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Impact of cerebral large-artery disease and blood flow in the posterior cerebral artery territory on cognitive function

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ABSTRACT

Objectives: The purpose of this study was to elucidate the association of cerebral large artery disease (CLAD) with cerebral blood flow (CBF) in the posterior cerebral artery (PCA) territory and cognitive performance.
Method: We prospectively registered patients with CLAD who had internal carotid or middle cerebral artery (MCA) with the degree of stenosis ≥50%. Automated brain segmentation was used to quantify CBF in the thalamus, hippocampus, and PCA and MCA territories. We measured cognitive function of patients using the Wechsler Memory Scale Revised (WMS-R), the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment. Patients were divided into 3 groups according to CBF of the cortical and subcortical PCA territory.
Results: There were 60 patients included in this study. The degree of stenosis was significantly correlated with CBF in the PCA territory ($\Gamma = 0.35$, $P = .006$) and hippocampus ($\Gamma = 0.34$, $P = .008$). Verbal memory, general memory, and reproduction on WMS-R and MMSE were significantly reduced areas with low CBF in the PCA territory compared with areas with middle and high CBF.
Conclusions: CBF of the PCA territory was significantly inversely correlated with the degree of stenosis in CLAD patients. Low CBF of the PCA territory was significantly associated with reduced cognitive and memory functions.

1. Introduction

Cerebrovascular disease is known to cause cognitive impairment. There are several categories of cognitive impairment in cerebrovascular disease, including parenchymal ischemic or hemorrhagic lesions, white matter lesions, microbleeds, and cerebral large artery disease (CLAD) [1]. There are increasing reports on the association of CLAD with cognitive function [2–4], as well as the status of cerebral hemodynamic impairment with cognitive performance [5–7]. CLAD is a known cause of cognitive impairment regardless of the history of stroke. We and others have reported that cerebral blood flow (CBF) of the middle cerebral territory (MCA) is significantly associated with cognitive dysfunction in patients with significant stenosis in either the internal carotid artery (ICA) or MCA [8,9].

There are 3 different mechanisms of collateral circulation in patients with steno-occlusive disease in the MCA or ICA [10]. The Willis circle is the most important collateral that can enhance CBF in the MCA territory, although flow from the external carotid artery and leptomeningeal anastomosis may compensate for reduced CBF. The leptomeningeal anastomosis is a network of blood vessels supplying the brain that follows a diffuse course over the superficial surface of the brain. The leptomeningeal anastomosis from the posterior cerebral artery (PCA), rather than the anterior cerebral artery, frequently develops on the ipsilateral side of the MCA territory [11,12]. CBF in the PCA territory may decrease as a result of collateral flow from the PCA to the MCA territory.

In the present study, we hypothesized that significant steno-occlusive CLAD may contribute to reduced CBF of the PCA territory, which may lead to dysfunction of the ipsilateral PCA territory including the hippocampus and thalamus. The aim of this study was to examine whether degree of stenosis in either the ICA or MCA is negatively related to CBF in the PCA territory in CLAD patients, and to examine the effect of CBF in the PCA territory on cognitive performance.

