Increased Sympathetic Nerve Activity Correlates With Neurovascular Compression at the Rostral Ventrolateral Medulla

Mauricio M. Sendeski, Fernanda Marciano Consolim-Colombo, Claudia Costa Leite, Marcelo Custódio Rubira, Patricia Lessa, Eduardo Moacyr Krieger

Abstract—We used microneurography to measure muscle sympathetic nerve activity (MSNA) in 25 hypertensive subjects and correlated these results with the presence or absence of signs of neurovascular compression (NVC) at the rostral ventrolateral (RVL) medulla on MRI. Subjects were divided into 3 groups based on MRI findings: NVC−, no MRI evidence of NVC (N=9); NVC+contact, image showing artery in contact but not compressing the RVL medulla (N=8); and NVC+compression, image showing arterial compression of the RVL medulla (N=8). The MSNA measurements were performed at rest, after a hypothermic stimulus, and during isometric exercise. The MSNA during rest in the NVC+compression group was significantly higher than that in the NVC+contact and NVC− groups (30.4±3.4 versus 17.5±1.1 and 21.4±3.2 spikes per minute, respectively). However, the blood pressure in the NVC+compression group was slightly but not significantly higher than that in the other 2 groups (183±7/115±8, 174±6/108±7, and 171±5/110±5 mm Hg, respectively). The increases in MSNA, blood pressure, and heart rate during the cold pressor and isometric exercise tests were similar. Our results show that, although resting MSNA is elevated in patients with true NVC of the RVL medulla, patients without NVC or with arterial contact but not overt compression of the RVL medulla have similar MSNA. These findings are important for identifying, among hypertensive patients with NVC, individuals who may have associated physiological repercussions, such as increased sympathetic activity. (Hypertension. 2006;47:988-995.)

Key Words: sympathetic nervous system ■ magnetic resonance imaging

Primary hypertension in humans has a high prevalence worldwide and is considered to be multifactorial and polygenic. Central sympathetic activation has been implicated in the pathogenesis of hypertension (HTN), although its mechanisms still remain unclear.1 Neurovascular compression (NVC) is a neuroanatomical anomaly of the brain stem classically associated with neurological diseases, such as hemifacial spasm and neuralgia of the trigeminal and glossopharyngeal nerves. NVC has also been related to neurogenic HTN when occurring at the rostral ventrolateral (RVL) medulla,2 a region identified as an important efferent pathway of the sympathetic nervous system.3–5 Various techniques for identifying NVC at RVL medulla in humans have been described since the first intraoperative reports by Jannetta and Gendell.6,7 Currently, MRI is the most effective method for studying details of the brain stem and surrounding vessels involved in NVC. In some studies, the frequency of signs of NVC has ranged from 7% to 22.2% in nonhypertensive subjects, from 11% to 16.6% in subjects with secondary HTN, and from 74% to 90% in subjects with primary HTN.8–11 These data suggest that NVC may be associated with primary HTN and not secondary to prolonged exposure to high blood pressure (BP). Other studies, which used different means of assessment, revealed no difference in the frequency of NVC in populations with and without primary HTN.12–15

Although the pathophysiological role of NVC in HTN remains controversial, evidence from surgical series and some case reports suggests that surgical treatment of NVC at the RVL medulla influences the control of HTN.16–20 Experimental data also have shown that artificial pulsatile compression of the RVL medulla in baboons and rats produces sympathetic hyperactivity and hyperdynamic responses.21,22 The presence of a similar mechanism in humans may explain why surgical treatment of NVC has successfully reduced BP in a subset of hypertensive patients.23 Few studies, with different approaches, have evaluated sympathetic activity in hypertensive subjects with and without signs of NVC on MRI.24–27 Their results pointed to the presence of increased sympathetic activity in hypertensive and normotensive subjects with NVC of RVL medulla.

At the moment, the data obtained from experimental studies demonstrate evidence for vessel compression playing a role in HTN. Human studies are scarce and indicate that
although the NVC at RVLM may not be the principal mechanism of primary HTN, it can play an important role in increasing central sympathetic nerve activity in a subgroup of hypertensive patients.

