Spectrum of Autonomic Cardiovascular Neuropathy in Diabetes

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OBJECTIVE — Diabetic patients with incapacitating orthostatic hypotension can have either a “hyperadrenergic” or “hypoadrenergic” presentation. Although the latter is related to overt autonomic neuropathy, the former is proposed to be explained by appropriate autonomic responses. We hypothesize, however, that both conditions are part of a spectrum of autonomic dysfunction.

RESEARCH DESIGN AND METHODS — We studied 16 consecutive diabetic patients with preserved renal function referred for incapacitating orthostatic hypotension and characterized their autonomic and neurohumoral cardiovascular regulation.

RESULTS — Six patients had a hyperadrenergic orthostatic response: systolic blood pressure fell 42 ± 15 mmHg, heart rate increased 20 ± 3 bpm, and plasma norepinephrine increased from 340 ± 80 to 910 ± 100 pg/ml. Ten patients had a hypoadrenergic response: systolic blood pressure fell 78 ± 5 mmHg, heart rate increased only 7 ± 3 bpm, and norepinephrine increased only from 130 ± 28 to 230 ± 40 pg/ml. Vagal (sinus arrhythmia, Valsalva ratio) and sympathetic (response to hyperventilation, postprandial hypotension) responses were impaired in both groups, but to a greater extent in the hypoadrenergic group. Notwithstanding severe orthostatic hypotension, the postural increase in plasma renin was blunted in both groups, more so in the hypoadrenergic group. Despite preserved renal function, patients had mild anemia due to impaired erythropoietin release, as seen in primary cases of autonomic failure.

CONCLUSIONS — Our results suggest that diabetic patients presenting with hyperadrenergic orthostatic hypotension have an initial stage of autonomic neuropathy, with overtly abnormal vagal function and early signs of sympathetic impairment. Furthermore, altered renin response can contribute to the patients’ orthostatic hypotension.

Two distinct clinical presentations of orthostatic hypotension have been described in diabetic patients, depending on their norepinephrine response to upright posture. The “hypoadrenergic” orthostatic hypotension form is associated with low plasma norepinephrine response to posture and is related to established autonomic failure. On the other hand, there is a group of patients in whom plasma norepinephrine can be greatly increased on standing (“hyperadrenergic” orthostatic hypotension) (7–9), but the underlying pathophysiology of this form of orthostatic hypotension has not been defined. Only a few such patients have been reported in the literature. It has been assumed that these patients have an intact autonomic function (10,11), but details of their autonomic and neurohumoral cardiovascular regulation have not been previously provided. A similar “hyperadrenergic” condition has been described in nondiabetic patients (12–14), and it is proposed to be due to a partial autonomic neuropathy (14–17). We hypothesize, therefore, that autonomic impairment also underlies the hyperadrenergic orthostatic intolerance described in diabetic patients. The goal of this study, therefore, was to investigate the autonomic function in diabetic patients with hyperadrenergic orthostatic hypotension and compare them with a hypoadrenergic group.

Whereas adrenergic responses to posture have been the focus of most previous studies, alterations in the renin-angiotensin-aldosterone system have also been explored as potential contributors of orthostatic hypotension in diabetic patients. These studies, however, have found low, normal, or high values of plasma renin activity (18,19). Furthermore, the correlation between these diverse levels of plasma renin activity and the two presentations of diabetic orthostatic hypotension are not known. A second goal of this study was to test the hypothesis that the renin-angiotensin-aldosterone system is altered in diabetic autonomic neuropathy. For this purpose, we compared diabetic patients who had hyper- and hypoadrenergic orthostatic hypotension with both a group of healthy control sub-
jicts and a group of patients with idiopathic orthostatic hypotension (pure autonomic failure).

