Decreased Response of Plasma Renin Activity to Orthostasis in Diabetic Patients with Orthostatic Hypotension

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SUMMARY

Plasma renin activity (PRA) was studied in eight patients maintained on a 100 mEq sodium diet who had diabetes mellitus with orthostatic hypotension (OH) and in eight diabetic matched controls without orthostatic hypotension. Signs of neuropathy and nephropathy were more frequent in patients with OH. Supine PRA was 1.2 ± .2 ng./ml. (S.E.M.) in OH and 3.0 ± .9 in controls ($P < .1$). Following upright posture for one-half hour, patients with OH demonstrated a fall in mean blood pressure from 102 ± 8 mm. Hg. to 72 ± 8 ($P < .001$). Despite this stimulus for renin release, PRA was 1.5 ± .3, significantly lower than controls, 4.2 ± .8 ($P < .01$). In patients with OH, mean blood pressures remained lower after four hours of upright posture (80 ± 8) than supine ($P < .005$). PRA was 2.5 ± .6, again lower than in control diabetic patients (5.6 ± .9) ($P < .02$). These results contrast with those in ten out of fifteen reported cases of idiopathic orthostatic hypotension who demonstrated an increase in PRA to the stimulus of upright posture. One explanation for decreased renin release in diabetic patients with OH would be defective catecholamine stimulation. In one patient who was given infusions of norepinephrine for one-half hour on two successive days, no increase in PRA was observed. The associated nephropathy in diabetic patients with OH suggests the possibility of defective renal renin stores or renin releasing mechanisms. When combined with other possible defects in blood pressure homeostatic mechanisms such as catecholamine deficiencies and blood volume abnormalities, an inadequate response of the renin-angiotensin system may be etiologically related to the OH in patients with diabetes. DIABETES *23*:835-40, October, 1974.

Orthostatic hypotension with or without supine hypertension may be a severe and disabling complication of diabetes mellitus. The precise mechanisms responsible for this abnormality in blood pressure homeostasis remain unknown. This report summarizes observations concerning the renin-angiotensin system which may shed light on the understanding of mechanisms involved in a group of diabetic patients with orthostatic hypotension.

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METHODS

Patient Source and Analysis

Informed consent for this study was obtained from sixteen patients with insulin dependent diabetes mellitus who were hospitalized at the New England Deaconess Hospital. Eight patients had diabetes mellitus complicated by orthostatic hypotension defined as a sustained fall in blood pressure of at least 50 mm. Hg. systolic and 20 mm. Hg. diastolic. Supine hypertension with orthostatic hypotension was present in four patients. Antihypertensive medications included Resperine in two of these patients (discontinued two weeks prior to study), methyldopa plus chlorothiazide in one patient (discontinued four days prior to study) and Ser-Ap-Es (Ciba) in one patient (discontinued four days prior to study). For comparison, eight patients with the duration of diabetes similar to those with orthostatic hypotension, but who had neither hypertension nor orthostatic hypotension were studied. The mean daily insulin requirement on the day of study was 37 ± 6 units and 37 ± 5 units for each group respectively. With the exception of two patients with orthostatic hypotension (L. J. treated with Furosemide and J. O. treated with Acetazolamide) no diuretics were used.

Each patient was maintained on a diet containing 100 mEq of sodium and 100 mEq of potassium for a minimum of four days. On the final day of this diet, twenty-four-hour urine collections were analyzed for sodium, potassium, and creatinine. Blood was also

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drawn into EDTA for determination of plasma renin activity (PRA) as follows: a) at 8 a.m. after the patient had been supine overnight, b) after the patient had been upright (sitting or walking) for one half-hour, and c) after being upright for four hours. Blood pressure and pulse were determined at half-hourly intervals.

In one patient with orthostatic hypotension (J. O.) the study diet was continued for two additional days. On the first of these days, tyramine 0.25 mg., 0.75 mg., and 1 mg., was injected intravenously at ten-minute intervals with the patient sitting and the blood pressure recorded each one-half minute. Following the tyramine injections, norepinephrine was infused in graded doses (from 2 to 12 mcg. per minute) with the patient sitting until the blood pressure was raised above control levels for thirty minutes. On the second day, norepinephrine was again infused as on the first day. PRA was determined on each day both in the supine position and after the blood pressure had been maintained above supine control levels for one-half hour.

