Correlation between angiographic transit times and neurological status on admission in patients with aneurysmal subarachnoid hemorrhage

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OBJECTIVE The use of digital subtraction angiography (DSA) for semiquantitative cerebral blood flow (CBF) assessment is a new technique. The aim of this study was to determine whether patients with aneurysmal subarachnoid hemorrhage (aSAH) with higher Hunt and Hess grades also had higher angiographic contrast transit times (TTs) than patients with lower grades.

METHODS A cohort of 30 patients with aSAH and 10 patients without aSAH was included. Relevant clinical information was collected. A method to measure DSA TTs by color-coding reconstructions from DSA contrast-intensity images was applied. Regions of interest (ROIs) were chosen over major cerebral vessels. The estimated TTs included time-to-peak from 0% to 100% (TTP_{0–100}), TTP from 25% to 100% (TTP_{25–100}), and TT from 100% to 10% (TT_{100–10}) contrast intensities. Statistical analysis was used to compare TTs between Group A (Hunt and Hess Grade I–II), Group B (Hunt and Hess Grade III–IV), and the control group. The correlation coefficient was calculated between different ROIs in aSAH groups.

RESULTS There was no difference in demographic factors between Group A (n = 10), Group B (n = 20), and the control group (n = 10). There was a strong correlation in all TTs between ROIs in the middle cerebral artery (M₁, M₂) and anterior cerebral artery (A₁, A₂). There was a statistically significant difference between Groups A and B in all TT parameters for ROIs. TT_{100–10} values in the control group were significantly lower than the values in Group B.

CONCLUSIONS The DSA TTs showed significant correlation with Hunt and Hess grades. TT delays appear to be independent of increased intracranial pressure and may be an indicator of decreased CBF in patients with a higher Hunt and Hess grade. This method may serve as an indirect technique to assess relative CBF in the angiography suite.

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KEY WORDS digital subtraction angiography; transit times; subarachnoid hemorrhage; Hunt and Hess; neurological outcome; vascular disorders

ANEURYSMAL subarachnoid hemorrhage (aSAH) remains a devastating disease with significant morbidity and mortality.^{21,23} The morbidity of aSAH depends on multiple factors that affect the postictal cerebral metabolism status,¹⁶ with alteration in cerebral perfusion, intracranial pressure (ICP), and cerebral blood flow (CBF).^{6,11,22,36} There are several techniques for noninvasive assessment of CBF including CT angiography^{11,19} and quantitative MR angiography.^{1–3,9,13,33,35} New computational methods have been developed to evaluate cortical tran-

sit times (TTs)^{15,28} However, not all of these methods are available in the angiography suite, and they often require additional radiation or contrast exposure. There are no prior studies that attempted to correlate the angiographic contrast TTs with the neurological exams of patients with aSAH.

In our current study, we sought to apply a computational method based on digital subtraction angiography (DSA) analysis to evaluate the relative CBF in patients with aSAH. This method does not require additional ra-

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; CBF = cerebral blood flow; DICOM = Digital Imaging and Communications in Medicine; DSA = digital subtraction angiography; EVD = external ventricular drain; GOS = Glasgow Outcome Scale; ICA = internal carotid artery; ICP = intracranial pressure; mRS = modified Rankin Scale; ROI = region of interest; TT = transit time; TTP = time-to-peak.

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diation or contrast exposure and may be applied during angiography in real-time. This technique is based on the analysis of DSA contrast TTs in multiple regions of interest (ROIs), corresponding to the major components of the anterior intracranial circulation. We report the correlation of DSA contrast TTs in patients with aSAH in relation to the clinical presentation graded by the Hunt and Hess classification.²⁰

