Pressor Factors and Responsiveness in Hypertension Accompanying Diabetes Mellitus

PETER WEIDMANN, CARLO BERETTA-PICCOLI, AND BERNHARD N. TROST

SUMMARY Hypertension accompanying diabetes mellitus may involve abnormalities in at least two major blood pressure-regulating systems: the body sodium-fluid volume state and cardiovascular reactivity. In metabolically stable nonazotemic diabetes, exchangeable sodium is increased by 10% on average, regardless of age, insulin dependence or nondependence, or the presence or absence of diabetic retinopathy or clinical nephropathy (proteinuria ≥ 0.3 g/24 hr). Possible contributing mechanisms include renal sodium retention and an extravascular shift of fluid and sodium; intracellular accumulation is not excluded. Circulatory volume is normal or low and the total exchangeable sodium/blood volume ratio increased. In hypertensive diabetes, the latter abnormality is particularly pronounced; systolic pressure tended to correlate with exchangeable sodium (r = 0.47, p < 0.001) and diastolic pressure with the plasma sodium/potassium ratio (r = 0.25, p < 0.05). Plasma aldosterone, renin, epinephrine, and norepinephrine levels are generally normal or sometimes low in metabolically stable nonazotemic diabetic patients with normal or high blood pressure; the plasma clearance of norepinephrine also appears to be unaltered. The cardiovascular pressor responsiveness to norepinephrine is often exaggerated relative to concomitant plasma concentrations, regardless of age, type of antidiabetic treatment, or presence or absence of diabetic retinopathy, peripheral neuropathy, or high blood pressure. Pressor responsiveness to angiotensin II also may sometimes be increased relative to plasma renin levels. Sodium retention and diabetic vasculopathy of resistance vessels could be important complementary mechanisms of hyperreactivity. In diabetes with mild hypertension, diuretic treatment restored exchangeable sodium, norepinephrine pressor responsiveness, and blood pressure toward normal. Thus sodium retention and cardiovascular hyperreactivity tend to occur even at the normotensive, nonazotemic stage of diabetes and may concomitantly predispose for the frequent development of hypertension in the diabetic population.

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KEY WORDS • body sodium-fluid volume state • sympathetic system • renin-angiotensin system • cardiovascular responsiveness • aldosterone • antihypertensive treatment

THE body sodium-fluid volume state, the sympathetic and renin-angiotensin pressor systems, the basal vascular tone and cardiovascular reactivity to vasoactive stimuli, and perhaps also vasodepressor prostaglandins and kinins are major complementary factors in the regulation of blood pressure (BP). Based on various adaptive mechanisms, a dynamic equilibrium between the control systems normally allows maintenance of BP homeostasis. Any persistent deviation from this equilibrium, however, with a relative or absolute excess in one or more pressor factors, exaggerated basal cardiovascular tone or reactivity, or possibly also a noncompensated vasodepressor deficiency, will result in hypertension.

Hypertension accompanying diabetes mellitus (DM) may involve abnormalities in at least two major BP-regulating systems: the body sodium-fluid volume state and cardiovascular responsiveness. This review considers their possible role and the interactions with the renin-angiotensin system and the catecholamines in diabetes-associated hypertension.

Body Sodium-Fluid Volume State

Nonazotemic (serum creatinine < 1.3 mg/dl or < 115 μmol/L) diabetes mellitus that is metabolically stable and uncomplicated by heart failure or edema is frequently associated with distinct sodium retention. We noted in such a study population a 10% increase in exchangeable body sodium34 (Table 1). This tendency
occurred regardless of the patient's age (Figure 1), dependence on insulin, sex or body habitus, or presence or absence of major complications such as diabetic retinopathy, peripheral neuropathy, or clinical nephropathy as evidenced by proteinuria greater than 0.3 g/24 hr. On the other hand, plasma and blood volumes were normal or sometimes slightly low (Figure 1), Table 1). Others have confirmed these findings.5 Thus nonazotemic diabetic humans differ from experimental rats with severe alloxan-induced DM in which circulatory volume as well as blood urea nitrogen are increased.6

