Visit-to-Visit Blood PressureVariations and Hemodynamic Deterioration in Atherosclerotic Major Cerebral ArteryDisease

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Objective: Visit-to-visit variations in blood pressure (BP) in patients with atherosclerotic major cerebral artery disease could impair the function of cerebral collaterals, leading to hemodynamic deterioration at follow-up. However, few studies have investigated the relationship between visit-to-visit BP variability and changes in hemodynamic parameters at follow-up. *Materials and methods:* We evaluated 35 medically treated patients with atherosclerotic internal carotid artery or middle cerebral artery disease with no ischemic episodes during follow-up (mean: 35 ± 20 months); these patients had a three-time visit for positron emission tomography examinations with ^{15}O-gas. Differences in the mean hemispheric values of hemodynamic parameters in the cortical territory of the diseased artery between the first and third examinations (changes at follow-up) were correlated with the coefficient of variation (CoV) in three systolic BP (SBP) values at the three examinations (BP variability during follow-up). *Results:* CoV values were negatively correlated with changes in oxygen metabolism or cerebral blood flow/cerebral blood volume (CBF/CBV) ratio. In 17 patients with higher CoV values (> group median, 0.072), decreases in CBF, cerebral metabolic rate of oxygen, and CBF/CBV ratio were observed at follow-up; CBV decreased in 18 patients without elevated CoV. A higher CoV was associated with a lack of statin use. *Conclusion:* In patients with atherosclerotic major cerebral artery disease, high visit-to-visit SBP variations during follow-up may be associated with deterioration in cerebral hemodynamics and metabolism.

Key Words: Carotid artery disease—Middle cerebral artery disease—Positron-emission tomography—Blood pressure variability—Cerebral blood flow

Introduction

In patients with atherosclerotic internal carotid artery (ICA) or middle cerebral artery (MCA) disease, chronic hemodynamic impairment is a predictor of subsequent ischemic stroke.[1–3] Furthermore, hemodynamic deterioration during follow-up increases the risk of ischemic stroke.[2,4,5] Therefore, preventing hemodynamic deterioration may be useful to improve patient prognosis.

Hypertension is a major risk factor for stroke. However, the optimal management of the blood pressure (BP) level in patients with atherosclerotic major cerebral artery disease remains unknown. Specifically, the level at which BP should be lowered to achieve maximal benefits among patients with atherosclerotic major cerebral artery disease and hemodynamic impairment is controversial.[6–9] There are concerns that lowering BP could impair cerebral perfusion in patients with atherosclerotic major cerebral artery disease. Our previous study in 89 patients with ICA or MCA disease showed that low BP levels were associated with hemodynamic deterioration during the follow-up period.[10] The contribution of low BP levels to the overall variance in hemodynamic changes over time was significant but was not so large; the correlation coefficients between mean systolic BP (SBP) values and changes in cerebral blood flow (CBF) or CBF/cerebral blood volume (CBV) ratio were 0.27 ($p < 0.01$) and 0.32 ($p < 0.005$),

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respectively. This finding suggested that some other factors might have also contribute to the variance in hemodynamic changes.

In addition to the BP level, appropriate control of BP variability could improve prognosis. Recent studies have shown that increased visit-to-visit variability in office BP is a powerful risk factor for stroke, which is independent of the BP level, despite the potential impact of hospital stress.[11,12] The mechanism by which visit-to-visit BP variability causes stroke remains unclear; however, several studies have shown that high visit-to-visit BP variability, as well as 24h ambulatory BP variability, is associated with arterial stiffness, endothelial dysfunction, and atherosclerosis, suggesting that alterations in vascular function may occur with high BP variability.[13–16] Hence, increased visit-to-visit BP variability could impair the function of cerebral collaterals in patients with atherosclerotic major cerebral artery disease, leading to hemodynamic impairment.[17,18] However, accurate evaluations of hemodynamic status are not feasible in clinical practice. Therefore, few studies have investigated the relationship between visit-to-visit BP variability and hemodynamic changes during follow-up.

