Severely Impaired Baroreflex-Buffering in Patients With Monogenic Hypertension and Neurovascular Contact

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Background—We identified a family with a monogenic syndrome of hypertension, brachydactyly, and neurovascular contact of the brain stem. Neurovascular contact of the ventrolateral medulla may lead to arterial hypertension by interfering with baroreflex function.

Methods and Results—In 5 patients with monogenic hypertension (18 to 34 years old), we conducted detailed autonomic function tests. Blood pressure during complete ganglionic blockade was 134±4.9/82±4.1 mm Hg and 90±6/49±2.4 mm Hg in patients and in control subjects, respectively. During ganglionic blockade, plasma vasopressin concentration increased 24-fold in control subjects and <2-fold in patients. In patients, cold pressor testing, hand-grip testing, and upright posture all increased blood pressure excessively. In contrast, muscle sympathetic nerve activity was not increased at rest or during cold pressor testing. The phenylephrine dose that increased systolic blood pressure 12.5 mm Hg was 8.0±2.0 µg in patients and 135±35 µg in control subjects before ganglionic blockade and 5.4±0.4 µg in patients and 13±4.8 µg in control subjects during ganglionic blockade.

Conclusions—In patients with monogenic hypertension and neurovascular contact, basal blood pressure was increased even during sympathetic and parasympathetic nerve traffic interruption. However, sympathetic stimuli caused an excessive increase in blood pressure. This excessive response cannot be explained by increased sympathetic nerve traffic or increased vascular sensitivity. Instead, we suggest that baroreflex buffering and baroreflex-mediated vasopressin release are severely impaired. (Circulation. 2000;102:2611-2618.)

Key Words: baroreceptors ■ genetics ■ hypertension ■ nervous system, autonomic ■ receptors

Bilginturan et al1 first described autosomal dominant hypertension and brachydactyly. The gene responsible for the syndrome was mapped to chromosome 12p2. Affected individuals exhibit a profoundly accelerated increase in blood pressure with age.3 We showed earlier that affected individuals are not salt sensitive and that plasma renin activity and aldosterone respond normally to volume expansion and depletion.3 We subsequently showed by MR tomography that all 15 affected family members tested had a left-sided loop of the posterior inferior cerebellar artery (PICA) impinging on the rostroventrolateral medulla, compared with none of 11 nonaffected family members.4 Pulsatile compression of the rostroventrolateral medulla may contribute to essential hypertension.5,6 This hypothesis is supported by the observation that neurosurgical decompression of the brain stem improves blood pressure control.7 Animal studies suggest that pulsatile compression of the rostroventrolateral medulla increases blood pressure through sympathetic activation.8 Whether similar autonomic abnormalities occur in humans is not known. We tested the hypothesis that in patients with monogenic hypertension, brachydactyly, and neurovascular contact, the hypertension is mediated through sympathetic activation. Furthermore, we tested whether these changes were caused by increased sympathetic nerve traffic or increased vascular sensitivity. Instead, we suggest that baroreflex buffering and baroreflex-mediated vasopressin release are severely impaired. (Circulation. 2000;102:2611-2618.)

Key Words: baroreceptors ■ genetics ■ hypertension ■ nervous system, autonomic ■ receptors

Methods

Subjects
Five younger family members with hypertension and brachydactyly traveled to Germany to participate in this study (3 men, 2 women, 26±3.4 years old, 57±4.0 kg, 152±2.4 cm tall). Their results were compared with those of healthy normotensive control subjects of similar age. Written informed consent was obtained. All studies were approved by the institutional review board.
Plasma catecholamines were determined after patients had been in the supine position overnight and again after 30 minutes standing. The test was repeated on a different day after volume loading with intravenous saline solution. In addition, plasma catecholamines were determined after complete ganglionic blockade achieved.

### Protocol

Three days before the study, volunteers received a 150-nmol sodium diet free of substances that could interfere with catecholamine measurements. All vasoactive medications were discontinued ≥5 half-lives before testing. The patients underwent a physical examination, MRI imaging of the brain stem, and a series of autonomic tests on separate days.

