て 3 カ月後の完全自立と負の関係にあった[11]．Japan Alteplase Clinical Trial II(J-ACT II)[5]では，中大脳動脈水平部の起始から 5 mm 未満に閉塞が存在すると，発症 24 時間以内の早期再開通は 25%，3 カ月後の完全自立は 8.3% と有意に少なかった．また，胸部大動脈解離や胸部大動脈瘤を伴う脳梗塞に rt-PA 静注療法を行った場合の転帰が不良であることを示すデータが集積されてきた．

急性期虚血性脳卒中患者評価における超音波検査のメリット・デメリット

rt-PA 静注療法は適正治療指針を遵守する必要があり，発症 3 時間以内に治療を開始する必要がある．現在の指針では，頭部画像検査で広範な早期虚血性変化を除外することになっているが，頭頸部の血管評価は含まれない．3 時間以内でも発症から治療までの時間がより短いほど完全自立が増え[9]，血管評価による治療開始の遅れは避けなければならない．この制限のなかでも，超音波検査を用いるとベッドサイドで主幹動脈閉塞の有無を評価できる．超音波検査のメリットは，検査の非侵襲性，簡便性，および治療中でも繰り返し行えリアルタイムに閉塞血管の再開通現象を評価可能なことである．日本人では側頭骨窓から超音波が入りにくく約 4 割の脳卒中患者で経頭蓋超音波が検査できないこと[14]，また一定の検査の修練や経験を要することなどがデメリットとしてあげられる．

rt-PA 静注療法時に注意すべき超音波所見

大動脈解離や大動脈瘤に rt-PA を投与して死亡した 10 例の集積を受けて，2007 年にアルテプラーゼの添付文書の警告欄に「胸部大動脈解離あるいは胸部大動脈瘤を合併している可能性がある患者では，適応を十分に検討すること」が追加された．2008 年には日本脳卒中学会がこのような可能性のある患者に対して，「頸部血管超音波を rt-PA 静注

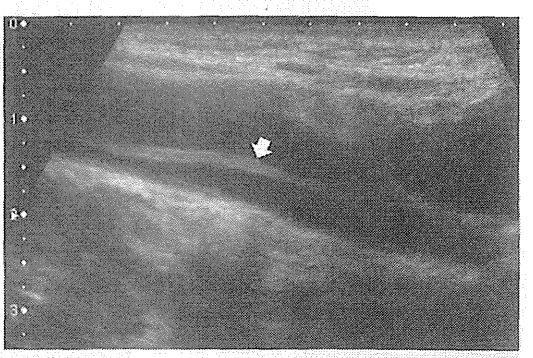

Fig. 1 頸部血管超音波による大動脈解離から波及する総頸動脈解離所見
右総頸動脈に解離が波及した大動脈解離患者の頸部血管超音波所見．右総頸動脈長軸像．総頸動脈内に intimal flap を認める(矢印)．

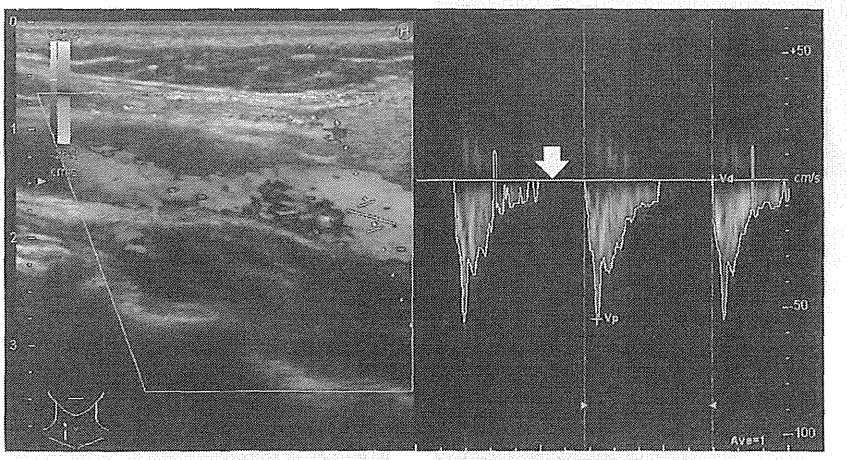

Fig. 2 頸部血管超音波による内頸動脈閉塞診断
右内頸動脈遠位部閉塞患者の頸部血管超音波所見．右内頸動脈起始部のカラードプラ像(左)と同部位でのパルスドプラによる血流速度波形(右)．拡張末期血流速度が消失しており遠位部内頸動脈閉塞の所見(矢印)．

