Temporary Reduction of Blood Pressure and Sympathetic Nerve Activity in Hypertensive Patients After Microvascular Decompression

Helga Frank, MD; Karsten Heusser, MD; Helmut Geiger, MD; Rudolf Fahlbusch, MD; Ramin Naraghi, MD; Hans P. Schobel, MD

Background and Purpose—Experimental studies suggested neurovascular compression of the brain stem as a cause of hypertension. The aim of our prospective study was to investigate the effect of microvascular decompression in patients with severe hypertension with neurovascular compression on blood pressure and central sympathetic nerve activity in the long-term.

Methods—Fourteen patients (4 males; mean age, 46±8 years) with essential hypertension underwent microvascular decompression of the brain stem. Vasoconstrictor muscle sympathetic nerve activity (recorded by microneurography: burst frequency, bursts/min) and blood pressure (24-hour profiles) were investigated before surgery and 7 days, 3 months, and every 6 months postoperatively.

Results—Muscle sympathetic nerve activity was preoperatively elevated and decreased significantly postoperatively (35±13 bursts/min vs 20±9 bursts/min; P<0.01). Sympathetic activity remained reduced 3 months (19±8bursts/min; P<0.01), 6 months (19±7bursts/min; P<0.01), and 12 months (23±9 bursts/min; P<0.01) postoperatively. However, in the long-term, sympathetic nerve activity increased again (18 months after surgery: 28±10 bursts, not significant; 24 months postoperatively: 34±12 bursts/min, not significant). Systolic and diastolic blood pressure decreased from 162±6/98±5 mm Hg preoperatively to 133±6/85±4 mm Hg (7 days postoperatively; P<0.01); 136±5/86±4 mm Hg (3 months postoperatively; P<0.01); 132±4/85±4 mm Hg (6 months postoperatively; P<0.01); 132±3/85±5 mm Hg (12 months postoperatively; P<0.01); 132±5/84±5 mm Hg; P<0.01). Twenty-four months after microvascular decompression, blood pressure increased again up to 158±7/96±6 mm Hg, corresponding to the sympathetic nerve activity course.

Conclusion—Sympathetic nerve activity and blood pressure are temporary reduced by microvascular decompression in patients with severe hypertension with neurovascular compression. The data are a hint for sympathetic overactivity as a pathomechanism in this subgroup of patients. (Stroke. 2009;40:47-51.)

Key Words: decompressive surgery ■ hypertension ■ sympathetic nervous system

Experimental data,1 microanatomical,2 and MR tomographical studies3 suggest an association between neurovascular compression (NVC) of the rostral ventrolateral medulla (RVLM) by looping arteries (eg, the posterior inferior cerebellar artery) and hypertension.

The RVLM is a major cardiovascular control center in regulating the level of arterial blood pressure. Sympathetic vasomotor nerves originating from the lower brain stem are critical components for the feed-forward cardiovascular responses to acute alerting stimuli and have been implicated in the development of chronic hypertension.4 It has been shown that in patients with essential hypertension with NVC, sympathetic vasoconstrictor discharges to skeletal muscle is markedly higher as compared to those with hypertension without NVC.5 These data raise the hypothesis that pulsatile compression of the RVLM may induce a sustained stimulation of the central sympathetic vasomotor or cardiac activity causing a secondary form of neurogenic hypertension.

In a limited collective of patients with severe hypertension for years and NVC who underwent microvascular decompression (MVD) of the RVLM, blood pressure levels had improved postoperatively in a subgroup of patients.6,7 However, the underlying mechanism and functional relevance of the looping artery at the left lower brain stem are not definitely known. Therefore, it is critical to assess whether the morphological finding NVC produces a form of hyper-

Received February 27, 2008; final revision received May 9, 2008; accepted May 30, 2008.
From Department of Nephrology (H.F.), Klinikum rechts der Isar, Technische Universitaet Muenchen, Germany; Department of Clinical Pharmacology (K.H.), Hannover Medical School, Hannover, Germany; Department of Nephrology (H.G.), University of Frankfurt, Germany; International Neuroscience Institute Hannover (R.F.), Germany; Department of Neurosurgery (R.N.), University of Erlangen-Nuremberg, Germany; Benedictus Krankenhaus Tutzing (H.P.S.), Germany.
Correspondence to Helga Frank, MD, Department of Nephrology, Klinikum rechts der Isar, Technische Universitaet Muenchen, Ismaninger Strasse 22, 81675 Munich, Germany. E-mail Helga.Frank@lrz.tum.de
© 2008 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.108.518670
tension mediated by the central nervous system. Therapeutic implications could be the preferred use of central sympatholytic agents or, in selected cases, MVD as a possible successful therapeutic alternative in intractable hypertension with NVC.

