Supplementary Information for

Poor Venous Outflow Profiles Increase the Risk of Reperfusion Hemorrhage after Endovascular Treatment

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Includes:

Supplementary Table 1-4

Supplementary Figure 1
Supplementary Figure 1. Flow chart of patient inclusion and exclusion criteria.

n = 796
Underwent EVT triage, assessed for eligibility

n = 167
Excluded
- No EVT (n = 90)
- No follow-up imaging (n = 68)
- Intraprocedural bleeding (n = 9)

n = 629
With pretreatment NCCT, CTA and CTP, anterior vessel occlusion (ICA, MCA), underwent EVT, follow-up imaging within 48 h after EVT

n = 382 VO-
n = 247 VO+

n = 33
Excluded from multivariable logistic regression
- Unknown blood glucose on admission (n = 25)
- Unknown Admission NIHSS (n = 1)
- Unusable CTP (n = 3)

n = 600
Included in multivariable logistic regression

model PH

n = 95
Excluded from multivariable logistic regression
- PH (n = 91)
- Unknown anesthesia (n = 4)

n = 505
Included in multivariable logistic regression

model HI

Abbreviations:
EVT, endovascular treatment; NCCT, non-contrast CT; CTA, CT angiography; CTP, CT perfusion; ICA, internal carotid artery; MCA, medial cerebral artery; HI, hemorrhagic infarction; PH, parenchymal hematoma; NIHSS, National Institutes of Health Stroke Scale
Supplementary Table 1. Patient characteristics dichotomized by early time window (ETW) and late time window (LTW). ETW was defined as ≤ 4.5 hours from symptom onset to imaging and LTW as > 4.5 hours or unknown symptom onset. As expected, ETW patients received intravenous lysis therapy more often. LTW patients exhibited a higher rate of hemorrhagic infarction (HI) [26.0% vs 18.4%, p=0.022], while there was no significant difference as regards the occurrence of more severe parenchymal hematomas (PH) [14.6% vs 14.3%, p=0.920].

| Patient characteristics | All patients (n = 629) | Early time window (n = 321) | Late time window (n = 308) | p value* |
|-------------------------|------------------------|-----------------------------|---------------------------|----------|
| Age (years), mean (SD)  | 72.6 (±14.1)           | 72.6 (±13.8)                | 72.7 (±14.5)              | 0.793 (1) |
| Male sex, n (%)         | 307/629 (48.8%)        | 157/321 (48.9%)            | 150/308 (48.7%)          | 0.958 (2) |
| Blood glucose on admission (mg/dL), mean (SD)† | 134.6 (±49.1)        | 129.2 (±45.8)              | 140.2 (±51.9)            | 0.001 (1) |
| Admission NIHSS, median (IQR)‡ | 15 (9-19)           | 15 (9-19)                  | 15 (10-19)               | 0.871 (1) |

| Imaging characteristics |                      |                             |                           |
|-------------------------|-----------------------|-----------------------------|---------------------------|
| Baseline ischemic core volume [CBF<30%] (mL), mean (SD)¶ | 24.1 (±35.3)        | 24.3 (±35.7)                | 23.9 (±35.0)              | 0.921 (1) |
| Favorable VO profile (COVES ≥ 3), n (%) | 247/629 (39.3%)     | 143/321 (44.5%)            | 104/308 (33.8%)          | 0.006 (2) |
| Favorable arterial collaterals (Maas ≥ 3), n (%) | 373/629 (59.3%)     | 193/321 (60.1%)            | 180/308 (58.4%)          | 0.668 (2) |

| Procedural characteristics |                      |                             |                           |
|---------------------------|-----------------------|-----------------------------|---------------------------|
| Time from symptom onset to imaging (min), median (IQR)Ω | 180 (90-362)         | 120 (68-180)               | 508 (350-718)             | <0.001 (1) |
| Time from imaging to groin puncture (min), median (IQR)§ | 64 (48-98)           | 65 (50-105)                | 60 (45-90)               | 0.120 (1) |
| Administration of tPA, n (%) | 320/624 (51.3%)     | 226/320 (70.6%)            | 94/304 (30.9%)           | <0.001 (2) |
| TICI 2b/2c/3, n (%) | 507/629 (80.6%)      | 253/321 (78.8%)            | 254/308 (82.5%)          | 0.247 (2) |

