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ABSTRACT

BACKGROUND AND PURPOSE: The relationship between reperfusion and clinical outcome is time-dependent, and the effect of reperfusion on outcome can vary on the basis of the extent of collateral flow. We aimed to identify the impact of time-to-reperfusion on outcome relative to baseline angiographic collateral grade in patients successfully treated with endovascular revascularization for acute large-vessel anterior circulation stroke.

MATERIALS AND METHODS: Two hundred seven patients were selected for analysis from our prospectively maintained registry. Inclusion criteria were M1 MCA ± ICA occlusions, onset-to-puncture time within 8 hours, and successful endovascular reperfusion. Baseline angiographic collateral grades were independently evaluated and dichotomized into poor (0–1) versus good (2–4). Multivariable analyses were performed to identify the effect of collateral-flow adequacy on favorable outcome on the basis of onset-to-reperfusion time and puncture-to-reperfusion time.

RESULTS: In the poor collateral group, the odds of favorable outcome significantly dropped for patients with onset-to-reperfusion time of >300 minutes or puncture-to-reperfusion time of >60 minutes (onset-to-puncture time: ≤ 300, 59% versus >300, 32%; OR, 0.24; \( P = 0.011 \); puncture-to-reperfusion time: ≤ 60, 73% versus >60, 32%; OR, 0.21; \( P = 0.011 \)), whereas the probability of favorable outcome in the good collateral group was not significantly influenced by onset-to-reperfusion time or puncture-to-reperfusion time. In the subgroup lesion-volume growth analysis by using DWI, the effect of puncture-to-reperfusion time of >60 minutes was significantly greater compared with the effect of puncture-to-reperfusion time of ≤ 60 minutes in the poor collateral group (\( \beta = 41.6 \text{ cm}^3, P = 0.001 \)).

CONCLUSIONS: Time-to-reperfusion including onset-to-reperfusion time and puncture-to-reperfusion time in patients with poor collaterals is an important limiting factor for favorable outcome in a time-dependent fashion. Future trials may benefit from a noninvasive imaging technique to detect poor collaterals along with a strategy for rapid reperfusion.

ABBREVIATIONS: HI = hemorrhagic infarction; OPT = onset-to-puncture time; ORT = onset-to-reperfusion time; PH = parenchymal hematoma; PRT = puncture-to-reperfusion time

The restoration of antegrade perfusion to the ischemic territory is the principal goal of current acute stroke treatments because it is associated with better clinical outcomes and reduced mortality. Also, the effect of reperfusion on outcome is time-dependent, and onset-to-reperfusion time (ORT) has emerged as an important time metric to show the benefit of endovascular treatment.

However, the effect of reperfusion on outcome can vary on the basis of the extent of collateral flow. Baseline collateral flow, which is an important determinant of clinical recovery, can mitigate potential injury to ischemic brain tissue. Before adequate reperfusion occurs, the penumbral area can continue to be salvageable depending on the robustness of collateral flow, and its impact on infarct growth and subsequent clinical outcome may be time-dependent, along with reperfusion status. It can be speculated that in patients with poor collaterals, the relationship between reperfusion and clinical outcome may be more dependent on time-to-reperfusion because the odds of potential brain injury may be higher until reperfusion occurs.

We hypothesized that differential clinical response to reperfusion can be driven by the quality of baseline collaterals in a time-
MATERIALS AND METHODS

Between May 2006 and April 2013, patients were retrospectively selected from a prospectively maintained acute stroke intra-arterial treatment registry at our institution. Eligibility for inclusion in this study was that patients met the following criteria: 1) They had an acute anterior circulation stroke with angiographically confirmed ICA-T or -L, MCA M1, or ICA/M1 tandem occlusion; 2) had evaluable angiographic collateral grading; 3) had arterial puncture from stroke onset within 8 hours; and 4) achieved a sufficient angiographic reperfusion. Treatment strategies were selected on the basis of available therapies at the time of angiography, which included intra-arterial thrombolytic infusion (urokinase or rtPA), mechanical clot disruption, mechanical thrombectomy including forced arterial suction thrombectomy or Solitaire thrombectomy (Covidien, Irvine, California), rescue intra-/extracranial stent, or a combination.16-18

Angiographic collateral-flow grade was evaluated with the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology collateral-flow grading system on pretreatment angiography. This angiographic scale assigns patients to grades 0–4 according to the completeness and rapidity of collateral filling in a retrograde fashion.13 The angiographic collateral-flow grade was independently evaluated by an experienced neuroradiologist (Y.-W.K.) and neuroradiologist (D.-H.K.) blinded to patient information and was dichotomized as poor (collateral-flow grades 0–1) and good (2–4). The κ coefficient for interobserver agreement was 0.864 for each collateral grade. Disagreement was resolved by consensus. Reperfusion status was measured by the same raters and methods for the TICI scale.13

