Research Article

The lower safety level of blood pressure evaluated by ^{123}I-IMP single-photon emission computed tomography in acute cerebral infarction patients

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Practice Points

- Guidelines for stroke management only mention that a patient who shows diastolic blood pressure (BP) >120 mmHg or systolic BP >220 mmHg should be treated. It is sometimes difficult to treat stroke patients who suffer from fluctuating neurological deficits depending on the systemic BP.
- A recent investigation (the CHHIPS trial) reported that early reduction of BP in acute stroke demonstrated not only no adverse effect, but also lowering of 3-month mortality.
- It is desirable to ascertain the lowest point of BP that will maintain effective cerebral blood flow in the ischemic lesion.
- There was a significant correlation between the cerebral blood flow (CBF) ratio (ischemic:intact) and systolic BP in patients with mild-to-moderate stenosis or occlusion at the corresponding artery.
- The CBF ratio showed a correlation with the diastolic BP in patients with occlusion at the lesion side and stenosis at the intact side.
- The lowest BP level that maintained the CBF ratio ≥0.6 was a systolic BP of 109 mmHg in patients with mild-to-moderate stenosis and 142/79 mmHg in patients with occlusion at the lesion side and stenosis at the intact side.
- BP control should be carefully managed in acute stroke patients with occlusion and stenosis in main arteries.

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SUMMARY **Aims:** At the acute phase of cerebral infarction, the autoregulation of cerebral blood flow (CBF) is compromised. In this study, we explored the lower safety level of blood pressure (BP) for maintaining optimal CBF in acute cerebral infarction patients. **Patients & methods:** Acute middle cerebral artery territorial infarctions were screened. Patients who had single-photon emission computed tomography performed within 7 days following onset were enrolled (n = 30). The CBF ratio (ischemic:intact) was calculated at the border zone of the middle cerebral artery. Vascular lesions were assessed by magnetic resonance angiography. **Results:** The lowest BP level that maintained the CBF ratio ≥0.6 was 109 mmHg in patients with mild-to-moderate stenosis and 142/79 mmHg in patients with occlusion at the lesion side and stenosis at the intact side by the linear regression analysis. **Conclusion:** BP control should be carefully managed in acute stroke patients with occlusion and stenosis in the main arteries of the brain.

Autoregulation of cerebral blood flow (CBF) has been reported to be compromised at the acute phase of cerebral infarction [1,2]. According to the guidelines of stroke management, the antihypertensive agents should be withheld unless the diastolic blood pressure (BP) is >120 mmHg or unless the systolic BP is >220 mmHg [3,4]. Moreover, a recent study reported that regional CBF of an ischemic lesion was not selectively affected by acute BP lowering [5]. Recently, it was reported that the aggressive treatment of BP did not improve the outcome of ischemic stroke patients [6]. Conversely, in the CHHIPS trial, early reduction of BP in acute stroke showed not only no adverse effect, but also lowering of 3-month mortality [7].

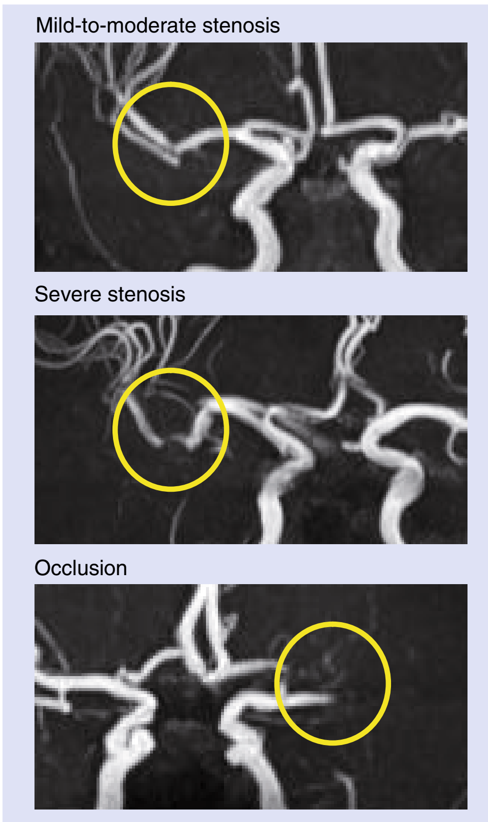

Figure 1. Arterial lesions on magnetic resonance angiography. Representative pictures of mild-to-moderate stenosis, severe stenosis and occlusion observed on the magnetic resonance angiography pictures.

