CT Perfusion Imaging as a Predictor for Cerebral Vasospasm and Neurological Deficits After Subarachnoid Hemorrhage

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A. Study Purpose and Rationale

Subarachnoid hemorrhage-induced cerebral vasospasm is a common occurrence following the rupture of an intracranial aneurysm. Vasospasm can occur from the time of hemorrhage up to two weeks after hemorrhage and frequently leads to diminished cerebral perfusion, with potential ischemia and cerebral infarction resulting in irreversible neurological injury. In North America, it is estimated that as many as 36,000 people develop Subarachnoid hemorrhage because of a ruptured intracranial aneurysm annually. While up to 70% of patients have evidence of arterial narrowing (angiography or Doppler Ultrasound), only 20-30% of these patients become symptomatic. Despite aggressive medical management, stroke or death occurs in up to 10-20% of symptomatic patients establishing cerebral vasospasm as the leading cause of morbidity and mortality after subarachnoid hemorrhage. The gold standard for detecting vasospasm is angiography. Angiographic vasospasm refers to radiographically visualized narrowing of the arterial vessel caliber. However, though there may be angiographic evidence of vasospasm, the patient may not manifest clinical deficits. Clinically symptomatic vasospasm or delayed ischemic neurological deficit is characterized by confusion or decreased level of consciousness and will often but not always demonstrate arterial narrowing and/or diminished contrast flow, as only larger arteries may be visualized angiographically. There is no reliable association between the degree of vasospasm demonstrated on angiography and symptom severity. Hence, detection of cerebral vasospasm and the identification of which patients are likely to become symptomatic is crucial.

Recently, CT perfusion has been introduced as a method for quantitative assessment of regional cerebral blood flow (rCBF). CT perfusion provides information concerning the functional state of the perfused tissue and changes occurring on the microvascular level. Vasospasm leads to alterations in cerebral blood flow and subsequently, these changes may manifest as neurologic dysfunction. Cerebral blood flow data has been useful in predicting the risk of vasospasm and in distinguishing those deficits caused by vasospasm. The viability of the cerebral parenchyma is dependent on cerebral blood flow. Mean cerebral blood flow values range approximately 50 ml / 100 g / minute, and must be maintained in order to meet the energetic needs of underlying neurons. Neurobiochemical mechanisms via autoregulation ensure a constant rCBF, and through compensatory dilatation of the arteriolar bed of the brain, an increase in cerebral blood volume occurs. Ischemia occurs when the rCBF falls below 20 cc per 100 g per minute, and infarction occurs below 10-15 cc per 100 g per minute. In response to a declining hemodynamic reserve, salvageable brain parenchyma demonstrates a decrease in the rCBF yet the cerebral blood volume is paradoxically increased due to vascular dilatation consistent with reversible ischemia. When autoregulatory mechanisms supplying collateral flow fail and both rCBF and cerebral blood volume are decreased, infarction occurs over a duration of time. CT perfusion data can be useful in the management of patients who have subarachnoid hemorrhage following aneurysm rupture by establishing those patients likely to develop vasospasm, those who become symptomatic, and patients who may benefit by early intervention and when to do so.

B. Study Objective

The aim of this prospective study is to determine the role of CT perfusion imaging as

1. an accurate and reliable method for diagnosing vasospasm and

2. as a predictor of clinical deterioration after subarachnoid hemorrhage. This is highly desirable before starting treatment.

