Hypertension in Patients with Neurovascular Compression Is Associated with Increased Central Sympathetic Outflow

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Abstract. Recent data suggest a causal relationship between essential hypertension and neurovascular compression (NVC) at the rostral ventrolateral medulla. An increase of central sympathetic outflow might be an underlying pathomechanism. The sympathetic nerve activity to muscle was recorded in 21 patients with hypertension with NVC (NVC+ group) and in 12 patients with hypertension without NVC (NVC− group). Heart rate variability, respiratory activity, BP, and central venous pressure at rest and during unloading of cardiopulmonary baroreceptors with lower-body negative pressure and during a cold pressor test were also measured. Resting sympathetic nerve activity to muscle was twice as high in the NVC+ group compared with the NVC− group (34 ± 22 versus 18 ± 6 bursts/min; P < 0.05). Resting heart rate (P = 0.06) and low-frequency power ratio values (P = NS) (as indicators of cardiac sympathovagal balance) tended to be augmented as well in the NVC+ group. The sympathetic nerve activity to muscle response to the cold pressor test was increased in the NVC+ group versus the NVC− group (+15 ± 11 versus 6 ± 12 bursts/min; P = 0.05), but hemodynamic and sympathetic nerve responses to lower-body negative pressure did not differ between the two groups. It is concluded that NVC of the rostral ventrolateral medulla in patients with essential hypertension is accompanied by increased central sympathetic outflow. Therefore, these data support the hypothesis described in the literature: in a subgroup of patients, essential hypertension might be causally related to NVC of the rostral ventrolateral medulla, at least in part, via an increase in central sympathetic outflow.

The central nervous system is not only responsible for the minute-to-minute regulation of arterial BP, but also has been implicated in the development of chronic hypertension (1). A novel mechanism for central nervous system–induced hypertension has been proposed. Janetta et al. (2) were the first to describe a possible association between essential hypertension and intraoperatively observed neurovascular compression (NVC) of the rostral ventrolateral medulla (RVLM) at the level of the root entry zone of cranial nerves IX and X on the left side. Animal-model studies (3–5), autopsy studies (6), and radiographic studies (7–9) confirmed these findings. Additionally, in a prospective study, we previously observed that microvascular brain stem decompression in the area of cranial nerves IX and X might improve BP control in patients with severe hypertension (10).

The RVLM is an important cardiovascular control center because it is a major source of supraspinal sympathetic outflow to heart, kidneys, and vessels (11,12). Thus, the hypothesis has been put forward, supported by experimental studies in rats (3), that pulsatile NVC in this region might induce arterial hypertension by means of enhancing central sympathetic outflow to cardiovascular effectors. Whether similar autonomic abnormalities occur in humans is not definitively known, however.

To further investigate this hypothesis in humans, we applied direct microneurographic measurements of intraneuronal sympathetic nerve activity to muscle (MSNA) in patients with essential hypertension who had neuroradiologically proven NVC and contrasted the results with those of control patients with hypertension without NVC. We also assessed cardiac sympathovagal balance (by spectral analysis of heart rate variability), ambulatory 24-h BP, and echocardiographic parameters. Because malfunctions of autonomic cardiovascular control might occur both at rest and during stress, we also applied lower-body negative pressure to test cardiopulmonary baroreflex mechanisms, and we used a cold pressor test as a nonspecific sympathoexcitatory stimulus.

Materials and Methods

Subjects

We consecutively recruited a total of 33 white patients (21 men and 12 women) with essential hypertension who were referred to our outpatient clinic (tertiary referral center) of the Erlangen University Hospital by general practitioners and internists for further hyperten-siologic work-up (especially to rule out renal hypertension). Patients were diagnosed as hypertensive if their systolic BP values were more than 140 mmHg, their diastolic BP readings were more than 90 mmHg on repeated clinic visits, or both; or if they had been receiving

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antihypertension medication for documented essential hypertension. Renal and other secondary forms of hypertension were excluded by appropriate tests. At the time of enrollment and throughout the study, all patients were receiving stable antihypertension medication according to international guidelines. Informed written consent was obtained before the study, and the protocol was approved by the ethics committee of the University of Erlangen-Nuremberg.