Given the variable degree of vascular compression produced in adjacent neural structures, additional studies are needed to evaluate the relationship between NVC and sympathetic outflow. Accordingly, this study investigated, by direct recording of muscle sympathetic nerve activity (MSNA) in hypertensive subjects with and without MRI evidence of NVC, whether NVC is associated with hyperactivity of the sympathetic nervous system at baseline and in response to standard physiological stress tests.

Methods

Population

Twenty-five outpatients with primary HTN, representing both sexes and ages 20 to 55 years, selected from the InCor Hypertension Outpatient Service were studied. A diagnosis of HTN was made according to the Joint National Committee criteria (VI) based on the presence of arterial BP measurements (>140 and 90 mm Hg for systolic and diastolic BP, respectively).28 All of the patients were submitted to general physical, neurological, and laboratory study. Individuals were free of clinical evidence of arterial disease, peripheral or neurological, and/or clinical conditions that increase sympathetic activity or alter MSNA (eg, diabetes mellitus, heart failure, obesity, or peripheral neuropathies). The committee of ethics on research of our institution approved the study, and all of the participants provided written, informed consent after receiving a detailed explanation of the study procedures.

MRI

The MRI was performed with a 1.5 T scanner (GE - Horizon), using a head coil; ≥3 sequences were obtained in each individual: fast spin-echo sagittal T1 localizer, axial T2, and coronal T2, with 3-mm–thick slices and an interslice interval of 1 mm. The field of view used was 20 cm, the matrix varied between 196 and 256×256, and the number of excitations ranged from 2 to 4. Occurrence of neurovascular contacts with the RVLM medulla was analyzed at the level of the root entry zones of the ninth and tenth cranial nerves. No evidence of NVC at the RVLM medulla (NVC”) was defined whenever the vessels and the nervous tissue were separated by a space, that is, there was a “white” cerebrospinal fluid between the “black” of the blood vessel and the “gray” of the medulla (Figure 1A). Two circumstances were considered positive signs of NVC according to different degrees of relationship between vessel position and the subjacent nervous tissue the medulla: (1) NVC+ contact was defined by presence of a vessel simply touching the RVLM medulla associated with a normal contour of the medulla, that is, by the absence of white cerebrospinal fluid between the black of the blood vessel and the gray of the medulla (Figure 1B); (2) NVC+ compression was defined when a vessel contacted the neural tissue indenting the surface of the medulla, that is, causing a depression of the normally regular adjacent tissue (Figure 1C). The number of vessels, laterality, and identity of the probable vessel involved in the NVC also were recorded.

Measurements

The BP (systolic, diastolic, and mean) was measured noninvasively and beat-to-beat using a photoplethysmographic finger device (Finapres-Ohmeda 2300, Ohmeda). A multichannel physiological recorder (Gould) and a computer coupled to a signal converter (Stemtech, Inc) were used to record the heart rate (HR; electrocardiography), BP, and MSNA. AT/MCA-CODAS software (DATAQ Instruments, Inc), with a sampling frequency of 500 Hz per channel, was used for signal acquisition and store; data from the latter were analyzed using Excel (Microsoft) worksheets.

The MSNA was obtained through multunit recordings of postganglionic sympathetic nerve activity; this involved the selective insertion of unipolar tungsten microelectrodes into muscle nerve fibers of the fibular nerve posterior to the fibular head, according to indirect inquiry, to detect possible harmful effects of medication withdrawal. The subjects also were instructed to avoid use of products containing alcohol, caffeine, and nicotine in the days preceding the protocol.

Microneurography Protocol

To avoid interference with measurements, all of the evaluations of sympathetic activity were made after withdrawal of antihypertensive medication in accordance with the half-life of each drug. Each subject was then surveyed, through repeated BP measurements and direct inquiry, to detect possible harmful effects of medication withdrawal. The subjects also were instructed to avoid use of products containing alcohol, caffeine, and nicotine in the days preceding the protocol.

