TABLE 5

Incidence of complications and DW MR imaging abnormalities after carotid revascularization, according to the CEA risk grade, surgical procedure, and presentation

	No. of Cases/Subgroup Total (%)					
	Symptomatic			Asymptomatic		
CEA Risk Grade	CEA	CASP	p Value	CEA	CASP	p Value
incidence of ischemic neurological complications						
I	0/37 (0)	0/11 (0)	0.229	0/26 (0)	1/21 (4.8)	0.366
II	0/11 (0)	0/3 (0)	—	0/4 (0)	1/7 (14.3)	1.000
III	1/25 (4.0)	2/16 (12.5)	0.550	1/17 (5.9)	3/31 (9.7)	1.000
incidence of new abnormalities on DW MR imaging						
I	2/37 (5.4)	4/11 (36.4)	0.019	0/26 (0)	2/21 (9.5)	0.194
II	0/11 (0)	1/3 (33.3)	0.214	0/4 (0)	3/7 (42.9)	0.506
III	1/25 (4.0)	8/16 (50.0)	0.001	2/17 (11.8)	14/31 (45.2)	0.026

dence in the Grade I risk group. Because of the small number of Grade IV cases treated with CASP, the incidence rate for lesions in this group seems to be unreliable.

Authors of a recent prospective study showed that DW MR imaging detects asymptomatic bright lesions at a significant rate even after diagnostic angiography, which is a much less invasive and time-consuming procedure than CASP. The rates of lesion appearance are related to the vascular risk profile,[6] suggesting the presence of a baseline risk of embolization during catheterization of supraaortic vessels. Data from several ex vivo studies have demonstrated the risk of embolism at various stages of CA angioplasty and stent insertion, even showing an increase in the size and number of particles as the procedure proceeds from guidewire and catheter passage to angioplasty with or without stent placement.[12,29] Authors of a systematic review of the early outcome after CASP reported a reduction in thromboembolic complications during the procedure from 4.8% without protection to 0.8% with protection.[22] There was no substantial decrease in ischemic events in CASP II compared with those in CASP I, suggesting the presence of a significant risk of embolism during placement of the guiding catheter and lesion crossing by the distal balloon catheter, especially in the Grade III risk group. The risk of particulate emboli to the brain during catheterization is increased in older patients with friable atherosclerotic walls and tortuous stenosis at the carotid bifurcation. In fact, results of a previous study showed that an age of 80 or more years was the best predictor of stroke (30 days posttreatment) and death after CASP.[30] Regarding cardiac comorbidity, atherosclerosis develops earlier in the coronary arteries than in the carotid and peripheral arteries.[21] A high incidence of lesions on imaging even in the CASP II group of patients with a Grade III risk may be explained by the presence of more advanced atherosclerosis along the access route because of an advanced age and coexistent coronary and peripheral vascular risk factors. Considering the results of the study on stenting and angioplasty with protection in patients at high risk for endarterectomy (SAPPHIRE), the indications for CASP in treating NASCET-ineligible cases of high-risk CA stenosis are now expanding.[38] However, data in the present study showed that the preoperative assessment of severe atherosclerotic change along the access route, especially in the aortic arch, is mandatory when considering CASP in high-risk patients, especially those with a Grade III risk.

Results Based on Symptomatic and Asymptomatic Presentations

The findings of randomized large trials led to the creation of guidelines indicating that after CEA the expected rate of stroke 30 days posttreatment and death in patients with symptomatic or asymptomatic CA stenosis should be lower

TABLE 6

*Summary of cases with periprocedural nondisabling stroke after CASP**

Age (yrs), Sex	Presentation	CEA Risk Grade	Risk Profile/Specific Cause of Stroke
64, M	A	I	bilat severe stenosis, echolucent plaque/in-stent thrombosis, MCA thromboembolism†
69, M	A	II	contralat ICAO, tandem stenosis, misery perfusion/thrombosis at proximal edge‡
69, M	S	III	contralat ICAO, PVD, long segment CCA stenosis, echolucent plaque/dissection at distal edge, hypotension
69, M	A	III	siphon stenosis, AP, echolucent plaque, CASP before CABG
73, M	A	III	AP, SMI, echogenic calcified plaque, off-pump bypass before CASP, complicated plaque at aortic arch
74, M	A	III	AP, thoracic aortic aneurysm, CASP before total arch replacement & CABG
79, F	S	III	SMI, DM, female, PCI before CASP, progressive stenosis of CCA/placement of guiding catheter

* A = asymptomatic; AP = angina pectoris; MCA = middle cerebral artery; PCI = percutaneous coronary intervention; S = symptomatic; SMI = silent myocardial ischemia.

† Successfully treated with percutaneous transluminal angioplasty and intraarterial infusion of urokinase.

‡ Additional stenting was performed to cover the proximal edge of the primary stent.

TABLE 7
Nonneurological complications in patients assigned to each treatment group

Complication	No. (%)		p Value
	CEA	CASP	
no. of patients	139	92	
AP	3 (2.2)	2 (2.2)	1.000
congestive heart failure	0	1 (1.1)	0.398
cholesterol embolism	0	1 (1.1)	0.398
cranial nerve injury	7 (5.0)	0	0.044*
permanent	1 (0.7)	0	1.000
deep venous thrombosis	2 (1.4)	0	0.519
hypotension/bradycardia	2 (1.4)	11 (12.0)	<0.001*
pseudoaneurysm	1 (0.7)	0	1.000
respiratory distress	1 (0.7)	0	1.000
renal failure	0	1 (1.1)	0.398
wound/groin hematoma	6 (4.3)	2 (2.2)	0.482

* Statistically significant (Fisher exact test).

than 6 and 3%, respectively.[8] One of the major limitations of the grading system by Sundt and colleagues is that it does not consider the surgical risk separately for symptomatic and asymptomatic patients.[33] Furthermore, it excludes patients with recurrent stenosis post-CEA, because of the extremely high surgical risk. Results of our subgroup analysis confirmed that ischemic neurological morbidity rates and the incidence of DW imaging abnormalities after CEA and CASP were similar based on the risk grading system, regardless of the mode of presentation. Notably, the risk of CASP in asymptomatic patients with vascular and medical risk profiles is virtually the same as that in symptomatic patients and exceeds the risk recommended by the American Heart Association.[8] This finding may support our hypothesis that more advanced atherosclerosis along the access route, which is caused by an advanced patient age and coexistent vascular risk factors, may play a role in the development of embolic events in CASP; intuitively, a lesion crossing asymptomatic plaque has less potential of embolizing than one crossing symptomatic plaque. A lower profile, or smaller caliber, stent system may improve the results in such high-risk patients. Given the previously reported unfavorable results of CEA for recurrent stenosis post-CEA,[27] such cases were exclusively treated with CASP in the present study and classified into the risk grading system based on other factors. Carotid artery stent placement for recurrent stenosis post-CEA was not associated with any morbidity or DW imaging abnormalities, suggesting the benefits of CASP in cases of high surgical risk with less embolic potential, although the benefit of revascularization in asymptomatic cases remains uncertain.

Importance and Limitations of This Study

Detailed analysis of neurological ischemic complications offers important information regarding the safety of CASP in patients with different surgical risks. Authors of previous studies have reported several patient characteristics and angiographic features as high risk for CASP. Characteristics such as an advanced age of 80 or more years, uncontrolled hypertension, a recent symptomatic stroke, renal insufficiency, unforgiving hemodynamic status (neurologically unstable conditions due to misery perfusion) as well as some angiographic risk factors such as thrombus, in general, also confer increased risk for CEA. Nonetheless, some of the angiographic risk factors are unique to CASP. Tortuosity or extensive atherosclerosis of the aorta, severity of stenosis and lesion size (> 10 mm), kinks and tortuosity of the internal CA, echolucent plaque, and dense concentric calcification of the lesion confer increased risk for CASP.[14] As in these reports, most of our complicated cases had several vascular and medical risk profiles that made CASP high risk even for asymptomatic stenosis. In complicated cases in the baseline risk group (Grade I), specific causes such as acute thrombosis played a major role in assigning patients to a particular treatment group. These results showed that patients in the Grades II and III groups, considered high surgical risk groups, also had a greater risk of adverse consequences from CASP even with an asymptomatic presentation, and that meticulous periprocedural management is especially important in these patients.

Nonneurological complications after CEA and CASP deserve some mention. Myocardial infarction and cardiac dysrhythmia are the main causes of death following CEA. Notably, there was no intra- or postoperative myocardial infarction in the present study, including the NASCET-ineligible cases (20.3%). This excellent outcome regarding medical complications may be attributable to the fact that CASP was indicated mainly in patients with high medical risk profiles. Carotid endarterectomy involves an inherent risk of cranial nerve palsy although most cases are transient and mild.[16] In the present study, permanent cranial nerve palsy was noted in only one case (0.7%) treated with CEA. In contrast, CASP, especially in cases involving vascular or medical risk profiles, can cause a cholesterol embolism (the embolization of cholesterol crystals from atherosclerotic plaques of the aorta or large arteries), which may cause serious problems such as acute renal failure with a high mortality rate of 64 to 87%.[19,31]

Although the role of CASP in high-risk NASCET-ineligible patients was established especially in symptomatic cases,[38] there remains much controversy regarding its place in an unselected population with CA stenosis. Results of the present study offer insight into the mechanisms of the neurological complications in patients with various risk profiles and provide valuable information regarding patient selection for CEA and CASP based on the well-established CEA risk grading system. Although distal protection was applied during the procedure in all CASP cases in the present study, total protection using the modern distal protection device (GuardWire Plus) was performed in only one fourth (CASP II) of the cases. A preliminary comparison between CASP I and II indicated similar revascularization risk profiles based on the risk grading system, despite the overall lower complication rates in the latter group of treated cases. Nonetheless, additional studies are necessary to determine whether such revascularization risk profiles for CASP, as based on the CEA risk grading system, can be generalized to a greater number of cases also treated with total protection using the modern distal protection device.