Importance of keeping the appropriate BP level to maintain effective CBF is still uncertain

Maintaining the appropriate BP level to keep the optimal CBF in ischemic lesions at the acute phase is still ambiguous. Meanwhile, physicians may sometimes have to treat stroke patients who show fluctuation of neurological deficits, depending on the systemic BP. Therefore, to reveal the lowest BP level to maintain the effective blood supply to ischemic lesions regarding the treatment of acute cerebral infarction, correlation between CBF of the lesion and systemic BP was explored using single-photon emission computed tomography (SPECT).

Patients & methods

■ Patients

Patients with acute internal carotid artery (ICA) or middle cerebral artery (MCA) territorial infarction were screened between January 2008 and December 2009, following the approval of the committee of medical ethics in the

Table 1. Background of all cases.

Characteristic	Mild-to-moderate stenosis	Severe stenosis	Occlusion	Occlusion with stenosis
Gender, n (M/F)	9 (6/3)	7 (7/0)	10 (9/1)	4 (4/0)
Age (years; mean ± SD)	69 ± 11.2	79 ± 6.0*	68 ± 13.0	63 ± 13.1
Type				
Cardioembolism (%)	11.1	0	20	0
Athrothrombotic (%)	44.4	100	80	75
Lacunar (%)	44.4	0	0	25
Risk				
Hypertension (%)	77.8	85.7	80	100
Diabetes (%)	30.0	42.9	40	50
Hyperlipidemia (%)	22.2	28.6	20	50
IHD (%)	11.1	14.3	0	0
AF (%)	0	0	20	0
BP				
Systolic (mmHg; mean ± SD)	142.0 ± 13.1	153.4 ± 29.5	152.1 ± 24.8	164.5 ± 20.9**
Diastolic (mmHg; mean ± SD)	83.3 ± 11.2	73.1 ± 11.3	81.3 ± 16.4	91.0 ± 11.6
Duration (days; mean ± SD)	4.8 ± 1.9	5.4 ± 1.8	4.1 ± 1.9	3.0 ± 1.6

*$p < 0.03$ compared with the occlusion with stenosis group.
**$p < 0.05$ compared with the mild-to-moderate group.
AF: Atrial fibrillation; BP: Blood pressure; IHD: Ischemic heart disease; M/F: Male/female; SD: Standard deviation.

Research Institute for Brain and Blood Vessels (Akita, Japan; n = 72). Ischemic stroke lesions were confirmed by MRI (Sigma 1.5T; GE Medical Systems, Tokyo, Japan) on admission. Transverse T2-weighted images (repetition time: 3600 s, echo time: 96 s) and diffusion-weighted images (repetition time: 5800 s, echo time: 76.2 s) were acquired with a slice thickness of 5 mm. Magnetic resonance angiography was performed using the 3D time-of-flight method, and images were rendered using the maximum intensity projection method. In this study, we aimed to assess the lesional CBF at the acute phase, therefore we sequentially selected the patients who had an infarct lesion in the anterior circulation territory and in whom SPECT was performed within 7 days following stroke onset (n = 30). Based on the magnetic resonance angiography findings, the vascular lesions were defined as mild-to-moderate stenosis (<70% stenosis), severe stenosis (70–99% stenosis) and occlusion. The representative pictures are shown in Figure 1. Following this, all cases were classified into four groups (Table 1):

- Mild-to-moderate stenosis group, <70% stenosis in ICA or MCA (M1) of the lesional side;
- Severe stenosis group, 70–99% stenosis in ICA or MCA (M1) of the lesional side;
- Occlusion group, occlusion in ICA or MCA (M1) of the lesional side;
- Occlusion with stenosis group, occlusion in ICA or MCA (M1) of the lesional side and severe stenosis in ICA or MCA (M1) of the intact side.

Neurological severity was assessed using the NIH Stroke Scale (NIHSS) on admission.