Figure 1. MRIs showing typical findings in our study: (A) T2 axial image of the medulla oblongata with the vertebral arteries in their normal positions (white arrow), away from the medulla, called NVC”; (B) T2 axial image of the medulla oblongata with the vertebral artery and posterior inferior cerebellar artery (white arrow), in contact with the medulla, but not compressing it, called NVC+ contact; (C) T2 axial image of the medulla oblongata with the left vertebral artery (white arrow), clearly indenting the surface of the left RVLM medulla, called NVC+ compression.
TABLE 1. Distribution of Probable Vessels Involved in NVC and Side of RVL Medulla Compromise

<table>
<thead>
<tr>
<th>MRI Finding (n=10)</th>
<th>Vessel</th>
<th>n</th>
<th>Side of Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular contact* (n=8)</td>
<td>Left PICA</td>
<td>3</td>
<td>Left</td>
</tr>
<tr>
<td></td>
<td>Right and left VA</td>
<td>2</td>
<td>Right and left</td>
</tr>
<tr>
<td></td>
<td>Left VA</td>
<td>1</td>
<td>Left</td>
</tr>
<tr>
<td></td>
<td>Right VA</td>
<td>1</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>Right PICA and right VA</td>
<td>1</td>
<td>Right</td>
</tr>
<tr>
<td>Vascular compression† (n=8)</td>
<td>Right VA</td>
<td>3</td>
<td>Right</td>
</tr>
<tr>
<td></td>
<td>Left VA</td>
<td>2</td>
<td>Left</td>
</tr>
<tr>
<td></td>
<td>Right and left VA</td>
<td>2</td>
<td>Right and left</td>
</tr>
<tr>
<td></td>
<td>VA + BA</td>
<td>1</td>
<td>Left and right</td>
</tr>
</tbody>
</table>

PICA indicates posterior inferior cerebellar artery; VA, vertebral artery; BA, basilar artery.
*Image showing vessel in contact with the RVL medulla but not distorting its outline.
†Image showing frank compression of the RVL medulla by a vessel with clear anatomical distortion.

After placement of the electrode and other devices, the patient was subjected to 10 minutes of rest to ensure that the BP, HR, and MSNA were at basal conditions. Activity was then recorded for 10 minutes (baseline conditions), and exposure to different stimuli (cold water and isometric exercise) was initiated. The cold pressor stimulus, which was applied immediately after the basal period, involved immersion of the hand up to the wrist in ice water for 2 minutes; this stimulus was followed by another 10-minute rest period to ensure that their BP, HR, and MSNA returned to basal conditions. After that, MSNA, BP, and HR were recorded for 2 minutes (baseline conditions), and the subjects were engaged in isometric exercise, which involved pulling a dynamometer at 30% of the subject’s maximum effort for 2 minutes.

The BP and HR are expressed in mm Hg and bpm, respectively. Baseline values represent the mean values obtained during all of the basal period (2 minutes). The highest values attained during 15-s periods during the tests are considered responses to the stimuli. The MSNA expressed as spikes per minute represents the mean value for each period. The MSNA expressed as spikes per heartbeat represents at baseline the ratio between MSNA and HR during basal period and, in response to stimuli, represents the ratio between the highest MSNA values attained during 15-s periods during the tests and the corresponding HR at this moment.

Statistical Analyses
The results from the clinical and laboratory tests are expressed as the mean±SD, and the results from the evaluation of sympathetic activity (hemodynamic and MSNA data) are expressed as the mean±SE. All of the categorical variables were analyzed using χ² or Fisher’s exact test. ANOVA and Tukey’s modified test were used to establish whether significant differences in baseline or continuous variables existed between groups. Values for P<0.05 were considered statistically significant.