**RESEARCH DESIGN AND METHODS** — The study group consisted of 16 consecutive patients with diabetes, age 53 ± 4 years, who were referred to the Autonomic Dysfunction Center at Vanderbilt University Medical Center for evaluation and treatment of symptomatic orthostatic hypotension. All patients complained of frequent and disabling presyncopal episodes; 50% had recurrent syncopal episodes. Orthostatic hypotension was defined by the American Autonomic Society criteria: a decrease in upright systolic/diastolic blood pressure of at least 20/10 mmHg in the setting of frequent orthostatic symptoms, such as lightheadedness, presyncope, and syncope (20). All medications were discontinued except for those required for glucose control. Patients with congestive heart failure, renal failure (glomerular filtration rate <40 ml/min), or apparent peripheral vascular disease were excluded. Patients with amyloidosis or other causes of autonomic failure were also excluded. Short-acting insulin was withheld at least 2 h before autonomic testing, and no patients had a recent episode of hypoglycemia before testing.

The control groups consisted of 12 age-matched normal subjects and 25 consecutive patients with disabling pure autonomic failure, who underwent the same investigational procedures described below. Diagnostic criteria for pure autonomic failure are described elsewhere (21). All investigational procedures were approved by the institutional review board, and subjects gave informed consent.

**Procedures**

Subjects were admitted to Vanderbilt’s General Clinical Research Center and were fed a low-monoamine caffeine-free diet containing 150 mEq sodium and 70 mEq potassium per day. Patients were kept off medications and in sodium balance for at least 3 days before evaluation. Autonomic function tests were performed as previously described (22). The respiratory arrhythmia ratio was used as a marker of cardiac parasympathetic activity. To assess cardiovascular sympathetic function, we used the response to hyperventilation for 30 s (23), coldpressor test, and isometric handgrip. We also determined the cardiovascular effects of ingesting a standardized meal, because postprandial hypotension is a sensitive indicator of autonomic failure (24).

Blood samples for catecholamine levels, plasma renin activity, and aldosterone were obtained through an indwelling catheter placed in an antecubital vein. Samples were obtained after patients had been lying down overnight (supine position) and after they had been standing for a maximum of 30 min (upright position). Patients were encouraged to stand as long as possible during this period but were allowed to sit at intervals if presyncopal symptoms developed. Plasma catecholamine levels were determined as previously described (25). Plasma renin enzymatic activity was assessed by the conversion of angiotensinogen to angiotensin I and expressed as nanograms of angiotensin I produced per milliliter of plasma per hour (26). Plasma aldosterone was measured by radioimmunoassay (Coat-a-Count; Diagnostic Products, Los Angeles, CA). Plasma erythropoietin was measured by an enzyme-linked immunosorbent assay method, using a commercial kit (Quantikine IVD; R&D Systems, Minneapolis, MN).

**Statistical analysis**

Results are expressed as mean ± SE. Data were analyzed with GraphPad Prism (version 3.0; GraphPad Software, San Diego, CA). Associations between two study variables were determined by linear regression. Group comparisons were made by paired or unpaired t tests as appropriate. Multiple group comparisons were made using ANOVA. Criterion for significance was P < 0.05.

**RESULTS**

**Clinical characteristics**

Seven patients had type 1 diabetes and nine had type 2 diabetes. Fourteen patients were being treated with insulin, and only 2 patients were receiving oral hypoglycemic drugs. The mean age was 53 ± 4 years, and the mean duration of the disease was 17 ± 2 years. The progression of orthostatic symptoms in these patients was gradual but variable, ranging from a few months to several years. Most patients had associated somatic and sensory symptoms of peripheral neuropathy. Regarding major complications of diabetes (target organ damage), peripheral neuropathy was found in all patients, retinopathy in 50%, symptomatic coronary heart disease in 35%, hypertension in 55%, gastroparesis in 30%, diarrhea in 15%, significant proteinuria (>300 mg/24 h) in 25%, and neurogenic bladder in two (15%) patients (Table 1). Four of the male patients had impotence, and these data were not available in the remaining three male patients. The information about diabetes complications was obtained as part of the clinical evaluation of these patients and not primarily as part of this research. We cannot be certain, therefore, that these complications were absent in the patients in whom it was not reported.