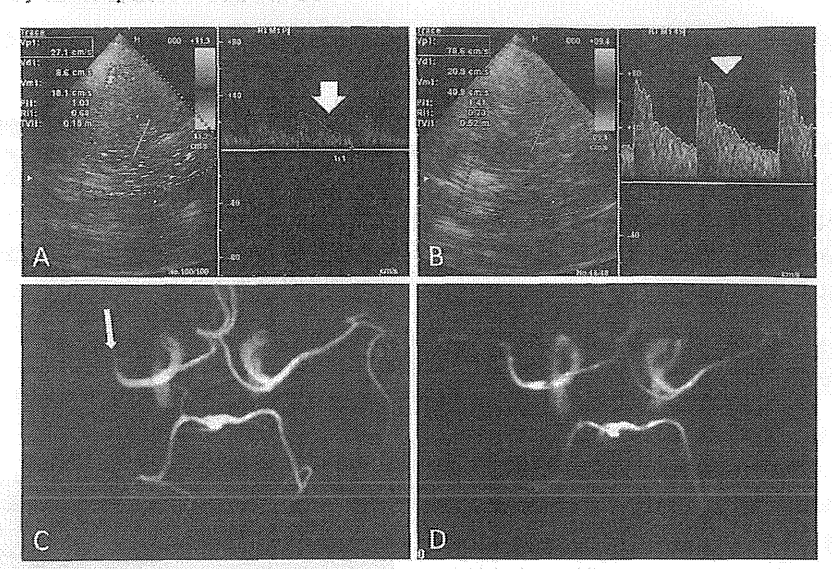

Fig. 3 経頭蓋カラードプラによる中大脳動脈閉塞の再開通評価
右中大脳動脈閉塞患者の rt-PA 静注療法前後での経頭蓋カラードプラ所見(**A, B**)と頭部 MRA 所見(**C, D**)．**A.** rt-PA 静注療法前の右中大脳動脈起始部血流速度は著明に低下している(矢印)．**B.** 治療開始 45 分で同血流速度は(健側と同程度まで)改善している(矢頭)．**C.** 治療前の MRA で右 M1 の閉塞を認める(矢印)．**D.** 治療後の MRA で右 M1 の再開通を認める．

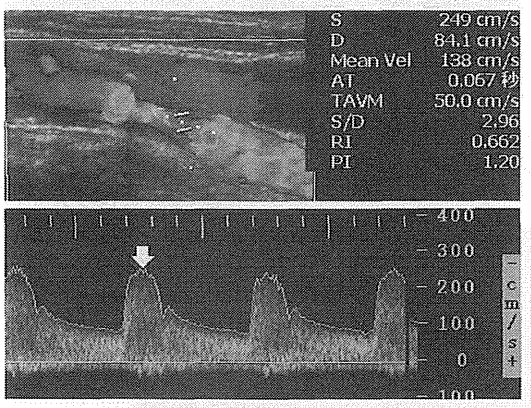

Fig. 4 頚部血管超音波による内頚動脈起始部狭窄診断
右内頚動脈起始部高度狭窄患者の頚部血管超音波所見．右内頚動脈起始部のカラードプラ像(上)と同部位でのパルスドプラによる血流速度波形(下)．収縮期最大血流速度 249 cm/s で高度狭窄の所見(矢印)．

療法前にルーチンで実施すること」を提言した．大動脈解離から波及する総頚動脈解離により脳梗塞を発症する場合には，頚部血管超音波により容易に診断可能である(**Fig. 1**)．特に，胸背部痛の存在や，四肢拍動触知不良，血圧左右差，胸部レントゲンによる上縦隔の拡大などがある場合には大動脈解離を疑い，必要に応じて胸部造影 CT を追加する．

前述したように内頚動脈閉塞は rt-PA 静注療法が奏効しにくく[6,11]，早期から診断できればその再開通の有無を評価しながら MERCI リトリーバーや PENUMBRA システムなどによる追加治療を検討する．頚部血管超音波では，内頚動脈起始部閉塞の場合には同部位から遠位部にかけてのカラードプラ完全消失，遠位部での閉塞は内頚動脈起始部での拡張末期血流消失(**Fig. 2**)として診断可能である[6]．遠位部閉塞の場合には心臓などからの塞栓性閉塞が多く，繰り返し血流速度を測定することが再開通のモニターに役立つ．

中大脳動脈水平部閉塞では，両側総頚動脈血流速度の拡張末期血流速度の左右比(健側/病側)が 1.3 を超えることが報告されており[13]，その閉塞と再開通の有無を評価できる可能性がある．閉塞部位が近位部か否かに関しては経頭蓋超音波や MRA などを組み合わせて評価する．経頭蓋超音波では血流波形や速度で中大脳動脈閉塞を診断し，その変化で再開通の有無を評価する(**Fig. 3**)．

内頚動脈起始部に高度狭窄(**Fig. 4**)[7]を伴うよう

なアテローム血栓性脳梗塞の場合には，rt-PA 静注療法が有効であっても，その後進行したり再発する可能性が高い．同療法後も積極的内科治療に加え内膜剝離術やステント留置術を含めた慎重な対応を検討する必要がある．

若年性の脳梗塞の原因として内頸動脈解離が重要であるが，rt-PA 静注療法の適否に関してはまだ結論は出ていない．頭頸部痛，下位脳神経麻痺やホルネル症候群を伴うようなテント上の脳梗塞の場合には，内頸動脈解離が原因となっている可能性があり，経口腔頸部血管超音波が診断に役立つ[8]．

