Sympathetically Mediated Hypertension in Autonomic Failure

John R. Shannon, MD; Jens Jordan, MD; Andre Diedrich, MD; Bojan Pohar,† MD; Bonnie K. Black, BSN; David Robertson, MD; Italo Biaggioni, MD

Background—Approximately 50% of patients with primary autonomic failure have supine hypertension. We investigated whether this supine hypertension could be driven by residual sympathetic activity.

Methods and Results—In patients with multiple system atrophy (MSA) or pure autonomic failure (PAF), we studied the effect of oral yohimbine on seated systolic blood pressure (SBP), the effect of ganglionic blockade (with trimethaphan) on supine SBP and plasma catecholamine levels, and the effect of α₁-adrenoreceptor blockade (phentolamine) on supine SBP. The SBP response to yohimbine was greater in patients with MSA than in those with PAF (area under the curve, 2248±543 versus 467±209 mm Hg · min; P=0.022). MSA patients with a higher supine SBP had a greater response than those with a lower supine SBP (3874±809 versus 785±189 mm Hg · min; P=0.0017); this relationship was not seen in PAF patients. MSA patients had a marked depressor response to low infusion rates of trimethaphan; the response in PAF patients was more variable. Plasma norepinephrine decreased in both groups, but heart rate did not change in either group. At 1 mg/min, trimethaphan decreased supine SBP by 67±8 and 12±6 mm Hg in MSA and PAF patients, respectively (P<0.0001). Cardiac index and total peripheral resistance decreased in MSA patients by 33.4±5.8% and 40.7±9.5%, respectively (P=0.0015). Patients having a depressor response to trimethaphan also had a depressor response to phentolamine. In MSA patients, the pressor response to yohimbine and the decrease in SBP with 1 mg/min trimethaphan were correlated (r=0.98; P=0.001).

Conclusions—Residual sympathetic activity drives supine hypertension in MSA. It contributes to, but does not completely explain, supine hypertension in PAF. (Circulation. 2000;101:2710-2715.)

Key Words: nervous system, autonomic • hypertension • trimethaphan • phentolamine • norepinephrine

Autonomic failure is characterized by orthostatic hypotension with an inadequate heart rate response and bowel, bladder, and erectile dysfunction. The primary autonomic failure syndromes, pure autonomic failure (PAF) and multiple system atrophy (MSA), can be distinguished by the presence (in MSA) or the absence (in PAF) of motor system degeneration, but both are associated with disabling orthostatic hypotension. It is less well appreciated, however, that half of these patients are hypertensive when supine. Supine hypertension complicates the treatment of autonomic failure by limiting the use of pressor agents and by causing a pressure diuresis, which exacerbates orthostatic symptoms. Understanding the mechanism of this paradoxical hypertension in the setting of profound loss of sympathetic function will improve our approach to the treatment of hypertension in autonomic failure, and it could also contribute to our understanding of hypertension in general.

Supine hypertension in patients with PAF seems to be driven by an increase in systemic vascular resistance, but the mechanisms responsible are not known. Plasma renin activity is low and unresponsive. Because sympathetic function is severely impaired, it seems an unlikely culprit. However, this possibility cannot be dismissed outright. It is conceivable, for example, that the pressor effect of residual sympathetic tone could be magnified by a combination of postsynaptic receptor hypersensitivity and the loss of baroreflex restraint. Plasma norepinephrine levels, an index of global sympathetic tone, can be extremely low in patients with PAF but only slightly reduced in those with MSA. Thus, residual sympathetic tone could be an important contributor to supine hypertension, particularly in MSA patients.

We hypothesized that residual sympathetic function indeed contributes to supine hypertension in patients with severe autonomic failure and that this effect is more prominent in patients with MSA than in those with PAF. We used complementary approaches to test this hypothesis. First, we reasoned that if residual sympathetic tone were present, patients should respond to yohimbine, an α₁-antagonist that acts primarily by enhancing central sympathetic tone and peripheral norepinephrine release. Second, we posited that if sympathetic tone contributes to supine hypertension, interrupting sympathetic transmission or blocking the effect of released norepinephrine should reduce supine blood pressure.
Methods

Study Subjects
We studied a total of 38 patients with autonomic failure: 23 had MSA (9 women and 14 men aged 66±1 years), and 15 had PAF (7 women and 8 men aged 70±3 years). Patients with secondary causes of autonomic failure were excluded. Written, informed consent was obtained before study entry. All studies were approved by the institutional review board.

