ORIGINAL ARTICLE

Blood pressure variability and prognosis in acute ischemic stroke with vascular compression on the rostral ventrolateral medulla (RVLM)

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One of the known causes of hypertension is vascular compression on the rostral ventrolateral medulla (RVLM). However, it remains unknown whether RVLM vascular compression causes the significant variability in blood pressure observed during acute ischemic stroke. The purpose of this study was to evaluate differences in blood pressure variability and prognosis in acute ischemic stroke patients based on the presence or absence of RVLM vascular compression. We evaluated 56 patients with acute ischemic stroke. Blood pressure was measured every 6 h for 72 h after admission and evaluated with successive variation (SV). The presence of RVLM vascular compression was evaluated using time-of-flight 3D magnetic resonance imaging. Neurological severity was evaluated using the National Institutes of Health Stroke Scale (NIHSS) at admission and 14 days after admission, and clinical improvement was determined by taking the difference in the NIHSS scores between admission and at 14 days. Patient clinical outcome was evaluated with the modified Rankin scale on discharge. Vascular compression of the RVLM was identified in 15 patients (26.8%). The proportion of patients showing clinical improvement was significantly higher in the non-compression group (odds ratio, 0.21 (95% CI=0.06–0.78); $P=0.01$). The SV value for systolic blood pressure was significantly higher in the compression group ($P<0.0001$). We found that patients with RVLM vascular compression had a greater variability in blood pressure during the acute ischemic stroke phase, which may be related to poorer prognosis.

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INTRODUCTION

Regardless of nationality or ethnicity, hypertension is a lifestyle-related disease afflicting patients throughout the world and is a major risk factor for stroke. Hypertension is a multifactorial disease. It has been reported that a large population of patients with vascular compression on the rostral ventrolateral medulla (RVLM) have hypertension.^{1–4} Surgical decompression of the RVLM reduced sympathetic nerve activity and normalized systemic blood pressure.^{5,6} Therefore, it is suggested that vascular compression on the RVLM influences the development or maintenance of hypertension. The RVLM has been experimentally shown to be a site of cardiac and vasomotor regulation. The mechanism of increased blood pressure in patients with vascular compression on the RVLM remains to be completely elucidated. It is currently hypothesized that chronic stimulation of this region with vascular compression can cause constitutive activation of the sympathetic nervous system and the development of hypertension.^{7,8}

More than 80% of acute stroke patients have elevated blood pressure. Several days following the incidence of stroke, however, the blood pressure in these patients returns to baseline levels.⁹ This blood pressure elevation varies depending on the subtype of ischemic stroke

and on the patient's medical history.¹⁰ In general, the cause of elevated blood pressure during the acute phase of ischemic stroke is presumed to be an increase in sympathetic nerve activity and stress from the ischemic insult that disrupts intracerebral autoregulation to maintain cerebral blood flow.¹¹ During acute ischemic stroke, the rapid decrease in blood pressure reduces cerebral blood flow in parallel to a decrease in the perfusion pressure that is sufficiently large to expand infarct volumes and worsen neurologic symptoms. Therefore, such an excessive lowering of blood pressure during acute ischemic stroke is not desirable. Even in studies examining the correlation between blood pressure and prognosis in the acute ischemic stroke phase, the variability in blood pressure has been shown to be an independent prognostic factor for a poor outcome.^{12,13}

RVLM vascular compression may cause significant variability in blood pressure during acute ischemic stroke by sympathetic nerve activation.¹⁴ However, to our knowledge, it remains unclear whether RVLM vascular compression influences blood pressure during acute ischemic stroke. Therefore, the purpose of this study was to evaluate differences in blood pressure variability and prognosis during acute ischemic stroke in the presence or absence of RVLM vascular

compression and to examine the influence of chronic sympathetic nerve activation on acute ischemic stroke.