超音波照射を併用した rt-PA 静注療法

2004 年に Alexandrov らが，rt-PA 静注療法時に経頭蓋ドプラを併用することにより，閉塞血管の再開通率が有意に改善することを CLOTBUST として報告した[2]．それ以来，超音波血栓溶解療法(sonothrombolysis)が注目されている．彼らは，超音波血栓溶解療法の有効性を示すために，検査者の技術によらない operator independent の経頭蓋超音波装置を開発し，多施設共同無作為介入試験である CLOTBUST-ER を 2012 年にも開始する．わが国では，東京慈恵会医科大学の古幡教授らが 500 kHz 連続波を用いた同療法を前臨床で評価してきた[3]．現在，簡便に装着できる治療用プローブを作成中であり，今後臨床評価が行われる予定である．

おわりに

rt-PA 静注療法の登場により，脳梗塞が救急疾患であることが広く認識されるようになってきた．救急の現場で，簡便に使用できる超音波検査を駆使することで rt-PA 静注療法時にも早期から血管病変の把握が可能であり，再開通現象の評価は追加治療の検討に役立つ．超音波血栓溶解療法は閉塞血管の rt-PA 静注療法の効果を促進する可能性が示されており，今後の臨床試験の結果が注目される．

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Admission hyperglycemia causes infarct volume expansion in patients with ICA or MCA occlusion: association of collateral grade on conventional angiography

T. Shimoyama[a], K. Shibazaki[a], K. Kimura[a], J. Uemura[a], T. Shiromoto[a], M. Watanabe[a], T. Inoue[a], Y. Iguchi[a] and S. Mochio[b]

[a]*Department of Stroke Medicine, Kawasaki Medical School, Kurashiki City Okayama; and* [b]*Department of Neurology, Jikei University School of Medicine, Tokyo, Japan*

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Background and purpose: Hyperglycemia (HG) is associated with infarct volume expansion in acute ischaemic stroke patients. However, collateral circulation can sustain the ischaemic penumbra and limit the growth of infarct volume. The aim of this study was to determine whether the association between HG and infarct volume expansion is dependent on collateral circulation.

Methods: We performed a retrospective analysis of 93 acute ischaemic stroke patients with internal carotid artery or middle cerebral artery occlusion within 24 h of onset were retrospectively studied. HG was diagnosed in patients with an admitting blood glucose value ≥140 mg/dl. Angiographic collateral grade 0–1 was designated as poor collateral circulation and grade 2–4 as good collateral circulation. Infarct volume was measured at admission and at again within 7 days using diffusion-weighted magnetic resonance images.

Results: Among 34 patients with poor collateral grade, the change in infarct volume was significantly greater in the HG group than in the non-HG group (106.0 ml vs. 22.7 ml, $P = 0.002$). Among the 59 patients with good collateral circulation, the change in infarct volume was greater in the HG group than in the non-HG group (53.3 ml vs. 10.9 ml, $P = 0.047$). Multiple regression analysis indicated that admission HG ($P = 0.004$), baseline National Institutes of Health Stroke Scale score ($P = 0.018$), and poor collateral circulation ($P = 0.040$) were independently associated with infarct volume expansion.

Conclusions: Infarct volume expansion was greater in individuals with HG on admission regardless of collateral circulation status.

Introduction

Hyperglycemia (HG) is common in acute ischaemic stroke patients, and often occurs without a preexisting diagnosis of diabetes [1]. Previous studies have shown that HG is associated with infarct volume expansion and poor outcomes in acute ischaemic stroke patients [2,3]. HG is thought to influence neuronal damage via the facilitation of lactic acid production in ischaemic tissue [2]. In animal studies, HG increases with oxidative stress and matrix metalloproteinase-9 activity and causes cerebral edema formation after ischaemia [4].

On the other hand, collateral circulation plays an important role in maintaining tissue viability during large vessel occlusion [5] and can limit infarct volume expansion and improve functional status in ischaemic stroke patients [5]. However, few previous studies have reported on collateral circulation grade in acute ischaemic stroke patients.

The aim of this study was to determine whether collateral circulation alters the relation between HG and the expansion of infarct volume and functional outcome in acute ischaemic stroke patients with internal carotid artery (ICA) or middle cerebral artery (MCA) occlusion.

Subjects and methods

Patients

Between April 2004 and July 2011, 426 acute ischaemic stroke patients with ICA or MCA occlusion were

Correspondence: T. Shimoyama, Department of Stroke Medicine, Kawasaki Medical School, 557 Matsushima, Kurashiki City Okayama 701-0192, Japan (tel.: +81 86 462 1111; fax: +81 86 4641128; e-mail: t.shimo0702@gmail.com).

admitted within 24 h of stroke onset according to our stroke registry. We retrospectively examined the records of patients who underwent conventional angiography. We excluded patients treated with intravenous tissue plasminogen activator (t-PA) or endovascular therapy, because early recanalization after thrombolysis should rescue the ischaemic penumbra and does not affect infarct volume expansion [6]. The protocol of this study was approved by the medical ethics committee of Kawasaki Medical School.