Protocol
Patients were admitted to the Vanderbilt University General Clinical Research Center. Vasopressors and medications and fluid coticortisone were discontinued ≥5 half-lives before testing. Patients were placed on a diet with 150 mEq of sodium and 70 mEq of potassium that was free of substances which could interfere with catecholamine measurements. Studies were conducted ≥2.5 hours after a meal. All blood samples were drawn from an antecubital heparin lock placed ≥30 minutes before the time of sampling. We determined supine and upright blood pressure, heart rate, and plasma catecholamine levels and assessed autonomic cardiovascular reflexes. In 19 MSA patients (7 women and 12 men aged 66±1 years) and 11 PAF patients (5 women and 6 men aged 68±3 years), we determined the seated blood pressure response to oral yohimbine. In a subgroup of patients with supine hypertension (10 with MSA [5 women and 5 men aged 67±1 years] and 9 with PAF [6 women and 3 men aged 75±3 years]), we assessed the response to trimethaphan and/or phenolamine.

Supine and Upright Blood Pressure, Heart Rate, And Plasma Catecholamines
Blood pressure and heart rate were measured after the patients had spent the night in a supine position and then after they spent 3 minutes standing. Plasma catecholamine levels were determined after the patients spent the night in the supine position and then after they spent 30 minutes in the upright position. Patients were instructed to stand motionless as long as possible during the standing period, but if symptomatic, they were permitted to walk or sit briefly until orthostatic symptoms abated.

Autonomic Reflex Testing
Heart rate and beat-to-beat blood pressure were determined by continuous ECG and photoplethysmography, respectively. Respiratory sinus arrhythmia was assessed during controlled breathing (5-second inhalation and 5-second exhalation). The sinus arrhythmia ratio was calculated as the ratio of the longest to the shortest RR-interval during controlled breathing. The blood pressure response to hyperventilation for 30 seconds was determined. Blood pressure and heart rate responses to the Valsalva maneuver, isometric handgrip, and the cold pressor test were assessed.

Oral Medication Trial With Yohimbine
Patients were studied seated in a chair. Brachial blood pressure and heart rate were determined every 5 minutes by an automated cuff (Dinamap, Critikon). After a 30-minute baseline measurement, 5.4 mg of yohimbine (Goldline) was administered orally, and blood pressure was monitored beat-to-beat by photoplethysmography and determined manually with a brachial cuff for subsequent analysis. After the subject had rested quietly for ≥20 minutes, sympathetic and parasympathetic ganglia were blocked by continuous infusion of the Nα-cholinergic antagonist trimethaphan (Trimetaphan, Cambridge Labs). The infusion was initiated at 0.5 or 1 mg/min and increased in 6-minute intervals to one of the following end points: presyncopal symptoms, no further decrease in blood pressure with increased infusion rates, or an infusion rate of 12 mg/min. Blood was obtained before and after the infusion. Plasma was analyzed for catecholamines by high-pressure liquid chromatography. During trimethaphan infusion in 10 subjects (7 with MSA and 3 with PAF), changes in cardiac index were estimated by segmental body impedance (Body Impedance Measurement Device, Heinemann & Gregory) using the first derivative of torso impedance.

α-Adrenoreceptor Blockade
Six patients (2 with MSA and 4 with PAF) tested with trimethaphan were also tested with phenolamine. Heart rate was determined with continuous ECG. Blood pressure was monitored continuously by photoplethysmography but measured for analysis with a brachial cuff. After a 20-minute baseline measurement, intravenous phenolamine (Regitine, Ciba Labs) was administered in incremental bolus doses (0.5, 1.0, 2.0, and 4.0 mg) at 3-minute intervals.

