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Delayed Orthostatic Intolerance

David H. P. Streeten, MB, DPhil, FRCP, Gunnar H. Anderson, Jr, MD

● In seven patients who presented with lightheadedness, fatigue, "weakness," and sometimes syncope, blood pressure was found not to fall after standing for 3 to 4 minutes but to fall severely, frequently with syncope or presyncopal symptoms, after 13 to 30 minutes when measured every minute with an automatic device. This delayed orthostatic hypotension could be corrected with inflation of a pressure suit to 45 mm Hg. Its mechanism was further investigated with measurements of plasma catecholamines, plasma cortisol and aldosterone responses to corticotropin, and the effects of norepinephrine infusions on blood pressure and venous contractility. There was normal or excessive orthostatic norepinephrine release in all patients, evidence of impaired venous innervation in the legs in some, and various disorders in the other patients. Since therapeutic improvement in the orthostatic hypotension greatly reduced the symptoms, we concluded that orthostatic hypotension occurring after more than 10 minutes of standing is a potentially debilitating and often correctable disorder. (*Arch Intern Med.* 1992;152:1066-1072)

When orthostatic hypotension is suspected as the cause of symptoms in a patient, it is customary to try to establish this diagnosis by measuring the blood pressure (BP) in the recumbent and the standing postures over a period of about 3 or 4 minutes. Characteristically, in patients with orthostatic hypotension, the BP will fall by at least 20 mm Hg systolic and 10 mm Hg diastolic¹ almost immediately after standing and will remain subnormal as long as the patient continues to stand. If there has been no convincing fall in BP by the end of a few minutes in the upright posture, the diagnosis of orthostatic hypotension is considered to have been eliminated.

For editorial comment see pp 919 and 1058.

In seven of approximately 110 patients during the past 5 years, we have been unable by such measurements to substantiate the presence of orthostatic hypotension despite symptoms that were highly suggestive of this disorder. In these seven individuals, the diagnostic enigma was solved by measuring the BP and heart rate automati-

cally every minute, while the patients remained standing for between 10 and 30 minutes. In all instances, the BP remained normal for 10 to 25 minutes and then gradually or rapidly declined to clearly hypotensive levels as impending or actual syncope occurred. The clinical and laboratory findings in these seven patients with delayed orthostatic hypotension are described in this report.

PATIENTS AND METHODS

Patients

The diagnosis of orthostatic hypotension was suggested by a history of one or more of the following complaints: lightheadedness, severe fatigue, "weakness of the legs," headaches, syncope episodes, palpitations, excessive sweating, and cutaneous flushing (Table 1). These symptoms occurred while the patients were in the upright posture. Since changes in BP and heart rate were consistently within the normal range after the patients stood for 3 to 4 minutes, measurements of BP and heart rate were obtained for a total of 30 to 40 minutes with an automatic device (Dinamap, Critikon Co, Tampa, Fla). A fall in BP below 92/58 mm Hg with a heart rate rising in the standing posture by more than 27 beats per minute or to more than 108 beats per minute was considered diagnostic of hyperadrenergic orthostatic hypotension¹ and was usually accompanied by severe symptoms typical of the presenting complaints, which terminated within 1 to 2 minutes of resuming recumbency.

Five of the patients were female and two were male. All were white, and their ages ranged from 15 to 70 years. Most of the patients had complained of their presenting symptoms for several years before the presence of delayed orthostatic hypotension was documented. Some had been considered neurotic, since no organic cause of their chronic fatigue could be found, and in three patients the presence of postprandial hypoglycemia had been suspected but could never be demonstrated.

Orthostatic changes in BP and pulse rate were documented in all patients with an automatic measuring device equipped with a printer. Measurements were made every minute while the patients were recumbent, with one pillow, for 30 minutes and thereafter while they stood at the bedside, without restrictions in leg movements, for an additional 30 to 40 minutes or until symptoms became severe and recumbency was resumed. In these initial studies, the patients were not wearing a pressure suit, which was used for later observations of the effect of external pressure on orthostatic maintenance of BP. The seven patients described herein were found among approximately 150 patients with symptoms suggestive of orthostatic intolerance, among whom 36 experienced a fall in BP within 3 minutes of standing.

