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Relative cerebral blood volume is associated with collateral status and infarct growth in stroke patients in SWIFT PRIME

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Abstract

We aimed to evaluate how predefined candidate cerebral perfusion parameters correlate with collateral circulation status and to assess their capacity to predict infarct growth in patients with acute ischemic stroke (AIS) eligible for endovascular therapy. Patients enrolled in the SWIFT PRIME trial with baseline computed tomography perfusion (CTP) scans were included. RAPID software was used to calculate mean relative cerebral blood volume (rCBV) in hypoperfused regions, and hypoperfusion index ratio (HIR). Blind assessments of collaterals were performed using CT angiography in the whole sample and cerebral angiogram in the endovascular group. Reperfusion was assessed on 27-h CTP; infarct volume was assessed on 27-h magnetic resonance imaging/CT scans. Logistic and rank linear regression models were conducted. We included 158 patients. High rCBV ($p = 0.03$) and low HIR ($p = 0.03$) were associated with good collaterals. A positive association was found between rCBV and better collateral grades on cerebral angiography ($p = 0.01$). Baseline and 27-h follow-up CTP were available for 115 patients, of whom 74 (64%) achieved successful reperfusion. Lower rCBV predicted a higher infarct growth in successfully reperfused patients ($p = 0.038$) and in the endovascular treatment group ($p = 0.049$). Finally, rCBV and HIR may serve as markers of collateral circulation in AIS patients prior to endovascular therapy.

Clinical Trial Registration: Unique identifier: NCT0165746.

Keywords

Acute ischemic stroke, collateral circulation, perfusion imaging, thrombectomy, cerebral blood volume

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Introduction

In patients with acute ischemic stroke (AIS) and a large-artery occlusion, collateral circulation is a key determinant of the rate of ischemic penumbra recruitment and cerebral infarct outgrowth.[1] Previous studies on AIS patients who received endovascular treatment have shown that good collateral status on cerebral

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angiography is associated with smaller baseline infarct cores and reduced final infarct volumes.[2–4] Therefore, assessing collateral circulation in advance may help estimate the life expectancy of the tissue at risk, and this information may have an added value when patients are being considered for endovascular reperfusion.

Ideally, collateral capacity should be noninvasively assessed as a part of the process to indicate reperfusion therapies. Visual scales have been developed that use computed tomography angiography (CTA), and these show a good correlation with 4-vessel cerebral angiography, which is considered the reference standard for assessing collateral circulation.[5,6] Other groups have used a CT perfusion (CTP) source image-based visual scale.[7] However, visual scales condense the entire spectrum of collateral capacity into a limited number of categories, and may be influenced by the rater's subjectivity. Therefore, there is a growing clinical need to develop an objective, operator-independent, automatic, and real-time way to assess collateral circulation status in AIS patients.

Given that perfusion imaging is tightly linked to collateral status, postprocessed brain perfusion parameters might emerge as good markers of collateral capacity.[8] The Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) randomized controlled trial (RCT)[9] used a multimodal imaging protocol and fully automated brain perfusion software (RAPID; iSchemaView, Menlo Park, CA, USA). The objectives of this post hoc study, approved by the SWIFT PRIME publications committee, were to evaluate how candidate brain perfusion parameters, such as relative cerebral blood volume (rCBV) and the hypoperfusion index ratio (HIR), correlate with collateral circulation status, and their capacity to predict infarct outgrowth in AIS patients eligible for endovascular therapy.

Methods

SWIFT PRIME protocol

The methodology and main results of the SWIFT PRIME trial have been published previously.[9,10] Eligible patients were randomized to receive treatment with an intravenous tissue-type plasminogen activator (tPA) alone vs. tPA plus endovascular therapy (using the Solitaire device). The baseline ischemic core lesion volume and hypoperfusion volume were generated in real time during the study using fully automated software (RAPID), which was installed at the study sites. The CTP and magnetic resonance imaging (MRI) diffusion/perfusion protocols were adjusted at each site to harmonize acquisition parameters. For patients with baseline CTP scans, the ischemic core was defined as tissue with a $>70\%$ reduction in cerebral blood flow when compared with normally perfused tissue. For patients who underwent MRI at baseline, the ischemic core was defined as tissue with an apparent diffusion coefficient (ADC) of $<620 \times 10^{-6}\,mm^2/s$. Hypoperfusion volume was identified as tissue with a T_{max} value >6 s; when necessary, the SWIFT PRIME imaging core laboratory corrected the automated T_{max} volume assessments to remove artifacts. The clinical trial was approved by the responsible ethics committees of the participating centers (please see complete list of enrolling sites at nejm.org, reference 9, supplementary appendix, pages 33–36). Enrolled patients provided written informed consent. The current research was conducted according to the principles of the Declaration of Helsinki.

