Contrasting Effects of Vasodilators on Blood Pressure and Sodium Balance in the Hypertension of Autonomic Failure

JEFF JORDAN,*† JOHN R. SHANNON,† BOJAN POHAR,† SACHIN Y. PARANJAPE,† DAVID ROBERTSON,† ROSE-MARIE ROBERTSON,† and ITALO BIAGGIONI†
*Clinical Research Center, Franz Volhard Clinic, Berlin, Germany; and †Autonomic Dysfunction Center, Vanderbilt University, Nashville, Tennessee.

Abstract. Supine hypertension, which is very common in patients with autonomic failure, limits the use of pressor agents and induces nighttime natriuresis. In 13 patients with severe orthostatic hypotension due to autonomic failure (7 women, 6 men, 72 ± 3 yr) and supine hypertension, the effect of 30 mg nifedipine (n = 10) and 0.025 to 0.2 mg/h nitroglycerin patch (n = 11) on supine BP, renal sodium handling, and orthostatic tolerance was determined. Medications were given at 8 p.m.; patients stood up at 8 a.m. Nitroglycerin was removed at 6 a.m. Compared with placebo, nifedipine and nitroglycerin decreased systolic BP during the night by a maximum of 37 ± 6 and 36 ± 10 mmHg, respectively (P < 0.01). At 8 a.m., supine systolic BP was 23 ± 7 mmHg lower with nifedipine than with placebo (P < 0.05), but was similar with nitroglycerin and placebo. Sodium excretion during the night was not reduced with nitroglycerin (0.13 ± 0.02 mmol/mg creatinine [Cr] versus 0.15 ± 0.03 mmol/mg Cr with placebo), but it was increased with nifedipine (0.35 ± 0.06 mmol/mg Cr versus 0.13 ± 0.02 mmol/mg Cr with placebo, P < 0.05). Nifedipine but not nitroglycerin worsened orthostatic hypotension in the morning. It is concluded that nifedipine and transdermal nitroglycerin are effective in controlling supine hypertension in patients with autonomic failure. However, nifedipine has a prolonged depressor effect and worsens orthostatic hypotension in the morning. The decrease in pressure natriuresis that would be expected with the substantial decrease in BP obtained with nitroglycerin and nifedipine may be offset by a direct effect of both drugs on renal sodium handling.

Primary autonomic failure can occur with central nervous system involvement and extrapyramidal or cerebellar manifestations (Shy-Drager syndrome or multiple system atrophy [MSA]) or without evidence of central nervous system involvement (pure autonomic failure [PAF]) (1). One of the most disabling symptoms of primary autonomic failure is orthostatic hypotension (2). It is less recognized that approximately 50% of these patients also have supine hypertension (3). The presence of supine hypertension complicates the treatment of autonomic failure, because pressor agents used for the treatment of disabling orthostatic hypotension aggravate supine hypertension (4,5). In addition, supine hypertension increases nocturnal natriuresis, which worsens orthostatic symptoms in the morning (6). The rationale to treat supine hypertension in autonomic failure is to prevent cardiovascular complications of hypertension, to allow the use of pressor agents, and to attenuate the sodium loss during the night. Nonpharmacologic treatments of supine hypertension (e.g., elevation of the head of the bed) are often used not only to reduce hypertension, but also to decrease nocturnal sodium loss, which will improve orthostatic hypotension in the morning (7). This approach, however, is often insufficient to treat supine hypertension. Relatively low doses of transdermal nitroglycerin delivered by a patch substantially decrease supine BP in autonomic failure patients (3). Nifedipine is sometimes used to treat supine hypertension but has not been systematically studied.

The aim of this study was to test the hypothesis that nitroglycerin or nifedipine would not only be effective in reducing supine hypertension but would decrease nocturnal diuresis and improve orthostatic hypotension in the morning.

Materials and Methods

Patients

We studied 13 patients with primary autonomic failure: seven MSA (4 men, 3 women; 72 ± 4 yr) and six PAF patients (2 men, 4 women; 76 ± 3 yr) (1). All patients had supine hypertension defined as supine diastolic BP >90 mmHg and/or supine systolic BP >150 mmHg. Patients were excluded if they had secondary causes of autonomic failure (e.g., diabetes mellitus, amyloidosis). Written informed consent was obtained before study entry. All studies were approved by the institutional review board.