Results

Autonomic Reflex Testing
With standing, SBP decreased by 76±10 and 78±7 mm Hg in PAF and MSA patients, respectively (Table). Respiratory sinus arrhythmia and the Valsalva heart rate ratios were markedly attenuated, indicating impaired parasympathetic innervation to the heart. Impaired sympathetic function was evident by the profound decrease in SBP during phase II of the Valsalva maneuver, the absence of blood pressure overshoot during phase IV, the reduced response to the cold pressor and handgrip stimuli, and the depressor effect of hyperventilation. The severity of parasympathetic and sympathetic dysfunction in the 2 groups of patients was not different.

Response of Seated Blood Pressure to Yohimbine
Yohimbine increases blood pressure by increasing central sympathetic nervous system outflow and by increasing peripheral norepinephrine release. If supine hypertension is driven by residual sympathetic tone, then yohimbine should cause a greater blood pressure increase in patients with supine hypertension than in those without it, and this relationship should be stronger in patients with MSA than in those with PAF. The increase in SBP was indeed greater in MSA patients than in PAF patients (2248±543 versus 467±209 mm Hg·min; P=0.022; Figure 1a).

MSA and PAF patients were then subdivided into 2 groups on the basis of supine SBP. In MSA patients, the median value was 162 mm Hg; the 10 patients at and below the median had a mean of 148±4 mm Hg (range, 116 to 162 mm Hg), whereas the mean of the 9 patients above the median value was 181±4 mm Hg (range, 168 to 202 mm Hg; P<0.0001). The pressor response to yohimbine was significantly greater in patients with a higher supine blood pressure (3874±809 versus 785±189 mm Hg·min; P=0.0017; Figure 1b). The median value among the 11 PAF patients was 142 mm Hg; the means
Results of Autonomic Reflex Testing

<table>
<thead>
<tr>
<th></th>
<th>PAF (n=15)</th>
<th>MSA (n=23)</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70±3</td>
<td>66±2</td>
<td></td>
</tr>
<tr>
<td>Male:female ratio</td>
<td>8:7</td>
<td>14:9</td>
<td></td>
</tr>
<tr>
<td>ΔSBP while standing, mm Hg</td>
<td>−76±10</td>
<td>−78±7</td>
<td>&lt;−20</td>
</tr>
<tr>
<td>ΔHR while standing, bpm</td>
<td>7±3</td>
<td>12±2</td>
<td></td>
</tr>
<tr>
<td>SA ratio</td>
<td>1.1±0.03</td>
<td>1.1±0.01</td>
<td>&gt;1.2</td>
</tr>
<tr>
<td>ΔSBP in Valsalva phase II, mm Hg</td>
<td>−67±7</td>
<td>−72±5</td>
<td>&lt;−20</td>
</tr>
<tr>
<td>ΔSBP in Valsalva phase IV, mm Hg</td>
<td>−10±5</td>
<td>−10±3</td>
<td>&gt;20</td>
</tr>
<tr>
<td>Valsalva HR ratio</td>
<td>1.1±0.03</td>
<td>1.2±0.03</td>
<td>&gt;1.4</td>
</tr>
<tr>
<td>ΔSBP with hyperventilation, mm Hg</td>
<td>−23±8</td>
<td>−21±4</td>
<td>&lt;−10</td>
</tr>
<tr>
<td>ΔSBP with cold pressor, mm Hg</td>
<td>8±4</td>
<td>6±4</td>
<td>&gt;20</td>
</tr>
<tr>
<td>ΔSBP with handgrip, mm Hg</td>
<td>11±6</td>
<td>10±3</td>
<td>&gt;15</td>
</tr>
</tbody>
</table>

HR indicates heart rate; SA ratio, sinus arrhythmia ratio.

among those below and above the median were 114±10 mm Hg (range, 81 to 142 mm Hg; n=6) and 175±6 mm Hg (range, 157 to 191 mm Hg; n=5), respectively (P<0.005). In contrast to MSA patients, no significant difference existed in the response to yohimbine between the 2 PAF subgroups (Figure 1b).

