First-pass effect in patients with acute vertebrobasilar artery occlusion undergoing thrombectomy: insights from the PERSIST registry

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Abstract

Background: Achieving rapid and complete vascular recanalization in patients with acute large vessel occlusion can significantly improve patients’ prognosis.

Objective: We aimed to investigate the potential contribution of the first-pass effect (FPE) to the clinical outcome of patients with acute vertebrobasilar artery occlusion (VBAO).

Methods: We retrospectively analyzed the data of patients who underwent endovascular thrombectomy (EVT) caused by VBAO in a multicentered retrospective registry dataset. FPE was defined as successful recanalization [modified thrombolysis in cerebral infarction (mTICI) 2b/3 as modified FPE (mFPE); mTICI 3 as true FPE (tFPE)] after one pass of the device without rescue therapy. The baseline characteristics and procedural and clinical outcomes were analyzed. Multivariate analysis was used to explore the predictors of FPE and the relationship between FPE and 90-day prognosis.

Results: A total of 508 patients (age, 63.7 ± 13.1 years, male, 71.6%) were finally included, 29.9% (152/508) of whom achieved mFPE, and 21.1% (107/508) of whom achieved tFPE. FPE was significantly associated with improved clinical outcomes, regardless of mFPE [odds ratio (OR): 0.601, 95% confidence interval (CI): 0.370–0.977, p = 0.040] and tFPE (OR: 0.547, 95% CI: 0.318–0.940, p = 0.029). The use of contact aspiration, favorable collateral status, cardioembolic etiology, and basilar artery occlusion were statistically significant predictors of mFPE and tFPE, whereas hypertension was a negative predictor. Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) prior to EVT was a positive predictor of mFPE but not of tFPE.

Conclusion: FPE was associated with significantly favorable outcomes in EVT patients with VBAO. The predictors of FPE include infarct etiology, the site of occlusion, collateral status, EVT strategies, and IV rt-PA bridging strategies.

Trial registration number: URL: http://www.chictr.org.cn/; Unique identifier: ChiCTR2000033211.

Keywords: recanalization, stroke, thrombectomy, vertebrobasilar artery occlusion

Introduction

Posterior circulation stroke occurs in approximately one-fifth of all ischemic strokes,1 which are supplied by the vertebrobasilar artery and result in severe disability or death in nearly two-thirds of patients.2

Previously, several randomized controlled studies have shown that endovascular thrombectomy (EVT) was a safe and effective treatment for large vessel occlusion stroke (LVOS) in the anterior circulation up to 24 h from stroke onset.3,4 However,
among patients with stroke from vertebrobasilar artery occlusion (VBAO), EVT treatment showed inconsistent results. Previous clinical trials failed to show significant advantages over medical therapy.\(^5,6\) However, the ATTENTION (EndovAscular TreaTmENT for acute basilar artery occlusion) study recently published at the European Stroke Conference showed that EVT was significantly better than medical therapy [an adjusted risk ratio of 2.1, 95% confidence interval (CI): 1.5–3.0]. One important reason was a significantly higher proportion of 'futile' reperfusion.\(^7\)

Achieving successful reperfusion of the target vessel occlusion is critical for improving patients’ prognosis. However, reperfusion can be achieved in single or multiple passes.\(^8\) Multiple passes are associated with a prolonged procedure time and aggravated arterial endothelial injury.\(^9\) Therefore, the concept of the first-pass effect (FPE) or modified FPE (mFPE) was introduced, which implies that ideally, EVT should achieve successful reperfusion [modified thrombolysis in cerebral infarction (mTICI) 2b/3] after a single pass.\(^8,10\) Several previous studies have investigated the clinical value and predictors of FPE in the treatment of EVT in patients with anterior circulation LVOS.\(^11,12\) Furthermore, a recent study showed that first-pass mTICI 2b/3 reperfusion was the only treatment-related factor predictive of clinical outcome.\(^12\) Therefore, it is important to identify the predictors associated with first-pass reperfusion in the posterior circulation stroke.\(^13\)

To address this question, we conducted a study comparing the baseline characteristics and clinical outcomes of patients with FPE with those of the remainder of the cohort. The aim was to identify factors that may influence the achievement of FPE in EVT patients with VBAO and the relationship between FPE and prognosis.

**Methods**

**Study population**

PERSIST is a retrospective registry program of consecutive patients who present with acute, symptomatic, radiologically confirmed VBAO treated with EVT (Registration: URL: http://www.chictr.org.cn/; Unique identifier: ChiCTR2000033211).\(^14\) PERSIST involved 21 stroke centers in 13 provinces of China between December 2015 and December 2018. The study was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (USTC) in Hefei, China (No. 2020–40). Due to its anonymized, retrospective nature, the need for patient consent was waived.

