Review Article

Pil-Woo Huh, M.D.

Do-Sung Yoo, M.D.

Department of Neurosurgery
The Catholic University of Korea
College of Medicine
Uijeongbu St. Mary's Hospital
Uijeongbu, Korea

Intracranial Atherosclerotic Disease; Current Options for Surgical or Medical Treatment

Recently, intracranial atherosclerosis has become a major cause of ischemic stroke, appearing more frequently in Koreans than Caucasians. Symptomatic or asymptomatic intracranial atherosclerosis is a disease that could recur readily even during the treatment with anti-platelet agents. When the symptoms develop, ischemic stroke can not be recovered readily. Therefore, aggressive treatments such as endovascular therapy and bypass surgery are required in addition to medical treatment for the intracranial artery stenosis. Recent intracranial stenting and drug eluting stenting have shown as very advanced effective therapeutic modalities. Nevertheless, until now, a randomized controlled study has not been conducted. Regarding bypass surgery, since the failed EC-IC bypass surgery study performed 20 years ago, extensive studies on its efficacy has not been conducted yet, and thus it has to be performed strictly only in hemodynamically compromised patients. Unless breakthrough drugs that suppress the progression of intracranial atherosclerosis and the formation of thrombi, and facilitate the regression of the arterial stenosis, the treatment concept of the recovery of the blood flow of stenotic arterial territory by mechanical recanalization or bypass surgery would be remained for the prevention as well as treatment of ischemic stroke caused by intracranial atherosclerosis.

KEY WORDS : Angioplasty and stenting · Bypass surgery · Intracranial atherosclerosis.

INTRODUCTION

In Korea, the number of individuals who die from cerebrovascular diseases is 34,000 persons annually, 13.9% of whole, and it is the second leading cause of death following the leading cause of death being cancer (2004 Korean National Statistics bureau data). For the first time in Korea, in December 2005, the Health Insurance Review Agency reported the 'stroke preliminary report'. According to the data, the number of patients of cerebral ischemia or hemorrhage in the year of 2003 was 118,667 patients, and among them, 18,288 patients (15.41%) died. Therefore, this value implies that the mortality caused by cerebral ischemia or hemorrhage is very high. In addition, cancer is the leading cause of death and cerebrovascular disease is the second leading cause; nonetheless, as death caused by a single disease, it is in the first place. The incidence of cerebral ischemia or hemorrhage in 100,000 persons of the entire age group was average 347 persons, the 50s was 578 persons, the 60s was 1,170 persons, the 70s was 3,023 persons, and a trend of rapid increase with aging. Among reported cerebral ischemia or hemorrhage, the number of patients with cerebral infarction was 69,348 patients (58% of the entire cerebral ischemia and hemorrhage). In the above statistics, the causality of 69,348 cerebral infarction cases has not been described clearly, nonetheless, it has been reported that the cases caused by intracranial atherosclerosis reaches to 8-10%^(42,55). Although, the incidence varies depending on races, however, in Korea, cerebral infarction patients whose causality is intracranial atherosclerosis could be estimated to be 6,000-7,000 patients annually. It has been reported that in the USA, annually, 700,000 stroke cases develop annually, and among them, the cases caused by intracranial atherosclerosis are approximately 70,000 patients⁽¹³⁾.

Recently, an important study on the conservative treatment of intracranial atherosclerosis has been reported. According to this Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study in patients with symptomatic intracranial atherosclerotic stenosis, despite of the administration of warfarin or aspirin, the ipsilateral stroke risk rate at 1.8 yr was reported to be 13-14%. According to this study, in 50-69% stenosis, the stroke risk in one year was 6%, and in 70-99% stenosis patients, the stroke risk was 19%^(7,49,54). With these results, the WASID study proposed the necessity of more aggressive additional therapies besides drug treatments

• Received : July 30, 2007
• Accepted : November 12, 2007
• Address for reprints :
Do-Sung Yoo, M.D.
Department of Neurosurgery
The Catholic University of Korea
College of Medicine
Uijeongbu St. Mary's Hospital
65-1 Geumo-dong, Uijeongbu
480-130, Korea
Tel : +82-31-820-3595
Fax : +82-31-846-3117
E-mail : pilbrain@ catholic.ac.kr

for symptomatic intracranial atherosclerotic stenosis.

The report of the North American Symptomatic Carotid Endarterectomy Study (NASCES)^{32,33} and the report of the European Carotid Surgery Trial (EST)¹², Veterans Affairs Cooperative Study Program^{1,22} have shown that stroke recurrence was smaller in the carotid endarterectomy (CEA) group than the group administered aspirin only, thus provided the base of CEA to become the gold standard for severe carotid stenosis. After it has been reported that, EC-IC bypass could be a technically feasible treatment method not only for internal carotid artery stenosis but also for middle cerebral artery stenosis⁴³, the result of multicenter trials of the effect of EC-IC bypass has been reported^{16,32,35,50}. Therefore, although it is still controversial, it became an opportunity for EC-IC bypass becoming one of important options. After the report on carotid angioplasty and stenting for carotid stenosis^{4,10}, through the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial^{38,59} and the Stent protected Percutaneous Angioplasty of the Carotid vs Endarterectomy (SPACE) Study³⁹, carotid stent has been established as a remarkable treatment method comparable to the gold standard CEA.