Clinical characteristics

Routine blood biochemistry, blood count, and electrocardiograph examinations were performed on admission. From these data, we obtained leukocyte, erythrocyte and platelet count, and hematocrit, plasma glucose and glycated hemoglobin levels. We classed patients as having HG if blood glucose levels were $\geq$140 mg/dl [7]. We also determined the presence of vascular risk factors including hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation. The ischaemic stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment criteria [8]. The severity of neurological deficits was graded on admission according to the National Institutes of Health Stroke Scale (NIHSS) [9].

Neuroimaging

Magnetic resonance imaging (MRI) was performed on admission (baseline) and within 7 days after admission (follow-up) using a 1.5-T Vision MRI (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI, USA). Diffusion-weighted imaging (DWI) MRI was used to determine infarct volume and T2* gradient echo MRI was used to determine the occurrence of hemorrhagic transformation at each time point. Two neurologists (T.S. and J.U.), who were blind to the clinical information, performed these evaluations. Infarct volume was quantified using image analysis software (NIH Image). The regions of hyperintense lesions were manually outlined on each slice, and multiplied by the slice thickness and inter-slice gap to obtain a volume measure. The window level and window width were chosen to obtain the best between the lesion and the normal surrounding tissue. The change in infarct volume (ΔInfarct) was considered the difference between baseline and follow-up MRI volumes (Fig. 1).

Hemorrhagic transformation was defined as the appearance of low intensity lesions that were at least partially in the ischaemic lesion on the follow-up image.

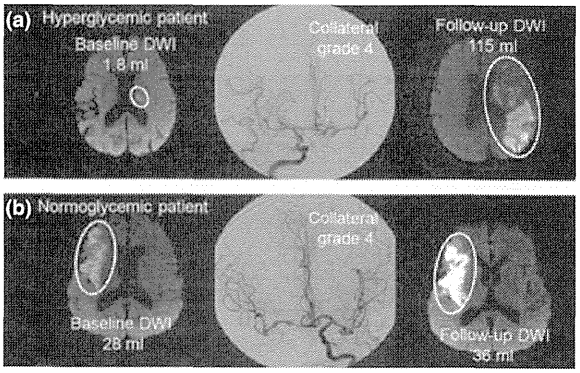

Figure 1 Representative diffusion weighted MRI at baseline (left) and follow-up (right) from a patient with HG (top panel; admission glucose level of157 mg/dl) and a patient without HG (bottom panel; admission glucose level 120 mg/dl). Both patients were classified as having good collateral circulation.

Magnetic resonance angiography (MRA) was performed on admission (baseline) and within 7 days after admission (follow-up) and used to identify spontaneous recanalization of the occluded arteries. Spontaneous recanalization was defined as complete (i.e., reappearance of the entire occluded artery and distal branches) or partial (i.e., resolution of part of the distal vessel supplied by an occluded artery) [10] on the follow-up MRA.

Conventional angiography

Conventional angiography included injection of both common carotid arteries and the dominant vertebral artery through the late venous phase. Two neurologists (T.S. and J.U.), who were blind to the clinical information, evaluated the collateral grade of occluded arteries according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System [11]. The grades assigned were 0) no collaterals visible to the ischaemic site, 1) slow collaterals to the periphery of the ischaemic site with persistence of some of the defect, 2) rapid collaterals to the periphery of the ischaemic site with persistence of some of the defect and to only a portion of the ischaemic territory, 3) collaterals with slow but complete angiographic blood flow of the ischaemic bed by the late venous phase, or 4) complete and rapid collateral blood flow to the vascular bed in the entire ischaemic territory by retrograde perfusion. Grades 0 and 1 were classified as poor collateral circulation, and grades 2–4 were classified as good collateral circulation [12]. The Kappa coefficient for inter-observer agreement was 0.817 for collateral grade.

Patient outcomes

Patient outcome was quantified using the modified Rankin Scale (mRS) score [13] at discharge. Poor outcome was defined as mRS score of 5 at discharge, or death during hospitalization.

Analysis

Patients were classified in the HG and non-HG groups according to admission glucose level. Patient characteristics were compared across these two groups using a Mann–Whitney U test for continuous variables and a chi-squared test for categorical variables. The primary outcome variables were ΔInfarct and the patient outcome. The secondary outcome measures were the presence or absence of spontaneous recanalization and hemorrhagic transformation.

Patients were further divided according to collateral circulation (poor; good). The primary outcome variables (ΔInfarct and patient outcome) were compared among four subgroups according to admission glucose level (HG; non-HG) and collateral circulation (poor; good).

Multiple regression analysis was performed to identify variables that predicted ΔInfarct. Regression models included HG status (HG; non-HG), collateral circulation grade (poor; good), and other potentially predictive variables (NIHSS score, baseline infarct volume, spontaneous recanalization, hemorrhagic transformation and past history of hypertension).

Statistical analyses were carried out using Statistical Package for the Social Science (SPSS version 17.0) software for Windows (SPSS, Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation in the text and tables. Values of $P < 0.05$ were considered statistically significant.