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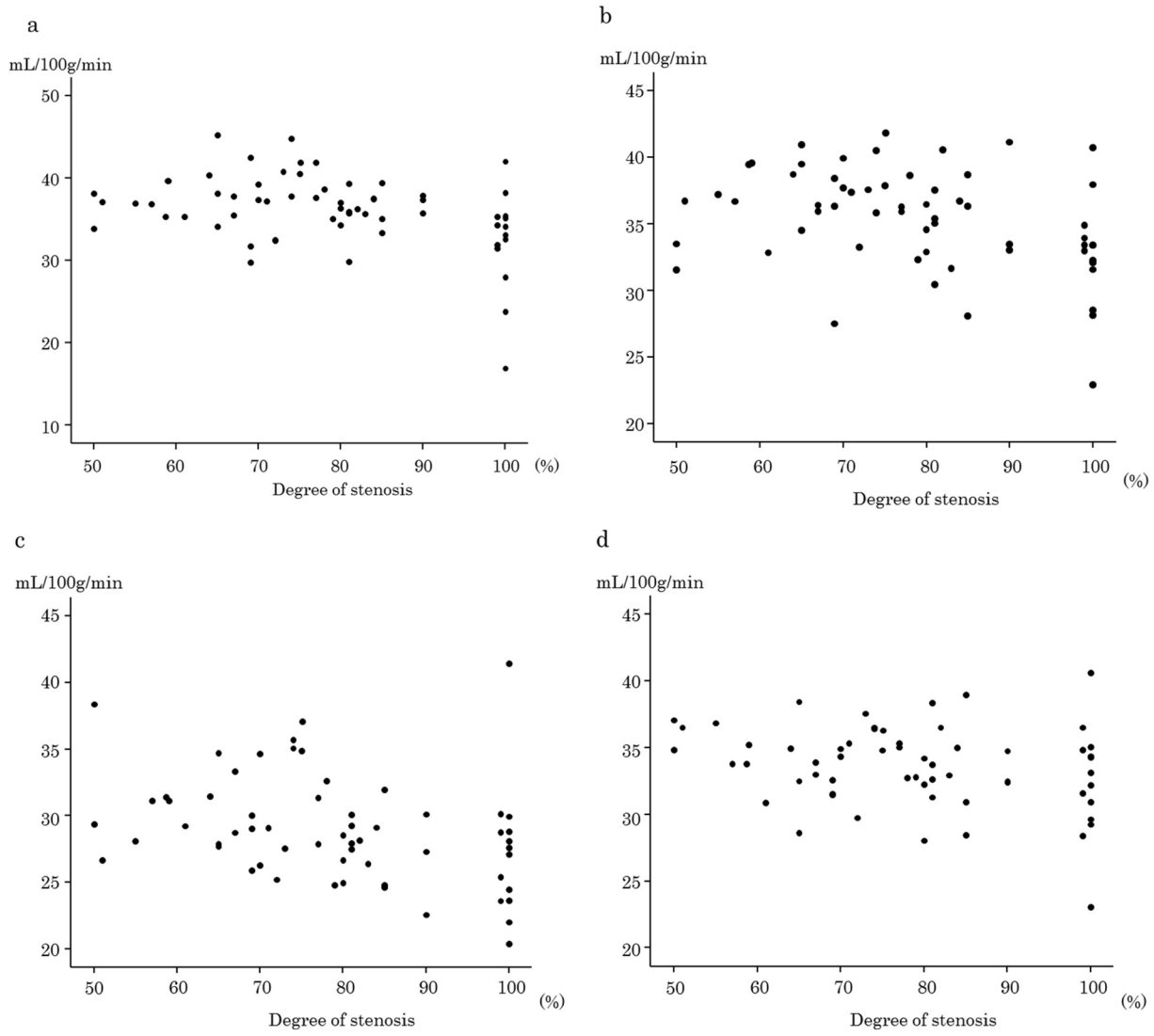

Fig. 1. Cerebral blood flow (CBF) of each territory depending on the degree of stenosis of either the internal carotid artery (ICA) or the middle cerebral territory (MCA). (A) CBF of the MCA territory ($\Gamma = 0.37$, $P = .003$). (B) CBF of the PCA territory ($\Gamma = 0.35$, $P = .006$). (C) CBF of the hippocampal area ($\Gamma = 0.34$, $P = .008$). (D) CBF of the thalamus area ($\Gamma = 0.25$, $P = .053$). Correlation coefficients and statistical values were calculated using Pearson's product moment.

2. Material and methods

We prospectively registered patients with stenosis or occlusion of either ICA or MCA of 50% or more who were hospitalized in the Neurocenter of Fukuoka University Hospital, Japan, from April 2014 to June 2016. They were hospitalized because some had atherothrombotic stroke while the others underwent carotid endarterectomy or arterial stenting. We excluded patients with dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, or those with a modified Rankin Scale ≥ 3. We previously performed a subanalysis of these patients to examine the association of microbleeds with vascular endothelial growth factor in CLAD patients (Ogata T et al.: Cerebrovascular Disease Extra, accepted). The present study was performed using the same dataset. The study protocol was approved by the Ethics Committee of Fukuoka University Hospital (IRB No. 14-1-07).

CLAD was defined when the degree of stenosis in either the ICA or MCA was $\geq 50\%$. Cerebral perfusion was measured by Technetium-99m ethyl cysteinate dimer single-photon emission computed tomography (SPECT). The SPECT scan was started 5 min after administration of 600 MBq of Technetium-99m ethyl cysteinate dimer, and data were collected for 20 min using a 3-head gamma camera. Automated brain segmentation was used to quantify CBF values in the thalamus, hippocampus, and the PCA and MCA territories. The CBF of the PCA territory was defined as the cortical and subcortical PCA territory, whereas CBF of the hippocampus and thalamus were determined separately. CBF in the whole MCA territory was also calculated.