Now, treatments for intracranial artery atherosclerosis patients utilize various methods applying extracranial carotid stenosis methods. The balloon angioplasty treatment performed successfully in 1980 by Sundt et al. on two medically refractory basilar artery stenosis patients⁴⁸ became the event to establish the intellectual framework of endovascular treatment to overcome intracranial atherosclerosis. Nevertheless, only after 10 years, the result showing the safety and effectiveness of percutaneous transluminal angioplasty intracranial atherosclerosis has been reported¹⁴. Afterward, by numerous investigators, good results of endovascular management for symptomatic intracranial atherosclerotic stenosis patients have been reported. On the other hand, however, substantial number of complications from stenting have also been reported.

Here, recent literatures on intracranial atherogenesis, natural history of intracranial arterial stenosis, acute infarction pattern in MCA and intracranial ICA stenosis, medical management of intracranial stenosis, endovascular treatment of intracranial stenosis, EC-IC bypass for flow augmentation in ischemia will be comprehensively reviewed along with summary of our experience.

INTRACRANIAL ATHEROGENESIS

The process of atherosclerosis is thought to occur at dividing or branching sites of intracranial and extracranial arteries secondary to the combined effects of turbulence, blood

stagnation, hemodynamic sheer stress, and boundary separation. The ratio of ICA area to common carotid artery area and the bifurcation angle result in a geometry at the bifurcation that produces vortex flow and increases contact of atherogenic substances and platelets with the site of maximal plaque development¹⁴. The current concept on atherogenesis is the "response to injury" hypothesis^{15,40}.

According to this hypothesis, endothelial injury is induced by the variety of forces and plaques are developed by inflammatory response to this injury. Factors that could induce endothelial injury are hypercholesterolemia, cigarette smoking, hypertension, oxidative stress, advanced glycation end products, and infection¹¹. Upon receiving endothelial injury, platelets and endothelial genes of adhesion molecule are expressed. In addition, molecules pertinent to the synthesis of growth factor, cytokine, and coagulation protein synthesis are induced^{9,34}. After endothelial injury, monocytes and low density lipoprotein enter the intima due to the increase of permeability. Monocyte derived macrophages secrete mitogens and the mitogens induce smooth muscle cells to egress to the intima. Smooth muscle cells egressed to the intima proliferates, and synthesizes extracellular collagen and proteoglycan. Oxidized lipoprotein is filled in macrophages more, and eventually, these cells become foam cells and rupture, and at that time, these cells release lipid and cytotoxic enzymes. This enhances fibroproliferation response of smooth muscle cells⁴⁴. Also, injured endothelium is more thrombogenic secondary to decreased expression of nitric oxide, prostacycline, and fibrinolytic and antithrombotic glycoprotein³⁴.

NATURAL HISTORY OF INTRACRANIAL ARTERIAL STENOSIS

In blacks and Asians, atherosclerosis is developed selectively in the intracranial artery than the extracranial artery⁵⁷. On the other hand, a trend is more extracranial lesions in Caucasians¹⁷. Risk factors of intracranial atherosclerosis are younger age, hypertension, smoking, diabetes, and lipid disorder^{5,23}. In comparison with extracranial atherosclerosis, intracranial stenosis is not associated with the typical risk factors of peripheral and coronary atherosclerosis, male sex and hypercholesterolemia⁴². According to survey reports in Korea⁴⁷, a trend is that intracranial stenosis is slightly more prevalent than extracranial stenosis in the atherosclerotic stenosis distribution. In addition, severe intracranial stenosis account for 52% of cases and extracranial stenosis 48%, being more prevalent in the intracranial artery. Furthermore, anterior circulation stenosis was more prevalent than posterior circulation stenosis by 20%⁴⁷. Single and severe stenosis has an increasing tendency toward intracranial involvement⁴⁷.

The dynamic nature of symptomatic middle cerebral artery (MCA) atherosclerotic stenosis has been reported in 1998 by Akins et al.²⁾ in a serial angiography study performed at average 26.7 months interval. According to this study, stenosis may be either progress or regress. In case with progression, it tends to occur more frequently in small vessels than large vessels. Average stenosis of intracranial ICA was stable from the beginning to the last time (51.2% versus 52.6%). Nevertheless, in anterior, middle, and posterior cerebral artery (PCA), it was progressed from the initial average 32.4% to last average 49.7%. Intracranial ICA does not progress more than other intracranial sites because of two reasons. First, the changes in percent stenosis will be greater for small vessels compared with large vessels. Second, in small vessels rather than intracranial ICA, local thrombus formation occurs more readily. In regression cases, 14% of the intracranial ICA group, and 28% of the ACA-MCA-PCA group were regressed. The pathological process that leads this angiographic improvement may attribute to regression of atherosclerosis or resolution of local thrombus or both.

In a study of the prevalence of asymptomatic MCA stenosis, it has been reported that, with transcranial Doppler ultrasound (TCD) and MRA, among total 3,057 patients with vascular high risk factors (elderly, hypertension, diabetes, hyperlipidemia), approximately 385 patients (12.6%) experienced asymptomatic MCA stenosis⁵⁸⁾. It is very difficult to select treatment principles for asymptomatic occlusive disease patients. For the best preventive therapy, the natural course of this disease, has to be understood first.

