ORIGINAL ARTICLE

Efficacy of an L- and N-type calcium channel blocker in hypertensive patients with neurovascular compression of the rostral ventrolateral medulla

Yasuko Aota[1], Satoshi Morimoto[1], Takao Sakuma[1], Tatsuyori Morita[1], Fusakazu Jo[1], Nobuyuki Takahashi[1], Minoru Maehara[2], Koshi Ikeda[2], Satoshi Sawada[2] and Toshiji Iwasaka[1]

The rostral ventrolateral medulla is an important regulation center of sympathetic nerve activity. Several clinical studies have indicated a possible association between essential hypertension and neurovascular compression of the rostral ventrolateral medulla. We have found that patients with essential hypertension and neurovascular compression of the rostral ventrolateral medulla by adjacent arteries have increased sympathetic nerve activity and that microvascular decompression of the rostral ventrolateral medulla normalizes blood pressure and sympathetic nerve activity. Although sympatholytic agents are expected to lower blood pressure in these patients, this remains to be clarified. In this study, we evaluated the effect of cilnidipine, a calcium channel blocker that blocks both vascular L-type and sympathetic N-type Ca^{2+} channels in hypertensive patients with neurovascular compression. Using high-resolution magnetic resonance imaging, 46 patients with untreated essential hypertension were distributed into those with and without neurovascular compression of the rostral ventrolateral medulla. All patients were prescribed 10 mg of cilnidipine for 16 weeks. Office and home blood pressure, plasma norepinephrine and left ventricular mass index were measured by echocardiography before and after cilnidipine treatment, and changes were compared between the two groups. At baseline, plasma norepinephrine was significantly higher in patients with neurovascular compression. Decreases in office and home blood pressure, plasma norepinephrine and left ventricular mass index were significantly greater in patients with neurovascular compression. These results suggest that cilnidipine lowers blood pressure by inhibiting enhanced sympathetic nerve activity and reduces left ventricular mass in hypertensive patients with neurovascular compression of the rostral ventrolateral medulla.

INTRODUCTION

The rostral ventrolateral medulla (RVLM) is an important center for the regulation of sympathetic and cardiovascular activities.[1,2] After the initial report by Jannetta and Gendell in 1978,[3] several clinical studies have suggested an association between neurovascular compression (NVC) of the RVLM and essential hypertension (EH).[4–10] We have reported that magnetic resonance imaging (MRI) with a high-resolution matrix revealed a significantly higher incidence of NVC of the RVLM in EH patients as compared with those with secondary hypertension or normotensive patients, although the degree of organ damage from hypertension was not significantly different between the two groups of hypertensive patients.[11,12] Jannetta et al.[13,14] and we[15] have reported that microvascular decompression (MVD) of the RVLM decreases blood pressure (BP) in hypertensive patients with NVC of the RVLM. Therefore, it is assumed that MVD

of the RVLM could be a useful therapeutic strategy to reduce BP in these patients. As MVD is an invasive therapeutic strategy, it seems worthwhile to seek useful antihypertensive agents for hypertensive patients with NVC of the RVLM. We and others have reported that EH patients with NVC of the RVLM show increased plasma levels of norepinephrine (NE).[15,16] Furthermore, these patients show an increased muscle sympathetic nerve activity (SNA).[17,18] Therefore, although sympatholytic agents are expected to lower BP in these patients, this remains to be clarified.

Cilnidipine is a unique Ca^{2+} channel blocker that not only inhibits vascular L-type and sympathetic N-type Ca^{2+} channels but is also used to treat patients with EH.[19–22] The N-type voltage-dependent calcium channel has an important role in sympathetic neurotransmission and regulates the release of NE from sympathetic nerve endings.[23] Cilnidipine inhibits SNA and heart rate and lowers BP in hypertensive

[1]Second Department of Internal Medicine, Kansai Medical University, Osaka, Japan and [2]Department of Radiology, Kansai Medical University, Osaka, Japan
Correspondence: Dr Y Aota, Second Department of Internal Medicine, Kansai Medical University, 2-3-1, Shin-machi, Hirakata, Osaka 573-1191, Japan.
E-mail: aotay@hitakata.kmu.ac.jp

patients. Therefore, in this study, we examined the effect of cilnidipine on BP in patients with EH with NVC of the RVLM.

METHODS

Case selection

Subjects were selected among patients with untreated essential hypertension who visited our hospital between April 2006 and March 2008. They were all Japanese and those with secondary hypertension (renal and endocrine sources of hypertension) were excluded by appropriate physical and laboratory evaluation. The patients had to have a systolic pressure of ⩾140 mm Hg and/or diastolic pressure of ⩾90 mm Hg on three consecutive office visits. Patients who had suffered a hemorrhagic stroke or cardiac infarction in the previous 6 months, as well as those with chronic renal failure (serum creatinine of ⩾1.5 mg dl^{-1}), pregnant women and those with peripheral vascular or malignant disease, were excluded.