Methods

Patient Data

Institutional review board approval was obtained prior to the initiation of the study. This is a retrospective study on prospectively collected data at a tertiary center. A cohort of 30 patients with aSAH and 10 recent consecutive patients without aSAH (control group) was included in the study period from November 2011–May 2013. The patients with aSAH were also part of a study that evaluated vasospasm treatment as they developed clinical vasospasm following hospital admission. Demographic variables, neurological status (Hunt and Hess grade) on admission, and medical comorbidities data were collected. To increase the prognostic power of our scale, patients with Hunt and Hess Grades I–II were defined as having mild aSAH (Group A), and patients with Hunt and Hess Grades III–V were considered to have severe aSAH (Group B).^{31,37} Outcomes were assessed at 6 months using the Glasgow Outcome Scale (GOS) and the modified Rankin Scale (mRS). Patients who underwent DSA within 24 hours of aneurysm rupture were included in this assessment. Patients who underwent angiography more than 24 hours after aSAH ictus, patients with non-aSAH (traumatic, angiogram negative), and those with angiographic vasospasm on presentation or associated with large hematomas were excluded from the study. Patients with hydrocephalus on admission or those with Hunt and Hess Grades III–V typically had an external ventricular drain (EVD) catheter inserted on admission prior to DSA. Only 3 patients in the cohort, all with Hunt and Hess Grade III, did not have EVDs inserted. All EVDs were opened to drain at 10 mm Hg during angiography as part of our routine practice.

Image Acquisition

All angiography was performed using the standard transfemoral approach. A 5F diagnostic catheter (Angiodynamics) was inserted into the internal cerebral arteries, and 12 ml of the iodine-based contrast agent iohexol (300 mg/ml) (Omnipaque, GE Healthcare) was injected into the internal carotid artery (ICA) over 2 seconds by a power contrast injector (Medrad, Bayer HealthCare). The power contrast injector was synchronized to a fluoroscopy angiographic machine with a 1.2-second delay in the contrast injection. A biplane neuroangiography suite (Artis zee, Siemens Medical Solutions) was used to capture DSA images at a rate of 4 frames/sec in standard anterior-posterior, lateral, and oblique transorbital projections. Digitally subtracted images were saved to the Picture Archiving and Communicating System. In addition, the entire unedited angiogram was archived on a separate DVD in Digital Imaging and Communications in Medicine (DICOM) format.

Estimation of TTs

To interpret relative blood flow within ROIs in the intracranial circulation, we developed a custom MATLAB-based software code (MathWorks). Representative consecutive DICOM images from DSA runs were loaded to a separate personal computer and analyzed for time-intensity using this novel method. The MATLAB-based software analyzed the image intensity throughout the entire angiogram and identifies various intensity plots including the maximum gray intensity in consecutive DICOM images. Various ROIs were selected throughout the major cerebral vessels: ICA, segments of anterior cerebral artery (A_1 and A_2), segments of the middle cerebral artery (M_1 and M_2). The ROI includes 3 to 4 pixels, and the average TT over individual ROIs was calculated. The time-intensity plots were analyzed at the selected ROI with regard to the image intensity over the angiography run-time. The time-intensity plot was divided into 3 components, and estimated TTs were defined as follows (Fig. 1): TTP 0%–100% (TTP_{0-100}) was defined as the time needed for the contrast density profile to reach maximum level (time to peak; TTP) from the time of the injection; TTP 25%–100% (TTP_{25-100}) was defined as the time needed for the contrast density profile to reach maximum (100%) from 25% of the maximum density, and TT_{100-10} was the time needed for the contrast density to reach 10% from its maximum value (100%) (Fig. 1). These 3 different TTs represent TTs during the early portion of the contrast passage in the intracranial circulation (TTP_{0-100} and TTP_{25-100}) as well as the late phase of the contrast curve (TT_{100-10}) as it transverse the intracranial circulation. Only data from the anterior circulation TTs (right and left hemispheres) were collected; no posterior circulation data were collected so as to avoid heterogeneity of the data in this manuscript (Fig. 2).

Statistical Analysis

Demographic variables were compared between Group A (Hunt and Hess Grade I–II), Group B (Hunt and Hess Grade III–V), and the control group. Patients with an altered level of consciousness (Hunt and Hess Grade III–V) were grouped together in an attempt to determine whether delayed TTs represent a common finding related to the neurological examination in DSA analysis. The

FIG. 1. Graph showing the time-contrast density profile and the portions of the curve representing the various TTs.

