Baroreflex Buffering and Susceptibility to Vasoactive Drugs

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Background—The overall effect of vasoactive drugs on blood pressure is determined by a combination of the direct effect on vascular tone and an indirect baroreflex-mediated effect, a baroreflex buffering of blood pressure. Differences in baroreflex function affect the responsiveness to vasoactive medications, particularly baroreflex buffering of blood pressure; however, the magnitude is not known.

Methods and Results—We characterized baroreflex function and responses to vasoactive drugs in patients with idiopathic orthostatic intolerance, patients with essential hypertension, patients with monogenic hypertension and brachydactyly, patients with multiple system atrophy, and control subjects. We used phenylephrine sensitivity during ganglionic blockade as a measure of baroreflex buffering. Phenylephrine (25 µg) increased systolic blood pressure 6±1.6 mm Hg in control subjects, 6±1.1 mm Hg in orthostatic intolerance patients, 18±3.9 mm Hg in patients with essential hypertension, 31±3.4 mm Hg in patients with monogenic hypertension, and 25±3.4 mm Hg in patients with multiple system atrophy. Similar differences in sensitivities between groups were observed with nitroprusside. The sensitivity to vasoactive drugs was highly correlated with baroreflex buffering function and to a lesser degree with baroreflex control of heart rate. In control subjects, sensitivities to nitroprusside and phenylephrine infusions were correlated with baroreflex heart rate control and sympathetic nerve traffic.

Conclusions—Our findings are consistent with an important effect of baroreflex blood pressure buffering on the sensitivity to vasoactive drugs. They suggest that even moderate changes in baroreflex function may have a substantial effect on the sensitivity to vasoactive medications. (Circulation. 2002;105:1459-1464.)

Key Words: baroreceptors • nervous system, autonomic • drugs • blood pressure

Changes in arterial blood pressure elicited by vasoactive drugs are sensed by carotid, aortic, and, perhaps, coronary baroreceptors. The signal generated in these baroreceptors is integrated in cardiovascular control centers in the brain stem and leads to compensatory adjustments in sympathetic and parasympathetic nerve traffic. Application of a vasoconstrictor is associated with a baroreflex-mediated increase in heart rate and sympathetic traffic to the vasculature. In contrast, a vasoconstrictor elicits a decrease in heart rate and sympathetic traffic. Thus, the baroreflex buffers the effect of vasoactive medications. In patients with damage to the afferent arc (baroreflex failure), the sensitivity to phenylephrine and nitroprusside is dramatically increased. Similarly, dysfunction of the efferent baroreflex arc, either caused by neuronal degeneration (autonomic failure) or ganglionic blockade, causes a profound increase in sensitivity to vasodilators and vasoconstrictors. Given the large effect of complete interruption of the baroreflex arc on drug sensitivity, even a moderate change in baroreflex function may have a substantial effect. However, the magnitude of the effect is not known. The purpose of our study was to determine the effect of baroreflex function on the sensitivity to vasoactive medications in healthy subjects and in patients with different degrees of baroreflex impairment. In addition to standard baroreflex tests, we developed a new strategy to assess baroreflex blood pressure buffering function. Finally, we sought to determine if baroreflex control of heart rate and of sympathetic outflow to the vasculature contribute individually to the variability in drug sensitivity and to what degree they influence blood pressure buffering.

Methods

Subjects We studied 15 patients with idiopathic orthostatic intolerance (OH) (14 women, 1 man; age, 34±2.4 years), 7 patients with essential hypertension (4 men, 3 women; age, 52±4.4 years), 5 patients with monogenic hypertension and brachydactyly (3 men, 2 women; age, 26±3.4 years), and 9 patients with a diagnosis of probable multiple system atrophy (MSA) (5 women, 4 men; age, 54±1.3 years). Nine healthy subjects served as the control group (7 women, 2 men; age, 24 to 37 years). Microneurography studies were conducted in 18 healthy subjects (14 women, 4 men; age, 26±6 years).
years). Written informed consent was obtained. The institutional review board approved all studies.

Protocol
Three days before the study, subjects ingested a diet free of substances that could interfere with catecholamine measurements. All vasoactive medications were discontinued at least 5 half-lives before testing. All tests were conducted with the subject recumbent at least 2.5 hours after the last meal. Initially, we determined the sensitivity to bolus application of phenylephrine and nitroprusside in patients and in control subjects. Testing with phenylephrine was repeated during ganglionic blockade. In patients with OI and in control subjects, we also determined the sensitivity to the depressor effect of isoproterenol before and during ganglionic blockade. In a separate study, we assessed the effect of phenylephrine and nitroprusside infusions on blood pressure and muscle sympathetic nerve activity.