Patients had a mean fasting glucose of 214 ± 14 mg/dl and a mean HbA1c of 10.5 ± 0.4%, suggesting poorly controlled diabetes (normal values 4.0–6.5%). Mean creatinine was 1.4 ± 0.2 mg/dl (median 1.1), blood urea nitrogen 25 ± 3 mg/dl, and glomerular filtration rate 78 ± 5 ml/min (median 76). Significant proteinuria (as defined above) was present in only four patients. Plasma total protein and albumin were in the normal range; serum sodium, potassium, and magnesium were 138 ± 8 mEq/l, 4.4 ± 0.1 mEq/l, and 2.0 ± 0.04 mg/ml, respectively. Urinary sodium and potassium were 134 ± 5 and 52 ± 3 mEq/24 h, respectively.

Mean hemoglobin was 12.8 ± 0.4 g/dl for the whole group. However, if the World Health Organization definition of anemia is followed (hemoglobin <12 g/dl for women and <13 for men), then anemia was present in 65% of the patients; three patients in the hyperagrengic group (50%) and seven in the hypoadrenergic group (70%), which is unexpected in the setting of normal kidney function. Mean hematologic values in the subset of patients with anemia were hemoglobin 11.5 ± 0.2 g/dl (range 10.7–12.5 g/dl), mean corpuscular volume 89 ± 2 μm³, mean corpuscular hemoglobin 30 ± 0.4 pg, reticulocytes 1.6 ± 0.2%, total iron binding capacity 234 ± 14 μg/dl, ferritin 246 ± 35 μg/l, serum iron 74 ± 10 μg/dl, folic acid 12.5 ± 1.5 mg/ml, and vitamin B₁₂ 660 ± 190 pg/ml. Only one patient had demonstrable iron-deficient anemia. All others had normocytic normochromic anemia of unknown etiology. Plasma erythropoietin was available in only four patients, for whom it was inappropriately low (5.5 ± 0.5 mU/ml) for their hemoglobin levels (11.2 ± 0.3 g/dl). Predicted
plasma erythropoietin levels for this level of hemoglobin should be 28 mU/ml (27).

**Autonomic response to posture**

Patients were classified as hyperadrenergic or hypoadrenergic depending on their plasma norepinephrine response to posture (8,28). Six patients with upright plasma norepinephrine 600 pg/ml or higher were considered hyperadrenergic and 10 patients with plasma norepinephrine <600 pg/ml were classified as hypoadrenergic. The mean patient age in these two groups was similar. The duration of the disease was shorter in the hyperadrenergic group (15 ± 3 years) than in the hypoadrenergic group (18 ± 1.5 years) (P = 0.07).

**Hemodynamic and neurohumoral characteristics**

The hemodynamic and humoral characteristics of the patients are shown in Tables 1 and 2. Although the mean supine systolic and diastolic blood pressure tended to be higher in the hypoadrenergic group than in the hyperadrenergic group, the upright systolic and diastolic blood pressures dropped significantly more in the hypoadrenergic group (Table 1 and Fig. 1). Supine heart rate was not different between the groups, but standing heart rate was significantly higher in the hyperadrenergic group (P = 0.01). The incidence of supine hypertension (systolic blood pressure >160 or diastolic blood pressure >95 mmHg) was similar in both the hyper- and hypoadrenergic groups (50% of the patients) and was also similar to that found in the patients with pure autonomic failure (57%).

Mean upright plasma norepinephrine levels were 253 ± 40 pg/ml in the hyperadrenergic group and 915 ± 100 pg/ml in the hypoadrenergic group (Table 2). Supine plasma norepinephrine was also significantly lower in hypoadrenergic patients than in the hyperadrenergic group (141 ± 30 and 324 ± 80 pg/ml, respectively, P < 0.005) (Fig. 2). Supine mean plasma epinephrine was similar in the hyper- and hypoadrenergic groups (23 ± 6 and 23 ± 7 pg/ml, respectively), but the upright values were higher in the hypoadrenergic group (50 ± 18 pg/ml) than in the hyperadrenergic group (25 ± 5, P = 0.04).

