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Evidence for Cerebral Hemodynamic Measurement-based Therapy in Symptomatic Major Cerebral Artery Disease

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Abstract

In patients with atherosclerotic internal carotid artery or middle cerebral artery occlusive disease, chronic reduction in cerebral perfusion pressure (chronic hemodynamic compromise) increases the risk of ischemic stroke and can be detected by directly measuring hemodynamic parameters. However, strategies for selecting treatments based on hemodynamic measurements have not been clearly established. Bypass surgery has been proven to improve hemodynamic compromise. However, the benefit of bypass surgery for reducing the stroke risk in patients with hemodynamic compromise is controversial. The results of the two randomized controlled trials were inconsistent. Hypertension is a major risk factor for stroke, and antihypertensive therapy provides general benefit to patients with symptomatic atherosclerotic major cerebral artery disease. However, the benefit of strict control of blood pressure for reducing the stroke risk in patients with hemodynamic compromise is a matter of debate. The results of the two observational studies were different. We must establish strategies for selecting treatments based on hemodynamic measurements in atherosclerotic major cerebral artery disease.

Key words: cerebrovascular disease, positron emission tomography, misery perfusion, blood pressure, bypass surgery

Introduction

In patients with either symptomatic extracranial internal carotid artery (ICA) occlusion or intracranial stenosis or occlusion of the ICA or middle cerebral artery (MCA), the evidence for therapeutic strategies to prevent recurrent strokes is limited. The severity of hemodynamic impairment distal to a diseased artery is the most important predictor of subsequent stroke.[1,2] Therefore, therapeutic strategies to prevent recurrent strokes should differ between patients with and without hemodynamic impairment. Here, we summarize recent reports on the strategies for selecting treatments based on hemodynamic measurements, and discuss the usefulness for the evaluation of hemodynamic status.

Hemodynamic Impairment and Stroke Risk

Studies in the 1990s demonstrated that chronic hemodynamic compromise, as indicated by increased oxygen extraction fraction (OEF; misery perfusion)[3] on positron emission tomography (PET) or severely decreased vasodilatory capacity, is a risk factor for subsequent ischemic stroke in atherosclerotic ICA or MCA occlusive disease.[4–11]

Improvement of medical secondary prevention in the 2000s may progressively decrease the recurrent stroke risk in patients with ICA or MCA occlusive disease.[12,13] To determine whether misery perfusion is still a predictor of subsequent stroke despite recent improvements in medical treatment for secondary prevention of stroke, we studied 130 non-disabled patients with symptomatic major cerebral artery disease.[2] Baseline hemodynamic measurements were obtained from ^{15}O-gas PET, and patients received medical treatment and were followed for 2 years or until stroke recurrence or death. The incidence of subsequent stroke was higher in patients with misery perfusion than in those without, under the use of recent standard medical treatments. In patients with and without misery perfusion, the 2-year incidence of ipsilateral ischemic stroke was 4/16 (25%) and 3/114 (2.6%), respectively ($P < 0.001$), and the all-stroke incidence was 4 (25%)

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and 9 (7.9%), respectively ($P < 0.05$). Between the study periods (1999–2010), patients without misery perfusion demonstrated a decrease in stroke rate, but patients with misery perfusion did not. In symptomatic major cerebral artery disease, misery perfusion remains the most important predictor of subsequent stroke. Thus, identification and strict management of patients with misery perfusion are essential steps to further improve prognosis.

In this observational study, we compared different PET methods to predict subsequent stoke risk.[2] We defined misery perfusion as increased OEF, decreased cerebral blood flow (CBF), and decreased CBF/cerebral blood volume (CBV). Such "complete" misery perfusion is a better predictor of stroke risk than increased OEF alone in patients with symptomatic major cerebral arterial occlusive disease. The recurrence rate in patients with increased OEF without decreased CBF/CBV was low. The increased ipsilateral-to-contralateral ratio of OEF was a predictor of stroke risk only when an appropriate cut-off value is selected in ICA occlusion, but it was not in intracranial major arterial disease. The "complete" misery perfusion defined by using quantitative measurements of CBF, OEF, and CBF/CBV allowed effective stratification of high-risk patients regardless of whether the arterial disease affected the extracranial or intracranial vasculature.

