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·Original Article·

Xenon-enhanced CT assessment of cerebral blood flow in stroke-in-progress patients with unilateral internal carotid artery or middle cerebral artery stenosis

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ABSTRACT

Carotid or cerebral artery stenosis resulting in low perfusion is a major cause of ischemic stroke. Understanding the unique hemodynamic features in each patient undergoing a stroke-in-progress (SIP) and the correlation between progression and cerebral blood flow (CBF) status would help in the diagnosis and treatment of individual patients. We used xenon-enhanced CT (Xe-CT) to examine cerebral perfusion in patients with or without SIP (30 patients/group), recruited from October 2009 to October 2010. Only SIP patients with unilateral stenosis in the internal or middle cerebral artery were recruited. The occurrence of watershed infarction was higher in the SIP group than in the non-SIP group (P <0.05). In the SIP group, larger hypoperfused areas were found around the lesions than in the non-SIP group. In the SIP group, the CBF values in the ipsilateral areas were significantly lower than those in corresponding regions on the contralateral side. CBF values in the contralateral hemisphere were significantly lower in the SIP group than in the non-SIP group. In SIP patients, infarctions were surrounded by larger hypoperfused areas than in non-SIP patients. These larger hypoperfused areas may result in pathological damage to the brain that is responsible for the progression of stroke.

Keywords: cerebral blood flow; stroke in progress; artery stenosis; xenon-enhanced CT; hypoperfusion

INTRODUCTION

Stroke is the third leading cause of death and disability in the USA[1] and the second leading cause of death in China[2]. Neurological deterioration is common during the acute phase, and early progression accounts for much of the total burden of death and long-term disability[3, 4]. The underlying mechanisms are largely unclear. Stroke-in-progress (SIP) is encountered in several major types of stroke[5]. It occurs in ~30% of patients with acute stroke and negatively affects the prognosis and mortality. The underlying pathogenesis is not well understood. It has been demonstrated that cerebrovascular stenosis is an important cause of SIP[5, 6]. The degree of vascular stenosis-induced brain perfusion directly determines the progression and outcome of stroke. Many patients suffer progressive neurological deterioration that is often accompanied by ongoing hemodynamic instability[7]. It is unknown whether the hemodynamic features differ between patients with and without SIP. Furthermore, few reliable measures are available for early diagnosis and appropriate treatment.

Xenon-enhanced CT (Xe-CT) systems equipped with

stable (non-radioactive) xenon and a standard CT scanner have been used to measure cerebral blood flow (CBF). These systems can be used for real-time imaging, making it possible to evaluate local and whole cerebral perfusion as a function of time. In this study, we aimed to quantify CBF by Xe-CT and evaluate the associated clinical signs and variations in patients with SIP.

METHODS

Participants

The study design was approved by the Ethics Committee of the First Norman Bethune Hospital of Jilin University. Informed consent was obtained from all participants. We carried out a prospective study of consecutive admissions to the Department of Neurology at the First Hospital of Jilin University during a 12-month period (October 2009 to October 2010), and 150 stroke patients (average age, 57.3 ± 12.3 years; 111 males and 39 females) with unilateral internal carotid artery (ICA) or middle cerebral artery (MCA) stenosis were recruited. ICA or MCA stenosis was diagnosed by transcranial Doppler (TCD; MultiDop X2, DWL, Sipplingen, Germany) and magnetic resonance imaging (1.5 T, Signa, General Electric, Milwaukee, WI). Subjects with other intracranial or extracranial arterial stenosis diagnosed using TCD and carotid ultrasound (IU22, Phillips, Andover, MA) were excluded. Clinical workup consisted of a thorough physical examination, electrocardiography, laboratory tests including liver and kidney function tests and hematology profiles, TCD, magnetic resonance imaging, and Xe-CT scanning. The patients were admitted within 24 h of the onset of stroke, when all examinations were carried out.

