Clonidine for the Treatment of Supine Hypertension and Pressure Natriuresis in Autonomic Failure

Cyndya Shibao, Alfredo Gamboa, Robert Abraham, Satish R. Raj, Andre Diedrich, Bonnie Black, David Robertson, Italo Biaggioni

Abstract—Patients with autonomic failure are disabled by orthostatic hypotension, which can be worsened by the nighttime pressure natriuresis induced by associated supine hypertension. Several pharmacological agents are available that effectively reduce nighttime hypertension, but none of them prevent pressure natriuresis. Because hypertension of autonomic failure can be driven by residual sympathetic tone, we hypothesized that clonidine would be effective in reducing blood pressure (BP) and nocturnal natriuresis. Therefore, we determined the effect of placebo, 0.1 mg clonidine, and 0.1-mg/h nitroglycerin transdermal patch on supine BP, orthostatic hypotension, and pressure natriuresis in 23 patients with primary autonomic failure and supine hypertension. Medications were given at 8:00 PM, and BP was recorded every 2 hours for 12 hours. The maximal decrease in BP was seen 6 to 8 hours after drug administration and was similar to clonidine and nitroglycerin (−29±9 and −30±10 mm Hg, respectively), as was the average fall in BP throughout the night. However, only clonidine effectively reduced nocturnal natriuresis (−0.09 mmol/mg Cr; 95% CI, −0.13 to −0.04; P=0.004), but this was not associated with improvement in morning orthostatic hypotension because of a residual hypotensive effect. The decrease in BP induced by clonidine was modestly but significantly correlated with the magnitude of residual sympathetic tone determined in 10 subjects by the fall in BP induced by ganglionic blockade (r=0.66; P=0.043). These results are consistent with residual sympathetic tone contributing to supine hypertension in autonomic failure, which can be targeted with clonidine to decrease BP and nocturnal natriuresis.

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Key Words: drugs ■ hypertension ■ autonomic nervous system ■ natriuresis

Primary autonomic failure is characterized by severe orthostatic hypotension defined by a fall in systolic blood pressure (BP) of ≥20 mm Hg or diastolic BP of ≥10 mm Hg and accompanied by disabling symptoms of cerebral hypoperfusion. Paradoxically, patients may also experience high BP when supine. Supine hypertension worsens orthostatic hypotension because it induces pressure natriuresis during the night causing volume depletion, can complicate the treatment of orthostatic hypotension because it limits the use of pressor agents during the day, and increases the risk of cardiovascular events and end-organ damage.

Several vasodilators are effective in decreasing BP at night, but none of them decrease nighttime pressure natriuresis or improve orthostatic hypotension the next morning. In many autonomic failure patients, supine hypertension is driven by residual sympathetic tone acting on hypersensitive receptors and unrestrained by the impairment of baroreflex buffering. Therefore, we hypothesized that clonidine, a selective α2-adrenergic agonist that acts centrally to reduce sympathetic outflow, would be effective in reducing supine hypertension and nocturnal natriuresis, resulting in improved orthostatic hypotension the next morning. This study was designed to test this hypothesis.

Methods

Study Subjects
We studied 23 patients with primary autonomic failure. Patients were diagnosed with multiple system atrophy (MSA; 12 patients) or pure autonomic failure (PAF; 11 patients) based on current diagnostic criteria. All of the patients had supine hypertension defined as supine systolic BP >150 mm Hg and/or supine diastolic BP >90 mm Hg. Patients were excluded if they had secondary forms of autonomic failure (eg, diabetes mellitus or amyloidosis) or renal failure. The study was approved by the Institutional Review Board at Vanderbilt University, and all of the participants provided written consent before enrollment.

Protocol
Patients were admitted to the General Clinical Research Center at Vanderbilt University Medical Center. Medications with cardiovascular/autonomic effects were discontinued for ≥5 half-lives before admission. Patients were placed on a metabolic ward and sodium balance. The diet consisted of low monoamine, caffeine-free food containing 150 milliequivalents of sodium and 70 milliequivalents of potassium per day. Studies were conducted ≥2.5 hours after a meal.
The screening consisted of a comprehensive medical history, physical examination, 12-lead ECG, and laboratory assessments. Standardized autonomic function tests were performed to assess the severity of autonomic impairment. These included orthostatic stress test, Valsalva maneuver, the cold pressor test, and handgrip to assess cardiovascular autonomic function and sinus arrhythmia (change in heart rate in response to controlled breathing) to assess cardiac parasympathetic activity. Brachial BP and heart rate during all of these tests were obtained using an automated sphygmomanometer (Dinamap, GE Medical Systems Information Technologies). Blood samples were obtained for catecholamines, renin, and aldosterone measurements while patients were supine and upright. Plasma catecholamine levels were determined by high-performance liquid chromatography with electrochemical detection. 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. Plasma aldosterone was measured by radioimmunoassay.