Protocol

Patients were admitted to the Elliot V. Newman Clinical Research Center at Vanderbilt University Medical Center. Vasoactive medications and fludrocortisone were discontinued at least five half-lives before testing. Patients were placed on a 150-mEq sodium and 70-mEq potassium diet free of substances that could interfere with catecholamine measurements. Studies were conducted at least 2.5 h after breakfast or lunch. Patients underwent a thorough autonomic
evaluation, including the determination of orthostatic vital signs, cardiovascular autonomic reflex testing, as well as supine and upright plasma catecholamines and plasma renin activity. In all patients, we obtained a 12-lead electrocardiogram (ECG) and a chest x-ray film on admission.

**Autonomic Evaluation**

Heart and brachial BP were determined with a brachial BP cuff kept at heart level after 10 min supine and then again after 3 min standing (or as long as tolerated). During autonomic reflex testing (8), BP and heart rate were measured beat to beat by photoplethysmography (Finapres, Ohmeda) and continuous ECG, respectively.

The degree of sinus arrhythmia was assessed during controlled breathing (5-s inhalation and 5-s exhalation for 90 s). The sinus arrhythmia ratio (SA ratio) was calculated as the ratio of the longest to the shortest RR interval during this 90-s period. The response of BP to rapid (approximately 60/min), shallow breathing for 30 s was determined. BP response to isometric handgrip (30% of maximum voluntary contraction for 1 min) was determined. To measure the BP response to pain, the cold pressor test was performed by immersing one hand in a 50/50 mixture of ice and water for 1 min. The systolic BP and heart rate responses to the Valsalva maneuver (40 mmHg pressure generated for 15 s) were also determined.

Plasma catecholamines and plasma renin activity were determined the morning after the patient remained in the supine position overnight, and again after 30 min in the upright position. Patients were instructed to stand as much as possible during this period. If standing without symptoms was not possible, they were permitted to walk or sit briefly until symptoms abated. Blood samples were drawn from a heparin lock placed at least 30 min before the first blood draw.

**Overnight Medication Trials**

We compared in a single blinded manner the effect of transdermal nitroglycerin (Nitro-Dur patch, Key Pharmaceuticals, Kenilworth, NJ) and 30 mg of oral nifedipine (Adalat, Miles, West Haven, CT) on supine BP and urinary excretion overnight to the effect of a placebo patch. The order of the interventions (placebo, nitroglycerin, nifedipine) was random. During the medication trials, BP and heart rate were measured by an automated brachial BP cuff (Dinamap, Criticon, Tampa, FL) at 1-h intervals throughout the night with care taken to avoid waking the patient. The nitroglycerin patch (or placebo patch) was placed at 8 p.m. The subjects remained supine from 8 p.m. until 8 a.m. the next day. The patch was removed at 6 a.m. The initial nitroglycerin dose was 0.025 mg/h. If necessary, the dose was increased on subsequent nights until a hypotensive effect was observed or a maximal dose of 0.2 mg/h was reached. An oral dose of 30 mg of nifedipine was given at 8 a.m. with approximately 50 ml of tap water.

At 8 a.m., after the medication trials were completed, patients stood up, and upright BP and heart rate were determined after 1 min standing (or as long as tolerated). To determine diurnal variation in sodium excretion, urine was collected from 8 a.m. to 8 p.m. before placebo was administered and from 8 p.m. to 8 a.m. after placebo was administered. To determine the effect of antihypertensive medications on nocturnal sodium excretion, urine was collected from 8 p.m. to 8 a.m. after the nitroglycerin patch was applied or patients took nifedipine.

**Analytical Methods**

Plasma was analyzed for catecholamines by a modification of a high-pressure liquid chromatographic method described previously (9). Plasma renin enzymatic activity was assessed by the conversion of angiotensinogen to angiotensin I and expressed as nanograms of angiotensin I produced per liter of plasma per hour (10).

**Statistical Analyses**

All data are expressed as mean ± SEM. Intraindividual and interindividual differences were analyzed by paired and unpaired t tests, respectively. ANOVA testing for repeated measures was used for multiple comparisons. A value of P < 0.05 was considered statistically significant.

