

Title:

Neurovascular compression: Sympathetic Activity in Severe Arterial Hypertension

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Neurovascular compression and arterial hypertension

Summary

Compression of the rostral ventrolateral medulla oblongata (RVLM) by an abnormally located artery is regarded as one possible cause of arterial hypertension. There exists a limited set of data suggesting that increased sympathetic activity in patients with RVLM compression may lead to arterial hypertension. Accordingly, we decided to assess the sympathetic activity in patients with severe arterial hypertension and to investigate any correlation with the presence of RVLM compression. Sixty-four patients with severe arterial hypertension were enrolled in our study. Sympathetic activity was evaluated using 24-hour urinary norepinephrine as measured by high-pressure liquid chromatography with electrochemical detection. The presence of RVLM compression was assessed with magnetic resonance imaging. Neurovascular compression of the RVLM was identified in 40 patients, 27 of whom presented left-sided compression. Twenty-four hour urinary norepinephrine averaged $263.6(\pm 135.9)$ nmol in patients with neurovascular compression - $255.6(\pm 137.3)$ nmol in those with left-sided compression and $251.6(\pm 138.5)$ nmol in patients without RVLM compression. We did not identify any increase in urinary norepinephrine in patients with severe arterial hypertension and neurovascular compression of the RVLM. Our results do not support the hypothesis that neurovascular compression of RVLM may exhibit a sympathetically mediated increase in blood pressure.

Keywords

Neurovascular compression, arterial hypertension, magnetic resonance imaging

Rostral ventrolateral medulla (RVLM) is a brainstem centre that is located below the retroolivary sulcus, anterior to the fibres of the glossopharyngeal and vagal nerves. The adrenergic neurons of the RVLM play a role in the control of blood pressure. It has been hypothesised that RVLM compression by an anomalous artery may be a cause of arterial hypertension in humans (Jannetta *et al.* 1985). However, systematic evaluations of brainstem morphology with magnetic resonance imaging (MRI) found no difference in the incidence of RVLM compression between hypertensive and normotensive subjects (Thuerl *et al.* 2001, Hohenbleicher *et al.* 2001, Zizka *et al.* 2004).

In contrast, the concept of neurogenic hypertension is supported by several reports. Increased plasma norepinephrine levels were observed in patients with arterial hypertension and neurovascular compression (Morimoto *et al.* 1999a). Moreover, neurosurgical decompression was associated with the decrease of both blood pressure (Geiger *et al.* 1998) and urinary norepinephrine concentration (Morimoto *et al.* 1999b).

The main limitation of morphological studies is the inability to assess the functional impact of vascular compressions on the RVLM. Therefore, we decided to assess sympathetic activity in patients with severe arterial hypertension, and to correlate any observations with the presence or absence of RVLM vascular compression.

All patients with arterial hypertension treated in our hypertension clinic were screened for the purpose of this study. The study included those individuals with arterial hypertension lasting for ≥ 2 years, who had documented systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg and who were undergoing treatment with a combination of 3 or more antihypertensive drugs. The

patients with a secondary form of arterial hypertension and/or a contraindication to MRI were excluded.

Based on these criteria, 64 patients (30 females) were enrolled. The study protocol evaluated sympathetic activity and aimed to identify any correlations with the presence or absence of RVLM compression. Antihypertensive medication was not discontinued; this decision was justified by ethical considerations.

The activity of the sympathetic nervous system was assessed using 24-hour urinary secretion of norepinephrine. Urinary norepinephrine was measured by high pressure liquid chromatography with electrochemical detection.

The presence of RVLM compression was evaluated with MRI; MRI examinations were performed on a 1.0 Tesla system (Magnetom Expert; Siemens, Erlangen, Germany). The imaging technique and the method of the assessment of RVLM vascular compression is described in detail elsewhere (Zizka *et al.* 2004). Briefly, RVLM compression was defined as either contact of the artery with the brainstem or pressure from the artery leading to apparent deformity of the brainstem contour. The patients with neurovascular contact and with pressure-induced deformation were evaluated separately.

Since it is unclear whether only the left side (Jannetta *et al.* 1985) or both sides of the RVLM may be involved in the development of arterial hypertension, all patients were evaluated both for the presence of any RVLM compression and for compression of the left RVLM.

Statistical analysis of the acquired data was performed by parametric tests using the Medcalc® version 9 software package.

The study was approved by the institutional review board and informed consent was obtained from all subjects.