**Magnetic Resonance Tomography Evaluations**

Magnetic resonance tomography was performed with a 1.5-T MagnetomAQ (Philips Gyroscan ACS-NT, Eindhoven, The Netherlands) in a head coil. We performed T2-weighted transverse and coronal turbo spin echo three-dimensional studies (TR 4000, TE 250). The slices were 1 mm thick without a gap. In addition, axial magnetic resonance angiography of the posterior fossa was performed (TR 39, TE 6.9, flip angle 20°) with a slice thickness of 0.5 mm and maximum intensity protection-reconstruction. A positive finding of NVC in essential hypertension was defined as the presence of a vascular signal at the ventrolateral medulla on the left, caused by a vascular loop according to the types of NVC as described previously (6,7) (Figure 1). The ventrolateral medulla extends in craniocaudal direction from the root entry zone of the cranial nerve IX down to the upper part of the cranial nerve XI. It is dorsolateral to the olive and medioventral to the root entry zone of the cranial nerves IX and X, as described previously (6).

Thus, the patients were classified into two groups according to the existence (NVC+/H11001) or nonexistence (NVC/H11002) of NVC. The magnetic resonance tomography studies were evaluated independently by a neurosurgeon familiar with the operation of NVC and a neuroradiologist, both of whom were unaware of the patients’ medical histories.

**Measurements**

Twenty-four-hour ambulatory BP measurements were achieved by use of an automated portable device (Spacelabs Medical, Redmond, WA). The measurements were carried out automatically every 15 min during the day and every 30 min during the night, yielding the 24-h pressure profile. In the laboratory, systolic, diastolic, and mean arterial pressure were measured noninvasively, beat to beat, by a photoplethysmographic finger device (Finapres; Ohmeda, Englewood, CO), as described in detail elsewhere (13). Heart rate (electrocardiogram), respiratory activity (pneumograph), central venous pressure (by an 18.5-gauge polyethylene catheter inserted peripherally in an antecubital vein and advanced to the superior vena cava), level of lower-body negative pressure, and MSNA were recorded on a direct-writing multichannel physiologic recorder (Gould, Oxnard, CA).

Multunit recordings of postganglionic sympathetic nerve activity were obtained with unipolar tungsten microelectrodes selectively inserted into muscle nerve fascicles of the peroneal nerve posterior to the fibular head by the microneurographic technique of Vallbo et al. (14). This technique has been validated and extensively described in many studies (14–20). For analysis, sympathetic bursts were identified by inspection of the filtered and mean voltage neurograms. The rate of sympathetic nerve discharge was expressed as the number of bursts per minute (burst frequency) and—corrected for heart rate—as bursts per 100 heart beats (burst incidence). All nerve recordings were analyzed by two investigators who were unaware of the group assignment (NVC+ versus NVC−) of the subjects. Similar to previous studies in our laboratory (15,16), the intraobserver and interobserver variability in identifying bursts were approximately 5% and less than 10%, respectively.

**Figure 1.** Magnetic resonance tomography images from a 38-yr-old woman. (A) Turbo spin echo (TSE) T2 axial image of the medulla oblongata with a prominent loop of the posterior inferior cerebellar artery (PICA) originating from the vertebral artery (AV), leading to a neurovascular compression (NVC) at the ventrolateral medulla on the left in a patient with essential hypertension. CN 9 and 10, cranial nerves 9 and 10; AV, vertebral artery. (B) TSE T2 coronal view of the medulla showing the convexity of the PICA loop at the ventrolateral medulla resulting into an NVC. (C) Axial magnetic resonance–angio-gram reconstruction showing the course of the PICA loop at the left ventrolateral medulla.

