

# Hemodynamics in Diabetic Orthostatic Hypotension

J. HILSTED, H.-H. PARVING, N. J. CHRISTENSEN, J. BENN, and H. GALBO, *Institute of Medical Physiology B, University of Copenhagen; Hvidøre Hospital; Department of Internal Medicine and Endocrinology, Herlev Hospital; Steno Memorial Hospital; Department of Clinical Physiology and Medical Department C, Bispebjerg Hospital, Copenhagen, Denmark.*

**ABSTRACT** Hemodynamic variables (blood pressure, cardiac output, heart rate, plasma volume, splanchnic blood flow, and peripheral subcutaneous blood flow) and plasma concentrations of norepinephrine, epinephrine, and renin were measured in the supine position and after 30 min of quiet standing. This was done in normal subjects ( $n = 7$ ) and in juvenile-onset diabetic patients without neuropathy ( $n = 8$ ), with slight neuropathy (decreased beat-to-beat variation in heart rate during hyperventilation) ( $n = 8$ ), and with severe neuropathy including orthostatic hypotension ( $n = 7$ ). Blood pressure decreased precipitously in the standing position in the diabetics with orthostatic hypotension, whereas moderate decreases were found in the other three groups. Upon standing, heart rate rose and cardiac output and plasma volume decreased similarly in the four groups. The increases in total peripheral resistance, splanchnic vascular resistance and subcutaneous vascular resistance were all significantly lower ( $P < 0.025$ ) in the patients with orthostatic hypotension compared with the other three groups. The increase in plasma norepinephrine concentrations in the patients with orthostatic hypotension was significantly lower ( $P < 0.025$ ) than in the patients without neuropathy, whereas plasma renin responses to standing were similar in the four groups. We conclude that in diabetic hypoadrenergic orthostatic hypotension the basic pathophysiological defect is lack of ability to increase vascular resistance, probably due to impaired sympathetic activity in the autonomic nerves innervating resistance vessels; cardiac output and plasma volume responses to standing are similar to those found in normal subjects and in diabetics without neuropathy.

## INTRODUCTION

Orthostatic hypotension, i.e. an excessive fall in arterial blood pressure upon change of body position from supine to standing, may occur as a primary (idiopathic) disease or may develop as a complication to other diseases (1). Considerable attention has been given to orthostatic hypotension, in part because it is an incapacitating disease, and in part because examinations of patients with orthostatic hypotension may give further insight into the complex physiological mechanisms involved in blood pressure homeostasis in man.

Irrespective of etiology, the basis for development of orthostatic hypotension is (a) defective contraction of resistance vessels in the standing position, (b) abnormal reduction in blood volume, or (c) diminished cardiac output (CO)<sup>1</sup> in the standing position due either to reduced venous return or to inability to accelerate the heart, or both. Long-term diabetes is a frequent cause of orthostatic hypotension (1), and, indeed, in diabetes all three factors may be involved, alone or in concert. Thus, autonomic neuropathy is common in diabetes and may affect the innervation of the heart as well as sympathetic vasomotor fibers innervating resistance vessels (2). Furthermore, capillary permeability to albumin may be increased (3).

Previous investigations have focused on only one of these three factors. The aim of the present study was to study simultaneous responses of the heart, sympathoadrenal system, resistance vessels, and plasma volume to change of position from supine to standing by means of measurements of blood pressure (BP), heart rate (HR), CO, pulmonary tissue volume, hepato-splanchnic blood flow, peripheral subcutaneous blood flow, plasma volume (PV), and plasma concentrations

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Address reprint requests to Dr. J. Hilsted, Institute of Medical Physiology B, University of Copenhagen, Copenhagen N, Denmark.

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<sup>1</sup>Abbreviations used in this paper: BP, blood pressure; CO, cardiac output; EV, erythrocyte volume; HR, heart rate; PV, plasma volume; R<sub>SPL</sub>, hepato-splanchnic vascular resistance; R<sub>SUBCUT</sub>, subcutaneous vascular resistance; TPR, total peripheral resistance.

of catecholamines and renin. The responses of long-term insulin-dependent diabetics with orthostatic hypotension, were compared with those of long-term insulin-dependent diabetics with signs of autonomic dysfunction (decreased beat-to-beat variation in heart rate, which is considered due to a cardiac parasympathetic defect [4]) but having normal blood pressure response to standing, and to those of long-term insulin-dependent diabetics without neuropathy and of healthy subjects.