Pharmacological Testing Before and During Ganglionic Blockade
Heart rate was determined with continuous ECG. Changes in blood pressure were determined either with an indwelling catheter in the radial artery or with photoplethysmography (Finapres, Ohmeda), which was adjusted to brachial blood pressure measurements. We determined the responses to phenylephrine, nitroprusside, isoproterenol, and trimethaphan, as described previously. Briefly, incremental intravenous bolus doses of nitroprusside, isoproterenol, and phenylephrine were applied before ganglionic blockade. Thereafter, we infused the ganglionic blocker trimethaphan (Cambridge Pharmaceuticals) starting at 1 mg/min. The infusion was increased at 6-minute intervals until the steepest part of the baroreflex was completely blocked. Bolus doses of phenylephrine, isoproterenol, and nitroprusside were then administered just as before blockade.

Pharmacological Testing With Microneurography
Heart rate was determined by continuous ECG and beat-by-beat blood pressure with a Finapres device. Brachial blood pressure was also determined (Dinamap, Critikon). Changes in cardiac stroke volume were determined by impedance cardiography. Muscle sympathetic nerve activity was recorded from the right peroneal nerve. A unipolar tungsten electrode ( uninsulated tip diameter of 1 to 3 μm, shaft diameter of 200 μm) was inserted into the muscle nerve fascicles of the peroneal nerve at the fibular head for multunit recordings. Nerve activity was amplified with a total gain of 100,000, bandpass-filtered (0.7 to 2 kHz), and integrated. After a stable baseline was reached, incremental infusions of sodium nitroprusside and phenylephrine hydrochloride infusions (0.2, 0.4, 0.8, and 1.6 μg/kg per minute over 5 minutes) were given. The infusions were stopped after the maximum dose had been given or after diastolic blood pressure had changed by >15 mm Hg. Phenylephrine sensitivity was determined by extrapolating the dose that would change systolic blood pressure 10 mm Hg from individual dose–response curves. Pharmacological baroreflex sensitivity was determined from the steepest part of the sigmoidal curve obtained during phenylephrine and sodium nitroprusside infusions. The spontaneous baroreflex sensitivity was calculated as the slope of the linear regression lines between the R-R intervals (RR1) and the systolic blood pressure values by use of the sequence technique.

Statistics
All data are expressed as mean±SEM. Intraindividual differences were compared by means of Wilcoxon’s matched pairs test. For comparisons between groups, the Kruskal-Wallis test followed by Dunn’s multiple comparison test was used. The relation between parameters was assessed by linear regression analysis. A value of P<0.05 was considered significant.

Results
Clinical Characteristics
In control subjects, supine blood pressure was 111±3.5/65±2.4 mm Hg. They did not exhibit any signs of autonomic dysfunction. In patients with OI, blood pressure was 110±3.6/66±2.6 mm Hg in the supine position and did not decrease with upright posture. Patients with OI had orthostatic tachycardia with an increase in heart rate by 48±4 bpm after 5 minutes of standing. Supine blood pressure was 162±5.6/92±5.6 mm Hg in patients with essential hypertension and 135±6.7/81±4.6 mm Hg in patients with monogenic hypertension and bradykarydactyly. All 9 patients with MSA had either parkinsonian symptoms or symptoms of cerebellar dysfunction. In this group, systolic blood pressure was 144±9 mm Hg in the supine position and decreased to 96±9 mm Hg after 3 minutes of standing, which is consistent with moderate to severe autonomic failure.