FIG. 2. Cerebral angiograms obtained in representative patients from Groups A and B. **A:** Diagnostic cerebral angiogram of a patient from Group A (Hunt and Hess Grade I). **B:** Corresponding reconstructed color-coded time-density TT_{100-10} of (A) showing corresponding ROIs (A_1 , A_2 , M_1 , M_2). **C:** Diagnostic cerebral angiogram of a patient from Group B (Hunt and Hess Grade V). **D:** Corresponding reconstructed color-coded time-density TT_{100-10} of (C) showing corresponding ROIs. Figure is available in color online only.

clinical data were compared between the 2 independent groups (Group A and Group B). The TTP_{0-100} , TTP_{25-100} , and TT_{100-10} for the corresponding ROIs were compared between Group A and Group B; TT_{100-10} were compared between aSAH patients groups and the control group, as well as to the control group. A Student t-test was used for analysis between Group A and Group B, and an ANOVA test was used to compare between the 3 groups. A p value < 0.05 was defined as a significant difference. All TT analysis was performed for all ROIs (ICA, M_1 , M_2 , A_1 , and A_2). The TT values for different ROIs were correlated with each other by using scatter plots and calculation of the coefficient of determination (R^2). The statistical analysis was performed using IBM SPSS Statistics for Macintosh, Version 21.0.

Results

There was no difference in demographic factors between the 3 groups: Group A ($n = 10$), Group B ($n = 20$), and the control group ($n = 10$). All patients with EVD catheters had a normal ICP documented during DSA (Table 1). Factors that might influence the baseline cerebral perfusion including age, sex, hypertension, diabetes, and smoking were comparable between the groups. General anesthesia was equally used during cerebral angiography

between aSAH groups. Outcomes at 6 months after patient discharge were significantly worse based on mRS and GOS in Group B patients (Table 1).

Analysis of the TTP_{0-100} time-density plot between different representative ROIs of ICA, M_1 , M_2 , A_1 , and A_2 of the same patients showed the weakest correlation between those ROIs (R^2 varied between 0.434–0.841) (Fig. 3A). The correlation between different ROIs was stronger in the TTP_{25-100} (R^2 varied between 0.656–0.931) (Fig. 3B). The strongest correlations were observed between the representative ROIs in the TT_{100-10} time-intensity plot (R^2 varied between 0.893–0.955) (Fig. 3C). The weak correlation in TTP_{0-100} may represent an inherent problem related to the fact that this portion of the time curve is the earliest and the most sensitive to the induced hemodynamic changes caused by the contrast power injector and to the limited frame rate of the angiography hardware. This artifact is less evident in the last portion of the time-intensity plot (TT_{100-10}). The correlation between different ROIs in TT_{100-10} is very close to 1, indicating that the TTs for each corresponding ROI are almost identical to the other regions, and might indicate comparable perfusion in different regions of the brain. This also indicates that the most sensitive TT is TT_{100-10} since it is least affected by the hemodynamic changes induced by the contrast injector (Fig. 3D).

TABLE 1. Patient demographic and clinical data*

Characteristic	Group A† (n = 10)	Group B‡ (n = 20)	Control Group (n = 10)	p Value
Female	5 (50)	10 (50)	7 (70)	0.545
Mean age in yrs ± SD	55.5 ± 14.7	57.7 ± 9.6	51.2 ± 10.1	0.690
Diabetes	1 (10)	2 (10)	1 (10)	0.112
Smoker	6 (60)	11 (55)	4 (40)	0.637
Hypertension	4 (40)	10 (50)	3 (30)	0.114
Hyperlipidemia	3 (30)	5 (25)	4 (40)	0.621
EVD placement	0	17	NA	NA
GA for diagnostic angiography	8 (80)	18 (90)	NA	0.407
LVEF <50% on admission	1	1	NA	0.483
mRS score 0–2 at 6 mos	9 (90)	7 (35)	NA	0.004

GA = general anesthesia; LVEF = left ventricle ejection fraction; NA = not applicable.

* Values are n (%) except where indicated. Bold type indicates statistical significance.

† Hunt and Hess Grade I–II.

‡ Hunt and Hess Grade III–V.