## METHODS

### Patients

23 insulin-dependent male diabetics and 7 healthy males volunteered for the study after giving informed consent (Table I). The patients were divided into three groups according to previously determined beat-to-beat variation in HR during hyperventilation (4) and to BP changes during change of position from supine to standing, both measurements carried out during HR and BP screening at outpatient clinics.

**Group 1.** ( $n = 8$ ). Control patients with normal beat-to-beat variation in HR ( $>15 \text{ min}^{-1}$ ) and normal orthostatic BP responses (decrease in systolic BP  $< 15 \text{ mm Hg}$  1 min after standing up).

**Group 2.** ( $n = 8$ ). Patients having signs of autonomic neuropathy (beat-to-beat variation in HR  $\leq 15 \text{ min}^{-1}$ ) but having normal orthostatic BP responses, as defined above.

**Group 3.** ( $n = 7$ ). Patients with orthostatic hypotension (decrease in systolic BP  $\geq 30 \text{ mm Hg}$  1 min after standing up) and decreased beat-to-beat variation. These were the first seven patients displaying orthostatic hypotension at the BP screening. Five of the patients had symptomatic postural hypotension under conditions of daily living. Vibratory per-

ception threshold was measured in the big toe with a Biothesiometer (Bio-Medical Instruments Co., Newbury, Ohio). The threshold is expressed in volts, a threshold  $>20 \text{ V}$  being indicative of neuropathy (5). Vibratory perception threshold was elevated in groups 2 and 3, while normal values were found in group 1 (Table I).

**Normals.** ( $n = 7$ ). Seven healthy males (Table I) were also investigated.

Duration of diabetes was similar in the three patient groups, yet group 1 patients had no clinical signs or symptoms of neuropathy. Two groups 2 patients lacked sweat secretion on feet and legs; one of these was impotent and the other had retrograde ejaculation. Two other group 2 patients lacked sweat secretion on feet and legs, but had no other clinical symptoms of neuropathy. In contrast, group 3 patients had gross clinical symptoms of neuropathy: five patients were impotent, six patients lacked sweat secretion as described above, four patients had atrophy of interdigital muscles and six patients had paresthesias. The number of patients having other long-term complications (nephropathy and retinopathy) is given in Table I.

No patients or normals had signs or symptoms of other endocrine, metabolic, or cardiovascular disease, nor did they take any drugs apart from insulin.

### Procedures

The patients and the normal subjects arrived fasting in the laboratory at 8 a.m. after a good night's sleep and at least 12-h abstinence from tobacco and alcohol. The patients took their last dose of insulin at 10 p.m. the preceding night. Throughout the preceding 24 h the patients had collected their urine, which was later analyzed for glucose and electrolytes. They were weighed and had a cannula inserted into a cubital vein in each arm, whereupon they rested supine on a couch. The subjects rested supine for 85 min and subsequently stood up (quiet standing) for 30 min, group 3 patients slightly sup-

TABLE I  
Anthropometric and Clinical Data Including Assessment of Neuropathy

	Age	Duration of diabetes	Daily insulin dose	Height	Weight	Sense of vibration	Beat-to-beat	Serum creatinine	Proteinuria (no. of subjects)	Proliferative retinopathy (no. of subjects)
	<i>yr</i>		<i>IU</i>	<i>cm</i>	<i>kg</i>	<i>V</i>	<i>min<sup>-1</sup></i>	<i>μmol/liter</i>		
Normals ( $n = 7$ )	30±2	—	—	182±2	74±2	6±0.4	30±4	—	—	—
Group 1 ( $n = 8$ )	27±1	16±1	39±3	180±2	72±2	7±0.4	32±3	84±2	0	0
Group 2 ( $n = 8$ )	36±2	20±3	37±2	176±2	67±1	23±3	8±2	86±4	4	5
Group 3 ( $n = 7$ )	40±2	19±3	36±3	176±2	67±3	23±4	4±2	93±6	4	4

Group 1. Insulin-dependent male diabetics without signs of neuropathy. Group 2. Insulin-dependent male diabetics having signs of autonomic neuropathy (decreased beat-to-beat variation in HR during hyperventilation, which is considered due to cardiac parasympathetic neuropathy) but having normal BP responses to standing (decrease in systolic BP  $< 15 \text{ mm Hg}$  1 min after standing up). Group 3. Insulin-dependent diabetics with decreased beat-to-beat variation and orthostatic hypotension (decrease in systolic BP  $\geq 30 \text{ mm Hg}$  1 min after standing up). Vibratory perception threshold (sense of vibration) was measured in the big toe with a Biothesiometer. The threshold is expressed in volts, a threshold  $>20 \text{ V}$  being indicative of neuropathy.

ported by a go-cart. The following variables were determined:

**BP.** BP was measured by means of the indirect auscultatory method, using a sphygmomanometer and a cuff. Diastolic BP were impossible to measure in patients with orthostatic hypotension in the standing position.