MRI evaluation

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 the posterior commissure. T2-weighted three-dimensional fast recovery fast spin echo (3D-FRFSE) 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, MM), who were blind to the individuals' medical histories, assessed all scans independently to check for the presence of NVC of the RVLM. In instances of disagreement between the reviewers, a consensus interpretation was used for the case. NVC of the RVLM was defined as an arterial vessel or vascular loop with its convexity contacting the surface of the RVLM. The anterior border of the RVLM was defined as the transitional point of the olivary convexity to the concavity of the retro-olivary sulcus, and the posterior border was at the junction of the parenchymal brain tissue to the nerve fibers. Upper and lower borders were determined by the uppermost and the lowest end of the glossopharyngeal and vagal nerve bundles entering the medulla.

Measurement of office BP and pulse rate (PR)

Office BP and PR were measured from 1100 to 1200 hours when the patient was seated after at least 5 min of rest with the use of 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 using an automated oscillometric sphygmomanometer according to the Japanese Society of Hypertension Guidelines for Self-Monitoring of Blood Pressure at Home;[24] within 1 h after waking, after micturiction, sitting after 1 to 2 min of rest, before drug ingestion, and before breakfast. Home BP and PR data were determined as the averages of the measurements for 3 days before the time of estimation.

Laboratory analyses

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 levels of urea nitrogen (BUN), creatinine, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were assessed by conventional methods at the clinical laboratory center of our hospital. Plasma NE concentration was measured by high performance liquid chromatography with electrochemical detection by an external laboratory (SRL Inc., Tokyo, Japan).

Echocardiography

M-mode and pulse Doppler echocardiography was performed blindly to the MRI findings using a 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,[25] and left ventricular mass index (LVMI) was obtained by dividing the left ventricular mass by the body surface area. On the pulse Doppler echocardiogram, the sample volume was placed between the anterior and posterior mitral leaflets to record the left ventricular inflow patterns; the maximum amplitudes of the early diastolic transmitral flow wave (E wave) and atrial systolic transmitral flow wave (A wave) were then estimated and used to calculate the E/A ratio. The E wave deceleration time (Dct) was also estimated. In addition, the percent fractional shortening (%FS) of the left ventricle was calculated using left ventricular internal dimensions (LVDd and LVds). The ejection fraction of the left ventricle was also calculated according to the American Society of Echocardiography's criteria using the area length method.[26]

Study design

At enrollment we collected information on age, gender, duration of hypertension, current diseases, medication, smoking history, body mass index (BMI), waist circumference, biochemical levels (BUN, creatinine, FBS, HbA1c, LDL-C, HDL-C, and TG), plasma NE level and echocardiographic findings. All patients were treated with 10 mg of cilnidipine monotherapy (once daily in the morning) for 16 weeks. During this study, additional treatment or change of dosing of concomitantly administered anti-hyperlipidemic, anti-diabetic or anti-platelet drugs was prohibited.

BMI, waist circumference, biochemical levels, plasma NE level and echocardiographic findings were measured at enrollment and at the end of therapy. Changes between pre- and post-treatment values were compared between patients without (NVC− group) and with (NVC+ group) NVC of the RVLM.

Office and home BP and PR were obtained at enrollment, and at 8 and 16 weeks of treatment. Changes in these values at weeks 8 and 16 in groups NVC− and NVC+ were also compared.

Safety

Information on adverse events was routinely recorded at each hospital visit; investigators were asked to give their opinion on causality.

Statistical analysis

To detect a 15 mm Hg between-group difference in systolic BP change with a power of 80% and a minimum level of significance of 0.05, given a s.d. of 10 mm Hg, 20 patients per group were necessary. Taking into account that about 10% of patients could not be evaluated, a total of 45 assigned patients were required.

Paired Student's t-test was applied to determine the significance of differences between pre- and post-treatment values. Chi-squared test and a non-paired Student's t-test were performed to assess the statistical differences between the NVC(−) and NVC(+) groups. Data are shown as the mean values ± 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 their integrity. All the authors have read the paper and agree with the content.

RESULTS

MRI evaluation and study subjects

The reviewers considered that out of the 48 MRI studies they analyzed, that of one patient with EH (2.1%) was inadequate for assessment because of poor images and was excluded from further evaluation. NVC was observed on the left side in 13 patients, right side in 7, and on both sides of the RVLM in 4 of 46 patients; there were 22 patients in the NVC(−) group and 24 in the NVC(+) group. The contacting artery was the vertebral artery (VA) in four patients, posterior inferior cerebellar artery (PICA) in seven, and the anterior inferior cerebellar artery in 10 of the 20 patients with NVC

of the ipsilateral RVLM. As for the three patients with NVC of the bilateral RVLM, the contacting arteries were VA and PICA in one, PICA and anterior inferior cerebellar artery in another and two PICAs in the third patient.

