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## **Permalink**

<https://escholarship.org/uc/item/09m786wr>

## **Journal**

Stroke, 44(10)

## **ISSN**

0039-2499

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## **Publication Date**

2013-10-01

## **DOI**

10.1161/strokeaha.113.001231

Peer reviewed



# NIH Public Access **Author Manuscript**

*Stroke*. Author manuscript; available in PMC 2014 September 08.

### Published in final edited form as:

*Stroke*. 2013 October ; 44(10): 2748–2754. doi:10.1161/STROKEAHA.113.001231.

# **Prognostic Evaluation Based on Cortical Vein Score Difference in Stroke**

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## **Abstract**

**Background and Purpose—**Multimodal imaging in acute ischemic stroke defines the extent of arterial collaterals, resultant penumbra, and associated infarct core, yet limitations abound. We identified superficial and deep venous drainage patterns that predict outcomes in patients with a proximal arterial occlusion of the anterior circulation.

**Methods—**An observational study that used computed tomography (CT) angiography to detail venous drainage in a consecutive series of patients with a proximal anterior circulation arterial occlusion. The principal veins that drain the cortex (superficial middle cerebral, vein of Trolard, vein of Labbé, and basal vein of Rosenthal) and deep structures were scored with a categorical scale on the basis of degree of contrast enhancement. The Prognostic Evaluation based on Cortical vein score difference In Stroke score encompassing the interhemispheric difference of the composite scores of the veins draining the cortices (superficial middle cerebral+vein of Trolard +vein of Labbé+basal vein of Rosenthal) was analyzed with respect to 90-day modified Rankin Scale outcomes.

**Results—**Thirty-nine patients were included in the study. A Prognostic Evaluation based on Cortical vein score difference In Stroke score of 4 to 8 accurately predicted poor outcomes (modified Rankin Scale, 3–6; odds ratio, 20.53; *P*<0.001). On stepwise logistic regression analyses adjusted for CT Alberta stroke program early CT score, CT angiography collateral grading and National Institutes of Health Stroke Scale score, a Prognostic Evaluation based on Cortical vein score difference In Stroke score of 4 to 8 (odds ratio, 23.598; *P*=0.009) and an elevated admission National Institutes of Health Stroke Scale (odds ratio, 1.423; *P*=0.023) were independent predictors of poor outcome.

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The online-only Data Supplement is available with this article at [http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/](http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.001231/-/DC1) [STROKEAHA.113.001231/-/DC1.](http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.001231/-/DC1)

**Conclusions—**The Prognostic Evaluation based on Cortical vein score difference In Stroke score, a novel measure of venous enhancement on CT angiography, accurately predicts clinical outcomes. Venous features on computed tomography angiography provide additional characterization of collateral perfusion and prognostication in acute ischemic stroke.

#### **Keywords**

angiography; brain ischemia; cerebral veins; collateral circulation; perfusion; stroke

Clinical and imaging markers that identify patients most likely to benefit from revascularization therapy are important. National Institutes of Health Stroke Scale (NIHSS) score at presentation is an established clinical predictor of outcome.<sup>1</sup> Similarly, imaging parameters derived from multimodal computed tomography (CT)/MRI have been used to delineate the infarct core to guide further management and evaluate prognosis.<sup>2–6</sup> The presence of increased leptomeningeal collaterals on CT angiography (CTA) is associated with good outcomes after revascularization,  $2.7-9$  providing additional information beyond noncontrast CT. Lack of standardized postprocessing is an important drawback of computed tomography perfusion (CTP).<sup>10</sup> Similarly, shortcomings of CTA are (1) poor sensitivity to identify incomplete occlusion<sup>11</sup> and (2) lack of information on the tissue state. Additional means to define the extent of collaterals and resultant perfusion may, therefore, have a prominent impact on management of the acute stroke patient.

We piloted a novel venous scale for CTA that would improve prognostic evaluation of patients with acute ischemic stroke. Venous correlates of collateral perfusion have been known for decades, yet often ignored because of overwhelming focus on arterial delivery via leptomeningeal anastomoses.12 In the setting of proximal arterial occlusion, these anastomoses supply blood flow to the downstream microcirculation and adjacent venous circuits. In fact, the majority of cerebral blood volume is maintained in the venous circulation. Evaluation and quantification of venous flow in the downstream territory of an ischemic territory may, therefore, improve our understanding and characterization of collateral perfusion.