Criteria of SIP and non-SIP

Standardized neurological assessments were performed daily for the first 3 days in the patients with acute stroke. Using the Scandinavian Stroke Scale scoring system, SIP was defined as a ≥2-point worsening in the conscious state and arm, leg, or eye movement scores and/or a ≥3-point worsening in speech score. Comparisons were made between the scores obtained from assessment on day 3 and baseline scores unless death occurred within 72 h of onset[3, 8]. If there was no improvement in the neurological assessment or scores did not reach the SIP standard, the condition was defined as non-SIP. Patients with poor Xe-CT CBF images and patients with serious consciousness disorders were excluded. Serious consciousness disorders included stupor, coma, or inability to cooperate sufficiently to complete the Xe-CT scans.

TCD Protocol

We insonated the terminal ICA, MCA, anterior and posterior cerebral arteries, bilateral vertebral arteries, and basilar arteries. Focal stenosis of the MCA or ICA was diagnosed as a focal elevation in peak systolic flow velocity >120 cm/s or a mean velocity >80 cm/s or a difference between the ipsilateral and contralateral mean velocities of >30 cm/s with or without turbulence/spectral broadening and vessel wall vibration[9, 10].

Measurement of CBF Using Xe-CT Scanning

CBF was measured on both the ipsilateral and contralateral hemispheres. Measurements were made using a CT scanner (Somatom plus 4, Siemens, Forchheim, Germany) equipped for detection of Xe-CT CBF images (Xe/TC system-2, Diversified Diagnostic Products, Inc. (DDPI), Houston, TX). The Xe-CT protocol was used to image four contiguous 10-mm slices (120 kVp, 200 mA, acquisition matrix 512 × 512, field of view 230 mm, 28% xenon gas) with the head aligned along the orbitomeatal plane. Two baseline scans separated by 30 s were obtained at each of the four chosen levels during room air inhalation. After a delay of 33 s, six additional Xe-CT scans were obtained over ~4.5 min at each level while the patient inhaled an air mixture containing 28% xenon[11-13]. Regional CBF was calculated using DDPI software. The largest slice of infarction from each patient was analyzed. Two regions of interest (ROIs) >1 cm² were drawn freehand on the CT scan; one area was around a low-density area, and the other was around a mirror region of normal-appearing brain tissue in the contralateral hemisphere. In each ROI, the CBF values were calculated and the means were expressed as milliliters per 100 g brain tissue per minute (mL/100 g/min). Two ranges of CBF were evaluated: 10–20 and 20–30 mL/100 g/min. The DDPI Xe-CT software was used to select the zones consistent with these ranges and then the total areas of the zones were calculated. We compared the CBF values in the ipsilateral and contralateral sides in each group.

Statistics

The Statistical Program for Social Sciences (SPSS) 17.0 was used for data analysis. Comparisons of regional CBF values between the ipsilateral and contralateral sides in the SIP and non-SIP groups were performed with the paired two-tailed *t*-test. The level of significance was set at $P < 0.05$.

RESULTS

Demographic Information

Of the 150 stroke patients admitted to the Department of Neurology at the First Hospital of Jilin University over a one-year period, 56 were classified as SIP and 94 as non-SIP. Twenty-six patients were further excluded from the SIP group (21 presented with consciousness disorders and five had poor Xe-CT CBF images), and the remaining 30 patients were available for the SIP group (58.73 ± 9.33 years old; 21 males and 9 females; 17 with MCA stenosis and 13 with ICA stenosis; Table 1). Seven patients were excluded from the non-SIP group due to poor Xe-CT CBF images. Of the remaining 87 patients, 30 were randomly selected as the final non-SIP group (60.40 ± 9.61 years old; 20 males and 10 females; 15 with MCA stenosis and 15 with ICA stenosis; Table 1).

