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 brachyactly, 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
3.4 mm Hg in patients with monogenic hypertension and brachydactyly. 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 μg) increased systolic blood pressure 6.2 ± 1.6 mm Hg in control subjects, 6.2 ± 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 with 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 6.2 ± 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 ± 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 $116 \pm 2.3/65 \pm 1.8 \text{ mm Hg}$ at baseline to $137 \pm 3.2/82 \pm 1.9 \text{ mm Hg}$ with $1.3 \pm 0.1 \mu g$/kg per minute phenylephrine. The pressor response was associated with an increase in R-R interval of 24 ms at baseline to 51 ms during maximal infusion ($P=0.0003$). Muscle sympathetic nerve activity decreased from 24 \pm 1.6 bursts/min at baseline to 10 \pm 1.6 bursts/min during the maximal infusion rate ($P=0.0005$). Stroke volume and cardiac output changed 18 \pm 5\% ($P=0.001$) and 2 \pm 5\% ($P=0.3$), respectively. The dose of phenylephrine that increased systolic blood pressure 10 mm Hg was $0.89 \pm 0.17 \mu g$/kg per minute. Nitroprusside was infused at a maximal rate of 1.3 \pm 0.1 \mu g$/kg per minute. Blood pressure decreased from $119 \pm 2.1/67 \pm 1.8 \text{ mm Hg}$ at baseline to $105 \pm 2.2/52 \pm 1.4 \text{ mm Hg}$. The response led to a baroreflex-mediated decrease in R-R interval from $920 \pm 17 \text{ ms}$ at baseline to $704 \pm 17 \text{ ms}$ ($P=0.0003$). Muscle sympathetic nerve activity increased from $27 \pm 1.7 \text{ bursts/min}$ at baseline to $51 \pm 3.7 \text{ bursts/min}$ during maximal nitroprusside infusion rate ($P=0.0002$). Stroke volume and cardiac output decreased $32 \pm 3.6\%$ ($P=0.0002$) and $11 \pm 3.4\%$ ($P=0.004$), respectively. The dose of nitroprusside that led to a 10–mm Hg decrease in systolic blood pressure was $0.88 \pm 0.19 \mu g$/kg per minute. Spontaneous baroreflex sensitivity with the sequence technique was 21 \pm 2.4 mmHg. Baroreflex RRI sensitivity determined during phenylephrine and nitroprusside infusions was 24 \pm 4.1 mmHg. Sympathetic baroreflex sensitivity was 9.4 \pm 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-RI 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 medica-

**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).

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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 medica-

**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 nitropruss-
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.\(^1,\)\(^2\) In addition, we determined baroreflex control of heart rate and muscle sympathetic nerve activity during phenylephrine and nitroprusside infusions.\(^1,\)\(^3\) 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.\(^1,\)\(^3\)\(^4\) 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.\(^3\)\(^,\)\(^22\)\(^,\)\(^23\) Patients with impaired baroreflex buffering function 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 (eg, caffeine), and medications.\(^24\)\(^,\)\(^25\) We have recently shown that baroreflex control of heart rate is strongly influenced by genetic factors.\(^24\) 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.\(^16\) 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.\(^26\)\(^,\)\(^27\) 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.

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**References**

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