We reviewed the venous drainage in patients with acute ischemic stroke who had multimodal CT as part of their emergent evaluation. The primary objective of our study was to determine whether the pattern of venous drainage on brain imaging immediately after an acute ischemic stroke caused by proximal arterial occlusion of the anterior circulation can determine patient prognosis.

#### **Materials and Methods**

#### **Study Design and Patients**

Patients with acute ischemic stroke satisfying the following criteria were included: (1) terminal internal carotid artery (ICA), M1 or proximal M2 middle cerebral artery occlusion, (2) CT criteria for adequacy of scan met (described below), (3) age >18 years, and (4) CTA acquired within 24 hours of onset. Patients with distal M2 occlusions and beyond, posterior

circulation stroke and in whom CT criteria for adequacy of scan not met, were excluded. The University of Alberta institutional review board had approved this study.

Demographic, clinical, and laboratory data were abstracted in a structured case record form. All patients had a minimum of 3-month follow-up and clinical assessment in form of NIHSS and modified Rankin Scale was done. The clinical outcome measure was based on the modified Rankin scale assessment at 90 days. A score of 0 to 2 represented a good outcome and a score of 3 to 6 a poor outcome.

#### **Imaging**

Multimodal imaging was obtained using a Siemens definition 64-slice, 128-channel scan. Eighty milliliters of contrast was injected at a rate of 5 mL/s and scanning would be triggered when contrast density in the arch of aorta was 50 HU. Scanning time was set to 11 seconds. The acquisition rate was 126/0.6 mm and reconstruction was at 0.6/0.4 mm using a soft kernel algorithm. The scan was considered adequate if there was (1) complete reconstitution of the venous sinuses up to the internal jugular vein on both sides, (2) maximal intensity projection axial, sagittal, and coronal reconstruct sequences available, and (3) a minimum contrast density of  $150 \text{ HU}^{13,14}$  in both internal jugular veins.

A filling defect on CTA was considered an occlusion. Terminal ICA is defined as the segment of ICA before division into anterior and middle cerebral arteries. M1 is defined as the sphenoidal segment<sup>15</sup> that extends from the bifurcation of ICA on the medial end to its bifurcation or trifurcation in the insular region. Proximal M2 is defined as the segment that starts immediately after M1 bifurcation and distal M2 is beyond this region.

Though scanning is not dynamic, contrast filling or nonfilling at the time of acquisition reflects on the delay in transit through the arterial—capillary—venous bed. This can be significant and an assessment done at a single point can give valuable information on transit times.

#### **Veins Assessed and Scoring System**

The following veins were assessed for filling of contrast (1) superficial middle cerebral vein (SMCV), (2) vein of Labbé (VOL), (c) vein of Trolard (VOT), (4) basal vein of Rosenthal (BVR), (5) thalamostriate vein, and (6) internal cerebral vein (Figures 1 and 2). The reconstitution of the abovementioned veins was scored on the basis of visual assessment of the level of contrast enhancement in them. A score of 2 for complete (contrast filling similar to opposite hemisphere), 1 for partial (intermediate contrast filling), and 0 for no reconstitution (density similar to brain parenchyma on maximal intensity projection images or vessel just visible because of stagnation of blood or a very faint trace of contrast with a HU<100) was assigned. The contrast filling rather than the caliber of the vessel was scored. The veins should be tracked for at least a third of the distance between the origin and drainage site. The anatomy, variability, and radiological identification scheme are described in the online-only Data Supplement.

The veins were grouped on the basis of structures they drain (cortical or subcortical). In addition to the deep structures, the BVR drains the cortex and hence included with the

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superficial veins.<sup>16</sup> Therefore, 2 groups were considered: group A: superficial (SMCV+VOT +VOL+BVR) and group B: deep (internal cerebral vein+thalamostriate vein). The composite scores in the affected hemisphere and the score differences between the 2 hemispheres were computed for both the groups. The rationale for using the score difference was to account for the variability in the superficial veins. We designed a new scoring system based on group A veins—Prognostic Evaluation based on Cortical vein score difference In Stroke score (PRECISE). The PRECISE score is determined from the interhemispheric difference of composite scores of group A (SMCV+VOT+VOL+BVR) veins.