This study aimed to determine whether high visit-to-visit BP variability during follow-up is associated with hemodynamic deterioration on positron emission tomography (PET) in patients with atherosclerotic ICA or MCA disease. We selected patients who had a three-time visit for PET examinations with ^{15}O-gas. We analysed the relationship between the variability in three BP values measured at three PET examinations and differences in PET variable values measured at the first and third PET examinations. Then, the BP variability and PET variable changes in the same period were correlated.

Methods

Patients

The relationship between visit-to-visit BP variability and changes in hemodynamic and metabolic parameters in 35 patients with atherosclerotic ICA or MCA disease was retrospectively analysed (Table 1). Patients were referred to our PET unit for evaluation of the hemodynamic effects of ICA or MCA disease as part of a comprehensive clinical evaluation to determine whether they required vascular reconstruction surgery. Thirty-five patients who had a three-time visit for PET examinations with ^{15}O-gas were selected. We considered at least three BP measurements were needed to evaluate visit-to-visit BP variability; three SBP values measured at three PET examinations were used for the analysis in this study. We calculated the coefficient of variation (CoV) values in the three SBP values as an index of long-term visit-to-visit BP variability. Long-term changes in cerebral hemodynamics and metabolism were evaluated using the first and third PET data. Thus, long-term visit-to-visit BP variability and changes in PET variables between the first and third PET examinations were correlated.

Inclusion criteria were: (1) occlusion or stenosis of the extracranial ICA (> 60% diameter reduction according to the NASCET criteria[19]) or intracranial ICA or MCA (> 50% diameter reduction according to the WASID criteria[20]) as documented by conventional or magnetic resonance angiography, (2) functional independence in daily life (a modified Rankin Scale score < 3), (3) for symptomatic patients, a history of transient ischemic attack (TIA) or minor completed stroke in the ICA or MCA distributions recorded during the first PET examination, (4) medically treated patients with no intervening TIA or stroke between the first and third PET examinations, and (5) availability and willingness to return for follow-up PET examination. TIA was defined as focal symptoms of presumed ischemic cerebrovascular origin lasting < 24 h. Exclusion criteria were: (1) infarction in the cerebral cortex detectable on routine magnetic resonance imaging (MRI) (T1-weighted, T2-weighted, or fluid-attenuated inversion recovery imaging) or computed tomography (CT) imaging at the first PET examination in the chronic stage, (2) a history of vascular reconstructive surgery, and (3) the presence of potential sources of cardiogenic embolism.

Of the 35 patients, 9 were asymptomatic, 9 had TIA, and 17 had a completed stroke. In the same patient cohort, 17, 4, and 14 had ICA occlusion, ICA stenosis, and MCA occlusion, respectively (Table 1). Patients with MCA occlusion had 10 proximal M1 occlusions, 2 distal M1 occlusions, and 2 M2 occlusions. In terms of vascular risk factors, hypertension, diabetes mellitus, ischemic heart disease, hyperlipidemia, and smoking were evaluated from the patient's history recorded during the first PET examination. Hypertension, diabetes mellitus, ischemic heart disease, or hyperlipidemia was considered present when there was a history of treatment.

All protocols in this study were approved by the Shiga Medical Center for Adults Institutional Review Board and the Human Study Committee (number 119). All participants provided written informed consent. All experiments were performed following the Declaration of Helsinki and the Good Clinical Practice guidelines.

PET measurements

PET scans were performed in each patient using an Advance whole-body scanner (General Electric Medical Systems, Wauwatosa, WI), which permits the simultaneous acquisition of 35 image slices with a 4.25 mm interslice spacing.[21] Performance tests revealed the intrinsic resolution of the scanner to be 4.6–5.7 and 4.0–5.3 mm in the transaxial and axial directions, respectively. A transmission scan using ^{68}Ge /^{68}Ga was performed for attenuation correction in each subject before tracer administration. To reconstruct PET data using filtered back projection, images were blurred to 6.0-mm full width