Information on demographic and clinical characteristics, medical history, admission blood pressure, and blood glucose levels was collected at baseline. The onset of stroke was defined as the time when the patient was last observed to be healthy. Stroke severity was assessed by using the NIHSS at baseline. The DWI at baseline was assessed by using ASPECTS.20 All patients underwent CT or MR imaging at 24–48 hours after the treatment. If there was evidence of hemorrhage, the subtype was classified as hemorrhagic infarction (HI), parenchymal hematoma (PH), SAH, intraventricular hemorrhage, or mixed.21 Symptomatic intracranial hemorrhage was defined as any type of hemorrhage associated with an increase in the NIHSS score of ≥4 within 24 hours.22 A subset of 160 patients had undergone both pretreatment and posttreatment DWI (3–7 days from stroke onset). One experienced neurologist (Y.-W.K.) who was blinded to clinical status performed DWI lesion-volume calculation by using an open source image-analysis software (OsiriX Imaging Software; http://www.osirix-viewer.com). Functional status was assessed by using the mRS at 3 months, and favorable outcome was defined as an mRS of ≤2 or equal to the prestroke mRS if the prestroke mRS was >2.22,23

Statistical Analysis

Statistical analysis was performed by using the SPSS statistical package (Version 20.0; IBM, Armonk, New York). Bivariate comparisons were made by using the χ² test or Fisher exact test as appropriate for categoric variables. The Student t test was used for continuous variables, and the Mann-Whitney U test was used for ordinal and continuous variables that had skewed distributions. Multivariable regression analysis was performed to identify the effect of collateral-flow grade on each outcome or lesion volume.

**FIG 1.** Flow chart description of patient selection and exclusion for the study. IAT indicates intra-arterial treatment.

**TABLE 1.** Flow chart description of patient selection and exclusion for the study. IAT indicates intra-arterial treatment.
RESULTS

During the study period, 207 patients were included for analysis, and the details of exclusion are described in Fig 1. Overall, 76 patients (37%) were assigned to the poor collateral group (collateral-flow grades, 0–1), and 131 patients (63%), to the good collateral group (collateral-flow grades, 2–4). The baseline characteristics and outcomes are described in the Table (On-line Table 1 in detail). Patients in the poor collateral group had a higher baseline NIHSS score, a lower baseline ASPECTSDWI score, a higher incidence of ICA-T or -L occlusion, and a lower rate of 3-month favorable outcome, all statistically significant.

Time-to-Reperfusion and Favorable Outcome

As shown in Fig 2A, the probability of favorable outcome decreased with every minute increase of ORT in the poor collateral group (OR, 0.99; 95% CI, 0.99–1.00; \(P = .021\)). The effect of ORT on the probability of favorable outcome in the good collateral group was also time-dependent, but it was not statistically significant (OR, 1.00; 95% CI, 0.99–1.00; \(P = .080\)). With 30-minute time intervals, the OR magnitude was 0.80 (95% CI, 0.67–0.96; \(P = .015\)) in the poor collateral group compared with the good collateral group (OR, 0.90; 95% CI, 0.80–1.02; \(P = .096\)) after adjustment for age, baseline NIHSS score, and posttreatment TICI 2b–3 reperfusion. With a time cutoff point of 300 minutes for ORT, ORT of \(\geq 300\) minutes remained as an independent predictor of decreased odds for favorable outcome in patients with poor collateral flow (OR, 0.24; 95% CI, 0.08–0.72; \(P = .011\)) compared with good collateral flow (OR, 0.47; 95% CI, 0.21–1.08; \(P = .074\)) after adjustment for age, baseline NIHSS score, and posttreatment TICI 2b–3 reperfusion (Fig 3A).