PRECISE score=composite score normal hemisphere<sub>SMCV+VOT+VOL+BVR</sub>−composite score affected hemisphere $_{SMCV+VOT+VOL+BVR}$  (Figure 3).

A high PRECISE score meant that there was poor superficial vein filling in the affected hemisphere and vice versa. Inter-rater agreement was evaluated on the basis of assessment of venous system in 20 scans by R.P. (Neurologist) and M.K. (neurologist), who were blinded to the outcome and each other's scores.

The following imaging and clinical data were recorded: (1) Alberta stroke program early CT score (ASPECTS), (2) CTA collateral grade, (3) follow-up infarct volume on imaging at 24 hours or later, (4) CTP measures, (5) recanalization grade,  $^{17}$  and (6) admission NIHSS score. A CT ASPECTS of 0 to 7 was categorized as low and 8 to 10 as good. CTA collaterals were graded good or reduced on the basis of Miteff et al<sup>8</sup> grading scale. The reduced category was further subclassified into moderate and poor.<sup>8</sup> The follow-up infarct volume was calculated on the basis of ABC/2 geometric model<sup>18</sup> and patients were grouped as having either small ( $50$  mL) or large ( $>50$  mL) infarct volumes.<sup>7,19</sup> CTP mismatch assessment (VPCT Neuro; Seimens Health Care) was done on the basis of qualitative visual analysis of color maps generated using cerebral blood flow and time-to-drain to define the tissue at risk (penumbra and core) and cerebral blood volume to define infarct core.<sup>20</sup> The presence of mismatch on CTP was defined as penumbral volume of a third or more of the volume of tissue at risk.

#### **Statistical Methods**

IBM SPSS version 20 was used to analyze the data. Chi-square statistics was used to analyze categorical data. An independent sample *t* test was used for parametric data. Stepwise logistic regression analysis was used to examine the effect of PRECISE score on outcome in univariate analysis and when adjusted for CT ASPECTS, CTA collateral grade, and admission NIHSS.

## **Results**

During a 3-year period (September 2009–September, 2012), 47 patients with proximal arterial occlusion of the anterior circulation were identified (Figure 4). Thirty-nine patients satisfied the inclusion criteria for this study and of them 21 (54%) were men. The median NIHSS in patients with good outcome was 12 (n and interquartile range, 17 and 8.25) and poor outcome was 18 (n and interquartile range, 22, 6). Fifteen (60%;  $n=25$ ) patients with a good ASPECTS and 1 (7.7%; n=13) patient with a low ASPECTS on the initial CT scan had

good outcomes at 3 months (the initial CT scan was inaccessible in 1 patient). Ten (66.7%; n  $=15$ ) patients with a good collateral grade had a good outcome and 17 (70.8%; n= 24) patients with a reduced collateral grade had poor outcomes. The mean infarct volume on follow-up scan done at 24 hours or later in patients with good and poor outcomes was 23.47 mL (n and SD, 15 and 26.766) and 213.48 (n and SD, 21 and 162.273; *P*<0.0001; there was no follow-up imaging at 24 hours or more in 3 patients). The site of occlusion was terminal ICA in 5 (12.8%), M1 in 30 (76.9%), and proximal M2 in 4 (10.3%). The mean HU on the right and left internal jugular veins was 228.86 (SD, 63.9; 152–416) and 222.08 (SD, 61.91; 151–377), respectively (Table 1).

#### **Venous Pattern in the Affected Hemisphere**

SMCV filling was absent, partial, and full in 23 (59%), 12 (30.8%), and 4 (10.3%) patients, respectively. Absent, partial, and full reconstitution of VOT was observed in 15 (38.5%), 22 (56.4%), and 2 (5.6%) patients, respectively. VOL filling was absent in 18 (46.2%), and was partly and fully reconstituted in 13 (33.3%) and 8 (20.5%) patients, respectively. Sixteen (69.6%; n=23), 12 (80%; n=15), and 14 (77.8%; n=18) patients had poor outcomes in the absence of enhancement of SMCV (*P*=0.048), VOT (*P*=0.024), and VOL (*P*=0.023), respectively. BVR filling was absent, partial, and full in 19 (48.7%), 14 (35.9%), and 6 (15.4%) patients, respectively. The absence of BVR filling (*P*=0.206) did not predict outcomes. In all patients there was internal cerebral vein or thalamostriate vein contrast enhancement. Partial reconstitution of thalamostriate vein (*P*=0.751) or internal cerebral vein (*P*=1.000) did not predict poor outcomes at 90 days (Table 2).