Patients were included in PERSIST registry if they were (1) over 18 years old; (2) had imaging evidence of VBAO obtained by computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography; (3) received endovascular revascularization treatment. In this study, patients were excluded if they (1) had an estimated time of VBAO beyond 24 h, (2) participated in other clinical trials, (3) had incomplete data, (4) had a preexisting disability with a modified Rankin Scale (mRS) score greater than 2, and (5) were treated with angioplasty or stent implantation as the first-line treatment.

All consecutive patients were retrospectively documented. The data included demographics, medical history (hypertension, diabetes mellitus), National Institute of Health Stroke Scale (NIHSS) score, the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, laboratory measures, and time from estimated occlusion to puncture and initial vessel occlusion. Patients with occlusion of the vertebra artery resulting in no flow to the basilar artery [e.g. functional basilar artery occlusion (BAO)] were also included, defined as the vertebral artery occlusion (VAO). The occlusion site of the ‘basilar artery’ was limited to only BAO.

Bridging therapy is decided by the stroke doctor. It was executed as follows: the patients received intravenous (IV) alteplase (0.9 mg/kg) if they met the criteria for IV thrombolysis within 4.5 h of stroke symptom onset. Then, endovascular preparation was initiated simultaneously with or soon after IV alteplase administration was started.

Reperfusion status was assessed with the modified Thrombolysis in Cerebral Infarction (mTICI) scale. Collateral status was evaluated using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral grading system, and collateral scores were categorized into ASITN/SIR grades 0–1 and 2–4.\(^15\)

For all enrolled subjects, the imaging characteristics were evaluated by two neurologists/interventionalists who were blinded to the clinical information.
According to previous studies, mFPE was defined as (1) one single pass of the device, (2) near-complete reperfusion of the large vessel occlusion and its downstream territory (mTICI 2b/3), and (3) no use of rescue therapy. True FPE was defined as complete reperfusion (mTICI 3) of the large vessel occlusion by one single pass of the device and without the use of rescue therapy.

**Clinical outcomes**

The clinical outcome was assessed by trained neurologists via face-to-face or telephone interviews at 90 days postprocedure. Clinical functional independence was defined as an mRS of 0–2. Favorable outcome was defined as an mRS of 0–3.

**Statistical analysis**

Patients were divided into the FPE group and non-FPE group or good and poor outcome groups. Demographics and clinical characteristics were compared between groups. Continuous variables are presented as the mean (SD) or median [interquartile range (IQR)] depending on the distribution. Categorical variables are presented as numbers and percentages. Continuous and ordinal categorical variables were compared with Student’s $t$ test or the Mann–Whitney $U$ test, and categorical variables were compared with the $\chi^2$ test or Fisher’s exact test, as appropriate. We further implemented backward stepwise logistic regression analysis to determine the predictors of FPE.

The association between FPE and clinical outcome at 90 days was also analyzed, and variables with a $p$ value $< 0.05$ were entered into the stepwise logistic regression analysis. Odds ratios (ORs) and 95% CIs were calculated. For all analyses, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Version 25.0 (IBM Corp, Armonk, NY) software package.

**Results**

**Baseline and characteristics of the study cohort**

A total of 609 patients with VBAO were treated with thrombectomy during the study period. Among them, 101 patients were excluded for various reasons, as listed in Figure 1. Finally, 508 patients were included in our study.

The mean age of the study population was 63.7 (SD, 13.1) years old, and 71.6% ($n = 361$) of them were males. The other baseline characteristics are shown in Table 1. All eligible patients underwent a 90-day follow-up, 29.1% ($n = 148$) of them had 90-day functional independence, 36.6% (186/508) of them had 90-day favorable outcomes, and 38.2% ($n = 194$) of them died (Table 1).

**Frequency and predictors of FPE**

As shown in Table 1, 29.9% (152/508) of all subjects achieved mFPE. The proportion of previous hypertension and collateral status significantly differed between the groups. The mFPE group was more likely to be treated with IV recombinant tissue plasminogen activator (rt-PA) and contact aspiration (CA) and had a higher proportion of cardioembolic etiology and BAO.