Conclusions

Data in this study provide a unique opportunity to compare the results of CEA and CASP among patients with dif-

ferent CEA risk grades and with symptomatic or asymptomatic presentations (separately) by using neurological complication rates and the incidence of lesions on DW MR imaging as outcome measures. Despite a higher incidence of ischemic lesions in the Grade IV risk group, there was no significant association between the risk grade and neurological morbidity rates after CEA. Vascular (Grade II) and medical (Grade III) risk profiles were associated with a higher incidence of neurological morbidity and ischemic lesions on DW MR imaging after CASP, in addition to the baseline risk (Grade I), regardless of the presentation (symptomatic or asymptomatic). Recurrent stenosis post-CEA is a sound indication for CASP given the associated low incidence of neurological morbidity and DW imaging abnormalities. However, CASP should be considered carefully in asymptomatic patients with a medical risk profile. Considering that no serious nonneurological complications were noted in the present study, CEA and CASP appear to be complementary methods of revascularization for CA stenosis with various risk profiles at the present developmental stage of distal protection techniques.

References

1. Anonymous: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. **N Engl J Med 325:**445–453, 1991
2. Anonymous: Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. **JAMA 273:**1421–1428, 1995
3. Anonymous: MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. **Lancet 337:**1235–1243, 1991
4. Anonymous: Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). **Lancet 351:**1379–1387, 1998
5. Ascher E, Hingorani A: Changing characteristics of carotid endarterectomy. **Ann Vasc Surg 15:**275–280, 2001
6. Bendszus M, Koltzenburg M, Burger R, Warmuth-Metz M, Hofmann E, Solymosi L: Silent embolism in diagnostic cerebral angiography and neurointerventional procedures: a prospective study. **Lancet 354:**1594–1597, 1999
7. Biasi GM, Froio A, Diethrich EB, Deleo G, Galimberti S, Mingazzini P, et al: Carotid plaque echolucency increases the risk of stroke in carotid stenting: the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study. **Circulation 110:**756–762, 2004
8. Biller J, Feinberg WM, Castaldo JE, Whittemore AD, Harbaugh RE, Dempsey RJ, et al: Guidelines for carotid endarterectomy: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. **Stroke 29:**554–562, 1998
9. Bond R, Rerkasem K, Rothwell PM: Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. **Stroke 34:**2290–2301, 2003
10. CARESS Steering Committee: Carotid revascularization using endarterectomy or stenting systems (CARESS): phase I clinical trial. **J Endovasc Ther 10:**1021–1030, 2003
11. Cheung RT, Eliasziw M, Meldrum HE, Fox AJ, Barnett HJ, et al: Risk, types, and severity of intracranial hemorrhage in patients with symptomatic carotid artery stenosis. **Stroke 34:**1847–1851, 2003
12. Coggia M, Goeau-Brissonniere O, Duval JL, Leschi JP, Letort M, Nagel MD: Embolic risk of the different stages of carotid bifurcation balloon angioplasty: an experimental study. **J Vasc Surg 31:** 550–557, 2000
13. Cunningham EJ, Bond R, Mehta Z, Mayberg MR, Warlow CP, Rothwell PM, et al: Long-term durability of carotid endarterectomy for symptomatic stenosis and risk factors for late postoperative stroke. **Stroke 33:**2658–2663, 2002
14. Dieter RS, Laird JR: Defining and minimizing the risk of complications during carotid artery interventions, in Henry M, Ohki T, Polydorou A, et al. (eds): **Angioplasty and Stenting of the Carotid and Supra-Aortic Trunks.** London: Martin Dunitz, 2004, pp 391–404
15. Featherstone RL, Brown MM, Coward LJ, ICSS Investigators: International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. **Cerebrovasc Dis 18:**69–74, 2004
16. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al: The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. **Stroke 30:**1751–1758, 1999
17. Fox AJ: How to measure carotid stenosis. **Radiology 186:** 316–318, 1993
18. Gray-Weale AC, Graham JC, Burnett JR, Byrne K, Lusby RJ: Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. **J Cardiovasc Surg (Torino) 29:**676–681, 1988
19. Hagiwara N, Toyoda K, Nakayama M, Inoue T, Yasumori K, Ibayashi S, et al: Renal cholesterol embolism in patients with carotid stenosis: a severe and underdiagnosed complication following cerebrovascular procedures. **J Neurol Sci 222:**109–112, 2004
20. Hobson RW II: CREST (Carotid Revascularization Endarterectomy versus Stent Trial): background, design, and current status. **Semin Vasc Surg 13:**139–143, 2000
21. Joseph A, Ackerman D, Talley JD, Johnstone J, Kupersmith J: Manifestations of coronary atherosclerosis in young trauma victims—an autopsy study. **J Am Coll Cardiol 22:**459–467, 1993
22. Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB: Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. **Stroke 34:**813–819, 2003
23. Malek AM, Higashida RT, Phatouros CC, Lempert TE, Meyers PM, Smith WS, et al: Stent angioplasty for cervical carotid artery stenosis in high-risk symptomatic NASCET-ineligible patients. **Stroke 31:**3029–3033, 2000
24. Mathur A, Roubin GS, Iyer SS, Piamsonboon C, Liu MW, Gomez CR, et al: Predictors of stroke complicating carotid artery stenting. **Circulation 97:**1239–1245, 1998
25. McCrory DC, Goldstein LB, Samsa GP, Oddone EZ, Landsman PB, Moore WS, et al: Predicting complications of carotid endarterectomy. **Stroke 24:**1285–1291, 1993
26. Mericle RA, Kim SH, Lanzino G, Lopes DK, Wakhloo AK, Guterman LR, et al: Carotid artery angioplasty and use of stents in high-risk patients with contralateral occlusions. **J Neurosurg 90:** 1031–1036, 1999
27. Meyer FB, Piepgras DG, Fode NC: Surgical treatment of recurrent carotid artery stenosis. **J Neurosurg 80:**781–787, 1994
28. Qureshi AI, Luft AR, Janardhan V, Suri MF, Sharma M, Lanzino G, et al: Identification of patients at risk for periprocedural neurological deficits associated with carotid angioplasty and stenting. **Stroke 31:**376–382, 2000
29. Rapp JH, Pan XM, Sharp FR, Shah DM, Wille GA, Velez PM, et al: Atheroemboli to the brain: size threshold for causing acute neuronal cell death. **J Vasc Surg 32:**68–76, 2000
30. Roubin GS, New G, Iyer SS, Vitek JJ, Al-Mubarak N, Liu MW, et al: Immediate and late clinical outcomes of carotid artery stenting in patients with symptomatic and asymptomatic carotid artery stenosis: a 5-year prospective analysis. **Circulation 103:**532–537, 2001
31. Scolari F, Tardanico R, Zani R, Pola A, Viola BF, Movilli E, et al: Cholesterol crystal embolism: a recognizable cause of renal disease. **Am J Kidney Dis 36:**1089–1109, 2000

32. Shawl F, Kadro W, Domanski MJ, Lapetina FL, Iqbal AA, Dougherty KG, et al: Safety and efficacy of elective carotid artery stenting in high-risk patients. **J Am Coll Cardiol 35:**1721–1728, 2000
33. Sundt TM, Sandok BA, Whisnant JP: Carotid endarterectomy. Complications and preoperative assessment of risk. **Mayo Clin Proc 50:**301–306, 1975
34. Terada T, Tsuura M, Matsumoto H, Masuo O, Yamaga H, Tsumoto T, et al: Results of endovascular treatment of internal carotid artery stenoses with a newly developed balloon protection catheter. **Neurosurgery 53:**617–625, 2003
35. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR: Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. **Ann Neurol 37:**231–241, 1995
36. Wholey MH, Al-Mubarek N, Wholey MH: Updated review of the global carotid artery stent registry. **Catheter Cardiovasc Interv 60:**259–266, 2003
37. Yadav JS, Roubin GS, Iyer S, Vitek J, King P, Jordan WD, et al: Elective stenting of the extracranial carotid arteries. **Circulation 95:**376–381, 1997
38. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al: Protected carotid-artery stenting versus endarterectomy in high-risk patients. **N Engl J Med 351:**1493–1501, 2004

Manuscript received September 6, 2005.
Accepted in final form March 9, 2006.
This work was supported in part by a Research Grant for Cardiovascular Diseases (No. 14A-3, Japan Carotid Atherosclerosis Study) from the Ministry of Health, Labor and Welfare.
Current address for Dr. Sakai: Kobe City General Hospital, Kobe, Japan.
Current address for Dr. Nagata: Nagasaki University Medical School, Nagasaki, Japan.
Address reprint requests to: Koji Iihara, M.D., Department of Neurosurgery, National Cardiovascular Center, 5–7–1 Fujishiro-dai, Suita, Osaka 565–8565, Japan. email: kiihara@hsp.ncvc.go.jp.

