

ORIGINAL ARTICLE

Efficacy of clonidine in patients with essential hypertension with neurovascular contact of the rostral ventrolateral medulla

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The rostral ventrolateral medulla (RVLM) is an important center for regulation of sympathetic nerve activity. Several clinical studies have suggested an association between neurovascular contact (NVC) of RVLM and essential hypertension. Microvascular decompression (MVD) of RVLM decreases blood pressure (BP) in hypertensive patients with NVC of this region. Therefore, MVD could be a useful therapeutic strategy to reduce BP in these patients. However, as MVD is an invasive procedure, it is worthy to seek useful antihypertensive agents for hypertensive patients with NVC. It is reported that sympathetic nerve activity is elevated in patients with hypertension accompanied by NVC of RVLM. It is anticipated that sympatholytic agents could be effective in lowering BP in these patients. In this study, we investigated the efficacy of clonidine, an α_2 adrenergic agonist, in essential hypertensives with NVC of RVLM. Thirty consecutive essential hypertensive patients with NVC and 30 consecutive essential hypertensive patients without contact were treated with clonidine for 4 weeks, and decreases in BP and plasma norepinephrine levels were compared between the two groups. Decreases in BP and plasma norepinephrine levels were significantly greater in patients with NVC than in those without contact. These results suggest that clonidine exhibits significantly greater reductions of BP and sympathetic nerve activity in essential hypertensive patients with NVC compared with those without contact of the rostral ventrolateral medulla.

Hypertension Research (2010) 33, 633–637; doi:10.1038/hr.2010.41; published online 9 April 2010

Keywords: essential hypertension; α_2 adrenergic agonist; clonidine; RVLM; sympathetic nerve activity

INTRODUCTION

Neurovascular compression has been widely accepted as a cause of trigeminal neuralgia and hemifacial spasm. In the majority of patients, an ectatic and elongated artery has been found in association with these syndromes. In trigeminal neuralgia and hemifacial spasm, neurovascular compression is mainly caused by the superior cerebellar artery and anterior inferior cerebellar artery, respectively. Microvascular decompression (MVD) is an appropriate technique to relieve the pain associated with these syndromes.^{1–4}

The rostral ventrolateral medulla (RVLM) is an important center for the regulation of sympathetic and cardiovascular activities.^{5,6} After the initial report by Jannetta and Gendell in 1978,⁷ several clinical studies have suggested an association between neurovascular contact (NVC) of RVLM and essential hypertension (EH).^{8–15} Jannetta *et al.*^{16,17} have reported that MVD of RVLM decreases blood pressure (BP) in hypertensive patients with NVC of RVLM. MVD of RVLM could be a useful therapeutic strategy to reduce BP in these patients. However, because MVD is an invasive procedure, it is worthy to seek useful antihypertensive agents for hypertensive patients with NVC of RVLM. Sympathetic nerve activity (SNA) is elevated in patients with

hypertension accompanied by NVC of RVLM.^{18–20} We have reported a patient with refractory hypertension and NVC of RVLM, who experienced prominent BP reduction by additional treatment with clonidine,²¹ which is an α_2 adrenergic agonist, and elicits hypotensive and sympathoinhibitory effects by acting mainly on RVLM.²² In this study, we investigated whether clonidine is effective in lowering BP in essential hypertensives with NVC of RVLM in a group study.

METHODS

Study subjects

Subjects were selected among patients with EH who visited our hospital between April 2006 and March 2008. They were all Japanese and they all had been diagnosed as having EH and were under treatment with antihypertensive drugs other than α_2 adrenergic agonists and still had a clinic BP of $\geq 140/90$ mmHg on three successive office visits and/or home BP of $\geq 135/85$ mmHg. Patients with secondary hypertension (renal and endocrine sources of hypertension) were excluded by appropriate physical and laboratory evaluation. Subjects who had suffered a hemorrhagic stroke or cardiac infarction in the previous 6 months, those with chronic renal failure (serum creatinine of ≥ 1.5 mg per 100 ml), pregnant women and those with peripheral vascular or malignant disease were excluded.

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Received 31 October 2009; revised 25 January 2010; accepted 15 February 2010; published online 9 April 2010

Measurement of clinic BP and PR

Clinic BP and pulse rate (PR) were measured from 1100 to 1200 h while the patient was seated and after at least 5 min of rest, using an automated oscillometric sphygmomanometer (MPV3301, Nihon Kohden, Tokyo, Japan). Three measurements were obtained 2 min apart at each time point. The average of the second and third readings was used for all analyses.