The results of backward stepwise logistic regression analysis for predictors of mFPE are reported...
### Table 1. Comparison of baseline demographic, clinical, and procedural characteristics between patients with and without FPE.

| Variables                              | ALL n = 508 | mFPE n = 152 | Non-mFPE n = 356 | p value | tFPE n = 107 | Non-tFPE n = 401 | p value |
|----------------------------------------|-------------|--------------|------------------|---------|--------------|------------------|---------|
| **Demographic**                        |             |              |                  |         |              |                  |         |
| Age, years [SD]                        | 63.7 [13.1] | 63.9 [13.4]  | 63.6 [13.0]      | 0.711   | 63.7 [13.8]  | 63.7 [12.9]      | 0.800   |
| Sex, male, n (%)                       | 361 [71.6]  | 99 [65.1]    | 262 [73.6]       | 0.054   | 66 [61.7]    | 295 [73.6]       | 0.016   |
| **Medical history, n (%)**             |             |              |                  |         |              |                  |         |
| Hypertension                           | 338 [66.5]  | 90 [59.2]    | 248 [69.7]       | 0.022   | 57 [53.3]    | 281 [70.1]       | 0.001   |
| Diabetes mellitus                      | 113 [22.2]  | 31 [20.4]    | 82 [23.0]        | 0.513   | 17 [15.9]    | 96 [23.9]        | 0.075   |
| Hypolipemia                            | 177 [34.8]  | 54 [35.5]    | 123 [34.6]       | 0.833   | 35 [32.7]    | 142 [35.4]       | 0.602   |
| Coronary heart disease                 | 50 [9.8]    | 12 [7.9]     | 38 [10.7]        | 0.336   | 6 [5.6]      | 44 [11]          | 0.098   |
| History of stroke                      | 99 [19.5]   | 29 [19.1]    | 70 [19.7]        | 0.879   | 21 [19.6]    | 78 [19.5]        | 0.968   |
| **Clinical features**                  |             |              |                  |         |              |                  |         |
| Admission SBP, mmHg, median (IQR)      | 149 [133–165]| 149 [132–162]| 149 [134–168]    | 0.283   | 145 [130–160]| 150 [135–168]    | 0.032   |
| Admission DBP, mmHg, median (IQR)      | 85 [76–95]  | 84 [76–96]   | 85 [76–95]       | 0.575   | 82 [76–93]   | 85 [77–95]       | 0.205   |
| Baseline NIHSS, median (IQR)           | 23 [14–29.5] | 22 [13–31]  | 23 [15–29]       | 0.665   | 23 [14–33]  | 23 [14–29]       | 0.645   |
| Baseline pc-ASPECT Score, median (IQR)| 9 [8–10]    | 9 [8–10]     | 9 [8–10]         | 0.931   | 9 [7–10]    | 9 [8–10]         | 0.219   |
| Baseline GCS Score, median (IQR)       | 7 [6–11]    | 7 [6–11]     | 7 [6–11]         | 0.726   | 7 [6–11]    | 7 [6–11]         | 0.668   |
| **TOAST classification, n (%)**        |             |              |                  | <0.001  |             |                  | <0.001  |
| Atherosclerosis                        | 316 [62.2]  | 76 [50.0]    | 240 [67.4]       | 44 [41.1]| 272 [67.8]  |                  |         |
| Cardioembolic                          | 117 [23.0]  | 55 [36.2]    | 62 [17.4]        | 46 [43] | 71 [17.7]   |                  |         |
| Others                                 | 75 [14.8]   | 21 [13.8]    | 54 [15.2]        | 17 [15.9]| 58 [14.5]   |                  |         |
| **Procedural data**                    |             |              |                  |         |              |                  |         |
| IV rt-PA, n (%)                        | 93 [18.3]   | 37 [24.3]    | 56 [15.7]        | 0.022   | 21 [19.6]   | 72 [18]          | 0.691   |
| Time from onset to puncture, median (IQR)| 342.5 [240–490]| 329.5 [246.5–461.5]| 349.5 [240–506]| 0.492 | 342 [251–471]| 343 [240–497.5] | 0.752   |
| First attempt approach, n (%)          |             |              |                  | <0.001  |             |                  | <0.001  |
| Stent retriever                        | 471 [92.7]  | 125 [82.2]   | 346 [97.2]       | 90 [84.1]| 381 [95]    |                  |         |
| Contact aspiration                     | 37 [7.3]    | 27 [17.8]    | 10 [2.8]         | 17 [15.9]| 20 [5]      |                  |         |
| Site of occlusion, n (%)               |             |              |                  | <0.001  |             |                  | <0.001  |
| BA                                     | 405 [79.7]  | 138 [90.8]   | 267 [75.0]       | 100 [93.5]| 305 [76.3]  |                  |         |
| VA                                     | 103 [20.3]  | 14 [9.2]     | 88 [24.8]        | 7 [6.5] | 95 [23.8]   |                  |         |
| Anesthesia mode, n (%)                 |              |              |                  | 0.066   |              |                  | 0.280   |