最近の大規模臨床試験の概要
外科的治療
JET study (Japanese EC-IC Bypass Trial)

小笠原邦昭　　小川　彰

Key words：バイパス術，血行力学的脳虚血，脳循環代謝

はじめに

脳主幹動脈の慢性的な閉塞・狭窄が原因で灌流域末梢の脳血流が低下し，脳梗塞を来す血行力学的脳虚血に関しては，脳梗塞の再発予防として脳血流を術直後より増加させることの可能なバイパス術が有効であろうと考えられてきた[1-3]．

本稿では，内頸動脈あるいは中大脳動脈の慢性閉塞性病変による血行力学的脳虚血の考え方およびこれに対するバイパス術の有効性を検討したJET study (Japanese EC-IC Bypass Trial) について述べる．

1. 血行力学的脳虚血の重症度分類

脳はあらゆる臓器の中で虚血に対し，最も脆弱である．このため，脳血流を維持しようとする機構（自動調節能）が存在する．脳血管の慢性閉塞性病変により末梢の脳灌流圧が徐々に低下していくと，細動脈を拡張させ血管抵抗を低下させる．これにより脳血流は維持される．しかし，この細動脈拡張には限界があり，この限界を超えてもなお，脳灌流圧が低下すると脳血流は低下し始める．一方，少ない脳血流ながらも脳組織が正常な生命活動をするに足る酸素が何とか供給されていれば，この段階でも脳梗塞に陥らない．この酸素需要に対し酸素供給が相対的に減少している状態を貧困灌流症候群といい[4]，脳梗塞発症の準備段階と考えられている．この状態から更に，脳灌流圧が低下すると，ついに脳血流の低下により脳に対する酸素供給が絶対的に不足し脳組織が生存できなくなり，不可逆的変化，すなわち脳梗塞を来す．

2. 内頸動脈あるいは中大脳動脈の慢性閉塞性病変に対するバイパス術の考え方の変遷

バイパス術は1969年にYasargil[5]によって導入され，1970年に入って多くの施設で内頸動脈あるいは中大脳動脈の慢性閉塞性病変に対し行われるようになった．しかし，その適応および効果に関しては不明であったため，1977-82年にかけ，世界的規模で多施設参加によるprospective randomized studyが行われた[6]．そして，1985年にバイパス術は内科的治療に勝る脳梗塞再発予防効果はないとする結果が発表された[6]．この研究結果に対し，多くの批判がなされた．すなわち，多数の登録外での治療例，症例数の不足，研究期間の長期化，多数の不適合例，追跡不能例，不完全な経過観察，周術期合

Kuniaki Ogasawara, Akira Ogawa: Department of Neurosurgery, Iwate Medical University　岩手医科大学 脳神経外科

0047-1852/06/¥40/頁/JCLS

併症の多さ，脳血流からみた適応決定の曖昧さなどである．最も大きな欠点は患者選択に際し，上述した貧困灌流症候群の概念が導入されていないことにあった．すなわち，血行力学的脳虚血以外の原因で脳梗塞が再発している症例にはバイパス術は当然無効であり，また，脳主幹動脈閉塞性病変による脳梗塞の発症機序として血行力学的脳虚血は全体の10％前後と少なく，これらが，国際共同研究の結果に影響しているものと考えられた．しかし，当時貧困灌流症候群を日常臨床で診断する方法が確立しておらず，国際共同研究の結果公表後，我が国を含め慢性脳主幹動脈閉塞性病変に対するバイパス術は急速に行われなくなった．

一方，1990年代になり，positron emission tomography(PET)，single photon emission CT(SPECT)あるいはtranscranial Doppler(TCD)などの普及により脳循環代謝の測定が一般臨床でも可能となった．本来，貧困灌流は‘一定の脳血流に存在する酸素の何％が脳組織で用いられているか’の指標である酸素抽出率(oxygen extraction fraction: OEF)の上昇で表され，PETでなければ検出できないとされていた．しかし，自動調節能の出動による細動脈の拡張状態を知ることで間接的に貧困灌流を検出できることがわかってきた[7]．すなわち，血管拡張物質による脳血流の増加率が著明に減少あるいは喪失している領域は貧困灌流を来している可能性が高いことが指摘されてきた．現在，血管拡張物質として二酸化炭素あるいはacetazolamide(Diamox)が，脳血流測定装置としてはPET，SPECT，cold Xe CT，TCDが用いられている[8-12]．これらの手法を用いた多数例の脳循環代謝の測定から，①内頸動脈あるいは中大脳動脈の慢性閉塞性病変をもつ患者のうちでも，貧困灌流の存在する患者では存在しない患者に比し，有意に脳梗塞再発作を来しやすいこと[8-12]，②貧困灌流の存在する患者にバイパス術を行うと貧困灌流は消失すること[4,7]などが証明されてきた．これらの結果から，貧困灌流の存在する症例のみを集め，検討を行えばバイパス術の有効性を証明できるのではないかという気運が日本のみならず，世界的に高まってきた．

3. JET study

上述のような脳循環代謝測定法の発達およびevidence based medicine(EBM)の普及に伴い，我が国で内頸動脈あるいは中大脳動脈の慢性閉塞性病変に対するバイパス術に関してevidenceを得ようと多施設共同によるrandomized controlled trialが行われた(JET study)[13]．本研究の特徴は以下のとおりである．①脳循環の測定を定量的に高い精度で行い，貧困灌流を有する患者のみを対象とする，②対象を薬物療法のみの群あるいは薬物療法＋バイパス術の群のいずれかに無作為に割り付け，2年間追跡し，脳梗塞再発作の頻度を比較する．本研究の具体的な対象症例は[13]，内頸動脈系の閉塞性脳血管病変による一過性脳虚血発作または完成卒中を3カ月以内に認めた症例で以下のinclusion criteriaを満たすものである．すなわち，臨床的criteriaとして，73歳以下・ADLがほぼ自立している(Rankin disability scale 1，2)，放射線学的criteriaとして，CTないしはMRIにて一血管支配領域にわたる広範な脳梗塞巣を認めない・血管撮影上内頸動脈，中大脳動脈本幹の閉塞あるいは高度狭窄(CEAの対象となる内頸動脈狭窄を除く)がある，脳血流criteriaとして，3次元的定量的脳血流測定法(PET，SPECT，cold Xe CT)にて病側中大脳動脈灌流域の安静時血流量が正常値の80％未満かつacetazolamide反応性が10％未満．なお，脳血流criteriaでは登録症例を更に脳虚血の程度で中等症(0≦acetazolamide反応性＜10％)と重症(0＞acetazolamide反応性)に分けて登録した．

本研究では，1998年11月から2002年3月の3年5カ月の登録期間中に206例の登録症例があった．1998年11月1日から2002年1月31日まで(3年3カ月)の196例についての中間解析を述べる[14]．薬物療法，外科治療とも98例ずつ割り付けられていた．中等度脳虚血は104例，重度脳虚血は92例であった．primary end pointに達した症例数は，平均追跡期間15カ月で薬物療法群14例(14.3％)，外科治療群5例(5.1

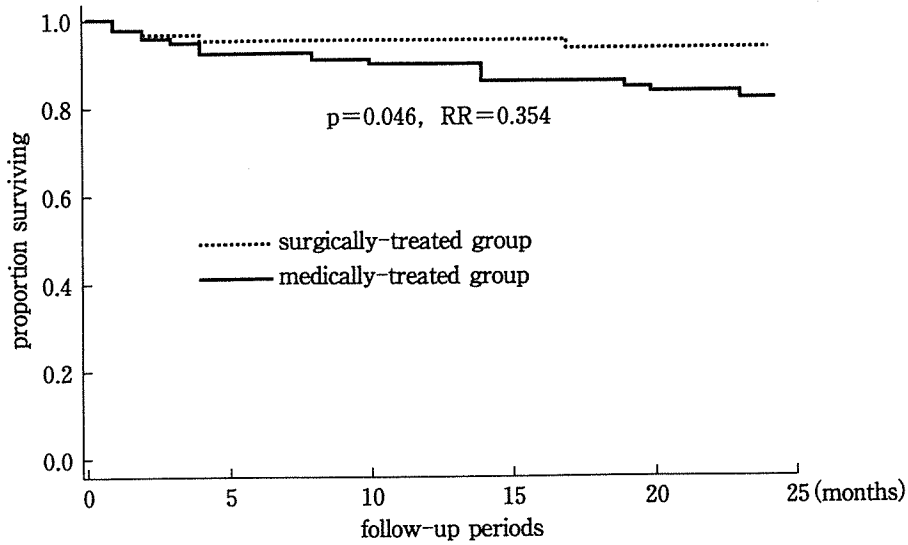


図1 JET study中間解析における primary end point の生存曲線
薬物療法群に比し外科治療群で primary end point 発生率が有意に低い.