The excess body sodium distinctly differentiates stable nonazotemic DM from uncomplicated essential hypertension. Table 1 provides an up-dated comparative analysis of our findings; these study populations and the methods used were described previously in detail.2,3,4 Exchangeable sodium (NaE), plasma volume, and blood volume are on average similar in patients with essential hypertension and healthy subjects, as noted previously.5,10 In the diabetic population, the increase in NaE is only minimally less pronounced in normotensive patients than in those with mild to moderate hypertension. The latter, however, are characterized additionally by plasma and blood volumes that on average are significantly contracted as compared to both the normal state and essential hypertension.

It follows that the ratios between total NaE and total plasma or blood volume are increased in nonazotemic DM, and this abnormality is significantly more pronounced in hypertensive than in normotensive patients (see Table 1). Moreover, the relationship between values of NaE and plasma or blood volume is quite similar in healthy subjects and patients with essential hypertension, but is displaced to the right (p < 0.01) in DM, and significantly (p < 0.05) more so in the hypertensive than in normotensive diabetics (Figure 2). This constellation points to a diabetes-associated abnormal accumulation of sodium, and with it possibly also fluid space, and an enhanced tendency for blood volume contraction in DM complicated by hypertension.

### Table 1. Blood Pressure, Electrolyte-Fluid Volume State, Plasma Renin, and Aldosterone in Healthy Subjects and Patients with Nonazotemic Diabetes Mellitus or Essential Hypertension (Mean ± so)

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>All</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>Essential hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>110</td>
<td>124</td>
<td>65</td>
<td>59</td>
<td>120</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>48/62</td>
<td>66/58</td>
<td>32/33</td>
<td>33/26</td>
<td>36/84</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39 ± 17</td>
<td>55 ± 13*</td>
<td>56 ± 14</td>
<td>55 ± 13</td>
<td>44 ± 16</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.78 ± 0.16</td>
<td>1.79 ± 0.19</td>
<td>1.78 ± 0.19</td>
<td>1.79 ± 0.18</td>
<td>1.85 ± 0.19†</td>
</tr>
<tr>
<td>Blood pressure, supine (mm Hg)</td>
<td>119/76 ± 10/8</td>
<td>148/85 ± 27/14†</td>
<td>133/77 ± 16/9</td>
<td>166/96 ± 26/11</td>
<td>156/100 ± 26/17</td>
</tr>
<tr>
<td>Plasma volume (%§)</td>
<td>100 ± 15.9</td>
<td>96.3 ± 16.3</td>
<td>99.4 ± 10.0</td>
<td>93.1 ± 16.2*</td>
<td>99.6 ± 15.8</td>
</tr>
<tr>
<td>Blood volume (%§)</td>
<td>100 ± 15.0</td>
<td>94.3 ± 15.0*</td>
<td>97.4 ± 14.6</td>
<td>90.7 ± 14.9*</td>
<td>99.2 ± 14.3</td>
</tr>
<tr>
<td>Exchangeable sodium (%§)</td>
<td>100 ± 6.7</td>
<td>109.7 ± 10.7#</td>
<td>109.3 ± 9.3*</td>
<td>110.3 ± 12.1#</td>
<td>100 ± 7.8</td>
</tr>
<tr>
<td>Total exchangeable sodium/plasma volume</td>
<td>1.12 ± 0.18</td>
<td>1.27 ± 0.22#</td>
<td>1.21 ± 0.20</td>
<td>1.31 ± 0.23#</td>
<td>1.17 ± 0.21</td>
</tr>
<tr>
<td>Total exchangeable sodium/blood volume</td>
<td>0.66 ± 0.10</td>
<td>0.77 ± 0.13#</td>
<td>0.73 ± 0.11</td>
<td>0.80 ± 0.14#</td>
<td>0.66 ± 0.10</td>
</tr>
<tr>
<td>Plasma sodium (mmol/L)</td>
<td>140 ± 2.1</td>
<td>137.9 ± 2.9‡</td>
<td>137.5 ± 3.0‡</td>
<td>138.5 ± 2.6‡</td>
<td>138.7 ± 2.7‡</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.06 ± 0.32</td>
<td>4.05 ± 0.38</td>
<td>4.10 ± 0.36</td>
<td>4.01 ± 0.39</td>
<td>4.07 ± 0.36</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.06 ± 0.21</td>
<td>0.93 ± 0.22‡</td>
<td>0.93 ± 0.19</td>
<td>0.96 ± 0.26</td>
<td>1.05 ± 0.19</td>
</tr>
<tr>
<td>Renin activity, supine (ng/ml/hr)</td>
<td>1.7 ± 1.2</td>
<td>1.7 ± 1.4</td>
<td>1.7 ± 1.3</td>
<td>1.6 ± 1.5</td>
<td>1.5 ± 1.7</td>
</tr>
<tr>
<td>Aldosterone supine (ng/dl)</td>
<td>6.7 ± 4.7</td>
<td>4.3 ± 3.2</td>
<td>4.1 ± 2.6</td>
<td>4.3 ± 3.1</td>
<td>7.6 ± 5.2</td>
</tr>
<tr>
<td>Urinary sodium, (mmol/24 hr)</td>
<td>135 ± 66</td>
<td>151 ± 68</td>
<td>157 ± 72</td>
<td>146 ± 63</td>
<td>152 ± 67</td>
</tr>
<tr>
<td>Urinary potassium, (mmol/24 hr)</td>
<td>64 ± 22</td>
<td>66 ± 23</td>
<td>68 ± 26</td>
<td>65 ± 26</td>
<td>62 ± 23</td>
</tr>
</tbody>
</table>

