

# Pulsatile Compression of the Rostral Ventrolateral Medulla in Hypertension

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**Abstract** The rostral ventrolateral medulla (RVLM) has been known to be a major regulating center of sympathetic and cardiovascular activities. An association between essential hypertension and neurovascular compression of the RVLM has been reported in clinical observations, including magnetic resonance imaging (MRI) studies. To reconfirm this relationship, we performed MRI using a high-resolution 512×512 matrix in patients with essential and secondary hypertension and in normotensive subjects. The duration of hypertension and the degree of organ damage by hypertension were not significantly different between the two hypertension groups. Neurovascular compression of the RVLM was observed in 74% of the essential hypertension group, and the incidence of compression was significantly higher than in the secondary hypertension group (11%) or in the normotensive group (13%) ( $P < .01$ ). These results from the clinical studies suggest that neurovascular compression of the RVLM is, at least in part, causally related to essential hypertension. Although blood pressure elevation by pulsatile compression of the RVLM in an experimental baboon model has already been reported, its un-

derlying mechanism is not well known. Accordingly, we performed experiments to investigate whether pulsatile compression of the RVLM would increase arterial pressure and to elucidate the mechanism of the pressor response in rats. Sympathetic nerve activity, arterial pressure, heart rate, and plasma levels of epinephrine and norepinephrine were increased by pulsatile compression of the RVLM. The pressor response was abolished by intravenous treatment with hexamethonium or RVLM injection of kainic acid. In summary, the results from the MRI studies suggest that neurovascular compression of the RVLM is, at least in part, causally related to essential hypertension. This was supported by the results from experimental studies using rats indicating that pulsatile compression of the RVLM increases arterial pressure by enhancing sympathetic outflow. (*Hypertension*. 1997;29[part 2]:514-518.)

**Key Words** • rostral ventrolateral medulla • neurovascular compression • magnetic resonance imaging • pulsatile compression • neurogenic hypertension • essential hypertension • sympathetic nerve activity

The rostral ventrolateral medulla (RVLM) contains neurons that are considered to be an origin of tonic sympathetic discharge and a major center regulating sympathetic and cardiovascular activities.<sup>1,2</sup> Chemical or electrical stimulation of the RVLM increases sympathetic nerve activities to elevate blood pressure, while its destruction causes hypotension.<sup>3-6</sup> Since the report by Jannetta and Gendell,<sup>7</sup> it has been shown that posterior inferior cerebellar artery, anterior inferior cerebellar artery, and vertebral artery occasionally compress the medulla oblongata and that patients with essential hypertension are associated with neurovascular compression of the ventrolateral medulla at the root-entry zone of glossopharyngeal and vagus nerves (ie, the RVLM) in clinical observations including magnetic resonance imaging (MRI) studies.<sup>8-16</sup> To reconfirm this relationship, we performed MRI using a high-resolution 512×512 matrix, a newly developed magnetic device, in patients with essential and secondary hypertension and in normotensive subjects. Jannetta et al<sup>10</sup> also reported blood pressure elevation by pulsatile compression of the RVLM in an experimental baboon model. However, the mechanism of the development of

hypertension was not investigated precisely. Therefore, we performed experimental studies to investigate whether pulsatile compression of the RVLM would increase arterial pressure and to determine the underlying mechanism of the pressor response in rats.

## Methods

### Clinical Studies

Nineteen patients with essential hypertension (8 women), 9 patients with secondary hypertension (3 women), and 16 normotensive subjects (5 women) were recruited. The present studies were approved by the ethics committee of Kyoto Prefectural University of Medicine. Informed consent was obtained from all subjects. In the secondary hypertension group, there were 6 patients with renal hypertension, 2 patients with primary aldosteronism, and 1 patient with pheochromocytoma. The mean age was not significantly different among the three groups ( $58 \pm 11$ ,  $53 \pm 18$ , and  $49 \pm 13$  years, respectively). All hypertension patients were receiving antihypertensive drugs. The duration of hypertension ( $147 \pm 114$  versus  $137 \pm 122$  months), the blood pressure level ( $136 \pm 11/77 \pm 11$  versus  $140 \pm 12/78 \pm 9$  mm Hg), left ventricular mass calculated using echocardiograms<sup>17</sup> ( $279 \pm 66$  versus  $269 \pm 102$  g), and stage of the "classification of hypertension by extent of organ damage"<sup>18</sup> were not significantly different between the two hypertension groups.