SPECT imaging

CBF images were acquired by a ring-type SPECT scanner (SET-080; Shimadzu, Kyoto, Japan) using intravenous injection of *N*-isopropyl-*p*-[^{123}I] iodoamphetamine. The images were in parallel with the orbitomeatal line, and measurement of SPECT counts was performed on the image slice 7 cm above the orbitomeatal line. The regions of interest (ROI) were set in 1-cm squares at the border zone of main arteries, that is between the MCA and anterior cerebral artery or between the MCA and posterior cerebral artery (PCA), as shown in Figure 2. The relative CBF ratio was calculated using the formula: total SPECT counts of ROI in ischemic hemisphere/total SPECT counts of ROI in intact hemisphere. This calculation was performed on the ROI of MCA–anterior cerebral artery and MCA–PCA, separately in each patient. Systemic BP was measured by an automatic brachial BP-monitoring

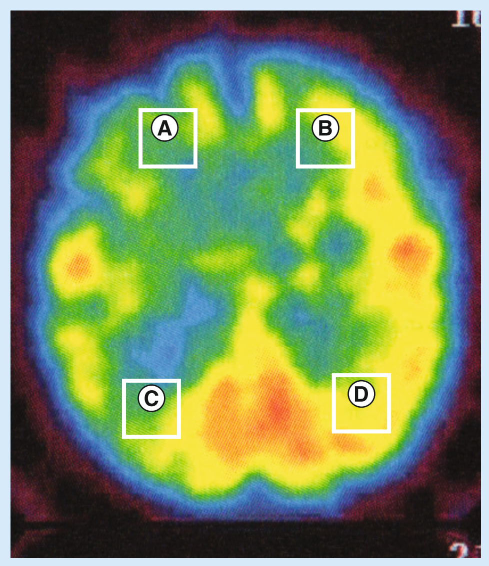

Figure 2. Representative picture of single-photon emission computed tomography image. The relative amount of cerebral blood flow is indicated by color gradation: red, yellow, light green, dark green and blue stand for plenty, proper, fair, poor and almost no amount, respectively. This patient has a severe stenosis at the right middle cerebral artery (MCA) horizontal portion. White squares (1 × 1 cm) indicate regions of interest representing the border zone of **(A)** MCA and anterior cerebral artery in lesion side; **(B)** MCA and anterior cerebral artery in intact side; **(C)** MCA and posterior cerebral artery in lesion side; and **(D)** MCA and posterior cerebral artery in intact side.

system (WEP-5208; Nihon Kohden, Tokyo, Japan) at the position of the patient lying on the bed. BP data were adopted from those measured on the morning of the SPECT examination before breakfast with at least 30-min rest. On checking the patient's BP was at first on both arms and their arterial pulsation on both radial arteries, it was confirmed that no BP laterality existed, excluding the risk of stenosis at subclavian artery.

In each group of stenosis severity, the correlation between relative CBF ratio and adopted BP was assessed. In all graphs, data of systolic and diastolic BP were presented in the same panel.

■ Statistical analysis

All data in the graphs are expressed as means ± standard deviation (SD). Patients' backgrounds were compared among four groups using Pearson's χ^2 test. Kruskal–Wallis one-way analysis of variance was used for the analysis of the difference in NIHSS on admission and the difference in CBF ratio among the four groups. Correlations of the CBF ratio with BP were assessed by simple regression analysis. All calculations were performed by the assistance of computer software (StatView-J 5.0; SAS Institute Inc., NC, USA). Values of $p < 0.05$ were considered significant.

Results

■ Patients' characteristics

The backgrounds of all patients are shown in **Table 1**. Average age in the severe stenosis group was relatively high compared with the mild-to-moderate and occlusion groups, and was significantly older compared with the occlusion with stenosis group ($p = 0.027$). Prevalence of stroke risks was not significantly different among the four groups. The average systolic BP on the morning of SPECT examination was significantly higher in the occlusion with stenosis group compared with the mild-to-moderate stenosis group ($p = 0.049$). There was no difference in the timespan between the day of admission and the day of SPECT examination. The neurological severity was compared among the four groups depending on the relative CBF ratio **(Table 2)**. According to a previous report in which relative CBF of the penumbral lesion was assumed to be between 0.4 and 0.6 [8], all patients were classified into the relative CBF ratio ≥0.6, between 0.6 and 0.4, and <0.4. The average NIHSS score was significantly worse in the occlusion group than those in the mild-to-moderate and severe groups ($p = 0.007$ and $p = 0.016$, respectively). There was no significant difference in NIHSS among the three relative CBF ratio categories in each vascular severity group.