Sensitivity to Phenylephrine, Isoproterenol, and Nitroprusside
The responses to phenylephrine were heterogeneous, both between groups and within groups (Figure 1, top). Phenylephrine (25 g/kg) increased systolic blood pressure 6±1.6 mm Hg in control subjects, 6±1.1 mm Hg in patients with OI, 18±3.9 mm Hg in patients with essential hypertension, 31±3.4 mm Hg in patients with monogenic hypertension, and 25±3.4 mm Hg in patients with MSA. The differences in phenylephrine sensitivity between groups were attenuated during complete ganglionic blockade. During complete ganglionic blockade, 25 μg phenylephrine increased systolic blood pressure 22±2.4 mm Hg in control subjects, 21±1.4 mm Hg in patients with OI, 32±1.5 mm Hg in patients with essential hypertension, 33±4.4 mm Hg in patients with monogenic hypertension, and 39±5.0 in patients with MSA. Thus, ganglionic blockade potentiated the effect of 25 μg phenylephrine 6±1.9-fold in control subjects, 4±0.9-fold in patients with OI, 2±0.5-fold in patients with essential hypertension, 1.6±0.3-fold in patients with monogenic hypertension, and 1.5±0.1-fold in patients with MSA (Figure 1, middle). The R-R baroreflex slope was 19±2.0 ms/mm Hg in control subjects, 17±1.4 ms/mm Hg in patients with OI, 8.9±4.7 ms/mm Hg in patients with essential hypertension, 6.2±1.0 ms/mm Hg in patients with monogenic hypertension, and 4.6±1.5 ms/mm Hg in patients with MSA (Figure 1, bottom). Sensitivities to nitroprusside showed a pattern similar to phenylephrine sensitivities (Figure 2). In the absence of ganglionic blockade, 0.4 μg/kg nitroprusside decreased systolic blood pressure 8±2.7 mm Hg in control subjects, 9±1.4 mm Hg in patients with OI, 20±3.4 mm Hg in patients with essential hypertension, 21±2.3 mm Hg in patients with monogenic hypertension, and 28±4.6 in patients with MSA. In 9 control subjects and in 5 patients with OI, we determined the potentiation of nitroprusside with ganglionic blockade (3.7±0.9-fold potentiation in patients with OI, 3±0.5-fold potentiation in control subjects). In this homogenous group, nitroprusside and phenylephrine potentiation were not significantly correlated.

We observed a strong nonlinear relation between potentiation of 25 μg phenylephrine during ganglionic blockade and the pressor effect of 25 μg phenylephrine before ganglionic blockade (Figure 3, top). When phenylephrine potentiation decreased below 3-fold, phenylephrine sensitivity increased dramatically. Similarly, the responses to 0.4 μg/kg nitroprusside and phenylephrine potentiation were correlated with
before ganglionic blockade, isoproterenol, phenylephrine, and nitroprusside responses were correlated with each other (Figure 6). The correlations between drug responses were abolished by ganglionic blockade.

### Regulation of Sympathetic Traffic and Drug Responsiveness

Changes in systolic blood pressure, R-R interval, and muscle sympathetic nerve activity with incremental infusion of phenylephrine and nitroprusside are illustrated in Figure 7. Blood pressure increased from 116±2.3/65±1.8 mm Hg at baseline to 137±3.2/82±1.9 mm Hg with 1.3±0.1 μg/kg per minute phenylephrine. The pressor response was associated with an increase in R-R interval from 945±35 ms at baseline to 1090±35 ms during maximal infusion (P=0.0003). Muscle sympathetic nerve activity decreased from 24±1.6 bursts/min at baseline to 10±1.6 bursts/min during the maximal infusion rate (P=0.0005). Stroke volume and cardiac output changed 18±5% (P=0.001) and 2±5% (P=0.3), respectively. The dose of phenylephrine that increased systolic blood pressure 10 mm Hg was 0.89±0.17 μg/kg per minute. Nitroprusside was infused at a maximal rate of 1.3±0.1 μg/kg per minute. Blood pressure decreased from 119±2.1/67±1.8 mm Hg at baseline to 105±2.5/2±1.4 mm Hg. The response led to a baroreflex-mediated decrease in R-R interval from 920±31 ms at baseline to 704±17 ms (P=0.0003). Muscle sympathetic nerve activity increased from 27±1.7 bursts/min at baseline to 51±3.7 bursts/min during maximal nitroprusside infusion rate (P=0.0002). Stroke volume and cardiac output decreased 32±3.6% (P=0.0002) and 11±3.4% (P=0.004), respectively. The dose of nitroprusside that led to a 10–mm Hg decrease in systolic blood pressure was 0.88±0.19 μg/kg per minute. Spontaneous baroreflex sensitivity with the sequence technique was 21±2.4 ms/mm Hg. Baroreflex RRI sensitivity determined during phenylephrine and nitroprusside infusions was 24±4.1 ms/mm Hg. Sympathetic baroreflex sensitivity was 9.4±1.0%/mm Hg. There was no correlation between spontaneous baroreflex sensitivity and sympathetic baroreflex sensitivity (r=0, P=0.75). Phenylephrine sensitivity was correlated with spontaneous baroreflex sensitivity (r=0.58, P=0.02), baroreflex RRI sensitivity determined during pharmacological testing (r=0.81,
P<0.0001), and sympathetic baroreflex sensitivity (r=0.56, P=0.02). Nitroprusside sensitivity was correlated with sympathetic baroreflex sensitivity (r=0.62, P=0.008). Correlations between nitroprusside sensitivity and spontaneous baroreflex sensitivity and baroreflex R-R sensitivity determined during pharmacological testing were borderline in significance (r=0.44 and P=0.08 for both).

