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Comparison of CT perfusion and digital subtraction angiography in the evaluation of delayed cerebral ischemia

Ronan P. Killeen, MB¹, Alvin I. Mushlin, MD ScM², Carl E. Johnson, MD¹, Joseph P. Comunale, MD¹, Apostolos John Tsiouris, MD¹, Holly Delaney, MB¹, Allison Dunning², and Pina C. Sanelli, MD MPH^{1,2}

¹Department of Radiology, NewYork-Presbyterian Hospital, Weill Cornell Medical College, 525 East 68th Street, Starr 8A, Box 141, New York, NY 10065, 212-746-2573, 212-746-8597 (fax)

²Department of Public Health, NewYork-Presbyterian Hospital, Weill Cornell Medical College, 402 East 67th Street, New York, NY 10065, 646-962-8009

Abstract

Rationale and Objectives—Delayed cerebral ischemia (DCI) is a devastating condition that occurs secondary to aneurysmal subarachnoid hemorrhage (A-SAH). The purpose is to compare CT perfusion (CTP) and digital subtraction angiography (DSA) for determining DCI in A-SAH.

Materials and Methods—A retrospective study of A-SAH patients admitted at our institution between December 2004 and December 2008 was performed. CTP and DSA were obtained at days 6–8 following aneurysm rupture. Both qualitative and quantitative analyses of CT perfusion deficits were performed. DSA was categorized as presence or absence of vasospasm. The reference standard for determining DCI was based on clinical deterioration or infarction on CT or MRI. The test characteristics of CTP and DSA were calculated and their graphs of conditional probabilities were constructed using Bayesian analysis.

Results—Fifty-seven patients were included; 79% (45/57) had DCI. Seventy percent (40/57) had CTP perfusion deficits; 80% (36/45) of the DCI and 33% (4/12) of no DCI patients. Sixty-three percent (36/57) had DSA demonstrating vasospasm; 73% (33/45) of the DCI and 25% (3/12) of no DCI patients. Quantitative analysis of the CTP data revealed a significant difference in cerebral blood flow values for the DCI (29.4 mL/100gm/min) and no DCI groups (40.5 mL/100gm/min, $p=0.0213$). The sensitivity, specificity, positive and negative predictive values for CTP were 0.80 (95% CI 0.68–0.92), 0.67 (95% CI 0.40–0.93), 0.90 (95% CI 0.82–0.96), 0.47 (95% CI 0.27–0.62) and for DSA were 0.73 (95% CI 0.60–0.86), 0.75 (95% CI 0.50–0.99), 0.92 (95% CI 0.82–0.98) and 0.43 (95% CI 0.26–0.53), respectively.

Conclusion—CTP and DSA have similar test characteristics and Bayesian analysis for determining DCI in A-SAH patients.

Keywords

Subarachnoid hemorrhage; Brain ischemia; Tomography, X-ray computed; Cerebral angiography; Bayes Theorem

Corresponding Author: Ronan P Killeen, ¹Department of Radiology NewYork-Presbyterian Hospital Weill Cornell Medical College, 525 East 68th Street Starr 8A, Box 141 New York, NY 10065. Tel: 212-746-2573, Fax: 212-746-8597, rokilleen@yahoo.com.

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Introduction

Cerebral vasospasm is a significant cause of morbidity in patients with aneurysmal subarachnoid hemorrhage (A-SAH), occurring in 20–50% of patients following successful surgical or endovascular treatment of the ruptured aneurysm.[1–3] Several terms have been used in the literature to describe this entity, including symptomatic vasospasm, angiographic vasospasm, transcranial Doppler vasospasm and delayed cerebral ischemia (DCI). In the past, the gold standard for vasospasm has been accepted as arterial narrowing documented on digital subtraction angiography (DSA). However, the presence of angiographic vasospasm does not always correlate with neurological deterioration or the development of infarction.[4, 5]