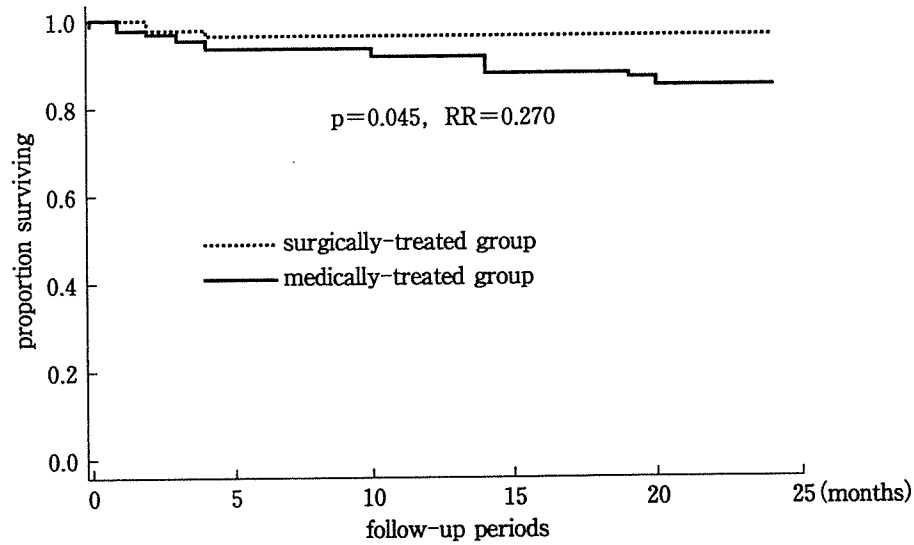


図2 JET study中間解析における secondary end point の生存曲線
薬物療法群に比し外科治療群で secondary end point 発生率が有意に低い.

%)であった. 脳虚血の重症度の比較では, 中等度脳虚血群と重度脳虚血群との間には primary end point に達した率には有意差はなかった. Kaplan-Meier analysis による解析では薬物療法群が外科治療群に比して有意に(p=0.046)高い頻度で primary end point に達していた(図1). relative risk は0.354であった. primary end point に達した症例の内訳は, 外科治療群ではプロトコール違反(登録時に既にRankin disability scale 4), 心筋梗塞による死亡, 腎不全による死亡が各1例であった. また, 同側脳梗塞再発による primary end point 例が2例あった. 薬物療法群では登録時と同じ責任血管が原因の脳梗塞再発による primary end point が11例認められた. また, 対側半球の脳梗塞および小脳脳幹部梗塞が各1例ずつ認められた. 更に, 急性心筋梗塞による primary end point が1例認められた. secondary end point である登録時と同側の脳梗塞再発のみについて解析すると, 薬物療法群は11.2%, 外科治療群は3.1%の頻度

でsecondary end pointに達していた．secondary end pointにおいてもやはり，脳虚血重症より中等症の方がend pointに達する頻度が高かった．Kaplan-Meier analysisによる解析では薬物療法群が外科治療群に比して有意に(p=0.045)高い頻度でsecondary end pointに達していた(**図2**)．relative riskは0.270であった．

以上のようにJET studyの中間解析では，バイパス術に脳梗塞再発予防効果がある可能性が報告されている．我が国でのJET studyに刺激され，米国でも同様の研究方法でCOSS (Carotid Occlusion Surgery Study)が組織され，患者登録が開始されている．

おわりに

JET studyは病側中大脳動脈灌流域の安静時血流量が正常値の80％未満かつacetazolamide反応性が10％未満という重度の脳虚血のみを対象にした研究である．現在これより軽症の血行力学的脳虚血をもつ症例が薬物療法のみでどういう経過をとるかの研究をJET2 studyとして継続中である．

文　献

1) Binder LM, et al: Behavioral effects of superficial temporal artery to middle cerebral artery bypass surgery: preliminary report. Neurology **32**: 422-424, 1982.
2) Younkin D, et al: Superficial temporal-middle cerebral artery anastomosis: effects on vascular, neurologic, and neuropsychological functions. Neurology **35**: 462-469, 1985.
3) Drinkwater JE, et al: Cerebral function before and after extra-intracranial carotid bypass. J Neurol Neurosurg Psychiatry **47**: 1041-1043, 1984.
4) Baron JC, et al: Reversal of focal "misery-perfusion syndrome" by extra-intracranial arterial bypass in hemodynamic cerebral ischemia: A case study with 150 positron emission tomography. Stroke **12**: 454-459, 1981.
5) Yasargil MG: Microsurgery Applied to Neurosurgery, p105-115, Georg Thieme, Stuttgart, 1969.
6) The EC/IC Bypass Study Group: Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial. N Engl J Med **313**: 1191-1200, 1985.
7) Vorstrup S, et al: Effect of acetazolamide on cerebral blood flow and cerebral metabolic rate for oxygen. J Clin Invest **74**: 1634-1639, 1984.
8) Grubb RL Jr, et al: Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. JAMA **280**: 1055-1060, 1998.
9) Kleiser B, Widder B: Course of carotid artery occlusions with impaired cerebrovascular reactivity. Stroke **23**: 171-174, 1992.
10) Kuroda S, et al: Long-term prognosis of medically treated patients with internal carotid or middle cerebral artery occlusion: can acetazolamide test predict it? Stroke **32**: 2110-2116, 2001.
11) Ogasawara K, et al: Cerebrovascular reactivity to acetazolamide and outcome in patients with symptomatic internal carotid or middle cerebral artery occlusion: a xenon-133 single-photon emission computed tomography study. Stroke **33**: 1857-1862, 2002.
12) Yamauchi H, et al: Evidence of misery perfusion and risk for recurrent stroke in major cerebral arterial occlusive diseases from PET. J Neurol Neurosurg Psychiatry **61**: 18-25, 1996.
13) JET Study Group: Japanese EC-IC Bypass Trial(JET Study): study designと中間解析．脳卒中の外科 **30**: 97-100, 2002.
14) JET Study Group: Japanese EC-IC Bypass Trial(JET Study): 中間解析結果(第二報)．脳卒中の外科 **30**: 434-437, 2002.

4 脳神経外科手術
—JET, MELT Japan など—

はじめに

近年では，脳神経外科領域においても，内頸動脈狭窄症に対する外科的治療と，内科的治療の大規模ランダム化比較試験や頭蓋外内血行再建術の有効性に関する大規模ランダム化比較試験の報告がなされている．本稿では，わが国で実施された，または進行中の大規模ランダム化比較試験として，Japanese EC-IC Bypass Trial(JET Study)とMCA-Embolism Local Fibrinolytic Intervention Trial Japan(MELT Japan)に関して述べる．

1 JET Study

頭蓋外—頭蓋内(EC-IC)バイパス術の有効性を証明すべく，1977～82年に世界的規模で大規模ランダム化比較試験が行われた．しかしその結果は，EC-ICバイパス術には内科的治療に優る脳梗塞再発予防効果はないとするものであった[1]．この研究結果の最も大きな欠点は，患者選択に際し貧困灌流症候群の概念が導入されていないことにあった．そこで貧困灌流の存在する症例のみを集めて検討を行えばバイパス術の有効性を証明できるのではないかと考えられ，JET Studyが開始された．本研究の特徴は以下の3点である．

①脳循環の測定を定量的に行い，貧困灌流を有する患者のみを対象とする．

②対象を薬物療法のみの群あるいは薬物療法＋EC-ICバイパス術の群のいずれかにランダムに割り付け，2

年間追跡し，脳梗塞再発作の頻度を比較する．

③両群間で高次脳機能の改善・悪化についても比較し，慢性虚血による高次脳機能障害に対するEC-ICバイパス術の有効性についても検討する．

本研究は1998年に開始され，2004年3月で経過観察期間を終了した．対象症例は，内頸動脈系の閉塞性脳血管病変による一過性脳虚血発作または完成卒中を3カ月以内に認めた症例で，以下のinclusion criteriaを満たすものである．

①73歳以下でADLがほぼ自立している(modified Rankin Scale；mRS 1,2)．

②CTないしはMRIにて一血管支配領域にわたる広範な脳梗塞巣を認めない．

③血管撮影上内頸動脈，中大脳動脈本幹の閉塞あるいは高度狭窄(内頸動脈内膜剝離術の対象となる内頸動脈狭窄を除く)がある．

④3次元的定量的脳血流測定法にて，病側中大脳動脈灌流域の安静時血流量が正常値の80％未満，かつアセタゾラミド反応性が10％未満であること．

高次脳機能障害に対するEC-ICバイパス術の有効性に関しては，いまだ最終報告がなされていないが，脳卒中再発率に関しては外科的治療群が内科的治療群に比べ有意に低いことが示された．さらに全死亡に関しても，外科的治療群のほうが有意に内科的治療群より少なかった．また，JET Studyの脳循環criteria内ではその重症度と再発頻度には相関がなく，より緩やかなcriteriaでも外科的治療の有効性が存在することが示唆されている．

貧困灌流を有する症例においてはEC-ICバイパス術の脳卒中予防効果が証明されたといえる．

2　MELT Japan

脳梗塞急性期にt-PA静脈投与を行うことにより，患者転帰が改善することが大規模ランダム化比較試験にて示されている．わが国においても，2005年10月に経静脈的投与に対して薬事認可された．しかし局所線溶療法に関しては，その有効性は十分検討されていない．

超急性期局所線溶療法多施設共同試験MELT Japanはウロキナーゼを用い，超急性期局所線溶療法の有効性を評価することを目的に2001年より開始された．対象は急性中大脳動脈閉塞による虚血性脳血管障害患者とした．選択基準は下記の通りである．

①血管撮影で急性中大脳動脈閉塞が確認された患者，
②発症時刻が特定可能で発症後6時間以内に局所線溶療法が開始できる患者，
③入院直後のCTでまったく変化を認めないか，病側に軽微な初期虚血変化のみを認めるもの，
④CT撮像後より2時間以内に局所線溶療法を開始できる患者，
⑤年齢20歳以上75歳以下．