PRA was determined by either the bioassay method of Boucher et al.[1] as previously modified[2] or by a radioimmunoassay using antibodies against angiotensin I raised in rabbits with the antigen prepared as previously described.[3] This antibody did not react with renin substrate, angiotensin II, ACTH, lysine vasopressin, arginine vasopressin, oxytocin, or bradykinin. The plasma samples were incubated at pH 7.5 in the presence of 5-hydroxyquinoline and dimercaptol for one hour at 37° C. Assays were performed in triplicate, incubating at 4° C. in TRIS acetate buffer containing 1 mg. per ml. of bovine serum albumin for thirty-six hours with I^{125} angiotensin I obtained from the Isoserve Division of Cambridge Nuclear Corporation. Free from bound angiotension I was separated using Dextran coated charcoal.[4] Bound/Free ratios were determined after counting in a Nuclear Chicago Gamma Counter. PRA was determined by reading the angiotensin I generated from a standard curve prepared with each assay and expressing the results of ng. per ml. per hr. incubation. The reproducibility of this method is 3.8 ± .6 (SD) (coefficient of variation 16 per cent) (n = 50). By application of a correction factor of 1.7 to the values obtained by bioassay, a high correlation was obtained between the bioassay and immunoassay methods over the entire physiologic range ($r = .90$, $P < .001$).[5] In this study, this factor was applied to all data obtained by bioassay. Therefore all the results were expressed in terms of the radioimmunoassay. In ten new diabetic patients (diabetes for two years or less) maintained on a 100 mEq sodium, 100 mEq potassium diet, PRA was 2.3 ± .6 ng. per ml. per hr. supine and 5.2 ± 1.1 after upright for four hours. In sixteen patients with diabetes for four to sixteen years wtihout obvious complications of their disease, PRA was 2.8 ± .5 ng. per ml. per hr. supine and 4.8 ± .8 after four hours of upright posture.

Mean blood pressure was defined as diastolic plus one-third systolic minus diastolic pressure. Statistical comparison between mean values was made by application of Student's t test.

RESULTS

Table 1 shows the clinical characteristics of the patients studied. The mean age, sex distribution and mean duration of diabetes was not significantly different between the groups. Symptoms of autonomic insufficiency and signs of peripheral neuropathy (absent ankle reflexes and diminished distal vibratory sensation) were more frequently observed in the patients with orthostatic hypotension. Although retinopathy was observed in each group, neovascularization was more frequent in the patients with orthostatic hypotension.

TABLE 1

Clinical characteristics

	Orthostatic Hypotension	Control
Number of patients	8	8
Male/Female	6/2	6/2
Age (Years)	48 ± 4 (S.E.M.)	38 ± 5 (S.E.M.)
Duration of Diabetes (Years)	19 ± 3 (S.E.M.)	18 ± 3 (S.E.M.)
Dizziness	7	0
Neuropathy	8	3
Impotence	6	1
Anhydrosis	6	0
Retinopathy	7	5
Background	7	5
Neovascularization	5	1
Supine Hypertension	4	0

The mean blood pressure and the pulse rate in the supine and upright positions are shown in table 2. Whereas the pulse rate increased with upright posture in both groups, the mean blood pressure was significantly decreased in those patients with orthostatic hypotension, and increased in those without this abnormality after assuming the upright posture.

Mean blood glucose (determined at 7 a.m. and 11 a.m. on the day of renin studies) was 128 ± 16 in

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TABLE 2

Mean blood pressure and pulse rate (mean ± S.E.M.)

	Supine	Upright Immediate	Upright 1/2 hour	Upright 4 hours
Mean Blood Pressure (mm. Hg.)				
Orthostatic hypotension	102 ± 8	67 ± 8‡	72 ± 8‡	80 ± 8†
Controls	87 ± 6	94 ± 6*	96 ± 7*	91 ± 4
Mean Pulse (per minute)				
Orthostatic hypotension	79 ± 3	85 ± 3*	93 ± 6*	93 ± 5*
Controls	75 ± 2	95 ± 5*	104 ± 4‡	98 ± 5*