In the SIP group, four patients (13.3%) presented with deterioration in level of consciousness (normal to somnolence, but were able to cooperate during Xe-CT imaging), twelve (40.0%) had impairment in movement alone, six (20.0%) presented with loss of speech alone, and eight (26.7%) had loss of function in both movement and speech. In the non-SIP group, no patients had consciousness disorders, sixteen (53.3%) had impairment in movement alone, eight (26.7%) presented with loss of speech alone, and six (20.0%) had loss of function in both movement and speech.

No significant differences between the SIP and non-SIP groups were found in most of the serious risk factors for stroke (age, sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, coronary artery disease, alcohol use, and family history). However, smoking was more common in the SIP group than in the non-SIP group (Table 2).

Analysis of the Lesion Sites

In the SIP group, five cases had lesions in the frontal, temporal, and parietal lobes; eight had lesions in the border zone of the fronto-parietal, parieto-occipital, and fronto-temporal lobes; two showed a large infarct involving the left frontal, temporal, and parietal lobes; in 11, lesions were found in the white matter lateral to the lateral ventricle; and in four the lesions were in the basal ganglia (Table 3).

In the non-SIP group, six cases had lesions in the frontal, temporal, and parietal lobes; in four the lesions were in the border zone of the fronto-parietal, parieto-occipital, and fronto-temporal lobes; three had a large infarct involving the left frontal, temporal, and parietal lobes; six had lesions in the white matter lateral to the lateral ventricle; and in 11 the lesions were in the basal ganglia (Table 3).

When the two groups were compared, the occurrences of infarction in watershed areas and in the white matter lateral to the lateral ventricle were higher in the SIP group than in the non-SIP group. However, the occurrence of infarcts among lobes and large infarcts was similar in the two groups. Finally, the occurrence of infarcts in the basal ganglia was lower in the SIP group than in the non-SIP group (Table 3).

CBF Values and Hypoperfused Areas in the Ipsilateral Hemisphere

In both groups, the CBF values in the ipsilateral areas were significantly lower than those in corresponding regions on the contralateral side. In the SIP group, the ipsilateral CBF was 14.40 ± 3.46 mL/100 g/min, and the contralateral CBF was 38.59 ± 9.45 mL/100 g/min ($P < 0.05$); whereas in the non-SIP group, the ipsilateral CBF was 25.51 ± 3.55 mL/100 g/min, and the contralateral CBF was 49.91 ± 11.34 mL/100 g/min ($P < 0.05$). The CBF values in the contralateral hemispheres were significantly lower in the SIP group than in the non-SIP group (38.59 ± 9.45 mL/100 g/min *vs* 49.91 ± 11.34 mL/100 g/min, $P < 0.05$). In the SIP group, the hypoperfused areas around lesions in the ipsilateral hemisphere were significantly larger than those in the contralateral hemisphere (Fig. 1). The size of the hypoperfused area in the ipsilateral hemisphere with CBF values in the 10–20 mL/100 g/min range was 1723 ± 528 pixels, whereas in the contralateral hemisphere, the size averaged 1100 ± 387 pixels ($t = 8.5$, $P < 0.05$; Fig. 2 and Table 1). For CBF values in the 20–30 mL/100 g/min range, the ipsilateral lesions averaged 1491 ± 424 pixels and the contralateral lesions averaged 1269 ± 437 pixels ($t = 3.6$, $P < 0.05$; Fig. 2 and Table 1). In the non-SIP