MRI studies were performed on these subjects with an SMT-150X (1.5 T, Shimadzu) Proton density-weighted fast SE images (repetition time/effective echo time, 5000/23 ms) were obtained in axial and coronal views. To obtain high-quality images, a high-resolution ( $0.4 \times 0.4$  mm/pixel) 512×512 matrix with 3-mm slice thickness was used. Two neuroradiologists, unaware of each subject's medical history, assessed all the MRI scans to determine whether there was neurovascular compression of the retro-olivary

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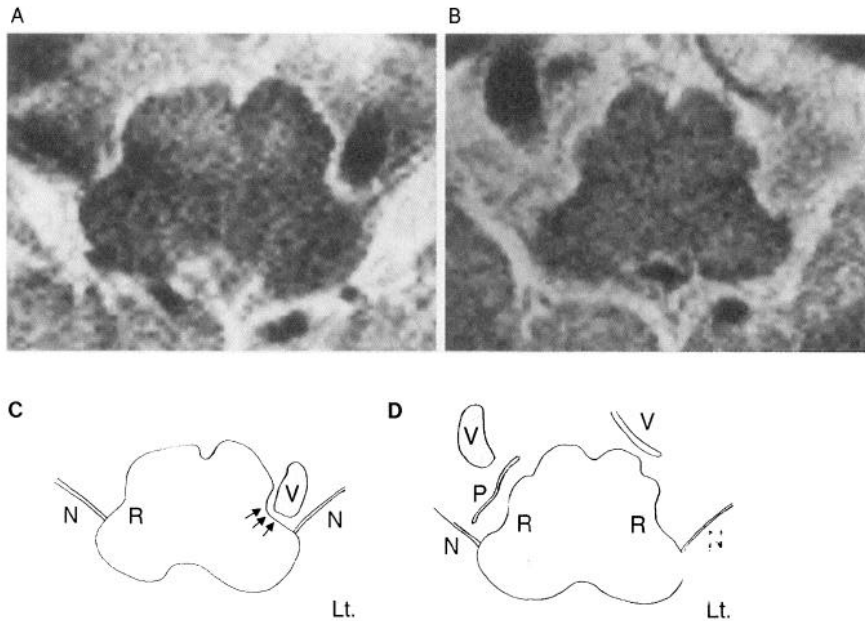


FIG 1. Axial views of magnetic resonance images. A, A case of a 60-year-old man with essential hypertension. Left vertebral artery compresses the left retro-olivary sulcus (RVLM) in the medulla oblongata. B, A case of a 62-year-old normotensive woman. No vascular structure apparently compresses the medulla oblongata. C, Schematic of Fig 1A. D, Schematic of Fig 1B. R indicates RVLM; V, vertebral artery; P, posterior inferior cerebellar artery; and N, the root-entry zone of the vagus nerve.

sulcus of the medulla oblongata at the level of the root-entry zone of the glossopharyngeal and the vagus nerves, assumed to be the surface of RVLM.<sup>14</sup> Compression was recognized when contact and depression of the RVLM was observed in the axial or coronal view.

### Experimental Studies

All experiments were carried out acutely in male Wistar rats weighing between 300 and 400 g purchased from Charles River Breeding Laboratories (Kanagawa, Japan). Animal care and procedures conformed to the position of the American Heart Association on research animal use. After anesthetized with urethane (100 mg/100 g IP), each rat was mounted on a stereotaxic apparatus (David Kopf Instruments) in the supine position. The lower trachea was cannulated, and the rats were artificially ventilated at a rate of 60 breaths/min with a respirator (Ealing Co, Ltd) and were paralyzed with decamethonium bromide (0.2 mg/100 g IV).