Table 1. *Patient characteristics.*

Characteristic		*High SBP CoV (> 0.072)* *Yes*	*No*
No. of patients	35	17	18
SBP CoV, mmHg	0.078 ± 0.038	0.111 ± 0.026	0.048 ± 0.014
Mean SBP, mmHg	145 ± 17	143 ± 16	147 ± 17
SBP, 1st	148 ± 20	150 ± 23	146 ± 17
SBP, 2nd	145 ± 17	141 ± 18	148 ± 18
SBP, 3rd	143 ± 21	139 ± 21	148 ± 20
Interval, 3rd−1st, mean ± SD, months	35 ± 20	38 ± 23	32 ± 18
Interval, 2nd−1st	17 ± 16	20 ± 19	15 ± 12
Interval, 3rd−2nd	17 ± 10	17 ± 11	16 ± 9
Age, (years)	63 ± 8	63 ± 6	63 ± 9
Sex, (men)	22	9	13
Symptomatic, (no.)	26	10	16
Cerebral ischemic lesion, (no.)	28	13	15
Qualifying artery, (no.)			
ICA (occlusion/stenosis)	21(17/4)	10 (7/3)	11 (10/1)
MCA occlusion (proximalM1/distalM1/M2)	14(10/2/2)	7 (5/1/1)	7 (5/1/1)
Other medical illness, (no.)			
Hypertension	24	12	12
Ca^{2+}-antagonist	13	5	8
ACE-inhibitor	3	1	2
ARB	12	4	8
Diuretics	2	1	1
β-blocker	3	1	2
Diabetes mellitus	10	6	4
Ischemic heart disease	14	3*	11
Hyperlipidemia	17	4**	13
Smoking habit (current and former), (no.)	12	5	7
Antiplatelet agents	28	12	16
Statins	13	2**	11

CoV, coefficient of variation; SD, standard deviation; ICA, internal carotid artery; MCA, middle cerebral artery; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

*$p < 0.05$,

**$p < 0.01$ vs. No group

at half maximum in the transaxial direction using a Hanning filter. Functional images were reconstructed as 128 × 128 pixels, with each pixel representing an area of 2.0 × 2.0 mm.

After a transmission scan, a series of ^{15}O-gas studies were conducted.[21] A small cannula was placed in the left brachial artery for blood sampling. $C^{15}O_2$ and $^{15}O_2$ were continuously delivered to the patient using a mask for the duration of a 5-min scan. Arterial blood was manually sampled from the brachial artery five times (at 0, 1, 2, 3, and 4 min) and three times (at 0, 2, and 4 min) during the scanning, respectively. The CBV was measured based on bolus inhalation of $C^{15}O$ with scanning for 3 min. Arterial samples were obtained manually twice (at 1 and 2 min) during scanning. Radioactivity of the radiotracer, oxygen content, and hematocrit were measured. BP was measured using an arterial catheter connected to a pressure transducer. Mean values of BP during $C^{15}O_2$ and $^{15}O_2$ scanning were used as the values of BP during PET examinations, and SBP values at each of the three examinations were used for the analysis in this study.

We used the steady-state method to calculate the CBF, cerebral metabolic rate of oxygen ($CMRO_2$), and oxygen extraction fraction (OEF).[22] The $CMRO_2$ and OEF were corrected based on the CBV.[23] The CBF to CBV ratio was calculated pixel-by-pixel as an indicator of cerebral perfusion pressure.[24,25]

To obtain normal control values of the ^{15}O-gas PET variables, we performed ^{15}O-gas studies with arterial sampling in seven normal volunteers (men: 4; women: 3), aged 47 ± 7 (mean ± standard deviation [SD]) years who underwent normal routine neurological examinations and MRI scans.

Data analysis

Ten tomographic planes, located 46.25−84.50 mm above and parallel to the orbitomeatal line were

analysed.[26] The lowest plane corresponded to the level of the basal ganglia and the thalamus, and the uppermost plane corresponded to the level of the centrum semiovale. The software for image analysis was programmed by a member of our research team.

A region of interest (ROI) was selected for the CBF images at baseline. Each image was examined by compactly placing 10−12 circular ROIs (diameter, 16 mm), over the gray matter of the outer cortex in each hemisphere. According to the atlas[27], the ROIs in all 10 images covered the distribution of the MCA as well as the external border zone regions.[10,26] The same ROIs were used for the $CMRO_2$, OEF, and CBV images at baseline and the PET images at the third examination co-registered with baseline PET images using the PMOD version 3.204 (PMOD Technologies Ltd., Zurich, Switzerland). The mean hemispheric value for the hemisphere affected by ICA or MCA disease was calculated as the average of all circular ROIs.