**HR** HR was registered with surface electrodes, both as an electrocardiogram and as a cardiogram. The cardiogram and electrocardiogram were recorded on an ultraviolet light recorder (Abem Ultralette 5651, Abem Instrument Group, Stockholm, Sweden).

**PV** PV was measured in the supine position by means of  $^{125}\text{I}$ -labeled human serum albumin, and changes in PV upon standing were calculated from determinations of peripheral hematocrit (6).

Plasma protein concentration was read refractometrically in triplicate with a total solid-meter (American Optical Corp., Scientific Instrument Div., Buffalo, N. Y.). None of the patients had interfering hyperlipemia.

**CO.** CO was measured as rate of freon-22 wash-in into pulmonary capillaries the subject rebreathing (5–10 forced respirations) from a rubber bag (7, 8). Gas was sampled from the mouthpiece of the rubber bag and continuously analyzed for freon, neon, argon, oxygen and nitrogen in a mass spectrometer (Centronic MGA 200, 20th Century Electronics, Croydon, England). Coefficient of variation in 12 measurements on separate days of CO in a normal subject was 8% in the resting supine position. In the present study CO was measured after 50 min of supine rest and after 25 min in the standing position.

**Pulmonary tissue volume.** Pulmonary tissue volume was calculated from gas fractions during rebreathing as the difference between distribution space for a water-soluble gas (freon) and a water-insoluble gas (neon) (9). Coefficient of variation in 12 measurements on separate days of pulmonary tissue volume in a normal subject was 7% in the supine position.

**Total peripheral resistance (TPR).** TPR was calculated from the equation  $\text{SAP} = \text{CO} \times \text{TPR}$ ; (SAP: systolic arterial pressure).

As previously mentioned, diastolic BP was impossible to obtain in patients with orthostatic hypotension, in the standing position; therefore, in all subjects TPR is calculated from systolic BP and CO and accordingly overestimated.

**Hepato-splanchnic vascular resistance ( $R_{\text{SPL}}$ ).** Hepato-splanchnic blood flow was estimated by measurements of peripheral Indocyanine Green ( $\text{ICG}^{(R)}$ ) clearance after a bolus injection (10).

Spectrophotometric analysis of urine from group 3 patients with added human serum albumin (collected after the experiment) showed that no Indocyanine Green was lost in urine. Plasma Indocyanine Green fractional clearance rate ( $k$ ) (disappearance rate constant) was calculated from the regression line (determined by the method of least squares) for the logarithmically transformed plasma concentrations vs. time (10). Coefficients of correlations for the regression lines were similar in the four groups. Plasma clearance (PC), which parallels hepatic blood flow, was then calculated from the equation,  $\text{PC} = k \times \text{PV}$ .

Estimated splanchnic vascular resistance  $R_{\text{SPL}}$  was calculated from the equation,  $R_{\text{SPL}} = \text{SAP}/(k \times \text{PV})$ ,  $R_{\text{SPL}}$  denoting resistance to plasma flow.

**Subcutaneous vascular resistance ( $R_{\text{SUBCUT}}$ ).** Subcutaneous blood flow was estimated by means of the local  $^{133}\text{Xe}$  wash-out technique (11). In the standing position, complete immobilization was not possible, and in 10 subjects (two group 1, three group 2, three group 3 and two normals), wash-out curves were discarded because of changes in counting geometry caused by movements.  $R_{\text{SUBCUT}}$  in the supine

position ( $R_{\text{SUBCUT}}$  supine) was calculated from the equation,  $R_{\text{SUBCUT}} \text{ supine} = \text{SAP} \text{ supine}/F \text{ supine}$ ,  $F$  denoting subcutaneous blood flow. Estimated  $R_{\text{SUBCUT}}$  in the standing position was calculated from the equation  $R_{\text{SUBCUT}} \text{ standing} = (\text{SAP} \text{ standing} + 100)/F \text{ standing}$ . (100 represents estimated hydrostatic pressure in millimeters of Hg [due to gravity] at the injection site in all subjects).