Similar measurements of BP and heart rate were obtained during 60 minutes of recumbency and 60 minutes of standing in nine healthy subjects aged 21 to 66 years, none of whom had any history or physical findings suggestive of orthostatic intolerance.

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Studies

The following studies were performed on as many of these patients as possible, in an attempt to determine the pathogenesis of delayed orthostatic hypotension.

1. Adrenocortical insufficiency was eliminated by measurements of plasma cortisol and aldosterone concentrations before and after the intravenous (IV) injection of furosemide, 40 mg, followed by recumbency for 1 hour to promote natriuresis, and standing or sitting for 1 to 2 hours. Cosyntropin (corticotropin, Cortrosyn), 0.25 mg in 5% dextrose solution, was then infused over 6 to 8 hours, with blood sampling for cortisol and aldosterone measurements by radioimmunoassay at 0, 4, and 6 or 8 hours.

2. Autonomic function was assessed by high-performance liquid chromatographic measurements of plasma norepinephrine and epinephrine concentrations² made on heparinized blood samples obtained through a previously inserted venous needle after 30 minutes of recumbency and after 5, 10, 15, and (usually) 30 minutes in the standing position. Coagulation of blood in the needle between samplings was prevented with a heparin lock.

3. Venous function and the presence of orthostatic venous pooling was studied by (a) observing the effect on the standing BP and heart rate when the pressure had fallen to abnormal levels, and/or heart rate had risen excessively, of inflating a pressure suit (MAST, Clarke Co, Worcester, Mass) worn by the patients to 45 to 50 mm Hg for 5 to 10 minutes^{3,4} and (b) using a linear variable differential transformer to measure the dose-related inhibition of venous dilatation by IV infusion of norepinephrine during inflation of a sphygmomanometer cuff to 45 mm Hg. The norepinephrine was infused into the same vein, 2 to 4 cm from the site of the linear variable differential transformer, at rates of 1, 4, 16, 64, and 250 ng/min.^{4,5}

4. Arteriolar responses to norepinephrine infusion were measured by recordings of diastolic (and systolic) BP with an automatic recorder every 1 minute, on one arm, during IV infusion of norepinephrine bitartrate (Levophed) into a large vein on the opposite arm. After a control period of 30 to 60 minutes in recumbency, norepinephrine (diluted in 5% dextrose solution) was infused at 1, 2, 4, 8, and (sometimes) 16 µg/min, for 20 to 30 minutes at each rate, by infusion pump (Harvard Apparatus Co, Millis, Mass).^{4,5}

Informed consent was obtained from all normal subjects and patients for the above studies, which were approved, in advance, by our Institutional Review Board for the Protection of Human Subjects.

RESULTS

Presenting Symptoms

As is evident from Table 1, lightheadedness and a feeling of impending syncope had been noticed at some time in the past by six of the seven patients, and three had fainted on one or more occasions. Associated with these symptoms, three patients had noticed palpitations, three had experienced transient blurring of vision, and one had sweated excessively. All of these are expected symptoms of hyperadrenergic orthostatic hypotension. However, six of the patients complained most strongly of severe fatigue, sometimes referred to as "weakness" and a feeling of utter exhaustion. Extreme symptoms of this type were complained of by the index patient (patient 1 in Table 1), who was a head nurse in a public hospital. She described getting up at 5:30 AM feeling reasonably well, starting work on a psychiatric ward at 7 AM, and becoming increasingly fatigued as her work continued, until she was able to go home at 3 PM, collapse on a bed, and sleep immediately for 3 or 4 hours or sometimes until 5:30 the next morning. Since she gave a history of lightheadedness and occasional fainting spells, her BP was measured fre-

Table 1.—Symptoms in Patients With Delayed Orthostatic Hypotension*

	Patient						
	1	2	3	4	5	6	7
Sex/age, y	F/46	F/35	F/32	F/62	F/45	M/70	M/15
Lightheadedness	+	+	+	—	+	+	+
Headaches	—	—	—	—	+	—	+
Weakness	—	+	+	—	+	—	—
Fatigue	++	++	+	+	+	+	—
Syncope	+	—	+	—	—	—	+
Palpitations	—	—	—	+	+	—	+
Blurred vision	+	+	—	—	—	—	+
Flushing	—	Pale	—	+	—	—	—
Excessive sweating	—	+	—	—	—	—	+
Aggravation by heat	—	—	—	—	—	—	+
Aggravation by exercise	—	—	—	—	—	—	++
Impaired thinking	+	—	—	—	+	—	—
Impaired memory	+	—	—	—	—	—	—
Somnolence	+	—	—	—	—	—	—
Improved by food	+	+	—	—	—	—	+

*Minus sign indicates absent; plus sign, present; and double plus signs, severe.