(Continued)
Table 1. [Continued]

| Variables                        | ALL n = 508 | mFPE n = 152 | Non-mFPE n = 356 | p value | tfPE n = 107 | Non-tFPE n = 401 | p value |
|----------------------------------|-------------|--------------|------------------|---------|--------------|------------------|---------|
| General anesthesia               | 117 (23.0)  | 25 (16.5)    | 92 (25.9)        |         | 19 (17.8)    | 98 (24.4)        |         |
| Local anesthesia                 | 251 (49.4)  | 80 (52.6)    | 171 (48.0)       |         | 54 (50.5)    | 197 (49.1)       |         |
| Conscious sedation               | 140 (27.6)  | 47 (30.9)    | 93 (26.1)        |         | 34 (31.8)    | 106 (26.4)       |         |

Collateral status, n (%)<0.001<0.001

| ASITN/SIR 0–1                    | 403 (79.3)  | 103 (67.8)   | 300 (84.3)       |         | 70 (65.4)    | 333 (83)         |         |
| ASITN/SIR 2–4                    | 105 (20.7)  | 49 (32.2)    | 56 (15.7)        |         | 37 (34.6)    | 68 (17)          |         |

Outcome

| Any HT                           | 103 (20.3)  | 27 (17.8)    | 76 (21.3)        | 0.357   | 16 (15)      | 87 (21.7)        | 0.123   |
| sICH, n (%)                      | 35 (6.9)    | 7 (4.6)      | 28 (7.9)         | 0.184   | 6 (5.6)      | 29 (7.2)         | 0.556   |
| 90-day mRS ≤ 2, n (%)            | 148 (29.1)  | 57 (37.5)    | 91 (25.6)        | 0.007   | 41 (38.3)    | 107 (26.7)       | 0.019   |
| 90-day mRS ≤ 3, n (%)            | 186 (36.6)  | 66 (43.4)    | 120 (33.7)       | 0.037   | 48 (44.9)    | 138 (34.4)       | 0.046   |
| 90-day death, n (%)              | 194 (38.2)  | 51 (33.6)    | 143 (40.2)       | 0.160   | 35 (32.7)    | 159 (39.7)       | 0.189   |

ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology System; BA, basilar artery; DBP, diastolic blood pressure; FPE, first-pass effect; GCS, Glasgow Coma Scale; HT, hemorrhagic transformation; IQR, interquartile range; IV, intravenous; mFPE, modified FPE; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECT, posterior circulation–Alberta Stroke Program Early CT; rt-PA, recombinant tissue plasminogen activator; sICH, symptomatic intracranial hemorrhage; SBP, systolic blood pressure; SD, standard deviation; tfPE, true FPE; TOAST, the Trial of ORG 10172 in Acute Stroke; VA, vertebral artery. Bold means p < 0.05.

In Table 2. We observed that the use of CA (OR: 8.518, 95% CI: 3.822–18.982, p < 0.001) and IV rt-PA (OR: 1.831, 95% CI: 1.108–3.025, p = 0.018) was a positive predictor of mFPE. Favorable collateral status (ASITN/SIR 2–4 versus 0–1: OR: 2.187, 95% CI: 1.350–3.542, p = 0.001), cardioembolic etiology (atherosclerosis versus cardioembolic: OR: 0.518, 95% CI: 0.316–0.849, p = 0.009; others versus cardioembolic: OR: 0.401, 95% CI: 0.200–0.803, p = 0.009) and BAO (BAO versus VAO: OR: 2.608, 95% CI: 1.369–4.966, p = 0.004) were statistically significant predictors of mFPE. Hypertension (OR: 0.579, 95% CI: 0.365–0.918, p = 0.020) was a negative predictor of achieving mFPE.