Exchangeable sodium was measured in 110 healthy subjects, all diabetics, and 91 patients with essential hypertension; blood volume was obtained in 107 healthy subjects, 110 diabetics (56 normotensive and 54 hypertensive), and 117 patients with essential hypertension.

*p < 0.05 vs healthy subjects and all diabetics.

†p < 0.01 vs healthy subjects.

§Percentage of mean normal value as related to body surface area and considering the sex of subjects.4

‖p < 0.02 vs normotensive diabetics.
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Certain correlations between BP and measured variables of the electrolyte-fluid volume state were also apparent. In our hypertensive diabetics, systolic BP correlated with NaE (r = 0.47, p < 0.001), while diastolic BP correlated weakly with the plasma sodium/potassium ratio (r = 0.26, p < 0.05). Similar tendencies were present in the entire diabetic population (r = 0.25 and 0.27 respectively, p < 0.01), but not in normotensive diabetic or healthy persons.

To evaluate further the relationship between the body sodium-blood volume state and BP, nonazotemic diabetic patients with mild hypertension were evaluated first in the untreated state (receiving placebo) and then again after 6 weeks of intervention with the thiazide-type diuretic chlorthalidone. Diuretic treatment normalized the initially increased NaE, further reduced blood volume, and restored blood pressure toward normal values (Figure 3). The distinct responses of body sodium (~8%) and circulatory volume (~11%) also differentiated hypertensive DM from uncomplicated essential hypertension, where NaE and blood volume were modified only minimally (~3% and ± 0% respectively) by identical therapy with chlorthalidone, which nevertheless effectively reduced BP (from 151/99 to 129/86; n = 23, p < 0.001). The sodium-blood pressure constellation before and after diuretic intervention in hypertensive nonazotemic diabetics resembles in part the profile in primary hyperaldosteronism, however, a condition considered to represent the prototype of sodium-induced hypertension.
The average increases in NaE (+10% vs +16%) and BP (166/96 vs 183/112 mm Hg) were both less pronounced in the hypertensive diabetics than in patients with untreated primary hyperaldosteronism. Circulatory volume is generally normal in the established phase of primary hyperaldosteronism. Whether and to what extent the absence of hyperaldosteronism and/or the tendency for blood volume contraction, at a given increase in NaE, may contribute to a milder degree of BP elevation in DM than in primary hyperaldosteronism deserves consideration.