Results

Of the 426 acute ischaemic stroke patients examined, 176 underwent conventional angiography. Of these 176 patients, we excluded 45 patients treated with endovascular therapy, 23 patients treated with intravenous t-PA and seven patients treated with combined endovascular and intravenous t-PA therapy. We also excluded four patients with pacemakers, three patients who did not undergo follow-up MRI because of severe stroke and one patient who did not undergo complete conventional angiography. The remaining 93 patients (65 men, age 67.7 ± 13.3 years) formed the sample for this study. There were 52 patients with ICA occlusion, 23 patients with M1 occlusion, and 18 patients with M2 occlusion (Table 1).

Table 1 Clinical characteristics and outcomes in the HG and non-HG groups

	HG group (n = 50)	non-HG group (n = 43)	P
Age (years)	68.5 ± 13.9	66.2 ± 13.3	0.500
Male, n (%)	35 (70.0)	30 (69.8)	1.000
Risk factors, n (%)			
Hypertension	45 (90.0)	25 (58.1)	0.001
Hyperlipidemia	10 (20.0)	16 (37.2)	0.104
Diabetes mellitus	23 (46.0)	6 (14.0)	0.001
Atrial fibrillation	19 (38.0)	9 (20.9)	0.112
Laboratory data			
Leukocytes (per μl)	7766.0 ± 2264.7	7252.1 ± 1796.5	0.363
Erythrocytes (× 10 000/μl)	434.3 ± 64.6	434.4 ± 50.0	0.994
Hematocrit (%)	39.5 ± 6.4	40.3 ± 5.0	0.450
Platelets (× 10 000/μl)	20.7 ± 5.2	21.7 ± 7.5	0.929
Glucose (mg/dl)	188.2 ± 67.8	114.3 ± 15.2	<0.001
HbA1c (%)	6.3 ± 1.3	5.6 ± 0.5	<0.001
Stroke type, n (%)			
Cardioembolic stroke	20 (40.0)	17 (39.5)	1.000
Large vessel disease	17 (34.0)	16 (37.2)	0.829
Others or undetermined stroke	13 (26.0)	10 (23.3)	0.813
Time from symptom onset to initial MRI (h)	5.4 ± 4.8	5.4 ± 5.0	0.761
Interval between initial and follow-up MRI (days)	4.5 ± 2.6	4.1 ± 2.4	0.437
Time from symptom onset to conventional angiography (h)	27.5 ± 43.5	29.6 ± 50.4	0.945
Occluded artery, n (%)			
ICA	27 (54.0)	25 (58.1)	0.834
M1	14 (28.0)	9 (20.9)	0.478
M2	9 (18.0)	9 (20.9)	0.795
Infarct volume (ml)			
Baseline	32.8 ± 65.3	36.3 ± 63.0	0.627
Follow-up	103.0 ± 116.6	52.1 ± 77.3	0.056
Δ(follow-up − baseline)	70.1 ± 86.4	15.8 ± 40.0	0.001
Spontaneous recanalization, n (%)	6 (12.0)	16 (37.2)	0.004
Hemorrhagic transformation, n (%)	12 (24.0)	9 (20.9)	0.806
Baseline NIHSS score	10.7 ± 7.9	8.2 ± 6.8	0.133
Poor outcome, n (%)	22 (44.0)	8 (18.6)	0.014

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale. MRI, magnetic resonance imaging; ICA, internal carotid artery; M1,M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery.

HG

Fifty patients (53.8%) were classified in the HG group and 43 patients (46.2%) in the non-HG group. The clinical characteristics and outcome variables for both

groups are shown in Table 1. Hypertension and diabetes mellitus were more prevalent in the HG group than in non-HG group (90.0% vs. 58.1%, $P = 0.001$ for hypertension and 46.0% vs. 14.0%, $P = 0.001$ for diabetes mellitus). Glycated hemoglobin level was higher in the HG group than in the non-HG group (6.3 ± 1.3% vs. 5.6 ± 0.5%, $P < 0.001$). The baseline infarct volume was similar in the two groups (32.8 ± 65.3 ml vs. 36.3 ± 63.0 ml, $P = 0.627$), as was the interval between baseline and follow-up MRI (4.5 ± 2.6 days vs. 4.1 ± 2.4 days; $P = 0.437$). ΔInfarct was larger in the HG group than in non-HG group (70.1 ± 86.4 ml vs. 15.8 ± 40.0 ml, $P = 0.001$) and poor outcome at discharge was more common (44.0% vs. 18.6%, $P = 0.014$). Spontaneous recanalization was less frequent in the HG group than in the non-HG group (12.0% vs. 37.2%, $P = 0.004$); however, hemorrhagic transformation was similar (24.0% vs. 20.9%, $P = 0.806$).