Results
On MRI, 9 of 25 had no evidence of NVC at the RVL medulla (NVC⁻ group). The other 16 patients were considered to have NVC⁺ at the RVL medulla and were separated in 2 groups according to different degrees of relationship between vessel position and the subjacent nervous tissue the MRI images: the NVC⁺ contact group (n=8) and the NVC⁺ compression group (n=8). Table 1 shows the side of medulla involved in the NVC, the probable vessel involved, and the type of findings suggestive of NVC. Figure 1 shows the typical appearance of MRIs in patients with no NVC (NVC⁻), vascular contact of the RVL medulla (NVC⁺ contact), and vascular compression of the RVL medulla (NVC⁺ compression).

Clinical and Laboratory Characteristics
Table 2 summarizes clinical and laboratory characteristics of the 3 study groups while under medication. The groups did not differ in regard to age; body mass index; duration of HTN; number of antihypertensive medications in use; systolic and diastolic BP; HR; and serum levels of glucose, sodium, potassium, uric acid, creatinine, and total cholesterol. Compared with the 2 other groups, the serum triglyceride level was higher in the NVC⁺ contact group.

Hemodynamic Parameters and Sympathetic Activity
The HR and BP values during the rest period were similar among groups: systolic BP in the NVC⁺ compression group was 183±7 mm Hg versus 174±6 and 171±5 mm Hg in the NVC⁺ contact and NVC⁻ groups, respectively. Diastolic BP in the NVC⁺ compression group was 115±8 mm Hg versus 108±7 and 110±5 mm Hg in the NVC⁺ contact and NVC⁻ groups, respectively (Figure 2A). The HR in the NVC⁺ compression group was 81±6 bpm versus 71±3 and 72±3 bpm in the NVC⁺ contact and NVC⁻ groups, respectively (Figure 2B).

Under resting conditions, the NVC⁺ compression group had significantly higher MSNA compared with the other 2 groups. The number of spikes per minute was 30±4±3.4 for the NVC⁺ compression group versus 17.5±1.1 and 21.4±3.2 in the NVC⁺ contact and NVC⁻ groups, respectively (Figure 2C). The number of spikes per heartbeat in resting conditions was also significantly higher in the NVC⁺ compression.
group, 0.41 ± 0.08 versus 0.25 ± 0.02 and 0.30 ± 0.05 spikes/heartbeat in the NVC+contact and NVC− groups, respectively (Figure 2D).

Cold Pressor Test

The NVC+compression group had significantly higher increases in systolic BP when compared with the NVC+contact group (respectively, 34.7 ± 7 mm Hg versus 10 ± 2.3 mm Hg; P = 0.02) and reached a P = 0.05 compared with the controls (NVC− group; respectively, 34.7 ± 7 mm Hg versus 21 ± 4.5 mm Hg; Figure 3A). The diastolic BP and HR responses were similar in all of the groups. The increase in diastolic BP in the NVC+compression group was 19 ± 4 mm Hg versus 12 ± 4 and 13 ± 3 mm Hg in the NVC+contact and NVC− groups, respectively (Figure 3A). The increase in HR in the NVC+compression group was 13 ± 2 bpm versus 17 ± 3 and 17 ± 4 bpm in the NVC+contact and NVC− groups, respectively (Figure 3B). The increase in MSNA in the NVC+compression group was 12.9 ± 2.8 spikes/min versus 11.8 ± 2.1 and 13.2 ± 2.2 spikes/min in the NVC+contact and NVC− groups (Figure 3C), respectively, and 0.15 ± 0.05 spikes/heartbeat versus 0.13 ± 0.05 and 0.10 ± 0.07 spikes/heartbeat in the NVC+contact and NVC− groups, respectively (Figure 3D). This test caused a similar increase in the MSNA in all groups analyzed by spikes/min and spikes/heartbeat (Figure 3D).

However, it is important to note that the NVC+compression group maintained higher sympathetic activity compared with other groups (respectively, 46 ± 5.2 bursts/min, 30 ± 2.7 bursts/min, and 35 ± 2.3 bursts/min, for NVC+compression, NVC+contact, and NVC− groups, respectively; P < 0.02), which represents, expressed in spikes/heartbeat, an MSNA of 0.61 ± 0.10, 0.37 ± 0.04, and 0.45 ± 0.04, respectively.

