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Research Article

Angiographic Collateral Score as an Independent Predictor of Clinical Outcome and Contrast Staining in Acute Large Vessel Ischemic Stroke

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Abstract

Background and Purpose: Improved endovascular techniques in patients with acute ischemic stroke (AIS), have led to improved reperfusion rates. Both the TICI score and the extent of pial collateralization have been shown to predict clinical outcomes. We sought to determine if change in pial collateral circulation before and after revascularization independently predicts clinical and imaging outcomes.

Materials and Methods: Retrospective review of imaging and charts was performed of patients with anterior circulation AIS. Contributions of post-procedure TICI score and change in leptomeningeal collaterals to patient clinical and imaging outcomes relative to known predictors of patient outcomes in AIS therapies were determined by logistic regression.

Results: Post-procedure change in pial collateral (CiPC = pre-procedure collateral score – post-procedure collateral score) scores (OR: 0.68, 0.66, and 0.75 for readers 1, 2, and 3, respectively) and TICI scores (OR: 1.25, 1.78, and 1.70 for readers 1, 2, and 3 respectively) are independent predictors of ΔmRS (p = 0.006, 0.009, and 0.134; p = 0.257, 0.011, 0.023, readers 1, 2, and 3 for CiPC; TICI, respectively), and CiPC scores (OR: 1.11, 1.59, and 1.85 for readers 1, 2, and 3, respectively) and TICI scores after intervention (OR: 1.28, 1.45, and 1.71 for readers 1, 2, and 3 respectively) are independent predictors of contrast staining on follow up imaging (p = 0.53, 0.017, 0.031; p = 0.28, 0.14, 0.05, readers 1, 2, and 3 for CiPC; TICI, respectively).

Conclusion: Final TICI score and CiP Cappear to be independent predictors of patient and imaging outcomes.

Keywords: Stroke; Angiography; Collateralization; Contrast; Staining

Abbreviations

AIS: Acute Ischemic Stroke; CiPC: Pre-procedure collateral score minus Post-procedure Collateral Score; ΔmRS: Discharge Modified Rankin score minus the admission modified Rankin Score; AV: Arteriovenous

Introduction

Patients with acute ischemic stroke (AIS) secondary to large vessel occlusion can be treated by several endovascular arterial recanalization methods using DSA as imaging guidance. Evaluation of AIS patients with head CT after recanalization therapy sometimes demonstrates abnormal high density within the brain parenchyma, much higher than the density of hemorrhage that conforms to a normal anatomic structure and is without mass effect. This has been termed contrast staining. A recent retrospective evaluation of our stroke patients demonstrated a large majority of brain parenchyma with contrast staining ultimately progresses to infarction [1].

Significant advancements have been made in stroke therapy including development of endovascular thrombectomy devices, improved patient selection by non-invasive imaging, and prognostic information with post-treatment non-invasive imaging. Studies have shown stent-retrievers are able to achieve recanalization rates ranging between 61 and 92% compared recanalization rates of 24-60% for the Merci device [2-7]. Pre-intervention imaging has demonstrated the presence of leptomeningeal collaterals to be strongly predictive of better patient outcomes after stroke therapy [8]. Post-therapy CT of the head may demonstrate the degree of irreversible cerebral infarction, reperfusion hemorrhage, or contrast staining in the parenchyma. However, there is relatively little data on the prognostic information that can be obtained from the angiographic images acquired during intervention.

One aspect that can be evaluated on DSA imaging during stroke intervention is the presence of pial collaterals, their flow pattern, and robustness. While these findings have been remarked upon in many previous studies, there is little published evidence as to their utility for patient prognosis. A recently published paper highlighted the potential role of leptomeningeal collaterals in improving patient outcomes with large vessel ischemic stroke [8]. We sought in this study to determine the prognostic value of analyzing collaterals in DSA imaging. In this paper we review stroke therapy at our institution to evaluate findings on DSA during and after endovascular recanalization that may

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Table 1: Occlusion Level or Point of Maximal Flow Limitation.

-1	Recanalization without any DSA intervention
0	At the vertebral artery or extra cranial ICA
1	At the intracranial ICA or basilar artery
2	At the M1, or A1 segment
3	At the M2, or A2 segment
4	At the M3, or A3 segment
5	More distal

Occlusion level, or point of maximal flow limitation in cases of incomplete occlusion, was scored on the initial angiographic run centered over the head prior to any intra-arterial intervention according to an anatomic scoring system with lower numbers corresponding to more proximal occlusion levels. Cases of complete or near complete, recanalization without intervention were scored -1. Occlusion of the vertebral artery or extra cranial ICA was scored 0. Intracranial ICA or basilar artery occlusion was scored 1. Scores 2, 3, and 4 correspond to occlusion of the first, second, and tertiary segmental levels of the MCA, PCA and ACA, respectively. Occlusions distal to the tertiary segmental level were scored 5.

predict patient imaging and clinical outcomes in an effort to identify those patients who may benefit most from recanalization.