In addition, 21.1% (107/508) of the patients achieved true FPE (tFPE). Similarly, we also found that the tFPE group was more likely to be treated with CA and had a higher proportion of cardioembolic etiology, BAO, favorable collateral status, and a lower rate of hypertension. However, IV rt-PA did not increase the proportion of tFPE. In addition, unlike mFPE, the proportion of males and admission systolic blood pressure (SBP) levels was significantly lower in the non-tFPE group. Multivariate analysis showed that CA (OR: 3.590, 95% CI: 1.679–7.674, p = 0.001), the favorable collateral status (ASITN/SIR 2–4 versus 0–1: OR: 2.070, 95% CI: 1.237–3.464, p = 0.006), cardioembolic (atherosclerosis versus cardioembolic: OR: 0.416, 95% CI: 0.242–0.713, p = 0.001; others versus cardioembolic: OR: 0.472, 95% CI: 0.230–0.971, p = 0.041) and BAO (OR: 3.105, 95% CI: 1.350–7.139, p = 0.008) were statistically significant predictors of tFPE. Hypertension (OR: 0.513, 95% CI: 0.309–0.851, p = 0.010) was also a negative predictor of achieving tFPE (Table 2).

Functional outcomes of FPE

Distribution of 90-day mRS in VBAO patients treated with EVT according to the FPE is listed in Figure 2. The mFPE group patients had significantly better 90-day clinical outcomes than those in the non-mFPE group (90-day mRS ≤ 2: 37.5% versus 25.6%, p = 0.007; 90-day mRS ≤ 3: 43.4% versus 33.7%, p = 0.037). Similar results
were found in the tFPE group (90-day mRS ≤ 2: 38.3% versus 26.7%, p = 0.019; 90-day mRS ≤ 3: 44.9% versus 34.4%, p = 0.046). However, the rates of any hemorrhagic transformation (HT), symptomatic intracranial hemorrhage (sICH), and 90-day mortality were not significantly different between the groups. Table 3 summarizes the univariate analysis of predictors for functional outcome at 3 months. After adjustment for confounding factors, FPE patients had significantly better 90-day clinical functional independence (mRS < 2) than those in the non-FPE population (mFPE: OR: 0.601, 95% CI: 0.370–0.977, p = 0.040; tFPE: OR: 0.547, 95% CI: 0.318–0.940, p = 0.029). However, a difference in 90-day favorable outcomes (mRS ≤ 3) was not found in multivariate analysis adjusted for prespecified confounders (Table 4).

Table 2. Multivariate analysis of predictors of FPE.

| Variables                     | Odds ratio | 95% confidence interval | p value |
|-------------------------------|------------|-------------------------|---------|
| **mFPE**                      |            |                         |         |
| Hypertension                  | 0.579      | 0.365–0.918             | 0.020   |
| TOAST classification          |            |                         |         |
| Atherosclerosis to cardioembolic | 0.518   | 0.316–0.849             | 0.009   |
| Others to cardioembolic       | 0.401      | 0.200–0.803             | 0.010   |
| IV rt-PA                      | 1.831      | 1.108–3.025             | 0.018   |
| Contact aspiration            | 8.518      | 3.822–18.982            | <0.001  |
| **Site of occlusion**         |            |                         |         |
| BA versus VA                  | 2.608      | 1.369–4.966             | 0.004   |
| **Collateral status**         |            |                         |         |
| ASITN/SIR 2–4 versus 0–1      | 2.187      | 1.350–3.542             | 0.001   |
| **tFPE**                      |            |                         |         |
| Hypertension                  | 0.513      | 0.309–0.851             | 0.010   |
| TOAST classification          |            |                         |         |
| Atherosclerosis to cardioembolic | 0.416   | 0.242–0.713             | 0.001   |
| Others to cardioembolic       | 0.472      | 0.230–0.971             | 0.041   |
| Female                        | 1.339      | 0.815–2.202             | 0.250   |
| Contact aspiration            | 3.590      | 1.679–7.674             | 0.001   |
| **Site of occlusion**         |            |                         |         |
| BA versus VA                  | 3.105      | 1.350–7.139             | 0.008   |
| **Collateral status**         |            |                         |         |
| ASITN/SIR 2–4 versus 0–1      | 2.070      | 1.237–3.464             | 0.006   |
| Admission SBP                 | 0.996      | 0.987–1.006             | 0.453   |

ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology System; BA, basilar artery; FPE, first-pass effect; IV, intravenous; mFPE, modified FPE; rt-PA, recombinant tissue plasminogen activator; tFPE, true FPE; SBP, systolic blood pressure; TOAST, the Trial of ORG 10172 in Acute Stroke; VA, vertebral artery.
Figure 2. Distribution of modified Rankin Scale scores at 3 months in VBAO patients treated with EVT according to the first-pass effect (FPE).