Both supine and upright plasma renin activity were significantly lower in the hyperadrenergic group than in the hyperadrenergic group. Plasma renin activity for the hypo- and hyperadrenergic groups were 0.5 ± 0.1 and 0.9 ± 0.2 ng·ml⁻¹·h⁻¹, respectively, in the supine posture (P = 0.04 for the difference between groups) and 0.6 ± 0.1 and 1.4 ± 0.6 pg·ml⁻¹·h⁻¹, respectively, in the upright posture (P = 0.03) (Fig. 2). Low plasma renin activity that was unresponsive to posture was also found in pure autonomic failure patients, as previously described (29). Supine and upright aldosterone levels in the hyper- and hypoadrenergic diabetic groups were not significantly different, although upright aldosterone tended to be higher in the hyperadrenergic group (Table 2 and Fig. 2). Both supine and upright plasma aldosterone values were significantly lower in both diabetic groups than in normal control subjects (P = 0.01 and 0.04, respectively). We found significant correlations between plasma renin activity and aldoste-
between plasma renin activity and norepinephrine ($r = 0.65$, $P = 0.008$).

**Characterization of autonomic function**

Autonomic cardiac vagal function, as determined by the Valsalva ratio and sinus arrhythmia, was abnormal in both diabetic groups and in pure autonomic failure patients (Table 3). On the other hand, indices of sympathetic function were not as affected in the hyperadrenergic group as they were in the hypoadrenergic and pure autonomic groups. A meal challenge produced profound postprandial hypotension in the hypoadrenergic group and pure autonomic failure patients. Hyperadrenergic patients also had significant postprandial hypotension compared with control subjects ($P < 0.01$), but this was less pronounced compared with hypoadrenergic patients ($P < 0.07$). These results suggest that both groups of diabetic patients with orthostatic hypotension had impaired cardiac vagal function and that sympathetic involvement was more severe in the hyperadrenergic group.

Long-term follow-up was available in one patient in the hyperadrenergic group (patient 3). This patient was seen 5 years after initial evaluation. His upright plasma norepinephrine had decreased from 663 pg/ml at his initial evaluation to 284 at follow-up. This was also associated with a blunting of orthostatic tachycardia. Heart rate increased by 26 bpm on standing during his initial evaluation but only by 5 bpm at follow-up.

**CONCLUSIONS** — This study highlights the wide spectrum of autonomic neuropathy seen in patients with diabetes. Two distinct clinical presentations of orthostatic hypotension have been described in diabetic patients. The distinction was based on their plasma norepinephrine response to standing ($r = 0.54$, $P = 0.015$) and between plasma renin activity and norepinephrine ($r = 0.65$, $P = 0.008$).
rocyte mass, whereas plasma volume was found normal (9). It has been assumed, therefore, that these patients have an intact autonomic function and that their hyperadrenergic state is an adequate compensatory response to a reduced intravascular volume (10,11).

Our results, however, challenge this notion. Our study is the first to correlate the "adrenergic state" of patients with diabetic orthostatic hypotension to their autonomic function and their renin-aldosterone system. As expected, diabetic patients with hypoadrenergic orthostatic hypotension had overt autonomic failure. This was evidenced by clearly abnormal responses to autonomic function tests, with a severity similar to that observed in patients with severe and disabling pure autonomic failure. A novel and seemingly paradoxical finding in our study is that patients with hyperadrenergic orthostatic hypotension also have evidence of autonomic impairment. This was most evident by their impaired sinus arrhythmia, which depends, to a large extent, on an intact parasympathetic function. Parasympathetic involvement can be the first evidence of autonomic impairment in diabetes, preceding evidence of sympathetic involvement. Hyperadrenergic patients also had significant postprandial hypotension, a sensitive indicator of autonomic impairment (24). We postulate, therefore, that this apparent "hyperadrenergic state" may be the initial presentation of neuropathic autonomic failure in some diabetic patients. The apparent conversion of a patient from a "hyperadrenergic" to a "hypoadrenergic" form of orthostatic hypotension 5 years after initial evaluation is in agreement with this interpretation, although this observation remains anecdotal. The longer duration of disease in the hypoadrenergic group also suggests that hyper- and hypoadrenergic forms of orthostatic hypotension represent extremes of the same spectrum of disease.