### Posture Study

After the patients had remained overnight in the supine position, venous samples for plasma renin activity and aldosterone concentrations were obtained from a heparin lock placed ≥30 minutes before the first blood draw. Blood samples were again obtained after 30 minutes in the standing position. Automated measurements of blood pressure and heart rate were made (Dinamap, Criticon). On a separate day, the study was repeated after an intravenous infusion of 1000 mL normal saline in 30 minutes.

### Autonomic Reflex Testing

Sinus arrhythmia was assessed during controlled breathing (5-second inhalation and 5-second exhalation for 90 seconds). The sinus arrhythmia ratio was calculated as the ratio of the longest to the shortest RR interval during these 90 seconds. Patients performed a Valsalva maneuver (40 mm Hg pressure for 15 seconds). Blood pressure and heart rate responses to isometric handgrip (30% maximum contraction for 1 minute) and cold pressor testing were also determined.

Pharmacological testing was conducted with the subject recumbent ≥2.5 hours after the last meal. Heart rate was determined with a continuous ECG, blood pressure by an indwelling catheter in the radial artery, and changes in stroke volume by impedance cardiography. Leg blood flow was determined before and during complete ganglionic blockade by occlusion plethysmography (EC 5R, Hokanson). Responses to incremental intravenous bolus doses of nitropusside and phenylephrine were evaluated before ganglionic blockade. Thereafter, we infused the ganglionic blocker trimethaphan (Cambridge Pharmaceuticals) starting at 1 mg/min and increasing at 6-minute intervals until the efferent arc of the baroreflex was completely blocked. Bolus doses of phenylephrine were then administered just as before blockade.

The baroreflex slope was determined at the linear portion of the sigmoidal relation between phenylephrine-induced blood pressure changes and changes in RR interval. The spontaneous baroreflex slope was determined by the sequence technique. The doses of each drug that would change blood pressure by 12.5 mm Hg were determined by extrapolation from individual dose-response curves.

### Microneurography

During the microneurography study, heart rate was determined by continuous ECG and beat-by-beat blood pressure by photothvelysmography (Finapres, Ohmeda). Microneurography recordings were obtained as described previously.

### Analytical Methods

Plasma and urinary catecholamines were determined by a modification of a high-performance liquid chromatographic method. Plasma vasopressin concentration was determined by a radioimmunoassay.

### Statistics

All data are expressed as mean±SEM. Intraindividual and interindividual differences were compared by paired and unpaired t tests, respectively. ANOVA testing for repeated measures was used for multiple comparisons. If necessary, data were logarithmically transformed before analysis. Relationships between parameters were assessed by linear regression analysis. A value of P<0.05 was considered significant.

### Results

#### Clinical Characteristics

All 5 patients had severe arterial hypertension. None had cardiovascular complications. All had a normal creatinine clearance, and none had microalbuminuria. Echocardiography showed normal systolic function. One patient had mild left ventricular hypertrophy. However, none had signs of impaired left ventricular filling. MRI of the brain stem showed a left-sided loop of the PICA in all affected subjects (Figure 1).

#### Posture Studies and Catecholamines

Figure 2 illustrates supine and upright blood pressure and heart rate. Without volume loading, blood pressure was 135±6.7/81±4.6 mm Hg and increased to 148±3.2/99±5.7 mm Hg after 5 minutes in the standing position (P=0.1 for systolic blood pressure and P=0.01 for diastolic blood pressure). This increase in blood pressure was associated with a change in heart rate from 59±3.2 bpm supine to 87±5.5 bpm upright. Before volume loading, supine blood pressure was 140±6.0/84±6.0 mm Hg and supine heart rate was 63±4 bpm. Immediately after volume loading, supine blood pressure was 140±5.8/84±4.0 mm Hg and supine heart rate was 66±5.0 bpm. With volume loading, the increase in blood pressure with standing was attenuated. After 5 minutes of standing, blood pressure was 141±3.9/94±4.4 mm Hg and heart rate was 71±4.2 bpm. Plasma norepinephrine and epinephrine concentrations were not excessively increased in

### Table

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Plasma catecholamines were determined after patients had been in the supine position overnight and again after 30 minutes standing. The test was repeated on a different day after volume loading with intravenous saline solution. In addition, plasma catecholamines were determined after complete ganglionic blockade.
the supine or upright position (Table). Urinary excretion of norepinephrine was 112 ± 624 nmol/d (normal range 136 to 621 nmol/d). Urinary epinephrine excretion was 38 ± 628.2 nmol/d (normal range 22 to 109 nmol/d).