■ CBF ratio is correlated with arterial BP in patients with critical vascular lesions

Although each value was dispersed among all groups, the average of the relative CBF ratio was significantly reduced in the occlusion group compared with the mild-to-moderate and severe stenosis groups (**Figure 3**; $p = 0.028$ and $p = 0.0498$, respectively). In the mild-to-moderate stenosis group, if data from two patients were deleted because they were counted on the ischemic core lesions, a significant correlation was observed between the relative CBF ratio and systolic BP (**Figure 4A**; $p = 0.048$).

Table 2. NIH Stroke Scale at admission.

Vessel lesion CBF ratio (%)	Mild-to-moderate stenosis (mean ± SD)	Severe stenosis (mean ± SD)	Occlusion (mean ± SD)	Occlusion with stenosis (mean ± SD)
≥60	3.2 ± 2.1	3.6 ± 3.0	10.0 ± 8.2	7.5 ± 7.1
40–60	–	–	8.5 ± 6.6	–
<40	–	–	16	–
Total	3.2 ± 2.1	3.6 ± 3.0	10.3 ± 7.4*	7.5 ± 7.1

*p < 0.01 compared with the mild-to-moderate stenosis group and p < 0.02 compared with the severe stenosis group.
CBF: Cerebral blood flow; SD: Standard deviation.

According to the formula of regression line ($y = 74.9x + 64.4$, $R^2 = 0.25$), the appropriate BP that could maintain the relative CBF ratio at 0.6 was 109.3 mmHg. However, there was no significant correlation of relative CBF ratio with diastolic BP ($p = 0.165$).

In the severe stenosis group, no correlation was observed between the relative CBF ratio and systolic BP or diastolic BP (**Figure 4C**). All systolic BP exhibited ≥0.6 of relative CBF ratio was >112 mmHg and all diastolic BP was >60 mmHg. In the occlusion group, correlation was not observed between the relative CBF ratio and systolic BP or diastolic BP (**Figure 4D**). Meanwhile, in the occlusion with stenosis group, relative CBF ratio was significantly correlated with both systolic and diastolic BP (**Figure 4B**; $p = 0.0425$ and $p = 0.0450$, respectively). Calculation of regression line formula: $y = 73.9x + 97.8$ ($R^2 = 0.52$) for systolic BP; and $y = 40.6x + 54.3$ ($R^2 = 0.52$) for diastolic BP, the appropriate systolic and diastolic BP that could indicate relative CBF ratio >0.6 were 142.1 and 78.7 mmHg, respectively. According to the correlation between the relative CBF ratio and the mean BP was also significant (data not shown), and according to the formula of regression line: $y = 51.7x + 68.8$ ($R^2 = 0.57$; $p = 0.031$), the relative CBF ratio of 0.6 was 99.8 mmHg.

Discussion

In this study, the correlation between CBF in the lesional hemisphere and systemic BP in the acute phase of ischemic stroke patients was analyzed. Our data demonstrated the trends in which the occlusion with stenosis group showed a correlation between CBF at the MCA watershed in the lesion hemisphere and systemic BP.

Autoregulation of CBF is compromised at the acute phase of cerebral infarction

In general, CBF is maintained at a constant amount by the autoregulation of the brain arteries independent of systemic BP [9]. However, it has been reported that CBF might be subject to systemic BP, once the autoregulation of CBF is compromised at the acute phase of stroke [1]. In particular, in cases with a critical stenosis in the ICA, there will be a risk of hemodynamic infarction [10]. According to the guidelines of stroke management, antihypertensive agents should be withheld unless the diastolic BP is >120 mmHg or unless the systolic BP is >220 mmHg [3,4]. Namely, the highest BP limit that should be treated is only mentioned, and the lowest BP level that could be enough for care is not described. Meanwhile, a recent study has reported that early reduction of BP in acute stroke demonstrated not only no adverse effect, but also lowering of 3-month mortality [7]. Therefore, the lower safety level of BP should be established for the management of hyper BP condition at the acute phase of stroke. In this study, we explored the relationship between the relative CBF ratio and systemic BP in the acute phase of brain infarction, using SPECT data acquired within 1 week following the onset.