Changes in baseline characteristics

Baseline characteristics were well matched in the two groups; as summarized in Table 1, age, gender, duration of hypertension, smoking status, BMI, waist circumference and biochemical parameters did not differ significantly between the two groups. The number of patients taking anti-hyperlipidemic drugs (three in NVC− and four in NVC+), anti-diabetic drugs (two and two) and anti-platelet drugs (three and two) did not differ significantly either.

Table 1 Characteristics of the subjects

	NVC− group (n=22)	NVC+ group (n=24)
Age (years)	53.8 ± 10.9	52.9 ± 15.1
Gender (male/female)	13/9	13/11
Duration of hypertension (years)	5.8 ± 6.4	4.2 ± 3.2
Smoking (yes/no)	5/17	6/18
Body mass index (kg m^{-2})	24.4 ± 3.3	24.2 ± 4.0
Waist circumference (cm)	84.8 ± 9.3	84.2 ± 10.5
Blood urea nitrogen (mg per 100 ml)	14.8 ± 4.3	13.0 ± 4.4
Creatinine (mg per 100 ml)	0.76 ± 0.16	0.71 ± 0.18
Fasting blood sugar (mg per 100 ml)	116 ± 30	110 ± 30
Hemoglobin A1c (%)	5.5 ± 0.8	5.5 ± 0.9
Low-density lipoprotein cholesterol (mg per 100 ml)	131 ± 34	130 ± 33
High-density lipoprotein cholesterol (mg per 100 ml)	61 ± 17	61 ± 24
Triglyceride (mg per 100 ml)	146 ± 96	135 ± 92
Norepinephrine (pg ml^{-1})	391 ± 152	512 ± 158*

NVC−, hypertensive patients without neurovascular compression of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular compression of the RVLM. *$P < 0.05$ compared with NVC− group.
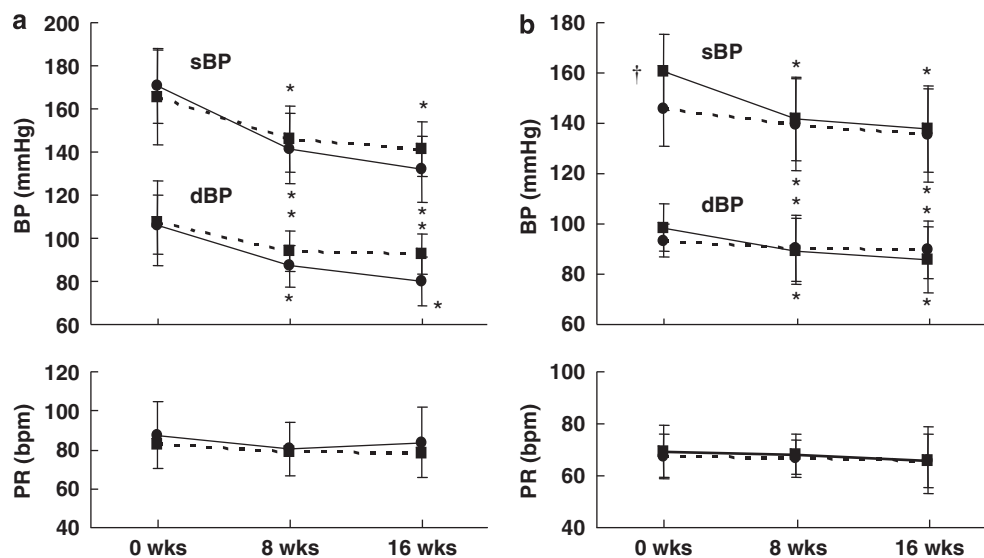
No subjects changed their smoking status during the study period. No patients had their anti-hyperlipidemic, anti-diabetic, or anti-platelet drugs changed during the study. BMI (24.2 ± 3.5 and 24.6 ± 4.2 kg m^{-2} in the NVC(−) and NVC(+) groups, respectively, after treatment), waist circumference (84.2 ± 9.5 and 83.8 ± 9.8 cm), BUN (15.2 ± 5.3 and 14.8 ± 4.9 mg dl^{-1}), creatinine (0.74 ± 0.12 and 0.72 ± 0.17 mg dl^{-1}), FBS (113 ± 7 and 112 ± 6 mg dl^{-1}), HbA1c (5.4 ± 0.7 and 5.3 ± 0.8%), LDL-C (132 ± 40 and 134 ± 38 mg dl^{-1}), HDL-C (65 ± 15 and 63 ± 19 mg dl^{-1}), and TG (147 ± 83 and 141 ± 78 mg dl^{-1}) did not change significantly because of treatment. Changes in these factors did not differ significantly between the two groups.

Changes in office BP and PR

Office systolic and diastolic BPs were not significantly different between the two groups (Figure 1a). Office systolic and diastolic BPs were significantly decreased at 8 and 16 weeks of treatment with cilnidipine in the NVC− and NVC+ groups (Figure 1a). The net changes and percentage changes in office systolic and diastolic BPs were significantly greater in the NVC+ group than in the NVC− group at 16 weeks of treatment (Table 2). Office PR did not differ significantly between the two groups before treatment and did not change significantly in either group at 8 and 16 weeks of treatment (Figure 1a). Neither the net change nor the percentage change in office PR differed significantly between the two groups (Table 2).