Table 1. Demographic features of participants

	SIP group (n = 30)						Non-SIP group (n = 30)					
Patient	Sex	Age (years)	Lesion hemisphere* 10–20	Lesion hemisphere* 20–30	Contralateral hemisphere* 10–20	Contralateral hemisphere* 20–30	Sex	Age (years)	Lesion hemisphere* 10–20	Lesion hemisphere* 20–30	Contralateral hemisphere* 10–20	Contralateral hemisphere* 20–30
1	M	66	2488	2200	1157	1909	F	53	1179	1247	1295	1722
2	M	50	1744	1407	1226	1075	M	68	2354	2122	2326	2112
3	M	62	1856	1157	986	787	M	50	1126	1564	949	1581
4	F	71	1932	1549	1164	1246	M	52	1448	2095	1462	1859
5	F	51	2430	2456	1702	2190	M	42	482	895	432	662
6	M	58	3029	1995	1666	2107	F	69	311	504	248	400
7	M	54	2680	2104	1777	2063	F	70	2297	2901	2027	2317
8	M	67	2232	1563	2096	1491	M	75	1329	1703	1871	1933
9	M	66	1591	1594	1150	1103	M	61	1414	2437	1698	2632
10	F	57	2175	1697	1540	1846	F	45	1655	1808	1976	2280
11	M	56	1755	2091	452	928	M	50	1400	2513	1596	2532
12	M	64	1266	1667	625	804	M	55	2441	2453	2181	2219
13	M	46	1820	1799	869	1203	M	56	1971	2011	1678	1538
14	M	54	1683	1921	822	1598	M	63	1506	1877	1059	1815
15	F	69	1469	1149	1343	1173	F	70	752	936	1273	1401
16	M	34	1826	1785	697	1224	M	67	1739	1996	1594	2365
17	F	75	1691	1049	1353	1233	M	65	1620	1581	1619	1703
18	M	62	1797	1543	814	1066	F	78	1342	1597	1396	1345
19	M	48	1370	1155	1070	801	F	47	555	1453	467	1445
20	M	57	1599	1575	865	2066	M	50	1166	2024	1350	1534
21	F	62	1066	1084	815	1190	M	71	1083	1483	1031	1302
22	M	56	1817	975	1358	887	M	68	1358	1678	1219	1626
23	F	54	2092	1379	935	998	M	58	1294	1285	1451	1181
24	M	42	900	1257	794	914	M	63	1698	1176	1513	1385
25	M	60	1404	1214	1007	952	F	60	1146	988	1343	1467
26	M	56	1493	1483	1284	1258	M	58	1205	1096	1010	1035
27	F	71	1446	1175	943	1172	F	49	733	1009	609	962
28	F	73	1477	1047	959	1201	M	72	823	1279	1254	1674
29	M	59	958	712	844	724	M	59	1557	1720	1416	1584
30	M	62	598	939	695	874	F	68	721	918	882	921

M, male; F, female. 10–20 and 20–30 are the cerebral blood flow thresholds (mL/100 g per minute). *Zones consistent with the range of CBF values were selected automatically using the instrument software. Total areas are given in pixels.

Table 2. Comparisons of risk factors in SIP and non-SIP patients

	SIP (*n* = 30)	Non-SIP (*n* = 30)	*P*
Age (years)	58.73 ± 9.33	60.40 ± 9.61	*P* >0.05
Male	21 (70.0%)	20 (66.7%)	*P* >0.05
Hypertension	19 (63.3%)	21 (70.0%)	*P* >0.05
Diabetes	13 (43.3%)	15 (36.7%)	*P* >0.05
Hyperlipidemia	12 (40.0%)	13 (43.3%)	*P* >0.05
Atrial fibrillation	5 (16.7%)	6 (20.0%)	*P* >0.05
Coronary artery disease	21 (70.0%)	17 (56.7%)	*P* >0.05
Smoking	26 (86.7%)	19 (63.3%)	*P* <0.05
Drinking	17 (56.7%)	15 (50.0%)	*P* >0.05
Family history	8 (26.7%)	9 (30.0%)	*P* >0.05