According to a previous report [8], we adopted the relative regional CBF of ≥0.6 and contrasted it with the intact hemispheric region as the normal limit. Unfortunately, as most of our cases demonstrated, with a relative CBF ratio >0.6, we could not conclude the lower safety level of BP, which can represent the threshold of normal CBF. In fact, in a lesion side where an infarcted area is included, there is a possibility that the CBF might be reduced due to the decreased demand of blood supply [11]. On the other hand, regional CBF was reported to be less affected by ischemia than the regional cerebral oxygen metabolism [12]. Moreover, it was reported that the hemispheric diaschisis was observed in the contralateral hemisphere in the MCA territory infarction [13,14]. Therefore, our data may contain the risk of underestimating the relative regional CBF in the ischemic hemisphere. Meanwhile, no significant

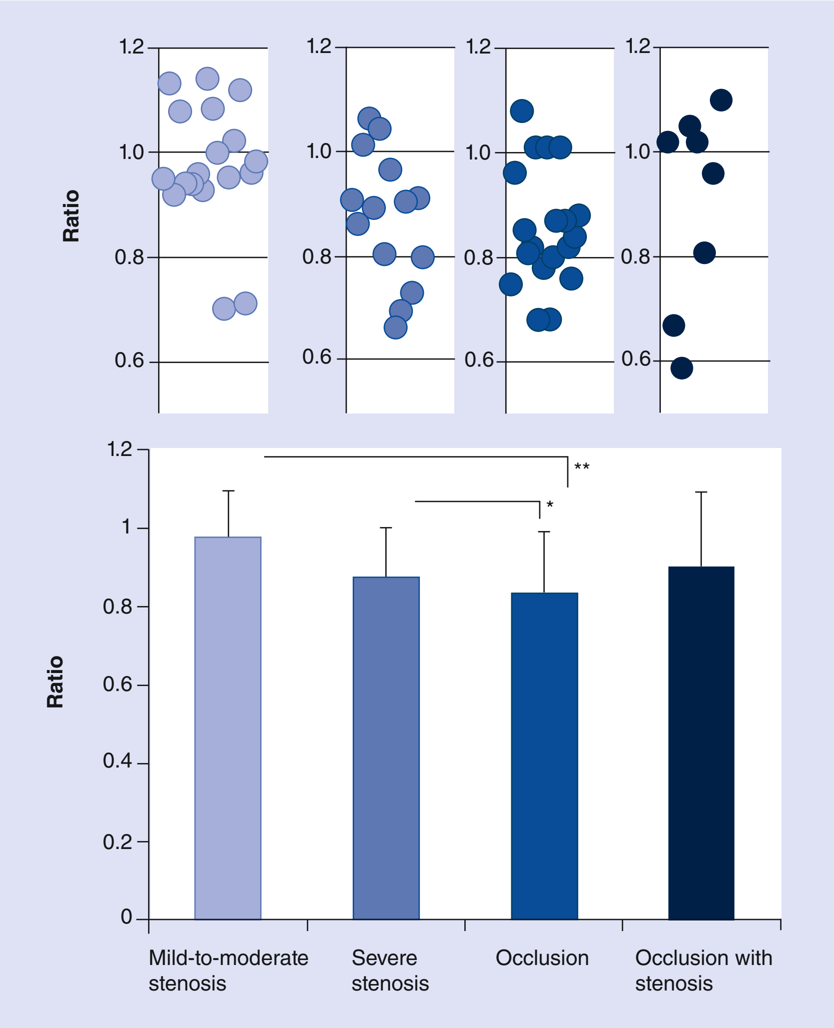

Figure 3. Relative cerebral blood flow ratio in each group. Scatter grams present individual data of relative cerebral blood flow ratio in the mild-to-moderate stenosis group, severe stenosis group, occlusion group and occlusion with stenosis group. The average of relative the cerebral blood flow ratio is presented in the bar graphs. The occlusion group is significantly lower than the mild-to-moderate and severe stenosis groups.
*$p < 0.05$; **$p < 0.01$.