Catheters were inserted separately in the right femoral artery for recording arterial pressure and heart rate and in the right femoral vein for drug injections. The splanchnic nerve was placed over a bipolar stainless steel electrode, and spike potentials were amplified and counted as described in detail elsewhere.<sup>19</sup> The ventral surface of the medulla oblongata was then exposed by occipital craniotomy. The RVLM was identified by the pressor response of more than 25 mm Hg of mean arterial pressure by microinjection of L-glutamate monosodium (300 ng, 100 nL saline).<sup>20,21</sup>

A polyurethane cannula (outer diameter: 1.5 mm) was connected to a computer-controlled pneumatic pump,<sup>22</sup> and a rubber membrane was stuck to the opposite end. By pumping air triggered with or without electrocardiogram (ECG), the membrane pulsated and the pressure wave inside the cannula became like that of an arterial pressure wave. The duration of air compression was set to be 50 ms. The rubber membrane of the cannula was lowered to the ventral surface of the medulla oblongata 1 mm dorsally from the line of the dura mater. Changes of arterial pressure, heart rate, and sympathetic nerve activity by pulsatile compression of the RVLM were monitored under several conditions: (1) ECG-triggered pulsatile compression of the RVLM (peak value of the pressure inside the cannula: 300 mm Hg); (2) ECG-triggered pulsatile compression of regions around the RVLM (peak value of the pressure inside the cannula: 300 mm Hg); (3) ECG-triggered pulsatile compression of the RVLM at various

strengths (ie, peak value of the pressure inside the cannula: 0, 100, 200, and 300 mm Hg); (4) pulsatile compression of the RVLM at various rates (ie, 0, 100, 200, 300, and 400 cycles/min; peak value of the pressure inside the cannula: 300 mm Hg); and (5) ECG-triggered pulsatile compression of the RVLM after intravenous injection with hexamethonium (2.5 mg/100 g) or RVLM injection of kainic acid (8 nmol, 100 nL saline).<sup>23,24</sup> Furthermore, plasma levels of epinephrine and norepinephrine were measured by high-performance liquid chromatography with electrochemical detection or by radioimmunoassay, respectively, after ECG-triggered pulsatile compression of the RVLM for 5 minutes.

### Statistical Analysis

A  $\chi^2$  test was applied to determine if there were significant differences between groups in neurovascular compression. Pulsatile compression-response curve data were analyzed by ANOVA followed by Fisher's multiple-range test. Pressor responses of pulsatile compression of the RVLM after pretreatment with hexamethonium or kainic acid were compared with sham rats by nonpaired *t* test. Plasma levels of catecholamines were also compared with sham rats by nonpaired *t* test.

## Results

### Clinical Studies

Fig 1A is a magnetic resonance image of a case with essential hypertension with neurovascular compression of the RVLM. The left vertebral artery compresses the left retro-olivary sulcus at the level of the root-entry zone of the vagus nerve (RVLM). Fig 1B is that of a normotensive subject without neurovascular compression of the RVLM.

Neurovascular compression of the RVLM was observed in 14 (74%) of 19 patients with essential hypertension. In contrast, neurovascular compression was observed in only 1 (11%) of 9 patients with secondary hypertension and in only 2 (13%) of 16 normotensive subjects. The incidence of observed neurovascular compression in the essential hypertension group was significantly higher than that in the secondary hypertension group or the normotensive group ( $P < .01$  for both groups, Fig 2).

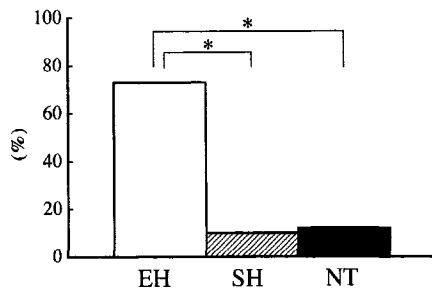


FIG 2 Observed neurovascular compression of the rostral ventrolateral medulla using magnetic resonance imaging. EH indicates essential hypertension (n=19), SH, secondary hypertension (n=9), and NT, normotensive (n=16). \* $P < 0.01$ .