Reviewing the natural course of asymptomatic occlusive disease (ICA or MCA occlusion), based on 79 months follow-up study showed that the symptomatic change rate in ICA occlusion cases was 5.9% and 22% in MCA occlusion cases²⁹⁾. The reason that symptomatic changes in MCA occlusion was higher than in ICA occlusion is thought to be that in ICA occlusion patients, possible collateral flow (anterior communicating artery, posterior communicating artery, leptomeningeal artery) is more abundant. The interval from the time of diagnosis to the time developing symptoms is average 32 months, and thus the follow up examination once in every 3 years at least is recommended²⁹⁾.

In patients with intracranial atherosclerosis, the increased risk of stroke, heart disease, and death has been consistently observed^{16,8,28,31,50)}. For example, mortality as high as 50% over an average 3.9-year period has been reported in patients with stenosis of the intracranial ICA²⁸⁾. According to the multicenter WASID study reported in 1995⁶⁾, the result of 19.3 months median follow up in 50-99% symptomatic patients with intracranial stenosis angiographically, during the administration of aspirin, showed that 24% developed

stroke, and 17% developed myocardial infarction or sudden death. According to the study reported by Arenillas et al. in 2001, patients with stenosis progressed showed a higher risk of clinical recurrence, a recurrence rate for ipsilateral ischemic events of 9.05% per year³⁾.

Based on pathological specimens, the luminal narrowing is generally caused by local atherosclerosis, but associated thrombus may also contribute. Emboli also causes luminal narrowing⁵⁾. The pathophysiological mechanism of ischemia should be taken into consideration in the assessment of the risk of recurrence of intracranial stenosis. Atherosclerotic process may differ between intracranial and extracranial arteries. In coronary or cervical arteries, ulceration or rupture of previously unstable atherosclerotic plaques causing thromboembolic phenomena would be much more relevant than intracranial arteries, where fibrous or fibrocalcific stable plaques are usually found. However, the reason that the progression of intracranial stenosis becomes the cause of ischemic recurrence is thought to be the cause of severe hemodynamic compromise. Because, microembolic signals were not detected during the TCD monitoring of long term chronic MCA stenosis³⁾, and in addition, because it has been reported that the group with the increased oxygen extraction fraction in PET was a high risk of subsequent stroke¹⁷⁾.

In symptomatic intracranial vertebral artery and basilar artery stenosis ($\geq 50\%$ stenosis), the subsequent stroke risk of any vascular territory stroke rate was 13.7%, 15% per 100 patient-years, stroke rate in the territory of stenotic artery 7.8%, 10.7% per 100 patient-years⁵¹⁾, which was higher than the subsequent stroke rate of symptomatic intracranial ICA or MCA stenosis patients.

ACUTE INFARCTION PATTERNS IN MCA AND INTRACRANIAL ICA STENOSIS

Possible mechanisms of cerebral infarction include thrombosis leading to complete occlusion, artery to artery embolism, hemodynamic compromise, local branch occlusion, or a combination of those factors⁵⁶⁾. Diffusion-Weighted Imaging (DWI) is the most sensitive diagnostic modality for the detection of acute ischemic lesions. In 2005, Lee et al.²⁶⁾ have reported, based on DWI study performed on 185 acute ischemic stroke patients, the infarction pattern and mechanism developed in association with MCA or ICA stenosis were investigated. According to this report, MCA stenosis patients with a single lesion were classified to perforating artery infarction (PAI), pial artery infarction (PI) pattern, large territorial, and border zone (BZ) pattern, and the cases with multiple lesions were classified to PAI+PI, PAI+PI+BZ, PAI+BZ, PI+PI, PI+BZ, and multiple BZ

Fig. 1. A : PAI+PI pattern : a 61-year-old man presented with transcortical sensory aphasia and right hemiparesis. B : PAI+PI pattern : a 67-year-old woman presented with lacunar syndrome (dysarthria and left hemiparesis). C : PAI+PI+BZ pattern : a 65-year-old man presented with transcortical mixed aphasia and right hemiparesis. Arrows indicate the site of MCA disease. From : Stroke. 2005; 36 : 2583.

Fig. 2. Large territorial infarction, in a 24-year-old man presented with left hemiplegia and decreased mentality. Arrow indicates the site of stenosis.

pattern. The pattern of ischemic stroke caused by MCA stenosis was primarily PAI pattern. On the other hand, in ICA stenosis cases, PI+BZ infarction was prevalent (Fig. 1). The infarction pattern caused by cardioembolism (CE) was primarily PI or large territorial infarction pattern in most cases different from the infarction pattern of ICA and MCA stenosis (Fig. 2).