#### **PRECISE Score and Composite Score (SMCV+VOT+VOL+BVR) of the Affected Hemisphere**

For both the PRECISE score and composite score (SMCV+VOT+VOL+BVR) on the affected hemisphere, a maximum and a minimum score of 8 and 0 are possible. Nineteen (82.6%; n=23) patients with a PRECISE score of 4 to 8 (odds ratio [OR], 20.5; *P*<0.0001) and 13  $(81.2\%; n=16)$  patients with a composite score of 0 to 2  $(OR, 6.7; P=0.013; 1$  vein or less filling) in the affected hemisphere had poor outcomes at 90 days (Figure 4). A PRECISE score of 4 to 8 meant that there were 2 veins not enhancing (or equivalent) on the affected hemisphere when compared with the normal hemisphere (Table 2; Figure 4).

When only the anastamotic veins, namely SMCV, VOT, and VOL were considered, a composite score of 0 to 2 (*P*=0.007) on the affected hemisphere and score difference of 4 to 6 (*P*<0.001) between the hemispheres predicted poor outcomes. Inter-rater agreement for the dichotomized venous score  $(0-3$  and  $4-8)$  was determined on 20 CT angiograms randomly selected from the study population by 2 independent raters (R.P. and M.K.) and was excellent (Cohen's  $\kappa$ =0.86 for the PRECISE score and  $\kappa$ =0.78 for 3 vein score difference). Neither the absolute score on the affected side (*P*=0.701) nor the score difference (*P*=0.168) of the group B (deep) veins predicted outcomes.

#### **Predictors of Poor Clinical Outcome**

The significant predictors of poor clinical outcome on univariate analysis were reduced arterial collateral grading score (OR [95% confidence interval {CI}], 4.857 [1.212, 19.416]; *P*=0.026), low ASPECTS score (OR [95% CI], 18 [2.012, 161.014]; *P*=0.010), high NIHSS

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score (OR [95% CI], 1.347 [1.105, 1.641]; *P*=0.003), and a high PRECISE score of 4 to 8 (OR [95% CI], 20.583 [3.934, 107.698]; *P*<0.0001). On stepwise logistic regression analysis, including the above variables, high NIHSS score on admission (OR [95% CI], 1.423 [1.051, 1.927]; *P*=0.023) and a PRECISE score of 4 to 8 (OR [95% CI], 23.598  $[2.179, 255.562]$ ;  $P=0.009$ ) were independent predictors of poor outcome.

#### **Relationship Between PRECISE Score and Collateral Grade/Follow-Up Infarct Volumes**

Eleven (73.33%) patients with a good collateral grade and 4 (20.83%) patients with a poor collateral grade had a low (0–3) PRECISE score. A good collateral grade predicted a low PRECISE score of 0 to 3 with significance (OR, [95% CI], 10.45, [2.30, 47.30]; *P*=0.002). Seventeen (77.27%) patients with a PRECISE score of 4 to 8 and 4 (28.57%) patients with a PRECISE score of 0 to 3 had a follow-up infarct volume of >50 mL. A PRECISE score of 4 to 8 predicted an infarct volume of >50 mL on follow-up scan with significance (OR [95% CI], 8.5 [1.84, 39.22]; *P*=0.006].

#### **Relationship Between PRECISE Score and Perfusion Patterns**

Sixteen  $(41.02\%; n=39)$  patients had CTP data. When the PRECISE score was 4 to 8, only 3/9 (33.3%) had mismatch on CT perfusion. Conversely, 6/7 (85.7%) patients with a PRECISE score of 0 to 3 had CTP mismatch. Univariate analysis indicated a trend to lower PRECISE scores being associated with CTP mismatch patterns (OR [95% CI], 12 [0.956, 150.68]; *P*=0.054). When only the anastamotic veins were considered (SMCV+VOT+VOL score difference), a score difference of 0 to 3 significantly predicted the presence of CTP mismatch (OR (95% CI), 48 (2.47, 932.84); *P*=0.011).