Extracranial-to-Intracranial (EC-IC) Bypass Surgery

I. Japanese EC/IC Bypass Trial (JET) and carotid occlusion surgery study

In 1985, a randomized clinical trial demonstrated that EC-IC bypass surgery has no benefit in patients with ICA or MCA occlusive disease, in general.[14] To determine whether bypass surgery prevents recurrent strokes in select patients with hemodynamic compromise, two randomized clinical trials have used hemodynamic criteria for patient selection.[15,16] EC-IC bypass surgery can improve misery perfusion.[3,17,18] However, operative risk may be high in patients with misery perfusion.

One study using single photon emission computed tomography (SPECT), the JET study (1998–2004), demonstrated a benefit of bypass surgery for preventing disabling stroke (modified Rankin scale > 2).[15] Two-hundred and six patients with decreased CBF and decreased CBF response to acetazolamide were selected. The 2-year ipsilateral disabling stroke rate of 2.9% (3/103) in the surgical group included perioperative stroke and was significantly lower than that of 10.6% (11/103) in the medically treated group ($P < 0.05$). No perioperative disabling stroke occurred, although some non-disabling stroke may have occurred. Because of the high prevalence of moyamoya disease, EC-IC bypass with postoperative management is an essential skill of neurosurgeons in Japan,[19] which may have resulted in the 0% perioperative disabling stroke rate of the JET.

Another study using PET (carotid occlusion surgery study; COSS) (2002–2010) in the United States and Canada reported a lack of benefit from bypass surgery in 195 patients with symptomatic carotid occlusion and misery perfusion (hemispheric OEF count ratio > 1.13).[16] The 2-year ipsilateral stroke rate was 22.7% (20/98) in the medical group and 21% (20/97) in the surgical group. The surgical group exhibited high rates of bypass graft patency, improved cerebral hemodynamics as measured by OEF ratio (from 1.258 ± 0.14 at baseline to 1.109 ± 0.101 at the 30- to 60-day), and much lower rates of recurrent ipsilateral ischemic stroke after postoperative Day 2 compared with the medical group (9% vs. 22.7%, respectively, at 2 years). However, the perioperative stoke rate in the COSS (15%, any stroke) was higher than that in the JET study (0%, disabling stroke) and nullified any benefit of bypass surgery.

The stroke rate in the medical group (23%) was much lower than the rate of 40% projected from a previous study carried out from 1992 to 1997,[5] which presumably reflects the overall increased efficacy of recent medical treatment for secondary stroke prevention, although there is an issue of the hemispheric OEF ratio method to detect high risk patients.[20]

The results of the two randomized clinical trials were inconsistent. EC-IC bypass surgery may be a useful treatment to improve misery perfusion. However, its benefit may depend on achieving low operative risk. The surgical complications rates must be needed to be very low. The third randomized clinical trial using hemodynamic criteria for patient selection with computed tomography (CT) perfusion imaging, Carotid and Middle Cerebral Artery Occlusion Surgery Study (CMOSS), is ongoing in China.[21]

II. Randomized Evaluation of Carotid Occlusion and Neurocognition (RECON) trial

In addition to prevention of recurrent strokes, EC-IC bypass may improve cognitive impairment that may be caused by cerebral hemodynamic impairment due to atherosclerotic ICA or MCA disease.[22,23] However, the treatment of cognitive impairment in this population has never been tested in a randomized controlled trial. RECON trial, an ancillary study of COSS, tested the hypothesis that EC-IC bypass can improve or preserve cognition over 2 years compared to best medical therapy alone in patients with symptomatic ICA occlusion and increased OEF ratio on PET.[24]

Patients were enrolled into RECON between 2005 and 2010. The COSS trial was terminated early for futility, thus discontinuing RECON enrollment. Eighty-nine patients were enrolled; 41 had increased OEF and were randomized. Two died, two were lost to follow-up, and two refused 2-year testing. Of the 35 remaining, 6 had ipsilateral stroke or death, leaving 13 surgical and 16 medical patients. Controlling for age, education, and depression, there was no difference in 2-year cognitive change between the medical and surgical arms. There was no evidence to support superiority of EC-IC bypass surgery plus best medical therapy in preserving or improving cognition over medical therapy alone in patients with recently symptomatic ICA occlusion and increased OEF.