**Results**

**Clinical Characteristics**

All patients were admitted for symptoms of severe autonomic failure. With further investigation, three patients (23%) had a history suggestive of cerebrovascular disease. Of these three patients, the first patient had a single episode of transient ischemic attack with a normal cranial computed tomography scan. The second patient had diffuse atherosclerotic disease and had had a carotid endarterectomy. The third patient had a cranial computed tomography scan that showed an old left occipital cerebral infarction that was currently asymptomatic. Three patients (23%) had ECG changes suggesting coronary artery disease (inverted T-waves in the precordial leads in one patient and R-wave reduction in precordial leads in two patients). Of these patients, one patient had a history of unstable angina and was angiographically shown to have significant coronary artery disease. Another patient had orthostatic angina that resolved with lying down, and a third patient had exertional dyspnea. The latter two patients had normal myocardial perfusion scans and no angiographically significant coronary artery disease. In four patients (31%), the 12-lead ECG was suggestive of left atrial enlargement (1), left ventricular hypertrophy (2), or both (1). On the chest x-ray films, two patients (15%) had mild cardiomegaly, but none of the patients had evidence of congestive heart failure.

**Autonomic Testing**

Orthostatic vital signs and the results of autonomic reflex testing are given in Table 1. Supine BP was 190 ± 9/95 ± 5 and 180 ± 9/91 ± 7 mmHg in patients with MSA and PAF, respectively. With standing, BP decreased profoundly by 72 ± 13 and 89 ± 16 mmHg in MSA and PAF, respectively. The compensatory heart rate increase with standing was inadequate considering the profound decrease in BP. Systolic BP decreased profoundly during phase II of the Valsalva maneuver in all patients. Likewise, the BP overshoot during phase IV of the Valsalva maneuver was markedly reduced or absent. The profound decrease in BP during phase II and the absence of the BP overshoot during phase IV of the Valsalva maneuver further evidence for impaired sympathetic function. Patients had markedly reduced respiratory sinus arrhythmia and a marked reduction in the Valsalva heart rate ratio consistent with impaired parasympathetic control of heart rate. Five patients had a normal cold pressor response (>20 mmHg), and seven patients had a normal BP increase with hand-grip testing. These findings may suggest that the loss of autonomic function
Table 1. Autonomic reflex testinga

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MSA</th>
<th>PAF</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine SBP (mmHg)</td>
<td>190 ± 9</td>
<td>180 ± 9</td>
<td></td>
</tr>
<tr>
<td>Supine HR (bpm)</td>
<td>73 ± 4</td>
<td>64 ± 15</td>
<td></td>
</tr>
<tr>
<td>ΔSBP standing (mmHg)</td>
<td>−72 ± 13</td>
<td>−89 ± 16</td>
<td>≤20</td>
</tr>
<tr>
<td>ΔHR standing (mmHg)</td>
<td>7 ± 2</td>
<td>8 ± 4</td>
<td></td>
</tr>
<tr>
<td>SA ratio</td>
<td>1.1 ± 0.04</td>
<td>1.2 ± 0.09</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>Valsalva phase II (mmHg)</td>
<td>−76 ± 14</td>
<td>−52 ± 16</td>
<td>≤20</td>
</tr>
<tr>
<td>Valsalva phase IV (mmHg)</td>
<td>−13 ± 8</td>
<td>−8 ± 9</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>1.1 ± 0.06</td>
<td>1.1 ± 0.06</td>
<td>&gt;1.4</td>
</tr>
<tr>
<td>Hyperventilation (mmHg)</td>
<td>−14 ± 5</td>
<td>−18 ± 8</td>
<td>≤10</td>
</tr>
<tr>
<td>Cold pressor (mmHg)</td>
<td>12 ± 3</td>
<td>23 ± 5</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Handgrip (mmHg)</td>
<td>14 ± 3</td>
<td>23 ± 6</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>

a Blood pressure responses during phase II and phase IV of the Valsalva maneuver are given as the blood pressure change compared with baseline. A negative blood pressure value during phase IV of the Valsalva maneuver indicates that the blood pressure overshoot was absent in most patients. MSA, multiple system atrophy; PAF, pure autonomic failure; SBP, systolic blood pressure; HR, heart rate; ΔSBP, systolic blood pressure change; ΔHR, heart rate change; SA ratio, sinus-arrhythmia ratio.

was severe but probably not complete. Plasma norepinephrine in the supine position was 72 ± 15 pg/ml in PAF and 450 ± 94 pg/ml in MSA. With upright posture, plasma norepinephrine increased to 123 ± 29 and 680 ± 110 pg/ml in PAF and MSA, respectively. Supine plasma renin activity was 0.4 ng/L per h and did not increase adequately with upright standing (0.7 ng/L per h), considering the profound decrease in BP.