FIG. 3. Scatter plots showing the TTPs and TTs across different ROIs and the corresponding correlation coefficients. **A:** Scatter plot showing TTP₀₋₁₀₀ TTs across different ROIs (ICA, M₁, M₂, A₁, A₂). There appears to be wide variability in the correlation coefficients between different ROIs. **B:** Scatter plot showing TTP₂₅₋₁₀₀ TTs between different ROIs. Higher correlation coefficients than those of TTP₀₋₁₀₀ are evident. **C:** Scatter plot showing TT₁₀₀₋₁₀ TTs between different ROIs. Higher correlation coefficients than those of TTP₀₋₁₀₀ and TTP₂₅₋₁₀₀ are evident. **D:** Scatter plot comparing multiple TTs (TTP₀₋₁₀₀, TTP₂₅₋₁₀₀, and TT₁₀₀₋₁₀) across M₁ and M₂ segments. For the same regions, the correlation coefficient is highest for TT₁₀₀₋₁₀ (R² = 0.951) and weakest for TTP₀₋₁₀₀ (R² = 0.817). Figure is available in color online only.

There was a statistically significant difference in TTs in the ROI M_1 : M_1 -TTP₀₋₁₀₀ between Groups A and B (1.98 vs 2.43 seconds, $p = 0.005$), M_1 -TTP₂₅₋₁₀₀ (1.78 vs 2.7 seconds, $p = 0.003$), and in M_1 -TT₁₀₀₋₁₀ (4.68 vs 6.27 seconds, $p = 0.012$), respectively (Fig. 4 left). Similar differences were observed in the ROI A_1 : A_1 -TTP₀₋₁₀₀ (1.84 vs 2.18 seconds, $p = 0.001$), A_1 -TTP₂₅₋₁₀₀ (1.63 vs 2.27 seconds, $p = 0.001$), and in A_1 -TT₁₀₀₋₁₀ (4.24 vs 5.12 seconds, $p = 0.0015$), respectively (Fig. 4 right), and for the ROI M_2 : M_2 -TTP₀₋₁₀₀ (2.03 vs 2.64 seconds, $p = 0.001$), M_2 -TTP₂₅₋₁₀₀ (1.83 vs 2.8 seconds, $p = 0.001$), and in M_2 -TT₁₀₀₋₁₀ (4.68 vs 6.2 seconds, $p = 0.012$). A statistically significant difference was observed in TT₁₀₀₋₁₀ between Group B and the control group, with significant TT delays in patients with aSAH. The TT₁₀₀₋₁₀ value in Group A (patients with Hunt and Hess Grade I–II) was shorter in all ROIs, without a significant difference compared with the control group. Results were unchanged by exclusion of patients without an EVD at the time of angiography. No significant difference was found between Groups A and B in estimated left ventricle ejection fraction percentage obtained within 24 hours after cerebral angiogram.

Discussion

In this study, we report a new algorithm of DSA image processing that is simple to incorporate, inexpensive, and available in angiography suites for real-time analysis. The results demonstrate strong correlations between all angiographic TTs and patient clinical presentation, and significant TT delays in patients with poor-grade aSAH (Hunt and Hess Grade III–V).

Postprocessing software similar to that used for our TTP₀₋₁₀₀ analysis has been developed by Siemens (iFLOW), Phillips (Allura Xper), and GE Healthcare (AngioViz), and is currently commercially available. To date, the successful use of this technique was reported following endovascular treatment of carotid cavernous fistulas,²⁷ carotid stenosis,²⁶

and cerebral vasospasm.²⁵ The main limitation of the commercially available postprocessing software is its reliance on the TTP portion of the DSA curve. As we have shown, this part of the curve is the least sensitive of the 3 TTs that we evaluated. It is believed that the early TT is heavily affected by the hemodynamic artifact from the contrast power injector and limited images acquisition speed, which alters the DSA TT in the early phase of the DSA curve. Our analysis has shown that the TT₁₀₀₋₁₀ is much less sensitive than TTP₀₋₁₀₀ to the above-mentioned factors.