Collateral grade

Thirty-four patients (36.6%) were classified as having poor collateral circulation and 59 patients (63.4%) as having good collateral circulation. The clinical characteristics and outcome variables for both groups are shown in Table 2. Hypertension and hyperlipidemia were more prevalent in patients with good collateral circulation than in patients with poor collateral circulation (83.1% vs. 61.8%, $P = 0.027$ for hypertension and 37.3% vs. 11.8%, $P = 0.009$ for hyperlipidemia). Atrial fibrillation was more prevalent in patients with poor collateral circulation than in patients with good collateral circulation (44.1% vs. 22.0%, $P = 0.035$). There was a higher prevalence of cardioembolic strokes (61.8% vs. 27.1%, $P = 0.002$) and a lower rate of large vessel disease (14.7% vs. 47.5%, $P = 0.002$) in patients with poor collateral circulation, and a lower rate of ICA occlusion (32.4% vs. 69.5%, $P = 0.001$). The severity of neurological deficits was also greater in patients with poor collateral circulation (NIHSS score; 11.4 ± 6.2 vs. 8.4 ± 7.9, $P = 0.026$).

Infarct volume was larger in patients with poor collateral circulation (63.9 ± 86.2 ml vs. 17.5 ± 38.1 ml, $P < 0.001$ at baseline, and 125.8 ± 127.4 ml vs. 52.8 ± 75.0 ml, $P = 0.001$ at follow-up), and ΔInfarct was similar across groups (61.9 ± 89.5 ml vs. 35.3 ± 61.8 ml, $P = 0.089$). Spontaneous recanalization and hemorrhagic transformation were more frequent in the poor collateral group than the good collateral group (41.2% vs. 13.6%, $P = 0.005$ for spontaneous recanalization and 35.3% vs. 15.3%, $P = 0.039$ for hemorrhagic transformation). The frequency of poor outcome was similar in the two groups (41.2% vs. 27.1%, $P = 0.175$).

Table 2 Clinical characteristics and outcomes of patients with poor collateral circulation and patients with good collateral circulation

	Poor collateral ($n = 34$)	Good collateral ($n = 59$)	P
Age (years)	69.0 ± 12.8	66.5 ± 14.1	0.219
Male, *n* (%)	21 (61.8)	44 (74.6)	0.242
Risk factors, *n* (%)			
Hypertension	21 (61.8)	49 (83.1)	0.027
Hyperlipidemia	4 (11.8)	22 (37.3)	0.009
Diabetes mellitus	7 (20.6)	22 (37.3)	0.109
Atrial fibrillation	15 (44.1)	13 (22.0)	0.035
Laboratory data			
Leukocytes (per μl)	7355.3 ± 1668.0	7628.1 ± 2272.6	0.895
Erythrocytes (× 10 000/μl)	422.3 ± 59.8	441.3 ± 56.3	0.080
Hematocrit (%)	39.6 ± 5.8	40.1 ± 5.8	0.836
Platelets (× 10 000/μl)	21.0 ± 5.8	21.3 ± 6.7	0.943
Glucose (mg/dl)	147.4 ± 43.4	157.9 ± 71.5	0.753
HbA1c (%)	5.8 ± 0.7	6.0 ± 1.3	0.506
Stroke type, *n* (%)			
Cardioembolic stroke	21 (61.8)	16 (27.1)	0.002
Large vessel disease	5 (14.7)	28 (47.5)	0.002
Others or undetermined stroke	8 (23.5)	15 (25.4)	1.000
Time from symptom onset to initial MRI (h)	5.3 ± 5.6	5.5 ± 5.4	0.274
Interval between initial and follow-up MRI (days)	4.1 ± 2.6	4.5 ± 2.5	0.493
Time from symptom onset to conventional angiography (h)	23.8 ± 43.4	31.2 ± 48.4	0.283
Occluded artery, *n* (%)			
ICA	11 (32.4)	41 (69.5)	0.001
M1	9 (26.5)	14 (23.7)	0.806
M2	14 (41.2)	4 (6.8)	<0.001
Infarct volume (ml)			
Baseline	63.9 ± 86.2	17.5 ± 38.1	<0.001
Follow-up	125.8 ± 127.4	52.8 ± 75.0	0.001
Δ(follow-up - baseline)	61.9 ± 89.5	35.3 ± 61.8	0.089
Spontaneous recanalization, *n* (%)	14 (41.2)	8 (13.6)	0.005
Hemorrhagic transformation, *n* (%)	12 (35.3)	9 (15.3)	0.039
Baseline NIHSS score	11.4 ± 6.2	8.4 ± 7.9	0.026
Poor outcome, *n* (%)	14 (41.2)	16 (27.1)	0.175

NIHSS, National Institutes of Health Stroke Scale. MRI, magnetic resonance imaging; ICA, internal carotid artery; M1,M1 segment of middle cerebral artery; M2, M2 segment of middle cerebral artery.