Table 3. Univariate analysis of predictors for functional outcome at 3 months.

|                      | mRS 0–2 (n = 148) | mRS 3–6 (n = 360) | p value | mRS 0–3 (n = 186) | mRS 4–6 (n = 322) | p value |
|----------------------|------------------|------------------|---------|------------------|------------------|---------|
| **Demographic**      |                  |                  |         |                  |                  |         |
| Age, years (SD)      | 61.4 (14.5)      | 64.6 (12.4)      | **0.028** | 61.7 (13.9)      | 64.8 (12.5)      | **0.017** |
| Sex, male, n (%)     | 115 (77.7)       | 246 (68.3)       | **0.034** | 137 (73.7)       | 224 (69.6)       | 0.327   |
| **Medical history**  |                  |                  |         |                  |                  |         |
| Hypertension, n (%)  | 91 (61.5)        | 113 (31.4)       | 0.122   | 116 (62.4)       | 222 (68.9)       | 0.130   |
| Diabetes mellitus, n (%) | 22 (14.9)    | 91 (25.3)        | **0.010** | 32 (17.2)        | 81 (25.2)        | **0.038** |
| Hyperlipemia, n (%)  | 56 (37.8)        | 121 (33.6)       | 0.364   | 67 (36)          | 110 (34.2)       | 0.672   |
| Coronary heart disease, n (%) | 10 (6.8)    | 40 (11.1)        | 0.134   | 14 (7.5)         | 36 (11.2)        | 0.183   |
| History of stroke, n (%) | 23 (15.5)   | 76 (21.1)        | 0.150   | 29 (15.6)        | 70 (21.7)        | 0.092   |
| **Clinical features**|                  |                  |         |                  |                  |         |
| Admission SBP, mmHg, median (IQR) | 149 [131.5–162.5] | 149 [134–166] | 0.408   | 149 [132–162]    | 149 [134–168]    | 0.234   |
| Admission DBP, mmHg, median (IQR) | 84 [76–95]   | 85 [77–95]       | 0.898   | 85 [76–95]       | 84 [77–95]       | 0.904   |
| Baseline NIHSS, median (IQR) | 15 [10–23]   | 26 [19–32]       | **<0.001** | 17 [10–24]      | 27 [20–33]       | **<0.001** |

(Continued)
Table 3. (Continued)

|                          | mRS 0–2 n = 148 | mRS 3–6 n = 360 | p value | mRS 0–3 n = 186 | mRS 4–6 n = 322 | p value |
|--------------------------|-----------------|-----------------|---------|-----------------|-----------------|---------|
| Baseline ASPECT score, median (IQR) | 9 [8–10]        | 9 [7–10]        | 0.143   | 9 [8–10]        | 9 [7–10]        | 0.002   |
| Baseline GCS score, median (IQR)   | 11 [8–13]       | 6 [5–10]        | <0.001  | 11 [7–13]       | 6 [5–9]         | <0.001  |
| TOAST classification, n (%)        |                 |                 | 0.065   |                 |                 | 0.195   |
| Atherosclerosis                | 43 [29.1]       | 74 [20.6]       |         | 108 [58.1]      | 208 [64.6]      |         |
| Cardioembolic                  | 81 [54.7]       | 235 [65.3]      |         | 51 [27.4]       | 66 [20.5]       |         |
| Others                        | 24 [16.2]       | 51 [14.2]       |         | 27 [14.5]       | 48 [14.9]       |         |
| Procedural data                |                 |                 |         |                 |                 |         |
| IV rt-PA, n (%)                | 36 [24.3]       | 57 [15.8]       | 0.025   | 43 [23.1]       | 50 [15.5]       | 0.033   |
| Time from onset to puncture, median (IQR) | 326 [240–460] | 353 [240–500] | 0.378   | 326 [240–459]  | 358 [240–506]  | 0.249   |
| First attempt approach, n (%)  | 0.296           |                 |         |                 |                 | 0.209   |
| Stent retriever               | 140 [94.6]      | 331 [91.9]      |         | 176 [94.6]      | 295 [91.6]      |         |
| Contact aspiration            | 8 [5.4]         | 29 [8.1]        |         | 10 [5.4]        | 27 [8.4]        |         |
| Tandem lesions, n (%)         | 21 [14.2]       | 41 [11.4]       | 0.381   |                 |                 |         |
| Site of occlusion, n (%)      | 0.383           |                 |         |                 |                 | 0.152   |
| BA                            | 121 [82.3]      | 284 [78.9]      |         | 154 [83.2]      | 251 [78]       |         |
| VA                            | 26 [17.1]       | 76 [21.1]       |         | 31 [16.8]       | 71 [22]        |         |
| Anesthetic, n (%)             | 0.972           |                 |         |                 |                 | 0.938   |
| General anesthesia            | 35 [23.7]       | 82 [22.8]       |         | 44 [23.7]       | 73 [22.7]      |         |
| Local anesthesia              | 73 [49.3]       | 178 [49.4]      |         | 90 [48.4]       | 161 [50]       |         |
| Conscious sedation            | 40 [27.0]       | 100 [27.8]      |         | 52 [28]         | 88 [27.3]      |         |
| Collateral status, n (%)      |                 |                 | <0.001  |                 |                 | <0.001  |
| ASITN/SIR 0–1                 | 98 [66.2]       | 305 [84.7]      |         | 124 [66.7]      | 279 [86.6]     |         |
| ASITN/SIR 2–4                 | 50 [33.7]       | 55 [15.3]       |         | 62 [33.3]       | 43 [13.4]      |         |
| mFPE, n (%)                   | 57 [38.51]      | 95 [26.4]       | 0.007   | 66 [35.5]       | 86 [26.7]      | 0.037   |
| tFPE, n (%)                   | 41 [27.7]       | 66 [18.3]       | 0.019   | 48 [25.8]       | 59 [18.3]      | 0.046   |