Table 2.—Orthostatic Blood Pressure (BP) and Pulse Rate (P) Changes in Patients*

Patient	Recumbent						Standing							
	1-10 min		11-20 min		21-30 min		1-10 min		11-20 min		21-30 min		31-40 min	
	BP	P	BP	P	BP	P	BP	P	BP	P	BP	P	BP	P
1	118/80	66	116/78	65	115/81	64	109/84	87	108/75	99	93/69	96	...	...
2	102/66	80	104/67	79	101/63	76	108/71	124	84/50	132+	...	...	...	...
3	116/69	61	122/78	67	117/77	71	113/77	147	108/87	153	116/94	150	78/61	144+
4	132/82	84	125/80	84	...	...	118/80	88	118/77	90	102/81	102	57/39	105+
5	109/64	55	107/62	56	113/65	54	110/75	80	95/59	78	...	...	...	...
6	144/84	60	141/81	58	...	...	140/85	64	139/86	65	95/58	61+	...	...
7	113/57	68	110/53	65	110/52	64	106/54	82	103/51	93	98/65	100	89/42	110+

*Values are means of 10 measurements in successive 10-minute periods. Blood pressure is in millimeters of mercury; pulse, beats per minute.

†Syncope or impending syncope.

Table 3.—Mean Blood Pressures During Six Successive 10-Minute Periods in Recumbency and Six 10-Minute

Subject	Mean Recumbent Blood Pressure, mm Hg						Mean Standing Blood		
	1-10 min	11-20 min	21-30 min	31-40 min	41-50 min	51-60 min	1-10 min	11-20 min	21-30 min
1	121/70	123/64	116/59	115/61	120/64	118/63	113/74	117/76	127/70
2	114/63	119/76	115/66	114/69	118/70	116/68	109/77	115/79	121/81
3	125/61	123/58	124/72	131/75	133/78	129/83	117/72	118/75	113/73
4	132/67	130/70	128/70	126/69	130/65	130/72	...	...	103/71
5	136/89	140/90	138/88	138/89	137/92	138/94	107/80	133/92	139/83
6	136/66	124/75	124/68	127/71	125/73	129/71	125/85	132/82	128/82
7	121/61	115/61	115/56	127/66	126/56	118/61	129/65	135/72	136/75
8	148/76	152/81	147/81	145/82	157/77	149/75	151/73	142/79	144/75
9	120/72	119/78	114/78	110/74	114/77	115/78	114/82	120/82	119/84
Mean	128.1/69.4	127.2/72.5	124.5/70.8	125.8/72.9	128.9/72.4	126.9/73.9	120.6/72.9	126.5/79.6	125.6/77.1
SEM	3.5/3.0	3.9/3.0	3.8/3.4	3.8/2.8	4.3/3.5	3.8/3.4	5.1/3.7	3.4/2.1	4.4/1.8

quently after a few minutes in the recumbent and the standing posture, and, like the rest of her physical findings, BPs were consistently normal. Psychotropic drugs were prescribed for a few weeks in the belief that her complaints were psychogenic, but no improvement was experienced. Other symptoms, listed in Table 1, were less frequently described.