Hyperglycemia and collateral grade

Table 3 shows infarct volume and patient outcome between poor and good collateral circulation in the HG group and non-HG group. Of the 50 patients in the HG

Table 3 Infarct volume and patient outcome between poor and good collateral circulation in the HG group and non-HG group

	HG group (n = 50)			Non-HG group (n = 43)		
	Poor collateral (n = 16)	Good collateral (n = 34)	P	Poor collateral (n = 18)	Good collateral (n = 25)	P
Infarct volume (ml)						
Baseline	66.2 ± 93.7	17.1 ± 39.2	0.002	61.8 ± 81.5	17.9 ± 37.2	0.010
Follow-up	172.2 ± 138.6	70.4 ± 89.7	0.005	84.5 ± 103.6	28.8 ± 37.2	0.085
Δ(follow-up – baseline)	106.0 ± 101.4	53.3 ± 74.1	0.018	22.7 ± 54.9	10.9 ± 24.4	0.730
Spontaneous recanalization, n (%)	4 (25.0)	2 (5.9)	0.074	10 (55.6)	6 (24.0)	0.055
Hemorrhagic transformation, n (%)	5 (31.3)	7 (20.6)	0.486	7 (38.9)	2 (8.0)	0.023
Baseline NIHSS score	13.3 ± 6.5	9.5 ± 8.2	0.116	9.7 ± 5.7	7.0 ± 7.4	0.084
Poor outcome, n (%)	9 (56.3)	13 (38.2)	0.360	5 (27.8)	3 (12.0)	0.247

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale.

group, 16 had poor collateral circulation and 34 had good collateral circulation. Infarct volume was larger in hyperglycemic patients with poor collateral circulation than in HG patients with good collateral circulation (66.2 ± 93.7 ml vs. 17.1 ± 39.2 ml, P = 0.002 at baseline and 172.2 ± 138.6 ml vs. 70.4 ± 89.7 ml, P = 0.005 at follow-up), as was ΔInfarct (106.0 ± 101.4 ml vs. 53.3 ± 74.1 ml, P = 0.018).

Of the 43 patients in the non-HG group, 18 had poor collateral circulation and 25 had good collateral circulation. Infarct volume at baseline was larger in non-hyperglycemic patients with poor collateral circulation than in non-hyperglycemic patients with good collateral circulation (61.8 ± 81.5 ml vs. 17.9 ± 37.2 ml, P = 0.010); however, infarct volume at follow-up was similar in the two groups (84.5 ± 103.6 ml vs. 28.8 ± 37.2 ml, P = 0.085). However, ΔInfarct was not statistically different (22.7 ± 54.9 ml vs. 10.9 ± 24.4 ml, P = 0.730).

Table 4 shows infarct volume and patient outcome between the HG group and non-HG group in poor and good collateral circulation. Of the 34 patients with poor collateral circulation, 16 were in the HG group and 18 were in the non-HG group. Of the 59 patients with good collateral circulation, 34 were in the HG group and 25 were in the non-HG group. Infarct volume at baseline was similar in the HG and non-HG groups, regardless of collateral circulation status (66.2 ± 93.7 ml vs. 61.8 ± 81.5 ml, P = 0.746 for patients with poor collateral circulation and 17.1 ± 39.2 ml vs. 17.9 ± 37.2 ml, P = 0.569 for patients with good collateral circulation). Among patients with poor collateral circulation, ΔInfarct was larger in the HG group than in the non-HG group (106.0 ± 101.4 ml vs. 22.7 ± 54.9 ml, P = 0.002), but the prevalence of poor outcome at discharge was similar (56.3% vs. 27.8%, P = 0.163). Among patients with good collateral circulation, ΔInfarct was also larger in the HG group than in the non-HG group (53.3 ± 74.1 ml vs. 10.9 ± 24.4 ml, P = 0.047) and poor outcome at discharge was more common (38.2% vs. 12.0%, P = 0.038).

Table 5 shows results of the multiple regression analysis of infarct volume change. Admission HG (P = 0.004), poor collateral circulation (P = 0.040), and baseline NIHSS score (P = 0.018) were independently associated with infarct volume expansion.

Table 4 Infarct volume and patient outcome between the HG group and non-HG group in poor and good collateral circulation

	Poor collateral (n = 34)			Good collateral (n = 59)		
	HG group (n = 16)	Non-HG group (n = 18)	P	HG group (n = 34)	Non-HG group (n = 25)	P
Infarct volume (ml)						
Baseline	66.2 ± 93.7	61.8 ± 81.5	0.746	17.1 ± 39.2	17.9 ± 37.2	0.569
Follow-up	172.2 ± 138.6	84.5 ± 103.6	0.036	70.4 ± 89.7	28.8 ± 37.2	0.206
Δ(follow-up – baseline)	106.0 ± 101.4	22.7 ± 54.9	0.002	53.3 ± 74.1	10.9 ± 24.4	0.047
Spontaneous recanalization, n (%)	4 (25.0)	10 (55.6)	0.092	2 (5.9)	6 (24.0)	0.061
Hemorrhagic transformation, n (%)	5 (31.3)	7 (38.9)	0.729	7 (20.6)	2 (8.0)	0.278
Baseline NIHSS score	13.3 ± 6.5	9.7 ± 5.7	0.135	9.5 ± 8.2	7.0 ± 7.4	0.190
Poor outcome, n (%)	9 (56.3)	5 (27.8)	0.163	13 (38.2)	3 (12.0)	0.038

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale.

Table 5 Multiple regression analysis of factors related to infarct volume expansion

	R^2	P
Admission HG	0.269	0.004
Baseline NIHSS score		0.018
Poor collateral		0.040
Spontaneous recanalization		0.073
Baseline infarct volume		0.339
Hemorrhagic transformation		0.482
Hypertension		0.571

HG, hyperglycemia; NIHSS, National Institutes of Health Stroke Scale.