ASITN/SIR, American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology System; BA, basilar artery; DBP, diastolic blood pressure; FPE, first-pass effect; GCS, Glasgow Coma Scale; IQR, interquartile range; IV, intravenous; mFPE, modified FPE; NIHSS, National Institutes of Health Stroke Scale; pc-ASPECT, posterior circulation–Alberta Stroke Program Early CT; rt-PA, recombinant tissue plasminogen activator; SBP, systolic blood pressure; SD, standard deviation; tFPE, true FPE; TOAST, Trial of ORG 10172 in Acute Stroke; VA, vertebral artery. Bold means p < 0.05.

Discussion

The main findings in our study were as follows: (1) in our multicentric cohort, the frequencies of tFPE and mFPE were 21.1% (107/508) and 29.9% (152/508), respectively; (2) patients achieving FPE were significantly associated with better clinical outcomes, regardless of tFPE and mFPE; and (3) multiple predictors of FPE were identified, including patient characteristics such as stroke etiology, the site of occlusion, collateral
status, and EVT strategies such as previously used IV rt-PA and the use of CA.

The concept of FPE was first reported by Zaidat et al.8 Furthermore, the benefits of FPE have been demonstrated in multiple cohorts of anterior circulatory stroke.11,12 However, limited studies have assessed the predictors and effectiveness of FPE in EVT patients with acute VBAO. Recently, four studies assessed the impact of FPE on efficacy and safety outcomes in acute BAO.16–19 Nevertheless, the main limitation of these studies is the limited sample size and the low proportion of VAO. In addition, there are some differences in the etiology of stroke between Asian and Western populations. Therefore, we again investigated the effectiveness of FPE in a large multiple EVT cohort with acute VBAO. We found that approximately 20–30% of VBAO patients can achieve FPE, which was consistent with previous studies. In addition, the proportion was similar to the rate of FPE in anterior circulation stroke.11,12 Moreover, we found that achieving an FPE was significantly associated with better clinical outcomes. Therefore, future studies should pay more attention to how to provide fast, complete, and safe reperfusion during EVT in VBAO patients.13

With such a question, we investigated the possible predictors that influence the achievement of FPE in patients with VBAO. We found that stroke etiology, the site of occlusion, collateral status, and EVT strategies were important predictors for FPE. First, the etiology of VBAO was an important predictor of FPE. In our study, cardiogenic embolism was more likely to achieve FPE than other etiologies, which was consistent with previous studies. Aubertin et al.16 and Terceno et al.17 showed that atherosclerotic etiology was a strong predictor of failure to achieve FPE. In addition, Aubertin et al.16 found that antiplatelet use before stroke onset, which indicated intracranial atherosclerotic disease, also predicted the failure of FPE. In our study, we did not collect a past medication history; however, we found that a previous history of hypertension was a negative predictor of achieving FPE. Hypertension is an independent risk factor for atherosclerotic lesions, which often occur with intrinsic stenosis, requiring an increased number of passes or rescue treatments.