In diabetics with azotemia, the prevalence of hypertension increases further, reaching 85% at serum creatinine values of about 8.5 mg/dl and almost 100% with end-stage renal failure; body sodium may tend to be increased even more than in nonazotemic diabetics, and removal of excess sodium and fluid volume by regular dialysis treatment almost always leads to satisfactory improvement of hypertension.

Several mechanisms may contribute to sodium retention in DM (Figure 4). Serum albumin concentration tends to be decreased even before the presence of clinical nephropathy, thus favoring a mild reduction in plasma oncotic pressure. The permeability of the microvasculature increases and a transcapillary escape of small and large molecules may be promoted further by an elevated filtration pressure in the presence of hypertension. Moreover, changes in collagen composition may enhance the avidity of tissues for sodium. These alterations could initially promote a shift of fluid and sodium from the intravascular to the interstitial space; the deficit in circulatory volume would in turn result in a finite degree of renal sodium retention, thus establishing a new steady state with increased extracellular sodium and fluid volume and an at least partly restored blood volume. Renal sodium excretion could potentially also be impaired due to functional consequences of diabetic vasculopathy in the kidneys, a deficiency of renal vasodilator prostaglandin E2 or kinins, increased renal blood levels of insulin in DM type II or early phase DM type I, or renal failure. Except for the last, the relevance of these mechanisms for altered sodium metabolism is at present speculative. The same is true for the possibility that insulin deficiency in established type I DM and tissue resistance to insulin in type II DM could compromise the transmembranous exchange of potassium and sodium, thus leading to intracellular accumulation of sodium and perhaps even an attendant increase in vascular muscle tone. Nevertheless, disturbed sodium transport has been noted in blood cells of subjects with obesity, a state commonly involving tissue resistance to insulin.

Diabetic patients tend to have high blood levels of growth hormone, which may have also a sodium-retaining effect. The normal values of total body potassium and nitrogen under stable metabolic conditions do not support an enhanced action of growth hormone on body composition, however. The excess sodium in diabetics clearly cannot be explained by increased secretion of aldosterone or other common corticosteroids.

The Renin-Angiotensin-Aldosterone System

Under stable metabolic conditions, plasma renin, angiotensin II, and aldosterone levels related to age and/or urinary sodium excretion are usually normal or sometimes low in nonazotemic DM and in normotensive and hypertensive diabetics (see Table 1, Figures 5 and 6). Restriction of the analysis to age-matched subgroups supports this notion; thus supine plasma renin activity averaged 1.3 ± 0.9 ng/ml/hr in 60 healthy subjects (mean age 49 ± 14 yr), 1.7 ± 1.3 ng/ml/hr in 60 diabetics (50 ± 15 yr), 1.8 ± 1.1 ng/ml/hr in 30 normotensive diabetics (50 ± 15 yr), 1.8 ± 1.5 ng/ml/hr in 30 hypertensive diabetics (51 ± 14 yr), and 1.3 ± 1.3 ng/ml/hr in 60 patients with essential hypertension (mean age 49 ± 15 yr). Others reported a tendency for low plasma renin levels in hypertensive diabetics or, in the opposite, slightly increased renin values in both normotensive and hypertensive diabetic patients. The hypertension in most diabetic patients obviously cannot be due to dis-
distinct activation of the renin-angiotensin system, although even normal renin and angiotensin II values could be inappropriately high relative to the excess in body sodium in some patients. In fact, a weak but significant positive correlation between plasma renin and both systolic and diastolic BP \(r = 0.30 \) and \(0.34\) respectively, \(p < 0.05\) in our hypertensive diabetics described in Table 1 may be consistent with a modulating influence of renin. This notion seems justified, since an interaction in the opposite direction, namely, a regulatory effect of BP and possible associated factors such as sodium retention and aging on renin release, would promote an inverse rather than positive relationship. Improved glycemic control in type II DM also resulted in lower plasma angiotensin II levels. On the other hand, the tendency for a hypoactive and/or hyporesponsive renin-angiotensin system in a proportion of diabetics may help to "protect" them from the development of malignant hypertension.