Methods

Patient selection

Our institution's Committee on Human Research approved this retrospective analysis of patient charts and imaging data. Stroke cases which took place between the years of 2002 and 2012 were evaluated. Patient inclusion criteria include patients with anterior circulation AIS who underwent cerebral angiogram and had at least one subsequent CT. Patients were not required to have undergone endovascular therapy to be included in the study; however those that did were selected for such based on the standard of care at the time. Because the study spanned a decade, there was no one set of indications for endovascular therapy. Patients were excluded from the study if their imaging studies were incomplete or non diagnostic due to motion or other artifacts. Patients with hemorrhage on CT prior to intervention were excluded.

Imaging analysis

Independent analysis of diagnostic cerebral angiograms was performed by 3 ACGME fellowship-trained neuro radiologists with additional subspecialty fellowship training in neuro interventional radiology. Angiograms were analyzed for the following parameters: occlusion level (Table 1), TICI score before and after intervention [9], collateral score prior to and after intervention (Table 2), hyperemia in the affected territory before and after intervention, arteriovenous (AV) shunting in the affected territory before and after intervention, the primary venous drainage pathway of the anterior circulation (supplemental table 1) [10], as well as the format of the angiogram, either on film or loaded as a stack of images in PACS to evaluate for consistency across these different formats. In the cases where a 4-vessel DSA was not performed or the collaterals were otherwise not able to be evaluated, no score was given and these patients were excluded from statistical analysis.

The length of procedure, time from stroke onset to beginning of intervention, IV tPA administration, IA tPA administration, and mechanical embolectomy were recorded for each procedure. All mechanical thrombectomy interventions such stent retriever embolectomy, MERCI thrombectomy (Stryker Neurovascular, Freemont, CA, USA), thrombus aspiration, angioplasty and attempts with stenting were all included in the category of mechanical embolectomy.

All follow-up brain imaging that patients had during their admission was evaluated for hemorrhagic transformation and contrast staining of brain parenchyma as a surrogate marker for parenchymal injury. Contrast staining was defined as high-density measuring greater than 40 HU, conforming to normal anatomic boundaries and without mass effect [1]. In keeping with the work of Yoon and colleagues, contrast staining measuring greater than 90 HU was also identified [11,12].

Patient medical records review

Patient medical records were evaluated by a member of the research team blinded to the outcome of recanalization for known vascular risk factors including: age, gender, presentation mRS, time of stroke onset, tobacco use, alcohol use, diabetes, previously known vascular disease, prior TIA, prior stroke, antecedent anticoagulation, family history of cerebrovascular disease or family history of cardiovascular disease. Patient's discharge mRS was calculated using discharge summaries and location of discharge. Transfer of patients to another acute care center was ranked as severe neurologic deficit (i.e. mRS = 5). Change in modified Rankin score (ΔmRS, defined as mRS at discharge minus mRS at admission) was the primary measure of clinical outcome.

Statistical analysis

Contributions of final TICI score after endovascular intervention, pial collateral circulation score prior to intervention, and CiPC to patient and imaging outcomes relative to known predictors of patient outcomes in AIS were determined by logistic regression.

Results

71 patients met our inclusion criteria with a mean age of 65.9 years (+/- 20.3). Of the 71 patients, 42 (59.2%) were female. The average time from stroke onset to arterial puncture was 7.4 hours (+/- 13.4). The median time from stroke onset to arterial puncture was 5 hours. Average procedure length was 210 minutes (+/- 68.9). 54 (76.1%) patients had mechanical intervention, 33 (46.5%) received intra-arterial tPA, 36 (50.7%) received intravenous tPA, and 16 patients

Table 2: Collateral Score.