The aim of the present prospective study was to investigate the sympathetic outflow to the cardiovascular effector organs in patients with hypertension with NVC and the effect of MVD on blood pressure and sympathetic nerve activity even in the long-term postoperative course. We analyzed direct microneurographic measurements of intraneural vasconstrictor sympathetic activity to muscle vessels in patients with severe essential hypertension and MRI-proven NVC preoperatively and postoperatively after MVD. We assessed the initial effects of MVD on blood pressure levels and on sympathetic activity to muscle vessels, as well as the long-term effect for 2 years after surgery.

Materials and Methods

Subjects
From 1992 to 2004, 14 patients with severe essential hypertension using ≥3 antihypertensive drugs without adequate blood pressure control, intolerable side effects, or both and a history of hypertension for 5 to 35 years were recruited at the Medical Department IV, University Erlangen-Nuremberg, Germany. All patients had at least 1 life-threatening hypertensive crisis. Secondary forms of hypertension (renal artery stenosis, endocrine abnormalities) were ruled out according to an extensive protocol. End-organ damage (left ventricular hypertrophy, proteinuria, hypertensive retinopathy, arteriosclerosis of the peripheral arteries) was assessed. Neurovascular compression at the root entry zone of cranial nerves IX and X was unveiled, the site of the neurovascular compression at the ventrolateral medulla and the root entry zone of cranial nerves IX and X was identified by axial and coronal double-echo (T2) and MRA sequences by 2 independent neuroradiologists. The study was approved by the Ethics Committee of the University of Erlangen-Nuremberg, and informed written consent has been obtained. Microvascular decompression was taken into consideration if blood pressure control was not achieved by far despite intensive antihypertensive management by experienced physicians according to the guidelines of the European Society of Hypertension. Microvascular decompression was performed at the Neurosurgery Department Erlangen according to the technique of Jannetta. After a left lateral subcircular cranectomy with the patient in a semi-sitting position, the site of the neurovascular compression at the ventrolateral medulla and the root entry zone of the cranial nerves IX and X was unveiled, and a Teflon felt was interposed between the brain stem surface and the looping artery. The protocol included physical examination, monitoring of casual and ambulatory blood pressure readings, blood chemistry, electrocardiography, and microneurography preoperatively and 1 month and every 6 months postoperatively. Type and dosage of antihypertensive medication were recorded at every visit. During the whole study period, the surgical team was the same. All patients were seen regularly and treated in the outpatient clinic of the Medical Department 4 of the University of Erlangen-Nuremberg; the diagnostic and therapeutic approach for hypertension was provided by a medical team working according to a detailed and settled preoperative and postoperative protocol to ensure that continuity of patient selection, enrollment, and medical practice were provided over the whole time period.

Measurements
Twenty-four hour ambulatory blood pressure measurements were obtained by use of an automated portable device (Space labs Medical). The measurements were performed automatically every 15 minutes during the day and every 30 minutes during the night, yielding the 24-hour pressure profile. In the laboratory, systolic, diastolic, and mean arterial pressure were achieved noninvasively, beat to beat, by a photoplethysmographic finger device (Finapres, Ohmeda). Multiunit recordings of postganglionic sympathetic nerve activity were measured by unipolar tungsten microelectrodes inserted selectively into muscle–nerve fascicles of the peroneal nerve posterior to the fibular head by the technique of microneurography of Vallbo et al. This technique has been validated and provides data of the direct, intraneural vasconstrictor sympathetic activity. The recording of sympathetic nerve activity was accepted when the neurogram revealed spontaneous, pulse-synchronous bursts of neural activity, with the largest bursts showing a minimal signal-to-noise ratio of 3:1. In each single study, we ascertained that sympathetic outflow to skeletal muscle rather than sympathetic discharge to skin was recorded by demonstrating that the neural activity did not change in response to arousal stimuli but showed a characteristic biphasic response to Valsalva maneuver. For analysis, sympathetic bursts were identified by inspection of the filtered neurograms. The rate of sympathetic discharge was expressed as the number of bursts per minute (burst frequency). All nerve recordings were analyzed by 2 independent investigators who were unaware of the study protocol. The intraobserver and interobserver variability in identifying bursts were ~5% and 7%, respectively. The recordings of sympathetic activity to muscle vessels were performed between 1:00 PM and 4:00 PM with the patient supine in a calm room with a temperature of 23°C to 25°C.