MEDICAL MANAGEMENT OF INTRACRANIAL STENOSIS

The efficacy of medical therapy to prevent stroke in patients who have intracranial stenosis has not been established. According to the WASID study which examined the efficacy of warfarin and aspirin on the subsequent major vascular events (stroke, myocardial infarction, or sudden death) in symptomatic intracranial stenosis⁷⁾, no benefit was detected in the warfarin administration group in comparison with the aspirin administration group, and, interestingly, major hemorrhage complications in the warfarin group were higher

than the aspirin group by approximately 2.5 times. Except the fact that warfarin treatment prevents cardioembolic events, it was not better than aspirin. In addition, according to the recent Warfarin-Aspirin Recurrent Stroke Study (WARSS) cohort⁴¹⁾, there were no treatment differences between two groups. In addition, the risk of warfarin causing bleeding was higher. Therefore, it is recommended to administer antiplatelets to non-cardioembolic stroke instead warfarin.

ENDOVASCULAR TREATMENT OF INTRACRANIAL STENOSIS

Angioplasty without stenting

Intracranial angioplasty can be performed with a high degree of technical success, usually resulting in immediate improvement in the observed stenosis and improved blood flow. Other benefits include reduced stroke risk as a result of normalization of oxygen extraction fraction and increased cerebral blood flow. Marks et al.²⁷⁾ in 2005, performed angioplasty without stenting on 36 patients with symptomatic intracranial stenosis refractory to medical therapy and reported the result. The duration of follow up was average 52.9 months (6-128month). Mean pretreatment stenosis was 84% before angioplasty and 43% after angioplasty. Periprocedural death and stroke rate was 8.3%. The annual stroke rate in the territory appropriate to the site of angioplasty was 3.36% and for those patients with residual stenosis of greater those 50% it was 4.5%. In their conclusion stroke recurrence rate could be lowered by balloon angioplasty only without stenting if stenosis were dilated more than 50%. However, percutaneous transluminal angioplasty are associated with complication such as intimal dissection, recoiling, thrombus formation, and vessel rupture. Stent can diminish vessel dissection and recoil of the stenosis after angioplasty, intraluminal thrombus and vessel rupture²¹⁾.

Stenting

According to the prospectively designed Stenting of Symptomatic atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVA) study⁴⁶⁾ performed in 2004 to evaluate a new stent (NeuroLink, Guidant) developed for the treatment of intracranial atherosclerosis, there was 95% technical and procedural success, and stroke rate within 30 days was 6.6%, 1 year was 13.1%, and none of patients died. However, 35% of patients developed restenosis, and among them, 61% was asymptomatic. Based on the probable benefit-to risk ratio, the US FDA granted a humanitarian device exemption to treat high risk patients with significant intracranial or extracranial atherosclerotic disease who have failed medical

Table 1. Recent major series of treatment of symptomatic patients with intracranial atherosclerotic disease*

	WASID, warfarin versus aspirin	Jiang et al., balloon-expandable stenting	SSYLVA, balloon-expandable stenting	Wingspan HDE, self expanding stenting	Marks et al., stand-alone angioplasty
No. of patients	569	40	43	45 (44 lesions)	36 (37 lesions)
Average% stenosis pretreatment	63.5	80.6	69.9 [†]	74.9	84.2
Index event					
TIA (%)	39.1	72.5	39.3 [†]	8.9	86
Stroke (%)	61.0	27.5	60.7 [†]	91.1	14
30-d ipsilateral stroke and/or death rate (%)	NA	10	6.6	4.5	8.3
1-yr ipsilateral stroke and/or death rate (%)	13.7 % [‡]	0 [§]	13.9	9.3 (44 patients)	10.8
Restenosis (%)	Not applicable	12.5	32.4	7.5	Not available

*WASID, Warfarin-Aspirin Symptomatic Intracranial Disease; SSYLVA, Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries; HDE, Humanitarian Device Exemption; TIA, transient ischemic attack. [†]No breakdown provided for intracranial versus extracranial vessels. [‡]Ipsilateral stroke risk at mean follow-up of 1.8 years. [§]Eight-month follow-up. From: Ecker : Neurosurgery, Volume 59(5) Supplement, November 2006. S3-210-S3-218

therapy using balloon angioplasty and stent placement. In 2005, Henkes et al. have examined the safety and device performance of new family of self expanding stents and reported the initial Wingspan trial⁵³. The result of the trial showed that 98% achieved technical and procedural success, and the 30 day death or ipsilateral stroke rate was 4.4% (2/44) and the 6-month death or ipsilateral stroke rate was 7.1%. Based on this study, US FDA granted a humanitarian device exemption approval for the Wingspan stent system in 2005 to treat symptomatic patients with an intracranial stenosis of >50%, refractory to medical therapy. Comparing with the major treatment studies on the above mentioned symptomatic intracranial stenosis, the treatment group who had received the Wingspan stent showed relatively good results (Table 1). However, all intracranial angioplasty or stenting studies are prospective studies without the control group, and in comparison with the WASID study, evidence is very weak. Therefore, randomized controlled trials are required for the examination of the safety of stenting of MCA stenosis and the effectiveness of stenting on the prevention of recurrent stroke in future.