Second, EVT strategies significantly impacted FPE. More recent studies challenge non-inferiority of direct MT.20 Our study first showed a higher rate of mFPE in patients treated with bridging therapy than in those treated directly with EVT in posterior circulation stroke. Furthermore, a recently published study based on VBAO patients of the Registration Study for Critical Care of Acute Ischemic Stroke after Recanalization (RESCUE-RE) study21 also suggested that Intravenous thrombolysis (IVT) leads to a higher rate of reperfusion and fewer passes. We speculated that the possible mechanism is that IVT before EVT changed the nature of the thrombus, dissolved distal emboli and improved reperfusion status. Unexpectedly, IVT plus EVT did not increase the rate of tFPE. We cannot fully explain the relationship. However, a possible explanation is that IVT before thrombectomy may lead to cacoethic clot migration, which may result in infarction in a new territory. In addition, fewer patients (18.3%) received bridging therapy in our cohort. This result may be caused by chance, and further research is needed to confirm this hypothesis.

In addition, we observed that CA was used in 15–18% of patients in the FPE group, while it was significantly less common in the non-mFPE group. Multivariate analysis showed that CA was a major predictor of FPE. The results were similar to the results of two recent studies.16,17 Moreover, previous studies have suggested that CA was more effective than stent retriever in producing complete and rapid recanalization in VBAO patients.22,23 As previously mentioned in the ASTER study (the effect of endovascular CA versus stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: The ASTER randomized clinical trial),24 when stent retriever was used for

| Table 4. Multivariable regression model for functional outcome at 3 months. |
|------------------|-----------------|------------------|
|                  | OR              | 95% CI           | p value |
| mFPE             |                 |                  |        |
| 90-day mRS ≤ 2   | 0.601           | 0.370–0.976      | 0.040  |
| 90-day mRS ≤ 3   | 0.782           | 0.492–1.243      | 0.298  |
| tFPE             |                 |                  |        |
| 90-day mRS ≤ 2   | 0.547           | 0.318–0.940      | 0.029  |
| 90-day mRS ≤ 3   | 0.675           | 0.400–1.136      | 0.139  |

FPE, first-pass effect; mFPE, modified FPE; mRS, modified Rankin Scale; tFPE, true FPE.
Thrombus retrieval, the guidewire needs to pass through the clot first, and this process could lead to thrombus fragmentation and cause embolism in the downstream region of the vessel. In contrast, when CA was used in the posterior circulation, the large-bore aspiration catheter may block the blood flow into the vertebral artery and may also lead to a transient reversal of blood flow in the contralateral vertebral artery, reducing the incidence of thrombus escape.\textsuperscript{16,25}

Third, collateral status was also an important predictor of achieving FPE in our study, which was consistent with the result in the anterior circulation.\textsuperscript{26} Possible explanations include that a strong collateral status can help deliver endogenous or exogenous thrombolytic substances, which could help to dissolve proximal segment thrombi.\textsuperscript{25} Moreover, in patients with severe cerebral hypoperfusion, the supplying vessels in the penumbral area would cause a higher clot burden due to stagnant blood flow,\textsuperscript{27} thus making the procedure more difficult with resultant lower recanalization rates.

Another important finding in our study was that BAO alone is easier to recanalize at one pass than VAO. This was not reported in previous studies due to the low proportion of VAO. We speculated that different causes of stroke may be the main reason for FPE in patients with only BAO. Aubertin \textit{et al.}\textsuperscript{16} reported that a significant proportion of BAO strokes are cardiogenic embolisms. Roberta \textit{et al.}\textsuperscript{28} also showed that thromboembolic disease is a more common mechanism of acute BAO. In addition, patients with VAO are prone to thrombus migration in the process of EVT, which reduces the probability of FPE.

The strengths of our study were the relatively intact data from multiple centers and the large sample size. Moreover, we included all baseline and procedural variables that may affect recanalization. However, due to the observational and non-randomized design, the results of our study should be interpreted with caution.

Conclusion

FPE could be achieved in one-fourth of patients with VBAO and was associated with significantly favorable outcomes. The predictors of FPE include infarct etiology, the site of occlusion, collateral status, bridging strategies, and EVT strategies. These results leave room for further improvement of current devices and technologies to increase the efficacy of EVT in patients with VBAO.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (USTC) in Hefei, China (No. 2020–40) and therefore conforms to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Due to the study’s anonymized, retrospective nature, the need for patient consent was waived.

Consent for publication

Not applicable.

Author contributions

Xianjun Huang: Conceptualization; Methodology; Writing – original draft.

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Min Li: Data curation; Methodology; Project administration; Writing – review & editing.

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**Competing interests**
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Availability of data and materials**
Data are available upon reasonable request.

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