We divided the ORT between onset-to-puncture time (OPT) and puncture-to-reperfusion time (PRT) to determine the effects of time spent on endovascular treatment. There was no time-dependent effect on favorable outcome based on a time cutoff point of 240 minutes of OPT. Rather, as shown in Fig 2B, the probability of favorable outcome decreased with every minute increase of PRT in the poor collateral group (OR, 0.99; 95% CI, 0.98–1.00; \(P = .038\)). The effect of PRT on the probability of favorable outcome in the good collateral group was also time-dependent, but it was not statistically significant (OR, 1.00; 95% CI, 0.99–1.00; \(P = .048\)). With 30-minute time intervals, the OR magnitude was 0.80 (95% CI, 0.67–0.96; \(P = .015\)) in the poor collateral group compared with the good collateral group (OR, 0.90; 95% CI, 0.80–1.02; \(P = .096\)) after adjustment for age, baseline NIHSS score, and posttreatment TICI 2b–3 reperfusion (Fig 3B).
increase of PRT in the poor collateral group (OR, 0.97; 95% CI, 0.96–0.99; \( P \leq 0.001 \)). The effect of PRT on the probability of favorable outcome in the good collateral group was also time-dependent (OR, 0.99; 95% CI, 0.98–1.00; \( P = 0.005 \)). According to a time cutoff point of 60 minutes, PRT of \( \geq 60 \) minutes remained an independent predictor of decreased odds of favorable outcome in patients with poor collateral flow (OR, 0.21; 95% CI, 0.06–0.70; \( P = 0.011 \)) compared with good collateral flow (OR, 0.80; 95% CI, 0.34–1.85; \( P = 0.601 \)) after adjustment for age, baseline NIHSS score, posttreatment TICI 2b–3 reperfusion, and OPT (Fig 3B). The cutoff time points for ORT and PRT were chosen on the basis of sensitivity and specificity analyses, and details are described in the On-line Figure.

**Time-to-Reperfusion and Mortality/Intracerebral Hemorrhage**

Unlike the significant relationship between the probability of favorable outcome and time-to-reperfusion, no statistically significant relationship was seen between the probability of mortality and prespecified time metrics based on collateral-flow grade. As to hemorrhage, the rate of HI was significantly increased in patients with ORT of \( >300 \) minutes in both the poor and good collateral groups. Likewise, a PRT of \( >60 \) minutes also increased the rate of HI, which remained as an independent predictor of increased odds of HI (OR, 6.60; 95% CI, 1.23–34.1; \( P = 0.024 \)) in the poor collateral group compared with the good collateral group (OR, 2.28; 95% CI, 0.88–5.95; \( P = 0.091 \)) after adjustment for age, baseline NIHSS score, posttreatment TICI 2b–3 reperfusion, and OPT (Fig 3C). The rate of PH was not significantly influenced by the prespecified time metrics based on collateral-flow grade (On-line Table 2).

**Time to Reperfusion and DWI Lesion Volume**

A subset of 160 patients (of 207, 77.3%) completed both pretreatment and posttreatment DWI (3–7 days from stroke onset). There was a significant imbalance regarding the completion of both DWIs between patients with a favorable outcome or those without; 108 of 117 (92.3%) in patients with a favorable outcome versus 52 of 90 (57.8%) in patients with an unfavorable outcome (\( P < 0.001 \)). At baseline, the median DWI lesion volume was 14.6 and 9.8 cm\(^3\) in the poor and good collateral group, respectively (\( P = 0.115 \)). The median DWI lesion volume at posttreatment and DWI lesion-volume growth were 56.6 cm\(^3\) and 31.1 cm\(^3\) versus 18.4 cm\(^3\) and 7.0 cm\(^3\) in the poor and good collateral groups, respectively (\( P = 0.002 \) and \( P = 0.001 \)). Multiple regression analysis was performed to elucidate the effect of prespecified time cutoff points on DWI lesion volume based on collateral-flow grade (On-line Table 3). PRT of \( >60 \) minutes in the poor collateral group was an independent predictor of larger final lesion volume (\( \beta = 46.8 \) cm\(^3\); \( P = 0.004 \)) and lesion-volume growth (\( \beta = 41.6 \) cm\(^3\); \( P = 0.001 \)) after adjustment for age, baseline NIHSS score, posttreat-
The results of this study should be interpreted with caution because it was not a randomized, controlled trial. Patients were treated with a variety of reperfusion therapies, including throm-
bolitics and different types of endovascular therapy. Furthermore, although our patients were enrolled prospectively, the decision for endovascular treatment was based on our institutional treatment protocol and the attending physician’s decision, so there was a chance of exclusion from our study if the patient had a sizable infarct volume with a large- vessel occlusion despite being within the treatable time window. Therefore, this study was limited by its retrospective nature and inherent case-selection bias. For example, for patients with poor collaterals at baseline, the chance of sizable infarct volume might be higher, and such a patient could be excluded from endovascular treatment. In addition, the exclusion of patients who failed reperfusion despite endovascular treatment might affect the results of our study because the chance of successful reperfusion could be higher in cases of good collaterals.11,30

CONCLUSIONS
In considering endovascular revascularization as a rescue treatment in patients with acute large-vessel occlusion, the status of baseline collateral flow at the time of angiography can be a crucial marker for favorable outcome and a limiting factor for lesion-volume increments in a time-dependent fashion (Fig 4). Therefore, limiting time-to-reperfusion, especially in patients with poor collaterals, is desirable in clinical practice, though our results should be confirmed in randomized trials or large datasets of prospective trials.

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