Drug eluting stenting

In SSYLVA study, angiographic restenosis was observed in 35% of patients and was symptomatic in more than one third of these patients. It could be predicted that with the increase of the stenting procedure for intracranial stenosis, restenosis would be increased higher. Drug eluting stents constitute a major breakthrough in restenosis prevention after percutaneous coronary intervention²⁵. Target lesion restenosis rates of less the 10% at 6months of follow-up have been reported with its use³⁶. Drug eluting stents have rapidly become the stent of choice for coronary intervention, constituting more than 85% of the stents used in the United

States²⁴. Drug eluting stents have a polymer coating that facilitates the release of a drug into the local vascular tissue. Mechanism of action and drugs used so far include anti-inflammatory (dexamethasone and methylprednisone), antiproliferative (angiopectin, actinomycin, paclitaxel, and sirolimus), migration inhibitor (batimastat), and healing promoter actions (estradiol, via vascular endothelial growth factor activation). In 2006, Qureshi et al.³⁷ have reported the result from 18 symptomatic intracranial stenosis patients ($\geq 70\%$ and/or medication failure); sirolimus-eluting stent in 14 cases and paclitaxel-eluting stent performed in 4 cases. One symptomatic angiographic restenosis was observed during 6-month follow-up period. In 2006, Gupta et al.²⁰ used drug eluting stents in 59 patients with 62 intracranial or extracranial atherosclerotic lesions. Two procedural complications were noted. During 3 months follow-up period, restenosis $\geq 50\%$ was seen in only 1 of 26 intracranial stent (5%). They have reported that, although a long term study is required, drug eluting stent is technically feasible and safe. Although initially considered a major advance in preventing late restenosis, drug eluting stents are also associated with subacute and late thrombosis, requiring prolonged antiplatelet therapy for at least 12 month. Further, polymer used as a vehicle for drug delivery may trigger vascular irritation, endothelial dysfunction, vessel hypersensitivity, and chronic inflammation at and around the stent⁵².

EC-IC BYPASS FOR FLOW AUGMENTATION IN ISCHEMIA

After the Cooperative Study on EC-IC bypass in 1985 failed to show a benefit from the bypass procedure over medical management for anterior circulation occlusive disease⁵⁰, the number of bypass procedures declined sharply.

Despite the disappointing findings of this study, a subpopulation of patients with ischemic vascular disease and poor hemodynamic reserve may benefit from EC-IC bypass. According to a long term chronic MCA stenosis TCD monitoring study⁴⁵⁾, microembolic signals in MCA were not detected. This suggests that clinical recurrence may be developed by a hemodynamic mechanism.

Therefore, if the stage of the hemodynamic compromise in stenosis arterial territory could be measured accurately, patients to be benefited by EC-IC bypass could be selected, and the result would be better than previous studies. Recently, by the Carotid Occlusion Surgery Study (COSS)¹⁹⁾ and the Japanese EC-IC bypass Trial (JET)³⁰⁾, the re-evaluation of STA-MCA anastomosis for cerebrovascular occlusive disease is being studied.

Homodynamic assessment

Among cerebrovascular occlusive disease patients, it is very important to understand the cerebrovascular reserve capacity of the affected arterial territory for the selection of patients whose benefit of blood flow augmentation may be larger by EC-IC bypass. There is a multitude of imaging modalities aimed at assessing adequacy of cerebral perfusion : PET, Xenon CT, SPECT, TCD, perfusion CT, and MR perfusion modalities. Degrees of cerebral hemodynamic impairment can be classified into two basic categories, designated as stage 1 and stage 2 hemodynamic compromises. Stage 1 compromise refers to autoregulatory vasodilatation, which occurs to maintain normal CBF by reducing vascular resistance. As perfusion pressure decrease further, the capacity for maintaining normal blood flow by autoregulatory vasodilatation is overcome and CBF decreases; the brain compensates by increasing the extraction of oxygen from the blood to maintain normal cerebral oxygen metabolism, referred to as stage 2 compromises (misery perfusion).

Parameters indicating misery perfusion are correlated with increased stroke incidence after carotid occlusion¹⁹⁾, and PET, therefore has emerged as the gold standard predictive and quantitative tool for assessing critical hypoperfusion. Demonstration of misery perfusion (stage 2 compromise) by PET in patients who have carotid artery

Fig 3. A 45-year-old man presented with presenting crescendo TIA (right hemiparesis and motor aphasia) A : ICA angiogram demonstrates left M1 stenosis (arrow). B : Preop. SPECT demonstrates a loss of vascular reserve capacity on left MCA territories. C : Postoperative, external carotid angiogram showing excellent filling of Left MCA territory by the widely patent STA bypass D : Postoperative, SPECT demonstrating normal blood flow without steal phenomenon.

occlusion is associated with a 30% 2-year stroke risk¹⁸⁾ and this subgroup now form the basis for the multicenter randomized COSS trial currently in progress to examine the usefulness of EC-IC bypass in reducing stroke risk¹⁹⁾. PET, however, is not a universally available imaging modality.

Another method to assess the misery perfusion time is Acetazolamide (vasodilatory drug) challenging test. In the cases with stage 2 compromise areas, more blood flow reduction occurs upon administering acetazolamide. It implies the poor cerebrovascular reserve capacity. Tests applicable to the two paired measurement of base-line CBF and CBF after acetazolamide stimulation are SPECT, xenon CT, etc.