Inclusion/exclusion criteria

In our study, we included all SWIFT PRIME patients who underwent baseline perfusion imaging and RAPID processing, and all non-exploratory analyses were prespecified before data examination. During the initial phase of SWIFT PRIME, enrollment was restricted to patients with a target-mismatch (TMM) profile, which was defined as an MRI- or CT-assessed ischemic core volume of ≤ 50 ml, $T_{max} > 10$ seconds-lesion volume ≤ 100 ml, mismatch volume (hypoperfusion volume minus ischemic core volume) ≥ 15 ml, and a mismatch ratio (hypoperfusion volume divided by ischemic core volume) >1.8. After 71 patients were enrolled, the protocol was modified to make perfusion imaging optional; however, the majority of patients continued to have perfusion imaging performed before randomization. Sites were encouraged to continue to follow the TMM criteria for patient selection if these results were available before randomization. Eight patients underwent CTP or multimodal MRI at the sites that did not have RAPID installed; these cases were postprocessed using RAPID at the core laboratory.

Pretreatment collateral circulation assessment

Pretreatment collateral status was centrally analyzed in SWIFT PRIME's imaging core laboratory, which was blind to clinical information and treatment allocation. Baseline CTA was used to assess collateral circulation in all patients included in both treatment arms. After visual inspection, the collaterals on CTA were graded as excellent, good, or poor according to previously published criteria.[11] In the endovascular group, the collaterals were also evaluated on pretreatment cerebral angiograms and categorized according to the

American Society of Interventional and Therapeutic Neuroradiology collateral scoring system (grades 0–4).[12] For analysis purposes, grades 3–4 were defined as good collaterals and grades 0–2 were categorized as poor collaterals.

Calculation of rCBV and HIR

The RAPID software provided CBV values from the $T_{max} > 6$ s area in the affected brain hemisphere. Mean rCBV was obtained by dividing the average of all CBV values from the Tmax > 6 s region within the ischemic hemisphere by the average of all CBV values from all tissue with Tmax ≤ 4 s. HIR was calculated as the quotient between the volumes with Tmax > 10 s and Tmax > 6 s.

Infarct outgrowth as the primary end point

The $\approx$ 27-h infarct volume was assessed by blinded readers who manually outlined the subacute fluid attenuation inversion recovery lesion or the subacute hypodense lesion on noncontrast CT. Regions of hemorrhagic transformation were included in the infarct volume. If both CT and an MRI were performed at $\approx$ 27 h, then the volume from the MRI lesion was selected. These manual outlines were performed before unblinding the treatment assignments. Infarct outgrowth was defined as the difference between the 27-h infarct volume and the baseline ischemic core volume. As previously reported, successful reperfusion was defined as a > 90% reduction in the hypoperfusion volume ($T_{max} > 6$ s) between baseline and $\approx$ 27 h.[13]

Statistical analysis

The statistical analysis was performed using SAS (version 9.3 or higher; SAS Institute, Cary, NC, USA). The baseline data are presented as the median value with interquartile range or mean value with standard deviation (SD). The Wilcoxon rank-sum test was used to compare pairs of subgroups within the patient population, whereas rank-ANOVA was used to analyze multifactorial sets of subgroups. Correlations between continuous variables were calculated using Spearman's rho. The associations between HIR, rCBV, and good vs. poor collaterals were evaluated using logistic regression models, where adjustment was done by baseline core and randomized group assignment. Multivariate-adjusted rank linear regression models were applied to assess the relationship between rCBV, HIR, and infarct outgrowth, where the baseline core and randomized group assignment (intravenous tPA alone vs tPA plus Solitaire) were included as required covariates. Due to observed nonnormality in the linear regression residuals caused by outliers in infarct outgrowth, a rank linear regression model was used transforming the dependent variable to ranks. After running the models using the whole sample, stratification by 27-h reperfusion status and treatment group (endovascular treatment using Solitaire) was performed. All p values were two-sided, and values < 0.05 were considered statistically significant.