Discussion
The overall effect of vasoactive drugs on blood pressure is determined by a combination of the direct effect on vascular tone and an indirect baroreflex-mediated effect. We tested the hypothesis that the indirect dampening effect of the baroreflex is a major contributing factor to interindividual variability in responsiveness to vasoactive drugs. To characterize the effect of the baroreflex on sensitivities to vasoactive medications, we assessed baroreflex function in different ways. Standard baroreflex tests do not measure baroreflex buffering. Instead, they characterize the relation between blood pressure and either heart rate or sympathetic nerve activity.1,19,20 We developed a new strategy to assess baroreflex buffering by comparing the pressor effect of phenylephrine on blood pressure before and during ganglionic blockade.16 The pressor effect of phenylephrine before ganglionic blockade is a function of vascular responsiveness and buffering by the baroreflex. Because the baroreflex loop is interrupted at the level of autonomic ganglia, phenylephrine sensitivity during trimethaphan infusion is mainly influenced by systemic vascular responsiveness.12 The ratio between phenylephrine potentiation and baroreflex function was highly correlated with the response to a single dose of 25 µg phenylephrine.

Figure 3. Changes in systolic blood pressure (SBP) with 25 µg phenylephrine (top) or 0.4 µg/kg nitroprusside (middle) were plotted against potentiation of 25 µg phenylephrine with ganglionic blockade. Below a value for phenylephrine potentiation of 3, sensitivity to phenylephrine and nitroprusside increased profoundly. Because phenylephrine responsiveness and potentiation are highly correlated, the response to a single dose of 25 µg phenylephrine will identify patients with impaired baroreflex function. Phenylephrine potentiation and baroreflex R-R slopes were weakly correlated (bottom).

Figure 4. Individual changes in systolic blood pressure (SBP) with 25 µg phenylephrine (top) and 0.4 µg/kg nitroprusside (bottom) plotted against baroreflex R-R slopes determined by phenylephrine and nitroprusside bolus application.

Figure 5. Individual changes in systolic blood pressure (SBP) with bolus application of 100 µg phenylephrine plotted over changes in systolic blood pressure with 0.4 µg/kg nitroprusside in control subjects, patients with OI, patients with essential hypertension, patients with monogenic hypertension and brachydactyly, and patients with MSA. Responses to phenylephrine and nitroprusside were highly correlated.
ephrine sensitivity during and before ganglionic blockade (ie, potentiation) is, therefore, a measure of baroreflex blood pressure buffering. Baroreflex buffering, baroreflex R-R slopes, and sympathetic baroreflex slopes correlated weakly or not at all in particular in individuals with intact baroreflex function. However, individuals with severely reduced baroreflex slopes always exhibited markedly reduced buffering function. Determination of buffering gives additional information on baroreflex function that is not available with standard baroreflex tests. We found a strong nonlinear relation between baroreflex buffering and phenylephrine sensitivity. Thus, bolus application of a single dose of 25 μg phenylephrine without ganglionic blockade can be used to identify individuals with reduced baroreflex buffering.