Changes in home BP and PR

Before cilnidipine treatment, home diastolic BP did not differ significantly between the two groups, whereas home systolic BP was significantly higher in the NVC+ group than in the NVC− group (Figure 1b). Home systolic and diastolic BPs were significantly decreased at 8 and 16 weeks of treatment with cilnidipine in both groups (Figure 1b). The net changes and percentage changes in home systolic and diastolic BPs were significantly greater in the NVC+ group than in the NVC− group at 16 weeks of treatment (Table 2). Home PR did not differ significantly between the two groups before treat-

Figure 1 Time courses of changes in blood pressure (BP) and pulse rate (PR) during treatment with cilnidipine. (**a**) Office BP and PR. (**b**) Home BP and PR. Dotted line, hypertensive patients without neurovascular compression of the rostral ventrolateral medulla (NVC−) (n=22); solid line, hypertensive patients with neurovascular compression of the rostral ventrolateral medulla (NVC+) (n=24). sBP, systolic blood pressure; dBP, diastolic blood pressure. *$P < 0.001$ vs. before treatment; †$P < P < 0.05$ vs. NVC− group.

Table 2 Net changes in office and home blood pressure and pulse rate (PR) at 8 and 16 weeks of treatment with cilnidipine

	After 8 weeks of treatment		After 16 weeks of treatment	
	NVC−	NVC+	NVC−	NVC+
Net changes in office sBP (mm Hg)	−19.2±20.8	−29.9±18.1	−24.1±16.7	−38.5±14.7*
Net changes in office dBP (mm Hg)	−13.1±11.8	−18.8±14.7	−14.3±11.8	−26±14.8*
Net changes in office PR (b.p.m.)	−3.9±14.3	−7±12.4	−4.6±10.7	−3.8±14.9
% Changes in office sBP (%)	−11.6±8.6	−17.5±9.5	−14.6±7.8	−22.6±7.2*
% Changes in office dBP (%)	−12.2±8.9	−17.7±10.5	−13.3±7.8	−24.5±8.8*
% Changes in office PR (%)	−4.7±14.3	−8±12.4	−5.6±10.7	−4.3±14.9
Net changes in home sBP (mm Hg)	−5.9±15.3	−18.4±13.2	−10.2±6.3	−22.6±14.2*
Net changes in home dBP (mm Hg)	−2.9±10.8	−9.4±10	−3.7±6.4	−12.9±11.4*
Net changse in home PR (b.p.m.)	−0.3±13.7	−1.6±10.3	−1.4±13.6	−3.8±10.5
% Changes in home sBP (%)	−4.1±9.8	−11.5±7.5	−7±5.7	−14.4±7.8*
% Chages in home dBP (%)	−3.1±10.8	−9.5±9.27	−4±7.3	−14.6±11*
% Changes in home PR (%)	−0.1±10.3	−2.3±12.9	−2.1±10.1	−5.5±9.9

NVC−, hypertensive patients without neurovascular compression of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular compression of the RVLM.
*$P<0.05$ compared with NVC− group.

ment and did not change significantly in either group at 8 and 16 weeks of treatment (Figure 1b). Neither the net change nor the percentage change in home PR differed significantly between the two groups (Table 2).

Changes in plasma NE level
Although the plasma NE level varied (coefficient of variation: NVC− group, 38.9%; NVC+ group, 30.9%), it was significantly higher in the NVC+ group than in the NVC− group before treatment (Table 1), in accordance with our previous data and those of others.[15,16] Plasma NE decreased significantly in the NVC+ group (326 ± 125 pg ml^{-1}, $P<0.01$) and slightly in the NVC− group (330 ± 110 pg ml^{-1}), showing no significant difference between the two groups at 16 weeks of treatment. The decrease in plasma NE was significantly greater in the NVC+ group than in the NVC− group (Figure 2).

Changes in echocardiographic findings
LVMI, a marker of left ventricular hypertrophy (LVH), E/A and Dct, markers of left ventricular diastolic function, and %FS and EF, markers of left ventricular systolic function, did not differ significantly between the two groups before treatment (Table 3). LVMI was significantly decreased in the NVC+ group but not in the NVC− group at 16 weeks of treatment with cilnidipine (Table 3). The decrease in LVMI was significantly greater in the NVC+ group than in the NVC− group (Figure 3). E/A, Dct, %FS or EF did not show a significant change, and neither did the changes differ significantly between the two groups.

Safety
No symptoms, adverse effects or abnormal laboratory findings were seen during the study. Patients in each group showed good tolerance, with no subjects discontinuing the study.