Results

Baseline characteristics

Of the 196 patients included in the SWIFT PRIME trial, the 158 patients (81%) who underwent baseline perfusion imaging and RAPID-derived perfusion mapping were included in this study. The main baseline characteristics of the study population are summarized in Table 1. The mean patient age was 66 years, 76 patients were included in the t-PA group and 82 in the t-PA plus Solitaire group, and the median baseline National Institutes of Health Stroke Scale (NIHSS) score was 16. Baseline characteristics did not significantly differ between treatment arms. CTA was available and of sufficient quality for collateral visual assessment for 95 patients (60%). Among the 82 patients included in the endovascular group, pretreatment cerebral angiograms were determined to have sufficient spatial and temporal resolution for the inspection of collateral circulation in 60 patients (73%). Regarding brain perfusion parameters, rCBV could be calculated in the entire population ($n = 158$), whereas HIR could be measured in 154 patients (97.5%). A statistically significant negative correlation was found between rCBV and HIR ($r = -0.28$; $p = 0.0005$), as shown in Supplemental Figure 1.

Association between rCBV, HIR, and pretreatment collateral status

The distributions of rCBV and HIR values according to the collateral circulation categories (as defined either by CTA or cerebral angiography) are shown in Figures 1 and 2. For additional details, see Supplemental Tables 1 to 4 and Supplemental Figures 2 and 3. A significant association between rCBV and higher collateral grades was observed, which was more pronounced when the cerebral angiography scoring system was used ($p = 0.01$). Both HIR ($p = 0.04$) and rCBV ($p = 0.02$) were significantly associated with good collateral status as assessed by CTA after the logistic regression models were applied, as shown in Table 2.

Table 1. Baseline characteristics of study sample.

Variable	iv tPA ($n=76$)	iv tPA + Solitaire ($n=82$)	Overall ($n=158$)
Age	66.7 ± 11.8	65.4 ± 13.1	66.0 ± 12.5
Baseline risk factors			
Hypertension	51.3%	67.1%	59.5%
Diabetes mellitus	14.5%	13.4%	13.9%
Hyperlipidemia	17.1%	24.4%	20.9%
Atrial fibrillation	32.9%	37.8%	35.4%
Myocardial infarction	7.9%	7.3%	7.6%
Baseline NIHSS	17.0 (8.0, 27.0)	16.0 (8.0, 28.0)	16.0 (8.0, 28.0)
Baseline glycemia	133.8 ± 51.0	132.0 ± 47.8	132.8 ± 49.2
Baseline SBP	149.0 ± 21.1	151.4 ± 25.6	150.3 ± 23.6
Collaterals (CTA)	$n=44$	$n=51$	$n=95$
Excellent	40.9% (18/44)	15.7% (8/51)	27.4% (26/95)
Good	47.7% (21/44)	56.9% (29/51)	52.6% (50/95)
Poor	11.4% (5/44)	27.5% (14/51)	20.0% (19/95)
Excellent/good	88.6% (39/44)	72.5% (37/51)	80.0% (76/95)
Collaterals (Angio)	NA	$n=60$	NA
1	NA	8.3% (5/60)	NA
2	NA	33.3% (20/60)	NA
3	NA	55.0% (33/60)	NA
4	NA	3.3% (2/60)	NA
3–4	NA	58.3% (35/60)	NA
Tmax > 6 s volume	126.2 ± 66.7	111.7 ± 59.3	118.8 ± 63.3
	128.0 (10.0, 378.0)	109.0 (17.0, 301.0)	124.5 (10.0, 378.0)
Tmax > 10 s volume	53.2 ± 37.0	51.1 ± 44.1	52.1 ± 40.7
	48.0 (0.0, 177.0)	39.0 (0.0, 211.0)	46.0 (0.0, 211.0)
HIR	0.393 ± 0.187	0.394 ± 0.224	0.394 ± 0.206
	0.442 (0.000, 0.750)	0.432 (0.000, 0.826)	0.434 (0.000, 0.826)
rCBV	0.936 ± 0.126	0.941 ± 0.171	0.938 ± 0.151
	0.960 (0.640, 1.300)	0.955 (0.520, 1.800)	0.960 (0.520, 1.800)

Note: Statistics shown are mean ± SD (n); median (minimum, maximum). SBP: systolic blood pressure; NIHSS: National Institutes of Health Stroke Scale; CTA: computed tomography angiogram; Angio: cerebral angiography; NA: not available; HIR: hypoperfusion index ratio; rCBV: relative cerebral blood volume.