Conversely, DCI has been shown to be the most clinically relevant term because of its strong associations with poor clinical outcome measures such as cognitive impairment and reduced quality of life.[1–3] DCI is defined as an otherwise unexplained clinical deterioration and/or new infarction demonstrated on imaging examinations. Clinical deterioration may manifest by alterations in consciousness, worsening on Glasgow coma scale, or new neurologic deficits. Other potential causes of clinical deterioration, such as hemorrhage, seizure activity or hydrocephalus, are not included in this definition. The second component of DCI is the presence of a new infarction documented on imaging examinations. This definition does not include infarctions present on the admission or the immediate post-operative imaging exams.[2,3,6] An important limitation to using this definition in clinical practice is that the diagnosis of DCI is retrospectively obtained once a neurologic deficit or infarction has already occurred. As a result, interventions to reduce the subsequent morbidity and mortality may have limited usefulness.[2] It has also been reported that the presence of DCI is associated with a more complicated hospital course resulting in prolonged hospitalization and extended length-of-stay in the intensive care unit (ICU).[1–3] Thereby, assessing the probability of a patient with DCI prior to developing a permanent neurological deficit and/or infarction is important for identifying patients that will maximally benefit from medical or interventional treatment.

Currently, DSA is used in clinical practice to identify patients with angiographic vasospasm, which clinicians often consider as a surrogate indicator of DCI in patients with A-SAH. Recently, some institutions are also using CT perfusion (CTP) for its ability to detect hemodynamic changes in the brain that may indicate vasospasm or DCI. A correlation with perfusion deficits on CTP and angiographic vasospasm on DSA has been described in the literature.[7–9] To our knowledge, there is no consensus to-date regarding the appropriate utilization of CTP or DSA in the evaluation of A-SAH patients for determining DCI.

The purpose of this study is to compare the test characteristics of CTP and DSA for determining DCI in A-SAH patients. The secondary purpose is to apply Bayesian analysis to these data in order to assist clinicians in making informed decisions regarding which diagnostic test is most valuable for specific clinical scenarios. The goal of this study is to guide clinicians toward the appropriate utilization of CTP and DSA in clinical practice.

Materials and Methods

Study Population

A retrospective study of A-SAH patients was performed from consecutive patients admitted at our institution between December 2004 and December 2008. Inclusion criteria were adult patients (18 years and older) with documented A-SAH at admission and who underwent both CTP and DSA during hospitalization. During the time of this study, CTP was performed as routine imaging for A-SAH patients. DSA was performed in patients who had

signs or symptoms of vasospasm and for follow-up evaluation of aneurysm treatment. A diagnosis of A-SAH was based on the initial noncontrast head CT, cerebrospinal fluid analysis, CT angiography (CTA) and/or DSA. In the retrospective data collection, there were no predetermined exclusion criteria. All enrolled subjects underwent standard-of-care surgical clipping and/or endovascular coiling for aneurysm repair. Institutional review board (IRB) approval and HIPAA compliance were obtained.

Study Design

A retrospective review of A-SAH patients was performed to compare the test characteristics of CTP and DSA for determining DCI. The time-frame at which imaging examinations were performed was defined in relation to the day of onset of A-SAH. Day 0 was defined as the day of the A-SAH event. Clinical and demographic data was collected by chart review.

CTP Scanning Protocol and Data Processing

CTP exams included in this study were performed prior to patients receiving treatment for vasospasm and prior to patients developing infarction to limit confounding bias. The standard scanning protocol for CTP at our institution utilizes GE Lightspeed or Pro-16 scanners (General Electric Medical Systems, Milwaukee, WI) with cine 4i scanning mode and 45 second acquisition at 1 rotation per second using 80 kVp and 190 mA. A scanning volume of 2.0 cm was used with its inferior extent selected at the level of the basal ganglia, above the orbits, to minimize radiation exposure to the lenses. Approximately 45 mL of nonionic iodinated contrast was administered intravenously at 5 mL/s using a power injector with a 5-second delay.

Post-processing of the acquired images into cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) maps were performed on a General Electric Advantage Workstation using CT Perfusion software version 3.0 (General Electric Medical Systems, Milwaukee, WI). This software employs a deconvolution method, which is considered most accurate for low contrast injection rates.[10] The post-processing technique was standardized for all patients according to recommended guidelines with the arterial input function as the A2 segment and venous function as the superior sagittal sinus.[11,12]

The perfusion maps were qualitatively evaluated by two neuroradiologists (with 8 years and 2 years experience) blinded to clinical and imaging data to determine the presence of perfusion deficits, defined as focal areas of decreased CBF and prolonged MTT. Focal perfusion abnormalities due to the primary hemorrhagic event and surgical intervention were not considered as perfusion deficits from DCI in this study. After reviewing the images independently, consensus judgment was determined.