After obtaining written informed consent from all patients, we measured cognitive function using the Japanese version of Wechsler Memory Scale Revised (WMS-R), the Mini-Mental State Examination (MMSE), and the Montreal Cognitive Assessment (MoCA). For the WMS-R [13], visual memory, verbal memory, general memory, attention and concentration, and delayed reproduction were evaluated separately, and the standardized scores weighted from the rough point of the 5 lower level examinations were then calculated. Based on the conversion table from score to index score, each standardized score was converted into the index score.

2.1. Statistics

The patients included in this study were divided into 3 groups according to the combined CBF of the cortical and subcortical PCA territory. First, we assessed the correlations between the degree of stenosis in either the ICA or MCA and CBF of the MCA, thalamus, hippocampus,

Table 1
The characteristics, imaging, and cerebral blood flow (CBF) findings of the patients according to CBF of the posterior cerebral artery (PCA) territory.

	Low CBF-P (n = 20)	Middle CBF-P (n = 20)	High CBF-P (n = 20)	P value
CBF-P	32 (29–33)	36 (35–36)	39 (38–41)	
Age	70.3 ± 10.3	72.7 ± 6.5	71.4 ± 9.2	0.691[a]
gender, male	16 (80%)	18 (90%)	14 (70%)	0.346
Neurological symptoms within 120 days	8 (40%)	4 (20%)	7 (35%)	0.47
Hypertension	15 (75%)	14 (70%)	18 (90%)	0.381
Diabetes mellitus	9 (45%)	9 (45%)	8 (40%)	1
dyslipidemia	14 (70%)	14 (70%)	12 (60%)	0.833
Current smoking	4 (20%)	3 (15%)	4 (20%)	1
Current drinking	6 (30%)	5 (25%)	6 (30%)	1
Cardiac ejection fraction	69.0 ± 8.8	70.0 ± 9.7	68.2 ± 10.8	0.84[a]
ICA lesion	17 (85%)	20 (100%)	18 (90%)	0.353
Side, right	11 (55%)	6 (30%)	9 (45%)	0.317
Left	9 (45%)	14 (70%)	11 (55%)	
Bilateral	3 (15%)	5 (25%)	1 (5%)	0.265
Degree of stenosis	95 (79 – 100)	77 (66–83)	74 (66–82)	0.006[a]
Vertebrobasilar stenosis	2 (10%)	6 (30%)	1 (5%)	0.122
PCA stenosis	4 (20%)	1 (5%)	0 (0%)	0.115
WMD of PCA territory	0 (0%)	3 (15%)	4 (20%)	0.144
ipsilateral MCA CBF	31 (28–32)	33 (32–33)	35 (33–37)	0.006[a]
CBF thalamus	32 (28–34)	38 (36–39)	43 (40–45)	< 0.001[a]
CBF hippocampus	25 (24–27)	29 (28–29)	32 (31–35)	< 0.001[a]
Education years	12 (9–13)	12 (10–15)	12 (9–16)	0.77[b]
MMSE	26 ± 4	28 ± 2	28 ± 2	0.048[a]
MoCA	22 ± 5	23 ± 3	23 ± 3	0.060[a]

CBF-P: CBF of the PCA; ICA: internal cerebral artery; MCA: middle cerebral artery; WMD: white matter disease; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.
[a] Analysis of variance.
[b] Mann-Whitney's *U*-test.

and cortical and subcortical PCA territories. Second, the patients were divided into 3 groups according to the CBF of the PCA territory (low CBF-P, middle CBF-P, and higher CBF-P groups). Univariate analyses were conducted to compare patients' characteristics, atherosclerotic risk factors, and imaging findings between the 3 groups. The same analyses were conducted to compare cognitive functions estimated by MMSE, MoCA, and WMS-R. Differences between the 3 groups were analyzed using one-way analysis of variance, Kruskal-Wallis analysis, and Fisher's exact test, as appropriate. Pearson's product moment was used to assess the correlation of the degree of stenosis with CBF of each territory. *P*-values < .05 were considered statistically significant. All statistical analyses were performed with statistical software (SPSS v.22.0; IBM Corp., NY, USA).

3. Results

Of the 66 patients who received analysis of cognitive function, 6 patients were excluded because of lack of CBF data. Thus, 60 patients were included in this study (71.4 ± 8.7 years, 48 men, 12 women). Fifty-five patients had stenotic lesions in the ICA. The median of degree of stenosis in CLAD was 80%.

