

Subarachnoid hemorrhage: effect on cerebral blood flow and cerebral metabolism

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1. ABSTRACT

Alterations in cerebral blood flow and metabolism after subarachnoid hemorrhage (SAH) are well known and have been extensively described. Many techniques exist in the intensive care setting to monitor for these alterations. Ranging from classic neurological exam to novel imaging studies a variety of modalities are available for intensive monitoring. Early identification of cerebral vasospasm is the key to prevention of its long term complications and as such the role of genetics and biochemical markers are currently being investigated. The dynamics of cerebral blood flow and metabolism following SAH are unique and require additional studies before any monitoring technique can be used as stand alone modality and supplant the DSA as the gold standard for detection of cerebral vasospasm.

2. INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH) is a recognized cause of premature and unexpected sudden death. Although the initial aneurysmal rupture carries significant mortality it is the delayed effects of cerebral vasospasm that cause an even greater amount of morbidity and mortality. Despite the significant improvement in the intensive care delivery, mortality following aneurysmal rupture is nearly 50% with an additional 1/3 of patients requiring long-term care.(1)

Under normal conditions the auto-regulatory system present at the level of the cerebral vasculature is able to provide constant rates of blood flow and metabolism in the brain. Following the onset of subarachnoid hemorrhage the autoregulation of cerebral

Table 1. Modalities for detection of cerebral vasospasm and alterations in blood flow dynamics post subarachnoid hemorrhage

Neurological monitoring
• Neurological Exam
• Intracranial Pressure
• Continuous EEG
Cerebral blood flow and metabolism
• Transcranial Doppler Ultrasound
• Microdialysis
• Jugular Venous Oxygen Saturation
• Brain Tissue Oxygenation
• Xenon CT
• Positron emission tomography
• Perfusion weighted MRI
• Single Photon Emission Computed Tomography
• CT Perfusion
• CT Angiography
• Cerebral Angiography

blood flow breaks down causing blood flow and metabolism mismatches that can cause brain injury. In addition to the acute effect of SAH blood flow and metabolism are further affected by the development of SAH-induced cerebral vasospasm. Although the pathway from aneurysmal rupture to the development of symptomatic vasospasm is a highly researched it is still not fully understood. However, the effects of vasospasm induced hypo-perfusion and cerebral ischemia is well described and can be lethal. Although the pathogenesis of cerebral vasospasm is not yet completely understood it appears to involve the activation of numerous biochemical cascades, cell to cell interactions and resulting inflammatory responses which are believed to play at least a partial role in the development of vasospasm. Animal and laboratory models exist and have provided invaluable information about the pathogenesis of SAH-induced cerebral vasospasm.

Detection of symptomatic vasospasm is key to beginning early treatment. Modalities for the detection of vasospasm range from non-invasive imaging examinations to more invasive cerebral angiography. (Table 1) Correlating the detection of vasospasm to clinically significant vasospasm however has proven to be challenging and remains up for much discussion.

The goal of the following chapter is a brief review of normal cerebral blood flow and metabolism as well as those acute and chronic changes exhibited post subarachnoid hemorrhage. An explanation of the monitoring methods available to evaluate changes in the normal cerebral metabolism dynamics will also be discussed.

3. NORMAL CEREBRAL BLOOD FLOW AND METABOLISM

The adult brain has a high rate of metabolism, using glucose as its energy substrate. For an organ weighing only 2-3% of the total adult body weight it utilizes nearly 20% of the cardiac output. Neurons demand nearly 90% of the cerebral energy while the parenchyma glial cells utilize the remaining 10%. Cerebral blood flow

(CBF) in the normal adult averages 50mL/100g brain tissue per minute.(2) The cerebral vasculature can tolerate significant decreases in CBF without effect on cerebral metabolic rate of oxygen (CMRO₂). Cerebral blood volume (CBV) and oxygen extraction fraction (OEF) also have role in maintaining CMRO₂.

In the normal adult brain tight regional control over CBF and neuronal demands for oxygen and glucose is maintained. Several chemical species have been related to increase neuronal and glial activity, including H⁺, K⁺, CO₂, ATP, and lactate. These chemical species are also known to have direct effect on vascular tone thus making them ideal targets for study in patients suffering cerebral perfusion alterations. The precise mechanism of cerebral autoregulation is to yet to be determined however an interaction between the myogenic and vasoactive chemical mediators such as CO₂ and H⁺ are believed to play a major role.(3) Alterations in CO₂ and therefore in pH have been shown to affect cerebral vasculature. A well described phenomenon is that a significant cerebral vasoconstriction results from decreases in PaCO₂. (4) A decreasing pH also has an effect on OEF. As the oxygen-hemoglobin curve shifts to the left an increase in delivery is O₂ to the target tissues is accomplished.