| Follow-up imaging |                      |                             |                           |
|-------------------|-----------------------|-----------------------------|---------------------------|
| Occurrence of HI, n (%) | 139/629 (22.1%)     | 59/321 (18.4%)             | 80/308 (26.0%)           | 0.022 (2) |
| Occurrence of PH, n (%) | 91/629 (14.5%)      | 46/321 (14.3%)             | 45/308 (14.6%)           | 0.920 (2) |
| Occurrence of sICH, n (%) | 20/629 (3.2%)       | 5/321 (1.6%)               | 15/308 (4.9%)           | 0.018 (2) |

| Clinical outcomes |                      |                             |                           |
|-------------------|-----------------------|-----------------------------|---------------------------|
| mRS score at 90-d follow-up, median (IQR)§ | 4 (1-5)            | 4 (1-5)                    | 4 (2-6)                   | 0.015 (1) |

* Characteristics were compared between ETW and LTW patients with the use of either a Mann-Whitney U test (1) for continuous variables or a chi-square test (2) for categorical variables. Statistical significance: p<0.05.

Abbreviations: HI, Hemorrhagic Infarction; PH, Parenchymal Hematoma; sICH, symptomatic Intraanrerial Cerebral Hemorrhage; NIHSS, National Institutes of Health Stroke Scale; CBF, Cerebral Blood Flow; COVES, Cortical Vein Opacification Score; VO, Venous Outflow; tPA, Tissue Plasminogen Activator; mRS, modified Rankin Scale; IQR, Interquartile Range; SD, Standard Deviation

† n = 309 ETW patients and n = 295 LTW patients
‡ n = 321 ETW patients and n = 307 LTW patients
¶ n = 321 ETW patients and n = 305 LTW patients
Ω n = 321 ETW patients and n = 166 LTW patients
§ n = 258 ETW patients and n = 201 LTW patients
§ n = 310 ETV patients and n = 293 LTV patients
Supplementary Table 2. Patient characteristics dichotomized by Thrombolysis in Cerebral Infarction (TICI) score (TICI 2b vs TICI 2c/3). There was no significant difference as regards the occurrence of HI and PH between the subgroups.

| Patient characteristics | All patients (n = 507) | TICI 2b (n = 224) | TICI 2c/3 (n = 283) | p value* |
|-------------------------|------------------------|------------------|---------------------|----------|
| Age (years), mean (SD)  | 72.4 (±13.9)           | 72.5 (±12.9)     | 72.3 (±14.7)        | 0.664 (1) |
| Male sex, n (%)         | 249/507 (49.1%)        | 109/224 (48.7%)  | 140/283 (49.5%)     | 0.856 (2) |
| Blood glucose on admission (mg/dL), mean (SD) | 135.4 (±50.8) | 134.6 (±52.0) | 136.1 (±49.9) | 0.517 (1) |
| Admission NIHSS, median (IQR) | 15 (9-19) | 15 (9-19) | 15 (9-19) | 0.673 (1) |
| Imaging characteristics |                        |                  |                     |          |
| Baseline ischemic core volume [CBF<30%] (mL), mean (SD) | 23.9 (±35.7) | 26.7 (±37.2) | 21.6 (±34.5) | 0.169 (1) |
| Favorable VO profile (COVES ≥ 3), n (%) | 216/507 (42.6%) | 84/224 (37.5%) | 132/283 (46.6%) | 0.039 (2) |
| Favorable arterial collaterals (Maas ≥ 3), n (%) | 296/507 (58.4%) | 137/224 (61.2%) | 159/283 (56.2%) | 0.259 (2) |
| Procedural characteristics |                        |                  |                     |          |
| Time from symptom onset to imaging (min), median (IQR) | 182 (88-355) | 213 (90-411) | 165 (88-335) | 0.156 (1) |
| Time from imaging to groin puncture (min), median (IQR) | 62 (45-95) | 60 (45-87) | 64 (48-100) | 0.215 (1) |
| Administration of tPA, n (%) | 258/503 (51.3%) | 114/223 (51.1%) | 144/280 (51.4%) | 0.945 (2) |
| Follow-up imaging |                        |                  |                     |          |
| Occurrence of HI, n (%) | 111/507 (21.9%) | 56/224 (25.0%) | 55/283 (19.4%) | 0.132 (2) |
| Occurrence of PH, n (%) | 72/507 (14.2%) | 33/224 (14.7%) | 39/283 (13.8%) | 0.761 (2) |
| Occurrence of sICH, n (%) | 15/507 (3.0%) | 7/224 (3.1%) | 8/283 (2.8%) | 0.844 (2) |
| Clinical outcomes |                        |                  |                     |          |
| mRS score at 90-d follow-up, median (IQR) | 3 (1-5) | 4 (2-5) | 3 (1-5) | <0.001 (1) |

* Characteristics were compared between TICI 0/1/2a/2b and TICI 2c/3 patients with the use of either a Mann-Whitney U test (1) for continuous variables or a chi-square test (2) for categorical variables. Statistical significance: p<0.05.