The mean OEF value obtained from the 14 control hemispheres in seven normal volunteers was 44.5% ± 3.8%. Hemispheric OEF values beyond the 95% upper limit defined in normal subjects (> 52.9%) were considered to represent increased OEF. Comparative values for CBF and CBF/CBV in normal controls were 44.6 ± 4.5 mL/100 g/min and 11.4 ± 1.8/min, respectively. Hemispheric CBF and CBF/CBV values below 35.0 mL/100 g/min and 7.6/min, respectively, were considered abnormal.

Patients with increased OEF, decreased CBF, and decreased CBF/CBV in hemispheres with arterial disease were categorized as having misery perfusion, whereas patients with decreased CBF/CBV were categorized as having decreased cerebral perfusion pressure (impaired perfusion). Patients were categorized by an investigator who was unaware of their clinical status.

The total change in CBF, $CMRO_2$, OEF, CBV, and CBF/CBV values in the MCA distribution with arterial disease was calculated by subtracting the values obtained at the baseline examination from those obtained at the third examination.

The CoV values (SD/mean) in three SBP values measured at the three PET examinations were calculated. CoV was selected as the measure of variability for its common use, simplicity, and relevance in clinical practice. Variability expressed by CoV is considered less affected by BP level than variability expressed by SD.

Statistical analysis

The statistical analysis was performed using the StatView™ (SAS Institute Inc., Cary, NC, USA). Clinical background or PET variable values were compared between groups using the Student's *t*-test or Fisher's exact test, as appropriate. PET variable values between the examinations were compared using paired *t*-tests. Relationships between variables were analysed using simple or multiple regression analyses. For all analyses, statistical significance was set at $p < 0.05$. A correction of multiple comparisons was not performed.

Results

Three SBP values measured at three PET examinations were used for the analysis in this study. We calculated the CoV values in the three SBP values as an index of long-term visit-to-visit SBP variations. Long-term changes in cerebral hemodynamics and metabolism were evaluated using the first and third PET data. The total change in in the mean hemispheric values of PET parameters in the cortical territory of the diseased artery values in the MCA distribution with arterial disease was calculated by subtracting the values obtained at the baseline examination from those obtained at the third examination.

In a simple regression analysis (Fig. 1), a negative linear relationship between changes in the $CMRO_2$ (r = -0.44; $p < 0.01$) or CBF/CBV (r = -0.41; $p < 0.05$) and the CoV for SBP during follow-up was noted. Using multiple regression analysis, the CoV for SBP during follow-up was also a significant predictor of the changes in $CMRO_2$ or the changes in CBF/CBV, after adjustment for the interval between the first and third PET examinations. Overall, the changes in CBF/CBV were significantly correlated with those in CBF (r = 0.71; $p < 0.001$) or OEF (r = -0.39; $p < 0.05$).

In a simple regression analysis, other BP variables (mean SBP, SBP 1st, SBP 2nd, SBP 3rd, SBP 3rd −1st) were not significantly correlated with the changes in CBF/CBV, while the SBP 3rd tended to be correlated with the changes in CBF/CBV (r = 0.30; p = 0.078). Using multiple regression analysis, the CoV for SBP during follow-up was also a significant predictor of the changes in CBF/CBV, after adjustment for the SBP 3rd values ($p < 0.02$). The CoV values were calculated by dividing SD by mean. When using SD instead of CoV, the SBP SD and the SBP 3rd were independently associated with changes in the CBF/CBV. Furthermore, SBP SD (coefficient, -0.142; standard error, 0.051; t = -2.791; $p < 0.01$) was negatively correlated with the CBF/CBV changes, whereas the SBP 3rd (coefficient, 0.031; standard error, 0.014; t = 2.303; $p < 0.05$) was positively correlated with the CBF/CBV changes: the CBF/CBV changes = − 0.142SBP SD + 0.031 (SBP 3rd) − 3.230 (a correlation coefficient of 0.51, $p < 0.01$). Thus, high SBP SD and low SBP 3rd were independent predictors of hemodynamic deterioration. Among the BP variables, only the CoV or SD for SBP during follow-up was a significant independent predictor of the changes in $CMRO_2$.