Another novel finding is that hyperadrenergic patients have a low renin response to posture compared with normal control subjects. This is remarkable considering that they should have a much greater renin response to compensate for diabietic orthostatic hypotension to their autonomic function and their renin-aldosterone system. As expected, diabetic patients with hypoadrenergic orthostatic hypotension had overt autonomic failure. This was evidenced by clearly abnormal responses to autonomic function tests, with a severity similar to that observed in patients with severe and disabling pure autonomic failure. A novel and seemingly paradoxical finding in our study is that patients with hyperadrenergic orthostatic hypotension also have evidence of autonomic impairment. This was most evident by their impaired sinus arrhythmia, which depends, to a large extent, on an intact parasympathetic function. Parasympathetic involvement can be the first evidence of autonomic impairment in diabetes, preceding evidence of sympathetic involvement. Hyperadrenergic patients also had significant postprandial hypotension, a sensitive indicator of autonomic impairment (24). We postulate, therefore, that this apparent "hyperadrenergic state" may be the initial presentation of neuropathic autonomic failure in some diabetic patients. The apparent conversion of a patient from a "hyperadrenergic" to a "hypoadrenergic" form of orthostatic hypotension 5 years after initial evaluation is in agreement with this interpretation, although this observation remains anecdotal. The longer duration of disease in the hypoadrenergic group also suggests that hyper- and hypoadrenergic forms of orthostatic hypotension represent extremes of the same spectrum of disease.

Table 3—Comparison of autonomic function tests between the different groups

<table>
<thead>
<tr>
<th>Test</th>
<th>Control subjects</th>
<th>Hyperadrenergic</th>
<th>Hypoadrenergic</th>
<th>Pure autonomic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva ratio</td>
<td>1.58 ± 0.08</td>
<td>←→</td>
<td>1.14 ± 0.04</td>
<td>1.1 ± 0.01</td>
</tr>
<tr>
<td>Sinus arrhythmia ratio</td>
<td>1.25 ± 0.03</td>
<td>←→</td>
<td>1.07 ± 0.01</td>
<td>1.04 ± 0.01</td>
</tr>
<tr>
<td>Hyperventilation ΔBP (mmHg)</td>
<td>–3/3 ± 2/1</td>
<td>←→</td>
<td>–14/–15 ± 2/4</td>
<td>←→ –29/–17 ± 4/4</td>
</tr>
<tr>
<td>Hyperventilation ΔHR (bpm)</td>
<td>6 ± 2</td>
<td>←→</td>
<td>10 ± 2</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Handgrip ΔBP (mmHg)</td>
<td>20/17 ± 2/2</td>
<td>←→</td>
<td>20/12 ± 8/4</td>
<td>←→ 5/5 ± 2/1</td>
</tr>
<tr>
<td>Cold pressor test ΔBP (mmHg)</td>
<td>21/15 ± 4/2</td>
<td>←→</td>
<td>13/7 ± 2/2</td>
<td>←→ 3/2 ± 2/1</td>
</tr>
<tr>
<td>Postprandial ΔBP (mmHg)</td>
<td>1/–4 ± 1/1</td>
<td>←→</td>
<td>–12/–7 ± 3/2</td>
<td>←→ –21/–13 ± 3/2</td>
</tr>
</tbody>
</table>