局所線溶療法群はウロキナーゼ動注を行い，対照群は局所線溶療法(動注，静注どちらも)以外の一般的治療を行うこととした．エンドポイントは発症3カ月でのmRSを比較することとした．

目標症例数は200例であるが，2005年10月時点で115例が登録されている．研究終了予定は2007年3月である．3カ月経過観察を終了した105例に対して，中間解析が施行された．その結果は，死亡および神経学的増悪を伴う脳内出血発生頻度において2群間に有意差は認めなかった．有効性に関しては，mRS 2以下(家庭内自立)となった頻度はウロキナーゼ群49.1％，対照群38.5％とほぼ同等であったが，mRS 1以下(社会復帰率)はウロキナーゼ群

41.5％，対照群21.2％とウロキナーゼ群に有意に多かった($P=0.035$)．

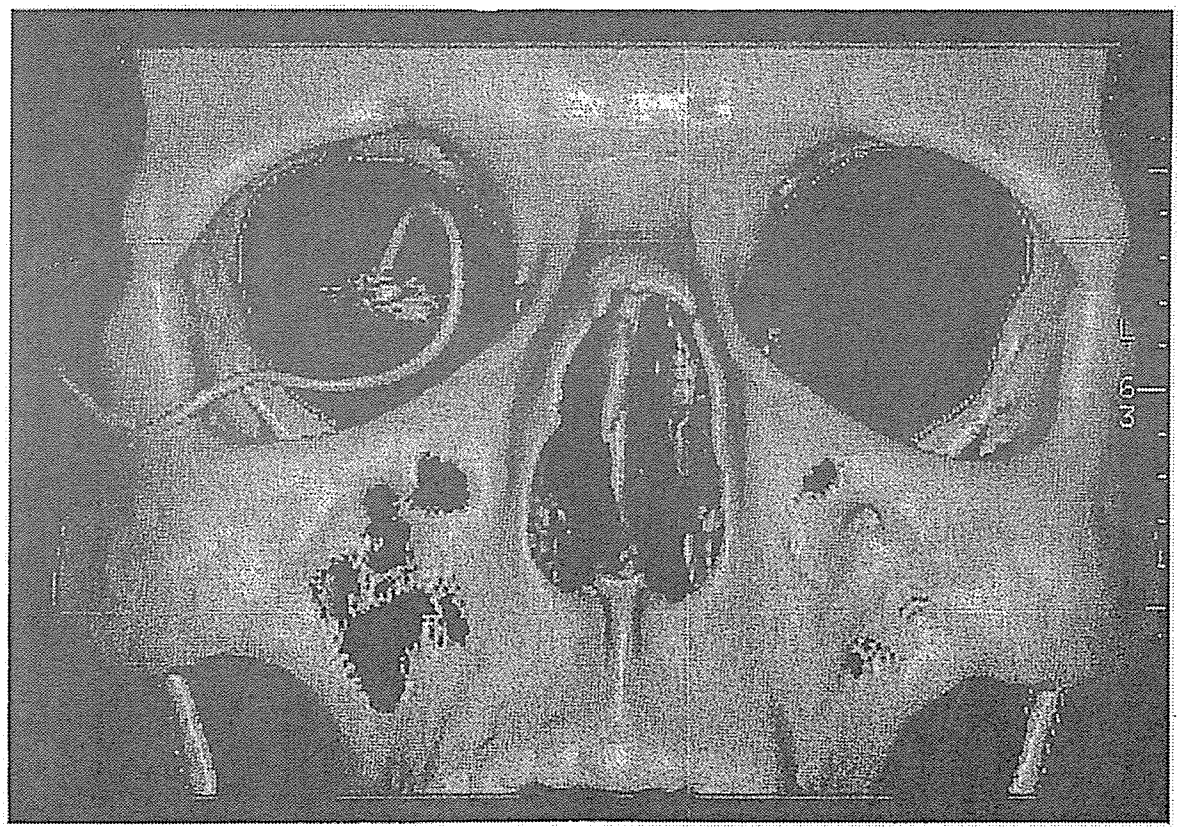
急性期中大脳動脈閉塞症例に局所線溶療法を行うことは社会復帰率を改善する可能性があると考えられる．

井上　敬／小笠原邦昭／小川　彰
(岩手医科大学医学部脳神経外科)

References

1) The EC/IC Bypass Study Group : Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *N Engl J Med* **313** : 1191-1200, 1985

Journal of Neurosurgery



APRIL 2006 Volume 104, Number 4

American Association of Neurological Surgeons

WWW.THEJNS-NET.ORG

Emmanuel Gérardin, MD, PhD
Stéphane Derrey, MD
Françoise Douvrin, MD
Erick Clavier, MD
Didier Hannequin, MD
Pierre Fréger, MD (Rouen University Hospital, France)

Introduction: The aim of this study was to evaluate the cognitive performance and the functional results in patients with AcoA aneurysms treated by different options such as microsurgical clipping (MC) and endovascular coiling (EC).

Methods: Between 2002 and 2004, 53 consecutive patients treated for a AcoA bleeding with a Glasgow Outcome Score of 4 or 5 (MC, n = 39 ; EC, n = 14) were prospectively selected in order to perform a neuropsychological and functional evaluation at 6 months. All patients were tested during a 3 h extensive neuropsychological battery of tests during 2 sessions (the patient alone and with a close relative). Statistical anlysis: t test, Mann Whitney Test.

Results: Any significant differences between the MC group and the EC was primarily found in global efficiency, memory tests [Badeley Doors test, Rey Complex Figure test, Gröber and Buschke tests] (pathologic in 51.3% vs 42.8% respectively) and executive test [Trail making test, Stroop test, Wisconsin Card sorting test, Verbal fluency and Brixton test](20.5% vs 28.5%). Surgically treated patients showed a significant impairment in their anosognosic symptoms (25.6% vs 0%, p = 0.019). Functional results were similar in both groups: RNLI (20.5% vs 14.3%, NS), modification of professional status (20,5% vs 14,3%, NS) and modified Rankin Score (0: 28.1% vs 28,6%, 1: 45,2% vs 14.3%, 2: 17.9% vs 50, 3: 7.7% vs 7.4%; NS).

Conclusions: Investigation of neuropsychological deficits showed impairment even in patients classified with a favorable outcome but no significant difference was observed as regards surgical or endovascular treatment.

PAPER 644
Effect of STA-MCA Bypass for the Ocular Ischemic Syndrome due to the Occlusive Internal Carotid Artery Diseases

Shoichiro Kawaguchi, MD
Hideaki Mishima, MD
Jun-ichi Iida, MD
Jun-ichi Nonaka, MD
Toshisuke Sakaki, MD (Kashihara, Nara, Japan)

Introduction: The authors examined the role of the STA-MCA bypass for chronic ocular ischemic syndrome (OIC) due to the occlusive internal carotid artery (ICA) diseases.

Methods: We examined the visual symptoms and the ophthalmic artery flow using color Doppler flow imaging (CDFI) in forty-four patients having the chronic OIS due to the occlusive ICA diseases treated with STA-MCA bypass. Visual symptoms were decline of visual acuity in 31 cases, frequent amaurosis fugax in 6 cases and both in 7 cases.

Results: 1. CDFI findings: 1) Preoperatively, 39 patients showed reversed ophthalmic artery flow (mean PFV: −0.32 m/sec). The other 5 patients showed antegrade ophthalmic artery flow (mean PFV: 0.09 m/sec). 2) At one month after bypass, 17 patients showed the antegrade ophthalmic artery flow. Mean PFV in the patients with preoperatively reversed ophthalmic artery flow significantly rose to −0.07 m/sec ($p < 0.05$). 3) At three months after surgery, 21 patients showed the antegrade flow. Mean PFV in the patients with preoperatively reversed ophthalmic artery flow significantly increased to 0.08 m/sec ($p < 0.05$). There was no significant change of CDF finding in patients with preoperative antegrade ophthalmic artery flow. 2. Visual symptoms: During the follow-up period (mean 4.9 years), visual acuity improved in 18 patients (47%) and did not worsen in any of the remaining 26 patients.

Conclusions: STA-MCA bypass was useful and important role for the improvement or prevention of progress of the OIS due to the occlusive ICA diseases, especially for the patients showing the reversed ophthalmic artery flow.

PAPER 645
Multimodality Management of 81 Pediatric Arteriovenous Malformations

Ruth E. Bristol, MD
Felipe C. Albuquerque, MD
Robert F. Spetzler, MD
Harold L. Rekate, MD
Cameron McDougall, MD
Joseph Zabramski, MD (Phoenix, AZ)

Introduction: Arteriovenous malformations are considered to be congenital in origin, though recent reports challenge the uniformity of this statement. Children make up between 3 and 20% of the patients with AVMs in the literature, however, AVMs are responsible for 30 to 50% of intracranial hemorrhages in children.

Methods: Between 1983 and 2005, 87 children (age 18 or under) were treated at St. Joseph's Hospital and Medical Center for intracranial arteriovenous malformations. The inpatient and outpatient charts of 81 patients were available for retrospective review.