Relationship between rCBV, HIR, and infarct growth

Baseline and 27-h follow-up CTP were available for 115 patients, of whom 74 (64%) achieved successful reperfusion. The rank linear regression models used to assess the relationship between rCBV, HIR, and infarct growth in the entire study population and after stratification by reperfusion status and treatment group are condensed in Table 3. The unadjusted models show that both high HIR and low rCBV in the entire study population and low rCBV in the group that achieved successful reperfusion and in the endovascular group were associated with infarct growth. After the multivariate adjustment was performed, low rCBV emerged as an independent predictor of infarct growth in the subgroup of patients who achieved successful reperfusion at 27 h (B − 73.9, 95% CI (−143.6 to −4.2), $p=0.038$) and in the endovascular treatment group (B − 86.8, 95% CI (−173.4 to −0.3), $p=0.049$). The overall relationship showing lower the rCBV value associated with higher infarct growth was statistically significant within the reperfused and endovascular treatment group subgroups.

Discussion

In this SWIFT-PRIME post-hoc study, two pretreatment cerebral perfusion parameters, HIR and rCBV, were independently associated with the degree of collateral circulation in anterior circulation AIS patients. Moreover, in response to our primary endpoint, rCBV emerged as a predictor of infarct growth in

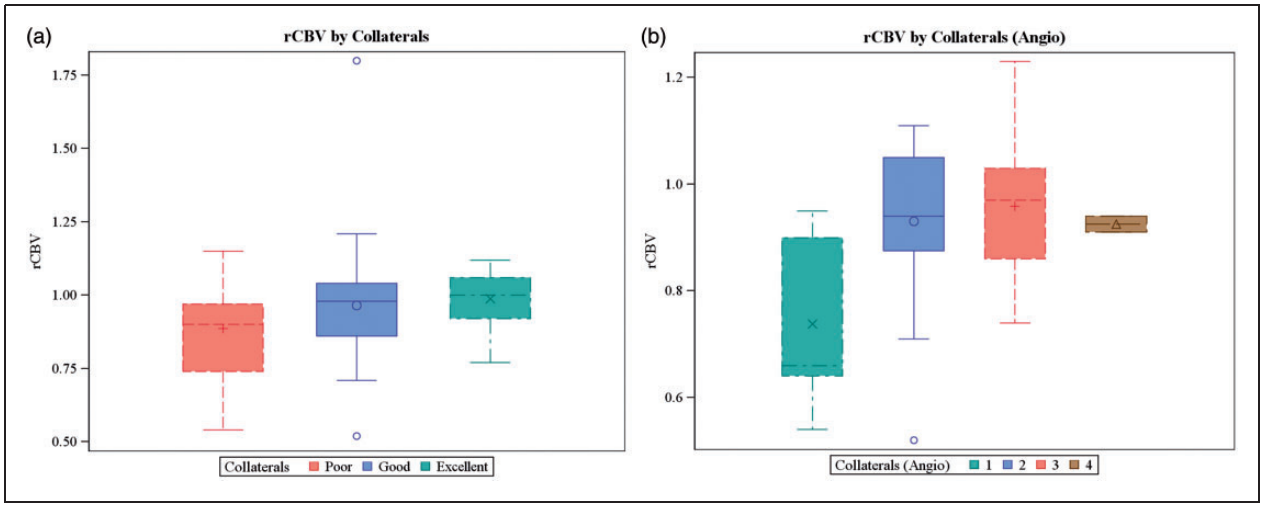

Figure 1. Boxplots showing the distributions of (a) the rCBV values across cerebral collateral categories as assessed by CTA in the core laboratory ($p = 0.08$ for all categories and $p = 0.008$ for excellent vs. poor collaterals) and (b) the rCBV values across cerebral collateral categories as assessed by cerebral angiography in the endovascular group ($p = 0.01$).