Patient Selection Criteria for EC-IC bypass

In general, the indications for STA-MCA anastomosis bypass for purpose of flow augmentation (Fig. 3) are as follows :

- Symptoms, stroke or TIA concordant with radiographic findings
- Failure of maximal medical therapy
- Compromised cerebrovascular reserve as demonstrated by any of the variety of perfusion imaging studies
- Lack of major medical comorbidities

Ongoing COSS trial in the US and JET study in Japan are assessing the usefulness of bypass in patients who have carotid occlusion and intracranial anterior circulation disease with hemodynamic impairment.

Author's experiences of STA-MCA anastomosis for the patients with intracranial atherosclerosis

In the past 5 years, we performed STA-MCA anastomosis on 52 patients with extracranial and intracranial atherosclerotic occlusive disease (not included other occlusive disease such as moyamoya disease, fibromuscular dysplasia). Long term follow up data (mean 3.5 years, from 5.0 year to 3 month) from consecutive series of 36 patients with intracranial atherosclerotic stenosis or occlusion were reviewed.

All patients presented with repeated transient ischemic attacks refractory to medical therapy. Angiographic findings included MCA stenosis or occlusion in 24 patients, intracranial ICA stenosis or occlusion in 12 patients. All patients for EC-IC bypass surgery were selected by SPECT with acetazolamide challenging test resulting in the decreased cerebral reserve capacity in the symptom related arterial territories.

The vast majority (94.5%) of patients experienced cessation of their ischemic events and stabilization of pre-existing neurological dysfunction. One patient died of pneumonia, and another patient had a severe atherosclerosis case that anastomosis was performed on the cortical artery with almost no blood flow, and eventually, the bypass became occluded.

There was 94.5% of patency rate. Presently, in most patients underwent bypass, new stroke lesions were not developed after surgery, nonetheless, antiplatelet agents are being administered continuously. According to our experience, the selection of patients is very important, and in the elderly (older than 70 years), the risk of pulmonary dysfunction and pneumonia is high and this it is better not to perform the procedure, and in severe intracranial atherosclerosis patients, the flow of the cortical recipient artery may be poor due to atherosclerosis, and thus even if bypass are performed, occlusion of bypass may occur. At this time, it is important to perform bypass by selecting another normal neighbor recipient artery. Even in the presence of intracranial atherosclerotic stenosis or occlusion, new stroke recurrence was hardly detected if collateral circulation is sufficient and thus even if CBF are decreased slightly, and if cerebral vascular reserve capacity is maintained well.

However, in the cases of young patients in their 30-40s if TIA caused by hemodynamic compromise were confirmed, it may be better to perform bypass as soon as possible to improve the active daily life of patient. Cerebral complications associated with bypass surgery such as hyperperfusion syndrome, ICH, local infarction due to recipient cortical or pial artery occlusion are not usually detected in such cases.

CONCLUSION

All symptomatic or asymptomatic intracranial atherosclerotic stenosis has a tendency to progress, and the risk of new stroke is very high. Thus, risk factors (hypertension, diabetes, smoking, hypercholesterolemia, hyperlipidemia, etc.) have to be comprehensively managed, and antiplatelets have to be taken daily. For asymptomatic cases, once every 3 years at least, MRA and perfusion study (SPECT, MR perfusion, CT perfusion) have to be followed up. However, in the cases with atherosclerotic stenosis in posterior circulation, the risk of subsequent stroke is very high in comparison with anterior circulation stenosis, therefore, it is better to conduct follow-up evaluation more frequently. If this lesion becomes occluded, it will be a very serious case, hence, it is better to educate their family to bring the patient to an emergency room upon development for emergent recanalization.

Intracranial stent is a promising therapeutic modality. In near future, the report of the result of randomized controlled trials providing evidences supporting this is anticipated. Presently, it is recommended to perform the procedure following the short segment M1 stenosis and intracranial distal ICA stenosis (asymptomatic $\geq 70\%$, symptomatic $\geq 50\%$).

The bypass procedure is thought to be a relatively safe surgical method. However, it is important to select patients carefully based on test modalities measuring the cerebral reserve capacity that are available to us presently (SPECT, Xenon CT, PET).

• Acknowledgement

This work was supported by Catholic Institute of Cell Therapy foundation (Project Number 35)

References

1. A Veterans Administration Cooperative Study : Role of carotid endarterectomy in asymptomatic carotid stenosis. A Veterans Administration Cooperative Study. *Stroke* 17 : 534-539, 1986
2. Akins PT, Pilgram TK, Cross DT 3rd, Moran CJ : Natural history of stenosis from intracranial atherosclerosis by serial angiography. *Stroke* 29 : 433-438, 1998
3. Arenillas JF, Molina CA, Montaner J, Abilleira S, Gonzalez-Sanchez MA, Alvarez-Sabin J : Progression and clinical recurrence of symptomatic middle cerebral artery stenosis : a long-term follow-up transcranial Doppler ultrasound study. *Stroke* 32 : 2898-2904, 2001
4. Babatasi G, Theron J, Massetti M, Payelle G, Rossi A, Khayat A : Value of percutaneous carotid angioplasty before cardiac surgery. *Ann Cardiol Angeiol (Paris)* 45 : 24-29, 1996
5. Caplan LR, Gorelick PB, Hier DB : Race, sex and occlusive cerebrovascular disease : a review. *Stroke* 17 : 648-655, 1986
6. Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, et al : The Warfarin-Aspirin Symptomatic Intracranial Disease Study. *Neurology* 45 : 1488-1493, 1995
7. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al : Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 352 : 1305-1316, 2005
8. Craig DR, Meguro K, Watridge C, Robertson JT, Barnett HJ, Fox AJ : Intracranial internal carotid artery stenosis. *Stroke* 13 : 825-828, 1982