Diurnal Variation of Urinary Excretion

Complete urine collections during the night and during the day were obtained in 12 patients (7 with MSA, 5 with PAF). Figure 1 illustrates urinary electrolyte, volume, and creatinine excretion during the day (8 a.m. to 8 p.m.) and during the night (8 p.m. to 8 a.m.) in patients with MSA and PAF. Creatinine clearance was similar during the day and during the night (MSA, 69 ± 8 and 76 ± 9 mg/min during day and night, respectively; PAF, 58 ± 11 and 67 ± 19 mg/min during day and night, respectively). The urine volume excreted during the day was 670 ± 120 ml in MSA and 670 ± 120 ml in PAF. A substantially greater urine volume was excreted during the night (1400 ± 160 ml in MSA, 940 ± 170 ml in PAF, *P <
0.05 for both). Similarly, urinary sodium excretion was increased approximately twofold during the night (MSA, day 0.06 ± 0.008 mmol/mg creatinine [Cr], night 0.13 ± 0.003 mmol/mg Cr; PAF, 0.09 ± 0.035 mmol/mg Cr; night 0.17 ± 0.05 mmol/mg Cr; P < 0.01 for both). In MSA, fractional sodium excretion was greater during the night in six of seven patients (0.38 ± 0.07% during the day and 0.75 ± 0.18% during the night, P = 0.08). In PAF, fractional sodium excretion increased in all patients during the night (0.56 ± 0.17% during the day, 1.0 ± 0.20% during the night, P < 0.01). There was no significant diurnal variation in potassium excretion or fractional potassium excretion. In MSA, electrolyte-free water clearance was not different between day and night (280 ± 90 and 620 ± 190 ml/12 h during day and night, respectively, P = 0.1). In contrast, in PAF, electrolyte-free water clearance was not different between day and night (220 ± 90 and 160 ± 120 ml/12 h during day and night, respectively).

**Hypotensive Effect of Nitroglycerin**

Supine systolic BP at 8 p.m. was 179 ± 5 mmHg before nitroglycerin was applied and 170 ± 7 mmHg before placebo was given. A sufficient hypotensive response was obtained with the first dose of nitroglycerin in nine patients, with the second dose in one patient, and with the third dose in one patient. Figure 2 illustrates the change in systolic BP with nitroglycerin compared with placebo. Nitroglycerin decreased systolic BP during the night substantially (P < 0.01 versus placebo by ANOVA). Compared with placebo, the maximal decrease in systolic BP was 36 ± 10 mmHg 4 h after the nitroglycerin patch was applied. Supine systolic BP at 8 a.m., 2 h after the nitroglycerin patch was removed, was 161 ± 7 mmHg with nitroglycerin and 173 ± 8 mmHg with placebo. The depressor response to nitroglycerin was similar in MSA and PAF patients. Systolic BP after 1 min standing was not significantly different between placebo or nitroglycerin treatment (88 ± 8 and 79 ± 7 mmHg with placebo and nitroglycerin, respectively).

**Hypotensive Effect of Nifedipine**

Supine systolic BP before placebo or nifedipine was similar (172 ± 8 mmHg with placebo, 163 ± 7 mmHg with nifedipine, P = 0.2). Figure 3 illustrates the changes in systolic BP with nifedipine and placebo. Nifedipine rapidly and profoundly decreased supine systolic BP (P < 0.001 versus placebo by ANOVA). The maximal decrease in systolic BP compared with placebo was 37 ± 9 mmHg (4 h after medication administration). The depressor effect was sustained throughout the night. At 8 a.m., 12 h after nifedipine was given, the decrease in systolic BP compared with baseline was still 23 ± 7 mmHg greater with nifedipine than with placebo (P < 0.05). The depressor response to nifedipine was similar in MSA and in PAF. With nifedipine, three of 10 patients were not able to stand up at 8 a.m. due to severe orthostatic symptoms (versus one patient with placebo). In the patients who were able to stand up, upright BP tended to be lower with nifedipine (91 ± 12 mmHg with placebo, 77 ± 3 mmHg with nifedipine). One patient with PAF and orthostatic symptoms but no prior history of frank syncope did lose consciousness while getting out of bed the morning after nifedipine.