Abbreviations: HI, Hemorrhagic Infarction; PH, Parenchymal Hematoma; sICH, symptomatic Intracranial Cerebral Hemorrhage; NIHSS, National Institutes of Health Stroke Scale; CBF, Cerebral Blood Flow; COVES, Cortical Vein Opacification Score; VO, Venous Outflow; tPA, Tissue Plasminogen Activator; mRS, modified Rankin Scale; IQR, Interquartile Range; SD, Standard Deviation

† n = 218 TICI 2b patients and n = 273 TICI 2c/3 patients
‡ n = 224 TICI 2b patients and n = 282 TICI 2c/3 patients
¶ n = 223 TICI 2b patients and n = 281 TICI 2c/3 patients
Ω n = 180 TICI 2b patients and n = 211 TICI 2c/3 patients
$ n = 168 TICI 2b patients and n = 196 TICI 2c/3 patients
§ n = 213 TICI 2b patients and n = 272 TICI 2c/3 patients
**Supplementary Table 3.** Univariable logistic regression to predict hemorrhagic infarction (HI), parenchymal hematoma (PH) and symptomatic intracranial cerebral hemorrhage (sICH) on follow-up imaging after endovascular treatment used for variable selection in multivariable logistic regression.

| Independent Variables | Dependent Variable: PH | Dependent Variable: HI | Dependent Variable: sICH |
|-----------------------|-------------------------|-------------------------|-------------------------|
|                       | n | OR   | 95% CI | p       | n | OR   | 95% CI | p       | n | OR   | 95% CI | p       |
| Admission NIHSS (per point) | 628 | 1.06 | 1.03-1.10 | <0.001 | 537 | 1.02 | 0.99-1.06 | 0.119 | 628 | 1.03 | 0.96-1.11 | 0.361 |
| Hypertension (yes) | 625 | 1.06 | 0.66-1.76 | 0.816 | 534 | 0.8 | 0.53-1.22 | 0.289 | 625 | 0.98 | 0.39-2.81 | 0.968 |
| Smoking (current/former) | 587 | 1.23 | 0.73-2.16 | 0.444 | 503 | 1.09 | 0.70-1.73 | 0.710 | 587 | 1.42 | 0.51-5.04 | 0.539 |
| Blood Glucose on admission (per 10 mg/dl) | 604 | 1.08 | 1.04-1.12 | <0.001 | 515 | 1.04 | 1.00-1.08 | 0.055 | 604 | 1.07 | 1.00-1.13 | 0.029 |
| Baseline Ischemic core volume [CBF<30%] (per 10 mL) | 626 | 1.09 | 1.03-1.15 | <0.001 | 535 | 1.05 | 0.99-1.10 | 0.084 | 626 | 1.12 | 1.02-1.22 | 0.007 |
| Penumbra volume [Tmax >6 s] (per 10 mL) | 626 | 1.00 | 0.97-1.02 | 0.936 | 535 | 1.00 | 0.98-1.02 | 0.967 | 626 | 0.99 | 0.94-1.04 | 0.804 |
| Unfavorable arterial collaterals (Maas ≤ 2) | 629 | 1.37 | 0.87-2.14 | 0.170 | 538 | 1.49 | 1.01-2.20 | 0.045 | 629 | 1.48 | 0.60-3.65 | 0.392 |
| Unfavorable VO profile (COVES ≤ 2) | 629 | 2.41 | 1.46-4.41 | <0.001 | 538 | 1.89 | 1.26-2.87 | 0.002 | 629 | * | * | * |
| Administration of tPA (yes) | 624 | 1.32 | 0.84-2.07 | 0.227 | 533 | 1.09 | 0.74-1.60 | 0.677 | 624 | 0.50 | 0.19-1.24 | 0.146 |
| Time from symptom onset to imaging ≤ 270 min [early time window] | 629 | 0.98 | 0.63-1.53 | 0.92 | 538 | 0.62 | 0.42-0.92 | 0.018 | 629 | 0.31 | 0.10-0.81 | 0.025 |
| Time from imaging to groin puncture (per 10 min) | 459 | 1.01 | 0.98-1.04 | 0.580 | 390 | 1.00 | 0.97-1.03 | 0.791 | 459 | 1.00 | 0.92-1.05 | 0.953 |
| General anesthesia (yes) | 623 | 1.31 | 0.84-2.05 | 0.240 | 532 | 1.31 | 0.89-1.93 | 0.173 | 623 | 1.64 | 0.67-4.24 | 0.286 |
| TICI 2b/2c/3 (yes) | 629 | 0.90 | 0.53-1.59 | 0.699 | 538 | 0.92 | 0.57-1.51 | 0.728 | 629 | 0.71 | 0.27-2.23 | 0.521 |
| Number of retrieval attempts | 569 | 0.97 | 0.82-1.12 | 0.674 | 484 | 1.03 | 0.90-1.17 | 0.677 | 569 | 0.99 | 0.70-1.30 | 0.935 |