Discussion

In this study, we retrospectively examined the medical records of acute ischaemic stroke patients and found that admission HG was associated with infarct expansion and poor outcome. These findings are consistent with previous reports [2,3]. The novel finding of this study is that admission HG is associated with infarct expansion regardless of collateral circulation status. This was confirmed by multiple regression analysis, where admission HG was independently associated with infarct expansion, regardless of collateral circulation grade and other factors. However, poor collateral circulation might not adversely affect infarct volume expansion in the non-HG group. Spontaneous recanalization occurred less frequently in patients with HG and good collateral circulation.

Our results show that admission HG is an important determinant of infarct expansion, even in patients with good collateral circulation. Only one previous report has examined the relationship between HG and infarct expansion at the same time as evaluating collateral circulation, and these authors found that serum glucose levels did not influence infarct size when collateral circulation was accounted for [14]. However, infarct expansion was evaluated using computer tomography, and angiographic findings were classified according to the presence or absence of collateral circulation rather than by detailed collateral grade. To the best of our knowledge, this study is the first to demonstrate the association between HG and infarct expansion according to collateral grade assessed using conventional angiography.

Collateral circulation plays a key role in maintaining tissue viability and rescues the ischaemic penumbra [5]. When collateral circulation was present, infarct volume was more strongly affected in patients with diabetics than patients with no diabetics [14]. The relation between HG and infarct expansion has been demonstrated in the available collateral circulation. Prado *et al.* [15] reported that cortical infarct regions are vulnerable to the deleterious effects of HG in the presence of collateral circulation, whereas striatum infarct regions are not. Variations in collateral circulation anatomy may be associated with infarct volume expansion in HG patients with good collateral circulation. There is limited accuracy in the evaluation of collateral circulation for end-arterial vascular territories by conventional angiography [5]. On the other hand, cortical circulation supplied by leptomeningeal collaterals is insufficient to sustain adequate cerebral perfusion pressure [16]. Therefore, HG may reduce pial collateral circulation and lead to cortical infarct volume expansion in patients with good collateral circulation.

Poor collateral circulation is insufficient to sustain cerebral perfusion in the penumbra and increased infarct volume [5]. In animal models, cerebral circulation in the penumbra is more reduced in the acute hyperglycemic state [17]. Therefore, HG may accelerate the reduction in cerebral circulation in the penumbra and lead to marked infarct expansion with poor collateral circulation. We found that poor collateral circulation affected infarct volume expansion in the HG group, but not in the non-HG group. These findings may support the hypothesis that HG causes fatal tissue damage in cases of poor collateral circulation. Previous reports showed that hemorrhagic transformation [12] and infarct growth [18] were more frequently observed in patients with poor collateral circulation, if recanalization has been achieved following endovascular therapy. Thus, management of HG may be a therapeutic option to limit infarct volume expansion in patients with poor collateral circulation.

Spontaneous recanalization occurred less frequently in patients with HG. This may be due to accelerated procoagulant activity in patients with HG [19]. A recent study demonstrated that acute HG decreased plasma fibrinolytic activity in rats and that this was associated with increased plasminogen activator inhibitor type 1 activity and decreased plasma t-PA activity [20]. The acute hyperglycemic state may hamper the fibrinolytic process, delaying reperfusion of the ischaemic penumbra in tPA-treated patients [21]. Delayed recanalization should rescue the ischaemic penumbra, but HG might not adversely affect patient outcome to the same extent as in patients without delayed recanalization [3]. The interval between baseline and follow-up MRIs in this study precluded assessment of early recanalization. Therefore, we did not observe any difference in spontaneous recanalization between patient outcomes in the two groups. Prospective studies that include detailed coagulant markers and a strict protocol of follow-up MRIs are needed to confirm our hypothesis.

We found that spontaneous recanalization was less frequent in patients with good collateral circulation. This differs from one previous report that angiographic collateral grade determined the recanalization rate after endovascular revascularization therapy [18]. In the present study, cardioembolic stroke was less frequent and large vessel occlusion was more frequent in patients with good collateral circulation. Moreover, ICA occlusion was more frequent in these patients. Kimura *et al.* [22] reported that the recanalization rate of ICA occlusions was lower than that of MCA occlusions after intravenous t-PA therapy. Differences in stroke etiology and the occluded artery may affect the rate of spontaneous recanalization and its relation to collateral circulation.

This present study is limited by the retrospective design. Patients were classified into HG and non-HG groups according to blood glucose levels measured at a single time point, whereas classification is more accurate with serial blood glucose measures. We did not perform perfusion weighted imaging. Although diffusion-perfusion mismatch volume is not dependent on collateral grade [23], evaluation of penumbral volume alongside angiographic collateral grade may provide new insights about the harmful effects of HG. Finally, the number of patients studied was small, and a larger sample is needed to more rigorously test our hypothesis.

In conclusion, admission HG was associated with infarct volume expansion and poor outcome in patients with ICA or MCA occlusion. Moreover, admission HG influenced infarct volume expansion regardless of collateral circulation.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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