**Catecholamines**

Under stable metabolic conditions, levels of age-related plasma and urinary norepinephrine (NE) or total plasma catecholamines are normal and sometimes low in patients with nonazotemic DM with normal or high BP (Figure 7). Plasma and urinary epinephrine is also normal or occasionally low. Mean values did not differ significantly among our diabetic groups, healthy subjects, and patients with essential hypertension. Table 2 further documents these aspects in groups of subjects in whom we simultaneously investigated plasma catecholamine concentrations, plasma renin activity related to age in 100 nonazotemic diabetic patients with a normal or high blood pressure. The shaded areas represent the 95% confidence ranges obtained from healthy subjects. The regression lines indicate statistically significant correlations \(r = -0.36 \) to \(-0.58, p < 0.01\) to \(< 0.001\). BP = blood pressure; BP ↑ = hypertension. (Reprinted from Beretta-Piccoli et al., 1979 with permission.)
ma NE clearance, and cardiovascular pressor responsiveness (see next section). Correction for the influence of the slightly higher mean age of the diabetics would, if anything, slightly lower their mean plasma NE compared to the values in the healthy subjects or patients with essential hypertension. Nevertheless, blood levels of NE depend not only on the rate of spillover from the synaptic cleft, but also on the rate of clearance from plasma. The latter, assessed during intravenous NE infusion, did not differ significantly among the healthy subjects, normotensive or hypertensive diabetics, or patients with essential hypertension (Table 2). This suggests that the plasma NE concentrations may approximately correlate with the overall spillover of neurotransmitter released from sympathetic nerves. Thus hypertension in a large majority of diabetics obviously is not due to sympathetic overactivity, although it may be that, as in the case of renin and angiotensin II, “normal” NE levels could be inappropriately high relative to a coexisting excess in body sodium53 in some patients.

**Cardiovascular Pressor Responsiveness**

Variations in cardiovascular reactivity modulate the responses to vasoactive stimuli and therefore are very important in BP regulation. Under normal conditions, BP responses to NE or angiotensin II (Ang II) are inversely related to their basal blood levels.54-55 Considering DM, an early study described increased pressor responses to NE.56 Others reported augmented responses to both NE and Ang II in nonazotemic diabetics with retinopathy, but normal responses in those without retinopathy.57 Increased Ang II responses, correlating inversely with low plasma renin levels, could be interpreted as being appropriate,57 however, and no simultaneous measurements of circulating NE were available.56,57

Studies from our laboratory suggested that the responsiveness to NE is often exaggerated relative to concomitant plasma NE concentrations in nonazotemic diabetics.3,58 The dose of intravenously infused NE required to elevate mean BP by 20 mm Hg in such patients was less than 50% of that needed in healthy

**FIGURE 7.** Plasma norepinephrine concentrations related to age in 51 nonazotemic diabetic patients with normal or high blood pressure. The shaded areas represent the 95% confidence ranges from healthy subjects.35 The regression lines indicate statistically significant correlations (r = 0.27 to 0.36; p < 0.05 to < 0.001). BP = blood pressure; BP ↑ = hypertension. Reprinted from Beretta-Piccoli et al., 1979 (with permission.)