Physical examination was almost always unrevealing except for orthostatic hypotension and tachycardia, which were clearly documented when BP and pulse rate were recorded every minute for several minutes in recumbency and for at least 15 to 30 minutes in the standing position. It is evident from Table 2 that the means of 10 consecutive measurements of BP every minute showed no impressive changes during the first 10 minutes of standing in any of the patients. Similarly, none of the *individual* measurements showed a fall in systolic BP of more than 20 mm Hg or in diastolic BP of more than 10 mm Hg.¹ The means of 10 BP readings in the second 10 minutes of standing were also within the normal range in four patients but fell excessively, with presyncopal symptoms, in patients 2 and 5 after 20 minutes of standing in each case. By the end of 30 minutes, BP had fallen by more than 20 mm Hg systolic and/or more than 10 mm Hg diastolic in all seven patients, associated with severe lightheadedness and/or fatigue and a request to be allowed to lie down. Orthostatic tachycardia (a rise of >27 beats per minute) preceded an abnormal fall in systolic or diastolic BP in four of the seven patients (Table 2). In all of the patients, severe symptoms of the types described on admission were present at the end of the 13 to 30 minutes of standing, and syncope or impending syncope was induced in five of the patients, with prompt disappearance of all symptoms after recumbency for 2 to 3 minutes. Purple discoloration of the legs was observed in the standing position in several patients. This was particularly severe in patient 3 and always disappeared rapidly in recumbency. Visible and palpable perspiration was evident when patients 2, 3, and 7 were standing.

Tendon reflexes were normal, heart rate responses to orthostasis were normal or excessive (except in patient 6), heart rate responses to the Valsalva maneuver were normal, and there was no evidence of parkinsonism or other

central nervous system disorders in any of these patients. There was no clinical or laboratory evidence of dehydration in any of the patients. Serum urea nitrogen, serum creatinine, and serum electrolyte concentrations were normal in all of them. Although the blood count was consistently normal, plasma volume and circulating red blood cell mass, measured by isotope dilution with iodinated I 125 serum albumin and chromium 51-labeled autologous erythrocytes, were both subnormal in three patients (patients 1, 2, and 6) studied with these methods.

BP Responses to Standing in Normal Subjects

In the nine healthy subjects, the mean systolic and diastolic BPs, recorded during successive 10-minute periods in both postures, are shown in Table 3. The normal subjects showed a slight fall in systolic and a slight rise in diastolic BP while they remained standing. In none was there a consistent downward trend in BP, and no subject developed lightheadedness or syncope while standing at the bedside for 1 hour.

The difference in the orthostatic responses of the healthy subjects compared with the patients with delayed orthostatic hypotension is depicted in Fig 1. The 10-minute mean BPs and the 95% confidence limits of these measurements in the normal subjects are shown in the shaded areas. The mean BPs over 10-minute periods in the patients with delayed orthostatic hypotension were within the normal range, both when the patients were reclining and when they stood for the first 10 minutes. Thereafter, the patients with delayed orthostatic hypotension, as a group, manifested a gradually progressive fall in systolic BP and a more delayed but eventually precipitous reduction in diastolic BP below the 95% confidence limits of these measures in the normal subjects.

Plasma Catecholamine Concentrations

Plasma epinephrine concentrations were consistently normal (180 to 530 pmol/L) in the recumbent and standing postures except in patient 5, who had primary hyperepinephrinemia.⁶ Her plasma epinephrine concentrations were 1398 pmol/L in recumbency and 625, 684, 566, and 1062 pmol/L after standing for 5, 10, 15, and 30 minutes. Plasma norepinephrine concentrations were slightly sub-

Periods While Standing in Normal Subjects

Pressure, mm Hg			Recumbent-Standing Blood Pressure, mm Hg	
31-40 min	41-50 min	51-60 min	21-30 min	51-60 min
128/75	97/58	118/77	+11/+11	0/+14
117/79	118/83	118/81	+6/+15	+2/+13
109/70	107/57	118/76	-11/+1	-11/-7
110/72	113/78	117/78	-25/+1	-13/+6
138/81	130/82	...	+1/-5	...
135/86	123/83	135/86	+4/+14	+6/+15
133/74	137/66	131/71	+21/+5	+13/+10
145/79	147/72	140/77	-3/-6	-9/+2
125/85	120/81	113/88	+5/+6	-2/+10
126.7/77.9	121.3/73.3	123.8/79.3	+1/+4.7	-1.8/+7.9
4.2/1.9	5.1/3.5	3.5/1.8	4.4/2.6	3.0/2.6

normal (0.51 nmol/L; reference range, 0.53 to 1.77 nmol/L) in recumbency in patient 5 but normal in the other patients and rose normally or excessively in the upright posture in all patients (Fig 2). The orthostatic rise in plasma norepinephrine concentration was maintained in all patients as long as they continued to stand.