**Urinary Excretion with Nifedipine and Nitroglycerin**

Table 2 gives the results of the overnight urine collections with nitroglycerin and placebo. Urinary output during the night and potassium excretion were similar with nitroglycerin and placebo. Creatinine clearance during the night was 62 ± 9 and 53 ± 5 ml/min with placebo and nitroglycerin, respectively (P = 0.3). Furthermore, there was no difference in sodium excretion (0.13 ± 0.02 mmol/mg Cr versus 0.15 ± 0.03 mmol/mg Cr with placebo) or fractional excretion of sodium (0.8 ± 0.1% versus 0.9 ± 0.2% with placebo). Nocturnal sodium excretion in seven patients who had a depressor re-

![Figure 2](image-url)  
**Figure 2.** Change in systolic BP (ΔSBP) with placebo and nitroglycerin patch (NTG) in autonomic failure patients. The medication was applied at 8 p.m. (0 h on the graph). The horizontal bar indicates the time the patch remained on the skin. Compared with placebo, the maximal decrease in SBP with nitroglycerin was 36 ± 10 mmHg 4 h after the patch was applied. Supine SBP at 8 a.m., 2 h after the nitroglycerin patch was removed, was similar with nitroglycerin and placebo.

![Figure 3](image-url)  
**Figure 3.** Change in systolic BP (ΔSBP) with placebo and nifedipine in autonomic failure patients. Medications were given at 8 p.m. (0 h on the graph). Nifedipine rapidly and profoundly decreased supine SBP. The maximal decrease in SBP compared with placebo was 37 ± 9 mmHg 4 h after medication administration. The depressor effect was sustained throughout the observation period.
response to the first nitroglycerin dose was 0.16 ± 0.04 and 0.12 ± 0.02 mmol/mg Cr with placebo and nitroglycerin, respectively (P = 0.4). In contrast, nifedipine substantially increased urinary sodium excretion during the night (0.35 ± 0.06 mmol/mg Cr [placebo, 0.13 ± 0.02 mmol/mg Cr]) and urine volume (Table 3). Fractional sodium excretion was increased twofold with nifedipine. Creatinine clearance during the night was 63 ± 10 and 48 ± 6 ml/min with placebo and nifedipine, respectively (P = 0.15). Figure 4 illustrates the relation between the depressor response to nifedipine or nitroglycerin and the change in urinary sodium excretion with each intervention. Six of seven patients had an increase in nocturnal sodium excretion with nifedipine. In contrast, only three of nine patients had an increase in urinary sodium excretion with nitroglycerin. Contrary to our initial hypothesis that BP reduction with nitroglycerin and oral nifedipine applied at bedtime decreases supine BP in patients with autonomic failure. However, none of the interventions prevented the pressure natriuresis during the night. Instead, nifedipine substantially increased the nocturnal sodium loss. Nifedipine, but not nitroglycerin, worsened orthostatic tolerance in the morning.

Coexistence of both supine hypertension and orthostatic hypotension in autonomic failure results from disordered short-term and long-term BP control. The impairment of short-term BP control is caused by a profound reduction in sympathetic and parasympathetic efferent function (11,12). Because sympathetic stimulation of the kidney causes renin release and provides an important trophic stimulus for renin generation, plasma renin activity is inappropriately low in most autonomic failure patients (13,14). Loss of sympathetic and parasympathetic efferent function is equivalent to interruption of the efferent arc of the baroreflex. In addition, patients with MSA may also have dysfunction of the afferent arc of the baroreflex (15).

Interruption of efferent (16) and afferent arc (17) of the baroreflex leads to a dramatic increase in the sensitivity to pressor and depressor stimuli. Therefore, autonomic failure is associated with impaired baroreflex buffering and extreme sensitivity to changes in vascular tone (18,19) or volume status (20). This brittleness of BP control is illustrated by the observation that some hemodynamic “stressors” that would be considered trivial in healthy subjects cause dramatic changes in BP in autonomic failure (21). For example, food intake, environmental heat, and exercise acutely decrease BP in autonomic failure patients. In contrast, water drinking elicits a potent and acute pressor effect in many autonomic failure patients (22).