Measurement of home BP and PR

Home BP and PR were measured in the morning and evening using an automated oscillometric sphygmomanometer according to the Japanese Society of Hypertension Guidelines for Self-Monitoring of Blood Pressure at Home;²³ within 1 h of waking, after urination, after 1- to 2-min rest in a seated position, before taking antihypertensive drugs and before breakfast in the morning, and before retiring and after 1- to 2-min rest in a seated position in the evening. The average of the first BP and PR values taken each morning and evening everyday for 7 days was used for the analysis.

MRI evaluation

Magnetic resonance imaging (MRI) studies were performed with a 1.5-T system (Signa Excite HD, GE Medical Systems, Milwaukee, WI, USA) and a neurovascular coil. The slices were axial, parallel to a line connecting the anterior commissure and posterior commissure. T2-weighted three-dimensional fast-recovery fast-spin echo images (repletion time [TR]/echo time [TE], 1500/15 msec; echo train length, 48) were obtained. The voxel size was 1.4×0.6×0.8 mm. Two experienced radiologists (KI and MM), who were blind to the individual's medical histories, assessed all scans independently to check the grade of NVC of RVLM. In instances of disagreement between the reviewers, a consensus interpretation was used for the case. NVC of RVLM was defined as an arterial vessel or vascular loop with its convexity contacting the surface of RVLM. The anterior border of RVLM was defined as the transitional point of the olivary convexity and the concavity of the retro-olivary sulcus; the posterior border was considered to be at the junction of parenchymal brain tissue and the nerve fibers. Upper and lower borders were determined by the uppermost and the lowest end of the glossopharyngeal and vagal nerve bundle entering the medulla.

Study protocols

In a preliminary study, MRI studies were performed in these subjects until 30 patients with and without NVC of the RVLM, respectively, were collected. Thereafter, 30 consecutive essential hypertensive patients with NVC of RVLM (NVC+) and 30 consecutive hypertensive patients without NVC of RVLM (NVC-) were enrolled into the main prospective study and were further evaluated.

At enrollment, we collected information on age, gender, duration of hypertension, current antihypertensive medications, smoking history, body mass index, waist circumference, urinary protein/creatinine ratio, biochemical parameters (blood urea nitrogen, creatinine, fasting blood sugar, hemoglobin A1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides), and plasma concentration of norepinephrine (NE), renin activity (PRA), aldosterone (Ald), brachial-ankle pulse wave velocity (baPWV), an index of arterial stiffness, carotid intima-media thickness (IMT), an index of atherosclerosis, and left ventricular mass index (LVMI), an index of left ventricular hypertrophy. All patients were treated with 225 µg per day of clonidine (t.i.d.) for 4 weeks. During this study, no additional treatment or change in the dose of concomitantly administered antihypertensive medications was allowed.

Clinic BP and PR, plasma NE, PRA and plasma Ald were determined again 4 weeks after treatment, and in each group, the values were compared with pretreatment values. Net changes and percentage changes in BP and PR were compared between the NVC- group and the NVC+ group. Net changes in plasma NE, PRA and PAC were also compared between these two groups.

Laboratory analyses

The concentration of protein and creatinine in random urine samples was measured by conventional methods at the clinical laboratory center of our hospital. Morning blood samples were collected from the antecubital vein after an overnight fast of > 12 h and after the subjects lay in a supine resting position for at least 20 min. Serum urea nitrogen, creatinine, fasting blood sugar,

hemoglobin A1c, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides were assessed by conventional methods at the clinical laboratory center of our hospital. Plasma NE was measured by high-performance liquid chromatography with electrochemical detection by an external laboratory (SRL, Tokyo, Japan). PRA and plasma Ald were measured by radioimmunoassay by the same external laboratory.

ABI and baPWV

The ankle-brachial index (ABI) and baPWV values were measured using a volume-plethysmographic apparatus PWV/ABI (Omron Healthcare, Kyoto, Japan) in accordance with a methodology described elsewhere.^{24,25} The lower and higher values were accepted as the ABI and baPWV values, respectively.