Table 3. Lesion sites in SIP and non-SIP patients

	SIP (*n* = 30)	Non-SIP (*n* = 30)	*P*
Lobes	5 (16.7%)	6 (20.0%)	*P* >0.05
Watershed areas	8 (26.7%)	4 (13.3%)	*P* <0.05
White matter lateral to the lateral ventricle	11 (36.7%)	6 (20.0%)	*P* <0.05
Basal ganglia	4 (13.3%)	11 (36.7%)	*P* <0.05
Large infarct (multiple sites)	2 (6.6%)	3 (10.0%)	*P* >0.05

patients, very small areas of hypoperfusion were observed around the lesions (Fig. 1F). For 10–20 mL/100 g/min, the hypoperfused areas were 1324 ± 529 pixels in the

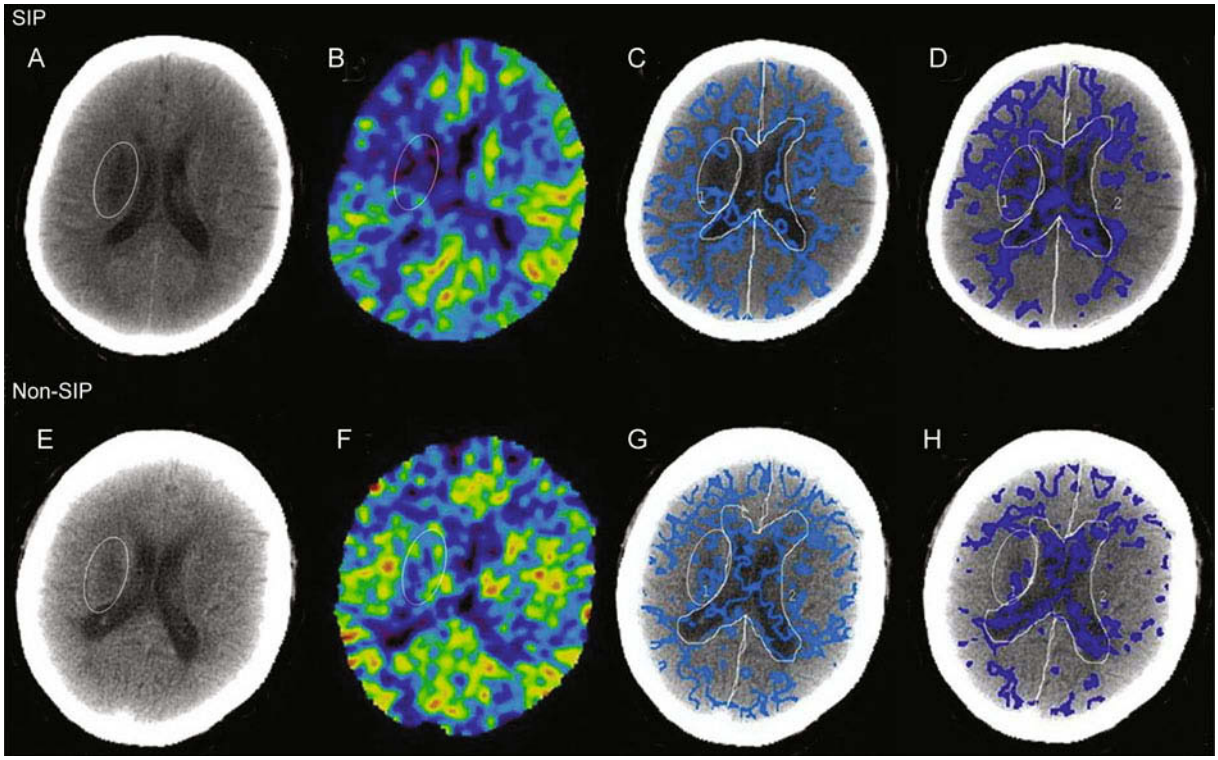

Fig. 1. Hemodynamic features in the patients with SIP and non-SIP. Xe-CT scan images showing that two stroke paients with MCA stenosis had similar infarction in terms of both location (the basal ganglia) and size (A and E). In the SIP group, the infarction lesions were surrounded with large hypoperfused areas (B), the sizes of the hypoperfused areas in the ipsilateral hemisphere with the CBF values ranging from 10–20 mL/100 g/min (C, light blue) to 20–30 mL/100 g/min (D, navy blue) were significantly larger than those in the contralateral hemisphere; Whereas in the non-SIP group, hypoperfusion area around the lesion was hardly visible (F), the sizes of hypoperfused areas in the ipsilateral hemisphere with the CBF ranging from 10–20 mL/100 g/min (G, light blue) to 20–30 mL/100 g/min (H, navy blue) were similar to those in the contralateral hemisphere.