Results: The majority of patients (48) 59% presented with hemorrhage. Another 17% presented with seizures, and 12% were found incidentally. Patients with brainstem lesions presented at a significantly younger age (p = 0.0015) than any other location. Lesions in the frontal lobes were significantly smaller than other locations, and thalamic lesions significantly larger (p = 0.01 and 0.005) Recurrences occured more frequently in the first 12 years than in the latter 12. Most patients with smaller lesions (grades I to III) underwent craniotomy alone, whereas nearly all patients with grade IV and V lesions underwent embolization, craniotomy and radiosurgery. Outcome was better for patients with grade I lesions than any other grade. Patients presenting with hemorrhage had a worse outcome than other presentations.

Conclusions: Children appear to be more prone to recurrence than adults with AVMs. The combination of endovascular, open surgical and radiosurgical techniques offers the best opportunity for cure with the lowest side effects. Long term follow-up is essential in all patients.

PAPER 646
Treatment of Traumatic Brain Injury in Rats with a Combination Therapy of Marrow Stromal Cells and Atorvastatin

Asim Mahmood, MD
Dunyue Lu, MD, PhD
Changsheng Qu, MD
Anton Goussev, MD
Michael Chopp, PhD (Detroit, MI)

Introduction: This study investigated the effects of combination therapy of marrow stromal cells (MSCs) and statins (atorvastatin) after traumatic brain injury (TBI) in rats.

Methods: 36 adult female Wistar rats were injured with controlled cortical impact and divided into four equal groups. Group I was injected with MSCs (1×10^6) intravenously 24 hrs after TBI. Group II was administered atorvastatin (0.5 mg/kg) orally for 14 days starting 24 hrs after TBI. Group III received MSCs (1×10^6) combined with atorvastatin (0.5 mg/kg), whereas Group IV (control) was injected with saline. MSCs were harvested from bone marrow of male Wistar rats in order to identify male donor cells within female recipient animals by localizing Y chromosomes within them. Functional analysis was performed using modified neurological severity scores and Morris Water Maze test. Animals were killed 35 days after injury and brain sections stained with immunohistochemistry.

Results: There was no improvement in functional outcome in animals treated with MSCs or atorvastatin alone (Groups I & II). However, in animals receiving combination therapy (Group III) significant functional improvement was seen with both testing modalities. Microscopic analysis showed that significantly more MSCs were present in animals receiving combination therapy than those receiving MSCs alone. Also, there was significant endogenous cellular

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2006;22:402–408
DOI: 10.1159/000094859

Received: December 21, 2005
Accepted: May 4, 2006
Published online: August 4, 2006

Effect of Carotid Artery Stenting on Ocular Circulation and Chronic Ocular Ischemic Syndrome

Shoichiro Kawaguchi[a] Toshisuke Sakaki[a] Hideaki Iwahashi[a] Kenta Fujimoto[a]
Jun-ichi Iida[a] Hideaki Mishima[a] Norikiyo Nishikawa[b]

[a]Department of Neurosurgery, Nara Medical University, Kashihara, and [b]Department of Ophthalmology, Osaka Police Hospital, Osaka, Japan

Key Words
Carotid artery stenting · Chronic ocular ischemic syndrome · Color Doppler flow imaging · Ophthalmic artery flow

Abstract
Background: The authors evaluated the effect of carotid artery stenting (CAS) on ocular circulation and chronic ocular ischemic syndrome. ***Methods:*** We examined 38 patients with carotid artery stenosis (>80%) at its origin treated with CAS. Ocular circulation and symptoms were examined before, within 24 h, and 1 week, 1 month, and 3 months after CAS based on ophthalmic artery color Doppler flow imaging and ophthalmological examinations. ***Results:*** Ocular circulation: Before CAS, 13 patients showed reversed ophthalmic artery flow, and 25 antegrade flow. Average peak systolic flow velocity was −0.038 m/s. Within 24 h after CAS, all patients showed antegrade ophthalmic artery flow; reversed flow before CAS was thus resolved. Average peak systolic flow velocity rose significantly to 0.36 m/s ($p < 0.05$). One week, 1 month and 3 months after CAS, there were no significant changes compared to the findings at 1 week after CAS. Ocular symptoms: Before CAS, 8 patients showed chronic ocular ischemic syndrome. During the follow-up period (mean: 2.8 years), the visual acuity improved in 7 cases. Average retinal artery pressure and arm-to-retina circulation time improved significantly to the normal level ($p < 0.05$). The other 30 patients complained of recurrent and worsened visual symptoms during the follow-up period. ***Conclusion:*** CAS was effective in improving ocular circulation, and also improved the chronic ocular ischemic syndrome caused by the severe carotid artery stenosis.

Introduction

The efficacy and safety of carotid endarterectomy for internal carotid artery stenosis at its origin has been confirmed previously by various prospective, randomized, and multicentered studies [1–4]. Recently, carotid angioplasty with stent placement has emerged as a potential safe and effective alternative to carotid endarterectomy [5–8]. Carotid artery stenting (CAS) can restore the cerebral perfusion pressure and improve the hemodynamic status of the brain [6, 9, 10]. One of the important clinical aspects of internal carotid artery stenosis at its origin is its influence on the flow dynamics of the ophthalmic artery. The disturbed ophthalmic artery flow correlates with the chronic ocular ischemic syndrome symptoms such as amaurosis fugax or a decline of visual acuity [11, 12]. Therefore, it is important to understand the ophthalmic artery flow and ocular symptoms in patients with internal carotid artery stenosis before and after CAS.

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/06/0226–0402$23.50/0

Accessible online at:
www.karger.com/ced

Shoichiro Kawaguchi, MD
Department of Neurosurgery
Nara Medical University, 840 Shijo-cho
Kashihara, Nara, 634-8522 (Japan)
Tel. +81 744 29 8866, Fax +81 744 29 0818, E-Mail skawaguc@naramed-u.ac.jp

In this study, the authors discussed and analyzed the effect of CAS on ocular circulation and chronic ocular symptoms in the patients with severe carotid artery stenosis.

Patients and Methods

Patients

From January 2002 to March 2005, the authors examined ophthalmic artery color Doppler flow imaging (CDFI) in 38 consecutive patients with internal carotid artery origin stenosis (>80%) treated with CAS. Thirty-two patients were male and 6 female. Ages ranged from 47 to 79 years, with a mean of 70 years. The clinical symptoms of the patients were transient ischemic attack in 29, and reversible ischemic neurological deficit in 9. According to the criteria of the NASCET study [4], the grades of angiographical internal carotid artery stenosis on the ipsilateral side were greater than 95% in 9 patients, 90% in 16 patients, and 80% in 13 patients. Stenosis of the ipsilateral external carotid artery at its origin was evaluated in each patient. Four patients had 30–50% stenosis, 9 patients had less than 30% stenosis, and the 25 patients did not show any apparent stenosis. The contralateral internal carotid artery was also evaluated. There was occlusion in 8 patients, 50–80% stenosis in 3 patients, less than 50% stenosis in 12 patients and no apparent stenosis in 15 patients.

Eight patients complained of chronic ocular ischemic syndrome. All 8 had a visual acuity of 20/40 or worse, and 2 had frequent amaurosis fugax. In these 8 patients, tiny or no iris rubeosis was seen, and intraocular pressure was normal (less than 25 mm Hg). No patients showed blindness. The exclusion criteria for chronic ocular ischemic syndrome were acute ocular ischemic symptoms such as sudden loss of vision, a single episode of amaurosis fugax, or ocular/orbital pain [13].

CAS was performed at least 4 weeks after the last attack for each patient using a smart stent. At the end of the procedure, the patency of the treated carotid artery lumen was confirmed in each case by angiography. No patient complained of permanent periprocedure neurological deficit due to the CAS procedure.

All patients were followed up for clinical symptoms after CAS. The follow-up period was 0.9 to 4.5 years (mean: 2.8 years). During this period, none of the patients had a recurrent neurological ischemic attack or worsening of the symptoms including ocular signs. At the final stage, no patients showed any neurological deficit.

Methods

To evaluate ocular circulation, the authors examined ophthalmic artery flow by color Doppler flow imaging (CDFI) with Computed Sonography 128XP/10 (Acuson Corp., Mountain View, Calif., USA). With a 5-MHz probe, the power was less than 50 mW/cm^2, and the examination was completed within 5 min in each eye. The ophthalmic artery CDFI findings from the ipsilateral side of CAS were analyzed. Ophthalmic artery CDFI was performed within 1 week before CAS, within 24 h (mean: 7.6 h), and 1 week, 1 month, and 3 months after CAS in each patient. These CDFI studies provided information regarding flow direction and peak systolic flow velocity of the ophthalmic artery.

The authors also performed ophthalmic artery CDFI on 36 normal healthy volunteers. Ages ranged from 37 years to 73 years, and the mean age was 62 years. 19 volunteers were male and 17 female. All volunteers showed normal flow direction, i.e. flow away from the orbital apex to the globe. Average peak systolic flow velocity was 0.36 ± 0.07 m/s.

All patients were examined for ocular symptoms such as visual acuity and amaurosis fugax before the CAS procedure and during the follow-up period. In patients showing chronic ocular ischemic syndrome before CAS, retinal artery pressure and arm-to-retina circulation time were also examined using fluorescent angiography before and after CAS.

The physiological data were compared using two-tailed paired or unpaired Student's t test, simple regression analysis, ANOVA and χ^2 test. $p < 0.05$ was considered as a threshold for statistical significance. All values are reported as means ± standard deviation (SD).