DISCUSSION
In this study, we found that plasma NE levels were significantly higher in the NVC+ group than in the NVC− group. In addition, chronic
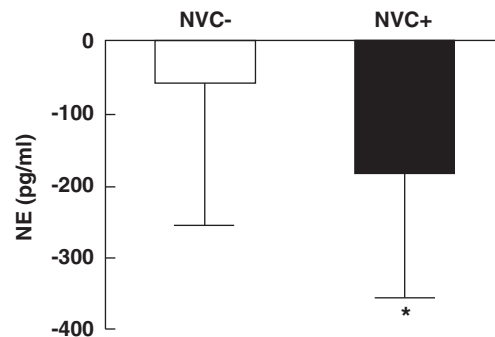

Figure 2 Changes in plasma norepinephrine (NE) levels after treatment with cilnidipine for 16 weeks. NVC−, hypertensive patients without neurovascular compression of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular compression of the RVLM. $n=22$ for the NVC− group and $n=24$ for the NVC+ group. *$P<0.05$ vs. NVC− group.

administration of cilnidipine led to regression of the left ventricular mass and to a significantly greater decrease in office and home BPs and plasma NE in the NVC+ group compared with the NVC− group, indicating that cilnidipine is effective, especially in hypertensive patients with NVC of the RVLM thanks to its inhibitory effect on enhanced SNA.

Since the initial report by Jannetta and Gendell[3] in 1978, several clinical studies have indicated a possible association between NVC of the RVLM and EH.[4–10] Using MRI, we found that the incidence of NVC of the RVLM in patients with EH was significantly higher than that in patients with secondary hypertension or in normotensive subjects, although the stage of hypertension did not differ significantly between the two hypertension groups.[11,12] We and others have reported that hypertensive patients show increased plasma levels of NE.[15,16] Therefore, it is assumed that NVC of the RVLM may be, at least in part, causally related to EH.

In the clinical report mentioned above,[10] Jannetta et al. described that of 51 patients with cranial neuralgia and hypertension, 42 underwent MVD of both the cranial nerves and the artery, and in 36 the results of the surgical procedure were adequate. The BP normalized in 32 of these patients and improved in the remainder,

Table 3 Echocardiographic findings

	NVC− group (n=21)		NVC+ group (n=22)	
	Before treatment	*16 weeks after treatment*	*Before treatment*	*16 weeks after treatment*
LVDd (cm)	4.8 ± 0.4	4.8 ± 0.6	4.8 ± 0.4	4.8 ± 0.6
LVDs (cm)	2.9 ± 0.4	3.0 ± 0.5	3.2 ± 0.7	2.8 ± 0.7
IVST (cm)	10.4 ± 1.9	10.0 ± 1.9	10.4 ± 1.7	9.1 ± 1.8
PWT (cm)	9.8 ± 1.7	9.9 ± 1.8	10.4 ± 1.4	9.3 ± 2.0
LVMI (g m^{-2})	127.2 ± 38.8	130.2 ± 35.5	134.1 ± 38.7	117.3 ± 38.5*
E (cm s^{-1})	68.8 ± 15.2	62.0 ± 16.9	62.9 ± 11.9	58.5 ± 13.7
A (cm s^{-1})	80.0 ± 10.9	85.5 ± 22.9	75.6 ± 15.3	81.3 ± 14.0
E/A ratio	0.86 ± 0.33	0.76 ± 0.22	0.86 ± 0.23	0.73 ± 0.15
E wave deceleration time (ms)	211 ± 62	214 ± 40	207 ± 47	219 ± 57
% FS (%)	38.9 ± 5.3	37.9 ± 6.9	37.9 ± 6.0	41.5 ± 6.3
EF (%)	69.0 ± 6.7	68.8 ± 7.0	67.9 ± 7.5	61.7 ± 13.3

NVC−, hypertensive patients without neurovascular compression of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular compression of the RVLM. LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; IVST, interventricular septatl thickness; PWT, posterior wall thickness; LVMI, left ventricular mass index; E, early diastolic transmitral flow velocity; A, atrial systolic transmitral flow velocity; Dct, E wave deceleration time; FS, fractional shortening; EF, ejection fraction.
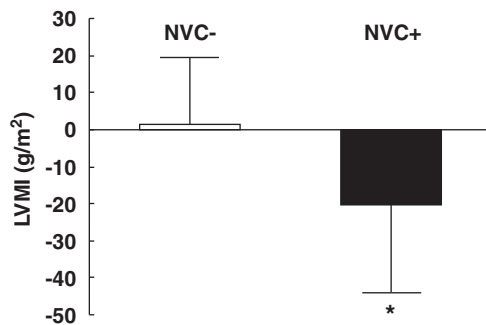*P<0.05 compared with before treatment.