Spectral parameters of heart rate variability were determined according to international guidelines (21). During stable rest in a recumbent position, the patients’ electrocardiograms were sampled at a
rate of 1 kHz for 5 min. From the occurrence times of the R-wave fiducial points, the discrete event series was calculated and was interpolated by a commercially available algorithm (monotonicity-preserving piecewise cubic hermite). After trend removal, the resulting, regularly sampled (more than 10 Hz) interpolant was fed without windowing into the fast Fourier transformation algorithm. The spectral powers of the low-frequency (LF; 0.05 to 0.15 Hz) and high-frequency (HF; 0.15 to 0.40 Hz) bands, as well as their normalized values, (nLF, nHF) and their ratio (LF/HF), were computed. The LF component predominantly represents sympathetic activity, whereas the HF component reflects parasympathetic activity. The LF/HF ratio is calculated as an indicator of cardiac sympathovagal balance.

Procedures and Protocol

All studies were performed at the same time of day, starting at 2:00 PM, with the subjects supine in the postabsorptive state (i.e., at least 90 min after the ingestion of a light meal) in a warm (22 to 24°C) and quiet room. Subjects were instructed to maintain their usual diet and medication before the study and to avoid alcohol, caffeine-containing beverages, and tobacco during the 12 h before the study. After a resting period of 20 min after the insertion of the nerve electrode and the application of the other monitoring devices, parameters were recorded continuously for at least 5 min at rest, and subsequently during 2 cardiovascular stress tests. First, orthostatic stress was simulated by the application of lower-body negative pressure for consecutive 2-min periods at levels of 0 (control), −5, −10, and −15 mmHg to reduce cardiac filling pressures without significantly altering arterial or pulse pressure (17,18). After a period of at least 5 min of rest to permit hemodynamic and MSNA parameters to return to baseline levels, responses to the cold pressor test were assessed by immersion of one of the subject’s hands up to the wrist in ice water for 2 min (19). The reported values represent the mean for each period.

Statistical Analyses

All data are presented as mean ± SD. Two-tailed t test for unpaired data were used to compare MSNA, heart rate variability indexes, and hemodynamic parameters at rest and in response to lower-body negative pressure and to the cold pressor test between the NVC+ and NVC− subjects. Relationships between parameters were assessed with multiple regression analysis. Statistical significance was considered as P < 0.05.

Results

Twenty-one (64%) of 33 patients with essential hypertension were identified to have NVC of the ventrolateral medulla at the root-entry zone of cranial nerves IX and X on the left side (NVC+ group). According to our classification of vascular loops (6,7), 13 patients had type I (posterior inferior cerebellar artery loop) NVC on the left side, 2 patients had type II (ectatic vertebral artery) NVC, 5 patients had type III (combination of type I and II) NVC, and 1 patient had a bilateral compression (left side, type III; right side, type I). Figure 1 shows a typical type I NVC in the axial and coronal slices.

Characteristics of the patients are given in Table 1. The two groups did not significantly differ with regard to age, gender, body-mass index, family history of hypertension, duration of hypertension, use of antihypertensive medication (including diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and central sympatholytics), degree of hypertensive end-organ damage, and average 24-h systolic and diastolic BP values. Hypertensive crises had occurred more often in the NVC+ group (81%) than in the NVC− group (36%).

In the laboratory, resting BP values were significantly higher in the NVC+ group as compared with the NVC− group (systolic pressure, 177 ± 31 versus 148 ± 20 mmHg; P < 0.01; diastolic pressure, 100 ± 22 versus 83 ± 13 mmHg; P < 0.05). The NVC+ subjects also had a faster heart rate than the NVC− subjects (77 ± 19 versus 66 ± 8 beats/min; P = 0.06), but the resting values of central venous pressure did not differ from each other (9 ± 2 versus 8 ± 2 mmHg; P = NS).