For further analysis, the 35 patients were arbitrarily assigned to two groups, defined as below or above the median SBP CoV (≤ 0.072 or > 0.072) (Table 1). For patient characteristics, patients with high SBP CoV had a

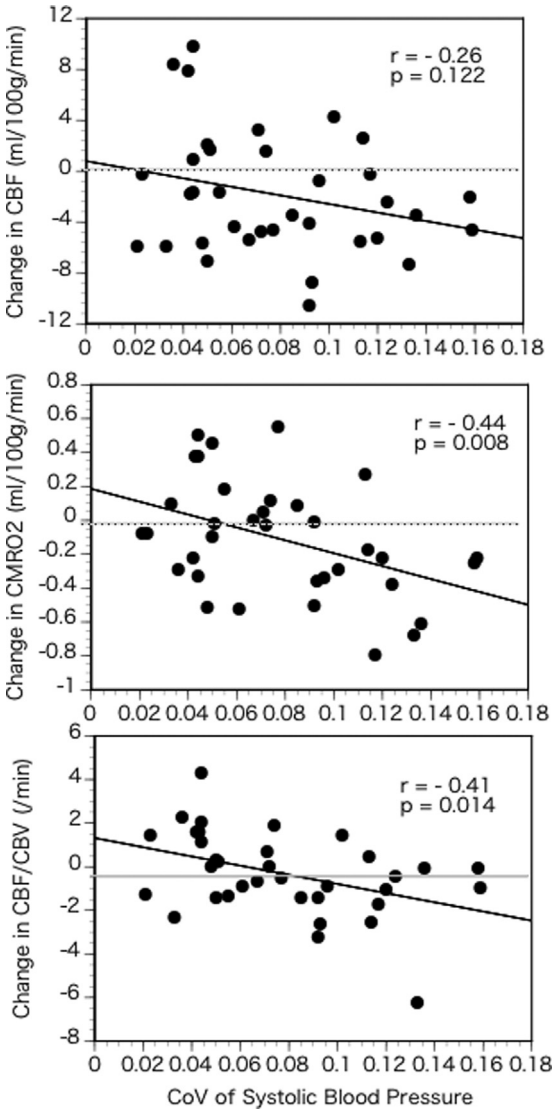

Fig. 1. *Scatter plot of the coefficient of variation (CoV) of systolic blood pressure and the changes in cerebral blood flow (CBF) (top), cerebral metabolic rate of oxygen ($CMRO_2$) (middle), and CBF/cerebral blood volume (CBV) ratio (bottom) in the hemisphere with arterial disease.*

significantly lower incidence of ischemic heart disease and hyperlipidemia and the use of statins ($p < 0.01$) than those without. No significant difference was found in the use of antihypertensive drugs between the two groups. Logistic regression analysis revealed that a low incidence of statin use was significantly associated with high SBP CoV after controlling for the presence of ischemic heart disease ($p < 0.05$).

At baseline, patients with high SBP CoV had a significantly higher $CMRO_2$ than those without (Table 2). The changes in $CMRO_2$ or CBF/CBV were significantly different between the two groups (Table 2). In patients with high SBP CoV, significant decreases in CBF, $CMRO_2$, and CBF/CBV were observed during follow-up (paired *t*-tests, $p < 0.05$) (Fig. 2), whereas a significant decrease in CBV in patients without high SBP CoV was observed.