Carotid artery ultrasonography

Carotid ultrasound examinations of the common carotid artery, bulb and internal carotid artery were performed bilaterally using the Prosound α10 ultrasound system (ALOKA, Tokyo, Japan). Subjects were examined in the supine position, with the head turned 45° from the site being scanned. Both carotid arteries were scanned longitudinally to visualize the IMT in the far wall of the artery and the maximum IMT was taken.

Echocardiography

M-mode echocardiography was performed using Vivid Seven scanner (GE VingMed, Milwaukee, WI, USA). The left ventricular end-diastolic dimension, left ventricular end-systolic dimension, end-diastolic interventricular septal thickness and posterior wall thickness were measured on the M-mode echocardiogram. The left ventricular mass was calculated using Devereux's formula,²⁶ and LVMI was obtained by dividing the left ventricular mass by the body surface area.

Statistical analysis

To detect an 8 mm Hg between-group difference in systolic BP change by clonidine treatment with a power of 80% and a minimum level of significance of 0.05, given an s.d. of 10 mm Hg, 24 patients per group were necessary. Considering that about 20% of patients could not be evaluated, a total of 60 patients were required. χ^2 -test and nonpaired Student's *t*-test were performed to assess the statistical differences between the NVC- and NVC+ groups. Paired Student's *t*-test was applied to determine the significance of differences between pre- and post-treatment values. Data are shown as mean values \pm s.d., and differences were considered statistically significant at $P < 0.05$.

The study was approved by the ethics committee of Kansai Medical University. Written informed consent was obtained from all individuals before their participation in the trial. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the paper as written.

RESULTS

Study subjects

In the preliminary study, to collect 30 essential hypertensive patients with and without NVC of RVLM, respectively, 77 patients were subjected to MRI studies. Thereafter, in the main study, 30 consecutive patients with and without NVC of RVLM, respectively, were treated with clonidine. Two of thirty essential hypertensive patients without NVC discontinued clonidine treatment due to general fatigue unrelated to BP reduction. Four of the thirty EH patients with NVC discontinued clonidine therapy: one patient due to general fatigue unrelated to BP reduction, two patients due to dizziness because of prominent BP reduction and one patient due to eczema. As a result, 28 and 26 patients were assessed in the NVC- group and NVC+ group, respectively.

Changes in baseline characteristics

Baseline characteristics are summarized in (Table 1). At baseline, age, gender, duration of hypertension, smoking status, body mass index,

Table 1 Characteristics of the subjects

	NVC- group (n=28)	NVC+ group (n=26)
Age (years)	59.3±11.5	61.8±9.3
Gender (male/female)	13/15	12/14
Duration of hypertension (years)	8.2±7.3	9.7±9.5
Smoking (yes/no)	5/23	4/22
Body mass index (kg m ⁻²)	24.5±3.7	24.0±3.8
Clinic systolic blood pressure (mm Hg)	147.9±18.3	148.1±13.2
Clinic diastolic blood pressure (mm Hg)	87.5±13.8	82.1±10.2
Clinic pulse pressure (b.p.m.)	77.4±11.6	78.1±12.6
Home systolic blood pressure (mm Hg)	141.3±17.4	142.2±14.5
Home diastolic blood pressure (mm Hg)	82.9±14.2	83.3±12.9
Home pulse pressure (b.p.m.)	74.8±9.9	75.5±11.3
Waist circumference (cm)	85.8±9.6	84.6±8.1
Urinary protein excretion (g per g cre)	0.28±0.32	0.26±0.29
Blood urea nitrogen (mg per 100 ml)	13.8±4.3	14.2±4.6
Creatinine (mg per 100 ml)	0.72±0.38	0.78±0.35
Fasting blood sugar (mg per 100 ml)	106±32	109±21
Hemoglobin A1c (%)	5.6±0.9	5.4±0.6
Low-density lipoprotein cholesterol (mg per 100 ml)	129±24	122±25
High-density lipoprotein cholesterol (mg per 100 ml)	57±18	57±11
Triglyceride (mg per 100 ml)	142±68	137±53
Plasma norepinephrine (pg ml ⁻¹)	382±181	485±198
Plasma renin activity (ng ml ⁻¹ h ⁻¹)	3.0±3.3	2.8±3.5
Plasma aldosterone (pg ml ⁻¹)	63.5±68.3	52.1±52.6
Ankle-brachial index	1.1±0.1	1.1±0.1
Brachial-ankle pulse wave velocity (cm s ⁻¹)	1732±345	1864±359
Intima-media thickness (mm)	0.88±0.35	0.85±0.24
Left ventricular mass index (g m ⁻²)	118±31	118±33

Abbreviations: b.p.m., beats per minute; cre, creatinine.