Figure 2 shows group resting sympathetic activities. Resting MSNA was almost twice as high in the NVC+ subjects compared with the NVC− subjects, both when expressed as burst frequency (34 ± 22 versus 18 ± 7 bursts/min; P < 0.05) and when expressed as burst incidence (44 ± 21 versus 29 ± 11 bursts/100 heart beats; P < 0.05). The LF/HF ratio tended to be higher as well in the NVC+ group compared with the NVC− subjects (3.3 ± 2.0 versus 2.1 ± 1.2; P = NS). In Figure 3, representative experimental recordings from two men are shown to illustrate resting hemodynamic and sympathetic activity. Despite similar age and body-mass index, the NVC+ subject had a considerably higher sympathetic nerve activity than the NVC− subject. MSNA was significantly correlated with systolic arterial pressure under laboratory resting conditions (r = 0.36, P < 0.05; Figure 4) but did not significantly correlate with age, body-mass index, or LF/HF ratio.

Figure 5 compares the MSNA responses to lower-body negative pressure at −15 mmHg and the cold pressor test.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NVC+ (n = 21)</th>
<th>NVC− (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46 ± 10</td>
<td>39 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/9</td>
<td>9/3</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.3 ± 4.9</td>
<td>27.3 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of hypertension (%)</td>
<td>83</td>
<td>73</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hypertension (yr)</td>
<td>10 ± 8</td>
<td>7 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertensive crises (%)</td>
<td>81</td>
<td>36</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Antihypertensive medication (Y/N)</td>
<td>21/0</td>
<td>12/0</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>110 ± 35</td>
<td>93 ± 36</td>
<td>NS</td>
</tr>
<tr>
<td>Mean stage of fundus hypertonicus</td>
<td>1.7 ± 0.7</td>
<td>1.6 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (24 hr) (mmHg)</td>
<td>158 ± 29</td>
<td>144 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (24 hr) (mmHg)</td>
<td>99 ± 19</td>
<td>90 ± 15</td>
<td>NS</td>
</tr>
</tbody>
</table>

*a NVC, neurovascular compression; NVC+, hypertensive with NVC; NVC−, hypertensive without NVC.
Although increases in sympathetic nerve activity were similar between the 2 groups during lower-body negative pressure, the MSNA response to the cold pressor test was augmented in the NVC+/H11001 group as compared with the NVC+/H11002 group ($15 \pm 11$ versus $+6 \pm 12$ bursts/min; $P = 0.05$). Hemodynamic responses during the 2 cardiovascular stress tests did not differ between the NVC+ and the NVC− subjects, apart from a tendency for a stronger increase in BP evoked by the cold pressor test in the NVC+ group ($+13 \pm 7$ versus $+10 \pm 13$; $P = \text{NS}$).

**Discussion**

We found that sympathetic vasoconstrictor discharge to skeletal muscle was markedly elevated in patients with essential hypertension with NVC as compared with those without NVC and that this parameter is correlated with systolic arterial pressure (Figure 4), although it explains only a minor proportion of BP variance. The patients with NVC also had augmented sympathetic nerve responses to the cold pressor test and tended to have a higher LF/HF ratio of heart rate variability. These findings favor the hypothesis described in the literature that in a subgroup of patients, NVC of the ventrolateral medulla might be causally related to essential hypertension, at least in part, by an increase in central sympathetic outflow. A case report by Morimoto et al. (22) strongly supports this hypothesis; this study demonstrated a reduction in sympathetic nerve activity to muscle, plasma, and urine norepinephrine levels, LF/HF ratio, and BP in a 47-yr-old man with essential hypertension who underwent microvascular decompression due to NVC of the RVLM.