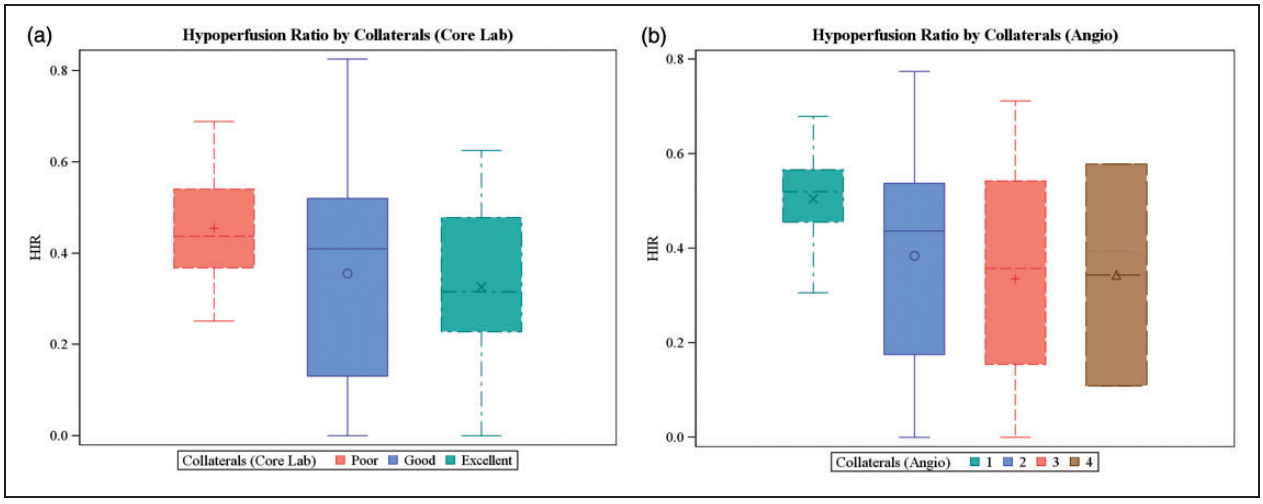

Figure 2. Boxplots showing the distributions of (a) the HIR values across cerebral collateral categories as assessed by CTA in the core laboratory ($p = 0.1$ for all categories and $p = 0.03$ for excellent vs. poor collaterals, respectively) and (b) Boxplots showing the distributions of the HIR values across cerebral collateral categories as assessed by cerebral angiography in the endovascular group ($p = 0.5$).

successfully reperfused patients and in the endovascular group. Both parameters were negatively correlated between each other, and therefore good collaterals correspond with a low HIR and a high rCBV, respectively. Previous publications suggested that HIR and rCBV might provide an estimate of collateral blood flow in anterior circulation AIS patients, which led us to select them as pre-specified parameters to be evaluated in this study. In the DEFUSE-2 cohort, HIR correlated with cerebral angiogram-assessed collaterals and predicted infarct growth.[14] High rCBV was found to be associated with a good collateral grade evaluated on CTP-source images in AIS patients treated with intravenous thrombolysis.[8] More recently, CBV-ASPECTS score emerged as the most robust indicator of collateral status in a retrospective series of AIS patients receiving endovascular therapy.[15] However, to the best of our knowledge, these promising parameters had not been tested as markers of collateral flow in the setting of a randomized control trial. As another strength of our study, collateral grading in SWIFT-PRIME was centrally performed and

assessed multi-modally by CTA and cerebral angiogram.

As the major finding of our study, rCBV predicted infarct growth in the subgroups of patients who achieved successful reperfusion and also in those who received endovascular treatment, independently of baseline core volume and treatment arm. This finding suggests that (1) infarct core continues its expansion from baseline imaging time until reperfusion occurs, or even after that time-point, and that (2) the velocity of infarct growth during that critical period depends on collateral circulation status. Thus, the poorer the collateral circulation as reflected by a lower rCBV, the fastest is the process of infarct growth taking place until reperfusion can be achieved. This observation is in line with recent studies showing that the impact of onset-to-reperfusion time on clinical and radiological outcomes is greater in AIS patients with poor collaterals.[16] Interestingly, HIR was not independently associated with infarct growth, although this negative finding might be related to reduced sample size and wide confidence intervals. We might also hypothesize that rCBV and HIR may reflect different aspects of collateral flow dynamics. HIR is based on arterial inflow delay within the ischemic brain tissue, and therefore it may evaluate predominantly the arterial phase of collateral flow. In contrast, rCBV might also reflect venous outflow capacity. Recent studies have underscored the prognostic importance of venous collaterals in AIS patients treated with endovascular therapies.[17] Moreover, angiographic collateral scores combining arterial plus venous information performed better than arterial scores alone in the prediction of long-term outcome.[18] As a speculative explanation for the higher prognostic value observed for rCBV in our study, this parameter could be integrating information about both arterial and venous phases of collateral flow, thus providing a more complete estimate of ischemic tissue viability. Anyhow, this hypothesis needs to be confirmed.