Endothelial derived factors have also been shown to function to either dilate (endothelium derived relaxing factor, EDRF) or constrict (endothelin-1, ET-1) cerebral vasculature as the oxygen and metabolic demands of the brain change. One mechanism endothelial agents utilize is to produce, alter or degrade the known vascular dilator nitrous oxide (NO) in response to alterations in cerebral oxygenation.(5)

Cerebral autoregulation is maintained utilizing changes in cerebral vessel diameter as well as the efficiency of unloading O₂, providing the ability to overcome variances in metabolism, cerebral perfusion pressure (CPP) and blood viscosity over a large range in CPP's.(6) Reversible damage to neurons occurs in the 15-20mL/100g brain tissue per minute range while irreversible damage occurs at just a slightly lower threshold of 10-15 20mL/100g/min.(7,8) The human brain is able to tolerate changes in mean arterial blood pressure from 80 to nearly 140 mmHg with only minimal changes in CBF. (Figure 1) When mean arterial blood pressures falls to the lower limits of the above range an increase in OEF is observed to maintain near constant delivery of oxygen to brain tissue. Only when CBF falls to its lower threshold and OEF has been maximized does the body begin to decrease CMRO₂ with a metabolic depression and ischemia soon following.

4. HEMODYNAMICS AND METABOLISM FOLLOWING SUBARACHNOID HEMORRHAGE AND VASOSPASM

First described over 60 years ago the ischemic changes following subarachnoid hemorrhage can cause profound destruction of neuronal tissue.(9) Subarachnoid hemorrhage alters multiple aspects of the normal cerebral vasculature and its autoregulation of CBF. Brain injury

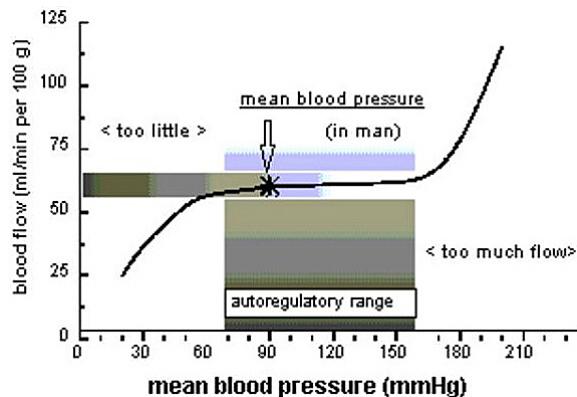


Figure 1. Autoregulation of cerebral blood flow in relation to mean arterial pressure.

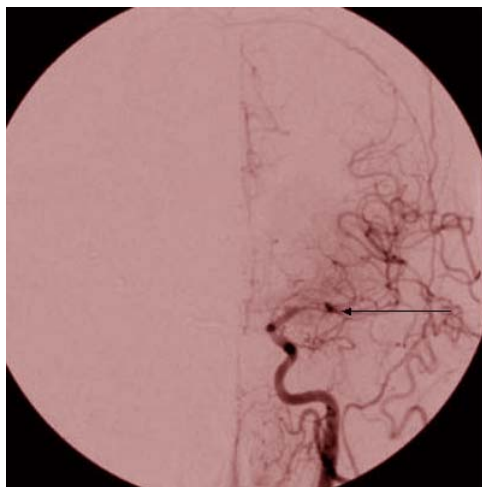


Figure 2. Cerebral Angiogram showing evidence of narrowing of left MCA.

after subarachnoid hemorrhage has been described as a biphasic event consisting of an acute phase due to distribution of blood in the subarachnoid space, elevation of intracranial pressure, reduced cerebral perfusion and cerebral blood flow (CBF) the second phase consists of the delayed injury or vasospasm phase.(10)

The earliest effect on CBF by SAH is caused by rapid increases in ICP due to either development of acute hydrocephalus or mass effect from expansion of an intracranial hematoma. It has been demonstrated that within 1-2 minutes of aneurysm rupture the ICP rises sharply to pressure near that of the diastolic blood pressure. It then takes an additional 10 minutes to stabilize this increase to a near normal level unless there has been an interval development of a hematoma.(11)