**Plasma concentrations of norepinephrine, epinephrine, and renin.** For catecholamine analysis blood was sampled 5 min before and 10 min after standing up. Plasma norepinephrine and plasma epinephrine concentrations were determined by a double-isotope derivative assay (12) with certain modifications (13). Plasma renin activity was measured by means of a commercially available radioimmunoassay kit (CEA-Sorin, Sorin Biomedica, Saluggia, Italy). Within assay coefficient of variation was 5.5%, between assay coefficient of variation was 16.8%.

**Glucose.** Glucose concentrations in urine were determined by the hexokinase method (14).

Statistical evaluation was made by Mann-Whitney's test for unpaired comparisons and by the Wilcoxon matched-pairs signed-ranks test for paired comparisons. Correlation analysis was made by the Spearman rank correlation coefficient test (15). Differences and correlations were considered to be significant if  $P < 0.05$  values were obtained.

## RESULTS

In the supine position systolic BP was higher in group 3 patients (orthostatic hypotension) than in group 1 patients (no neuropathy),  $P < 0.01$ , and in the normal subjects,  $P < 0.025$  (Fig. 1), whereas no significant difference was found between group 3 and group 2 patients (having slight neuropathy). After standing up, BP in group 1, group 2, and in the normals decreased slightly, whereas a marked fall in BP was found in group 3 patients. No significant differences were found in decrease in systolic BP after standing up between groups 1 and 2 and normals, although the decrease after 30 min in the standing position tended to be greater in group 2 patients (mean decrease  $23 \pm 8$  mm Hg (mean  $\pm$  SE)) compared with group 1 patients ( $11 \pm 3$ ) ( $P < 0.1$ ) and normal subjects ( $11 \pm 4$ ).

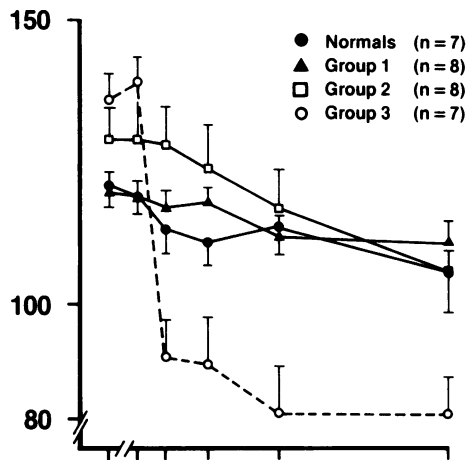
HR in the supine position was higher in group 2 and group 3 patients compared with group 1 patients and normal subjects ( $P < 0.01$ ) (Fig. 1). The increase in HR upon standing up was similar in the four groups.

Cardiac index in the supine position was similar in the four groups (Table II). CO decreased uniformly upon standing up in the four groups (Fig. 2).

Pulmonary tissue volume decreased significantly and similarly upon standing in all four groups ( $616 \pm 51$  ml [lying] vs.  $507 \pm 73$  [standing] [normal subjects]  $574 \pm 28$  vs.  $365 \pm 43$  [group 1],  $631 \pm 35$  vs.  $511 \pm 50$  [group 2],  $553 \pm 93$  vs.  $390 \pm 67$  [group 3]).

Erythrocyte volume (EV) was significantly lower in group 3 patients compared with group 1 patients and normal subjects ( $P < 0.05$ ), whereas EV was intermediate in group 2 (Table II). Total blood volume tended to be lower ( $P < 0.15$ ) in group 3 patients compared with group 1 patients and normal subjects (Table

## Systolic Blood Pressure (mmHg)



## Heart Rate (min<sup>-1</sup>)

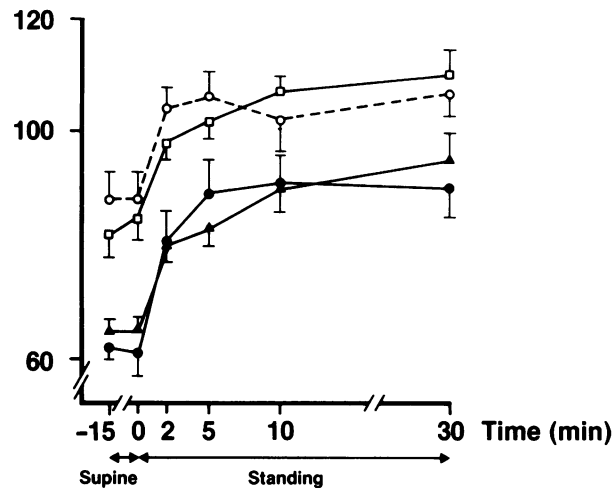


FIGURE 1 Responses of systolic BP (upper panel) and of HR (lower panel) to change of body position from supine to standing in diabetics with severe autonomic neuropathy including orthostatic hypotension (group 3), in diabetics with slight autonomic neuropathy (decreased beat-to-beat variation in heart rate during hyperventilation) (group 2), in diabetics without neuropathy (group 1) and in normal subjects. Values are mean  $\pm$  SE.