METHODS

Subjects and study design

This study was conducted in consecutive patients with acute ischemic stroke admitted between April 2008 and March 2010 to Hiroshima University Hospital within 24 h of stroke onset. Exclusion criteria included the inability to undergo magnetic resonance imaging (MRI) examination, the administration of thrombolysis, an National Institutes of Health Stroke Scale (NIHSS) score ≥ 23 on admission, the use of anti-hypertensive or vasopressor medicines within 72 h after admission, and surgery within 72 h after admission. In addition, we excluded patients with medullary infarctions, which might have effects on RVLM. The stroke subtype was determined based on MRI findings, electrocardiography, and carotid artery and cardiac ultrasound findings by at least two stroke specialists according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.¹⁵ The acute treatment was determined based on the stroke subtype in accordance with the established guidelines. Neurological severity was evaluated using the NIHSS upon admission and 14 days after admission.¹⁶ Their clinical outcome was evaluated with the modified Rankin scale at the time of discharge.¹⁷ The study was approved by the institutional review board of Hiroshima University Hospital.

Hypertension was defined as the use of any anti-hypertensive medicines before admission or a confirmed blood pressure of $\geq 140/90$ mm Hg at rest after 2 weeks from stroke onset. Diabetes mellitus was defined as HbA1c $\geq 6.5\%$, fasting blood sugar ≥ 126 mg dl⁻¹, or the use of any anti-diabetic medicines. Hyperlipidemia was defined as total cholesterol ≥ 220 mg dl⁻¹, low-density lipoprotein cholesterol ≥ 140 mg dl⁻¹ on admission, or the use of any anti-hyperlipidemic medications. For 72 h after admission, blood pressure and pulse rate were measured every 6 h on the unaffected arm in a resting supine position using a standard automated sphygmomanometer without any anti-hypertensive medicines. Blood pressure and pulse rate variability was evaluated with successive variation (SV), defined as the square root of the averaged squared differences between two successive measurements.¹⁸

The presence or absence of RVLM vascular compression was evaluated on a 3T MRI unit (GE, Fairfield, CT, USA) using 3D time-of-flight (slice thickness of 1.0 mm, TR/TE/flip angle, 23/3.4/18°). The RVLM was located at the root-entry zone of cranial nerves IX and X (Figure 1). The location was defined as follows: upper and lower borders of the root-entry zone were determined by the uppermost and lowest fibers of the IX/X nerve bundle entering the medulla; the anterior border of the root-entry zone was defined as the transition of the olivary convexity to the concavity of the retro-olivary sulcus; and the posterolateral border was located at the junction of parenchymal brain tissue and individual nerve fibers.² Arterial compression (vertebral artery or posterior-inferior cerebellar artery) within this defined area was considered 'positive' for RVLM, and patients with no arterial compression were considered 'negative.' We defined arterial compression as deformation of the medulla surface. Therefore, instances in which the artery just contacted the surface of the medulla were excluded from the criteria for RVLM vascular compression. The presence of RVLM vascular compression was evaluated by two neurologists who were unaware of each patient's medical history.

Statistical analysis

Data are shown as the mean $\pm$ s.d. or median (minimum-maximum) for continuous variables. Statistical analysis for comparison of the two groups was performed using Student's *t*-test or the Mann-Whitney *U*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. *P*-values < 0.05 were considered statistically significant. Receiver operating characteristic curves were configured to establish cut-off points for SV that optimally predicted RVLM compression.

RESULTS

Of the 86 enrolled patients, 11 did not undergo MRI, 4 had missing data, 3 received thrombolysis, 4 had an NIHSS score ≥ 23 on admission, 5 received anti-hypertensive or vasopressor medicines,

Figure 1 Axial 3D time-of-flight (TOF) images are shown (a) compression case, (b) non-compression case. The RVLM extends in a craniocaudal direction from the root entry zone of cranial nerve IX down to the upper part of cranial nerve XI. The RVLM is dorsolateral to the olive and medioventral to the root entry zone of cranial nerves IX and X (arrowhead). The compression of vertebral artery (arrow) or posterior-inferior cerebellar artery within this defined area was considered 'positive' for RVLM.

and 3 had surgery within 48 h of hospital admission. Thus, all analyses were performed on the remaining 56 patients. MRI was performed at a mean time of 32.3 h after symptom onset (range, 4–50 h). Table 1 shows the baseline characteristics of all patients. Vascular compression on the RVLM was identified in 15 (26.8%) patients (hereafter, referred to as the compression group). Age was not significantly different between the patients with and without RVLM vascular compression. In the compression group, the proportion of males was significantly higher (93.3 vs. 63.4%, $P=0.03$). The prevalence of hypertension was significantly higher in the compression group (93.3 vs. 61.0%, $P=0.02$). At the time of admission, there was no significant difference