Quantitative analysis was conducted using a standardized method with contiguous regions-of-interest (ROI) placement, measuring 157 mm², sampling the cortex and basal ganglia. Each CTP slice had up to approximately 28 ROIs distributed in the following territories: 6 ROIs in anterior cerebral artery, 12 ROIs in middle cerebral artery, 6 ROIs in posterior cerebral artery, and 4 ROIs in basal ganglia. In order to minimize the contribution of vascular pixels from large vessels, CBF values > 100 mL/100gm/min were excluded from the statistical analysis and not used in calculating the mean CBF, CBV and MTT parameters, as this method has been employed for evaluation of ischemia.[13]

DSA

Biplane DSA with or without 3D rotational views were performed using standard techniques (Innova 3100, GE Medical systems, France). The angiographic criteria for vasospasm were based on the arterial luminal narrowing compared with the normal parent vessel and

comparison with DSA performed on admission. Mild angiographic vasospasm was considered at less than 50% arterial narrowing, moderate vasospasm as 50–75% narrowing, and severe vasospasm as greater than 75% narrowing. Two observers, an interventional neuroradiologist who performed the exam (with either 10 or 25 years experience) and a neuroradiologist blinded to all patient information (22 years experience), performed interpretation of DSA. For disagreements, a third neuroradiologist (10 years experience) independently reviewed the exam in a blinded fashion.

Reference Standard

DCI was used as the reference standard in this study employing both clinical and imaging criteria. The clinical criteria consisted of development of a new neurological deficit that was clinically distinct from the baseline deficit caused by the A-SAH or surgical intervention. This clinical deterioration was judged to be not attributable to other causes, such as aneurysm rebleeding, intracranial hemorrhage, hydrocephalus, infection, metabolic disturbance and seizure. Noncontrast CT of the head was performed in patients who developed new or worsening clinical signs or symptoms to assess for other potential causes. For patients with limited clinical examination, particularly in patients who were comatose or mechanically ventilated, continuous monitoring of laboratory data, neurologic and systemic parameters were used to assess for clinical deterioration. The imaging criteria consisted of new infarction on CT or MRI after day 4. This criterion has been used to effectively exclude primary brain damage from A-SAH and/or surgical intervention.[2,14] A diagnosis of DCI was assigned by the reference standard if either or both of the clinical or imaging criteria above were met. If neither of these criteria were met then a diagnosis of no DCI was assigned.

Statistical Analysis

All statistics were performed using SAS version 9.2 (Cary, NC). Categorical variables are presented as frequencies and percentages while continuous variables are presented as means $\pm$ 1 standard deviation. Independent Student's T-tests were performed on continuous variables to test for differences in means between patients with DCI and patients without DCI. Odds ratios for all variables were provided from univariate logistic regression analyses predicting the probability of DCI. P-values less than 0.05 were considered statistically significant for all analyses conducted. We calculated the sensitivity, specificity, and likelihood ratios CTP and DSA. Bayesian analysis was performed to estimate the conditional probabilities following positive and negative test results for each using an available data analysis web-based spreadsheet.[15, 16]

Results

Study population characteristics

A total of 108 patients were admitted to our institution with A-SAH from December 2004 and December 2008. CTP was performed in 104 patients and DSA was performed in 57 of these 104 patients. Therefore, 57 patients (those who had both CTP and DSA) were included in this study. Seventy-nine percent (45/57) were classified as DCI and 21% (12/57) as no DCI according to the reference standard. The clinical and demographic characteristics of the study population are presented in Table 1. The age and gender distribution in the study population are in accordance with the literature with a reported age of 45–55 years and female preponderance.[17, 18]

The imaging characteristics of the study population are shown in Table 2. CTP was performed during the typical time-period expected for vasospasm in all groups. A qualitative perfusion deficit was identified in 70% (40/57) patients. Eighty percent (36/45) of patients in

the DCI and 33% (4/12) of patients in the no DCI groups had a qualitative perfusion deficit. Sixty-three percent (36/57) of patients had DSA demonstrating vasospasm. Seventy-three percent (33/45) of patients in the DCI and 25% (3/12) of patients in the no DCI groups had angiographic vasospasm. Not surprisingly, DSA was performed slightly earlier in the DCI compared to the no DCI group.