*P < .05
†P < .005 compared with supine levels
‡P < .001

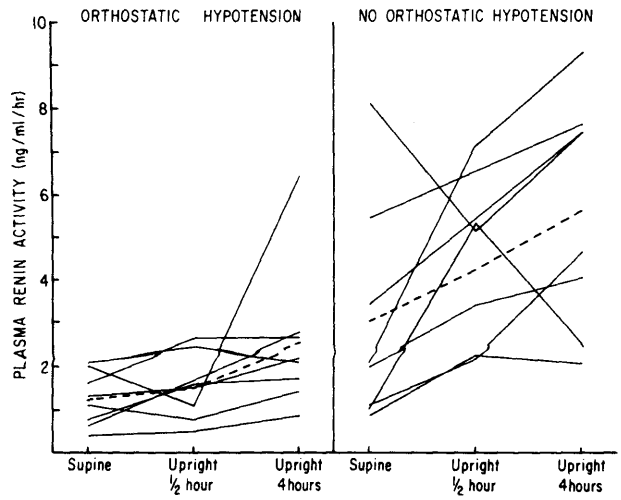

FIG. 1. Individual changes in plasma renin activity after assuming the upright posture in diabetic patients with orthostatic hypotension (left) and in control diabetic patients (right). Interrupted lines represent mean values.

patients with orthostatic hypotension and 188 ± 22 in controls (P < .05). Other mean laboratory characteristics are shown in table 3. The groups were similar with the notable exceptions of creatinine clearance, hematocrit, serum albumin, one-half hour upright plasma renin activity, and four hour upright plasma renin activity. These were significantly decreased in the patients with orthostatic hypotension. Each patient with orthostatic hypotension had proteinuria and/or decreased creatinine clearance. Individual changes in PRA with upright posture are shown in figure 1. Two patients who were unable to stand because of symptomatic orthostatic hypotension were maintained in the sitting position during the time required for the upright studies. The remainder of the patients in both study groups remained upright. Although the supine PRA was similar in the two groups, in only one patient with orthostatic hypotension did the PRA show an appropriate response at four hours, the one-half hour response being blunted.

In patient J. O., tyramine injections produced no increase in blood pressure. Norepinephrine infusions sufficient to increase the sitting blood pressure above control levels failed to result in an increase in PRA on either infusion day (table 4).

TABLE 3

Laboratory characteristics (mean ± S.E.M.)

	Orthostatic Hypotension	P	Control
Proteinuria (No. patients)	5		0
Serum albumen	3.6 ± .2	P < .01	4.4 ± .2
BUN (mg. per cent)	37 ± 14		15 ± 1
Creatinine (mg. per cent)	2.5 ± 1		1.0 ± .1
Creatine Clearance (cc/min.)	47 ± 10	P < .005	105 ± 12
Hematocrit	38 ± 2	P < .02	45 ± 2
Serum			
Sodium (mEq/1)	137 ± 2		141 ± 1
Potassium (mEq/1)	4.5 ± .2		4.5 ± .2
Urine			
Sodium (mEq/24 hours)	87 ± 8		94 ± 10
Potassium (mEq/24 hours)	63 ± 8		69 ± 10
Plasma Renin Activity (ng./ml./hr.)			
Supine	1.2 ± .2	P < .1	3.0 ± .9
1/2 hour upright	1.5 ± .3	P < .01	4.2 ± .8
4 hours upright	2.5 ± .6	P < .02	5.6 ± .9

DISCUSSION

Blood pressure regulation in the errect posture involves a complex interplay of both neural and humoral factors which have recently been reviewed by Guyton et al.[6] Baroreceptors located in the arch of the aorta and in the carotid sinuses are stimulated by a fall in blood pressure with upright posture, sending signals via the vasomotor center of the brain to the autonomic nervous system resulting in increased cardiac output and vasoconstriction, returning blood pressure toward normal. With more severe decreases in blood pressure (shock), chemoreceptors in the carotid and aortic bodies respond to hypoxia and hypercapnea again via the vasomotor center and autonomic nervous system with the resultant increases in blood pressure. These systems are aided by humoral factors including catecholamines and the renin-angiotension-aldosterone system.

Orthostatic hypotension could result when there is a failure of one or more of these compensatory blood

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TABLE 4

Norepinephrine (NE) infusion in patient J.O.