Table 1 Baseline characteristics, blood pressure and NIHSS on admission, and ischemic stroke subtypes

Variables	Compression (n=15)	Non-compression (n=41)	P-value
Age, mean years $\pm$ s.d.	71.6 $\pm$ 9.37	73.2 $\pm$ 9.5	0.59
Male, n (%)	14 (93.3%)	26 (63.4%)	0.03
<i>Risk factors</i>			
Hypertension, n (%)	14 (93.3%)	25 (61.0%)	0.02
Diabetes mellitus, n (%)	9 (60.0%)	17 (41.5%)	0.22
Hyperlipidemia, n (%)	7 (46.7%)	27 (65.9%)	0.19
Baseline NIHSS	4 (0–8)	4 (0–20)	0.29
Baseline SBP, mean mm Hg $\pm$ s.d.	159.1 $\pm$ 8.9	149.5 $\pm$ 26.1	0.17
Baseline DBP, mean mm Hg $\pm$ s.d.	81.1 $\pm$ 14.7	75.4 $\pm$ 15.2	0.88
<i>Ischemic stroke subtype</i>			
Atherothrombotic, n (%)	5 (33.3%)	13 (31.7%)	0.17
Cardioembolic, n (%)	2 (13.3%)	17 (41.5%)	
Small vessel, n (%)	3 (20.0%)	5 (12.2%)	
Other etiology, n (%)	5 (33.3%)	6 (14.6%)	

Abbreviations: DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

Table 2 Relationship between RVLM vascular compression and clinical improvement at 14 days

	Improved (NIHSS ≥ 4 improvement or NIHSS=0)	Unimproved	OR (95% CI) probability
Compression	4 (26.7%)	11 (73.3%)	0.21 (0.06–0.78) $P=0.01$
Non-Compression	26 (63.4%)	15 (36.6%)	

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; RVLM, rostral ventrolateral medulla.

in NIHSS scores, and no significant difference was observed in systolic or diastolic blood pressure between the groups. In addition, the subtype of ischemic stroke was not significantly different between the groups ($P=0.17$).

The patients were defined as clinically improved when their NIHSS score decreased more than four points or recovered to 0 on day 14 (ref. 19). The proportion of clinically improved patients was 26.7% in the compression group and 63.4% in the non-compression group (Table 2), with a significantly lower rate of improvement in the compression group (odds ratio, 0.21 (95% CI=0.06–0.78); $P=0.01$).

Figures 2 and 3 show the systolic and diastolic blood pressures and the SV values of the patients up to 72 h after admission. At all time points, no significant differences were observed in mean systolic or diastolic blood pressures between the two groups. However, the SV value of the systolic blood pressure was significantly higher in the compression group during the first 24 h after admission ($P<0.0001$) and during the 72 h period after admission ($P<0.0001$). Conversely, there were no significant differences in the diastolic blood pressure SV value between the groups at any time point. The pulse rate SV value was significantly higher in the compression group during the 72 h period after admission (8.7 ± 2.7 b.p.m. vs. 7.3 ± 2.2 b.p.m., $P<0.05$).

In the explanatory analysis, the best cutoff SV value of the systolic blood pressure during the 72 h period after admission obtained from the Receiver operating characteristic curve was 15.3 mm Hg, which

Figure 2 Average blood pressures during 72 h of hospitalization in the compression group ($n=15$) and the non-compression group ($n=41$). (a) Systolic blood pressure, (b) diastolic blood pressure.

predicted RVLM compression with a sensitivity of 67% and a specificity of 88% (area under the curve=0.783; $P=0.0002$). In the compression group, the patients with SV <15.3 mm Hg tended to show a more favorable outcome, defined using modified Rankin scale, than the patients with SV ≥ 15.3 mm Hg ($P=0.10$) (Figure 4).