Hemodynamic Effects of Ganglionic Blockade

To test the hypothesis that residual sympathetic tone supports supine blood pressure, we measured the decrease in SBP after the removal of residual sympathetic tone with trimethaphan. All MSA patients had a marked depressor response at relatively low infusion rates of trimethaphan (range, −60 to −130 mm Hg; Figure 2a). The decrease in SBP in response to trimethaphan was more variable in PAF patients (range, −10 to −84 mm Hg; Figure 2b). In one patient, the trimethaphan infusion was stopped because SBP increased by 43 mm Hg. This unusual patient had a normal sinus arrhythmia and a heart rate increase from 45 to 73 bpm with trimethaphan, indicating preserved parasympathetic innervation to the heart.

The maximal decrease in SBP was 90±8/42±6 mm Hg in MSA patients (P<0.0001) and 35±13/11±8 mm Hg in PAF patients (P=0.026). A lower rate of trimethaphan infusion was needed in MSA patients (compared with PAF patients) to obtain the maximal decrease (3.5±0.8 versus 9.3±1.1 mg/min; P=0.0003). At a rate of 1 mg/min, SBP decreased by 67±8 and 12±6 mm Hg in MSA and PAF patients, respectively (P<0.0001 between groups; Figure 2c). In neither group did heart rate change significantly; heart rates before and after the infusion, respectively, were 78±3 and 78±5 bpm in MSA patients and 65±3 and 69±2 bpm in PAF patients.

Plasma Catecholamines

Baseline plasma norepinephrine concentrations were greater in MSA patients than in PAF patients (376±70 versus 124±26 pg/mL; P=0.003), as reported previously. With the trimethaphan infusion, the plasma norepinephrine concentration decreased in all patients. Individual changes are illustrated in Figure 3. The plasma norepinephrine concentration decreased from 124±26 to 58±16 pg/mL (P=0.03) in PAF patients at the end of the infusion (9.3±1.2 mg/min). A similar decrease (from 180±20 to 39±8 pg/mL) was observed in normal subjects receiving trimethaphan at 6 to 8 mg/min. Plasma norepinephrine concentrations also decreased in MSA patients (from 376±70 to 210±69 pg/mL; P=0.0006), but the final infusion rate (3.5±0.8 mg/min) was limited by profound hypotension. Plasma norepinephrine concentrations tended to be correlated with the decrease in blood pressure at 1 mg/min in PAF.
patients ($r=0.69; P=0.055; n=8$) but not in MSA patients ($r=0.17; P=NS; n=7$).

### Effects of Trimethaphan on Cardiac Output and Peripheral Resistance
Changes in cardiac index and total peripheral resistance during trimethaphan infusion were estimated in 7 MSA and 3 PAF patients. Cardiac index and total peripheral resistance decreased in all MSA patients by $33.4\pm5.8\%$ and $40.7\pm9.5\%$, respectively (Figure 4; $P=0.0015$ for both). These trends were not observed in the 3 PAF patients.

### Hemodynamic Effects of Phentolamine
To confirm that the blood pressure response to trimethaphan was due to the blockade of sympathetic traffic rather than some other mechanism, we administered incremental doses of phentolamine to 6 patients (4 with PAF and 2 with MSA). With a cumulative phentolamine dose of $5.0\pm0.8$ mg, SBP decreased by $30\pm9/12\pm6$ mm Hg ($P<0.05$) in all patients. Five patients who had a depressor response to trimethaphan had a similar response to phentolamine. The patient whose blood pressure did not decrease with trimethaphan did not respond to phentolamine either.