The relationship between the degree of stenosis and CBF is shown in Fig. 1. As expected, the degree of stenosis was significantly associated with CBF in the MCA territory (Γ = -0.38, P = .003), and with CBF in the PCA territory (Γ = -0.35, P = .006) and hippocampus (Γ = -0.34, P = .008), but not in the thalamus (Γ = -0.25, P = .053). Based on categorizing the 60 patients into 3 groups according to CBF of the PCA, the median CBF of the low CBF-P, middle CBF-P, and higher CBF-P groups were 32, 36, and 39 mL/100 g/min, respectively. Patients in the low CBF-P group have significantly lower CBF in the thalamus and hippocampus compared with the middle CBF-P and higher CBF-P groups.

Atherosclerotic risk factors and the side of the lesion of CLAD were similar between the 3 groups (Table 1). In groups with low CBF-P, MMSE was significantly reduced while MoCA was reduced insignificantly (Table 1). As to the WMS-R, significant difference was not seen in the attention/concentration between the 3 groups (Fig. 2d). However, verbal memory, general memory, and reproduction of WMS-R were significantly different between the 3 groups, while visual memory showed a trend towards a decrease in the lower CBF-P group compared with the other groups (Fig. 2a–c, e). According to the verbal, visual, general, and reproduction scores of WMS-R in each group, the low CBF-P group had a significantly lower cognitive function compared with the other groups.

4. Discussion

Cerebral primary collaterals lie in the circle of Willis, whereas blood flow from the external carotid artery and leptomeningeal anastomosis constitute secondary collaterals [10]. An anatomical study noted the absence of an anterior communicating artery in 1% of subjects, while the absence or hypoplasia of either posterior communicating artery was up to 30% [11]. The degree of collateral flow depends on the caliber and patency of primary pathways, and the opening of collaterals likely depends on several compensatory hemodynamic, metabolic, and neural mechanisms [10]. CBF of the ipsilateral MCA is inversely related to the degree of the stenosis in patients with symptomatic ICA stenosis [14], indicating that the presence of secondary collateral pathways may be a marker of insufficient cerebral hemodynamics. However, the degree of stenosis can also markedly influence angiogenesis [12], which was associated with the formation of leptomeningeal anastomosis. Presuming that CBF of the PCA territory compensates CBF in the MCA via the leptomeningeal anastomosis, then this may decrease CBF of the PCA territory. In the present study, we found that the degree of stenosis in the ipsilateral ICA or MCA was inversely correlated with CBF of the PCA territory and hippocampus, as well as of the MCA territory.

A recent study reported that ICA stenosis exacerbates cerebral hypoperfusion, brain atrophy, cognitive decline, and dementia [2,15,16]. The reduction in cortical volume may help to explain the association of cerebral hypoperfusion with cognitive impairment [15,17]. In rodents, bilateral occlusion of the carotid artery induced cerebral hypoperfusion and neuropathological changes in the hippocampus, with associated learning and memory disturbances [18]. Thus, the inverse correlation of the severity of CLAD with CBF of the PCA territory and hippocampus observed in the present study may influence cognitive function, especially memory.

WMS-R is suitable for systematic examination of memory function. Auditory or visual memory may depend on the side of the CLAD. In the present study, the reduction in the general memory and reproduction scores were likely because of decreased CBF in the hippocampus. By contrast, we found no change in attention/concentration with the PCA territory, likely because impaired attention function relates to frontal hypoperfusion [19]. Our findings are unique in that the CBF in the hippocampus and PCA territory mediate the association of steno-occlusive disease of the ICA or MCA with cognitive, especially memory, function. Further studies are required to assess the role of CBF in the hippocampus and PCA territory.

There are several limitations in this study. First, the number of participants was small. Second, angiography was not performed in all patients; thus, the type and degree of collateral were not precisely evaluated. Third, the association of the side of stenosis with types of cognitive function was not accurately investigated, as a number of patients had bilateral ICA/MCA lesions. Another limitation was the lack of any controls in this study. Furthermore, we did not perform a positron emission spectroscopy or SPECT study, and acetazolamide reactivity and cerebral vasoreactivity were not evaluated. Thus, our