This study was limited by the small sample size. Furthermore, there was only a relatively modest reduction in OEF ratio achieved by the bypass. The OEF PET ratio in the surgical group had a statistically significant decrease from an average of 1.24 at baseline to 1.14 at 30 days postoperatively. However, only 3 of the 13 surgical patients had 30-day PET OEF ratios < 1.13, the COSS threshold for randomization into the study, and none of the 13 achieved OEF ratio < 1.067, the upper limit of normal for the COSS cohort overall. Further studies are needed to determine whether vascular reconstruction surgery can improve or preserve cognition in association with hemodynamic improvement.

Control of Blood Pressure (BP)

To improve the prognosis of high-risk patients with symptomatic major cerebral artery disease and hemodynamic impairment, best medical management is important. In addition to the use of antiplatelet drugs, an appropriate control of vascular risk factors is necessary. Hypertension is the most important, modifiable risk factor for stroke. Antihypertensive therapy provides general benefit to patients with a history of stroke. However, the benefit of strict BP control is controversial.[25–27] There had been concern that lowering BP might impair cerebral perfusion in patients with atherosclerotic ICA or MCA occlusive disease and thereby increase stroke risk.[17,28] Previous studies have demonstrated that the risk of stroke increases with BP in the great majority of patients with stenosis of the extracranial ICA or intracranial large artery, although the relationship is less steep than in patients without major cerebral artery disease.[29–31] In patients with symptomatic intracranial large artery stenosis, the risk of ischemic stroke was high only when patients with moderate stenosis had the systolic blood pressure (SBP) 160 mmHg or above.[31] Furthermore, patients with symptomatic bilateral carotid stenosis > 70% exhibited an inverse relationship between BP and stroke.[30] These findings suggest that the BP stroke-risk relationship may have been influenced by the presence of impaired perfusion. Notably, these studies did not include direct evaluations of baseline patient hemodynamic status. They also did not include patients with symptomatic occlusion of the major cerebral arteries, in which the incidence of impaired perfusion is greater than in patients with stenosis of the major cerebral arteries. Thus, the interpretation of these studies was limited by the fact that the proportion of patients with impaired perfusion was unknown and potentially low.

In our observational study of 130 medically-treated patients with symptomatic major cerebral artery disease described above, we analyzed the relationships among follow-up BP, impaired perfusion as indicated by a decreased CBF/CBV ratio at baseline,[32] and 2-year stroke risk to determine whether the relationship between follow-up BP level and recurrent stroke risk differs between patients with or without hemodynamic impairment.[26] Impaired perfusion implies that autoregulatory response to reduction in BP is disturbed. BP during the follow-up period was defined as the value of BP obtained just before stroke recurrence, death, or the end of the follow-up period. Continuous SBP measurements were categorized as follows: < 130 mmHg, 130–149 mmHg, 150–169 mmHg, and ≥170 mmHg.

There was a negative linear relationship between SBP and risk of stroke in the territory of the diseased artery; the hazard ratio (HR) per 20 mmHg was 0.27 [95% confidence interval (CI), 0.08–0.93, $P < 0.05$). On the other hand, there was a positive linear relationship between SBP and risk of stroke in the other vascular territory; the HR per 20 mmHg was 4.02 (95% CI, 1.48–10.87, $P < 0.01$). The 2-year incidence of ischemic stroke in the territory in patients with normal SBP (< 130 mmHg) (5/32; 15.6%) was significantly higher than in patients with high SBP (2/98, 2.0%, $P < 0.005$). Multivariate analysis revealed that normal SBP and impaired perfusion were independently associated with increased risk of stroke in the previously affected territory, while risk of stroke elsewhere was positively correlated with SBP. High total stroke risk was observed at lower BPs in patients with impaired perfusion and at higher BPs in patients without. Thus, the relationship between follow-up BP level and recurrent stroke risk differed between patients with or without impaired perfusion (interaction, P < 0.01; Fig. 1).

Overall, the relationship between SBP and total stroke recurrence was J-shaped. The incidence of total strokes was lowest in patients with SBP values within the 130–149 mmHg range. This J-shaped association was caused by the combined effects of the negative association with recurrent stroke in patients with impaired perfusion and the positive association with recurrent stroke in patients without impaired perfusion. The presence of a J-shaped association between BP and risk of recurrent stroke is a matter of debate.[33–35] The difference of the proportion of patients with impaired perfusion may contribute to the discrepant results among previous studies investigating the development of a J-shaped association between BP and stroke recurrence.