### Pressor Effect of Yohimbine in Trimethaphan Recipients
In MSA patients, a strong correlation existed between the pressor response to yohimbine and the decrease in SBP with 1 mg/min trimethaphan ($r=0.98; P=0.001; n=6$), but no such correlation was observed in PAF patients ($r=0.06, P=NS, n=4$).
Discussion

The novel finding of this study is that in MSA patients, blood pressure decreases profoundly with low doses of the ganglionic blocker trimethaphan or with the α₁-adrenoreceptor antagonist phentolamine. This decrease in blood pressure is due to a decrease in both cardiac output and peripheral resistance. Larger doses of trimethaphan are necessary to evoke a milder depressor response in PAF patients. The depressor response to trimethaphan in all MSA patients and in several PAF patients was substantially greater than the ≈25 mm Hg decrease in SBP previously reported in normal, healthy subjects of a similar age.16

The depressor effect of trimethaphan is primarily due to the blockade of postsynaptic N₂-cholinergic receptors in autonomic ganglia, which results in an interruption of sympathetic and parasympathetic traffic.17 Some have suggested that a direct vasodilatory effect and histamine release may contribute to the depressor effect of trimethaphan. However, the concentrations of trimethaphan needed for direct vasodilation in vitro are 10 to 100 times greater than those necessary to achieve ganglionic blockade,18,19 and histamine release does not seem to contribute to the hypotensive effect of trimethaphan with continuous infusion.20 Complimentary findings in this study support the conclusion that the decrease in blood pressure with trimethaphan in patients with autonomic failure, especially those with MSA, was due to the blockade of sympathetic traffic. These findings include the following: trimethaphan decreased plasma norepinephrine concentrations in all patients tested, the response to trimethaphan correlated with the response to phentolamine, and those patients who had a greater depressor response to trimethaphan had a greater pressor response to yohimbine.21

These results indicate that residual sympathetic tone is present in MSA patients and that it mediates supine hypertension, despite the profound orthostatic hypotension and autonomic reflexes consistent with profound autonomic failure. The contribution of residual sympathetic tone to supine hypertension in PAF patients seems to be less uniform. The correlation of supine norepinephrine concentration to the decrease in blood pressure with trimethaphan in PAF patients, however, supports the idea that residual sympathetic tone is contributory. The lack of this correlation in MSA patients may be due to a combination of factors. Plasma norepinephrine concentrations were measured at the end of the infusion, when MSA patients were receiving lower doses of trimethaphan than PAF patients. In addition, the decrease in cardiac index observed in MSA patients with no change in heart rate is consistent with decreased venous return and a resultant decrease in norepinephrine clearance causing higher plasma norepinephrine levels.22

Sympathetic tone can increase blood pressure by increasing either cardiac output or peripheral resistance. Therefore, the decrease in blood pressure with trimethaphan could result from a decrease in either of these parameters. Cardiac output is determined by heart rate and stroke volume. Because heart rate did not change during trimethaphan infusion, the decrease in cardiac output must have been due to a decrease in stroke volume, which could result from a decrease in either preload or cardiac contractility. A decrease in venous return (preload) is likely with trimethaphan.23 Because cardiac sympathetic nerves may be intact in MSA patients,24 a withdrawal of sympathetic tone could decrease cardiac contractility as well.

Given the heterogeneity of the response to trimethaphan in PAF patients and the limited number of patients in whom cardiac output data during trimethaphan infusion are available, definitive conclusions about the mechanisms of the depressor response to trimethaphan in this group cannot be made. Because PAF is associated with the loss of cardiac sympathetic innervation25 and the loss of neurons in the intermediolateral columns of the spinal cord,25 perhaps it is surprising that any decrease in blood pressure occurred with the blockade of sympathetic traffic. However, PAF patients demonstrated a modest increase in blood pressure with yohimbine, and previous studies in PAF patients using regional norepinephrine spillover have shown that sympathetic denervation may not be complete in all vascular territories.26 Those PAF patients having a greater decrease in blood pressure with trimethaphan could have less complete denervation.

It is difficult to conceptualize how residual sympathetic function could cause supine blood pressures >200/120 mm Hg. A sympathetically-mediated increase in blood pressure would require an increased norepinephrine release, adrenoreceptor hypersensitivity, impairment of baroreflex buffering, or a combination of these mechanisms. In the supine position, norepinephrine release is decreased in PAF patients,22 but the release in MSA patients is similar to that of normal subjects.24 This difference may result from the fact that in MSA, central nervous system autonomic neurons are primarily affected,27 whereas in PAF, the number of postganglionic sympathetic neurons is significantly reduced.28 Thus, the relative sparing of postganglionic neurons in MSA may explain the greater sensitivity to the hypotensive effect of trimethaphan in MSA patients.