**Overnight Medication Trials**

We compared the antihypertensive effect of 0.1 mg clonidine PO and 0.1 mg/h transdermal nitroglycerin on overnight supine BP to the effect of placebo. As a secondary end point, we determined changes in pressure natriuresis. The order of the intervention was random. The medication was administered with 50 mL of tap water at 8:00 PM and 2.5 hours after the last meal. Patients were instructed to remain supine throughout the night, fluid intake was restrained, and a research nurse collected urine for 12 hours after drug administration (clonidine, nitroglycerin, or placebo). BP was measured at 2-hour intervals by an automated sphygmomanometer. The nitroglycerin patch was removed at 6:00 AM. At 8:00 AM, patients were asked to stand up as long as tolerated or for up to 10 minutes, and BP and heart rate were measured at 1, 3, 5, and 10 minutes to assess orthostatic tolerance. Nocturnal sodium excretion was determined by the ratio of urinary sodium to urinary creatinine to correct for the incomplete bladder emptying seen in these patients.

**Evaluation of Residual Sympathetic Tone**

We used ganglionic blockade to gauge residual sympathetic tone in 6 patients with MSA and 4 patients with PAF in whom the effect of clonidine on BP and pressure natriuresis was also determined. Patients were studied in the supine position. Heart rate was monitored with continuous ECG. BP was measured with an automated sphygmomanometer. After the subject had rested quietly for ≥20 minutes, autonomic ganglia were blocked by continuous infusion of the N2-cholinergic antagonist trimethaphan (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 additional decrease in BP with increased infusion rates, or an infusion rate of 5 mg/min. The fall in systolic BP induced by autonomic blockade was used to measure the importance of tonic sympathetic modulation of BP.

**Statistics**

Power calculation was based on preliminary data obtained in 5 subjects. The nadir of systolic BP was 138±22 mm Hg during clonidine compared with 175±12 mm Hg during placebo 6 hours after drug administration. A sample size of 16 subjects had an 80% power to detect a difference in means of 17.6 mm Hg assuming that the common SD is 15.6 using a paired t test with 0.05 2-sided significance level (PS Version 2.1.30).

Data are reported as mean±SEM. For continuous variables, differences between groups were compared with the Mann-Whitney U test or Wilcoxon signed-rank test for univariate statistics. A 2-tailed P<0.05 was considered significant. All of the analyses were performed using SPSS for Windows (version 13.0; SPSS).

**Results**

**Patient Clinical Characteristics and Autonomic Function Tests**

The clinical characteristics of the patients are presented in Table. All of the patients were classified as having MSA or PAF based on current diagnostic criteria. Our cohort consisted of patients between 52 and 86 years of age, with an averaged body mass index of 26±1 kg/m². Only 5 patients were females. Hemodynamic responses to posture are shown in Figure 1. Mean systolic and diastolic BP were 170±6/91±2 mm Hg while supine and decreased to 79±4/52±3 mm Hg on standing, respectively. The compensatory increase in heart rate was inadequate considering the profound decrease in BP, indicating failure in baroreflex modulation. In all of the patients, systolic BP decreased significantly during phase II of the Valsalva maneuver (from 159±5 to 88±5 mm Hg; P<0.001) and did not increase as expected during phase IV. Both findings indicate an impaired sympathetic function. Respiratory sinus arrhythmia was reduced (1.1±0.1 mm Hg; normal values, >1.2) consistent with parasympathetic dysfunction. Furthermore, the BP response to the cold pressor test was blunted (6±0.05 mm Hg; normal, >20 mm Hg). As expected, plasma norepinephrine was lower in patients with PAF compared with patients with MSA. Despite the
profound decrease in upright BP, plasma renin activity was low (Table), but plasma aldosterone was preserved, as described previously.13

**Hypotensive Effect of Clonidine and Nitroglycerin**

At baseline (8:00 PM), no significant difference was found in supine systolic BP between placebo (177±6 mm Hg) and clonidine (166±8 mm Hg; *P*=0.148). The maximum decrease in systolic BP induced by clonidine compared with placebo was 26±6 mm Hg (95% CI, −39 to −12; *P*=0.003) and was observed 6 hours after drug administration (Figure 2, top).

Similarly, we found no statistical difference in supine systolic BP between placebo and nitroglycerin at baseline (187±5 and 179±5 mm Hg, respectively; *P*=0.245). The maximum decrease in systolic BP induced by nitroglycerin compared with placebo was 20±6 mm Hg (95% CI, −32 to −7 mm Hg; *P*=0.008) and was observed 8 hours after drug administration (Figure 2, bottom).

**Urinary Sodium Excretion During Clonidine or Nitroglycerin Administration**

The results of the overnight urine collection during nitroglycerin and clonidine administration are represented in Figure 3. Clonidine decreased pressure natriuresis significantly compared with placebo (−0.09 mmol/mg Cr; 95% CI, −0.13 to −0.04; *P*=0.004). In contrast, transdermal nitroglycerin did not significantly decrease pressure natriuresis (−0.02 mmol/mg; *P*=0.388). The average hypotensive effect throughout the night was similar with both interventions.