Neurosurgical observations in patients who underwent microvascular decompression because of hemifacial spasm or trigeminal neuralgia (2) first suggested an association between essential hypertension and NVC of the RVLM at the root entry zone of cranial nerves IX and X on the left side. The hypothesis that this phenomenon is not just secondary to long-standing arterial hypertension causing vascular elongation or ectasia but might have a causal relation to hypertension is supported by the following: first, NVC of the RVLM occurs more often in patients with essential hypertension than in those with secondary hypertension of similar degree and duration (3,6,7,23–26). Second, NVC by looping vessels occurs more often at the left side (6,7). Third, the prevalence of NVC of other cranial nerves is not increased by the existence of arterial hypertension. Fourth, microvascular decompression is a successful treatment, at least in some patients with severe hypertension and NVC (1,10). Fifth, simulation of pulsatile NVC at the RVLM of baboons caused severe arterial hypertension that normalized when the simulator was switched off (5). Consequently, recent research in this field focused on elucidating the potential mechanism or mechanisms by which NVC of the RVLM might be linked to essential hypertension.

Experimental studies in rats indicated that pulsatile compression of the RVLM increases arterial pressure by enhancing sympathetic outflow (3). These data are in agreement with the anatomic fact of the RVLM being a major site of origin of central sympathetic outflow. To date, only limited human data exist to support this concept. Morise et al. (27) found an elevated LF power of heart rate variability in patients with essential hypertension with NVC as compared with either patients with essential hypertension without NVC or patients without hypertension with NVC. Furthermore, a few recent studies found elevated venous norepinephrine levels at rest in

**Figure 2.** Bar graphs comparing group values for resting levels of sympathetic nerve activity to muscle (MSNA) between the patients with hypertension with neurovascular compression (NVC+ group) and those without (NVC− group). The NVC+ patients had significantly higher levels of MSNA compared with the NVC− patients, both when expressed as burst frequency and when expressed as burst incidence.

**Figure 3.** Recordings showing the resting levels of sympathetic nerve activity to muscle (MSNA) in a representative man with hypertension with neurovascular compression (NVC; NVC+) and a representative man with hypertension without NVC (NVC−) of similar age and body-mass index (BMI). The NVC+ patient had a markedly higher level of sympathetic activity than the NVC− patient.
patients with NVC of the RVLM (28–30). Venous catecholamines, however, constitute only insensitive measures of sympathetic activity that are influenced by many factors, such as efferent neural activity, synaptic transmitter release, reuptake mechanisms, and regional blood flow (30,31). Furthermore, sympathetic outflow to all organs is not uniform, and local, organ-specific increases and decreases in sympathetic activity can occur with different reflexes and in different disease states. Venous norepinephrine levels merely represent the algebraic sum of these changes and thus convey rather imprecise physiologic information.

Therefore, to gain more precise, quantitative, and reproducible information on sympathetic activity (32), we used the microneurographic approach of directly recording sympathetic outflow to muscle vascular beds—that is, a district where peripheral vascular resistance is largely determined. We also performed measurements of cardiac sympathovagal balance by spectral analysis of heart rate variability. The results were unequivocal: sympathetic nerve activity to muscle was almost twice as high in patients with hypertension with NVC than in those without NVC. Furthermore, resting levels of heart rate and the LF/HF heart rate variability ratio tended to be higher in the NVC+ group as well, indicating that enhancement of central sympathetic outflow in these patients is not solely restricted to the peripheral resistance vessels but might be directed to the heart, too. Although this measure of sympathovagal balance in cardiac regulation did not reach significance in our study, it is in line with the results of another group (27).

Because MSNA responses to lower-body negative pressure were not different between the two groups, the higher level of resting sympathetic activity in the NVC+ patients cannot be explained by a decrease in cardiopulmonary baroreflex sensitivity. This finding most likely rules out the hypothesis of an NVC-induced blockage of cardiac vagal C-fibers with resulting partial deafferentation of the nucleus tractus solitarii, which is the primary site for processing the afferent signals from the baroreceptors. The fact that MSNA responses to the nonbaroreflex-mediated cold pressor test were enhanced in the NVC subjects indicates an increase in generalized sympathetic reflex responsiveness in these people.