II). No significant correlation was found between blood volume or EV and decrease in CO upon standing up. PV decreased uniformly in the standing position in the four groups (Fig. 3). The total intravascular protein mass was not affected by standing ( $221 \pm 9$  g [lying] vs.  $216 \pm 9$  [standing] [normal subjects],  $205 \pm 8$  vs.  $205 \pm 8$  [group 1],  $187 \pm 5$  vs.  $185 \pm 4$  [group 2] and  $209 \pm 6$  vs.  $205 \pm 5$  [group 3]).

The calculated vascular resistances did not change upon standing in group 3. Accordingly, the ratios TRP standing/TRP supine,  $R_{SPL}$  standing/ $R_{SPL}$  supine and  $R_{SUBCUT}$  standing/ $R_{SUBCUT}$  supine were all significantly lower in group 3 compared with group 1 and 2, as well as with normal subjects ( $P < 0.025$ ) (Fig. 4). The change in splanchnic vascular conductance ( $1/R_{SPL}$  supine -  $1/R_{SPL}$  standing) upon standing was in percent of the change in total peripheral conductance ( $1/TPR$  supine -  $1/TPR$  standing):  $32 \pm 12$  (normal subjects),  $36 \pm 10$  (group 1),  $27 \pm 11$  (group 2) and  $30 \pm 12$  (group 3). Significant correlations were found between fall in systolic blood pressure upon standing and TPR standing/TPR supine ( $r_s = 0.76$ ,  $P < 0.01$ ,  $n = 23$ ),  $R_{SPL}$  standing/ $R_{SPL}$  supine ( $r_s = 0.67$ ,  $P < 0.01$ ,  $n = 23$ ),  $R_{SUBCUT}$  standing/ $R_{SUBCUT}$  supine ( $r_s = 0.72$ ,  $P < 0.01$ ,  $n = 15$ ), respectively.

Plasma norepinephrine concentrations in the supine position were similar in the four groups (Fig. 5). The increase in plasma norepinephrine upon standing was significantly smaller in group 3 patients ( $0.18 \pm 0.07$  ng  $\times$  ml<sup>-1</sup>) compared with group 1 patients ( $0.44 \pm 0.05$ ) ( $P < 0.025$ ), but not with group 2 patients ( $0.31 \pm 0.05$ ) ( $P < 0.2$ ) or with normal subjects ( $0.36 \pm 0.06$ ) ( $P < 0.1$ ). No significant increases were found in plasma epinephrine in any of the four groups (Fig. 5). A significant correlation existed between beat-to-beat variation in HR and increase in plasma norepinephrine upon standing in the diabetics ( $r_s = 0.44$ ,  $P < 0.05$ ,  $n = 23$ ) as well as between vibratory perception threshold and increase in plasma norepinephrine ( $r_s = -0.41$ ,  $P < 0.05$ ,  $n = 23$ ).

The responses of plasma renin activity to standing were similar in the four groups (Fig. 5). Urinary excretion of Na<sup>+</sup> (mean  $195 \pm 23$  meq/24 h) and K<sup>+</sup> (mean  $85 \pm 12$  meq/24 h) and glucose (mean  $28 \pm 9$  g/24 h) were identical in the three patient groups.

## DISCUSSION

The present study indicates that orthostatic hypotension in juvenile-onset diabetics may be due to lack of increase in TPR upon standing up. Decrease in CO as well as in PV were similar in diabetics with and without orthostatic hypotension and therefore abnormal changes in these variables do not seem to be involved in the pathogenesis of diabetic orthostatic hypotension.