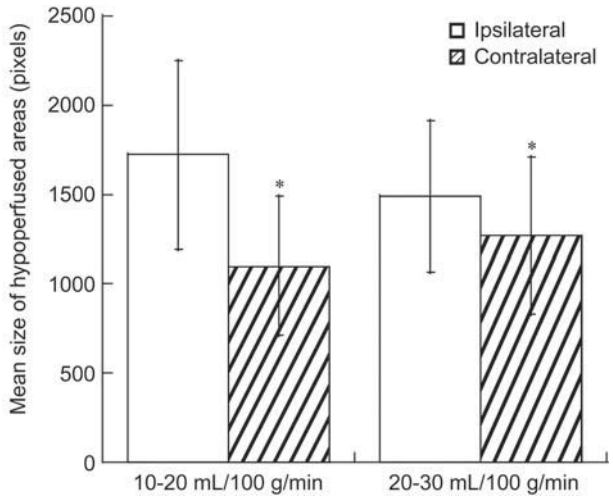

Fig. 2. Size of hypoperfused areas in the SIP group. In the SIP group, the sizes of the hypoperfused areas in the lesioned hemisphere with CBF values ranging from 10 to 20 mL/100 g/min and 20 to 30 mL/100 g/min were significantly larger than those in the contralateral hemisphere (*P <0.05).

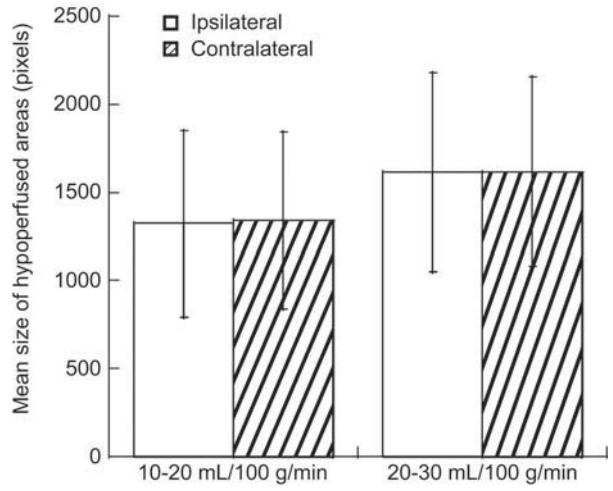

Fig. 3. Sizes of the hypoperfused areas in non-SIP patients. The sizes of the hypoperfused areas in the lesioned hemisphere with CBF ranging from 10 to 20 mL/100 g/min and 20 to 30 mL/100 g/min were similar to those in the contralateral hemisphere.

ipsilateral region *vs* 1341 ± 503 in the contralateral region (t = 0.4, P >0.05; Fig. 3; Table 1). For CBF values from 20–30 mL/100 g/min, the hypoperfused areas were 1612 ± 565 in the ipsilateral hemisphere and 1618 ± 534 pixels in the contralateral hemisphere (t = 0.1, P > 0.05; Fig. 3; Table 1). Thus, CBF values in the ipsilateral hemisphere were similar to those in the contralateral hemisphere for non-SIP patients.