Results

Ophthalmic Artery Color Doppler Flow Imaging

Before CAS

The ophthalmic artery flow was reversed in 13 patients and antegrade in 25 patients. Peak systolic flow velocities ranged from −1.63 to 0.54 m/s, with an average of −0.038 ± 0.47 m/s. Average peak systolic flow velocity in the patients with reversed flow was −0.57 ± 0.40 m/s, and in those with antegrade flow 0.24 ± 0.12 m/s. The average stenosis of the internal carotid artery was 87.0 ± 5.16% in the patients with antegrade flow, and 95.3 ± 2.10% in those with reversed flow. There was a significant difference between these two stenosis values ($p<0.00001$) using two-tailed unpaired t test.

The relationship between the degree of internal carotid artery stenosis and peak systolic flow velocity of the ophthalmic artery was examined. There was a statistically significant negative correlation using simple regression analysis ($p = 0.0002$) (fig. 1a). To evaluate the effect of the contralateral internal carotid artery stenosis, the 38 patients were divided into two groups according to the degree of stenosis. Group A consisted of 11 patients with more than 50% stenosis. Group B consisted of 27 patients with less than 50% or no apparent stenosis. In each group (fig. 1b, c) there was a statistically significant negative correlation between the degree of the internal carotid artery stenosis and ophthalmic artery peak systolic flow velocity on simple regression analysis ($p = 0.02$ in group A, $p = 0.0002$ in group B). Moreover, there was a significant difference between these two regression lines in groups A and B using ANOVA ($p = 0.0002$).

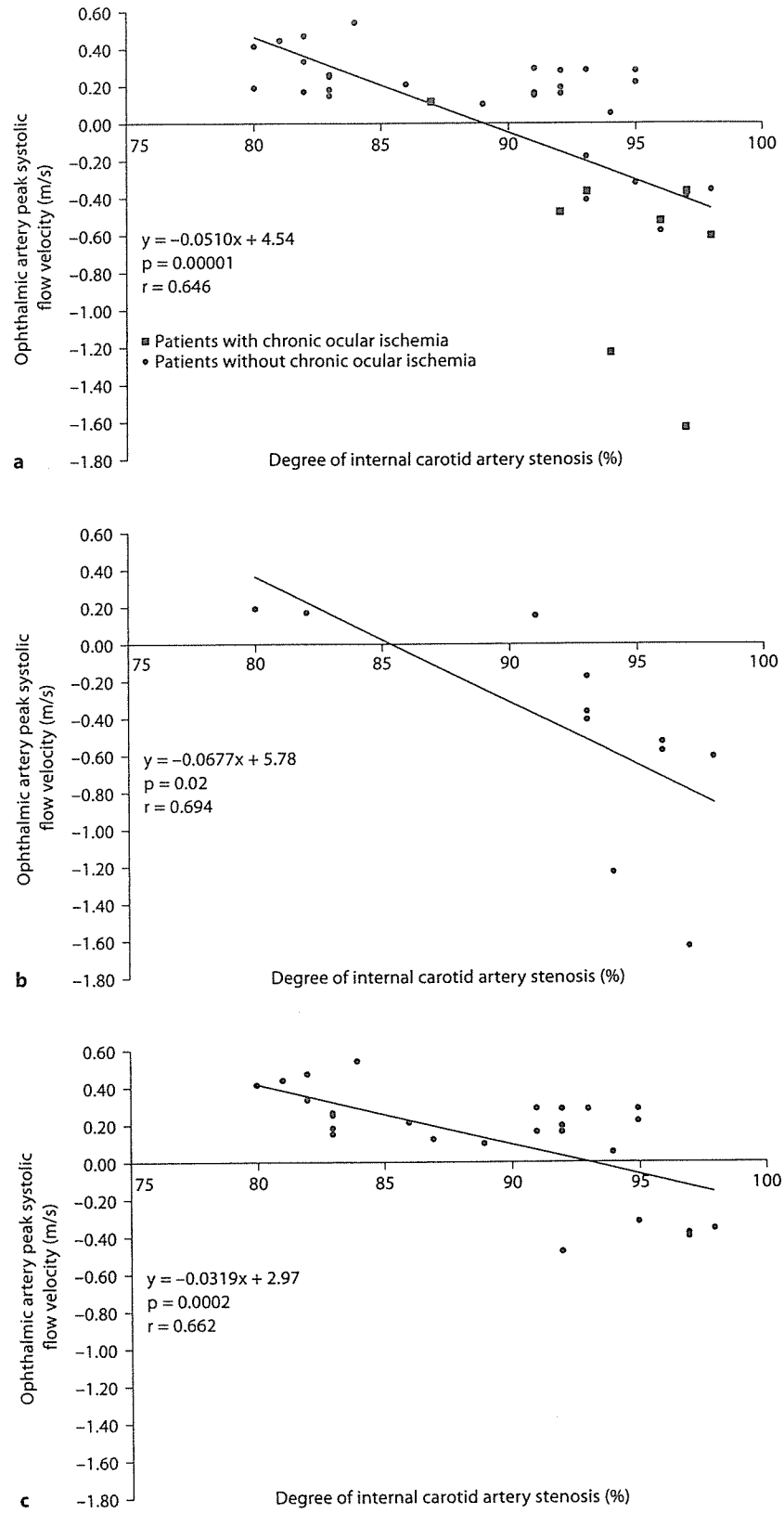


Fig. 1. Graphs showing the correlation between the degrees of internal carotid artery stenosis and the ophthalmic artery peak systolic flow velocities in all 38 patients (**a**), in group A consisting of 11 patients with contralateral internal carotid artery occlusion or more than 50% stenosis (**b**), and in group B consisting of 27 patients with less than 50% or no contralateral internal carotid artery stenosis (**c**).

Within 24 h after CAS

The patients showing reversed ophthalmic artery flow before CAS all returned to the normal antegrade flow following CAS. Peak systolic flow velocities ranged from 0.16 to 0.64 m/s. The overall average flow velocity rose to 0.36 ± 0.13 m/s, which is statistically significant compared with the level before CAS using two-tailed paired t test ($p = 0.00002$). Moreover, average peak systolic flow velocity did not significantly differ from that of controls on two-tailed unpaired t test.

One Week after CAS

In all patients, flow in the ophthalmic artery was antegrade. The peak systolic flow velocities ranged from 0.15 to 0.57 m/s. The overall average flow velocity was 0.35 ± 0.12 m/s, but this was not significantly different from the value obtained within 24 h after CAS using two-tailed paired t test.

One Month after CAS

In all patients, flow in the ophthalmic artery was antegrade. The peak systolic flow velocities ranged from 0.13 to 0.58 m/s. The overall average flow velocity was 0.35 ± 0.12 m/s. This was not significantly different from the value at 1 week after CAS using two-tailed paired t test.

Three Months after CAS

In all patients, flow in the ophthalmic artery was antegrade. The peak systolic flow velocities ranged from 0.15 to 0.58 m/s. The overall average flow velocity was 0.35 ± 0.11 m/s. This was not significantly different from the value at 1 month after CAS using two tailed-paired t test.

Ocular Symptoms

Before CAS

Eight patients complained of chronic ocular ischemic syndrome. These 8 patients were given careful ophthalmological examinations before and after CAS. Of these 8 patients, 6 showed reversed ophthalmic artery flow, and 2 antegrade flow. The relationship between the chronic ocular ischemic syndrome and the reversed ophthalmic artery flow was significant using the χ^2 test ($p = 0.006$). Ischemic changes of the optic fundi in the 8 patients were neovascularization on the disc in 5 patients (63%), cotton wool patches in 3 (38%), and peripheral hemorrhage in 2 (25%). Average arm-to-retina circulation time was 54.6 ± 12.3 s, and average retinal artery pressure was 39.6 ± 8.00 mm Hg.

Three Months after CAS

Seven of eight patients with the chronic ocular ischemic syndrome before CAS showed improvement in visual acuity, but one showed no improvement despite the normal ophthalmic flow after CAS. Six patients had a visual acuity between 20/40 and 20/20, and 2 a visual acuity less than or equal to 20/40.

Final Stage (Mean 2.8 Years after CAS)

Of the 8 patients, 6 had visual acuities between 20/40 and 20/20, and 2 had visual acuities less than or equal to 20/40. Ischemic changes of the optic fundi seen before CAS were improved during the follow-up period. Examination of the optic fundi showed neovascularization of the disc in 1 case (13%), whereas the remaining 7 cases (87%) were normal. The average arm-to-retina circulation time dropped to 16.3 ± 2.82 s, which was significant on two-tailed paired t test ($p = 0.004$), and the average retinal artery pressure increased to 54.6 ± 12.3 mm Hg, which was also significant on two-tailed paired t test ($p = 0.001$).

Thirty patients showed no chronic ocular ischemic syndrome before CAS. During follow-up, these 30 patients complained of no chronic ocular ischemic syndrome such as disturbance of the visual acuity or frequent amaurosis fugax. CAS could prevent the presentation of the chronic ocular ischemic syndrome due to the severe carotid artery stenosis in these patients.