Statistical Analysis
All results are presented as means±SD. Paired t tests (2-tailed) were used for the statistical comparisons of study parameters before and after microvascular decompression. All data were analyzed by using the SPSS/version 14.0 of the statistics package for social sciences. Statistical significance was indicated by P<0.05.

Results
Patient characteristics are shown in the Table. Four of the 14 patients who underwent microvascular decompression were male. The mean age was 46±9.5 years. Mean follow-up duration after MVD was 26±3 months.

Systolic and diastolic blood pressure levels decreased from 159±6/98±8 mm Hg preoperatively to 134±11/88±9 mm Hg (1 month postoperatively; P<0.05), 144±14/92±10 mm Hg (3 months postoperatively; P<0.05), 139±6/91±10 mm Hg (6 months postoperatively; P<0.05), and 138±4/93±3 mm Hg (12 months postoperatively; P<0.05). Eighteen months after

<table>
<thead>
<tr>
<th>Table. Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Office systolic blood pressure, mm Hg</td>
</tr>
<tr>
<td>Office diastolic blood pressure, mm Hg</td>
</tr>
</tbody>
</table>

†Calcium antagonists n=10, angiotensin-converting enzyme inhibitors n=11, alpha-adrenergic blockers n=7, beta blockers n=8, central sympatholytic agents n=9, diuretics n=10.
*Indicates calcium antagonists n=2, angiotensin-converting enzyme inhibitors n=2, beta blockers n=3, central sympatholytic agents n=3, diuretics n=4.

Lozenge button indicates calcium antagonists n=6, angiotensin-converting enzyme inhibitors n=5, beta blockers n=3, central sympatholytic agents n=1, diuretics n=2.
decompression, systolic and diastolic blood pressure levels increased and reached 24 months after surgery the levels at the preoperative state (Figure 1). At this point, amount and dosage of the antihypertensive drugs were less than those used preoperatively. Number and classes of antihypertensive medication preoperatively as well as 12 and 24 months after surgery are shown in the Table.

Sympathetic nerve discharge was preoperatively high (30±12 bursts/min) and decreased significantly 1 month after successful decompression (19±9 bursts/min; P<0.05), as well as 3 months postoperatively (19±5 bursts/min; P<0.05), 6 months (19±6 bursts/min; P<0.05), and 12 months postoperatively (22±4 bursts/min; P<0.05). Yet 24 months after MVD, burst frequency increased to 24±2 bursts/min. Results for the course of sympathetic activity to muscle vessels are given in Figure 2. Figure 3 shows a representative single study of a hypertensive male with NVC before and after microvascular decompression. Preoperatively, sympathetic burst frequency was elevated (42 bursts/min). Three months after surgery the sympathetic discharge was decreased (12 bursts/min). Two years after microvascular operation, micro-neurography revealed an increase of the central sympathetic nerve activity again (21 bursts/min).

Discussion

We found in our prospective study that in a subgroup of patients with severe refractory arterial hypertension, history of hypertensive crises and neurovascular contact at the left ventrolateral medulla oblongata, systolic and diastolic blood pressure decreased after microvascular decompression, and the need for antihypertensive medication was reduced. In parallel, central sympathetic nerve activity was elevated preoperatively and was reduced significantly by surgical treatment. However, these effects were limited in time; for 18 months after MVD, sympathetic vasoconstrictor activity increased again and achieved the high baseline level before surgery. These nerval effects were accompanied by a renewed increase in systolic and diastolic blood pressure 24 months postoperatively as well. These data give evidence for an association between neurovascular contact at the circulatory centers of the ventrolateral medulla oblongata and an increase of blood pressure. The elevated central sympathetic nerve activity appears as a link for the neurogenic pathomechanism in this specific subgroup of refractory hypertension mediating an increase of blood pressure by the elevated vasoconstrictor activity.