**TABLE 2. Mean Plasma Catecholamine Concentrations and Plasma Clearance Rates of Norepinephrine (Mean ± sd)**

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects</th>
<th>Diabetes mellitus</th>
<th>All</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>Essential hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>34</td>
<td>27</td>
<td>17</td>
<td>10</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>39 ± 16</td>
<td>52 ± 15*</td>
<td>51 ± 12*</td>
<td>55 ± 16*</td>
<td>42 ± 14</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>119/74 ± 11/10</td>
<td>131/74 ± 20/10</td>
<td>123/69 ± 12/8</td>
<td>146/87 ± 16/10</td>
<td>146/96 ± 23/14</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>63 ± 10</td>
<td>74 ± 10*</td>
<td>72 ± 12</td>
<td>78 ± 12*</td>
<td>69 ± 10</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>71 ± 11</td>
<td>74 ± 15</td>
<td>72 ± 15</td>
<td>77 ± 14</td>
<td>74 ± 12</td>
<td></td>
</tr>
<tr>
<td>Plasma epinephrine (ng/dl)</td>
<td>3.2 ± 1.7</td>
<td>3.4 ± 3.4</td>
<td>2.6 ± 2.0</td>
<td>4.8 ± 3.5</td>
<td>4.0 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Plasma norepinephrine (ng/dl)</td>
<td>22 ± 9</td>
<td>21 ± 13</td>
<td>17.5 ± 15</td>
<td>26 ± 13</td>
<td>24 ± 10</td>
<td></td>
</tr>
<tr>
<td>Clearance of norepinephrine from plasma (L/min)</td>
<td>5.3 ± 2.6</td>
<td>6.0 ± 3.4</td>
<td>5.9 ± 3.3</td>
<td>6.1 ± 3.5</td>
<td>5.6 ± 2.5</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05 vs healthy subjects and patients with essential hypertension.
PATHOGENESIS OF HYPERTENSION ACCOMPANYING DIABETES/Weidmann et al.

subjects, despite the absence of any significant difference in endogenous preinfusion plasma NE levels (Figure 8). Moreover, the relationship between increases in plasma NE and concomitant changes in mean arterial pressure was significantly displaced to the left in the diabetic group compared with healthy persons (Figure 9). The NE hyperresponsiveness was unrelated to variations in age, known duration of diabetes, or type of antidiabetic treatment and was almost equally pronounced in the presence or absence of diabetic retinopathy or peripheral neuropathy, or in diabetic subjects with normal BP or mild to moderate hypertension (Figure 8). Exaggerated NE responsiveness is also a well-established abnormality in some nondiabetic normotensive offspring of hypertensive families and in borderline or established essential hypertension. This disturbance may tend to be even more pronounced in DM than in mild to moderate essential hypertension (see Figures 8 and 9).

Compared to healthy subjects, doses of intravenously infused Ang II required to increase diastolic BP by 20 mm Hg also were significantly reduced in our nonazotemic diabetic patients; this trend was on average associated with a mild although statistically insignificant decrease in basal (preinfusion) plasma renin (Figure 10). Both values tend to decrease with increasing age. Nevertheless, it is possible that Ang II reactivity in diabetics exceeds a physiological adapta-

**Figure 8.** Norepinephrine pressor doses and basal (preinfusion) plasma norepinephrine concentrations in healthy subjects, nonazotemic diabetics with normal blood pressure or mild to moderate hypertension, and patients with mild to moderate essential hypertension. Norepinephrine pressor dose is defined as the infusion rate required to increase mean arterial pressure by 20 mm Hg. Mean values + SEM are shown. Same study populations as in Table 2.

**Figure 9.** Relationship between plasma norepinephrine levels and increases in blood pressure during norepinephrine infusion in healthy subjects, nonazotemic diabetics, and patients with mild to moderate essential hypertension. Horizontal and vertical bars indicate ± SEM. Same study populations as in Table 2.