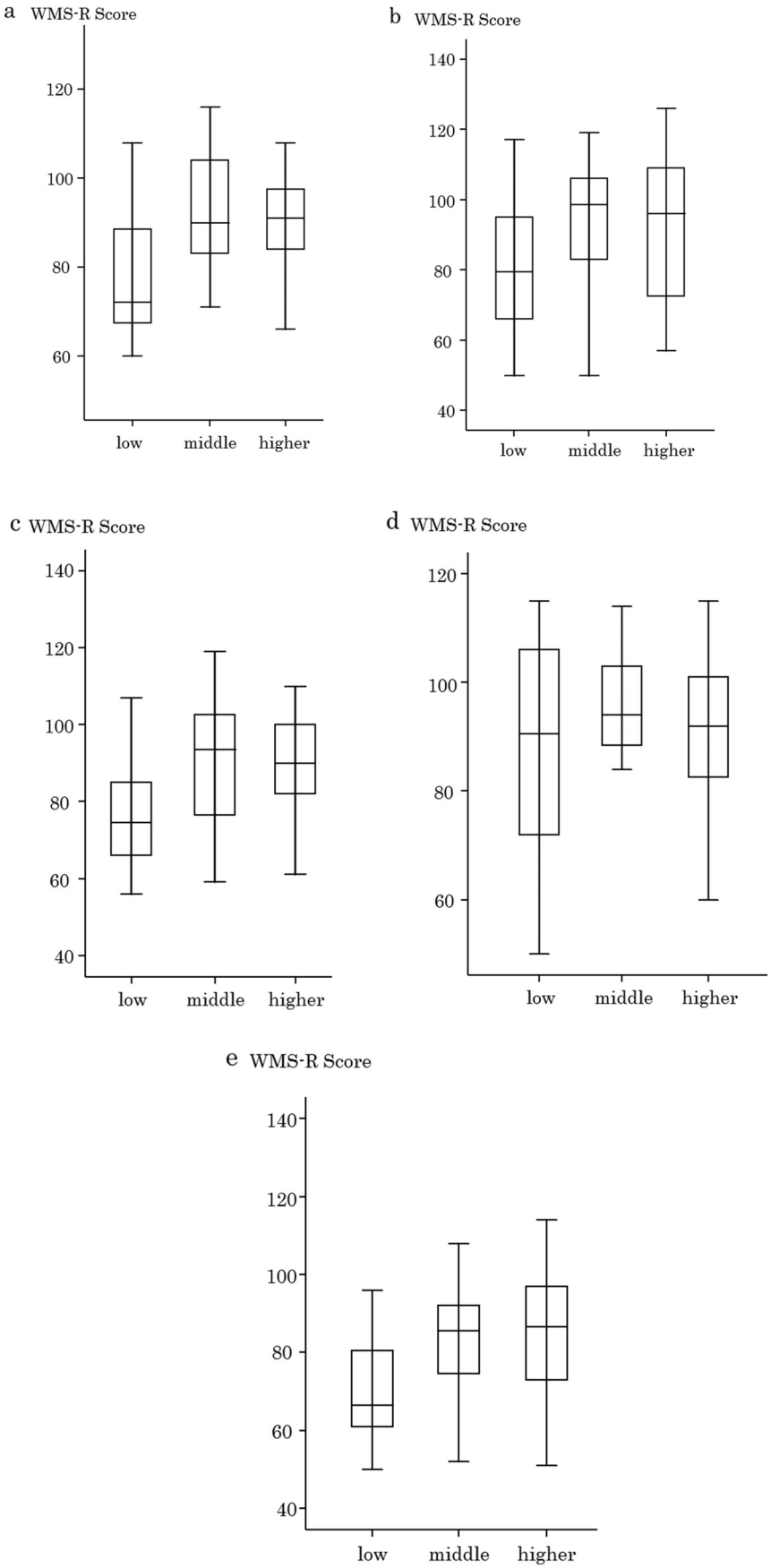

Fig. 2. Cognitive function evaluated using the Wechsler Memory Scale Revised (WMS-R) depending on posterior cerebral artery (PCA) CBF. (A) Verbal memory ($P = .017$). (B) Visual memory ($P = .064$). (C) General memory ($P = .016$). (D) Attention/concentration ($P = .407$). (E) Reproduction ($P = .025$). Data were assessed using the Kruskal-Wallis test.

evaluation of vasoreactivity may be inaccurate.

In conclusion, CBF in the PCA territory was inversely correlated with the severity of CLAD, and significantly associated with cognitive function, especially memory. Thus, the severity of CLAD may contribute to cognitive impairment and memory loss because of decreased CBF in the PCA territory and hippocampus.

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Statement of ethics

This study was approved by the Ethics committee in our hospital.

Disclosure statements

The authors have no conflict of interest to disclose.

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Author contributions

J.W., drafting the manuscript for content and study concept; T.O., drafting the manuscript for content, study design, statistical analysis, study supervision, and obtaining funding; Y.T, critical revision of the manuscript for intellectual content and obtaining funding; T.I., study supervision.

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