DISCUSSION

This study found that blood pressure variability during the acute ischemic stroke phase was significantly greater in patients with RVLM vascular compression than in those without. In addition, decreased improvement in neurologic symptoms was observed in patients with RVLM vascular compression compared with patients without RVLM vascular compression. In the compression group, patients with high SV values were more likely to have unfavorable outcomes. The association between blood pressure variability and acute ischemic stroke outcome has previously been reported.^{12,13} To our knowledge, this study is the first to clearly show an association between RVLM vascular compression, blood pressure variability and functional prognosis.

It has been reported that a large proportion of patients with RVLM vascular compression have hypertension.^{1–4} Mechanical stimulation of the RVLM causes glutamate release from RVLM vasomotor neurons, thereby increasing sympathetic nerve activity.²⁰ RVLM vascular compression was observed in 7–22.2% of healthy individuals without

Figure 3 Successive variation (SV) of blood pressure during 72h of hospitalization in the compression group ($n=15$) and the non-compression group ($n=41$). (a) Systolic blood pressure (SBP), (b) diastolic blood pressure (DBP).

Figure 4 Box plot showing median modified Rankin scale (m-RS) on discharge (solid bar), interquartile range (bar width), and minimum/maximum values across SV < 15.3 mmHg or ≥ 15.3 mmHg in compression group.

hypertension and in 74–90% of patients with hypertension.^{3,4,21,22} Our results demonstrated that the prevalence of hypertension was 93.3% (14/15) in patients with RVLM vascular compression, and it was higher than that in patients without RVLM vascular compression,

which is consistent with previous studies. The prevalence of hypertension was 60.5% (25/41) in patients without RVLM vascular compression, which is similar to other previous population-based studies of ischemic stroke.^{23,24} We propose that RVLM vascular compression is one of the important factors related to hypertension. However, it is still unknown whether RVLM vascular compression is the cause of hypertension because no study has prospectively followed young normotensive subjects with RVLM vascular compression to evaluate the incidence of hypertension. Conversely, several reports have demonstrated that surgical decompression of the RVLM reduced sympathetic nerve activity and normalized systemic blood pressure.^{5,6} In addition, in our study, the patient with RVLM vascular compression who did not show hypertension ($n=1$) had higher blood pressure variability than patients without RVLM vascular compression and had a poor prognosis on discharge. In the other target organs (the heart), it has been reported that the regression of left ventricular hypertrophy depends on not only blood pressure levels, but also the reduction of cardiac sympathetic drive.²⁵ Therefore, we think that chronic sympathetic nerve activation influences target organ damage even when patients are not hypertensive.

In the present study, the compression group had a significantly higher SV value and a significantly lower proportion of clinically improved patients. In the compression group, the sympathetic nerve may be chronically activated. Hypertension is likely one of the markers of this chronic sympathetic nerve activation, which explains the significantly higher rate of hypertension in the compression group. In patients with chronic hypertension, cerebral blood flow decreases rapidly with cerebral ischemia in association with an increasing cerebral oxygen extraction fraction.²⁶ Therefore, blood pressure variability may change cerebral blood flow. This pathological response may deteriorate the improvement of neurological symptoms in patients with RVLM vascular compression.

Our findings demonstrated that the difference in blood pressure between the groups was not significant, although it tended to be slightly higher in the compression group. Interestingly, the variability in blood pressure was significantly greater in the compression group. The sympathetic nervous system is generally persistently activated during acute ischemic stroke, leading to increased blood pressure regardless of the presence or absence of RVLM vascular compression. Therefore, it is difficult to detect a difference in blood pressure with or without RVLM vascular compression during the acute ischemic stroke phase. By contrast, RVLM vascular compression clearly activates the sympathetic nervous system, leading to increased burst-like firing of sympathetic nerves,²⁷ which is thought to have a role in blood pressure variability.