Table 2. *^{15}O-gas PET variables.*

	High SBP CoV (> 0.072)	
Characteristics	*Yes (n = 17)*	*No (n = 18)*
First examination		
CBF (ml/100 g/min)	34.3 ± 6.7	31.4 ± 7.6
$CMRO_2$ (ml/100 g/min)	3.16 ± 0.30[a]	2.81 ± 0.42
OEF (%)	51.7 ± 6.3	52.8 ± 7.3
CBV (ml/100 g)	3.60 ± 0.61	3.54 ± 0.69
CBF/CBV (/min)	10.12 ± 2.62	8.96 ± 2.06
Impaired perfusion, (no.)	4	7
Third examination		
CBF (ml/100 g/min)	32.1 ± 6.4[c]	30.8 ± 5.8
$CMRO_2$ (ml/100 g/min)	2.94 ± 0.40[d]	2.80 ± 0.45
OEF (%)	53.6 ± 7.9	54.2 ± 4.8
CBV (ml/100 g)	3.61 ± 0.53	3.30 ± 0.45[d]
CBF/CBV (/min)	8.97 ± 1.83[d]	9.39 ± 1.72
Impaired perfusion, (no.)	6[b]	1
CBF change (ml/100 g/min)	-3.20 ± 3.9	-0.57 ± 5.2
$CMRO_2$ change (ml/100 g/min)	-0.22 ± 0.34[b]	-0.008 ± 0.30
OEF change (%)	1.84 ± 6.64	1.38 ± 6.71
CBV change (ml/100 g)	0.018 ± 0.54	-0.243 ± 0.43
CBF/CBV change (/min)	-1.14 ± 1.88[b]	0.43 ± 1.64

PET, positron emission tomography; SBP, systolic blood pressure; CoV, coefficient of variation; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; OEF, oxygen extraction fraction; CBV, cerebral blood volume.

[a] $p < 0.01$,

[b] $p < 0.05$, vs. No group (Student's *t*-test or Fisher's exact test)

[c] $p < 0.01$,

[d] $p < 0.05$, vs. First examination (paired *t*-test)Normal values for CBF, $CMRO_2$, OEF, CBV and CBF/CBV in the seven controls were 44.6 ± 4.5 ml/100g/min, 3.43 ± 0.33 ml/100 g/min, 44.5 ± 3.8 %, 3.98 ± 0.48 ml/100 g and 11.4 ± 1.8/min, respectively.

Based on the CBF/CBV values in the hemisphere supplied by the diseased artery, 11 patients (31%) (4 in patients with high SBP CoV vs. 7 in patients without high SBP CoV) had decreased cerebral perfusion pressure (impaired perfusion) at baseline, and 24 (69%) did not. Of the 11 patients with decreased CBF/CBV, 8 had misery perfusion. At the last follow-up, 2 of the 11 patients had impaired perfusion, and 5 of the 24 patients had apparent impaired perfusion. Of the 7 patients with decreased CBF/CBV, 3 had misery perfusion. At the last follow-up, patients with high SBP CoV had a significantly higher incidence of impaired perfusion ($p < 0.05$) than those without (6 in patients with high SBP CoV vs. 1 in patients without high SBP CoV) (Table 2).

In most patients, all risk factors were well-controlled during the follow-up period. Some patients showed changes in treatments due to changes in the conditions of risk factors. For hypertension, two patients in the high SBP CoV group changed the dose or type of Ca^{2+}-antagonist during the follow-up period. One patient in the high