Quantitative analysis of the CTP data revealed the mean quantitative CBF, CBV and MTT for the DCI group were 29.4 mL/100gm/min (SD 13.7), 1.9 mL/100gm (SD 0.6), and 6.6 sec (SD 2.7), respectively. The mean CBF, CBV and MTT for the no DCI group were 40.5 mL/100gm/min (SD 16.9), 2.0 mL/100gm (SD 0.4), and 5.5 sec (SD 3.2), respectively. There was a significant statistical difference between the DCI and no DCI groups in only the CBF values ($p=0.0213$). The P-values for CBV and MTT were 0.47 and 0.22, respectively. Table 3 is a comparison of the test characteristics for CTP and DSA.

Figure 1 demonstrates the graphs of conditional probabilities for CTP for determining DCI. By incorporating the sensitivity and specificity of CTP, Bayesian analysis can be used to calculate the post-test probability of DCI for any given pre-test probability. For the entire spectrum of pre-test probabilities (range 0–1.0), the post-test probability can be determined for both a positive and negative CTP result. Figure 1b and 1c illustrate different clinical scenarios for using this data. Figure 2 demonstrates the graphs of conditional probabilities for DSA for determining DCI and the same clinical scenarios in Figure 2b and 2c to compare with CTP.

Discussion

DCI is a devastating condition that occurs secondary to A-SAH and contributes to significant morbidity and mortality in this patient population. A diagnosis of DCI is based on clinical criteria for the presence of clinical deterioration not explained by other causes or imaging criteria for new infarction not attributed to the initial hemorrhagic event or post-operative changes.[2] The difficulty with using this definition of DCI in clinical practice is that once infarction has occurred, treatment interventions have limited ability to improve clinical outcomes. Thereby, surrogate indicators for DCI, such as angiographic vasospasm on DSA and perfusion deficits on CTP, may provide information on cerebral blood flow prior to the development of infarction. Identifying these patients is valuable to initiate prompt medical treatment with hypervolemia-hemodilution-hyperdynamic (HHH) therapy or further testing with DSA and interventional vasodilator treatment. Both of these treatment regimens have known neurologic and systemic complications that may further add to the morbidity and mortality of A-SAH patients.[19, 20] Thereby, appropriate patient selection is emphasized when considering these treatments along with their risks and benefits in this patient population. An important consideration in this decision process is the probability of the patient actually having DCI. This post-test probability is related to both the pre-test probability of DCI and the accuracy of the test being used to determine this diagnosis.

In current clinical practice, there is variability in the utilization of DSA and CTP in A-SAH patients. This may partly be due to uncertainty about the diagnostic accuracy of these modalities and the lack of appropriate utilization guidelines. In this study, we compared the test characteristics of CTP and DSA for determining DCI. Our results revealed that a perfusion deficit on CTP has greater sensitivity but lower specificity compared to vasospasm on DSA. The sensitivity and specificity of CTP were 0.80 (95% CI 0.68–0.92) and 0.67 (95% CI 0.4–0.93), respectively. These results are concordant with similar studies in the literature with sensitivity and specificity of 0.84 (95% CI 0.65–0.93) and 0.79 (95% CI 0.52–0.92), respectively.[21] The sensitivity and specificity of DSA in determining DCI were 0.73 (95% CI 0.60–0.86) and 0.75 (95% CI 0.5–0.99), respectively. To our knowledge,

no studies to-date have been published regarding the diagnostic accuracy of DSA in determining DCI. Furthermore, there are no studies in the literature comparing the test characteristics of CTP and DSA and its application in determining the probability of DCI.

