rates of i.v. norepinephrine infusion, with increases in diastolic BP in six patients with hyperadrenergic orthostatic hypotension (lower curves) and four patients with diffuse autonomic 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.

percentage changes in venous distensibility in the hand and foot veins of the normal subjects. The 95% confidence limits of these relationships in the normal hand veins corresponded very closely with previous determinations of these limits in 15 other normal subjects (3). It is evident that all except two of the data points obtained on the foot veins fell within the 95% confidence limits of the data obtained on the hand veins in the

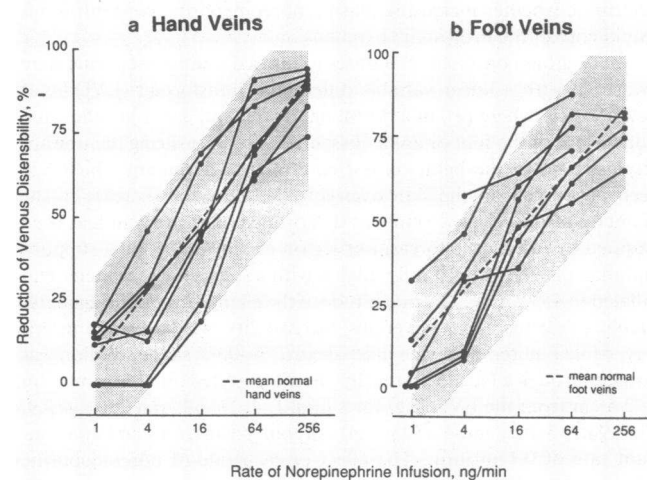


Figure 3. Relationship between increasing rates of norepinephrine infusion (log plot) and reduction in venous distensibility of (a) dorsal hand veins and (b) dorsal foot veins of seven normal subjects. In Figs. 3, 4, and 6 the shaded areas enclose the 95% confidence limits of the regressions of these 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 46×10^{-2} mm to 46.5, 47, 41, 27, and 21.5×10^{-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 22.3 to 8, 4.5, and 3.5×10^{-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 hy-

potension. 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% (ED_{50}) 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 ED_{50} 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 ED_{50} 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 $-34.2 \pm 8.4\%$, foot vein $-13.7 \pm 6.9\%$), or at 33 ng/min (hand vein $45.5 \pm 10.4\%$, foot vein $36.8 \pm 12.6\%$), or at 330 ng/min (hand vein $54.8 \pm 9.0\%$, foot vein $58.1 \pm 6.1\%$).

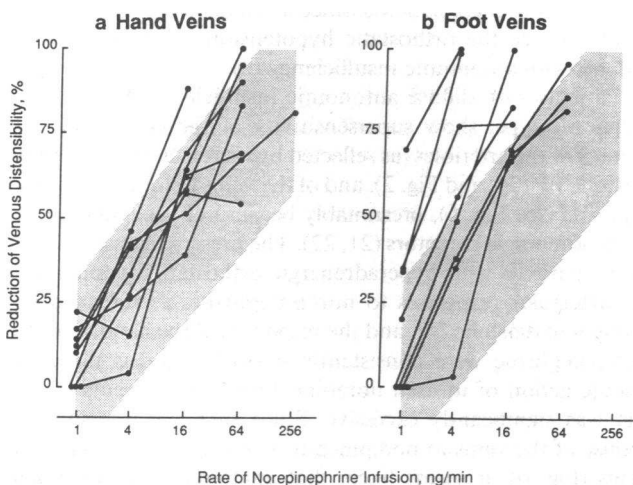


Figure 4. Relationships between increasing rates of norepinephrine infusions and reduction in venous distensibility in (*a*) hand veins and (*b*) foot veins of eight patients with hyperadrenergic orthostatic hypotension. Note that the patients' hand vein data fit within the 95% confidence limits of the normal hand veins (shaded area), whereas the foot vein results frequently rose above the normal limits.