Although the MSNA response to the cold pressor test was higher in the NVC+ group, the elevation of arterial pressure did not reach significance. This discrepancy might be due to the following. First, rising sympathetic nerve activity does not release a proportional amount of norepinephrine because higher levels of the transmitter within the synaptic cleft inhibit its own release via presynaptic α-2 receptors. Second, vasoconstriction is modulated by the release of cotransmitters—for example, ATP and neuropeptide Y. Thus, microneurography—which allows for a direct assessment of sympathetic activity—is able to detect states of sympathetic activation more accurately than by measuring effector organ responses.

The exact mechanism by which NVC of the RVLM and central sympathetic outflow in humans is linked, however, cannot be determined from our study. Recent animal data suggest that pulsatile compression of the RVLM increases sympathetic activity by activating postsynaptic RVLM neurons through stimulation of local glutamate receptors (33).

From Figure 4, we infer that in patients whose NVC is responsible for arterial hypertension, NVC is not the major diagnosis but rather a subsidiary one. This is further supported by the fact that the relief of hypertension by neurosurgical microvascular decompression is not guaranteed. We suggest that NVC diagnosed by magnetic resonance tomography overestimates the number of pathophysiologically relevant NVC. Furthermore, in a subgroup of patients with essential hyper-
tension, NVC might only aggravate the disease (by approxi-
mately 20 mmHg, according to Figure 4), but might not explain
it in full detail.

Most interestingly—and a potential weakness of the study—
together with sympathetic activation, the patients with NVC
exhibited higher BP levels under resting laboratory condi-
tions than did the patients without NVC, although they did not
significantly differ from each other with regard to their amбу-
latory 24-h BP profiles or their degree of hypertensive end-
organ damage. The higher MSNA in patients with NVC should
not be interpreted as part of an alerting response to the BP
measurement in the laboratory; rather, it is more likely a
feature of the disease. Grassi et al. (34) have shown that
although skin sympathetic nerve activity increased, muscle
sympathetic nerve activity was suppressed in response to BP
measurement in the laboratory. Rather, our findings might
suggest the existence of a positive feedback control of sympa-
thetic activity in these patients; thus, any stress-induced rise in
BP might lead to a stronger pulsatile neurovascular contraction
and compression, thereby enhancing sympathetic outflow,
which in turn increases BP. This hypothesis would also explain
the higher incidence of BP crises in the patients with NVC than
those without, as well as the fact that patients with severe,
pharmacologically uncontrollable hypertension and NVC
might benefit from neurosurgical decompression (10).

Furthermore, ongoing medication is unlikely to be the rea-
son for the sympathetic overactivity found in the NVC+ pa-
tients, because the antihypertensive drug classes used were
similar in both groups. This also holds for the relation of drugs
dampening (i.e., central sympatholytics) and activating (i.e.,
vasodilators) central sympathetic outflow. We decided to
maintain stable long-term treatments because in some patients,
withdrawal did not seem safe, and discontinuing medication
could produce unforeseeable alterations in cardiovascular reg-
ulation, with distortion of the results occurring to an even
greater extent.

In conclusion, our data show that NVC of the RVLM in
patients with essential hypertension is accompanied by a sig-
ificantly augmented central sympathetic outflow. Taking into
account the findings described in the literature, our results
concur with the hypothesis that a subgroup of patients with
essential hypertension exists whose increase in BP might, at
least in part, be causally related to NVC of the RVLM via an
increase in central sympathetic outflow. These patients seem to
be at a particularly high risk for the occurrence of hypertensive
crises.

Nevertheless, the subject of this work is far from being
completely clear. Advanced imaging techniques and a more
comprehensive characterization of patients with hypertension
with NVC of the RVLM are necessary to gain more insight.
Quantification of sympathetic vasomotor activity might play a
crucial role in this puzzle.

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