NVC-, hypertensive patients without neurovascular contact of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular contact of RVLM.

waist circumference, clinic BP and PR, home BP and PR, biochemical parameters, plasma NE, PRA, plasma ALd, ABI, baPWV, IMT and LVMI did not differ significantly between the two groups. No patients showed ABI <0.9. No subjects changed their smoking status during the study period. Body mass index (24.7±3.5 and 24.3±3.9 kg m⁻² in the NVC(-) and NVC(+) groups, respectively, after treatment), waist circumference (85.8±9.2 and 83.8±9.5 cm), blood urea nitrogen (14.3±4.8 and 14.0±4.5 mg per 100 ml), creatinine (0.77±0.29 and 0.79±0.33 mg per 100 ml), fasting blood sugar (102±33 and 105±29 mg per 100 ml), hemoglobin A1c (5.6±0.9 and 5.5±0.9%), low-density lipoprotein cholesterol (132±30 and 129±29 mg per 100 ml), high-density lipoprotein cholesterol (59±17 and 59±21 mg per 100 ml) and triglycerides (145±73 and 139±60 mg per 100 ml) did not change significantly because of treatment. Changes in these factors did not differ significantly between the two groups. Antihypertensive agents administered before clonidine therapy were identical between the two groups (Tables 2 and 3).

Changes in clinic BP and PR

Systolic BP was significantly decreased after treatment in the NVC- group, and both systolic and diastolic BPs were significantly reduced after treatment in the NVC+ group (Figure 1). Decreases in systolic BP were significantly greater in the NVC+ group than in the NVC- group (Figures 2a and b). Decreases in diastolic BP tended to be greater in

Table 2 Antihypertensive medications administered at baseline

	NVC- group	NVC+ group
Calcium channel blockers	18	15
Angiotensin-receptor antagonists	16	12
Angiotensin-converting enzyme inhibitors	3	4
Diuretics	7	5
α-Blockers	1	2
β-Blockers	3	4
Others	0	0

NVC-, hypertensive patients without neurovascular contact of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular contact of RVLM.

Table 3 Number of antihypertensive agents administered at baseline

Number of agents	NVC- group	NVC+ group
1	13	12
2	10	10
3	4	2
4	1	1
5	0	1

NVC-, hypertensive patients without neurovascular contact of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular contact of RVLM.

the NVC+ group than in the NVC- group, although there was no significant significance. PR did not show a significant change in either group (Figure 1). Changes in PR were not significantly different between the two groups (Figures 2a and b).

Changes in NE, PRA and Ald

After treatment with clonidine, plasma NE was significantly decreased in both groups (Figure 3a). The decrease in NE was significantly greater in the NVC+ group (Figure 3b). PRA (Figure 3c) and plasma Ald (Figure 3e) did not decrease significantly after treatment with clonidine in either group. Changes in PRA (Figure 3d) and plasma Ald (Figure 3f) were not significantly different between the two groups.

DISCUSSION

In this study, we found that administration of clonidine shows significantly greater reductions of BP and plasma NE levels in the NVC+ group compared with the NVC- group, indicating that clonidine is effective especially in hypertensive patients with NVC of RVLM due to its inhibitory effect on SNA.

Jannetta *et al.*^{13,16} reported that most patients with cranial neuralgia and hypertension with NVC of RVLM undergoing MVD of RVLM showed prominent BP reduction. We reported a patient with EH and hemifacial nerve spasms who exhibited NVC of RVLM and facial nerve.²⁷ MVD of RVLM successfully reduced BP and indices of SNA such as plasma and urine NE, low-frequency to high-frequency ratio obtained by power spectral analysis and muscle SNA.²⁷ Interestingly, Jannetta *et al.* also performed MVD of RVLM in 12 patients with EH without cranial neuralgia and observed a reduction in BP in 10 of them.¹⁷ Therefore, MVD of RVLM is expected to be a useful therapeutic strategy to reduce BP in these patients. However, as MVD is a highly invasive procedure, it seems quite unlikely to be applicable in all hypertensive patients with NVC of RVLM. It is more rational to use hypotensors with higher efficacy to treat such patients. We and others have reported that essential hypertensive patients with NVC of RVLM show increased plasma levels of NE.^{18,19} Furthermore,