An additional early effect of blood in the subarachnoid space is first a reduction in $CMRO_2$ and later reduction in CBF due to decreases in O_2 demand. In a classic description of alterations in $CMRO_2$ and CBF, Voldby showed that a more significant decrease in $CMRO_2$

precedes the smaller decrease in rCBF thus providing evidence for an uncoupling of normally tightly matched CBF and $CMRO_2$.(12) This luxury perfusion state is the time when the cerebral tissue is able to overcome decreases in cerebral blood flow while still maintaining cerebral metabolism. Once this cascade is started regional ischemia from decreased O_2 delivery may follow even in the face of decreasing $CMRO_2$. Infarction of cerebral tissue is known to occur when CBF falls below the 15-20ml/100g/min level.

During the vasospasm phase significant alterations in blood flow can cause areas of ischemia. When the ischemic areas become permanent and produce neurologic symptoms they have been described as delayed ischemic neurologic deficits (DIND). The exact mechanism from aneurysm rupture to neurologic ischemia and resulting DIND has yet to be elucidated. The uncoupling of CBF to cerebral metabolism is likely to play a major role this pathway however is still under investigation.

Vasospasm can peak in the 5th to 9th day post rupture but it is not unusual to have evidence of vasospasm at even 21 days post aneurysmal rupture.¹¹ The period immediately after subarachnoid hemorrhage is marked by a CBF decreases as early as post subarachnoid hemorrhage day 2 and remain low for three weeks.(13) The prediction of outcome following SAH has been correlated to patients presenting condition and amount of blood on CT images upon presentation but a direct correlation between a patient's neurologic condition on presentation and development of vasospasm does not exist.(14,15)

Cerebral infarction associated with vasospasm is the irreversible result of the cascade of events discussed above. The reactivity of cerebral vasculature is often abnormal in patients post subarachnoid hemorrhage and its ability to adapt to alterations in CBF becomes more difficult. Cerebral autoregulation in response to hypotension is abnormal even in mild cases of SAH and becomes globally disturbed in severe vasospasm.(11) Early identification of cerebral vasospasm is key to prevention of the long-term sequelae and will be the focus of the following material.

5. NEUROLOGICAL MONITORING

In an ideal situation neurological monitoring of the subarachnoid hemorrhage patient would consist of non-invasive, affordable and widely available testing modalities that will identify the earliest stages of cerebral vasospasm that would become symptomatic and go on to produce delayed ischemic neurologic deficits (DIND). The early identification would provide a mechanism for early intervention to prevent the ischemic sequelae. Digital subtraction angiography (DSA) remains the gold standard for detection of cerebral vasospasm. (Figure 2) This invasive test is not without problems and also does not provide information on cerebral blood flow or metabolism but rather is only able to evaluate vessel diameter. These

pitfalls of DSA have provided the motivation for evaluation of a neurological monitoring technique that could better evaluate cerebral metabolism and blood flow.

Many modalities currently exist for aid in neurological monitoring. Pitfalls are plentiful as most if not all the monitoring devices do not have the support of randomized clinical trials thus providing information that may have limited clinical utility.

5.1. Neurological exam

The neurological exam even in the purest and most ideal sense is only able to identify cerebral vasospasm after a neurological deterioration has occurred. The neurological exam leaves much to be desired in regards to the “typical” subarachnoid hemorrhage patient in which altered mental status, sedation and baseline deficits may already be present. Vasospasm often manifests in symptoms of alterations in level of consciousness and focal neurologic deficits such as hemiplegia or aphasia. Many non-specific symptoms are also often present and their relation to the presence of vasospasm is not completely clear. These nonspecific symptoms include restlessness, unusual behaviors, and impulsive behavior.(16) However non-specific the neurologic exam may be, it is of great importance to closely follow the exam for changes so that further investigations or therapies may be offered and is one of the few “continuous” monitoring modalities available.

5.2. Intracranial pressure

Elevated intracranial pressure (ICP) is associated with aneurysm rupture due to either mass effect from enlarging hematoma or to development of hydrocephalus. The management of many high grade SAH patients involves placement of an ICP monitor and/or CSF diversion drain into the ventricular system with the goal of maintaining a normal ICP. It is these high grade patients that are most likely to suffer the effects of cerebral vasospasm and has long been suspected, but not proven, that elevated ICP play an important role in the development of cerebral vasospasm.