The rostral ventrolateral medulla regulates tonic sympathetic activity and plays a critical role in baroreflex arcs. Current knowledge indicates that nerval blood pressure regulation is determined by the balance of powerful tonic excitatory and inhibitory inputs. The concept of disturbance of this opposing forces by vascular compression is verified by the results of clinical trials that demonstrated that sympathetic
nerve activity in patients with essential hypertension with NVC is significantly higher as compared to that in patients with hypertension without NVC.\textsuperscript{5,15} It has been shown in a group of patients with a monogenic syndrome of hypertension, brachydactyly, and neurovascular compression that the ability of the baroreflex to buffer changes in vascular tone is severely impaired in these subjects.\textsuperscript{16} A microanatomic correlate for these results is given by the finding that the RVLM contains a high number of sympathoexcitatory bulbospinal neurons that increase the pressor effect on sympathetic effector organs.\textsuperscript{17} This hypothesis requires a close contact between the pulsatile artery and the RVLM. In our prospective study, blood pressure and sympathetic nerve activity were reduced by surgical intervention with microvascular decompression over a time period of 24 months postoperatively. These data underline the role of sympathetic overactivity caused by a looping artery impinging on the surface of the RVLM and activating sympathoexcitatory neurons by

Figure 2. Muscle sympathetic nerve activity before, 4 weeks, and 3, 6, 12, 18, and 24 months after microvascular decompression (burst frequency: bursts/min). *Statistical significance (P<0.05).

Figure 3. Representative original recording of muscle sympathetic nerve activity in a 49-year-old man with neurovascular compression and severe hypertension before and after microvascular decompression. Bursts are marked with a dot.
pulsatile compression in this selected subgroup of patients. However, the improvement of blood pressure was only transient and the reasons for the repeated increase of sympathetic nerve activity 18 months after surgery are not clear.

Differences in the applied neurosurgical technique among the operated patients is probably not a relevant cause because this procedure always was performed by the same experienced neurosurgeons. Furthermore, MRIs of the brain stem were performed postoperatively to confirm the surgical success and correct position of the Teflon felt in cases of increasing blood pressure. The rebound of hypertension may be attributable to the fact that our selected patients had a long history of severe high blood pressure with secondary end-organ damage. At this stage of “fixed” hypertension, recovery of adequate blood pressure control is rendered more difficult because of a progressively disturbed interplay of regulatory and counterregulatory neurohumoral and neural mechanisms.

It can be considered that the reduction of sympathetic nerve activity by surgical decompression may elicit an increased cardiovascular adrenergic responsiveness, as has been shown for pharmacological sympathetic neuron blockade. Other components of the pathogenesis of essential hypertension such as genetic factors, overweight, neurohumoral function, vasopressor–receptor resetting, and stress, which may all interact together and with the sympathetic nervous system, have to be considered as reasons for the repeated increase of blood pressure.

Our findings may suggest a positive feedback control of sympathetic activity in neurogenic hypertension with enhancing sympathetic outflow by an increased pulsatile compression caused by elevated blood pressure. The data conform with the understanding that central sympathetic nerve activity is important not only for the beat-to-beat regulation of blood pressure but also for the long-term circulatory control and counterregulatory neurohumoral and neural mechanisms. It can be considered that the reduction of sympathetic nerve activity by surgical decompression may elicit an increased cardiovascular adrenergic responsiveness, as has been shown for pharmacological sympathetic neuron blockade. Other components of the pathogenesis of essential hypertension such as genetic factors, overweight, neurohumoral function, vasopressor–receptor resetting, and stress, which may all interact together and with the sympathetic nervous system, have to be considered as reasons for the repeated increase of blood pressure.

Our work is a hint for the concept that neurovascular compression of the RVLM causes neurogenic hypertension mediated by a central sympathetic overactivity and that microvascular decompression reduces central sympathetic outflow that is accompanied by a reduction of blood pressure. Yet the results have to be interpreted cautiously because the operative effect is limited and neither blood pressure improvement nor sympathetic deactivation is sustained effectively for the long-term. Reliable criteria for accurate and reproducible imaging techniques to visualize compression are not established. It is necessary to create algorithms for the comprehensive characterization and identification of the subgroup of patients who may respond to decompression. Until then, MVD is not recommended as a procedure for the cure of hypertension and should be performed only in prospective study protocols.

**Sources of Funding**

The study was supported by a grant of the Deutsche Forschungsgemeinschaft (DFG FR 1602/1-1) and by a grant of the Johannes und Frieda Marohn-Stiftung of the University of Erlangen-Nuremberg (Nar/02).

**Disclosures**

None.

**References**

Temporary Reduction of Blood Pressure and Sympathetic Nerve Activity in Hypertensive Patients After Microvascular Decompression
Helga Frank, Karsten Heusser, Helmut Geiger, Rudolf Fahlbusch, Ramin Naraghi and Hans P. Schobel

Stroke. 2009;40:47-51; originally published online October 16, 2008;
doi: 10.1161/STROKEAHA.108.518670
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/1/47

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/