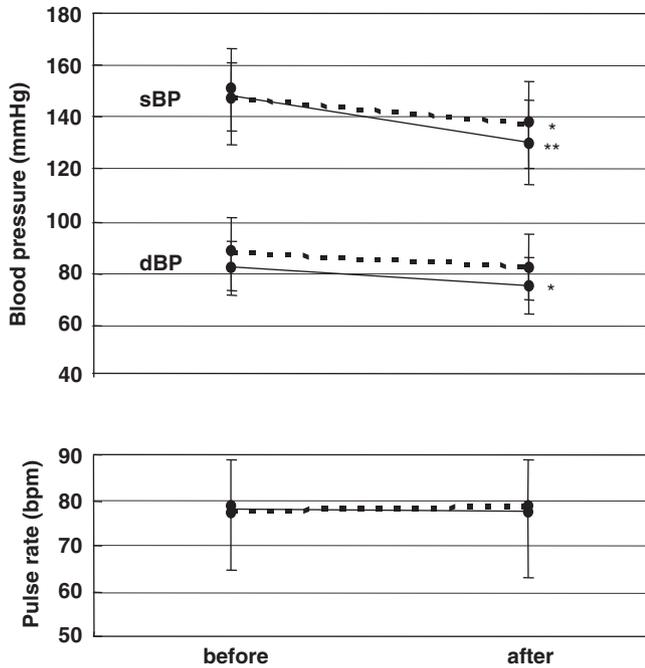


Figure 1 Clinic BP and pulse rate before and after clonidine therapy. sBP, systolic BP; dBP, diastolic BP. Dotted line: essential hypertensive patients without neurovascular contact (NVC) of the rostral ventrolateral medulla (RVLM) (NVC-, $n=28$); solid line: essential hypertensive patients with NVC of RVLM (NVC+, $n=26$). * $P<0.0005$ and ** $P<0.0001$ vs. before treatment.

muscle SNA is increased in essential hypertensive patients with NVC of RVLM.^{20,28} We have reported a patient with refractory hypertension and NVC of RVLM, who showed BP reduction by additional treatment with clonidine.²¹ Therefore, drugs capable of suppressing SNA among hypotensive agents are expected to reduce BP. In this study, we assessed the efficacy of clonidine in patients with EH in a group study. Although plasma NE was slightly higher in the NVC+ group than in the NVC- group, the difference failed to achieve statistical significance (Figure 3a). Considering that untreated essential hypertensive patients with NVC of RVLM show significantly increased concentrations of plasma NE,^{18,19} it is assumed that baseline antihypertensive medications before administering clonidine affected the concentration of plasma NE. Nevertheless, additional treatment with clonidine showed greater reduction in BP (Figures 2a and b) and plasma NE (Figures 3a and b) in the NVC+ group, suggesting that this agent reduces BP by inhibiting SNA in essential hypertensives with NVC more than in those without NVC of RVLM when coadministered with other antihypertensive agents. However, our previous study in rats revealed that BP elevation by pulsatile compression of RVLM becomes more marked in a pressure-dependent manner.¹⁵ Therefore, we cannot rule out the possibility that a decrease in arterial stimulation of RVLM by BP reduction led to a further reduction of BP. At present, there is an ongoing clinical study designed to compare the pressure-lowering effects of L-type calcium antagonists, which do not have sympathetic effects, in NVC+ and NVC- patients.

The antihypertensive drug to be first administered alone or concomitantly with other drugs should be selected from calcium channel antagonists, angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, diuretics and β -blockers.²⁹ As clonidine is not considered as a standard drug in the treatment of hypertension, we