### Experimental Studies

Sympathetic nerve activity (rising ratio:  $8.0 \pm 1.2\%$ ,  $P < 0.01$ ), mean arterial pressure (from  $88 \pm 22$  to  $105 \pm 22$  mm Hg,  $P < 0.01$ ), and heart rate (from  $325 \pm 37$  to  $335 \pm 39$  bpm,  $P < 0.01$ ) were increased by ECG-triggered pulsatile compression of the RVLM (peak value of the pressure inside the cannula 300 mm Hg), and these changes were normalized after cessation of the compression (Fig 3). On the other hand, these changes were not induced by pulsatile compression of regions around the RVLM (1 mm lateral, 1 mm medial, and 1 mm rostral). When the frequency of the compression or the pressure inside the cannula was changed, sympathetic nerve activity, mean arterial pressure, and heart rate were increased in a frequency-related or pressure-related manner, respectively. When the peak value of the pressure inside the cannula was 0 mm Hg or the rate of the pulsatile compression was 0/min, changes in sympathetic and cardiovascular activities were insignificant. The pressor response was abolished by ganglion blockade with hexamethonium or destruction of RVLM neurons with kainic acid (Fig 4). Plasma levels of epi-

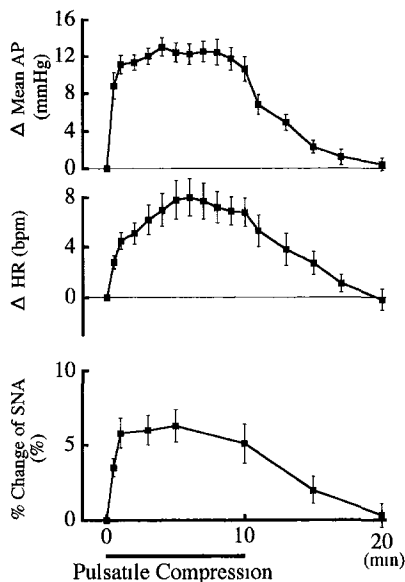


FIG 3 Effects of pulsatile compression of the rostral ventrolateral medulla on cardiovascular and sympathetic activities in rats (n=20). AP indicates arterial pressure, HR, heart rate, and SNA, sympathetic nerve activity.

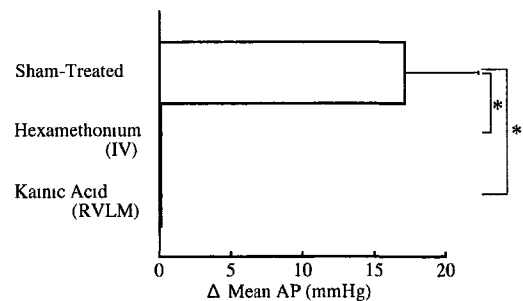


FIG 4 Effects of ganglion blockade (n=6) or kainic acid (n=6) on pressor response of pulsatile compression of the rostral ventrolateral medulla (RVLM) in rats. \* $P < 0.01$  compared with sham-treated rats (n=20). AP indicates arterial pressure.

nephrine and norepinephrine were significantly increased by pulsatile compression of the RVLM (Fig 5).

At the end of the experiments, 100 nL of methylene blue dye was injected into the RVLM and 150 mL of 10% phosphate-buffered formaldehyde solution was transcardially infused. Serial sections (50  $\mu$ m) were stained with Cresyl violet and examined by light microscopy for the location of injection sites with reference to a standard rat brain atlas.<sup>25</sup> The methylene blue injection sites were located ventral to the nucleus ambiguus, caudal to the facial nucleus, and rostral to the lateral reticular nucleus, which was comparable to the RVLM.

### Discussion

Our results from the MRI studies suggest that neurovascular compression of the RVLM is a cause of high blood pressure at least in some patients with essential hypertension. Our results from experimental studies with rats suggest that pulsatile compression of the RVLM causes a pressor response by enhancing sympathetic outflow, supporting the presumption from the clinical studies.

Jannetta et al<sup>9</sup> reported that neurovascular compression of the RVLM was found in 51 of 53 hypertensive patients and in none of the 50 normotensive patients who underwent microvascular decompression for unrelated cranial nerve dysfunction such as hemifacial spasm or trigeminal neuralgia. Since then, several observations have indicated an association between essential hypertension and neurovascular compression of the RVLM.<sup>11-16</sup> In the present clinical studies as well, the incidence of observed neurovascular compression in the