C. Study Design and Procedure

This will be a prospective study to assess the objectives as outlined above. All patients will undergo standard treatment. After confirmation of SAH via noncontrast CT and angiography, informed consent will be obtained. Patients will be informed of the imaging protocol, and informed of the minimal increase in exposure to radiation. Multisection dynamic contrast enhanced CT perfusion will be performed using a multidetector scanner and table toggling technique. Using a field of view of 25 cm, 120 kVp 30-60 mA, 40 ml nonionic contrast agent with a flow rate of 4ml/sec, a target slice for CT perfusion will be selected, containing the upper parts of the lateral ventricles**.** CT perfusion imaging will be performed on day 0, the day of the subarachnoid hemorrhage. Dynamic CT measurements of cerebral blood flow (rCBF), cerebral blood volume (rCBV), and mean transit time (MTT) will be obtained and calculated based on the central volume principle. The patient will be monitored closely and the neurosurgical team will keep a log of neurological examinations. Evidence of neurologic decline includes any features on the neurologic examination consistent with diminished cerebral blood flow, either diffusely or in an arterial territory distribution. This included any significant change in sensorium or level of consciousness. Documentation will be obtained regarding whether the patient clinically manifests the appropriate criteria defining symptomatic vasospasm.

All routine CTs and neurovascular interventions will be assessed by the same team of two interventional neuroradiologists.

D. Study Subjects

The patient population will include all patients presenting with subarachnoid hemorrhage as a result of ruptured cerebral aneurysm. The diagnosis of aneurismal SAH will be made by noncontrast CT and conventional 4 vessel angiography. Only patients with known day/time of onset of subarachnoid hemorrhage will be included in the study. The patient's creatinine and history of allergies will be obtained. Patients with a creatinine greater than 1.8 and contrast allergy will be excluded from the study. Subjects less than 18 years and greater than 85 years of age will be excluded.

E. Outcomes and Statistical Analysis

There will be three measures of outcome:

1. +/- CT Perfusion imaging: Perfusion CT examination with data analysis according to the central volume principle allows accurate quantitative assessment of the rCBF, the rCBV, and the MTT. Based on the literature, rCBF is superior to rCBV and MTT in sensitivity and specificity in predicting the extent of cerebral infarction, and therefore we will chose an rCBF threshold/cutoff as the outcome measure to indicate whether CTP imaging was positive or negative. This value will be 34 ml/100g/min, with a score of 34 or less as a positive result and a score of >34 a negative result. This cutoff was estimated from the literature.
2. Moderate/severe vasospasm vs absence of/mild vasospasm: Initial angiography on day 0. Angiographically mild, moderate, or severe vasospasm will be diagnosed if the arterial caliber reduction is 0-25%, 25-50%, or >50%, respectively of the adjacent normal vessel.
3. presence or absence of clinical vasospasm: Patients will be monitored and classified into 2 groups: no clinical signs/symptoms (irrespective of angiographic evidence of vasospasm) and positive clinical vasospasm. Clinical vasospasm will be defined as the new onset of neurological signs and symptoms not explained by rebleed or hydrocephalus.

The data will be collected and two 2x2 tables will be developed. The first will compare CT Perfusion with angiographically determined vasospasm and the second will compare CT Perfusion with clinical vasospasm. The sensitivity and specificity for CT Perfusion for each arm will be computed. Statistical significance will be set at the P<0.05 level and 80% power.

F. Sample Size

This study will require the enrollment of 51 patients to detect statistical significance set at the P<0.05 level and 80% power. This calculation was derived from the one-sample Chi-square test based on proportions.

1. CTP vs angiographic vasospasm.	True sensitivity = 90%	Useful sensitivity = 70%	n=36
	True specificity = 70%	Useful specificity = 50%	n=*51*
2. CTP vs clinical vasospasm.	True sensitivity = 90%	Useful sensitivity = 70%	n=36
	True specificity = 95%	Useful specificity = 80%	n=44

G. Confidentiality of Study Data

All personal identifiers of patient data will be removed and kept strictly confidential.

H. Potential Conflicts of Interest

None

I. Potential Risks and Benefits

The overall effective dose equivalent required for dynamic CT perfusion is only slightly higher than for routine CT. The potential risks for this study are minimal. The benefit is a more accurate and reliable way for diagnosing vasospasm which may play a role in determining the treatment of choice. The advantage of a CT technique is easy accessibility, tolerability, and not time-consuming.