Table 2. Effect of nitroglycerine patch on nocturnal urine excretion (n = 9)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nitroglycerine Patch</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml/12 h)</td>
<td>870 ± 170</td>
<td>880 ± 120</td>
</tr>
<tr>
<td>Creatinine (mg/12 h)</td>
<td>430 ± 52</td>
<td>470 ± 54</td>
</tr>
<tr>
<td>Ccr (ml/min)</td>
<td>53 ± 5.0</td>
<td>62 ± 9</td>
</tr>
<tr>
<td>Na/creatinine (mmol/mg)</td>
<td>0.13 ± 0.02</td>
<td>0.15 ± 0.03</td>
</tr>
<tr>
<td>K/creatinine (mmol/mg)</td>
<td>0.04 ± 0.004</td>
<td>0.05 ± 0.006</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>8.2 ± 0.85</td>
<td>8.7 ± 1.1</td>
</tr>
<tr>
<td>C\text{e}_{CH\text{2}O} (ml/12 h)</td>
<td>303 ± 100</td>
<td>290 ± 54</td>
</tr>
</tbody>
</table>

* Abbreviations as in Table 2.

Table 3. Effect of nifedipine on nocturnal urine excretion (n = 7)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nifedipine (30 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td>1300 ± 204</td>
<td>840 ± 110</td>
</tr>
<tr>
<td>Creatinine (mg/12 h)</td>
<td>390 ± 25</td>
<td>520 ± 76</td>
</tr>
<tr>
<td>Ccr (ml/min)</td>
<td>48 ± 6</td>
<td>63 ± 10</td>
</tr>
<tr>
<td>Na/creatinine (mmol/mg)</td>
<td>0.35 ± 0.06</td>
<td>0.13 ± 0.02b</td>
</tr>
<tr>
<td>K/creatinine (mmol/mg)</td>
<td>0.08 ± 0.01</td>
<td>0.04 ± 0.004b</td>
</tr>
<tr>
<td>FENa (%)</td>
<td>2.1 ± 0.4</td>
<td>0.9 ± 0.2b</td>
</tr>
<tr>
<td>FEK (%)</td>
<td>15 ± 2.5</td>
<td>8.2 ± 1.3b</td>
</tr>
<tr>
<td>C\text{e}_{CH\text{2}O} (ml/12 h)</td>
<td>170 ± 126</td>
<td>210 ± 63</td>
</tr>
</tbody>
</table>

A Ccr , creatinine clearance; FENa , fractional excretion of sodium; FEK , fractional excretion of potassium; C\text{e}_{CH\text{2}O}, electrolyte-free water clearance.
Thus, a relatively small increase in vascular tone or plasma volume could cause a substantial increase in supine BP.

Supine hypertension does not seem to be caused by an increase in plasma volume (3). Nevertheless, sodium retention can exacerbate supine hypertension (5). In PAF patients, supine hypertension seems to be driven by an increase in systemic vascular resistance (23); there are insufficient data on the hemodynamics of supine hypertension in MSA. However, excessive coldness of the hands in MSA might be suggestive of excessive peripheral vasoconstriction (24). It has been speculated that the increase in systemic vascular resistance in severe autonomic failure is probably not mediated by the sympathetic nervous system or the renin-angiotensin-aldosterone system because these pressor systems are severely impaired (3). This hypothesis, however, needs to be reevaluated because recent studies suggest that residual autonomic function is retained in most autonomic failure patients (25). Indeed, several patients in the present study had a normal BP response to cold pressor and hand-grip testing, despite severe orthostatic hypotension, consistent with residual sympathetic activity.

Loss of autonomic function not only makes patients extremely volume-sensitive, it also causes fluctuations in volume status (6). These diurnal changes in volume status seem to be related to large fluctuations in systemic BP with exaggerated pressure natriuresis. An increase in atrial natriuretic factor (26) or mineralocorticoid deficiency (27) seems to be less important. Increased natriuresis during the night and sodium retention during the day might be considered appropriate but are nevertheless insufficient responses to achieve BP control. However, the sodium loss overnight is maladaptive in that it leads to worsened orthostatic hypotension the next morning. Similarly, sodium retention during the day would exacerbate supine hypertension.

Nifedipine and nitroglycerin decrease supine BP substantially in patients with autonomic failure. In contrast, minoxidil and hydralazine are relatively ineffective in the treatment of supine hypertension (3). A further increase in sodium excretion during the night would complicate control of orthostatic hypotension. Conversely, pharmacologic reduction in pressure natriuresis would theoretically improve daytime orthostatic hypotension. Therefore, the effect of antihypertensive medications on urinary sodium handling is an important study end point.