DISCUSSION

Hemodynamic compromise has long been regarded as the primary mechanism underlying deep watershed infarction. In the present study, we showed that the occurrence of infarction in watershed areas and white matter lateral to the lateral ventricle was higher in the SIP group than in the non-SIP group. Our data suggest that abnormal hemodynamics occur in the SIP group, as previously proposed[14]. We found that the hemodynamic features in patients with SIP differed from those in non-SIP patients. In the SIP group with ICA or MCA stenosis, infarcts were surrounded by large hypoperfused areas with CBF ranged from 10 to 30 mL/100 g/min. Previous studies have shown that if the CBF is <10 mL/100 g/min, this area develops into a permanent infarction; if the CBF ranges 10 to 20 mL/100 g/min, the area is defined as a “penumbra”, and the outcome is variable; finally, a CBF from 20 to 30 mL/100 g/min indicates a mildly ischemic area that would likely not cause permanent symptoms[15-17].

In the present study, we mainly examined the penumbra and mildly ischemic area in patients with SIP by Xe-CT imaging, as these areas represent foci of potential pathological damage that might be responsible for the progression of stroke. In the SIP patients, the deterioration of these hypoperfused areas may directly cause the progression. If reperfusion of the penumbra occurs rapidly, neurons may recover and the patient may improve quickly. In contrast, if no reperfusion occurs, an irreversible infarction will result in permanent neuronal damage[16]. We found that the CBF values in the contralateral hemispheres were significantly lower in the SIP group than that in the non-SIP group. The reason for this difference may be that the infarcts in SIP patients were surrounded by larger hypoperfused areas and, because of the difference in pressure, blood flow from the contralateral side into the ipsilateral side through the anterior communicating artery compensated for the loss of blood flow on the ipsilateral side[18]. Thus, our data provide indirect evidence of reduced blood flow in SIP patients compared to non-SIP patients.

In patients with SIP, it is necessary to understand the

mechanisms underlying each case in order to determine the optimal therapeutic regimen. From the evidence gathered in the present study, it appears that no general guidelines for treatment can be made for such patients because of the complicated conditions and variable pathological changes such as lacunae, distal field infarctions, thrombotic and embolic infarcts, and cerebral hemorrhages[5]. Based on our results, treatment of the emergent hypoperfusion should be considered. To achieve this, intravenous and intra-arterial thrombolysis, anticoagulation, and anti-platelet agents can be used for reperfusion therapy. However, the simplest and most critical treatment is to maintain adequate blood pressure. Although hypertension contributes to the pathogenesis of stroke, and many patients with acute stroke have elevated blood pressure, attempts to reduce the blood pressure in stroke patients can lead to disastrous results. A rapid decrease in blood pressure may reduce cerebral perfusion resulting in profound worsening of the neurologic deficits[19-22], especially in patients with SIP. Therefore, lowering blood pressure should be performed carefully in these patients.

Our study characterized the hemodynamics of SIP in patients with ICA or MCA stenosis. The underlying pathogenesis of SIP is not well understood; we found that the infarcts were surrounded by large hypoperfused areas, which may contribute to the progression of stroke. Importantly, the early prediction of SIP is very difficult. If we could identify and manage SIP at an early stage, the risk of further damage would be reduced. We analyzed the characteristics of infarction and the Xe-CT features of hemodynamic abnormalities in patients with SIP in the hope that identification of measureable characteristics would allow doctors to rapidly identify the condition[23]. We did not analyze the ICA stenosis and MCA stenosis separately due to the small sample size. Further studies are necessary to explore the correlation between the progression and the CBF status as well as the potential of Xe-CT maps in the diagnosis of SIP.

In summary, the occurrences of infarction in watershed areas and the white matter lateral to the lateral ventricle were higher in the SIP group than in the non-SIP group. In the SIP group, the infarctions were surrounded by large hypoperfused areas, indicating potential pathological damage that may be responsible for the progression of stroke. Hemodynamic features observed with Xe-CT may allow us to identify and manage SIP early, which could reduce the risk of subsequent adverse events in these patients.

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