**Figure 10.** Angiotensin II pressor doses and basal (preinfusion) plasma renin levels in healthy subjects, nonazotemic diabetics with normal blood pressure or mild to moderate hypertension, and patients with mild to moderate essential hypertension. Angiotensin pressor dose is defined as the infusion rate required to increase diastolic arterial pressure by 20 mm Hg. Mean values + SEM are shown. Same study populations as in Table 2.
Attenuation to lower levels of circulating renin. Evidence for abnormally exaggerated Ang II responsiveness was also observed previously in a group of nonazotemic diabetics with mild hypertension (Figure 11), as well as in normotensive patients with uncomplicated insulin-dependent DM. The presence of hyperreactivity to both NE and Ang II already at the normotensive stage of DM differs from the constellation in nondiabetic normotensive offspring of hypertensive families who responded abnormally to NE but normally to Ang II.

Apart from blood levels of NE, Ang II, and plasma renin, additional factors must be considered as possible correlates or determinants of pressor responsiveness in DM. The tendency for sodium retention in such patients could contribute to enhanced Ang II receptor affinity and pressor responses to infused NE or Ang II. In nonazotemic diabetic patients with mild hypertension, removal of excess body sodium after 6 weeks of treatment with chlorthalidone (see Figure 3) was associated with restoration of NE pressor responsiveness to normal (Figure 11); since diuretic treatment had no significant effect on basal (preinfusion) plasma NE levels, it probably was improving the initially disturbed relationship between NE reactivity and prevailing sympathetic nervous activity. On the other hand, removal of excess sodium by chlorthalidone did not appear to improve the relationship between Ang II reactivity and the activity of the renin-angiotensin system; thus a possible net depressor influence from the restoration of Ang II pressor dose was probably offset by the pressor potential of the accompanying marked increase in circulating renin. The possibility of an abnormality of cations in blood vessels of diabetics (see Figure 4) and its correction by a thiazide is presently speculative, however.

Thickening of blood vessel walls induced by high BP is believed to be a secondary factor contributing to exaggerated cardiovascular reactivity in essential hypertension. Certain alterations in resistance vessels also develop early in the course of DM. Therefore diabetic vasculopathy may conceivably increase the responsiveness to pressor agents. Moreover, structural alterations in the afferent renal arterioles and the juxtaglomerular area may interfere with renin release in diabetic patients. Chronic sodium retention and diabetic vasculopathy could both favor a constellation in which, with progressive course of the disease, an increased Ang II pressor response is accompanied and perhaps partly compensated for by decreased plasma renin and Ang II levels, or vice versa; but exaggerated cardiovascular NE responsiveness is not accompanied and therefore not compensated for by a concomitant decrease in plasma NE.

Disturbed parasympathetic cardiac innervation or other dysfunction of the autonomic reflex arc develops commonly during long-term DM and may then also promote exaggerated pressor responses to vasoactive stimuli. The potential contribution of additional factors such as a deficiency in vasodilator prostaglandins or kinins is at present speculative.

Conclusion and Therapeutic Relevance

Whatever the exact underlying mechanisms leading to sodium retention and exaggerated cardiovascular reactivity are, it is evident that these alterations tend to occur even at the normotensive, nonazotemic stage of DM. Both disturbances may concomitantly predispose toward the frequent development of hypertension in the diabetic population. Moreover, consideration of these abnormalities may help in the choice of appropriate treatment of diabetes-associated hypertension. Blood pressure is an important prognostic factor in the long-term outcome of diabetic patients. A diet with low sodium, low fat, and high fiber content has been noted to exert a distinct antihypertensive effect and thus may be a useful nonpharmacological baseline approach. Treatment with a thiazide diuretic may often simultaneously improve BP, body sodium, and the
exaggerated cardiovascular responsiveness to NE in hypertensive nonazotemic diabetics; while removal of excess body sodium with dialysis almost always provides satisfactory BP control in patients with terminal renal failure. Unfortunately, thiazide or loop diuretics are not ideal step-1 drugs in DM since they tend to impair the glucose tolerance further and may have additional unwanted metabolic side effects. It is therefore of practical clinical interest that certain calcium-enzyme blockers may also improve cardiovascular hyperreactivity and provide effective long-term control of BP without adversely affecting carbohydrate metabolism.

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P Weidmann, C Beretta-Piccoli and B N Trost

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