In one study, patients with high ICP tended to have severe, prolonged, and diffuse vasospasm compared with a lower ICP group, however, only the duration of vasospasm was proven to be statistically different.(17) The relationship between cerebral perfusion pressure (CPP) and the development of vasospasm was also examined in this study and was shown to have a less significant effect than ICP on development of vasospasm. The fact that elevated ICP worsens vasospasm suggests that normalizing ICP may have potential for avoiding the development of severe vasospasm although this point has yet to be validated.

It is difficult to isolate elevated ICP from the CSF metabolites that have been shown to be present patients following SAH. Many of these metabolites are vasoactive and studies have suggested that it is the removal of these products rather than decrease in ICP alone that decreases the incidence of vasospasm.(18)

The effects of elevated ICP on brain tissue regardless of etiology can be catastrophic. The perceived increased risk of vasospasm with elevated ICP notwithstanding, management goals of all SAH should strive for normalization of ICP with either medical modalities or use of CSF diversion devices.

5.3. Continuous EEG

Continuous electroencephalographic (cEEG) is gaining favor among neurointensivists for the monitoring and identification of non-convulsive status epilepticus in the neurointensive care setting. The use of cEEG for monitoring of the subarachnoid hemorrhage patient can be looked at for multiple potential benefits.

The technique of cEEG is not only non-invasive but prior studies have shown that changes detected on cEEG correlate with cerebral metabolism and can be sensitive for detection of early cerebral ischemia.(19,20) The high rate of non-convulsive status epilepticus post aneurysm rupture has been documented and provides an additional benefit of cEEG monitoring.(19,20,21) cEEG monitoring correlates with cerebral topography providing additional information about the vasculature first beginning to show changes associated with vasospasm.(19,20) In fact cEEG has not only been shown to detect changes in metabolism prior to clinical deterioration but also to correlate with cerebral angiography once vasospasm has developed.(22,23)

As cEEG becomes more available in the neurosurgical intensive care unit its routine use for surveillance of the subarachnoid patient will increase. The detractors for its routine usage will point to introduction of operator error, requirement of capable neurologists to read the exams and susceptibility to artifacts as reasons to be skeptical. Universal use of cEEG on all SAH patients is yet to be determined but the potential multi-faceted benefits of detecting early changes in cerebral metabolism and identification of non-convulsive status should not be overlooked.

6. CEREBRAL BLOOD FLOW AND METABOLISM: MODALITIES FOR DETECTION IN THE SAH PATIENT

6.1. Transcranial Doppler Ultrasound

For over 20 years transcranial Doppler (TCD) have been used in the detection of alterations in blood flow velocity and therefore diameter of intracranial blood vessels.(1) The physics behind the technique are straightforward as a blood vessel begins to spasm the cross sectional diameter shrinks and blood velocity increases through this section of vessel. The *Lindgaard Ratio* comparing the intracranial velocities to extracranial velocities was thought to help to differentiate global hyperdynamic states from those more consistent with vasospasm.(24) Even with usage of the *Lindgaard Ratio* studies have shown poor correlation between high velocity calculated by the *Lindgaard Ratio* and angiographic proven vasospasm.(25,26) Reports in the literature have

shown both a high degree of correlation between elevations in velocity(27) and weak correlation(28) to degree of angiographic vasospasm. Vora *et al* have shown that only low or very high (<120 or >200 cm/s) velocities correlate with angiography for the detection of cerebral vasospasm.(26)

The sensitivity of TCD's to detect vasospasm is also widely variable on location of aneurysm rupture as well as operator specific. Sensitivity based on location range from 55% in anterior communicating artery aneurysm to nearly 95% in middle cerebral artery aneurysm rupture.(29) TCD's are often monitored throughout the SAH patient's hospital stay and evaluating the TCD's for trends, i.e. increasing velocities have shown promise of predicting development of vasospasm.(30)

The use of TCD's alone to *reliably* screen for cerebral vasospasm has not been scientifically validated. TCD's as a non-invasive, bedside testing modality are included in the monitoring of many SAH patients and one can include the result of TCD flow studies with additional investigations and with the clinical picture in order to better guide treatment decisions.