In a variety of clinical conditions associated with different degrees of baroreflex dysfunction, we observed that phenylephrine, nitroprusside, and isoproterenol sensitivities were highly variable. We found a close relation between baroreflex buffering and nitroprusside and phenylephrine sensitivities. Patients with impaired baroreflex buffering caused by monogenic hypertension or multiple system atrophy were particularly hypersensitive to phenylephrine and nitroprusside. Furthermore, even in a relatively homogeneous group of control subjects, individual sensitivities to the effect of vasoactive drugs varied 10- to 20-fold. Interruption of the baroreflex arc with ganglionic blockade attenuates differences in phenylephrine, nitroprusside, and isoproterenol sensitivities, both between and within groups. Based on the relation between phenylephrine potentiation and drug sensitivities, we estimate that roughly three quarters of the variability in phenylephrine sensitivity and one half of the variability in nitroprusside responsiveness can be explained by differences in baroreflex buffering. Phenylephrine, nitroprusside, and isoproterenol influence vascular tone by different mechanisms. Yet, responses to these drugs were highly correlated with each other. This correlation suggests that the magnitude of these responses is influenced by a common mechanism. Disappearance of the correlation during tri-methaphan infusion suggests that this common mechanism is buffering changes in vascular tone through the baroreflex. Our observations do not exclude the possibility that buffering of pressor and depressor stimuli is in part regulated differentially at least in healthy subjects.

The buffering function of the baroreflex is mediated through adjustments in cardiac function (ie, heart rate and contractility) and changes in sympathetic outflow to the vasculature. In our first set of experiments in patients and control subjects, we characterized baroreflex control of heart rate by using phenylephrine and nitroprusside bolus application. The patient groups with impaired baroreflex buffering also exhibited reduced baroreflex R-R slopes. However, the correlation between baroreflex R-R slope and drug responsiveness was much weaker than the correlation between phenylephrine potentiation and drug responsiveness. Thus, the effect of the baroreflex on responsiveness to vasoactive drugs cannot be simply explained by compensatory heart rate changes. To further address this issue, we characterized the relation between baroreflex control of heart rate and muscle sympathetic nerve activity and phenylephrine and nitroprus-
side sensitivity in a group of young control subjects. Baroreflex control of heart rate was assessed with the use of the sequence technique under baseline conditions. In addition, we determined baroreflex control of heart rate and muscle sympathetic nerve activity during phenylephrine and nitroprusside infusions. As expected, phenylephrine infusion was associated with a baroreflex-mediated decrease in heart rate and sympathetic traffic. Nitroprusside infusion led to an increase in heart rate and sympathetic traffic. None of the subjects had any evidence for impaired autonomic function. Yet, baroreflex function and sensitivities to phenylephrine and nitroprusside were highly variable. Individuals with more efficient baroreflex control of heart rate and muscle sympathetic nerve activity were less sensitive to the pressor effect of phenylephrine and to the depressor effect of nitroprusside. Thus, changes in baroreflex control of heart rate and vascular tone may individually or collectively contribute to the variability in drug sensitivity.

Our findings are consistent with an important effect of baroreflex blood pressure buffering on the sensitivity to vasoactive drugs. They suggest that even moderate changes in this baroreflex function may have a substantial effect on the sensitivity to vasoactive medications. Impaired baroreflex function has been described in a variety of common conditions such as congestive heart failure, arterial hypertension, and obesity. Patients with impaired baroreflex buffering are also more likely to have an increase in vascular sensitivity. Baroreflex function is not only influenced by disease states but also by age, physical fitness, body weight, dietary factors (e.g., caffeine), and medications. We have recently shown that baroreflex control of heart rate is strongly influenced by genetic factors. A study in patients with monogenic hypertension and brachydactyly drew our attention to blood pressure buffering because these patients had only mildly altered heart rate responses after phenylephrine, but regulated blood pressure hardly at all. All the factors that influence baroreflex control of heart rate and sympathetic tone have the potential to impair baroreflex blood pressure buffering, which may increase the risk of adverse effects to vasoactive medications. Even some healthy young subjects are sensitive to vasoactive agents because of low buffering capacity of the baroreflex. Possibly, these individuals are at an increased risk of side effects from over-the-counter medications such as phenylpropanolamine or other ephedra alkaloids. In contrast, individuals with particularly efficient baroreflex buffering may be resistant to standard doses of cardiovascular medications. Our findings may also have important implications for physiological and pathophysiological studies. For example, even substantial changes in vascular function may be ameliorated by compensatory adjustments by the baroreflex. The change in vascular function may become apparent as baroreflex buffering deteriorates.

Acknowledgments
This work was supported in part by Deutsche Forschungsgemeinschaft grants Jo 284/3-1 and Jo 284/4-1 and a grant-in-aid from AstraZeneca, Wedel, Germany. Dr. Jordan is recipient of a Helmholtz fellowship of the Max-Delbrueck-Center of Molecular Medicine.

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Circulation. 2002;105:1459-1464; originally published online March 4, 2002; doi: 10.1161/01.CIR.0000012126.56352.FD
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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