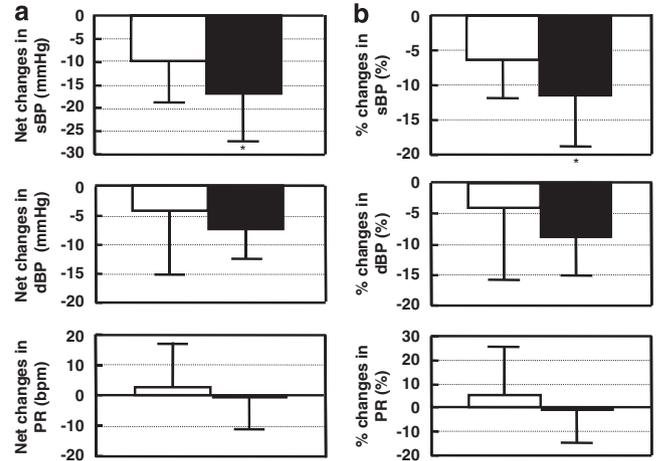


Figure 2 Changes in clinic BP and pulse rate after treatment with clonidine for 4 weeks. Open columns: essential hypertensive patients without neurovascular contact (NVC) of the rostral ventrolateral medulla (RVLM) (NVC- group, $n=28$); closed columns: essential hypertensive patients with NVC of RVLM (NVC+ group, $n=26$). * $P<0.05$ vs. NVC- group.

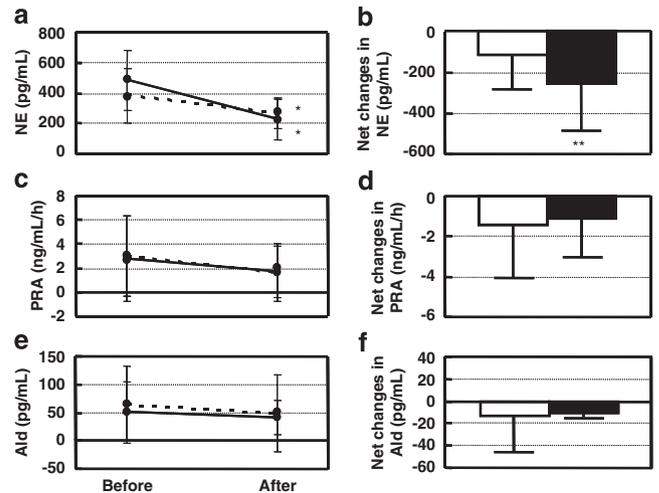


Figure 3 Plasma norepinephrine (NE) (a), renin activity (PRA) (b) and aldosterone (Ald) (c) before and 4 weeks after treatment with clonidine, as well as net changes in plasma NE (d), PRA (e) and Ald (f). Dotted lines and open columns: essential hypertensive patients without neurovascular contact (NVC) of the rostral ventrolateral medulla (RVLM) (NVC-, $n=28$); solid lines and closed columns: essential hypertensive patients with NVC of RVLM (NVC+, $n=26$). * $P<0.01$ vs. before treatment; ** $P<0.05$ vs. NVC- group.

limited the term of clonidine administration to 4 weeks in this pilot study. Clonidine showed greater reduction in BP and SNA during this short time period, which may not be enough to observe final effect of this therapy, in the NVC+ group than in the NVC- group. Studies testing the effect of clonidine >4 weeks are required to determine the real efficacy of this agent. Furthermore, effects of clonidine on the regression of target organ damages such as proteinuria, arterial stiffness (baPWV), atherosclerosis (carotid IMT) and left ventricular hypertrophy (LVMI), which could not be investigated in this short-period study, are needed. In addition, studies examining the effects of other α_2 adrenergic agonists such as guanfacine, guanabenz and α -methyl dopa are required. We have found that cilnidipine, a calcium

channel antagonist that blocks not only L-type channels but also N-type channels and inhibits SNA by inhibiting the release of NE from the peripheral sympathetic nerve endings, reduces BP and plasma NE more significantly in untreated EH with NVC than in those without NVC of RVLM.³⁰ Accordingly, it is possible that any antihypertensive agent that reduces SNA activity may decrease BP especially in hypertensive patients with NVC of RVLM. To test this hypothesis, clinical studies examining the effects of other sympatholytic agents such as α -blockers and β -blockers are also needed, and if this hypothesis is confirmed, it will become necessary to evaluate hypertensive patients for the presence of NVC of RVLM before deciding the treatment for hypertension.

In conclusion, therapy with clonidine resulted in significantly greater reductions of BP and SNA in essential hypertensives with NVC compared with those without NVC of RVLM, suggesting that sympatholytic agents might be especially effective in hypertensives with NVC of RVLM. It could be worthwhile to select hypotensive agents based on the presence or absence of NVC of RVLM when treating patients with EH. As normalization of BP has been reported in hypertensive patients with NVC of RVLM after MVD,^{16,17,27} hypertension due to NVC of RVLM could be classified as secondary hypertension.³¹ To establish this condition as a new type of secondary hypertension, it is essential to conduct further studies on its pathophysiology to establish reasonable treatment methods.

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