6.2. Microdialysis

Cerebral microdialysis is a minimally invasive bedside tool for sequential measurement of cerebral metabolic chemical substrates. Typically hourly analyses of glucose, pyruvate, lactate, aspartate and glutamate levels are performed using a bedside device that is placed into the brain parenchyma that is most likely to suffer the effects of vasospasm.(31) The microdialysis technique relies on its ability to detect the metabolic changes and diffusion of metabolites in the extracellular fluid associated with ischemia. Metabolic disturbances associated with ischemia include those associated with hypometabolism of glucose including higher than normal levels of glutamate, lactate, glycerol as well as increases in the lactate to pyruvate concentration ratio. These alterations have been shown to be amplified in comparing of the symptomatic cerebral vasospasm patient to asymptomatic patient.(32)

Microdialysis has a specificity and sensitivity for detection the ischemic effects of vasospasm that is comparable to TCD and DSA.(32) The high rate of vasospasm detection however does require the probe to have been placed close to area with alterations in perfusion and hence metabolic rate.(33) This fact is likely the findings in another study that concluded that microdialysis was unable to reliably predict the development of vasospasm.(33)

The current inability to predict the precise area that will suffer the ischemic effects of vasospasm is an issue that has yet to be resolved and provides an argument against the routine use of the microdialysis catheter. A positive trend for use of microdialysis in monitoring for ischemic events in SAH patients exists but studies demonstrating the clinical value of microdialysis as a stand alone modality are still needed.

6.3. Jugular venous oxygen saturation

Jugular venous oxygen saturation measurements (SjvO₂) provide an estimate of global cerebral oxygen delivery and metabolism. SjvO₂ measurements are obtained by placing a fiber optic catheter into the internal jugular vein and advancing to near the base of the skull. This minimally invasive technique allows for frequent blood sampling techniques and calculation so arteriovenous oxygen difference, delivery of cerebral oxygen and metabolic markers of the brain may be measured.

The reliability and especially reproducibility of SjvO₂ remain up for debate. To this point most of the studies examining the utility of measurements of SjvO₂ have been in the head injured patient. Complications in measurements may occur with misplaced catheters, clot formation on catheter, and alterations in blood sampling techniques provide a significant amount of variability that have been shown in regards to measurements in the head injured patient. SjvO₂ even in the ideal situation is only able to measure global cerebral oxygenation and metabolism providing no information on small alterations in *regional* blood flow or metabolism, those changes most frequently encountered along with the development of cerebral vasospasm in the SAH patient. With a reported false positive rate approaching 50% the use of SjvO₂ as the sole method for identifying vasospasm is not advisable.(34) Further studies in the SAH patient are necessary before SjvO₂ can be relied upon for vasospasm detection.

6.4. Brain tissue oxygenation

The idea of placing a monitor either into on the surface of the brain to measure CBF and cortical perfusion is a technique that has been around since the early 1980's. An early technique that has since fallen out of favor is one that involved placement of a probe in the subdural space onto the cortical surface of the brain. This technique used a probe with two electrodes that was able to quantify cerebral blood flow from detection of a temperature difference between the probes.(35) Although early studies verified the use of this subdural grid system for detecting alterations in cerebral blood flow it has been replaced by monitors that are placed directly into brain parenchyma.

The use of brain tissue oxygenation (PbO₂) monitoring is a modality that has been used to assess the autoregulation of blood flow in the traumatic brain injury patient.(36) Measurement of PbO₂ involves placement of a catheter into brain parenchyma through a small burr hole. Once in place, the catheter allows for measurement of local changes in PbO₂ as well as pCO₂, pH and temperature. Studies have hypothesized that continuous monitoring of PbO₂ in the subarachnoid hemorrhage patient would detect early changes in cerebral autoregulation.(37,38) Although validated in the traumatic brain injury patient the pitfalls of the subdural system may befall the parenchyma monitoring system in the SAH patient. Questions regarding ideal probe location and ability to monitor for local oxygenation changes require further clinical trials in the

SAH and cerebral blood flow and metabolism

SAH patient before PbO₂ monitoring gains a more universal acceptance.