←→ denotes significant differences between adjacent groups. ΔBP, blood pressure changes; ΔHR, heart rate changes.
the magnitude of their orthostatic hypotension. The dissociation between the exaggerated norepinephrine response to posture and this impaired renin response is also noteworthy. Renin impairment was even greater in hypoadrenergic patients. This finding raises the possibility that the low plasma renin activity may be due to autonomic denervation of the kidney, as suggested in patients with pure autonomic failure (29). This “relative hyporeninemia” may contribute to these patients’ orthostatic hypotension through lack of vascular actions normally provided by angiotensin II, as well as indirectly through altered sodium handling. We excluded patients with overt renal failure, but we cannot completely exclude that subtle impairment of renal function can contribute to our findings. Of interest, Hoeldtke et al. (30) recently found that diabetic patients without overt autonomic impairment had a decrease in plasma renin activity during a 3-year follow-up. The possibility that impaired renin secretion is an early marker of autonomic neuropathy deserves further study.

Previous reports (31,32) have suggested that erythropoietin, another renal hormone, is also impaired in diabetic autonomic neuropathy. We found a high incidence of low-production anemia in our patients, and this was associated with impaired erythropoietin production in the patients in whom this was measured. This type of anemia is also present in pure autonomic failure, and its magnitude correlates with the severity of autonomic impairment (33). The reduced erythropoietin response may explain the reduced red cell mass previously found in hyperadrenergic patients (9). Recombinant erythropoietin has been successfully used to treat diabetic patients with hypoadrenergic neuropathy (34) and patients with primary autonomic failure (33–35). The goal of this approach would not be to treat the anemia, which is usually mild, but to improve intravascular volume.

If, as we propose, hyperadrenergic patients have initial autonomic failure, how can we explain the increased upright plasma norepinephrine? We speculate that autonomic neuropathy in these patients is not global but circumscribed to a subpopulation of noradrenergic neurons; thus, some vascular beds may be relatively spared. A similar pattern of “partial dysautonomia” has been described in patients with idiopathic orthostatic intolerance (13,14,16,17,28,36,37). The clinical presentation of this condition is similar to that of diabetic patients with the hyperadrenergic syndrome: orthostatic intolerance, postural tachycardia, and increased upright norepinephrine. It should be noted that an increased plasma norepinephrine could be the result of a reduction in its clearance rather than an increase in norepinephrine release (38). Antecubital vein norepinephrine may overestimate overall norepinephrine release in these patients, and plasma norepinephrine may be lower if sampled from other sites.

In summary, we propose that diabetic autonomic neuropathy is associated with reduced renin release to upright posture and that all of these factors contribute to the severity of orthostatic hypotension. Our results suggest that autonomic function is impaired in diabetic patients with hyperadrenergic orthostatic hypotension. Their abnormal vagal function, the presence of postprandial hypotension, and their impaired renin response to upright posture are consistent with this conclusion. We propose that hyperadrenergic orthostatic hypotension is the clinical presentation of a partial autonomic neuropathy.

Potential clinical implications

The presence of autonomic neuropathy is a recognized risk factor that worsens the prognosis in diabetic patients. Intensive insulin treatment remains the most effective treatment for this condition. Overt autonomic failure, however, can theoretically increase the incidence of hypoglycemic episodes because of impaired counterregulatory mechanisms. Early recognition of autonomic neuropathy would be clinically desirable. Our results suggest that hyperadrenergic orthostatic hypotension is an early form of autonomic impairment. Before making this diagnosis, it is important to rule out first volume depletion and medications that can induce this condition. Impaired renin response to upright posture also appears to be an early indicator of autonomic impairment. The high incidence of low-production anemia found in diabetic patients with autonomic neuropathy provides a rationale for the use of recombinant erythropoietin as a therapeutic trial for those in whom impaired erythropoietin production is documented, as suggested in recent publications. The goal is not only to reverse the anemia, which is usually mild, but also to treat orthostatic hypotension.

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