Nineteen (48.71%; n=39) patients were treated with intravenous thrombolysis. The median onset to treatment (intravenous thrombolysis) time was 160 (interquartile range, 110, 240) minutes. Mechanical thrombectomy was attempted in 13 patients and was successful in 10 patients (in all Solitaire FR device was used) with a greater than or equal to thrombolysis in myocardial infarction 2 grade flow.<sup>17</sup> One patient who had mechanical thrombectomy did not receive intravenous thrombolysis. Recanalization data were available in 29 patients on the basis of either Transcranial Doppler or imaging. A thrombolysis in brain ischemia 2 or more or a thrombolysis in myocardial infarction 2 or more grade recanalization was achieved only in 13 patients. Neither the time to thrombolytic therapy nor recanalization status predicted outcomes with significance.

#### **Venous Pattern in the Normal Hemisphere**

The most common pattern observed was that of a dominance of all 3 veins (SMCV, VOT, and VOL) in 17 (43.7%) patients. The other patterns observed were as follows: (1) codominant VOL and VOT in 6 (15.4%), (2) dominant VOL in 5 (12.8%), (3) codominant SMCV and VOT in 4 (10.3%), (4) dominant VOT in 2 (5.1%), (5) codominant VOL and VOT and absent SMCV in 3 (7.6%), and (5) absent VOL in 1 (2.6%). In the 39 hemispheres examined, there were a total 4 absent superficial veins.

### **Discussion**

Our study provides quantifiable data on the impact of venous outflow identified by routine CTA on the prognosis in acute ischemic stroke. We established specific venous drainage patterns that predicted clinical outcomes. The cortical venous drainage, as opposed to deep venous drainage pattern predicted clinical outcomes. When there were 2 veins not filling (other combinations possible) on the affected hemisphere as compared with the normal hemisphere resulting in a high PRECISE score of 4, the outcome was poor. The PRECISE score and not the composite score on the affected hemisphere was an independent predictor of outcome on regression analysis and the likely reason for this is the variability in the venous structures. The subcortical structures drained by the deep veins are supplied by the anterior, middle, posterior cerebral, and anterior choroidal and posterior communicating arteries.

In our study group, the PRECISE score significantly correlated with arterial collateral status and follow-up infarct volumes, and the anastamotic veins score difference with perfusion mismatch. There are animal data on the significance of the venous circulation changes and prognosis in stroke. In a nonhuman primate model, when blood flow was evident in the cortical veins after M1 occlusion, the severity of hemiparesis and infarct volumes was low.<sup>21</sup> On the contrary, no venous flow predicted larger infarct volumes and poor outcomes. It was hypothesized that venous outflow was present in the collateral-rich group and absent in the collateral poor group.<sup>21</sup> Venous phase timing has been used during balloon test occlusion as a surrogate marker of adequacy of circle of Willis collaterals and cerebral blood flow to prognosticate outcomes if the ICA has to be sacrificed.<sup>22</sup> There is limited data on description of venous patterns in acute ischemic stroke.23,24

Collateral grading plays a crucial role in determining further management as collateral extent is an independent predictor of infarct growth<sup>8,25–27</sup> and clinical outcome at 3 months.<sup>8</sup> Although, good collateral status significantly predicted smaller baseline infarct volume and a minimal infarct expansion, it predicted good outcomes in <50% of patients in this category.<sup>8</sup> A potential explanation is that a single-phase CTA is not time resolved. When there is contrast filling beyond the occlusion site, a single-phase CTA cannot reliably differentiate between forward flow through an incomplete occlusion and retrograde collateral flow in complete occlusion. A single-phase CTA can predict incomplete occlusions with a sensitivity and specificity of 40% and  $87.2\%$ .<sup>11</sup>

In our patient group, the PRECISE score was an independent predictor of outcome (when compared with CTA collateral status) and the likely explanation is that in patients with inherently poor collaterals, spontaneous partial recanalization of an initially occlusive thrombus can give the appearance of good collaterals beyond the site of occlusion on a single-phase CTA (not sensitive to identify incomplete occlusions) because of forward flow. Whence the occlusive thrombus persists for a sufficiently long time to cause brain injury, reperfusion may not be achieved in spite of partial recanalization and good-appearing collaterals. Likewise, other than collateral extent, there are other factors that determine perfusion and the evolution of the ischemic penumbra to infarction.28,29 Thrombus propagation, embolization, and microvascular obstruction secondary to activation of

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microvessels are additional factors.29 Hence, venous outflow assessment is likely to represent a combined assessment of both the extent of collaterals and perfusion through the microcirculation. Another key advantage is that to assess veins one might not require dynamic scanning because absence of venous flow at a given point in time is likely to be significant as it represents delay in transit times.