correlation was observed between the relative CBF ratio and systemic BP in both the severe stenosis and occlusion groups. These findings could be explained by collateral blood flow into the ischemic lesions. The collateral circulation will be developed for compensating the reduced blood flow from the brain major arteries with stenosis or occlusion [15]. Next, the amount of collateral flow was reported to influence the viability after brain ischemic insult [16,17]. Patients with chronic hypertension were reported to show that the lower limit of autoregulation of CBF was shifted to a higher arterial BP compared with the normotensive patients [18]. Taking these pathological phenomena into account, it is still very difficult to set the lower arterial BP to keep optimal CBF in the ischemic brain.

The appropriate lowest BP is 142/79 mmHg in patients with critical vascular lesions

Our data suggest that the lowest level of systolic BP was approximately 110 mmHg in the mild-to-moderate stenosis group, and the systolic/diastolic BP and the mean BP, which might keep relative CBF ratio at 0.6 in the occlusion with severe stenosis group, was approximately 142/80 and 100 mmHg, respectively. A previous study, in which alteration of CBF autoregulation was observed in chronic hypertensive patients, reported that the lowest mean BP that stood for 70% of CBF was 68 mmHg and the lowest mean BP that could maintain the ability of autoregulation was 120 mmHg [2]. Computerized curve-fitting analysis had reported the lower limit BP of autoregulation at 85 mmHg in normal volunteers and 113 mmHg in chronic hypertensive patients [19]. Thus far, our findings suggested that CBF autoregulation in acute ischemic stroke patients with mild-to-moderate vascular lesions might not be compromised. Moreover, a calculated BP, which indicated a relative CBF of 0.6 in the occlusion with severe stenosis group was higher than other groups, suggesting that clinical doctors should pay attention when controlling BP in acute-phase stroke patients with severe arterial stenosis or with arterial occlusion.

This study was retrospective and patients who were unable to undergo SPECT within 1 week following onset were excluded from this study. We have to consider possibilities of some bias regarding the selection of patients. Moreover, in this study, we evaluated the data regarding systemic BP, which was acquired on the morning of SPECT examination. Ideally, the BP should be measured on site during SPECT examination. In this regard, our data are not interpretable. We have to pay attention to the fact that our results did not indicate the ideal value of arterial BP for preventing forthcoming brain ischemic trouble. However, systemic BP based on the data from brachial BP measurements could be associated with the ordinary condition of brain circulation [20]. Therefore, our data might still show the correlation between usual BP and the