Adrenocortical Function

Adrenocortical function was evaluated in six patients. Except in patient 6, plasma cortisol and aldosterone concentrations were normal at 8 AM and rose normally in response to corticotropin (cosyntropin, 0.25 mg), given by IV infusion over 6 to 8 hours, 3 hours after IV administration of 40 mg of furosemide (Table 4).

In patient 6, plasma aldosterone concentration rose only to 182 pmol/L after IV administration of furosemide (40 mg) and sitting for 1 hour, and to 220 pmol/L (normal, >640 pmol/L) after a subsequent 8-hour infusion of cosyntropin (0.25 mg). After IV angiotensin amide infusion in a dose sufficient to raise diastolic BP by 20 mm Hg over 2 hours, this patient's plasma aldosterone concentration rose only from 0 to 105 pmol/L (normal, >440 pmol/L). His plasma renin activity⁷ rose subnormally to 0.11 ng·L⁻¹·s⁻¹ after IV administration of furosemide and sitting for 1 hour (normal, 0.47 to 2.36 ng·L⁻¹·s⁻¹). All of these results indicated the presence of hyporeninemic hypoaldosteronism (with normal plasma cortisol responses) in this patient.

BP and Pulse Rate Responses to IV Norepinephrine Infusion

Blood pressure responses to norepinephrine infusions were measured in four patients. When the BP changes were related to the induced rise in plasma norepinephrine concentration at the end of each 20- to 30-minute period of infusion, the changes in systolic and diastolic BP were found to fall within the 95% confidence limits of the changes observed in 15 normal subjects studied in the same way (Fig 3). Heart rate fell appropriately as plasma norepinephrine concentration and BP increased, except in patient 1, whose heart rate rose from 64 to 66, 70, 67, 73, and 75 beats per minute at successively increasing rates of norepinephrine infusion. In each of the four subjects,

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Fig 1.—Mean systolic and diastolic blood pressure in successive 10-minute periods in recumbent and standing positions (each for 30 minutes) in seven patients with delayed orthostatic hypotension (closed symbols) compared with the mean and 95% confidence limits (shaded areas) of the blood pressures in nine normal subjects (open symbols) (60 minutes in each posture).

Fig 2.—Plasma norepinephrine concentrations after recumbency for 30 minutes and standing for 5, 10, 15, and 30 minutes in seven patients with delayed orthostatic hypotension.

when the patients assumed the erect posture while norepinephrine infusion continued at the highest rate used, BP fell and heart rate rose to levels similar to those that had previously been observed in the upright posture in the absence of norepinephrine infusion.

Effects of External Compression of Lower Limbs and Abdomen

The patients wore a pressure suit, and after the BP had fallen excessively or the heart rate had increased excessively in the upright posture, the responses to inflation of the suit to 45 mm Hg (and, later, deflation) for 5 to 10 minutes were observed (Table 5). The data show consis-

Table 4.—Adrenocortical Steroid Responses to Corticotropin Infusion*

Patient	Plasma Cortisol, nmol/L			Plasma Aldosterone, pmol/L		
	0	4 h	8 h	0	4 h	8 h
1	524	828	1048	560	...	1046
2	229	1214	883	272	...	560
3	593	2042	2759	316	610	630
4	...	...	...	...	...	...
5	403	...	1545	247	...	655
6	883	...	1766	105	...	222
7	414	...	1435	311	...	...
Reference range	193-690	...	966-2069	222-416	...	416-1110

*Cosyntropin, 0.25 mg intravenously over 8 hours, starting 3 hours after administration of furosemide.

Fig 3.—Relationship between increases in plasma norepinephrine concentrations induced by increasing rates of intravenous infusion of norepinephrine and mean changes in diastolic blood pressure in four patients with delayed orthostatic hypotension. The results almost all fell within the 95% confidence limits of the corresponding changes in 15 normal subjects (semilogarithmic plot; shaded area).

tent increases in systolic and diastolic BP and reductions in orthostatic tachycardia when the suit was inflated in the six patients in whom these measurements were made (except for negligible BP changes in patient 1).