We continued the follow-up of the patients for 5 years.[26] Stroke recurrence occurred mainly in the territory of the diseased artery within 2 years in patients with impaired perfusion, while most recurrent strokes occurred in the other vascular territory after 1 year in patients without impaired perfusion (Fig. 2). Normal SBP (< 130 mmHg) was associated with an increased risk of ipsilateral ischemic strokes in patients with impaired perfusion (including misery perfusion). On the other hand, in patients without impaired perfusion, SBP outside the 130–149 mmHg range was associated with an increased risk of all strokes and most strokes in the other vascular territory occurred at the level of SBP 150 mmHg or above.

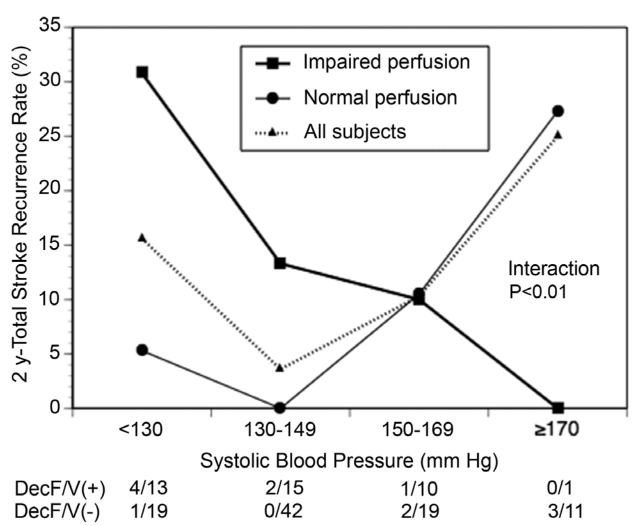

Fig. 1 Line graph showing subgroup comparisons of 2-year (y) total stroke recurrence rate as a function of systolic blood pressure, based on the presence of impaired perfusion, as indicated by decreased cerebral blood flow (CBF)/cerebral blood volume (CBV) [DecF/V].[26]

The Japanese Society of Hypertension (JSH 2014) guidelines recommend that the target level of BP control should be < 140/90 mmHg in the chronic phase of cerebral infarction in general.[36] This may be true for patients without impaired perfusion. Our data suggest that control of BP to the level of < 140/90 mmHg within 1 year would reduce recurrent strokes in the other vascular territory after 1 year. Optimal SBP targets may be near 130 mmHg. However, in patients with impaired perfusion, including those with misery perfusion, an aggressive BP reduction and a strict control of BP (< 130 mmHg) may be hazardous and may increase stroke recurrence in the territory of the diseased artery, especially during the first 2 years after presentation. BP should be mildly controlled depending on the level of BP in

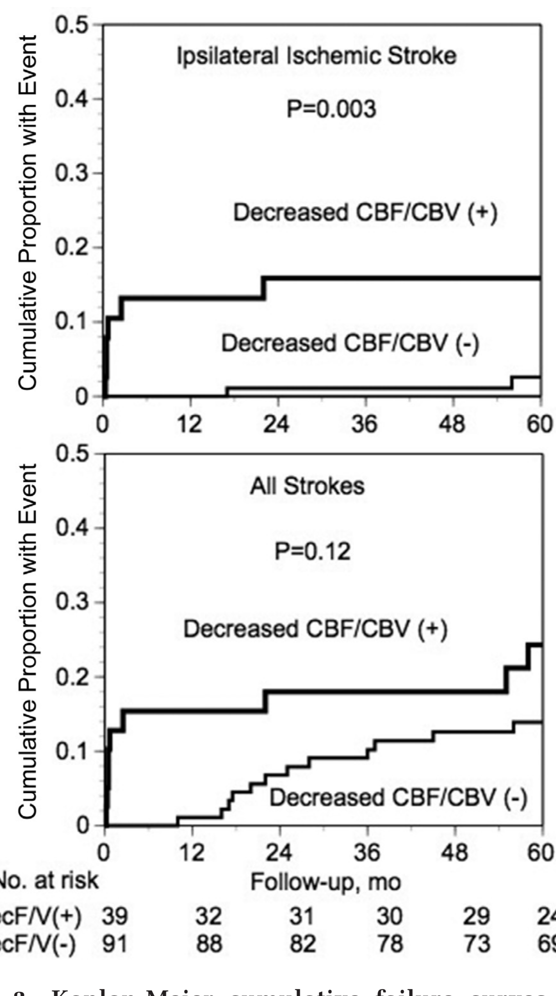

Fig. 2 Kaplan-Meier cumulative failure curves for ipsilateral ischemic stroke (*upper row*) and all strokes (*lower row*) in patients with and without decreased cerebral blood flow (CBF)/cerebral blood volume (CBV) [DecF/V]. The number of patients who remained event-free and available for follow-up evaluation is shown at the bottom of the graph.