It has been reported that patients with RVLM vascular compression have increased sympathetic nerve activity.⁸ In addition, the increased sympathetic nerve activity may induce high blood pressure variability because it was reduced after ganglion blockade with trimethaphan.²⁸ In parallel to this response, when sympathetic nerve activity increases, the baroreflex counteracts this activation in normal subjects. However, it is still unknown whether the increase in sympathetic nerve activity is caused by increased sympathetic nerve traffic, increased vascular sensitivity, or impaired baroreflex buffering in patients with RVLM vascular compression. It has been reported that baroreflex buffering and baroreflex-mediated vasopressin release are severely impaired in patients with RVLM vascular compression.⁷ When the impaired baroreflex is associated with RVLM vascular compression, blood pressure variability may increase with increased sympathetic nerve activity. It has been suggested that restoration of baroreflex sensitivity may prevent stroke in the animal model.²⁹ It is possible that the

restoration of baroreflex sensitivity reduced blood pressure variability and, therefore, stroke incidence. However, blood pressure variability was not examined in the experiment by Liu *et al*. Therefore, it is unknown whether stroke prevention with the restoration of baroreflex sensitivity was mediated by the reduction of blood pressure variability. In our study, we evaluated the association of blood pressure variability at the acute ischemic stroke phase and its prognosis for patients with or without RVLM vascular compression. However, we were unable to evaluate blood pressure variability at the pre-ischemic stroke period. Therefore, further studies are needed to clarify the association between blood pressure variability and the occurrence of stroke in patients with RVLM vascular compression.

Various measures of variability of individual blood pressure profiles have been used. The most common measures of variations are the extreme values, such as maximum, minimum, range (difference between maximum and minimum), s.d., or coefficient of variation (s.d. over mean).³⁰ In the present study, we selected SV as a parameter of within-patient blood pressure variability. This parameter includes the serial variation on a time sequence, whereas other measures, such as s.d. and coefficient of variation, ignore the sequential nature of such a data set. Therefore, when analyzing the sequential nature of data, as in the present study, it is better to use SV. If not, time-invariant measures, such as s.d. or coefficient of variation, can result in a misleading prediction of prognosis and is less informative for blood pressure management.

In the present study, we evaluated RVLM vascular compression with MRI images. However, it is possible that cases in which there appeared to be RVLM vascular compression had a low degree of compression that did not result in sympathetic nerve activation. Thus, we examined the association between SV and prognosis in the compression group, which was divided into two groups using the best cutoff SV value of the systolic blood pressure during the 72 h period after admission. As a result, the patients with high SV values tended to show more unfavorable prognosis than the patients with low SV values. Therefore, large-scale studies are required to confirm the influence of the SV value on the compression group prognosis.

The present study has several limitations. First, a selection bias may exist because of the small sample size at a single institution. Therefore, it will be necessary to conduct a similar multi-center study to confirm whether these results can be generalized. In addition, our results may not reflect all ischemic stroke patients because of the frequent exclusion of severe cases. It is highly possible that the severe cases have poor prognoses regardless of the presence of RVLM vascular compression or that the influence of RVLM vascular compression might be low. To study these issues, we are planning a multi-center, large-scale trial to define the association of RVLM vascular compression with the prognosis of ischemic stroke patients. Another limitation of the current study is that we did not examine the correlation between RVLM vascular compression and SV value with the use of anti-hypertensive medications before stroke onset. In particular, medications that inhibit sympathetic nerve activation may influence blood pressure and blood pressure variability. However, the half-lives of these anti-hypertensive medications are not more than 24 h, and their effects decrease with time. In our study, the SV value for blood pressure variability was calculated at 72 h after admission. Therefore, pre-medication with anti-hypertensives should have had a limited effect on the SV value. Finally, the correlation with ischemic location was not fully investigated. A previous study demonstrated that patients with infarctions involving the insular cortex tended to suffer from autonomic dysfunction,³¹ which may influence blood pressure. However, in the present study, few patients had infarctions involving

the insular cortex, and the proportion of patients with infarctions involving the insular cortex was similar between the compression and non-compression groups (two in the compression group (13.3%) and five in the non-compression group (12.2%)). Thus, the influence of ischemic location in the present study may also be limited.

In conclusion, this study found that patients with RVLM vascular compression had greater variability in blood pressure during the acute ischemic stroke phase, which may be a factor related to poorer prognosis. In the future, larger scale prospective studies are required to confirm the influence of RVLM vascular compression in acute ischemic stroke.

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