Table 2. Perfusion parameters and collateral assessment.

Collaterals	Independent Covariate	OR (95% CI)	*p*
CTA scale	rCBV	73.696 (1.664, >999)	0.0262
Angio	rCBV	31.945 (0.624, >999)	0.0845
CTA scale	HIR	0.056 (0.003, 0.915)	0.0432
Angio	HIR	0.232 (0.022, 2.463)	0.2254

Note: The table shows the results of the logistic regression analyses that evaluated the relationship between relative cerebral blood volume (rCBV) and collateral circulation status and between hypoperfusion index ratio (HIR) and collateral circulation status. Collateral circulation was categorized as good vs. poor according to CT angiography (CTA) or cerebral angiography (Angio) visual scales. Poor was classified as a 0–2 on the American Society of Interventional and Therapeutic Neuroradiology and good as a 3–4. Multivariable adjustment was done by baseline core and treatment arm.
HIR: hypoperfusion index ratio; rCBV: relative cerebral blood volume; CTA: CT angiography.

Table 3. HIR and rCBV as predictors of infarct growth.

Linear regression	Unadjusted B (95% CI)	*p*	Adjusted B (95% CI)	*p*
Entire population	Crude models (only rCBV or HIR)		Adjustment by core volume, treatment group and reperfusion success	
rCBV	−47.1 (−92.5, −1.7)	0.042	−54.8 (−111.4, 1.8)	0.058
HIR	51.7 (18.8, 84.6)	0.002	28.1 (−11.3, 67.6)	0.161
27 h reperfusion success group			Adjustment by core volume and treatment group	
rCBV	−84.6 (−144.4, −24.8)	0.006	−73.9 (−143.6, −4.2)	0.038
HIR	38.8 (−5.7, 83.2)	0.086	22.7 (−28.7, 74.1)	0.382
27 h reperfusion failure group			Adjustment by core volume and treatment group	
rCBV	−27.8 (−122.0, 66.4)	0.554	−33.4 (−130.8, 64.1)	0.492
HIR	35.5 (−31.0, 102.0)	0.287	30.5 (−33.9, 94.9)	0.344
Endovascular group			Adjustment by core volume and TICI 2b − 3	
rCBV	−17.1 (−76.4, 42.2)	0.568	−86.8 (−173.4, −0.3)	0.049
HIR	26.2 (−19.5, 71.9)	0.257	21.4 (−37.6, 80.4)	0.472

Note: Statistics show the parameter estimates with associated 95% confidence intervals and p values determined from the rank linear regression models for the outcome of infarct growth.
HIR: hypoperfusion index ratio; rCBV: relative cerebral blood volume.

A growing body of evidence supports the preeminent role of collateral circulation determining clinical and radiological outcomes in AIS patients who receive endovascular reperfusion therapies.[19] Therefore, rapid assessment of collateral status is critical to refine therapeutic decision making in AIS patients with a large-artery occlusion. Onset to reperfusion time, including intrahospitalary latencies, should be minimized to optimize clinical outcomes, as the pivotal randomized clinical trials of endovascular therapy have stressed.[20–23] Therefore, there is a need to develop fast, simple, automatic, objective and reproducible methods to assess collateral circulation status in hyperacute AIS. There have been previous attempts to develop quantitative perfusion-based imaging techniques to assess collateral flow, most of which were MRI-based.[14,23] In agreement with this concept, both rCBV and HIR can be fast, automatically and easily obtained after processing either CT or MR brain perfusion source images with the RAPID software. Another advantage of these perfusion parameters over visual reading collateral scales is their potentially wider generalizability as estimates of collateral flow. In our study, whereas rCBV could be obtained in the whole sample, CTA and cerebral angiogram assessed collaterals were considered not optimal for visual inspection in several patients. Nevertheless, further technical development is needed to improve the applicability of brain perfusion quantitative parameters, to allow their use for clinical decision making as objective measures of collateral status and predictors of infarct growth in AIS patients.