	Blood Pressure (mm. Hg.)				Plasma Renin Activity (ng./ml./hr.)			
	Supine	Upright			Supine	Upright		
		1/2 hr.	4 hr.	with NE		1/2 hr.	4 hr.	with NE
Day 1 (Control)	130/70	60/30	70/30	—	0.4	0.5	0.8	—
Day 2 (NE 12 ng./min.)	140/70	60/30	—	180/90	0.6	—	—	0.6
Day 3 (NE 8 ng./min.)	120/70	50/20	—	150/70	0.5	—	—	0.6

pressure regulatory responses or a defect in blood volume regulation. This entity may occur without known cause (idiopathic orthostatic hypotension), or can be associated with established disease states, both neurological and nonneurological. Among these disorders are amyloidosis, syphilis, adrenal insufficiency, spinal cord transection, and diabetes mellitus.

The present report is concerned with defining the role of one of the humoral mechanisms in patients with diabetes mellitus associated with orthostatic hypotension, namely plasma renin activity. Although the precise mechanisms of renin release from the juxtaglomerular cells of the kidney have not been defined, it is clear that a decrease in blood pressure or a decrease in effective plasma volume will increase PRA. Conditions such as hypotension, sodium depletion and upright posture cause increased PRA in normal subjects and in patients with essential hypertension and/or renal disease.[7,8] When released, renin splits angiotensin I from renin substrate, a polypeptide of hepatic origin. Angiotensin I is converted to angiotensin II, the most potent vasoconstrictor known and in turn, will increase blood pressure toward normal. In addition to its vasoconstrictor properties, angiotensin II is a potent stimulus to the adrenal gland for aldosterone secretion. Increased aldosterone results in increased sodium resorption from the distal renal tubule, thereby increasing body sodium. The increased sodium potentiates vascular reactivity to exogenous angiotensin II and norepinephrine[3] and stimulates ADH secretion with water retention, increased fluid volume and a return of blood pressure toward normal.

The patients studied were maintained on a constant sodium diet. Because of possible marked potentiation of orthostatic hypotension, which could occur with severe sodium restriction, 100 mEq Na was given daily. In patients with orthostatic hypotension, a fall in blood pressure would be expected to stimulate PRA markedly. Because blood volume may be increased with hyperglycemia[17] the significantly higher blood glucose in the control diabetic subjects might be expected to decrease their PRA. Despite the significantly decreased blood pressure in the patients with orthostatic hypotension, all patients demonstrated a blunted renin response to the stimulus of upright posture for one-half hour and seven out of eight to upright posture for four hours. In view of the observation that supine normal subjects can increase PRA fivefold with sodium depletion without changing physical activity,[7] the hypotension in the two subjects maintained sitting rather than standing ordinarily would be expected to increase PRA appropriately. The mean PRA at each study period remained significantly lower than in diabetic patients with similar age and duration of diabetes, but without orthostatic hypotension.

The PRA in diabetic patients with orthostatic hypotension has not been reported previously. A summary of the literature concerning the renin-angiotensin-aldosterone axis in patients with idiopathic orthostatic hypotension and the one reported patient with orthostatic hypotension and amyloidosis is presented in table 5. Ten of the fifteen patients with idiopathic orthostatic hypotension demonstrated an increase in PRA to the stimulus of upright posture and four out of four to the stimulus of sodium depletion. The patient with amyloidosis failed to increase PRA appropriately after these stimuli.

Diabetics with orthostatic hypotension therefore differ from most patients with idiopathic orthostatic hypotension in that they failed to increase PRA appropriately. Such a defect in an important hormone system for renal blood pressure volume regulation in diabetics raises two basic questions. First, what mechanisms are responsible for the blunted plasma renin activity response and second, what is the relationship between decreased renin and the orthostatic hypotension?

Possible mechanisms for decreased renin activity in human diabetics and in the alloxan-diabetic rat have been reviewed recently.[17] Three are pertinent to this discussion: a) deficiency of renin substrate, b) lack of catecholamine stimulation of renin release, and c) de-

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TABLE 5

Plasma renin activity and aldosterone in orthostatic hypotension—review of literature