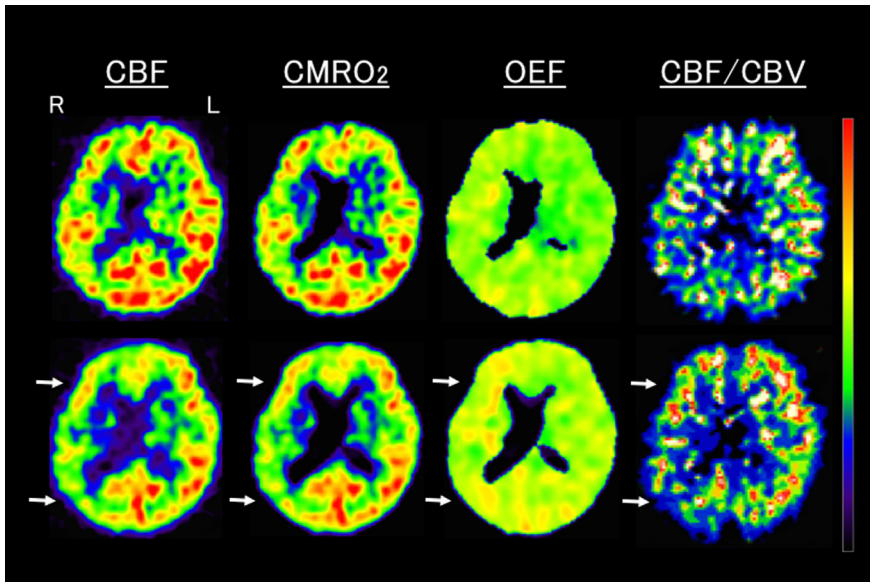

Fig. 2. *Representative PET images of hemodynamic deterioration in a patient with right internal carotid artery occlusion and left internal carotid artery stenosis (mild) who showed high coefficient of variation of systolic blood pressure (0.12). The first PET study (first row) revealed mild decreases in cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), and CBF/cerebral blood volume (CBV), with a slight increase in oxygen extraction fraction (OEF) in the right (R) hemisphere with internal carotid artery occlusion. A follow-up 44 months later (second row) revealed decreased CBF, $CMRO_2$, and CBF/CBV with increased OEF in the R hemisphere (arrows).*

SBP CoV group and one patient in the low SBP CoV group started using an angiotensin receptor blocker during the follow-up period. For hyperlipidemia, one patient in the low SBP CoV group started statin use during the follow-up period.

All patients underwent routine MRI and MRA examinations in clinical use at the first and third PET examinations. In the hemisphere affected by arterial disease, by visual inspection, T2-weighted MRI revealed no apparent MRI changes, including white matter lesions and silent infarctions, during follow-up in all patients. Follow-up findings on MR angiography, by visual inspection, showed apparent stenosis in only one patient in the high SBP CoV group (severe stenosis of the temporal branch of the ipsilateral MCA)

All patients were followed up for 2 years after the third PET examinations. Recurrent ipsilateral ischemic stroke occurred in only one patient with ICA occlusion in the high SBP CoV group.

Discussion

This study demonstrated that high visit-to-visit SBP variations were associated with hemodynamic deterioration in patients with atherosclerotic ICA or MCA disease. This study investigated the relationship between visit-to-visit SBP variations and changes in cerebral hemodynamics on PET at follow-up. A higher visit-to-visit SBP CoV was associated with greater decreases in $CMRO_2$ or CBF/CBV. In patients with higher visit-to-visit SBP CoV, significant decreases in CBF, $CMRO_2$, and CBF/CBV were observed at follow-up. A higher visit-to-visit SBP CoV during follow-up was associated with a lack of statin use.

In this study, the CBF to CBV ratio was used as an indicator of cerebral perfusion pressure.[24,25] A previous experimental PET study showed a linear relationship between CBF/CBV and mean arterial pressure.[18] In patients with ICA occlusion, decreases in CBF/CBV were early changes in response to decreased perfusion pressure due to ICA occlusion before decreases in CBF and increases in OEF occurred.[26] Therefore, changes in CBF/CBV are considered a sensitive index of hemodynamic changes during follow-up. Abnormal decreases in CBF/CBV (impaired perfusion) can be used as a predictor of subsequent ischemic stroke in patients with ICA and MCA diseases.[8,9,28,29] In this study, we showed that higher visit-to-visit BP variability was associated with decreases in CBF/CBV and the apparent impaired perfusion at follow-up. In contrast, patients with low visit-to-visit BP variability showed a decreased incidence of impaired perfusion and tended to improve CBF/CBV at follow-up.

The specific mechanisms for hemodynamic deterioration in patients with higher visit-to-visit SBP variations are unclear in this study. However, several studies have demonstrated that high visit-to-visit BP variability, even with as few as three BP measurements, is associated with arterial stiffness, endothelial dysfunction, and atherosclerosis, suggesting that alterations in vascular function may occur with high visit-to-visit BP variability.[13–16] The reason why visit-to-visit BP variability, a marker of longitudinal BP change, is associated with vascular dysfunction remains unclear, although a shorter-term BP fluctuation

may be associated with oscillating shear stress, leading to vascular dysfunction. One study showed that separate but similar relationships for measures of 24 h ambulatory BP variability and visit-to-visit BP variability with measures of smooth muscle function, suggesting that 24 h BP variability and visit-to-visit BP variability could have some similar underlying causes and/or sequelae.[13] Thus, in patients with atherosclerotic major cerebral artery disease, increased visit-to-visit BP variability could impair the function of cerebral collaterals and impede collateral growth, leading to hemodynamic impairment.[17,18] However, it is unclear whether this speculation is appropriate for the visit-to-visit BP variability in the present study because we have no data on the relationships between the visit-to-visit BP variability in the present study and BP fluctuations evaluated with 24 h ambulatory BP monitoring. The visit-to-visit BP variability evaluated in the present study and 24 h ambulatory BP variability are completely different in nature. In the present study, we only showed the association between the visit-to-visit BP variability evaluated with only 3 BP measurements and hemodynamic changes.