Figure 3 Changes in left ventricular mass index (LVMI) after treatment with cilnidipine for 16 weeks. NVC−, hypertensive patients without neurovascular compression of the rostral ventrolateral medulla (RVLM); NVC+, hypertensive patients with neurovascular compression of the RVLM. *n*=21 for the NVC− group and *n*=22 for the NVC+ group. *P<0.05 *vs*. NVC− group.

allowing a reduction of the hypertensive medication. Of the 36 patients whose decompression was deemed adequate, 30 were still available for follow-up 7 years later, and 26 were either normotensive or had improved the control of their hypertension.[13] They also performed MVD of the RVLM in 12 patients with EH without cranial neuralgia and observed a reduction in BP in 10 of 12 patients.[14] We reported a patient with EH and hemifacial nerve spasms who showed NVC of the RVLM and facial nerve. MVD of the RVLM successfully reduced BP and indices of SNA such as plasma and urine NE levels, low-frequency to high-frequency ratio obtained by power spectral analysis and muscle SNA.[27] Therefore, MVD of the RVLM is expected to be a useful therapeutic strategy to reduce BP in these patients.

However, as MVD is a highly invasive therapy, it seems quite unlikely to be applicable in all hypertensive patients with NVC of the RVLM. It seems more rational to use hypotensors with higher efficacy to treat such patients. It has been reported that SNA is elevated in patients with hypertension accompanied by NVC of the RVLM.[15–17] This study endorsed this previous finding (Table 1). We have reported a patient with refractory hypertension and NVC of the RVLM, who revealed prominent BP reduction by additional treatment with clonidine, an α2 adrenergic agonist.[28] Therefore, drugs capable of suppressing SNA among hypotensive agents are expected to reduce BP. In this study, we assessed the efficacy of cilnidipine, which is known to suppress SNA through N type calcium channel antagonism. Its hypotensive action and plasma NE-lowering effect were higher in the NVC+ group than in the NVC− group, suggesting that cilnidipine exerts a particularly potent hypotensive action in NVC+ patients. However, our previous study in rats revealed that BP elevation by pulsatile compression of RVLM becomes more marked in a pressure-dependent manner.[12] Therefore, we cannot rule out that a decrease in arterial stimulation of the RVLM led to a further reduction in BP. At present, there is an ongoing clinical study designed to compare the pressure-lowering effects of L type calcium antagonists in NVC+ and NVC− patients. The ultimate goal of antihypertensive therapy is the suppression of cardiovascular complications.[29,30] Achieving BP reduction is quite important in hypotensive therapy, and it is known that a strict reduction of BP can improve the prognosis.[31,32] We may therefore expect cilnidipine to be a useful means of treatment, particularly in NVC+ patients, and to suppress cardiovascular complications more potently in the NVC+ group than in the NVC− group.

LVH is one of the risk factors of cardiovascular complications.[16,33] In this study, the reduction of LVMI was greater in the NVC+ group than in the NVC− group; although in the whole study population the reduction of LVMI was not statistically significant (*P*=0.13). Although the 16-week period was not long enough to reduce in the NVC− group, this period was adequate for obtaining such change in the NVC+ group. Thus, cilnidipine would be particularly useful in EH patients with NVC+ to reduce LVH. An association between elevated SNA and LVH has been reported.[34,35] It is probable that in addition to hypotensive activity, suppression of SNA may be partially involved in the potent reduction of a left ventricular myocardial mass induced by cilnidipine in NVC+ patients. However, there was no significant correlation between LVMI reduction and plasma NE level reduction in this study (*r*=0.288, *P*=0.2925). The effects of cilnidipine in suppressing and reducing cardiovascular complications warrant more in-depth studies using a detailed analysis of the mechanism of action of cilnidipine.

Keeping in view that in these cases BP elevation was associated with increased SNA[15–18] and that BP usually normalizes following decompression,[13,14,27] we may say that the elevated BP seen in patients with NVC of the RVLM is attributable to the compression itself. This means that hypertension in these cases may be classified as secondary hypertension.[36] It might be worthwhile to select hypotensive agent based on the presence/absence of NVC of the RVLM when dealing with patients with EH. However, several MRI studies showed similar prevalence of NVC of the RVLM between patients with EH and normotensives.[37–41] In addition, the prevalence of NVC of the RVLM varied from 30 to 90% in essential hypertensives and from 7 to 55% in normotensives.[4–7,9,11,12,18,37–43] The reason for the variation of the estimated prevalence of NVC of the RVLM may be due to the inability of MRI for the perfect and adequate assessment of the presence of NVC of the RVLM and to a lack of standardized classification of NVC of the RVLM. Investigation to establish adequate methods to assess whether NVC of the RVLM exists or not, and whether the compression is functional or not, will be needed.