9. Cybulsky MI, Gimbrone MA Jr : Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. *Science* 251 : 788-791, 1991
10. Diethrich EB, Ndiaye M, Reid DB : Stenting in the carotid artery : initial experience in 110 patients. *J Endovasc Surg* 3 : 42-62, 1996
11. Drexler H : Endothelial dysfunction : clinical implications. *Prog Cardiovasc Dis* 39 : 287-324, 1997
12. European Carotid Surgery Trial (ECST) : Randomised trial of endarterectomy for recently symptomatic carotid stenosis : final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 351 : 1379-1387, 1998
13. Ferris A, Robertson RM, Fabunmi R, Mosca L : American Heart Association and American Stroke Association national survey of stroke risk awareness among women. *Circulation* 111 : 1321-1326, 2005
14. Fisher M, Fieman S : Geometric factors of the bifurcation in carotid atherosclerosis. *Stroke* 21 : 267-271, 1990
15. Fuster V, Badimon L, Badimon JJ, Chesebro JH : The pathogenesis of coronary artery disease and the acute coronary syndromes (2). *N Engl J Med* 326 : 310-318, 1992
16. Futrell N : EC-IC Bypass : The Failure of a Clinical Trial? Applicability to PFO Closure Trials. *Curr Treat Options Cardiovasc Med* 9 : 173-179, 2007
17. Gorelick PB, Caplan LR, Hier DB, Parker SL, Patel D : Racial differences in the distribution of anterior circulation occlusive disease. *Neurology* 34 : 54-59, 1984
18. Grubb RL Jr, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, et al : Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. *JAMA* 280 : 1055-1060, 1998
19. Grubb RL Jr, Powers WJ, Derdeyn CP, Adams HP Jr, Clarke WR : The Carotid Occlusion Surgery Study. *Neurosurg Focus* 14 : e9, 2003
20. Gupta R, Al-Ali F, Thomas AJ, Horowitz MB, Barrow T, Vora NA, et al : Safety, feasibility, and short-term follow-up of drug-eluting stent placement in the intracranial and extracranial circulation. *Stroke* 37 : 2562-2566, 2006
21. Hartmann M, Jansen O : Angioplasty and stenting of intracranial stenosis. *Curr Opin Neurol* 18 : 39-45, 2005
22. Hobson RW 2nd, Goldstein JE, Jamil Z, Lee BC, Padberg FT Jr, Hanna AK, et al : Carotid stenosis : operative and endovascular management. *J Vasc Surg* 29 : 228-235; discussion 235-238, 1999
23. Holme I, Enger SC, Helgeland A, Hjermann I, Leren P, Lund-Larsen PG, et al : Risk factors and raised atherosclerotic lesions in coronary and cerebral arteries. Statistical analysis from the Oslo study. *Arteriosclerosis* 1 : 250-256, 1981
24. Isenbarger DW, Resar JR : Drug-eluting versus third-generation bare metal stents : the US strategy. *Int J Cardiovasc Intervent* 7 : 171-175, 2005
25. Klein LW : Are drug-eluting stents the preferred treatment for multivessel coronary artery disease? *J Am Coll Cardiol* 47 : 22-26, 2006
26. Lee DK, Kim JS, Kwon SU, Yoo SH, Kang DW : Lesion patterns and stroke mechanism in atherosclerotic middle cerebral artery disease : early diffusion-weighted imaging study. *Stroke* 36 : 2583-2588, 2005
27. Marks MP, Marcellus ML, Do HM, Schraedley-Desmond PK, Steinberg GK, Tong DC, et al : Intracranial angioplasty without stenting for symptomatic atherosclerotic stenosis : long-term follow-up. *AJNR* 26 : 525-530, 2005
28. Marzewski DJ, Furlan AJ, St Louis P, Little JR, Modic MT, Williams G : Intracranial internal carotid artery stenosis : longterm prognosis. *Stroke* 13 : 821-824, 1982
29. Miyazawa N, Hashizume K, Uchida M, Nukui H : Long-term follow-up of asymptomatic patients with major artery occlusion : rate of symptomatic change and evaluation of cerebral hemodynamics. *AJNR* 22 : 243-247, 2001
30. Mizumura S, Nakagawara J, Takahashi M, Kumita S, Cho K, Nakajo H, et al : Three-dimensional display in staging hemodynamic brain ischemia for JET study : objective evaluation using SEE analysis and 3D-SSP display. *Ann Nucl Med* 18 : 13-21, 2004
31. Moufarrij NA, Little JR, Furlan AJ, Leatherman JR, Williams GW : Basilar and distal vertebral artery stenosis : long-term follow-up. *Stroke* 17 : 938-942, 1986
32. North American Symptomatic Carotid Endarterectomy Study Group : Carotid endarterectomy : three critical evaluations. *Stroke* 18 : 987-989, 1987
33. North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators : Clinical alert : benefit of carotid endarterectomy for patients with high-grade stenosis of the internal carotid artery. National Institute of Neurological Disorders and Stroke, Stroke and Trauma Division. *Stroke* 22 : 816-817, 1991