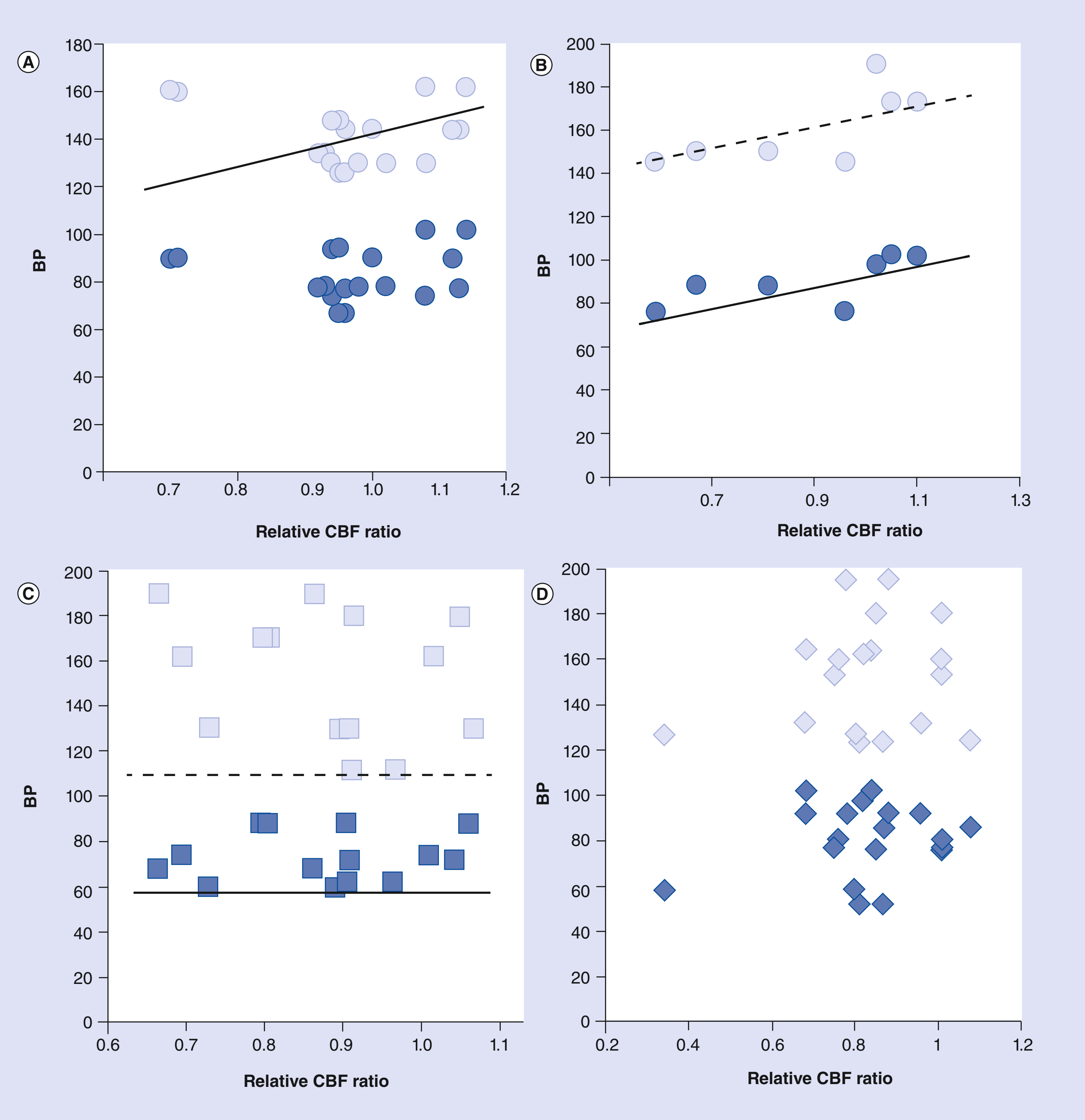

Figure 4. Relative cerebral blood flow ratio to arterial blood pressure. Scatter graph of relative CBF ratio in the **(A)** mild-to-moderate stenosis group, **(B)** occlusion with stenosis group, **(C)** severe stenosis group and **(D)** occlusion group. Light blue and dark blue markers stand for systolic BP and diastolic BP, respectively. A solid line in **(A)** indicates the regression line between relative CBF ratio and systolic BP ($y = 74.9x + 64.4$; $R^2 = 0.25$; $p = 0.048$), if two outliers with a relative CBF ratio of 0.7 are excluded. In **(B)**, a dotted line ($y = 73.9x + 97.8$; $R^2 = 0.52$, $p = 0.043$) and a solid line ($y = 40.6x + 54.3$; $R^2 = 0.52$; $p = 0.045$) indicate the regression line between relative CBF ratio and systolic and diastolic BP, respectively. In **(C)**, a dotted line indicates 112 mmHg and a solid line indicates 60 mmHg project the lowest amount of systolic and diastolic BP, respectively. There is no significant correlation between BP and relative CBF ratio both in the severe stenosis group and the occlusion group.
BP: Blood pressure; CBF: Cerebral blood flow.

amount of cerebral blood perfusion. Moreover, the number of patients in this study was quite small, and it did not have enough power to extract statistical consideration. In the future, a prospective study must be conducted to confirm our findings. In conclusion, maintaining a high BP may not be needed, even in acute ischemic stroke patients. However, BP control should be carefully managed in acute stroke patients with occlusion and stenosis in the main arteries of the brain.

Conclusion & future perspective

The optimal BP that can maintain effective blood supply to the ischemic penumbra of the brain is still ambiguous. Furthermore, our data can provide evidence that stroke patients who have mild stenosis at the corresponding artery may not show any influence regarding the autoregulation of CBF. It can be said that a higher BP should be kept for maintaining appropriate CBF in the acute phase of stroke patients with occlusion and severe stenosis in the major arteries of the brain.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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