Early studies on flow analysis with DSA¹⁸ showed that time-intensity curve geometry depends on the flow, vessel size, amount of iodine injected, and framing rate. It is not affected by volume, concentration, or rate of injection.¹⁸ This is true if the area under the curve is used as a surrogate of the flow in the ROI. We evaluated only the TT (not the area under the curve) in our method; thus, the vessel size and amount of iodine injected did not affect our results. The time-intensity curve in cerebral angiography is not symmetric but rather skewed to the right, with a longer negative slope run-time (longer TT₁₀₀₋₀ as compared with TT₀₋₁₀₀). Therefore, changes in the flow are easier to detect within the negative slope run-time. This observation was made using DSA on different flow rates in a basic plastic model.¹⁷

The Hunt and Hess scale was introduced in 1968 with the initial purpose of assessing the surgical risk in patients with aSAH based on patient clinical status on presentation prior to surgery.²⁰ Several studies showed high correlation between Hunt and Hess scores and clinical outcomes, with higher grades corresponding to increasingly poor prognosis.^{7,29} A patient's clinical presentation after aSAH is a reflection of the global CBF. In aSAH cases, the CBF is considerably affected by a combination of factors including brain exposure to blood product, elevated ICP, mechanical distortion of the blood vessels, and impaired cerebral vessel autoregulation.^{4,5,8,34} Previous as-

FIG. 4. Box plots comparing differences between groups in TT₁₀₀₋₁₀ for ROIs M_1 and A_1 . **Left:** Box plot comparing the TT₁₀₀₋₁₀ ROI over M_1 between Group A, Group B, and the control group. **Right:** Box plot comparing the TT₁₀₀₋₁₀ ROI over A_1 between Group A, Group B, and the control group. For each of the box plots, asterisks represent a statistically significant difference between Groups A and B but not between Group A and the control group. The boxes represent the interquartile range, horizontal rule the median, and the whiskers the minimum and maximum values. H&H = Hunt and Hess Grade.

sumptions about the intact CBF autoregulation during the early period of aSAH³⁸ have been challenged by several animal studies showing CBF impairment even in the early phase after ictus.^{4,12,32} Clinical studies with PET scans have demonstrated impairment of CBF in early aSAH in the absence of radiographic vasospasm, along with decreases in metabolic rate of oxygen.^{10,24} MR images performed early after ictus (within 0–3 days) have shown an approximately 60% incidence of diffusion-weighted imaging (DWI)–detected lesions. The presence of any early DWI/apparent diffusion coefficient lesion and increasing lesion volume were associated with a worse H&H grade and correlated with future poor neurological outcomes.¹⁴ The mechanism of ischemic infarcts in those patients is thought to be related to the early development of microcirculatory vasoconstriction⁵ that leads to hypoperfusion, oxidative cell injury, and subsequent cell death.³⁰ The vasoconstriction phenomenon seems to be independent of elevated ICP, and it is accompanied by considerable CBF decreases.⁵

Our data are in line with the abovementioned observations: TT delays were not associated with ICP status nor related to general anesthesia per se, nor related to early myocardial stunning with low left ventricle contraction. Therefore, the determination of the relative CBF status by measuring angiographic TT in the angiography suite could have prognostic value in patients with aSAH and provides further insights into the pathophysiology of cerebral injury following aSAH.

Conclusions

The DSA TTs showed significant correlation with Hunt and Hess grades. Patients with altered mental status (Hunt and Hess Grades III–V) are found to have considerable DSA TT delays in comparison with patients with minimal clinical symptoms (Hunt and Hess Grades I–II) and patients without aneurysm rupture. The TT appears to be independent of general anesthesia and increased ICP and may be an indicator of decreased CBF in patients with aSAH. This method may serve as an indirect technique available in the angiography suite for assessing relative CBF changes.

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Disclosure

Dr. Charbel reports direct stock ownership in Vassol Inc.

Author Contributions

Conception and design: Alaraj. Acquisition of data: Ivanov. Analysis and interpretation of data: Ivanov, Linninger, Hsu. Drafting the article: Ivanov, Hsu. Critically revising the article: Alaraj, Ivanov, Linninger, Amin-Hanjani, Aletich, Charbel. Reviewed submitted version of manuscript: Alaraj, Ivanov, Linninger, Amin-Hanjani, Aletich, Charbel. Approved the final version of the manuscript on behalf of all authors: Alaraj. Statistical analysis: Ivanov. Study supervision: Alaraj, Linninger.

Supplemental Information

Previous Presentation

Portions of this work were presented in the form of a poster at the CNS Annual Meeting (October 18–22, 2014, Boston, MA).

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