In conclusion, our data suggest that cilnidipine lowers BP by inhibiting enhanced SNA and reduces left ventricular mass in hypertensive patients with NVC of the RVLM. It is possible that antihypertensive treatment to reduce SNA may be useful in hypertensive patients with NVC of the RVLM. However, it is also possible that the effect of cilnidipine in hypertensive patients with NVC of the RVLM is due to a blockade of vascular L-type Ca^{2+} channels. Similar studies examining the effects of other antihypertensive agents to inhibit SNA or other Ca^{2+} channel blockers that do not reduce SNA are needed to test this presumption.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Dampney RA, Goodchild AK, Robertson LG, Montgomery W. Role of ventrolateral medulla in vasomotor regulation: a correlative anatomical and physiological study. *Brain Res Rev* 1982; **249**: 223–235.
2 Oshima N, Kumagai H, Onimaru H, Kawai A, Pilowsky PM, Iigaya K, Takimoto C, Hayashi K, Saruta T, Itoh H. Monosynaptic excitatory connection from the rostral ventrolateral medulla to sympathetic preganglionic neurons revealed by simultaneous recordings. *Hypertens Res* 2008; **31**: 1445–1454.
3 Jannetta PJ, Gendell HM. Neurovascular compression associated with essential hypertension. *Neurosurgery* 1978; **2**: 165.
4 Yamamoto I, Yamada S, Sato O. Microvascular decompression for hypertension–clinical and experimental study. *Neurol Med Chir (Tokyo)* 1991; **31**: 1–6.
5 Kleineberg B, Becker H, Gaab MR, Naraghi R. Essential hypertension associated with neurovascular compression: angiographic findings. *Neurosurgery* 1992; **30**: 834–841.
6 Naraghi R, Gaab MR, Walter GF, Kleineberg B. Arterial hypertension and neurovascular compression at the ventrolateral medulla. A comparative microanatomical and pathological study. *J Neurosurg* 1992; **77**: 103–112.
7 Naraghi R, Geiger H, Crnac J, Huk W, Fahlbusch R, Engels G, Luft FC. Posterior fossa neurovascular anomalies in essential hypertension. *Lancet* 1994; **344**: 1466–1470.
8 Kleineberg B, Becker H, Gaab MR. Neurovascular compression and essential hypertension. An angiographic study. *Neuroradiology* 1991; **33**: 2–8.
9 Akimura T, Furutani Y, Jimi Y, Saito K, Kashiwagi S, Kato S, Ito H. Essential hypertension and neurovascular compression at the ventrolateral medulla oblongata: MR evaluation. *Am J Neuroradiol* 1995; **16**: 401–405.
10 Jannetta PJ, Segal R, Wolfson SK. Neurogenic hypertension: etiology and surgical treatment. I. Observations in 53 patients. *Ann Surg* 1985; **201**: 391–398.
11 Morimoto S, Sasaki S, Miki S, Kawa T, Itoh H, Nakata T, Takeda K, Nakagawa M, Kizu O, Furuya S, Naruse S, Maeda T. Neurovascular compression of the rostral ventrolateral medulla related to essential hypertension. *Hypertension* 1997; **30** (part 1): 77–82.
12 Morimoto S, Sasaki S, Miki S, Kawa T, Itoh H, Nakata T, Takeda K, Nakagawa M, Naruse S, Maeda T. Pulsatile compression of the rostral ventrolateral medulla in hypertension. *Hypertension* 1997; **29** (part 2): 514–518.
13 Jannetta PJ, Hamm IS, Jho HD, Saiki I. Essential hypertension caused by arterial compression of the left lateral medulla: a follow-up. *Perspect Neurol Surg* 1992; **3**: 107–125.
14 Levy EL, Clyde B, McLaughlin MR, Jannetta PJ. Microvascular decompression of the left lateral medulla oblongata for severe refractory neurogenic hypertension. *Neurosurgery* 1998; **43**: 1–6.
15 Morimoto S, Sasaki S, Itoh H, Nakata T, Takeda K, Nakagawa M, Furuya S, Naruse S, Fukuyama R, Fushiki S. Sympathetic activation and contribution of genetic factors in hypertension with neurovascular compression of the rostral ventrolateral medulla. *J Hypertens* 1999; **17**: 1577–1582.
16 Makino Y, Kawano Y, Okuda N, Horio T, Iwashima Y, Yamada N, Takayama M, Takishita S. Autonomic function in hypertensive patients with neurovascular compression of the ventrolateral medulla oblongata. *J Hypertens* 1999; **17**: 1257–1263.
17 Smith PA, Meaney JFM, Graham LN, Stoker JB, Mackintosh AF, Mary DASG, Ball SG. Relationship of neurovascular compression to central sympathetic discharge and essential hypertension. *J Am Coll Cardiol* 2004; **43**: 1453–1458.
18 Sendeski MM, Consolim-Colombo FM, Leite CC, Ribira MC, Lessa P, Krieger EM. Increased sympathetic nerve activity correlates with neurovascular compression at the rostral ventrolateral medulla. *Hypertension* 2006; **47**: 988–995.
19 Oike M, Inoue Y, Kitamura K, Kuriyama H. Dual action of FRC8653, a novel dihydropyridine derivative, on the Ba2+ current recorded from the rabbit basilar artery. *Circ Res* 1990; **67**: 993–1006.