**Autonomic Reflex Testing**

Respiratory sinus arrhythmia was 1.3 ± 0.055. During Valsalva maneuver phase II, blood pressure increased 12 ± 11/26 ± 9.8 mm Hg. Blood pressure increased 45 ± 12/24 ± 6.3 mm Hg during phase IV. The Valsalva heart rate ratio was 1.4 ± 0.19. With hand-grip testing, blood pressure increased 36 ± 5.0/24 ± 2.7 mm Hg. After 1 minute of cold pressor testing, blood pressure increased 46 ± 8.8/27 ± 5.5 mm Hg. In 4 patients, blood pressure increased profoundly with cold pressor testing (range 45 to 66/22 to 41 mm Hg); 1 patient had a clearly abnormal response (9/7 mm Hg change) but had no pain during the test. The pressor responses to hand-grip exercise and to cold were exaggerated compared with control subjects.15

**Responses to Complete Ganglionic Blockade**

Before trimethaphan infusion, blood pressure was 150 ± 4.9/86 ± 1.8 mm Hg and heart rate was 67 ± 6.3 bpm. Figure 3 illustrates changes in blood pressure, heart rate, and stroke volume with increasing trimethaphan infusion. When complete ganglionic blockade was achieved, blood pressure and heart rate were 134 ± 4.9/82 ± 4.1 mm Hg and 90 ± 2.6 bpm, respectively. In control subjects, blood pressure in the supine position was 129 ± 4.0/65 ± 3.0 mm Hg before trimethaphan. With complete ganglionic blockade, blood pressure decreased to 90 ± 6/49 ± 2.4 mm Hg (P<0.01 compared with patients). Decreases in both systolic (P<0.05) and diastolic blood pressure (P<0.01) were smaller in patients than in control subjects. In patients, the decrease in blood pressure was associated with a 7.5 ± 5.3% decrease in cardiac output. Stroke volume decreased 31 ± 5.0%. Leg blood flow increased from 5.9 ± 0.6 mL·100 mL⁻¹·s⁻¹ at baseline to 11 ± 2 mL·100 mL⁻¹·s⁻¹ during complete ganglionic blockade. Plasma norepinephrine concentration decreased profoundly during ganglionic blockade (Table). In patients, plasma vasopressin concentration was 0.47 ± 0.02 pg/mL at baseline and 0.84 ± 0.13 pg/mL during complete ganglionic blockade (Figure 4). In control subjects, in contrast, plasma vasopressin concentration increased profoundly during ganglionic blockade (1.6 ± 0.17 pg/mL at baseline, 39 ± 13 pg/mL during ganglionic blockade).

**Sensitivity to Phenylephrine and Nitroprusside and Baroreflex Slope**

Before ganglionic blockade, patients were extremely hypersensitive to the pressor effect of phenylephrine (Figure 5). The phenylephrine dose that increased systolic blood pressure...
12.5 mm Hg was 8.0 ± 2.0 µg in patients and 135 ± 35 µg in control subjects (Figure 6). During ganglionic blockade, the phenylephrine dose that increased systolic blood pressure 12.5 mm Hg was 5.4 ± 0.4 µg in patients and 13 ± 4.8 µg in control subjects (P < 0.001 between groups, P < 0.001 between interventions, P < 0.01 for the interaction between group and intervention). Ganglionic blockade potentiated the pressor effect by factors of 1.5 ± 0.5 and 15 ± 4.3 in patients and control subjects, respectively (P < 0.01). Without ganglionic blockade, patients were hypersensitive to the depressor effect of nitroprusside (Figure 7). The nitroprusside dose that decreased systolic blood pressure 12.5 mm Hg without ganglionic blockade was 0.20 ± 0.066 µg/kg in patients and 1.8 ± 0.50 in control subjects (P < 0.01) (Figure 8). The baroreflex slope determined by phenylephrine bolus application was 9.4 ± 1.6 ms/mm Hg. Baroreflex slope determined by the sequence technique was 12 ± 2.0 ms/mm Hg. In 3 patients, baroreflex slope was above the 90th percentile for age, and in 2 patients, it was between the 90th and 95th percentiles.12