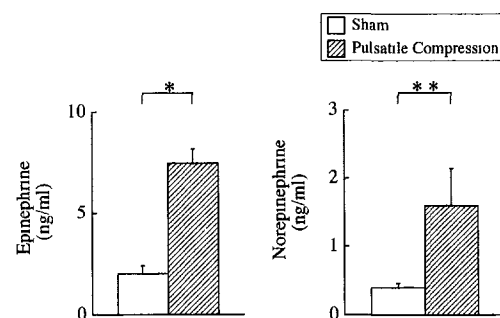


FIG 5 Effects of pulsatile compression of the rostral ventrolateral medulla on plasma levels of epinephrine (n=6) and norepinephrine (n=6) in rats. \* $P < 0.01$ , \*\* $P < 0.05$ .

essential hypertension group was significantly higher than that in the secondary hypertension group or the normotensive group. In general, prolonged blood pressure elevation makes arteries elongated and tortuous. Therefore, it should be discussed whether neurovascular compression of the RVLM is a result or a cause of essential hypertension. In the present studies, however, the duration of hypertension and the degree of organ damage by hypertension were not significantly different between the two hypertension groups. Thus, it is not likely that neurovascular compression of the RVLM is the natural outcome of a chronic blood pressure elevation. Accordingly, we assume that neurovascular compression of the RVLM is a cause rather than a result of high blood pressure, at least in some patients with essential hypertension from the clinical studies.

It has been reported that chemical or electrical stimulation of the RVLM increases sympathetic nerve activity to elevate blood pressure.<sup>3-5</sup> In the present experimental studies, we found that pulsatile compression of the RVLM increases sympathetic and cardiovascular activities. This finding is considered to be important because it implies that physical stimulation of the RVLM also increases sympathetic nerve activity and arterial pressure. Furthermore, although we cannot assume the long-term effects of pulsatile compression of the RVLM by the present acute experimental studies, these results support our presumption from the clinical studies described above.

Whether the pressor response in the present experimental studies is due to Cushing's response need to be discussed. Cushing's response is now considered to be from stretching of the receptive elements under the floor of the fourth ventricle by tissue distortion, either by direct pressure or by axial displacement of the brain stem.<sup>26</sup> In the present studies, however, the pressor response was not induced by pulsatile compression of regions around the RVLM, and it was abolished after RVLM injection of kainic acid. Accordingly, it seems to be due to specific effects to the RVLM but not to Cushing's response. On the other hand, when the peak value of the pressure inside the cannula was 0 mm Hg or the rate of the pulsatile compression was 0/min, sympathetic and cardiovascular activities were not significantly increased. Thus, it is likely that pulsatile compression but not nonpulsatile compression of the RVLM is important in the pressor response.

What is the mechanism of the pressor response by pulsatile compression of the RVLM? The following evidences indicate that it is via increased sympathetic nerve activity: (1) RVLM neurons are reported to project to the spinal preganglionic sympathetic neurons,<sup>27,28</sup> (2) pressor response by pulsatile compression of the RVLM was accompanied by an increase of sympathetic nerve activity in the present study, (3) plasma levels of epinephrine and norepinephrine were significantly increased by pulsatile compression of the RVLM, and (4) the pressor response was abolished after ganglion blockade with intravenously injected hexamethonium.

Microvascular decompression of the RVLM has been reported to improve hypertension.<sup>9-11</sup> Jannetta et al<sup>9</sup> reported that high blood pressure returned to normal in 32 and improved in 4 of 42 patients who were treated with left microvascular decompression of the RVLM. They re-

ported development of hypertension by pulsatile compression of the RVLM and normalization of blood pressure by cessation of the pulsatile compression in a chronic experimental baboon model as well.<sup>10</sup> We also observed normalization of increased sympathetic and cardiovascular activities by cessation of pulsatile compression of the RVLM in the present studies, although they were carried out acutely. Collectively, it is suggested that high blood pressure by pulsatile compression of the RVLM is reversible. Therefore, it might be possible that neurovascular decompression of the RVLM is selected as a therapy in the future for those who have neurovascular compression of the RVLM and antihypertensive medicine-resistant hypertension complicated with progressive target organ diseases.

In summary, the results from the MRI studies suggest that neurovascular compression of the RVLM is, at least in part, causally related to essential hypertension. This was supported by the results from the experimental studies indicating that pulsatile compression of the RVLM increases arterial pressure by enhancing sympathetic outflow.

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