20 Uneyema H, Takahara A, Dohmoto H, Yoshimoto R, Inoue K, Akaike N. Blockade of N-type Ca2+ current by cilnidipine (FRC-8653) in acutely dissociated rat sympathetic neurons. *Br J Pharmacol* 1997; **122**: 32–42.
21 Takahara A, Fujita S, Moki K, Ono Y, Koganei H, Iwayama S, Yamamoto H. Neuronal Ca2+ channel blocking action of an antihypertensive drug, cilnidipine, in IMR=32 human neuroblastoma cells. *Hypertens Res* 2003; **26**: 743–747.
22 Takahara A, Iwasaki H, Nakamura Y, Sugiyama A. Cardiac effects of L/N-type Ca2+ channel blocker cilnidipine in anesthetized dogs. *Eur J Pharmacol* 2007; **565**: 166–170.
23 Hirning LD, Fox AP, McCleskey EW, Olivera BM, Thayer SA, Miller RJ, Tsien RW. Dominant role of N-type Ca2+ channels in evoked release of norepinephrine from sympathetic neurons. *Science* 1988; **239**: 57–61.
24 Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, Fukiyama K. Japanese Society of Hypertension (JSH) Guidelines for Self-Monitoring of Blood Pressure at Home. *Hypertens Res* 2003; **26**: 771–782.
25 Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986; **57**: 450–458.
26 Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2**: 358–367.
27 Morimoto S, Sasaki S, Takeda K, Furuya S, Naruse S, Matsumoto K, Higuchi T, Saito M, Nakagawa M. Decreases in blood pressure and sympathetic nerve activity by microvascular decompression of the rostral ventrolateral medulla in essential hypertension. *Stroke* 1999; **30**: 1707–1710.
28 Morimoto S, Aota Y, Sakuma T, Ichibangase A, Ikeda K, Sawada S, Iwasaka T. Efficacy of clonidine in a patient with refractory hypertension and chronic renal failure exhibiting neurovascular compression of the rostral ventrolateral medulla. *Hypertens Res* 2009; **32**: 227–228.
29 World Health Organization International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; **21**: 1983–1992.
30 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Chapter 3. Principles of treatment. *Hypertens Res* 2009; **32**: 24–28.
31 Moser M, Hebert PR. Prevention of disease progression, left ventricular hypertrophy and congestive heart failure in hypertension treatment trials. *J Am Coll Cardiol* 1996; **27**: 1214–1218.
32 Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997; **277**: 739–745.
33 Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990; **322**: 1561–1566.
34 Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. *Circulation* 2003; **108**: 560–565.
35 Burns J, Sivananthan MU, Ball SG, Mackintosh AF, Mary DASG, Greenwood JP. Relationship between central sympathetic drive and magnetic resonance imaging-determined left ventricular mass in essential hypertension. *Circulation* 2007; **115**: 1999–2005.
36 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, Imai Y, Imaizumi T, Ito S, Iwao H, Kario K, Kawano Y, Kim-Mitsuyama S, Kimura G, Matsubara H, Matsuura H, Naruse M, Saito I, Shimada K, Shimamoto K, Suzuki H, Takishita S, Tanahashi N, Tsuchihashi T, Uchiyama M, Ueda S, Ueshima H, Umemura S, Ishimitsu T, Rakugi H. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). Chapter 12. Secondary hypertension. *Hypertens Res* 2009; **32**: 78–90.
37 Watterws MR, Burton BS, Turner GE, Cannard KR. MR screening for brain stem compression in hypertension. *Am J Neuroradiol* 1996; **17**: 217–221.
38 Colon GP, Quint DJ, Dickinson LD, Brunberg JA, Jamerson KA, Hoff JT, Ross DA. Magnetic resonance evaluation of ventrolateral medullary compression in essential hypertension. *J Neurosurg* 1998; **88**: 226–231.
39 Johnson DR, Coley SC, Brown J, Moseley IF. The role of MRI in screening for neurogenic hypertension. *Neuroradiology* 2000; **42**: 99–103.
40 Hohenbleicher H, Schmitz SA, Koennecke HC, Offermann R, Offermann J, Zeytountchian H, Wolf KJ, Distler A, Sharma AM. Neurovascular contact of cranial nerve IX and X root-entry zone in hypertensive patients. *Hypertension* 2001; **37**: 176–181.
41 Zikka J, Ceral J, Elias P, Tintera J, Kizo L, Solar M, Straka L. Vascular compression of rostral medulla oblongata: prospective MR imaging study in hypertensive and normotensive subjects. *Radiology* 2004; **230**: 65–69.
42 Goldmann A, Herzog T, Schaeffer J, Muehling M, Haubitz B, Haller H, Becker H, Radermacher J. Prevalence of neurovascular compression in patients with essential and secondary hypertension. *Clin Nephrol* 2007; **68**: 357–366.
43 Morise T, Horita M, Kitagawa I, Shinzato R, Hoshiba Y, Masuya H, Suzuki M, Takekoshi N. The potent role of increased sympathetic tone in pathogenesis of essential hypertension with neurovascular compression. *J Hum Hypertens* 2000; **14**: 807–811.