In our study, the average time it took for the scanner to reach the skull base from the aortic arch was 7.35 seconds (SD, 1.5, 5–12). On the basis of transit times reported in the literature,  $30-33$  the approximate arch to retinal circulation time for contrast was 0.77 seconds. From the above the approximate cerebral transit time for the contrast before the scanner reaches the skull base was 6.58 seconds (4.23–11.23). This was the rationale behind assessing veins on a CTA. Although, at the lower end of extremes, it is possible that some of the veins did not fill because of the short scanning time, it solely represents delay in transit through the microvasculature. A second-phase scanning from the skull base to vertex at 6 seconds mainly to assess the venous structures is likely to overcome this issue with a minimum 10-second transit time when extreme values were factored in.

The other limiting factors are that of a small sample size and the variability in the cortical venous structures. The variability in venous structures in this study was accounted for by calculating the score difference (PRECISE score). A venous grading scale is likely to give us extremely useful information over and above arterial collateral assessment to base further management decisions.

## **Conclusions**

Cortical venous outflow grading strongly predicted outcomes at 90 days. A high PRECISE score as opposed to composite hemispheric score on the affected side was an independent predictor of outcome. Quantifying venous outflow is likely to represent an assessment of both the extent of collaterals and perfusion and may play a key role in influencing management decisions. Further prospective studies will help in determining whether the venous score described above will help in determining prognosis in acute ischemic stroke.

### **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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## **Figure 1.**

Superficial veins on CTA. **A**, Vein of Trolard in axial, coronal, and sagittal sections. **B**, Vein of Labbé in axial, coronal, and sagittal sections. **C**, Superficial middle cerebral vein in axial, coronal, and sagittal sections.



### **Figure 2.**

Veins draining into the deep venous system. (**A**) Internal cerebral vein (ICV), (**B**) thalamostriate vein, (**C**) basal vein of Rosenthal (BVR), and (**D**) coronal section demonstrating ICV (bold arrow) and BVR (arrow).



#### **Figure 3.**

Demonstration of Prognostic Evaluation based on Cortical vein score difference In Stroke (PRECISE) score calculation in 2 patients with proximal occlusion in the anterior circulation. **A**, 1—Right terminal internal carotid artery (ICA) occlusion, 2—part reconstitution of right superficial middle cerebral vein (SMCV) and full reconstitution of left SMCV, 3—part reconstitution of right vein of Trolard (VOT) and full reconstitution of left VOT, 4—full reconstitution of both right and left vein of Labbé, and 5—full reconstitution of both right and left basal vein of Rosenthal (BVR). PRECISE=left (SMCV+VOT+VOL +BVR)–right (SMCV+VOT+VOL+BVR)=left (2+2+2+2)–right (1+1+2+2)=left (8)–right (6)=2. **B**, 1—Right terminal ICA occlusion, 2—absent filling of right SMCV and full reconstitution of left SMCV, 3—absent right VOT filling and full reconstitution of left VOT, 4—absent right VOL filling and full reconstitution of left VOL, and 5—part reconstitution of right BVR and full reconstitution of left BVR. PRECISE=left (SMCV +VOT+VOL+BVR)–right (SMCV+VOT+VOL+BVR)=left (2+2+2+2)–right  $(0+0+0+1)=left (8)-right (1)=7.$ 



#### **Figure 4.**

Patient inclusion and Prognostic Evaluation based on Cortical vein score difference In Stroke (PRECISE) score. mRS indicates modified Rankin Scale.

#### **Table 1**

### Demographics



BP indicates blood pressure; ICA, internal carotid artery; and NIHSS, National Institutes of Health Stroke Scale.

*\**Mean (n; SD).

#### **Table 2**

### Venous Patterns in the Affected Hemisphere and Venous Scoring



BVR indicates basal vein of Rosenthal; ICV, internal cerebral vein; mRS, modified Rankin Scale; OR, odds ratio; SMCV, superficial middle cerebral vein; TSV, thalamostriate vein; VOL, vein of Labbé; and VOT, vein of Trolard.

*\** Composite score of SMCV+VOT+VOL+BVR.