Reference	Diagnosis	Age/Sex	Plasma Renin Activity		Response to Catechol. Infusion	Response to Sodium Depletion	Aldosterone	
			Supine	Upright			High Sodium Diet	Low Sodium Diet
9	IOH*	68M	N	No response in 2 min.	None		N	N
	IOH	52M	N	↑ ↑	None		N	N
	IOH	55M	N	↑	None		N	N
	IOH	56M	N	No response in 2 min.	None		N	N
10	IOH	20F	N	↑ ↑				
	IOH	50M	N	↑ ↑				
	IOH	55M	N	No Response				
	IOH	48M	N	No Response				
11	IOH	49M	N	↑ ↑		↑ ↑	N	N
	IOH	69F	N			↑ ↑	N	N
12	IOH	56F	Low		↑ ↑	↑ ↑	Low	N
	IOH	41F	Low	↑ ↑	↑ ↑	↑ ↑	N	N
13	IOH	60M	N	↑ ↑				
14	IOH	45M	N	↑ ↑			N	N
15	IOH	50M						
	IOH	77F		↑				
	IOH	70M		↓	None			
16	OH†	68M	Low	No response	↑ ↑	Low	Low	Low

*IOH = Idiopathic orthostatic hypotension
†OH = Orthostatic hypotension with amyloidosis and macroglobulinemia
N = Normal

struction of juxtaglomerular cells. Although measurements of renin substrate were not made, the absence of liver disease would make the first possibility unlikely. Christensen has found decreased levels of circulating catecholamines in patients with long duration diabetes mellitus and peripheral neuropathy.[18] Additionally, vascular responsiveness to norepinephrine is increased in patients with diabetes of long duration accompanied by retinopathy, thus suggesting decreased circulating levels of this hormone.[19] In that norepinephrine can stimulate release of renin,[20] a deficiency of this hormone could lead to decreased responsiveness of the renin releasing mechanism to ordinary stimuli. In the one patient with orthostatic hypotension receiving tyramine injections, no increase in blood pressure occurred. Because tyramine normally will increase blood pressure due to release of stored norepinephrine in nerve endings,[21] this would suggest a deficiency of norepinephrine stores. Ordinarily a hormonal deficiency state will produce hyper-responsiveness to exogenous hormone. Norepinephrine infusions in this patient in amounts sufficient to increase the upright blood pressure above supine levels, however, failed to increase renin on two successive infusion days. One plausible explanation for blunted renin release revolves around the basic renal pathological process. Patients with orthostatic hypotension differed from those without orthostatic hypotension in that each had renal disease manifested by either proteinuria and/or decreased creatinine clearance. In light of the duration of diabetes in these patients, it is reasonable to assume that these patients had diabetic nephropathy. The juxtaglomerular cells lie adjacent to the glomerulus in the afferent arterioles. Hyalinization of the afferent arteriole which occurs in diabetic nephropathy frequently replaces these juxtaglomerular cells.[17] Additionally, Schindler and Sommers[22] reported abnormal separation of the macula densa from the juxtaglomerular cells by interposed sclerotic tissue and also fibrosis around individual juxtaglomerular cells in diabetic nephropathy. Because of this, they postulated that renin production would be lowered. Provided a sufficient number of afferent arterioles are involved, the renin storage and releasing apparatus of the kidney could be severely compromised and impaired renin responsiveness would ensue. A similar process could be postulated for patients with amyloidosis and orthostatic hypotension. In the one patient reported with this abnormality, however,[16] the renin responded normally to infu-

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sions of catecholamines.

The second question regarding the relationship between decreased renin and the pathogenesis of orthostatic hypotension in diabetic persons is complex. Patients who have no measurable renin or angiotensin II following nephrectomy for nondiabetic renal disease have normal blood pressure responsiveness after assuming the upright posture, provided fluid balance is adequate.[23] Therefore, deficient renin itself does not result in loss of blood pressure homeostasis. When several defects occur simultaneously, normal upright blood pressure cannot be maintained. In view of nervous system involvement, patients with diabetes could have compromised baroreceptor and chemoreceptor reflexes. There could also be compromised renal volume regulating mechanisms, and decreased intravascular volume related to hypoalbuminemia.

In diabetic patients with orthostatic hypotension, clinical and laboratory evidence is presented suggesting that this abnormality occurs in the course of long standing diabetes with diabetic nephropathy and neuropathy; that multiple defects in the mechanisms maintaining upright blood pressure may be present, including inability to adequately stimulate the renin-angiotensin system. The precise role of the renin-angiotensin system in the etiology of orthostatic hypotension in diabetic patients must await observations on the blood pressure response in such patients after undergoing renal transplantation.

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