Orthostatic hypotension in juvenile diabetics may be associated with exaggerated sympathetic responses, as measured by plasma catecholamine concentrations, i.e. hyperadrenergic orthostatic hypotension (16). In this condition the basic defect seems to be a reduction in the intravascular volume, specifically in the erythrocyte mass (17). However, most diabetic patients with severe orthostatic hypotension have been shown to

TABLE II  
Selected Hemodynamic Variables during Supine Rest

	EV	PV	Blood volume	Cardiac index	TPR PRU	Systolic BP
		<i>l/m<sup>2</sup></i>		<i>l/min/m<sup>2</sup></i>		<i>mm Hg</i>
Normals ( <i>n</i> = 7)	1.38±0.06	1.76±0.07	3.14±0.11	3.2±0.2	21±1	119±3
Group 1 ( <i>n</i> = 8)	1.36±0.05	1.61±0.07	2.97±0.10	3.2±0.3	22±2	119±3
Group 2 ( <i>n</i> = 8)	1.29±0.09	1.57±0.04	2.86±0.12	3.5±0.3	21±2	129±7
Group 3 ( <i>n</i> = 7)	1.18±0.06	1.73±0.03	2.91±0.07	3.1±0.3	26±2	139±5

EV, PV, and blood volume are given as liter per square meter body surface. Cardiac index is given as liter per minute per square meter body surface. TPR, calculated from the equation  $\text{systolic BP} = \text{TPR} \times \text{CO}$ . PRU, peripheral resistance units (millimeter Hg per liter per minute. For further details, see legend to Fig. 1.

have markedly reduced plasma norepinephrine responses to standing (17–19). In our patients with orthostatic hypotension, the increment in plasma norepinephrine was blunted (Fig. 5) (the highest concentration in the standing position was 0.57 ng/ml); thus, our patients had hypoadrenergic orthostatic hypotension (16). Nevertheless, our patients with orthostatic hypotension had, in fact, a reduced erythrocyte mass and a mean intravascular volume slightly but insignificantly lower than the normal subjects and group 1 patients (Table II). The decrease in PV upon standing up was similar in the four groups (Fig. 3); thus, probably neither diminished intravascular volume nor abnormal reductions in PV upon standing up are major

pathogenetic factors in diabetic hypoadrenergic orthostatic hypotension. Rather a lack of increase in TPR resulting from an impaired sympathetic nervous activity was the primary pathogenic abnormality accounting for the orthostatic hypotension in our group 3 patients. Also in patients with diabetic orthostatic hypotension selected for an exaggerated norepinephrine response to standing (hyperadrenergic orthostatic hypotension) has the presence of a neuro-pathic limitation to the compensatory sympathetic response been suggested (20). Conversely, in our patients with orthostatic hypotension may other factors, such as low blood volume (due to anemia), have converted individual patients with relatively mild sym-

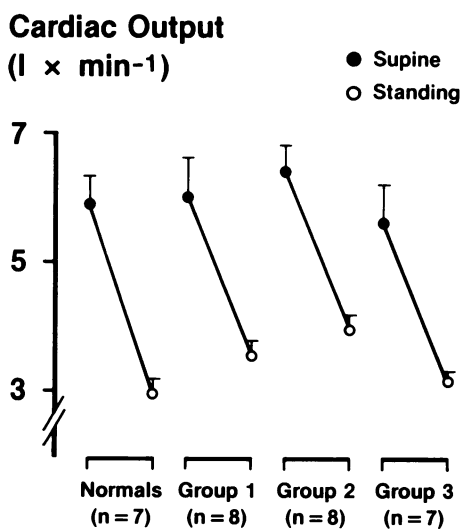


FIGURE 2 CO in the supine position and after 30 min of standing in diabetics with (group 3) and without (groups 1 and 2) orthostatic hypotension and in normals. Values are mean±SE.

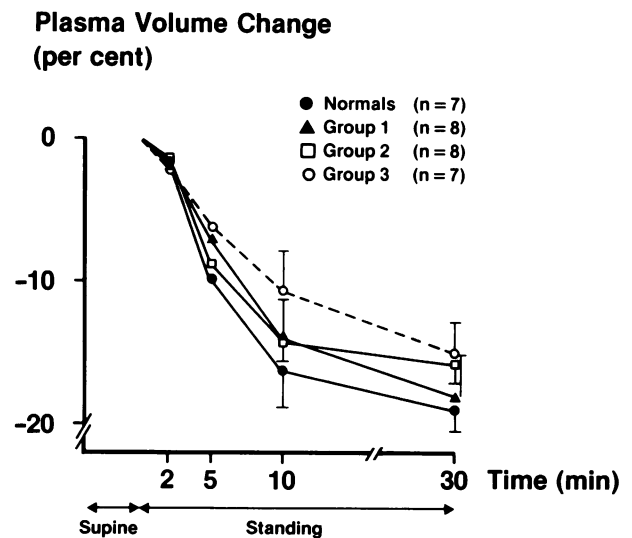


FIGURE 3 PV decrease upon standing up in percent of supine PV in diabetics with (group 3) and without (groups 1 and 2) orthostatic hypotension and in normal subjects. Value are mean±SE.