Microneurography
Representative microneurography recordings are illustrated in Figure 9. Baseline sympathetic activity in the supine position was 15 ± 4.6 bursts/min. In a previous study, resting muscle sympathetic nerve activity was 12 ± 6 bursts/min in young normotensive control subjects and 14 ± 9 bursts/min in young borderline hypertensives.13 Microneurography incidence was 22 ± 6.5 bursts/100 heartbeats. With cold pressor testing, muscle sympathetic nerve activity increased 7.5±6.8 bursts/min (11 ± 10 bursts/100 heartbeats). By comparison, cold pressor testing elicited an increase in muscle sympathetic nerve activity by 14 ± 10 bursts/min in normotensive control subjects and by 11 ± 8.0 bursts/min in patients with borderline hypertension.13 With lower-body negative pressure, muscle sympathetic nerve activity increased from 19 ± 5.8 bursts/min (31 ± 8.6 bursts/100 heartbeats) at 0 mm Hg to 24 ± 6.5 bursts/min (36 ± 9.0 bursts/100 heartbeats) at −10 mm Hg suction (n = 4). This increase in sympathetic nerve traffic during lower-body negative pressure was associated with a decrease in forearm blood flow from 8.7 ± 1.4 mL/100 mL to 6.6 ± 0.8 mL/100 mL. Blood pressure was 131 ± 4.6/74 ± 2.6 mm Hg at 0 mm Hg and 134 ± 3.3/76 ± 2.0 mm Hg at −10 mm Hg lower-body negative pressure.

Discussion
Our main finding was that in patients with monogenic hypertension, brachydactyly, and neurovascular contact,
blood pressure during complete ganglionic blockade was 44 mm Hg greater than in control subjects. However, sympathetic stimuli caused an excessive increase in blood pressure. This increase was not due to increased sympathetic nerve traffic. The patients were extremely hypersensitive to phenylephrine and nitroprusside. With ganglionic blockade, the pressor effect of phenylephrine was only slightly augmented in patients but increased dramatically in control subjects. Furthermore, with ganglionic blockade, plasma vasopressin concentration increased profoundly in control subjects but changed little in patients.

We used trimethaphan to determine the contribution of autonomic nervous system activity to blood pressure control.\(^1\) Ganglionic blockade at the level achieved in this study abolishes sympathetic and parasympathetic modulation of heart rate and blood pressure.\(^1\) Even with substantial changes in blood pressure, heart rate does not change and muscle sympathetic nerve activity is abolished.\(^1\) The blockade is associated with decreased plasma norepinephrine concentrations as low as seen in patients with severe pure autonomic failure.\(^1\) Plasma catecholamines and muscle sympathetic nerve activity were low normal in our patients, suggesting that the sympathetic contribution to supine blood pressure was not increased. In this regard, our patients resemble patients with secondary hypertension rather than patients with essential hypertension.\(^1\) Because sympathetic nerve traffic is

![Graph showing plasma vasopressin concentrations at baseline and during ganglionic blockade with trimethaphan in patients and in young control subjects.](image)

**Figure 4.** Plasma vasopressin concentrations at baseline and during ganglionic blockade with trimethaphan in patients and in young control subjects. In control subjects, ganglionic blockade is associated with a profound baroreflex-mediated increase in plasma vasopressin concentration. A similar increase was observed in a previous study by Baylis and Robinson.\(^3\) In patients, plasma vasopressin concentration increased slightly or not at all during ganglionic blockade.