Illustrative Cases

A 73-year-old man was referred to the authors' hospital complaining of transient left hemiparesis and right visual acuity decline (20/160). The right retinal artery pressure was 43 mm Hg, and right arm-to-retina circulation time was 25 s. The optic fundi on the right side showed tiny neovascularizations on the disc and cotton wool patches. Right carotid angiography showed 98% stenosis of the right internal carotid artery at its origin (fig. 2a). The right ophthalmic artery CDFI showed reversed flow, and the peak systolic flow velocity was −0.36 m/s (fig. 2b). Right CAS was performed. At the end of the procedure, dilatation of the stenosis and stenting were confirmed on right carotid angiography (fig. 2c). Within 24 h after CAS, the right ophthalmic artery CDFI showed resolution of the reversed flow, and the peak flow velocity was 0.44 m/s (fig. 2d). The peak systolic flow velocity of the ophthalmic artery was 0.42 m/s at 1 week after CAS (fig. 2e), 0.41 m/s at 1 month after CAS (fig. 2f), and 0.43 m/s at 3 months after CAS (fig. 2g). Three months after CAS, right visual acuity gradually improved to 20/40,

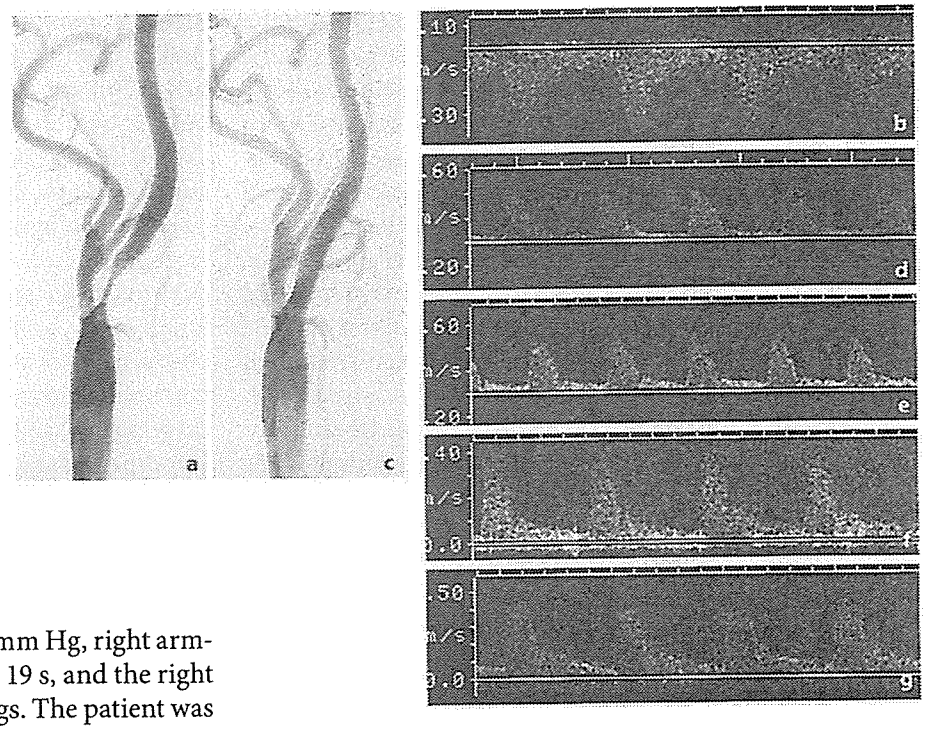


Fig. 2. a Before carotid artery stenting (CAS), right carotid angiography showing severe stenosis of the right internal carotid artery at its origin. **b** Before CAS, right ophthalmic artery color Doppler flow imaging (CDFI) showing the reversed ophthalmic artery flow direction. **c** After CAS, right carotid angiography showing the good patency of the CAS. **d** Right ophthalmic artery CDFI within 24 h after CAS showing the restoration of the normal ophthalmic artery flow pattern. **e** Right ophthalmic artery CDFI at one week after CAS. **f** Right ophthalmic artery CDFI at one month after CAS. **g** Right ophthalmic artery CDFI at 3 months after CAS.

right retinal artery pressure rose to 65 mm Hg, right arm-to-retina circulation time shortened to 19 s, and the right side optic fundi showed normal findings. The patient was followed up for 2.8 years after CAS, and there were no ischemic events, including visual symptoms.

Discussion

Occlusive internal carotid artery diseases exhibit ophthalmic artery flow disturbance [14]. The hemodynamic reduction of the ocular circulation due to severe internal carotid artery stenosis causes ocular ischemic syndrome. Therefore, it is significant to evaluate ophthalmic artery flow in the patients with internal carotid artery stenosis treated with CAS. The authors previously reported the effect of carotid endarterectomy on ophthalmic artery flow and ocular ischemic syndrome [15, 16]. However, there have been few reports about the effect of CAS on ocular circulation [17, 18]. To evaluate the effect of CAS on the ophthalmic artery flow, the authors examined the ophthalmic artery CDFI before and after CAS, including the follow-up period.

In the present series, 13 patients showed reversed ophthalmic artery flow before CAS. In these patients, the ophthalmic artery might function as collateral circulation from the extracranial to the intracranial circulation [19, 20]. In this series, there was a significant relationship between the degree of stenosis and the ophthalmic artery flow direction. Therefore, the flow of the ophthalmic artery as a collateral pathway for intracranial circulation depends on the degree of the primary carotid artery stenosis. The authors demonstrated the significantly increased flow velocity and correction of the flow direction in all patients immediately after CAS. This significant improvement also explains the correction of the ocular hemodynamic compromise.

In the present study, a negative correlation was demonstrated between the degree of the internal carotid artery stenosis and ophthalmic artery peak systolic flow velocity. The progress of the internal carotid artery stenosis revealed a stepwise decrease of the ophthalmic artery flow. Ultimately, the ophthalmic artery flow direction became reversed. Disturbance of the ophthalmic artery flow due to the progress of the internal carotid artery stenosis could be affected by the ipsilateral external carotid artery flow and the degree of stenosis of the contralateral internal carotid artery. In the present series, patients with contralateral internal carotid artery occlusion or more than 50% stenosis showed significantly more serious ophthalmic artery flow disturbance than patients without contralateral internal carotid artery stenosis or even those with less than 50% stenosis. However, in the present series, there were no patients showing significant stenosis of the ipsilateral external carotid artery. The effect of ipsilateral external carotid artery stenosis could not be clarified by the presenting study.

Reversed ophthalmic artery flow seen in the patients with severe carotid artery stenosis may contribute to the development of ocular ischemic syndrome [11, 21]. The reversed flow was significantly seen in the patients showing the chronic ocular ischemic syndrome before CAS in this series. For patients with chronic ocular ischemic syndrome due to reversed flow, it is vital to develop normal flow to prevent ocular ischemia [22]. In this series, 8 patients showed the chronic ocular ischemic syndrome. Among them, 6 patients initially showed the reversed ophthalmic artery flow. After CAS, all 6 patients showed normal flow. Therefore, CAS is the appropriate treatment for patients with ocular ischemic syndrome caused by reversed ophthalmic artery flow due to severe internal carotid artery stenosis. The other 2 patients with chronic ocular ischemic syndrome showed antegrade ophthalmic artery flow with reduction of peak systolic flow velocity before CAS. In these 2 patients, peak systolic flow velocity significantly increased immediately after CAS procedure. Seven patients showed an improvement of visual symptoms after CAS. Only one patient failed to show improvement of chronic ocular ischemic syndrome, due to the irreversible optic apparatus lesion. The authors report clear evidence of the effect of CAS on the improvement and prevention of chronic ocular ischemia due to internal carotid artery stenosis, based on data obtained from ophthalmic artery CDFI and clinical symptoms. Therefore, there is a good correlation between the course of ocular ischemic syndrome and the improvement of the ophthalmic artery CDFI findings during the follow-up period. CAS is effective for the treatment and prevention of ocular ischemic syndrome and is most beneficial if performed early, before the onset of irreversible neovascular glaucoma or irreversible ischemic optic fundi [14, 17].

In this study, improvement in the peak systolic flow velocity and normalization of the reversed ophthalmic artery flow occurred within 24 h after CAS. Subsequently, there was no significant change in the ophthalmic artery peak systolic flow velocity. This effect of CAS was highly expected. The authors clarified the chronological correction of the disturbed ophthalmic artery flow direction and peak systolic flow velocity after CAS based on the ophthalmic artery CDFI findings. The ophthalmic artery CDFI provides clear evidences of hemodynamic compromise in occlusive internal carotid artery lesions.

Cerebral hyperperfusion syndrome after CAS is a serious complication [23, 24]. Fortunately, in the authors' series, none of the patients showed hyperperfusion syndrome or hyperperfusion phenomenon perioperatively. The authors examined the ophthalmic artery flow within 24 h after CAS. During this period, the mean ophthalmic artery peak systolic flow velocity was not significantly higher than the control value in each group. One week after CAS, the mean ophthalmic artery peak systolic flow velocity was slightly decreased compared to the value obtained within 24 h. However, this decrease was not significant. Thus, there was a tendency toward slight hyperperfusion phenomenon but no significant hyperperfusion phenomenon in the ophthalmic artery flow velocity within 24 h after CAS in this study. This study was a very small series, and therefore these data are preliminary. In the future, a hyperperfusion phenomenon may be seen in the ophthalmic artery CDFI within 24 h after CAS in a large series. Therefore, management and prevention of hyperperfusion phenomenon of the ophthalmic artery flow after CAS should be kept in mind.

Conclusion

CAS achieved normalization of the disturbed ophthalmic artery flow, whether the flow direction of the ophthalmic artery was reversed or antegrade, immediately after CAS procedure. CAS improved the chronic ocular ischemic syndrome revealed from the severe carotid artery stenosis, and it also prevented the progress and onset of the chronic ocular ischemic syndrome.