34. O'Brien KD, McDonald TO, Chait A, Allen MD, Alpers CE : Neovascular expression of E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 in human atherosclerosis and their relation to intimal leukocyte content. *Circulation* 93 : 672-682, 1996
35. Ogasawara K, Ogawa As : JET study (Japanese EC-IC Bypass Trial). *Nippon Rinsho* 64 Suppl 7 : 524-527, 2006
36. Popma JJ, Leon MB, Moses JW, Holmes DR Jr, Cox N, Fitzpatrick M, et al : Quantitative assessment of angiographic restenosis after sirolimus-eluting stent implantation in native coronary arteries. *Circulation* 110 : 3773-3780, 2004
37. Qureshi AI, Kirmani JF, Hussein HM, Harris-Lane P, Divani AA, Suri MF, et al : Early and intermediate-term outcomes with drug-eluting stents in high-risk patients with symptomatic intracranial stenosis. *Neurosurgery* 59 : 1044-1051; discussion 1051, 2006
38. Rajagopal V, Yadav JS : Management of carotid artery disease in the high-risk patient with emphasis on the SAPHIRE study. *Curr Cardiol Rep* 9 : 20-24, 2007
39. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, et al : 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients : a randomised non-inferiority trial. *Lancet* 368 : 1239-1247, 2006
40. Ross R : The pathogenesis of atherosclerosis : a perspective for the 1990s. *Nature* 362 : 801-809, 1993
41. Sacco RL, Prabhakaran S, Thompson JL, Murphy A, Sciacca RR, Levin B, et al : Comparison of warfarin versus aspirin for the prevention of recurrent stroke or death : subgroup analyses from the Warfarin-Aspirin Recurrent Stroke Study. *Cerebrovasc Dis* 22 : 4-12, 2006
42. Sacco RL, Roberts JK, Boden-Albala B, Gu Q, Lin IF, Kargman DE, et al : Race-ethnicity and determinants of carotid atherosclerosis in a multiethnic population. The Northern Manhattan Stroke Study. *Stroke* 28 : 929-935, 1997
43. Samson DS, Boone S : Extracranial-intracranial (EC-IC) arterial bypass : past performance and current concepts. *Neurosurgery* 3 : 79-86, 1978
44. Schussheim AE, Fuster V : Antibiotics for myocardial infarction? A possible role of infection in atherogenesis and acute coronary syndromes. *Drugs* 57 : 283-291, 1999
45. Sliwka U, Klotzsch C, Popescu O, Brandt K, Schmidt P, Berlit P, et al : Do chronic middle cerebral artery stenoses represent an embolic focus? A multirange transcranial Doppler study. *Stroke* 28 : 1324-1327, 1997
46. SSYL VIA : Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYL VIA) : study results. *Stroke* 35 : 1388-1392, 2004
47. Suh DC, Lee SH, Kim KR, Park ST, Lim SM, Kim SJ, et al : Pattern of atherosclerotic carotid stenosis in Korean patients with stroke : different involvement of intracranial versus extracranial vessels. *AJNR* 24 : 239-244, 2003
48. Sundt TM Jr, Smith HC, Campbell JK, Vlietstra RE, Cucchiara RF, Stanson AW : Transluminal angioplasty for basilar artery stenosis. *Mayo Clin Proc* 55 : 673-680, 1980
49. Taylor RA, Kasner SE : Treatment of intracranial arterial stenosis. *Expert Rev Neurother* 6 : 1685-1694, 2006
50. 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
51. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group : Prognosis of patients with symptomatic vertebral or basilar artery stenosis. *Stroke* 29 : 1389-1392, 1998
52. Virmani R, Farb A, Guagliumi G, Kolodgie FD : Drug-eluting stents : caution and concerns for long-term outcome. *Coron Artery Dis* 15 : 313-318, 2004
53. Weber W, Mayer TE, Henkes H, Kis B, Hamann GF, Schulte-Altdorneburg G, et al : Stent-angioplasty of intracranial vertebral

- and basilar artery stenoses in symptomatic patients. *Eur J Radiol* 55 : 231-236, 2005
54. Weinberger J : Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *Curr Cardiol Rep* 8 : 7, 2006
  55. Wityk RJ, Lehman D, Klag M, Coresh J, Ahn H, Litt B : Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke* 27 : 1974-1980, 1996
  56. Wong KS, Gao S, Chan YL, Hansberg T, Lam WW, Droste DW, et al : Mechanisms of acute cerebral infarctions in patients with middle cerebral artery stenosis : a diffusion-weighted imaging and microemboli monitoring study. *Ann Neurol* 52 : 74-81, 2002
  57. Wong KS, Huang YN, Gao S, Lam WW, Chan YL, Kay R : Intracranial stenosis in Chinese patients with acute stroke. *Neurology* 50 : 812-813, 1998
  58. Wong KS, Ng PW, Tang A, Liu R, Yeung V, Tomlinson B : Prevalence of asymptomatic intracranial atherosclerosis in high-risk patients. *Neurology* 68 : 2035-2038, 2007
  59. 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