This study has several limitations. First, collaterals on CTA and cerebral angiography were available only in a subset of the study sample, due to technical reasons. It might have been interesting to use CTP source data to assess collaterals in the other patients, but we preferred to rely only on one non-invasive method to avoid heterogeneity. Moreover, cerebral angiogram collateral assessment was often based on a single-culprit vessel angiography in order to minimize groin to reperfusion time. Four-vessel angiography would have been desirable for an optimal assessment of collaterals. Second, SWIFT-PRIME inclusion criteria may have skewed the study towards a relatively benign sample in terms of collateral status, with an underrepresentation of patients with poor collaterals. This fact could have limited the prognostic value of the studied parameters. Third, although the image acquisition process was highly standardized, brain perfusion images were obtained using different CT and MR machines at the study sites. Fourth, the specific perfusion parameters and definition of HIR assessed in this study were prespecified in the statistical analysis plan. Other HIR definitions, such as using higher Tmax thresholds, or a mean Tmax value, might perform better and should be assessed in future studies. Fifth, the multivariable models provided wide confidence intervals, which may be due to small subgroup sizes. Finally, our methodology uses perfusion imaging to infer collateral status, which may be sufficient for clinical decision-making in the hyperacute stroke scenario, but for other purposes such as direct research on collateral therapeutic modulation, direct automated quantitative collateral imaging would be needed.

In conclusion, rCBV and HIR may serve as markers of collateral circulation status in AIS patients eligible for endovascular therapy. rCBV correlated with infarct growth in successfully reperfused patients. The effects of early reperfusion are likely modulated by collateral status, which can be non-invasively assessed using CTP. Further research is needed to validate our findings and prospectively evaluate the prognostic impact of these parameters.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Levy serves as a scientific consultant to Medtronic; has shareholder/ownership interest with Intratech Medical Ltd and Blockade Medical LLC; has received fees from Abbott for carotid training; and has served as an expert witness for Renders Medical/Legal opinion. Dr Saver serves as a scientific consultant about trial design and conduct for Covidien and Stryker and is an employee of the University of California, which holds a patent on retriever devices for stroke. Dr Goyal served as a consultant to Medtronic for design and conduct of the SWIFT PRIME trial; has also received honoraria from Medtronic/Covidien for speaking and teaching engagements; and was also one of the Principal Investigators for the ESCAPE trial. The ESCAPE trial was partially funded by Covidien through an unrestricted research grant to the University of Calgary. Dr Jahan has been a consultant and speaker for Covidien. Dr Albers has an equity interest and is a consultant for iSchemaView, which provided the RAPID software and Core Laboratory services for the SWIFT PRIME study and has been a consultant for Covidien. The other authors report no conflicts.

Authors' contributions

Juan F Arenillas: Study design, SWIFT PRIME investigator, data analysis, interpretation of results, writing of the manuscript, manuscript edit, manuscript submission.

Elisa Cortijo: Study design, SWIFT PRIME investigator, interpretation of results, comments to the manuscript.

Pablo García-Bermejo: Study design, SWIFT PRIME investigator, interpretation of results, comments to the manuscript.

Elad Levy: SWIFT PRIME investigator, conduct of the trial, interpretation of results, comments to the manuscript.

Reza Jahan: SWIFT PRIME investigator, imaging protocol, publications committee, conduct of the clinical trial, interpretation of results, comments to the manuscript.

Mayank Goyal: SWIFT PRIME steering committee, imaging protocol, study design, publications committee, conduct of the clinical trial, interpretation of results, comments to the manuscript.

Jeffrey L Saver: SWIFT PRIME steering committee, principal investigator, publications committee, conduct of the clinical trial, data analysis, interpretation of results, comments to the manuscript.

Gregory W Albers: SWIFT PRIME steering committee and principal investigator, imaging protocol, perfusion imaging assessment, RAPID system, study design, data analysis, interpretation of study results, manuscript writing.

Supplementary material

Supplementary material for this paper can be found at the journal website: http://journals.sagepub.com/home/jcb

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