Isometric Exercise

The responses to the isometric exercise were similar in the 3 groups. The increase in systolic BP in the NVC+compression group was 16 ± 3 mm Hg versus 12 ± 2 and 19 ± 5 mm Hg in the NVC+contact and NVC− groups, respectively. The increase in diastolic BP in the NVC+compression group was 9 ± 3 mm Hg versus 9 ± 1 and 12 ± 5 mm Hg in the NVC+contact and NVC− groups, respectively (Figure 4A). The increase in HR in the NVC+compression group was 8 ± 2 bpm versus 21 ± 4 and 13 ± 3 bpm in the NVC+contact and NVC− groups, respectively (Figure 4B). The increase in
MSNA in the NVC+compression group was 4.4 ± 2.8 spikes/min versus 7.4 ± 2.0 and 7.9 ± 2.0 spikes/min in the NVC+contact and NVC groups, respectively (Figure 4C), and 0.02 ± 0.03 spikes/heartbeats versus 0.10 ± 0.03 and 0.08 ± 0.04 spikes/heartbeats in the NVC+contact and NVC− groups, respectively (Figure 4D).

Discussion

The major finding in this study is that hypertensive subjects with clear signs of NVC of the RVL medulla have higher levels of sympathetic activity, measured directly by microneurography, than hypertensive subjects without deformation or with only vascular contact of the medulla visible on MRI. The anatomic variability of NVC at the RVL medulla has already been documented in initial studies by Jannetta and Gendell6,7 and in necropsy studies by Naraghi et al.30 Nevertheless, this topic was not considered in detail in other studies; in these prior investigations, the main interest was in determining whether MRI was capable of detecting a higher frequency of NVC in hypertensive subjects versus evaluating the different physiological consequences of NVC.

Previous reports, based on intraoperative descriptions, necropsy findings, and several MRI techniques,6–11,30 have described an association between HTN and NVC. However, some reports have documented no difference in the frequency of signs of NVC between populations with and without HTN,12–14 indicating the complexity of this type of study. MRI findings of NVC in hypertensive subjects have usually been described in anatomic terms, with no attempt to correlate MRI findings with clinical variables, such as hemodynamic data or sympathetic activity. Furthermore, investigators who used classification methods similar to the one used in the present study12,13 did not find a significant difference in the frequency of MRI signs of NVC between hypertensive and nonhypertensive subjects. The failure of others to have detected signs of NVC in subjects with HTN does not totally exclude the possibility that NVC at the RVL medulla could have physiological repercussions, contributing to an increase in sympathetic activity. Indeed, surgical treatment of NVC has shown that hypertensive patients submitted to microsurgical decompression of the RVL medulla experience long-lasting improvement in the control of their HTN, as well as a reduction in sympathetic hyperactivity.17,18 Conversely, studies in animals have demonstrated a positive relation among NVC at the medulla, increased sympathetic activity, and HTN.21,22

Figure 3. Responses to cold pressor test: the NVC+compression group had significantly higher increase in systolic BP when compared with the NVC+contact group (P < 0.02) and, although not significantly different, was also higher compared with the NVC− group (reaching a P = 0.05; A); HR (bpm; B) and MSNA expressed as spikes/min (C) and MSNA expressed as spikes/heartbeat (D) showed a similar increase in all groups (NVC−, n = 8; NVC+contact, n = 6; and NVC+compression, n = 6).
Makino et al. were the first to describe increased sympathetic activity in hypertensive subjects with NVC at the RVL medulla. Plasma norepinephrine levels were significantly higher, and baroreflex sensitivity (phenylephrine test) was slightly lower in the group with NVC, suggesting an increase in sympathetic activity. Although there was no significant difference between the groups in their BP and HR responses to mental stress, cold pressor, isometric exercise (hand grip), Valsalva maneuver, phenylephrine infusion, and clonidine suppression test, the values in the group with NVC were more globally elevated.24 The MRI finding considered suggestive of NVC was the presence of a vascular loop associated with deformation of the RVL medulla, which is similar to the findings of compression found presently. However, no attempt was made to correlate MRI findings with sympathetic activity.