each patient. Optimal SBP targets may be around 140 mmHg. For appropriate BP control, patients with and without impaired perfusion should be treated differently. Thus, identification of patients with impaired perfusion is essential for regulating BP to reduce stroke recurrence.

No previous studies have compared the BP stroke-risk relationship between patients with and without hemodynamic impairment. Recently, Powers et al. evaluated the BP stroke-risk relationship in 91 non-surgical controls from the COSS.[27] All patients had an increased OEF ratio ipsilaterally to recently symptomatic carotid occlusion. The target goal for BP was 130/85 mmHg in the COSS. They excluded four patients who had ipsilateral ischemic strokes before the first BP recording at the 30- to 35-day follow-up visit. The exclusion of such patients who had possible unstable hemodynamic status may have affected the results. They reported that three ipsilateral ischemic strokes occurred in the 41 patients with mean follow-up BP of ≤ 130/85 mmHg compared with 13 in the remaining 50 patients with mean follow-up BP of > 130/85 mmHg (HR, 3.74; 95% CI, 1.07–13.15; P = 0.027), which is inconsistent with our results.

Because the imaging feature of ipsilateral ischemic strokes in the COSS was not reported, the mechanism of stroke is unclear. Thus, we can only speculate the reason of the difference. If ipsilateral ischemic strokes in the COSS were low-flow infarcts, it is suggested that patients with an increased OEF and a higher BP may be more susceptible to low-flow infarcts due to a reduction in BP than in those with a lower BP, which may cause stroke before BP can reach the target (130/85 mmHg). However, Derdeyn et al. reported that most recurrent stokes occurred in the MCA core territory and were thromboembolic in patients with ICA occlusion and an increased OEF ratio.[37] They suggested that thromboemboli might cause infarction more readily in the setting of poor collateral circulation. In the COSS, embolic stroke may have occurred more frequently in carotid occlusion patients with a higher BP than in those with a lower BP. In our cohort, subcortical infarcts were a major type of recurrent ipsilateral stokes, in which the embolic mechanism was less likely.[2,27]

The population of the patients in the COSS might have more widespread systemic atherosclerosis than our cohort, which was associated with higher risk for thromboembolism. For example, the incidence of the patients using any lipid-lowering drugs in the COSS (89%) was higher than that in our cohort (30%).[16] On the other hand, our cohort included intracranial large artery diseases and might have more widespread arteriosclerosis of the intracranial arteries. Under the use of antiplatelet drugs, the patients in the COSS might have the tendency to cause embolic strokes at the higher level of BP, while the lower level of BP may have caused subcortical low-flow infarcts in our cohort.

In any case, a randomized controlled trial is needed to determine the level at which the BP should be lowered to achieve maximal benefits in patients with or without hemodynamic compromise. Evidence in the United States may differ in the background of atherosclerotic major cerebral artery disease from that in Japan. Therefore, more evidences in Japan are needed to establish strategies for selecting treatments based on hemodynamic measurements in Japanese patients with atherosclerotic major cerebral artery disease.

Conclusion

In Japan, strategies for selecting treatments based on hemodynamic measurements, including bypass surgery or appropriate control of BP, may improve prognosis of patients with atherosclerotic major cerebral artery disease. Expert neurosurgeons in Japan can perform bypass surgery with low perioperative stroke rate, which will reduce stroke recurrence in high-risk patients with hemodynamic impairment.[38] Hemodynamic measurements with SPECT, perfusion magnetic resonance imaging, or CT as well as ^{15}O-gas PET are covered by health insurance in Japan. Thus, we can establish strategies for selecting treatments based on hemodynamic measurements in atherosclerotic major cerebral artery disease.

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Conflicts of Interest Disclosure

None.

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