Candidate variables with a p-value of ≤0.2 in the univariate logistic regression analysis were included as independent variables into the multivariable regression models.

* Complete separation of data points. All sICH patients presented with unfavorable VO profiles (COVES ≤2). Please note that the complete separation might be caused by the small number of sICH patients (n=20).

Abbreviations: HI, Hemorrhagic Infarction; PH, Parenchymal Hematoma; sICH, symptomatic Intracranial Cerebral Hemorrhage; VO, Venous Outflow; CBF, Cerebral Blood Flow; Tmax, Time to maximum; COVES, Collateral Venous Opacification Score; tPA, Tissue Plasminogen Activator; TICI, Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale.
### Supplementary Table 4. Univariable and multivariable logistic regression to predict good clinical outcomes (90-day modified Rankin Scale [mRS] score ≤ 2).

| Independent Variables | Univariable Logistic Regression | Multivariable Logistic Regression |
|-----------------------|---------------------------------|----------------------------------|
|                       | n  | OR  | 95 % CI | p value | n  | aOR | 95 % CI | p value |
| Age (per 1 year)      | 603| 0.96| 0.95-0.97| <0.001  | 574| 0.96| 0.94-0.97| <0.001  |
| Sex (male)            | 603| 1.72| 1.23-2.41| 0.002   | 574| 1.32| 0.82-2.15| 0.252   |
| Admission NIHSS (per point) | 602| 0.85| 0.82-0.88| <0.001  | 574| 0.90| 0.86-0.94| <0.001  |
| Time from symptom onset to imaging (per 10 min) | 471| 1.00| 0.99-1.01| 0.546   | -  | -   | -      | -      |
| Blood Glucose on admission (per 10 mg/dl) | 581| 0.92| 0.87-0.96| <0.001  | 574| 0.94| 0.89-0.99| 0.030   |
| Baseline Ischemic core volume [CBF<30%] (per 10 mL) | 601| 0.82| 0.76-0.88| <0.001  | 574| 0.96| 0.87-1.05| 0.375   |
| Unfavorable arterial collaterals (Maas ≤ 2) | 603| 0.30| 0.21-0.43| <0.001  | 574| 0.60| 0.34-1.05| 0.074   |
| Unfavorable VO profile (COVES ≤ 2) | 603| 0.07| 0.05-0.10| <0.001  | 574| 0.12| 0.07-0.20| <0.001  |
| Administration of tPA | 599| 1.54| 1.10-2.16| 0.013   | 574| 0.98| 0.59-1.62| 0.937   |
| General anesthesia    | 597| 1.10| 0.78-1.53| 0.595   | -  | -   | -      | -      |
| TICI 2b/2c/3          | 603| 3.74| 2.24-6.56| <0.001  | 574| 4.56| 2.31-9.45| <0.001  |
| HI on follow-up imaging | 603| 0.52| 0.34-0.80| 0.004   | 574| 0.32| 0.17-0.60| <0.001  |
| PH on follow-up imaging | 603| 0.25| 0.12-0.45| <0.001  | 574| 0.26| 0.11-0.57| <0.001  |

Statistical significance: p<0.05

Abbreviations:
VO, Venous Outflow; CBF, Cerebral Blood Flow; Tmax, Time to maximum; COVES, Collateral Venous Opacification Score; tPA, Tissue Plasminogen Activator; TICI, Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; HI, Hemorrhagic Infarction; PH, Parenchymal Hematoma; mRS, modified Rankin Scale