Because hypertension in autonomic failure cannot be explained by increased norepinephrine release, the sensitivity to endogenously-released norepinephrine must be increased. Patients with autonomic failure are hypersensitive to adrenoreceptor agonists.29−31 Adrenoreceptor upregulation may contribute to this hypersensitivity,32 but the loss of baroreflex restraint likely contributes significantly. An interruption of the afferent33 or the efferent34 arc of the baroreflex profoundly increases the sensitivity to pressor agents and vasodilators. Sympathetic and parasympathetic efferents (the efferent arc of the baroreflex) are disrupted in both MSA and PAF. In addition, MSA patients may have dysfunction of afferent baroreflex pathways.35

Supine hypertension in autonomic failure, therefore, results from residual sympathetic tone acting on hypersensitive postsynaptic adrenoreceptors, an action that is unopposed because of a loss of baroreflex restraint. Residual sympathetic tone in MSA, therefore, is inappropriately high for the level of blood pressure. Supine hypertension in PAF can occur, even in the absence of residual sympathetic function, as evidenced by the lack of a depressor response to trimethaphan and phentolamine in some PAF patients. The cause of supine hypertension in these PAF patients remains to be determined.

The findings of this study have important implications for understanding the pathogenesis of hypertension and for the diagnosis and treatment of autonomic failure. It is evident that, even in the setting of severely impaired sympathetic function, hypertension can be driven by the sympathetic nervous system. It is difficult to assess the role of the sympathetic nervous system...
in the pathogenesis of hypertension using standard cardiovascular autonomic reflex tests, plasma catecholamines, or even such techniques as microneurography and norepinephrine spillover. As illustrated in this study by the observation that patients with PAF and MSA had similar responses to autonomic reflex tests yet markedly different sensitivities to the depressor effect of trimetaphan, these techniques can be useful in characterizing autonomic function, but misleading in the setting of abnormal baroreflex buffering and adrenoreceptor sensitivity.

Ganglionic blockade permits a distinction between patients with and without residual sympathetic function. In patients who have residual sympathetic function, as indicated by a depressor response to trimetaphan, orthostatic hypotension could be treated with medications that raise sympathetic tone (eg, yohimbine),31 and supine hypertension could be treated with medications that either decrease sympathetic tone or block a1-adrenergic receptors. Patients who fail to have a significant depressor response with trimetaphan infusion, indicating minimal residual sympathetic activity, are not likely to respond to medications that modulate sympathetic tone. In this group of patients, direct vasoconstrictors (eg, phenylephrine, indicating minimal residual sympathetic activity, are not useful in treating the symptoms of orthostatic hypotension, and direct vasodilators (eg, transdermal nitroglycerin) would be a reasonable choice for the treatment of supine hypertension. There is often reluctance to treat supine hypertension in autonomic failure patients. However, recent studies suggest that end-organ damage does occur in these patients.36

We conclude that even in patients with severe autonomic impairment, hypertension can be driven by the sympathetic nervous system. In patients with MSA, residual sympathetic activity is the cause of supine hypertension. In patients with PAF, residual sympathetic activity contributes significantly to supine hypertension in some, but it does not completely explain supine hypertension in all of these patients. The hypersensitivity to the depressor effect of ganglionic blockers in patients with MSA may also be useful to help distinguish them from PAF.

Acknowledgments

This work was supported in part by National Institutes of Health grants RR00095, 1PO1 HL56693, and 1U01 NS 33460 and by the Nathan Blaser Shy-Drager Research Program. Dr Jordan is supported by the Deutsche Forschungsgemeinschaft.

References

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Circulation. 2000;101:2710-2715
doi: 10.1161/01.CIR.101.23.2710

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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