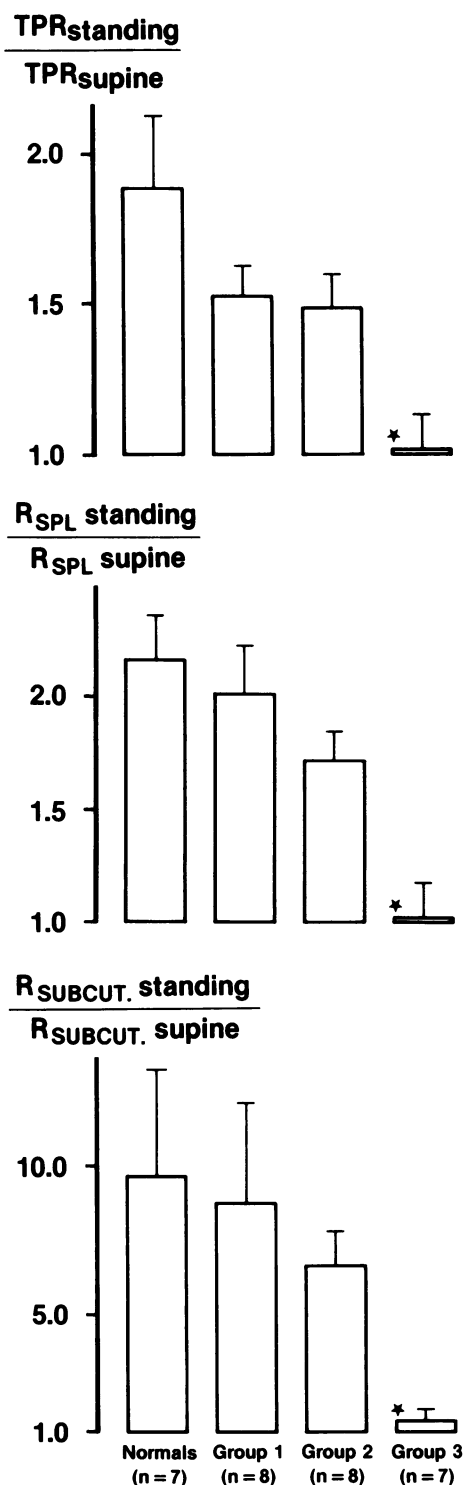


FIGURE 4 The ratios between TPR in the standing and in the supine position (upper panel), between  $R_{SPL}$  in the standing and in the supine position (lower panel) and between  $R_{subcut}$  in the standing and in the supine position in diabetics with (group 3) and without (groups 1 and 2) orthostatic hypotension and in normal subjects. Asterisks denote significant

pathetic defects from a compensated to a decompensated (hypotensive) state. Furthermore, orthostatic hypotension may have been aggravated by defective responsiveness of the arterioles to sympathetic stimulation, for example on the basis of arteriolar hyalinosis, which is not uncommon in diabetics (21). Compatible with a defective responsiveness of arterioles to sympathetic stimulation in diabetics with orthostatic hypotension, significant differences could not be demonstrated in norepinephrine responses, yet TPR ratio was clearly different in normals compared with group 3 patients (Figs. 4 and 5). On the other hand, norepinephrine infusions in patients with hyperadrenergic orthostatic hypotension induced normal increments in BP (20).

Lack of increase in TPR in the patients with orthostatic hypotension was accompanied by lack of increase in  $R_{SPL}$  and  $R_{SUBCUT}$  (Fig. 4). Increase in  $R_{SPL}$  has been shown to be of major importance for the maintenance of arterial BP upon standing up, the decrease in splanchnic vascular conductance being about one-third of decrease in total vascular conductance (22), a figure which is in agreement with our results in normal subjects and in diabetics without neuropathy. The finding of a  $R_{SPL}$  defect in diabetic orthostatic hypotension is in accordance with anatomical evidence of splanchnic neuropathy in diabetics (23). The lack of increase also in  $R_{SUBCUT}$  in the patients with orthostatic hypotension (Fig. 4), indicates that a vasoconstrictor defect exists also in the subcutaneous tissue in these patients. Similarly impaired reflex subcutaneous vasoconstriction has previously been found in the ankle region in diabetics with orthostatic hypotension during change of position of the ankle from cardiac level of 50 cm below the heart (11). Lack of increase in  $R_{SPL}$  and  $R_{SUBCUT}$  cannot completely account for lack of increase in total vascular resistance. Accordingly, a vasoconstrictor defect is also present in other areas. However, some increase in forearm vascular resistance occurs during lower-body negative pressure in diabetics with orthostatic hypotension (24). Thus, some vasoconstriction may occur during standing in diabetics with orthostatic hypotension.