0	Forward flow (either through direct anastomoses or previously blocked vessel)
1	Leptomeningeal collaterals reconstitute the distal portion of the occluded segment
2	Leptomeningeal collaterals reconstitute proximal portion of segment adjacent to occluded segment
3	Leptomeningeal collaterals reconstitute distal portion of segment adjacent to occluded segment
4	Leptomeningeal collaterals reconstitute two segments distal to occluded segment
5	Little or no significant reconstitution of the territory served by the occluded vessel segment

Collateral scoring system adapted from Christoforidiset al [8]. The scoring is from 0 to 5 and increases with progress of collateral flow based on vessel segment. Forward flow either directly through the circle of Willis, or antegrade through the previously blocked vessel was scored 0. A score of 5 corresponds to little or no significant reconstitution of the territory of the occluded vessel via pial collaterals. Change in pial collateral circulation (CiPC) was defined as initial collateral score minus final collateral score.

received both intravenous and intra-arterial tPA. Median change in mRS was 1 (lower quartile -1, upper quartile 4, and a range of 8).

The average time from stroke onset to end of procedure was 16.1 hours (+/- 34.4). The average time from end of procedure to CT follow up was 29.1 hours (+/- 100.1) with a median time of 13.0 hours. Hemorrhagic transformation was identified on follow-up imaging in 7 of the patients, (9.9%). Contrast staining was demonstrated on post-procedural CT for 45 of the patients (63.4%).

With regard to clinical outcomes, logistic regression analysis revealed that post-procedure CiPC scores (odds ratio [OR]: 0.68, 0.66, and 0.75 for readers 1, 2, and 3, respectively) and TICI scores (OR: 1.25, 1.78, and 1.70 for readers 1, 2, and 3 respectively) are independent predictors of ΔmRS ($p = 0.006$, 0.009, and 0.134; $p = 0.257$, 0.011, 0.023, readers 1, 2, and 3 for CiPC; TICI, respectively) (see supplemental table 2).

With regard to imaging outcomes, logistic regression analysis revealed that CiPC scores (OR: 1.11, 1.59, and 1.85 for readers 1, 2, and 3, respectively) and TICI scores after intervention (OR: 1.28, 1.45, and 1.71 for readers 1, 2, and 3 respectively) are independent predictors of contrast staining on follow up imaging ($p = 0.53$, 0.017, 0.031; $p = 0.28$, 0.14, 0.05, readers 1, 2, and 3 for CiPC; TICI, respectively) (see supplemental table 3).

The full list of clinical and imaging covariates that were evaluated and also included in the logistic regression model is provided in supplemental table 4. The only factor that appeared may have impact was preexisting diabetes mellitus. Including diabetes in the ordinal logistic regression model tended to increase the significance of the post-procedural TICI's and CiPC's impact on imaging (supplemental table 5) and clinical outcomes (supplemental table 6). Other clinical and imaging covariates did not have such an effect (see supplemental tables 7 and 8).

Discussion

CiPC appears to be an independent predictor of both contrast staining and clinical outcome in patients with acute anterior large vessel strokes. CiPC predicts patient outcomes independent of both the amount of forward flow upon revascularization (TICI score), as well as clinical risk factors for stroke such as prior CVA/TIA. This suggests that CiPC may provide prognostic information in conjunction with the TICI score in assessing revascularization at the time of stroke intervention in cases of large vessel acute ischemic stroke. Diagnostic cerebral angiography during stroke has a significant amount of prognostic information, which may assist practitioners in making decisions for further therapeutic interventions.

Many systems of grading blood flow with respect to vessel occlusion exist. The most commonly used grading system to evaluate flow in a thrombosed or partially thrombosed vessel is the TICI score, originally proposed for use in evaluating the effectiveness of thrombolytic therapy [9]. While several scoring systems have also been proposed for grading collateral blood flow in AIS, a standardized score has yet to be adopted [13]. The scoring system used in this study is a modified version of that published by Christoforidis et al [8]. While the original scoring system equated occlusions at M1, A1, and P1, our study chose to exclude evaluation of posterior circulation because it was unclear where a basilar or vertebral occlusion would fall in the original scoring scheme. We continued the original system of equating M1 with A1 and so on despite the fact that occlusions in these territories produce distinct symptoms and thus distinct morbidities because the scoring sytem had been previously validated as such.

Leptomeningeal collateral scoring remains inconsistent, but several publications demonstrate robust collaterals to be associated with decreased core infarct volume, better outcome following acute ischemic stroke, and decreased hemorrhagic transformation of acute ischemic stroke [14-17]. In addition, two recently published studies have shown that some of these collateral scoring systems correlate well with clinical outcomes [18,19]. This work expands the literature by confirming this correlation between collateral scores and clinical outcomes after stroke procedure as well as demonstrating that this information can be derived from the TICI score and leptomeningeal collaterals independent of each other. While the mechanism for leptomeningeal collateral opening in AIS is unclear, and the exact relationship between leptomeningeal collaterals and AIS patient outcomes is also unclear, a reproducible effect is seen independent of the degree of large vessel revascularization.