Venous Contractile Responses to IV Norepinephrine

Linear variable differential transformer studies were performed on only two of the seven patients. Both individuals showed supersensitivity of the contractile response to infused norepinephrine in a foot vein, similar in severity to the previously reported findings in patients with hyperadrenergic orthostatic hypotension.⁵

Symptomatic Responses to Therapy

Considerable reduction or complete correction of the delayed orthostatic hypotension resulted from treatment with fludrocortisone in patients 2, 4, 6, and 7 and with octreotide in patient 1. The patient with hyperbradykininism (patient 3) was unimproved by any therapy. Three of the four patients whose orthostatic hypotension was improved either by fludrocortisone or octreotide (patients 2, 6, and 7) experienced considerable reduction in the chronic fatigue that had been so troublesome before orthostatic hypotension was corrected.

COMMENT

It is well known that the BP may fall transiently after standing in otherwise healthy subjects and usually falls rapidly and persistently in most patients with orthostatic hypotension of the hypoadrenergic and hyperadrenergic types. However, there are no published guidelines indicating how many times or how long after standing the BP should be measured to detect orthostatic hypotension. The present results show, contrary to previous experience, that in some patients orthostatic hypotension may become evident and progressively severe only after standing for more than 10 and up to 30 minutes. These findings make it difficult to detect such types of delayed orthostatic hypotension under usual conditions of outpatient or even inpatient practice. Since the presenting complaints of patients with delayed orthostatic hypotension may be limited to such nonspecific symptoms as fatigue, weakness, and exhaustion, it is important to inquire about the presence of orthostatic lightheadedness and syncope even in patients with such nonspecific complaints. When the history suggests there is a reasonable possibility of delayed orthostatic hypotension, the BP and heart rate should be measured repeatedly, preferably with an automatic device (such as the one we used [Dinamap]) or with ambulatory BP equipment, during at least a 30-minute period. In the absence of such equipment, the diagnosis of delayed orthostatic hypotension would require repeated BP measurements by manual sphygmomanometry while the patient remained standing for up to 30 minutes or until adverse orthostatic symptoms were experienced.

The observations on our patients have shown that orthostatic hypotension of the delayed type may arise as an end result of a variety of pathogenetic mechanisms. Thus, patient 1 had extremely high levels of plasma norepinephrine with normal plasma epinephrine concentrations and was suspected of having an extra-adrenal pheochromocytoma, though none was evident on computed tomographic scanning, and ametaiodobenzylguanidine test had not yet been performed on this patient. Patients 2, 4, and 7 had hyperadrenergic orthostatic hypotension of unknown pathogenesis, and patient 3 appeared to have hyperbradykininism.⁸ Patient 5 was one of an unusual group of individuals with primary hyperepinephrinemia.⁶ One of her first cousins had multiple endocrine neoplasia type IIA, a condition in which adrenal medullary hyperplasia is common,^{9,10} which was presumably responsible for the hyperepinephrinemia. Patient 6 had hypoadosteronism, as well as impairment of baroreflex

Table 5.—Blood Pressure (BP) and Pulse (P) Responses to External Compression by Pressure Suit*

Patient	Standing					
	Recumbent		Pressure Suit Deflated		Pressure Suit Inflated	
	BP	P	BP	P	BP	P
1	108/68	84	102/80	116	103/78	84
2	104/67	70	101/60	118	107/67	95
3	112/73	82	113/76	134	120/81	93
4						
5	133/77	71	102/65	96	125/75	87
6	133/80	72	90/60	80	124/79	70
7	112/49	71	96/45	91	108/60	77
Mean	117.0/69.0	75.0	100.7/64.3	105.8	114.5/73.3	84.3
SEM	2.5/4.5	2.6	3.1/5.1	8.2	3.9/3.3	3.9

*Blood pressure is in millimeters of mercury; pulse, beats per minute.

function or, perhaps, cardiac denervation causing absence of orthostatic tachycardia. It is evident, therefore, that orthostatic hypotension may occur as a delayed phenomenon whether it originates from any of several possible causes.