Vascular compression of the RVLM was identified in 40 patients (62.5%), of which 27 (67.5%) exhibited compression on the left side. The neurovascular compression was described as contact-related in 34 patients and as pressure-induced brainstem deformation in a further six individuals. All of the latter cases were left-sided. We found no vascular compression of the RVLM in 24 patients (37.5%) and these individuals served as the control group. Patients with and without RVLM compression did not differ with regard to age, body mass index or the number of antihypertensive drugs used (**Table 1**).

No difference in 24 hour norepinephrine secretion was found between the group without RVLM compression and the patients who exhibited any or left-sided RVLM compression (**Table 1**).

No differences were observed when comparing those patients who exhibited pressure-induced brainstem deformation with both patients suffering from neurovascular contact-related RVLM compression and no-compression controls.

As the morphological studies failed to confirm the hypothesis regarding the neurovascular origin of arterial hypertension, we searched for other parameters to identify those patients for whom blood pressure elevation may result from neurovascular compression. Our study enrolled only those patients with established severe arterial hypertension and without any evidence of secondary causes. The logic behind this selection was that – if the results of our study had been positive – candidates for neurosurgical decompression would be selected mainly from this cohort.

Although there is no method that is universally recommended for the assessment of central sympathetic activity, we are aware of the limitations regarding our chosen diagnostic method of urinary norepinephrine secretion (Grassi and Esler 1999).

However, in patients with neurovascular compression and arterial hypertension, other researchers have observed increased plasma norepinephrine levels (Morimoto *et al.* 1999a) and the decrease of urinary norepinephrine after neurosurgical decompression (Morimoto *et al.* 1999b).

Several reports have used sophisticated methods to measure central sympathetic outflow. A number of authors have used such approaches to describe increased sympathetic activity in hypertensive patients with RVLM compression (Smith *et al.* 2004, Schobel *et al.* 2002, Sendeski *et al.* 2006). However, the numbers of patients enrolled in individual studies have been rather small, and researchers have been unable to identify any discriminative value that may associate elevated sympathetic activity with neurovascular compression and arterial hypertension. Moreover, there exists little uniformity among the reports in respect to MRI techniques, the definitions of neurovascular compression and the anatomic extent of the RVLM. Not all the studies differentiate the neurovascular compressions into contact-based phenomena and pressure-induced deformations when the artery is indented into the surface of the medulla. Sendeski *et al.* (Sendeski *et al.* 2006) reported increased sympathetic activity only in the latter group. However, the number of patients for whom this held true was low in the aforementioned study. Our study also included a relatively small number of these subjects.

The blood pressure-lowering effect of surgical decompression is another argument that is often used to support the existence of neurogenic hypertension. However, data from neurosurgical interventions should be treated with caution. First, there exist no controlled randomised studies. Second, the number of operations performed to date is rather low and a lowering of blood pressure was not observed in all patients (Frank *et al.* 2001). A postoperative blood pressure reduction may be explained not

only by neurovascular decompression itself but also as a non-specific functional effect of neurosurgical intervention on the brainstem centres. A recent report by Frank (Frank et al. 2008) suggested only a transient effect of neurosurgical decompression on blood pressure and sympathetic control.

In conclusion, we maintain that currently available data do not support the role of neurovascular compression as a definite causal factor in arterial hypertension. We did not identify increased sympathetic activity in patients with severe arterial hypertension and neurovascular compression of the RVLM.

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Table 1. Evaluation of sympathetic activity in patients with severe arterial hypertension, with and without neurovascular compression

	Any RVLM compression (contacts + pressure-induced deformations)	Left RVLM compression (contacts + pressure-induced deformations)	RVLM pressure-induced deformation	No RVLM compression
Number of patients	40	27	6	24
Age (years)	54 ± 11	55 ± 11	62 ± 10	50 ± 12
BMI (kg/m ²)	28.6 ± 4.5	28.5 ± 3.4	27.5 ± 1.2	29.5 ± 3.9
Number of antihypertensive drugs	4.2 ± 1.2	3.9 ± 0.9	3.7 ± 0.5	4.1 ± 1.1
Urinary norepinephrine (nmol/24-h)	263.6 ± 135.9	255.6 ± 137.3	200.7 ± 82.9	251.6 ± 138.5

Table 1 describes the principal group characteristics and 24-h urinary norepinephrine secretion in patients with and without RVLM compression. Values are expressed as number of patients or means (±standard deviation). We observed no statistically significant difference in any parameter evaluated between the study groups. BMI, body mass index; RVLM, rostral ventrolateral medulla.