HR increased in all patients with orthostatic hypotension and the mean increase was similar to the increase in the other three groups (Fig. 1). This is in accordance with earlier observations (25, 26); apparently few diabetics with orthostatic hypotension have no increase in HR upon standing up (26). Nevertheless, the fact that HR did not increase more in group 3 patients than in other groups in spite of markedly

differences ( $P < 0.025$ ) between group 3 (orthostatic hypotension) and group 2, group 1 and normal subjects. Values are mean  $\pm$  SE.

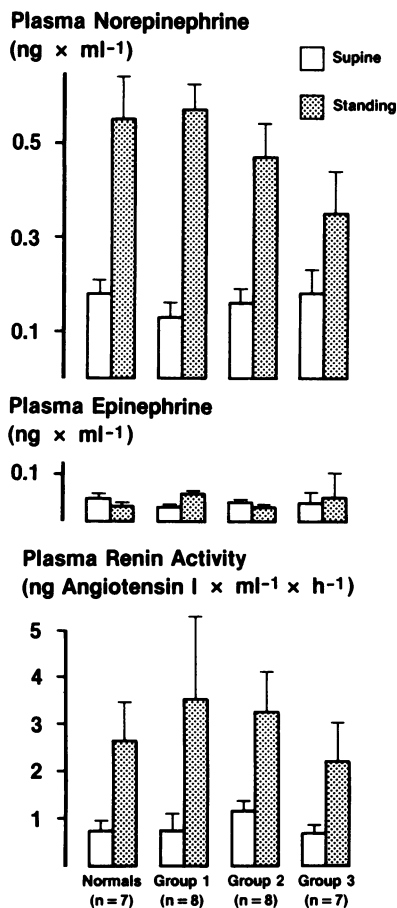


FIGURE 5 Plasma catecholamine concentrations (upper panels) and plasma renin activity (lower panel) in the supine and in the standing position in diabetics with (group 3) and without (groups 1 and 2) orthostatic hypotension and in normal subjects. Values are mean  $\pm$  SE.

lower arterial BP indicates a defect in the baroreceptor reflex arch. Also the reductions in CO upon standing were similar in the four groups (Fig. 2). Thus, an abnormal decrease in CO does not seem to be a pathogenetic factor in diabetic orthostatic hypotension.

The pulmonary tissue volume reflects the central venous pressure. Accordingly, the findings in the different groups of similar pulmonary tissue volume in the supine position as well as of similar decreases in response to standing indicate that central venous pressure was similar in the four groups.

Systolic BP was significantly higher in the supine position in the diabetics with orthostatic hypotension compared with diabetics without neuropathy and normal subjects (Table II). This is most likely explained by occurrence of nephropathy (persistent proteinuria) in the patients with orthostatic hypotension, since nephropathy in diabetics is associated

with supine hypertension (27). In group 3 patients the anemia might also be explained by nephropathy.

Diabetics with presumably slight autonomic neuropathy (group 2 patients) have abnormal cardiovascular responses to graded exercise (28). In these patients, BP decrease upon standing was somewhat, although not significantly, greater than in diabetics without neuropathy. This intermediate response can in part be explained by intermediate increments in TPR (also the increments in  $R_{SPL}$  and  $R_{SUBCUT}$  being intermediate) (Fig. 4) as judged by intermediate increments in plasma norepinephrine concentrations (Fig. 5). It is conceivable that some of these patients do develop frank orthostatic hypotension.

Plasma renin responses to standing have been reported to be blunted in diabetic orthostatic hypotension and sympathetic neuropathy has been held responsible for this reduction (29, 30). Yet, in the present study we found that the plasma renin responses to standing were similar in diabetics with and without orthostatic hypotension. Also patients with cervical cord transections have plasma renin responses to standing similar to those of normals but probably elicited by another mechanism, i.e. by the renal baroreceptor (31). It has been suggested that if blunted renin responses to standing occur in diabetics with orthostatic hypotension the reduction in plasma renin response is due to severe nephropathy affecting the juxtaglomerular apparatus and not to sympathetic neuropathy (32). This explanation is in accordance with the finding in the present study of normal plasma renin responses to standing in diabetics with orthostatic hypotension having slight nephropathy, as judged from serum creatinine measurements (Table I).

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