![Graph showing changes in systolic blood pressure with incremental bolus doses of phenylephrine before (top) and during (bottom) ganglionic blockade in patients with monogenic brachydactyly and hypertension (HTN) and in young normotensive control subjects. Before ganglionic blockade, patients were extremely hypersensitive to pressor effect of phenylephrine. During ganglionic blockade, sensitivity to phenylephrine was not significantly different between patients and control subjects.](image)

**Figure 5.** Changes in systolic blood pressure with incremental bolus doses of phenylephrine before (top) and during (bottom) ganglionic blockade in patients with monogenic brachydactyly and hypertension (HTN) and in young normotensive control subjects. Before ganglionic blockade, patients were extremely hypersensitive to pressor effect of phenylephrine. During ganglionic blockade, sensitivity to phenylephrine was not significantly different between patients and control subjects.

![Graph showing doses of phenylephrine that increased systolic blood pressure 12.5 mm Hg before and during ganglionic blockade with trimethaphan in patients with monogenic brachydactyly and hypertension (HTN) and in young normotensive control subjects. In control subjects, sensitivity to pressor effect of phenylephrine increased 15-fold after interruption of baroreflex with trimethaphan. Patients were extremely hypersensitive to pressor effect of phenylephrine before ganglionic blockade; with ganglionic blockade, sensitivity to phenylephrine increased only 1.5-fold.](image)

**Figure 6.** Doses of phenylephrine that increased systolic blood pressure 12.5 mm Hg before and during ganglionic blockade with trimethaphan in patients with monogenic brachydactyly and hypertension (HTN) and in young normotensive control subjects. In control subjects, sensitivity to pressor effect of phenylephrine increased 15-fold after interruption of baroreflex with trimethaphan. Patients were extremely hypersensitive to pressor effect of phenylephrine before ganglionic blockade; with ganglionic blockade, sensitivity to phenylephrine increased only 1.5-fold.
not evenly distributed throughout the body,\textsuperscript{14} muscle sympathetic nerve activity may not necessarily reflect overall sympathetic tone. Yet, blood pressure decreased with complete ganglionic blockade to a lesser degree than in control subjects,\textsuperscript{15,19} which further supports there being no increase in basal sympathetic tone. Blood pressure during ganglionic blockade was still greater in patients than in control subjects. Thus, the increase in basal blood pressure is not entirely explained by sympathetic nervous system activation. We cannot completely exclude chronic sympathetic stimulation and vascular remodeling. Stroke volume, on the other hand, decreased sharply in our patients, which may be due to a decrease in cardiac preload or cardiac contractility.

Several lines of evidence suggest that the autonomic nervous system contributes to hypertension in our patients. Perhaps the strongest evidence is the profound increase in blood pressure with standing. The increase was attenuated with volume loading, suggesting that the excessive increase in blood pressure was due to overcompensation of a reduction in cardiac preload. Similarly, leg compression prevents the orthostatic increase in blood pressure in patients with orthostatic hypertension.\textsuperscript{21} Moreover, stimuli such as cold pressor testing and hand-grip exercise led to a greater than normal pressor response. Although blood pressure responses to these stimuli were excessive, the increase in muscle sympathetic nerve activity was moderate. Thus, a smaller increase in sympathetic nerve traffic may elicit a greater pressor response.

If a smaller increase in sympathetic nerve traffic is associated with an excessive pressor response, the amount of norepinephrine with a given stimulus must be increased or the same amount of norepinephrine elicits a greater response. Plasma and urinary norepinephrine concentrations were not increased in our patients, evidence against increased norepinephrine release. Less likely is the explanation that increased norepinephrine release could be masked by changes in norepinephrine clearance.\textsuperscript{22} Therefore, the same amount of norepinephrine may elicit a greater pressor response. Indeed, our patients were extremely hypersensitive to the phenylephrine pressor response before ganglionic blockade. Ganglionic blockade can be used to study vascular responses in the absence of baroreflex-mediated changes in autonomic tone.\textsuperscript{11} The fact that the sensitivity to phenylephrine was similar in patients and in control subjects during ganglionic blockade challenges the concept that increased vascular sensitivity underlies the hypersensitivity to phenylephrine.