Alternatively, high visit-to-visit SBP CoV may be associated with large decreases in SBP during follow-up, which may lead to hemodynamic deterioration. In patients with higher CoV, the decrease in SBP from the baseline to the third examination tended to be larger than in patients without. However, the difference in SBP between the first and third examinations was not significantly correlated with changes in the PET variables.

In this study, decreases in cortical oxygen metabolism along with hemodynamic deterioration were associated with high visit-to-visit SBP variations during follow-up, which suggested the development of some cerebral damage. Although the patients who were evaluated showed no increase in apparent ischemic lesions in the cerebral cortex or the white matter on routine MRI and no apparent functional worsening on routine neurological examinations, high visit-to-visit SBP variations could cause silent damage of cortical neurons[30] or white matter fibre integrity,[31] which might cause decreased cortical oxygen metabolism. One possible underlying mechanism may be that transient BP reductions beyond the autoregulatory range in the setting of hemodynamic impairment may cause cerebral ischemia leading to brain damage in patients with unstable BP control. As we selected patients with no ischemic episodes of ischemic stroke during the follow-up period, the changes in hemodynamics and metabolism in patients with high visit-to-visit SBP variations during the follow-up period were not so large. Sophisticated MRI methods or detailed cognitive examinations could reveal morphological or functional correlates of decreased oxygen metabolism during longer follow-up periods.

Medical treatment strategies to control visit-to-visit BP variations could be important for hemodynamic improvement. Visit-to-visit BP variations can, in principle, be reduced by iteratively adjusting antihypertensive therapy.[32,33] In this study, no significant relationship was found between antihypertensive drugs and visit-to-visit BP variations. However, statin use was associated with low SBP CoV values. In animal experiments, statins reduced BP variability.[34] The decreased BP variability may be associated with the beneficial effects of statins on cerebral circulation, which may reduce the occurrence of neuronal damage and infarction due to large artery atherosclerosis.[35,36]

Limitations

This study was a post-hoc analysis of an observational study. Therefore, we cannot exclude the possibility that unmeasured confounding variables may explain some of our findings. The data were obtained in selected patients with no cortical infarction at baseline and no ischemic episodes of ischemic stroke during follow-up. However, these two factors affect the changes in hemodynamics and metabolism in the affected cortical territories and should be controlled to investigate the effect of visit-to-visit BP variations on the changes in hemodynamics and metabolism. Furthermore, the BP of patients included in this study was measured at only three PET examinations. Although accurate BP measurements using an arterial catheter connected to a pressure transducer were performed in a similar condition at three PET examinations, visit-to-visit SBP variation at PET examinations may be different from those in the clinic. Therefore, it is unclear whether the results can be generalized. We did not perform correction of multiple comparisons in the statistical analysis, because this was an exploratory study, which may lead to increased Type I error. Additional studies with a larger number of patients and more BP measurements are needed to confirm the results.

Conclusions

In patients with atherosclerotic ICA or MCA disease, high visit-to-visit SBP variations were associated with hemodynamic deterioration. High visit-to-visit SBP variations were also associated with decreased cortical metabolism. These findings suggested that the control of visit-to-visit SBP variations may be important to prevent the deterioration of cerebral hemodynamics and metabolism which could lead to poor patient prognosis.

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Declarations of Competing Interest

None.

CRediT authorship contribution statement

Hiroshi Yamauchi: Visualization, Data curation, Formal analysis, Writing – original draft. **Shinya Kagawa:** Data curation, Writing – original draft. **Kuninori Kusano:** Data curation, Formal analysis, Writing – original draft. **Miki Ito:** Data curation, Formal analysis, Writing – original draft. **Chio Okuyama:** Data curation, Writing – original draft.

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