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 ^{99m}Tc -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

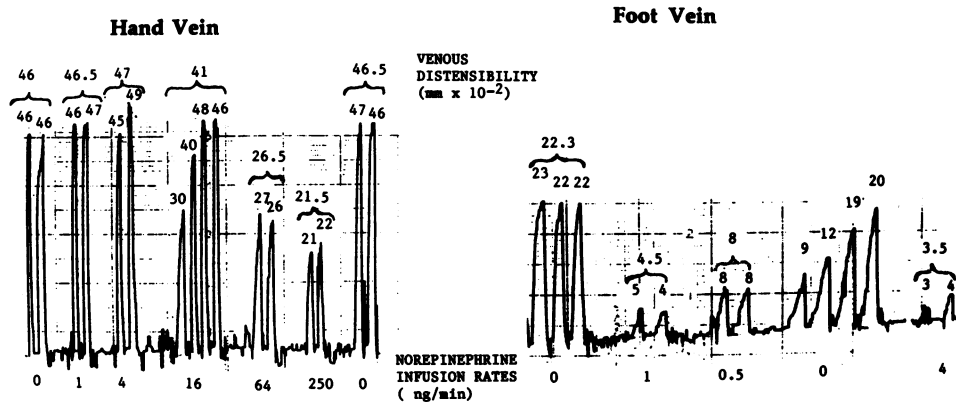


Figure 5. Effect of increasing rates of i.v. norepinephrine infusion on reduction in venous distensibility in (a) dorsal hand vein and (b) dorsal foot vein in a patient with hyperadrenergic orthostatic hypotension. At infusion rates of 0, 1, 4, 16, 64, and 250 ng/min, norepinephrine changed venous distensibility of the hand vein from 46 to 46.5, 47, 41, 26.5, and 21.5 $\times 10^{-2}$ mm, while norepinephrine infusion reduced the foot vein distensibility more dramatically from 22.3 to 8, 4.5, and 3.5 $\times 10^{-2}$ mm at infusion rates of 0.5, 1, and 4 ng/min, respectively.

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 repro-

ducible 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 postganglionic 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-

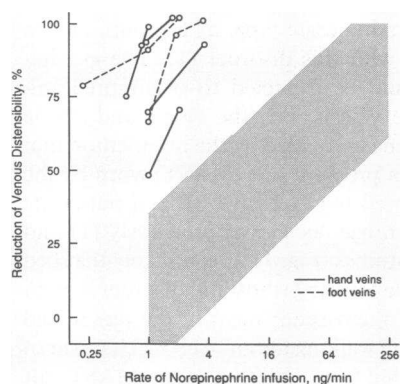


Figure 6. Effect of norepinephrine infusion on hand and foot vein distensibility in patients with "global" autonomic failure showing supersensitivity of the venous contractile response in all patients compared with the 95% confidence limits obtained in normal hand veins (shaded area).

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

	Hand veins					Foot veins					Foot minus hand vein data		
	r	Intercept	Slope	ED ₅₀		r	Intercept	Slope	ED ₅₀		Slope	ED ₅₀	
				log	antilog				log	antilog		log	antilog
A. Normal subjects													
Mean	0.96	4.3	35.5	1.27	23.5	0.97	15.6	30.5	1.11	19.0	-5.0	-0.17	-4.5
SEM	0.006	5.2	1.3	0.12	6.5	0.004	6.0	2.4	0.18	5.7	3.2	0.22	8.3
t								↑		↑	↑		↑
P								3.158		2.344	1.563		0.754
								<0.02		<0.05	N.S.		N.S.
								↓		↓			
B. Patients with hyperadrenergic orthostatic hypotension													
Mean	0.97	4.6	46.4	1.03	11.6	0.98	1.55	80.2	0.63	5.29	33.8	-0.41	6.35
SEM	0.01	3.6	5.3	0.069	1.6	0.010	12.13	15.5	0.116	1.23	13.1	0.16	2.42
t											↑		↑
P											2.580		2.624
											<0.05		<0.05

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 protrusion 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 low thoracic or lumbar sympathetic neurons."

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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