The most likely explanation for phenylephrine hypersensitivity in our patients is impaired baroreflex buffering. The main purpose of the baroreflexes is to buffer changes in cardiac preload or vascular tone. In patients with damage to the afferent arc (baroreflex failure), the sensitivity to phenylephrine and nitroprusside is dramatically increased.\textsuperscript{23} Similarly, impaired function of the efferent arc, due to either neuronal degeneration (autonomic failure)\textsuperscript{24–27} or ganglionic blockade,\textsuperscript{11,28,29} causes a profound increase in sensitivity to vasodilators and vasoconstrictors. In our patients, phenylephrine sensitivity was similar to the sensitivities observed in patients with baroreflex failure\textsuperscript{23} or autonomic failure\textsuperscript{25} or in control subjects during ganglionic blockade.\textsuperscript{30} Furthermore, the sensitivity to phenylephrine increased only slightly during complete ganglionic blockade, suggesting that the restraining effect of the autonomic nervous system was profoundly impaired. The finding that plasma vasopressin concentration did not increase despite a marked depressor response is further evidence for impaired baroreflex function.\textsuperscript{30,31} We\textsuperscript{15} and others\textsuperscript{32} have shown that in healthy subjects, ganglionic blockade with trimethaphan leads to a profound baroreflex-mediated increase in vasopressin concentrations. Paradoxically, the baroreflex control of heart rate was only mildly impaired, suggesting that the baroreflex dysfunction involved primarily control of vascular tone and of vasopressin release. The wide spontaneous fluctuations in blood pressure typical for patients with baroreflex failure\textsuperscript{23,31} were not observed in our patients. These findings suggest that noninvasive or invasive determination of the baroreflex–heart rate slope\textsuperscript{34,35} does not give sufficient information on baroreflex control of vascular tone and vasopressin release.\textsuperscript{36} Reliance on this
parameter alone in our subjects would have led to faulty conclusions regarding their baroreceptor reflex function.

The location of the lesion to the baroreflex in our patients is difficult. Absence of orthostatic hypotension and the results of autonomic reflex testing suggest that the efferent limb of the baroreflex is at least in part intact. Impaired baroreflex-mediated vasopressin release suggests that the lesion is proximal to sympathetic efferent neurons in the rostroventrolateral medulla. Because baroreflex control of heart rate was only slightly impaired, whereas control of vascular tone was severely affected, we suggest that the lesion must be located at a place where heart rate and blood pressure control are in part separated.

All patients studied and other affected family members had a left-sided vascular PICA loop impinging on the rostroventrolateral medulla, whereas nonaffected family members had no such loops.4 Animal studies have shown that pulsatile compression of the rostroventrolateral medulla exerted by a balloon increases blood pressure, which may be mediated through alteration of afferent neurons traveling from baroreceptors to the nucleus tractus solitarius or through direct activation of efferent sympathetic neurons.8,37 Our study demonstrates that in humans, neurovascular contact of the rostroventrolateral medulla can be associated with baroreflex dysfunction and changes in sympathetic nervous system activation. However, neurosurgical decompression of the brain stem would be necessary to prove a causal relationship between neurovascular contact and baroreflex dysfunction in these patients.5,38,39

We conclude that in patients with monogenic hypertension, brachydactyly, and neurovascular contact of the rostroventrolateral medulla, basal blood pressure was increased even during interruption of sympathetic and parasympathetic nerve traffic. However, sympathetic stimuli such as standing and cold pressor testing caused an excessive increase in blood pressure. This excessive response cannot be explained by increased sympathetic nerve traffic or increased vascular sensitivity. Instead, we suggest that the ability of the baroreflex to buffer changes in vascular tone is severely impaired in these subjects.

Acknowledgment

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References


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