**Residual Sympathetic Tone**

Residual sympathetic tone was determined in 10 patients who received clonidine and consented to this procedure; 6 had MSA, and 4 had PAF. The average decrease in supine systolic BP induced by clonidine was calculated for the 12-hour data collection. There was a considerable variability in the decrease in supine systolic BP induced by 1 mg/min trimethaphan, an indicator of residual sympathetic tone in these patients.6 We found a significant association between the decrease in systolic BP induced by ganglionic blockade and the average change in systolic BP induced by clonidine compared with placebo (*r*=0.66; *P*=0.043).

**Effect of Treatment on Orthostatic Hypotension**

We determined the effect of treatment on orthostatic tolerance by evaluating the decrease in systolic BP on standing, the morning after the trial was performed. We did not find a statistically significant improvement on orthostatic hypotension after clonidine compared with placebo (−87±6 versus −94±6 mm Hg, respectively; *P*=0.268). The orthostatic decrease in systolic BP was also similar between nitroglycerin and placebo (−91±5 versus −94±9 mm Hg, respectively; *P*=0.677).

**Discussion**

The clinical picture of autonomic failure is dominated by orthostatic hypotension because of its association with syncope and the disability it causes. The consequences of supine
hypertension, which is observed in 50% of patients, are more subtle but equally important. Supine hypertension has been associated with left ventricular hypertrophy, suggesting it can lead to end-organ damage in this patient population. Preliminary observations indicate that long-term prognosis is poorer in patients with autonomic failure and supine hypertension. In addition, supine hypertension can worsen orthostatic hypotension by inducing pressure natriuresis. This explains the observation that patients with autonomic failure lose twice as much urinary volume and sodium at nighttime compared with daytime, a reversal of the normal diurnal rhythm. As a consequence, symptoms of orthostatic hypotension are worse early in the morning in patients with autonomic failure. Treatment of nighttime supine hypertension, therefore, may result in improvement in orthostatic hypotension in the morning.

Indeed, head-up tilt is an effective way to decrease supine hypertension and nighttime diuresis and is associated with improved orthostatic tolerance the next morning. Unfortunately, patients with severe supine hypertension require levels of tilt that are not practically achieved, limiting the usefulness of this approach. It would be ideal, therefore, to identify an antihypertensive agent that would reduce supine BP and pressure natriuresis, inducing a "pharmacological tilt." A drug with a short duration of action would be required so that its antihypertensive effects would wane by the next morning.

We have been unsuccessful in previous studies to find such a drug. Nifedipine and nitroglycerin are effective in reducing BP but do not reduce and may even increase renal sodium excretion through a decrease in tubular reabsorption. In this study we demonstrate that clonidine fulfills some of the characteristic of this ideal drug. It is effective in lowering BP and is the only antihypertensive we have found that reduces nocturnal pressure natriuresis.

We were unable, unfortunately, to demonstrate an improvement in orthostatic tolerance the morning after clonidine administration. It is likely that this is because of residual hypotensive effects of clonidine carried over into the morning, opposing any potential beneficial effect that would be achieved by decreasing nighttime natriuresis. Given that the decrease in BP was delayed, being observed 6 hours after drug administration, clonidine could be given earlier in the day resulting in less residual hypotension in the morning. It may also be possible to counteract any residual effect of clonidine (partial α2-adrenergic receptor agonist) by giving yohimbine (α2-adrenergic receptor antagonist) the next morning. Either approach would require experimental validation before being recommended to patients.

We have shown previously that the pathogenesis of the supine hypertension of autonomic failure depends on the underlying pathophysiology. In MSA, the lesion is in the central nervous system proximal to the origin of sympathetic tone. Therefore, their hypertension is because of residual sympathetic tone unrestrained by the lack of baroreflex buffering. In PAF, the lesion involves postganglionic sympathetic neurons. The cause of the hypertension is not known but is less dependent on sympathetic tone. We expected, therefore, that clonidine would be a more effective antihypertensive in patients with MSA compared with PAF. We were not able, however, to see such a clear difference in this cohort, likely because of the inclusion of PAF patients with some degree of residual sympathetic tone. We find the response to trimethaphan to be a better tool to discriminate the contribution of residual sympathetic tone to supine hypertension. In contrast, we have reported previously on a patient with very severe PAF in whom BP increased with clonidine given at higher doses than those used in the current study. This is likely because of the pressor agonist effect of clonidine on the vascular α2-adrenergic receptor. Indeed, we observed that BP did not change or actually increased modestly in 2 patients with PAF. At the doses used in this study, we do not believe this raises safety concerns but highlights the need to individualize treatment in these patients. This can be achieved in clinical practice using ambulatory BP monitoring.

**Perspectives**

We found that clonidine effectively reduces BP and nighttime natriuresis in patients with supine hypertension and autonomic failure. Responses vary among patients and tend to be less or absent in patients who lack residual sympathetic tone, and, therefore, this treatment needs to be individualized. We were unable to demonstrate improvement of orthostatic tolerance after clonidine treatment. It is possible, but unproven, that clonidine administration earlier in the day or reversal of its actions with morning administration of yohimbine may improve orthostatic tolerance in these patients. Clonidine can be added as an alternative in the individualized management of these patients. Whether or not clonidine would provide a long-term benefit in the management of these patients should be addressed in future studies.

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