Our evaluation of leptomeningeal collaterals in acute ischemic stroke expands our understanding of collateral circulation and leptomeningeal collateral blood flow as a dynamic system such that a regression of leptomeningeal collateral flow after revascularization may be a positive predictive indicator of patient outcomes. More specifically, patients were more likely to improve if more robust leptomeningeal collaterals were seen on initial DSA and those collaterals were no longer visible on post-intervention DSA than those with robust collaterals, but no change in the collateral circulation after intervention. Change in collateral score may be a more physiologic predictor of adequate tissue perfusion or an indicator of adequate microvascular revascularization while TICI score is an anatomic indicator of large vessel revascularization.

The extent of the leptomeningeal collateral network might be a combination of inherent characteristic of individual patients, environmental factors, and time from stroke onset to intervention, or comorbidities and medications. While some anatomical studies have described the development of native collateral circulation through childhood [20], current literature shows a wide range of variability both in anatomy and function of these native collaterals [21]. Diabetic small vessel vasculopathy is well described, and may account for the decrease in collateral flow seen in diabetics and possibly account for the potential significance identified by the ordinal logistic regression [22]. One study found that patients on statins are more likely to have collateral flow [23]. Another study demonstrated no difference in collateral robustness as determined by CTA based on time from stroke to imaging [24]. However, cases of chronic ischemia, or slowly progressive vessel occlusion, are often some of the most robust cases of collateralization [25-27]. Long standing hypertension may impair the growth of leptomeningeal collaterals [28,29]. It is surprising, therefore, that in our cohort, presence of hypertension, CAD, prior TIA or CVA seemed to show no correlation with cerebral collateral formation. This may be due to the fact that all instances of these diseases were included in our analysis, with no accounting for variation in severity or any degree of treatment.

Similarly, it is unclear what portion altered hemodynamic scan account for greater CiPC in patients with the greatest clinical recovery. Perhaps the leptomeningeal collateral pathway is a backup mechanism where the leptomeningeal collaterals are always available, but merely collapsed by high pressure from the normal anterograde sources that are only evident with decrease in the antegrade pressure head. Return of the anterograde pressure head (secondary to revascularization) may overwhelm the retrograde pial collateral pressure head effectively reversing the pial collateral formation process putting them back into a resting collapsed state.

Interestingly, we identified several cases of post-intervention TICI 2b where pial collateralization did not regress. DSA has spatial resolution limits: the cerebral microvasculature cannot be seen directly. CiPC may be a useful, if indirect, measure of the adequacy of circulation in the microvasculature. Comparison of CiPC with intra procedural perfusion studies, such as those now possible using flat panel detector angiography suites, may provide further insights into their utility for predicting clinical outcomes.

The retrospective nature of this study is a limitation. Because of this, we were limited in our determination of patient outcome. While using the NIH stroke scale to judge severity of symptoms before and after intervention would have been ideal, this information was not recorded in all charts over the course of the study. Likewise, follow up data at 90 days was not always available for the early cases and thus we were limited to obtaining the mRS at discharge to evaluate patient outcome. A more powerful prospective trial to validate this hypothesis could further elucidate the relationship between leptomeningeal collateral circulation and patient outcomes in stroke interventions. This study however, demonstrates the collateral circulation to be a dynamic process.

The results of our analysis revealed a notably long average time from stroke onset to start of intervention (7.4 hours). The data is skewed with a median of 5 hours. Additionally, the interventions included in this study took place between 2002 and 2012. During the decade studied, several advances in understanding of stroke physiology have been made and patients are now more frequently excluded if presenting in a much delayed fashion. Were a prospective trial to be conducted of current procedures, the length of time from stroke to procedure start would likely be much shorter. Our study also found notably long procedure lengths. It should be noted that these measurements include the length of time from when the patient arrives in the DSA suite to when the patient has left the room, rounded up to the nearest half hour. Additionally, all of our stroke procedures are performed under general anesthesia. We are also finding that advances in endovascular tools and techniques have significantly shortened the procedure lengths [30].

Devices have progressed, noninvasive imaging has progressed, but more information can be gleaned from the DSA images that are acquired during interventions. Our study suggests that there is prognostic value to the data that can be gathered from procedural DSA.

Conclusions

CiPC appears to be an independent predictor of both imaging and clinical outcomes in patients with acute anterior circulation large vessel ischemic strokes. CiPC may be a useful predictive indicator in conjunction with the TICI score in assessing revascularization at the time of stroke intervention.

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