The studies described herein have shown that the autonomic response to the erect posture was normal or excessive in all of our patients. This was evident from the occurrence of orthostatic tachycardia, sometimes with excessive sweating and a normal or excessive orthostatic rise in plasma norepinephrine concentration. Moreover, it seems unlikely that delayed failure or delayed reduction of autonomic stimulation of arteriolar contractility is responsible for the eventual fall in BP in these patients, since plasma norepinephrine concentration remained normal or above normal when orthostatic hypotension supervened. It is doubtful that there was a delayed impairment of the arteriolar or cardiac inotropic response to endogenous norepinephrine release, in view of the normal BP responses to infused norepinephrine.⁵ Further evidence against any role of widespread autonomic insufficiency in patients with delayed orthostatic hypotension may be derived from findings in patients with diffuse autonomic failure. Not only have no such patients been found to have delayed orthostatic hypotension, but all patients with diffuse autonomic failure, in our experience, have had consistent, immediate, and sustained orthostatic reductions in systolic and diastolic BP on every occasion when they have been tested.¹

The basic defect in most of these patients was probably similar to that in many patients with orthostatic hypotension of the immediate type: excessive gravitational pooling of blood in the dependent veins.^{3,5} This hypothesis was supported by the observation that external compression to 45 mm Hg with a pressure suit almost invariably reduced or abolished the orthostatic hypotension and tachycardia in these patients, as it does in virtually all patients with hyperadrenergic orthostatic hypotension.³ This phenomenon was associated with supersensitivity of foot veins to the constrictor action of norepinephrine in two of our patients, as in a recently reported series of patients with hyperadrenergic orthostatic hypotension of the immediate (not delayed) type.⁵ It seems likely, therefore, that impaired sympathetic innervation of the veins of the lower limb plays a cardinal role in the pathogene-

sis of delayed orthostatic hypotension in at least some patients. An additional pathogenetic factor, the presence of which was supported by measurements in two of our patients, was the subnormal red blood cell mass; by aggravating the effects of orthostatic pooling on cardiac filling, this factor might be important in these patients, as it appears to be in patients with hyperadrenergic orthostatic hypotension of the immediate type.¹¹

Vasovagal syncope has been shown to occur several minutes after head-up tilt to between 60° and 80° on a tilt table. The delay between the onset of tilt and the occurrence of syncope has varied from 2 to 18 minutes in one study¹² and as long as 29 minutes in another.¹³ Although bradycardia was normally observed at the time of syncope in most of these studies, this was not always of vagal origin, since it was not preventable with atropine.¹⁴ In many instances tachycardia has occurred during syncope provoked by upright tilt, as it did in our patients with delayed orthostatic hypotension when they stood by the bedside.

Although it was not the only complaint, severe fatigue was the presenting symptom in six of the seven patients described here, as has frequently been found in other patients with orthostatic hypotension.¹ The fatigue was much improved by treatment that reduced or corrected the orthostatic hypotension in five of the six patients who had complained of fatigue. On the basis of these observations, it might be reasonable to speculate that the fatigue and exhaustion associated with several other debilitating disorders, including the enigmatic "chronic fatigue syndrome,"^{15,16} might result, at least in part or in some individuals, from the failure to maintain BP in the upright posture. Since anemia is known to cause hyperadrenergic orthostatic hypotension,¹¹ it is possible that the weakness, fatigue, and lethargy of many debilitated patients might be the results of delayed orthostatic intolerance caused by their anemia of chronic disease. The validity of these speculations will require more consistent measurements of orthostatic BP changes in debilitated subjects in the future.

CONCLUSIONS

Orthostatic hypotension may be delayed in onset, starting only 10 to 30 minutes after standing, and frequently eluding diagnosis. Such delayed orthostatic hypotension may present as severe fatigue, exhaustion, and weakness, all rapidly relieved by recumbency with or

without lightheadedness or syncope. Delayed orthostatic hypotension is usually hyperadrenergic and is relieved by a pressure suit. Its pathogenesis is not unique but involves known mechanisms of immediate orthostatic hypotension: hypovolemia (plasma or red blood cell) or excessive venous pooling probably due to impaired venous innervation. Since the symptoms are reduced or abolished by treatment that corrects the BP changes, it is concluded that the symptoms result from the orthostatic hypotension, which should be recognized and corrected whenever possible.

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