Nifedipine and other dihydropyridine calcium channel blockers cause vasodilation through blockade of vascular calcium channels. In addition to this vascular effect, they have been reported to increase renal sodium excretion independent of a hemodynamic effect through a decrease in tubular reabsorption (28–31). In our study, nifedipine caused an increase in urinary sodium excretion and an increase in fractional sodium excretion. Although statistically not significant, there seemed to be a reduction in creatinine clearance during the night with nifedipine. These findings suggest that nifedipine substantially decreased tubular reabsorption of sodium. With intact function of the autonomic nervous system and the renin-angiotensin-aldosterone system, the sodium loss with nifedipine can be attenuated through a compensatory increase in sodium reabsorption at the proximal (α1-adrenoreceptor-mediated) and distal tubules (renin-angiotensin-aldosterone system) (28). Both, sympathetic nervous system responses and release of plasma renin activity with hypotensive stimuli were impaired in the patients in this study. Therefore, dysfunction of both of these compensatory mechanisms is one possible explanation for the substantial increase in sodium excretion with a single dose of nifedipine. Our study suggests that the relative contribution of vasodilatation and increased sodium excretion to the BP-lowering effect of nifedipine may depend on the degree of autonomic impairment. For example, the depressor effect of immediate release nifedipine was sustained for more than 12 h, although the plasma half-life of the nifedipine preparation used was only 2 h. These observations suggest that in patients with autonomic failure, increased sodium excretion contributes significantly to the depressor effect of nifedipine.

Nitric oxide is important in the regulation of renal sodium excretion and has been suggested to mediate pressure natriuresis (32,33). The mechanism by which nitric oxide increases sodium excretion is imperfectly understood but may involve changes in kidney perfusion, changes in sodium uptake from the tubular lumen, and, perhaps, a decrease in Na-K-ATPase activity (33,34). Therefore, nitric oxide donors have the potential to increase renal sodium excretion in animals (33). With the substantial decrease in BP obtained with nitroglycerin in the present study, one might expect a concomitant decrease in urinary sodium excretion. However, urinary sodium excretion was similar with placebo and the nitroglycerin patch. This finding might suggest that the beneficial effect of BP reduction on urinary sodium excretion is in part offset by a direct effect of nitroglycerin on renal sodium handling, which has not been previously recognized in human studies. An alternative explanation for this finding is that there is some other cause of nocturnal natriuresis that is unaffected by BP reduction with nitroglycerin.

Although potent agents for the treatment of supine hypertension are available, their role in the management of autonomic failure patients has not been defined (3). It is not known whether supine hypertension in autonomic failure is associated with excess cardiovascular morbidity, and these data will be difficult to obtain given the low prevalence of primary autonomic failure. However, a relatively large proportion of patients in this study had some evidence for coronary artery disease, cerebrovascular disease, or left ventricular hypertrophy. Because the life expectancy of patients with MSA is rather limited (35), cardiovascular long-term complications of supine hypertension are less of a concern than in PAF. All pharmacologic treatments of supine hypertension will increase orthostatic hypotension during the night. Thus, patients have to be advised to use great caution if they must get up during the night, and pharmacologic treatment of supine hypertension may not be prudent in patients who are not able to follow these instructions. Despite these difficulties, pharmacologic treatment of supine hypertension is useful in selected patients with supine hypertension. In these patients, the use of antihypertensive medications overnight permits the use of long-acting pressor agents such as fludrocortisone (36) and erythropoietin (37).
for the treatment of disabling orthostatic hypotension. Our results suggest that the nitroglycerin patch has an advantage over nifedipine, because it does not increase sodium excretion during the night. Moreover, the nitroglycerin patch, when removed 2 h before arising, does not seem to worsen orthostatic hypotension in the morning.

We conclude that nifedipine and nitroglycerin patch decrease supine BP overnight in patients with autonomic failure. However, the duration of the depressor effect of nifedipine is prolonged, which worsens orthostatic hypotension in the morning. The decrease in urinary sodium excretion that would be expected with the substantial decrease in BP obtained with nitroglycerin and nifedipine may be offset by a direct effect of both drugs on renal sodium handling.

Acknowledgments

This work was supported in part by National Institutes of Health Grants RR00095, 1PO1 HL56693, and 1UO1 NS 33460, and the Nathan Blaser Shy-Drager Research Program. Dr. Jordan is supported by the Deutsche Forschungsgemeinschaft.

References

31. Luft FC, Fineberg NS, Weinberger MH: Long-term effect of nifedipine and hydrochlorothiazide on blood pressure and so-
dium homeostasis at varying levels of salt intake in mildly hypertensive patients. Am J Hypertens 4: 752–760, 1991