The application of probability theory in this study allows the direct comparison of CTP and DSA and also assesses the effect these imaging modalities have on the treatment decision making for subgroups of patients. This post-test probability is based on both the sensitivity and specificity of the test (CTP or DSA) and the pre-test probability of the disease in the population (prevalence). The calculation of the post-test probability can be performed using Bayesian analysis [22–24] with the results displayed as graphs of conditional probabilities. Application of Bayesian analysis in clinical practice is particularly useful when a test has an imperfect sensitivity and specificity, as is the case with both CTP and DSA in determining DCI. A probability calculation is performed to determine the post-test probability of DCI given a positive or negative test result. The pre-test probability is initially based on the prevalence of DCI in the A-SAH population. However, to individualize a pre-test probability for a given patient, additional factors such as the patient's history, symptoms, physical examination, laboratory testing and imaging studies are incorporated. In the absence of any clinical indicators suggesting an increased or decreased probability of DCI, the pre-test probability may be assumed to be the prevalence of DCI in the population. In our study population, the prevalence of DCI is 79%. For example, if a patient with a pre-test probability of 79% has a positive DSA, then the post-test probability of DCI increases to 92%. In contrast, if the same patient has a negative DSA then the post-test probability of DCI decreases to 57%. In comparison to CTP, if this patient has a positive CTP, the post-test probability of DCI increases to 90%. If the CTP is negative, then the post-test probability of DCI decreases to 53%. In determining the post-test probability of DCI, it is important to recognize its dependence on the pre-test probability for specific clinical scenarios.

In clinical practice, the Hunt and Hess (HH) grading scale is a clinical criterion used in A-SAH patients to evaluate the severity of the subarachnoid hemorrhage for an individual patient and to assess their risk of developing DCI.[25, 26] Hidra et al found that A-SAH patients with low HH grades (Grade 1 and 2) had a 24% prevalence of DCI, whereas patients with high HH grades (Grades 3–5) had a 40% prevalence.[26] Figures 1 and 2 demonstrate the effect of the pre-test probability for CTP and DSA, respectively, using the HH grades to define the pre-test probability for an individual patient. For example, in A-SAH patients with low HH grades who have a 24% pre-test probability of DCI, if the CTP exam is positive for a perfusion deficit, then the post-test probability increases to 43%. However, if the CTP exam is negative then the post-test probability decreases to 9% (Figure 1b). In comparison, for this same patient a positive DSA increases the post-test probability to 48% whereas a negative DSA decreases the posttest probability to 10% (Figure 2b). Conversely, A-SAH patients with high HH grades have a 40% pre-test probability of DCI. If the CTP exam is positive for a perfusion deficit, then the post-test probability increases to 62%. However, if the CTP exam is negative then the post-test probability decreases to 17% (Figure 1c). In comparison, for this same patient a positive DSA increases the post-test probability to 66% whereas a negative DSA decreases the post-test probability to 19% (Figure 2c). Therefore, at these pre-test probability levels, there is no clinically significant difference in using CTP or DSA for determining the post-test probability of DCI.

The clinical significance of these results is partly determined by the treatment thresholds clinicians use to manage individual patients. Treatment threshold decisions are variable according to clinicians' practice patterns and their patient population. The risks and benefits of treatment are considered in defining this threshold. For example, if a clinician's treatment threshold is 60%, then there is no clinically significant difference in using CTP or DSA in A-SAH patients with high HH grades. However, A-SAH patients with low HH grades will

not meet the treatment threshold using either CTP or DSA alone. Therefore, the clinician will need to consider additional patient factors (symptoms, physical examination, laboratory tests or other imaging exams) in order to increase the pre-test probability in patients with low HH grades to reach the same treatment threshold. This Bayesian analysis illustrates that CTP and DSA are most useful for determining DCI in A-SAH patients with high HH grades. In contrast, patients with low HH grades require consideration of additional patient factors in order to reach the same treatment threshold and for the test to be useful.

Even though the test characteristics of CTP and DSA are similar in determining DCI, CTP may provide an attractive alternative testing modality in A-SAH patients. CTP has specific advantages in the setting of critically ill patients because of its widespread availability, rapid acquisition time, few patient contraindications, less adverse events compared with DSA and concurrent performance with standard-of-care imaging protocols for A-SAH patients.

There are several limitations in this study. A high prevalence of DCI was seen in the study population which may be partly attributed to using DSA as an inclusion criteria. Since DSA is an invasive procedure with known neurologic complications, patients who undergo DSA may be more likely to have vasospasm and DCI because of clinical indicators. Another limitation inherent to CTP imaging is the limited brain coverage with the possibility of perfusion deficits not included in the area imaged. This may partly explain the slightly reduced specificity of CTP compared to DSA, which by contrast allows whole brain imaging.