In our study, the NVC+compression group had a higher increase in systolic BP compared with other groups in response to cold test. However, it is not possible to affirm the presence of a hyperreactive state in the compression group, because the number of patients in our groups is small, and other hemodynamic parameters were similar in response to this test, including the increase in MSNA.

Morimoto et al. reported the case of a man with primary HTN, hemifacial nerve spasms, and NVC of the RVL medulla and facial nerve. Microvascular decompression of the RVL medulla in this patient decreased MSNA, BP, and plasma and urinary norepinephrine levels, and the pattern of HR variability changed from low frequency to high frequency. These changes are indicative of a marked decrease in sympathetic activity.31

In humans, microneurography is the usual method for recording the direct efferent postganglionic sympathetic activity outflow to specific vascular territories, the muscle or skin vascular beds. Although it represents the sympathetic activity of a specific and limited territory, it positively correlates with the heart, brain, and kidney norepinephrine spillover in healthy individuals.32–34 In 2002, Schobel et al. were the first to compare the MSNA of hypertensive subjects with (n=21) and without (n=12) signs of NVC on MRI. The resting and posthypothermic stimulus values for MSNA were higher in the group with NVC. However, MSNA was measured during the use of antihypertensive medication. Based on MRI findings, the hypertensive subjects were divided into groups with and without NVC. A positive finding of NVC was defined as the presence of a vascular signal close to the RVL.
medulla but on the left side only. Although not clearly stated in the text, this definition seems to encompass both the contact and compression findings described here. The probable vessel involved was also described, but comparisons of clinical, hemodynamic, and MSNA data were limited to those between groups with and without vascular signs of NVC.

More recently, Smith et al. compared the MSNA of 83 subjects separated in groups of normotensive (NVC) or hypertensive (n = 59) subjects, with and without evidence of NVC on MRI. The MSNA was significantly higher in the group with NVC, thus implying a pathogenic role for NVC in HTN. Further supporting this notion was the finding that both the prevalence of NVC and the magnitude of sympathetic hyperactivity were greatest in the patients with mild essential HTN. There was no significant difference in confounding variables (eg, age, severity of HTN, and control of HTN) between the groups. These investigators’ criteria for considering MRI results as suggestive of NVC included findings of both contact (NVC+contact) and compression (NVC+ compression). However, no attempt was made to consider the possibility of a more or less accentuated compression, whether by ≥ 1 vessels, on 1 or 2 sides, or with or without functional repercussions on the neural circuitry. This is of potential significance, because there are some normotensive subjects who have signs of NVC on MRI and, at least by currently available evidence, no associated sympathetic hyperactivity.

It is important to analyze the possibility that the withdrawal of antihypertensive medication could have had an effect over sympathetic activity of the hypertensive patients. To avoid the discontinuation syndromes, we radmed the medication in a step by step sequence during a month period: first, we asked the patients to stop diuretics; after 1 week, a second pretreatment levels, a rebound of the BP plus symptoms and the hypertension of the left lateral medulla oblongata for severe refractory neurogenic hypertension. Decrease of blood pressure by ventrolateral medullary decompression in hypertension. Hypertension. 1997;29:514–518.


Conclusion and Perspectives

In our study, it was possible to identify, among those with MRI evidence of NVC, subjects who had actual functional consequences of NVC. Our results also indicate that patients with NVC can be divided, based primarily on MRI findings, into 2 subgroups with different levels of sympathetic activity: (1) an NVC+contact group that has BP, HR, and MSNA data similar to the NVC- group in our study, and (2) an NVC+compression group that has significantly higher MSNA levels than both the NVC- and NVC+contact groups in our study. Our results also contributed to the identification, within the heterogeneous NVC+ group, of subjects whose NVC has significant physiological repercussions. This may open a window of opportunity for investigating different clinical characteristics (eg, BP control and response to specific antihypertensive medications), as well as possible benefits of surgical treatment in selected cases of this population of patients.

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References


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