Conclusion

In summary, this study demonstrates that CTP and DSA have similar test characteristics for determining DCI in A-SAH patients. Performing Bayesian analysis in this study population illustrates the situations when testing with CTP and DSA will likely be useful. This application of probability theory provides a better understanding of the appropriate utilization of CTP and DSA in clinical practice for patients with low and high HH grades.

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Figure 1.

Graph of conditional probabilities (GCP) for CTP determining DCI in A-SAH patients.

Bayes theorem has been used to calculate the post-test probability of DCI for any given pre-test probability by using the patient-based sensitivity and specificity derived from this study (A). The blue line indicates a positive test result with a perfusion deficit on CTP. The pink line indicates a negative CTP test result. The GCPs are applied to patients with (low grade based on Hunt and Hess grading scale) low pre-test probabilities (24%) (B) and (high grade based on Hunt and Hess grading scale) intermediate pre-test probabilities (40%) (C). The post-test probabilities (dotted line) are interpreted on the Y-axis.

B

C

Figure 2.

Graph of conditional probabilities (GCP) for DSA determining DCI in A-SAH patients. Bayes theorem has been used to calculate the post-test probability of DCI for any given pre-test probability by using the patient-based sensitivity and specificity derived from this study (A). The blue line indicates a positive test result with arterial narrowing on DSA. The pink line indicates a negative DSA test result. The GCPs are applied to patients with (low grade based on Hunt and Hess grading scale) low pre-test probabilities (24%) (B) and (high grade based on Hunt and Hess grading scale) intermediate pre-test probabilities (40%) (C). The post-test probabilities (dotted line) are interpreted on the Y-axis.

Table 1

Clinical and demographic characteristics of the study population

		Study Population n=57		
		All n=57	DCI n=45	No DCI n=12
Age (years)	median range	51 28–80	55 29–80	48 28–78
Gender		% (n)	% (n)	% (n)
Male		25 (14/57)	27 (12/45)	17 (2/12)
Female		75 (43/57)	73 (33/45)	83 (10/12)
Aneurysm location				
Anterior		95 (54/57)	93 (42/45)	100 (12/12)
Posterior		5 (3/57)	7 (3/45)	0 (0/12)
Treatment type				
Surgical clipping		65 (37/57)	62 (28/45)	75 (9/12)
Coil embolization		35 (20/57)	38 (17/45)	25 (3/12)
Hunt Hess Grade				
Low (Grades 1 and 2)		46 (26/57)	44 (20/45)	50 (6/12)
High (Grades 3, 4 and 5)		54 (31/57)	56 (25/45)	50 (6/12)

Table 2

Imaging characteristics of the study population

		Study Population (n=57)		
		All n=57	DCI n=45	No DCI n=12
Day of CTP	median	7	7	6
Qualitative CTP deficit	% (n)	70 (40/57)	80 (36/45)	33(4/12)
Time-frame between Symptoms and CTP in days	median	0	0	0
Day of DSA	median	8	8	9
Time-frame between CTP and DSA in days	median	1	1	3

Table 3

Comparison of test characteristics for CTP and DSA.

	CTP	DSA
Sensitivity	0.80 (95% CI 0.68–0.92)	0.73 (95% CI 0.60–0.86)
Specificity	0.67 (95% CI 0.40–0.93)	0.75 (95% CI 0.50–0.99)
PPV	0.90 (95% CI 0.82–0.96)	0.92 (95% CI 0.82–0.98)
NPV	0.47 (95% CI 0.27–0.62)	0.43 (95% CI 0.26–0.53)
LR +	2.4 (95% CI 1.06–5.41)	2.9 (95% CI 1.08–7.94)
LR –	0.3 (95% CI 0.15–0.61)	0.4 (95% CI 0.20–0.64)
Odds Ratio	8.0 (95% CI 1.96–32.6)	8.25 (95% CI 1.91–35.67)

PPV is positive predictive value, NPV is negative predictive value, LR + is likelihood ratio of a positive result, LR – is likelihood ratio of a negative result.