6.5. Xenon CT

Gaseous Xenon is a fat soluble tracer molecule that when administered to a patient via a closed inhalation system acts as a contrast material. The differing densities demonstrated on CT scans correlate with arterial concentrations of Xenon and therefore cerebral perfusion.(39) Xenon enhanced CT (Xe-CT) scanning was first used to show CBF abnormalities in patients with ischemic strokes.(40) This information was then adapted to be used to detect alterations in CBF in those patients at risk of vasospasm following subarachnoid hemorrhage.(41)

Verification of Xe-CT findings were made by comparing hypodensities on plain CT to the results of Xe-CT. Irreversible cerebral ischemia on CT imaging is presented by a hypodense signal. These hypodensities are known to represent cerebral ischemia and the resulting cytotoxic edema.(42) Hypodensities on CT have been shown to correlate with CBF alterations detected on Xe-CT. In the post SAH patient that has suffered ischemic injury secondary to vasospasm Xe-CT has demonstrated an abnormally low CBF.(41,43) New information exists that shows hypodensities on CT may not always correlate with hypoperfusion and that within these hypodense areas a range of cerebral blood flow patterns may exist.(44)

The time course and correlation between alterations in CBF as detected on Xe-CT and irreversible ischemia are yet to be fully determined in the SAH patient. The ability to predict areas of cerebral ischemia from early alterations in CBF as detected by Xe-CT would provide information prior to development of symptomatic vasospasm and hence allow for early interventions. It was thought that Xe-CT could provide a reliable and non-invasive measurement of CBF in the SAH patient, however this has yet to be proven in the clinical setting and with the advent of both CT and MR perfusion may never have its clinical utility proven.

6.6. PET

Positron emission tomography (PET) scanning provides an accurate, quantitative measurement of regional hemodynamics and has been used for identification in flow abnormalities in cerebrovascular disease.(45) PET scanning is simultaneously able to measure regional CBF, CMRO₂, OEF, and CBV. The CBF measurements determined by PET scanning involve mainly large vessel flow characteristics.

PET scanning has been used to identify abnormal patterns of CBF and metabolism in cerebral vasospasm post SAH.(46) This study demonstrated symptomatic vasospasm may or may not be associated with PET scan detected blood flow abnormalities and also lacked a correlation to TCD detected abnormalities. This study provides evidence for the growing theory that large vessel vasospasm is only one part in the development of ischemia and DIND. It has been suggested that PET scanning is best utilized when serial studies are conducted and both regional

CBF and cerebral metabolism are examined for changes.(46)

PET scanning has provided much information regarding the development of cerebral ischemia and DIND following SAH but it is most likely availability and lack of large clinical studies that have kept it from becoming a standard of care in management of the SAH patient.

6.7. Magnetic resonance imaging

The use of Magnetic Resonance Imaging (MRI) for detection of blood flow abnormalities in the SAH patient is a relatively new technique. Perfusion and diffusion weight imaging techniques will be considered as they are able to provide information on CBF and metabolism.

Perfusion weighted MRI (PWI) is a non-invasive imaging technique to visualize regions of cerebral hypervolemia or hypovolemia, providing information on relative tissue perfusion. Cerebral blood volume, cerebral blood flow and meant transit time are parameters evaluated by PWI. PWI can be obtained in one of two ways. Images can be obtained with either the use of contrast material, dynamic susceptibility contrast imaging, or using arterial proton spin labeling technique that does not utilize contrast material.(47) Ease of use in relation to length of study and improved resolution have made the dynamic susceptibility technique the most commonly used of the two PWI techniques.

Diffusion weighted MRI (DWI) has also been utilized to detect early signs of irreversible brain ischemia. Combining PWI and DWI have the unique ability to identify brain tissue that is at risk of ischemia prior to the development of infarction, one of the few studies able to identify the ischemic penumbra.(48)

The use of DWI and PWI in detecting vasospasm has been described in a few studies.(49,50) One study determined that PWI not only had a higher sensitivity to detection of cerebral vasospasm than TCD but also was able to detect vasospasm earlier.(51) Information obtained by MRI regarding CBF and CBV obtained have shown that while the relative CBF is decreased in areas of vasospasm, relative CBV remains stable post ischemia, providing evidence for a breakdown in cerebral autoregulation.(52,53)

A few caveats specific to MRI must be noted. Artifacts from either blood products or aneurysm clips or coils can affect the MRI results. With no clear threshold for determining the threshold when infarction occurs one must use care when interpreting the data from DWI and PWI. Like many imaging techniques only relative measurements of regional cerebral blood flow are able to be detected. These measurements are only snapshot of cerebral perfusion and do not allow for minute to minute bedside evaluation with our current technology. As opposed to CT scanning MRI typically requires longer scan times, 15-20 minutes for DWI and PWI, higher associated costs and less availability.

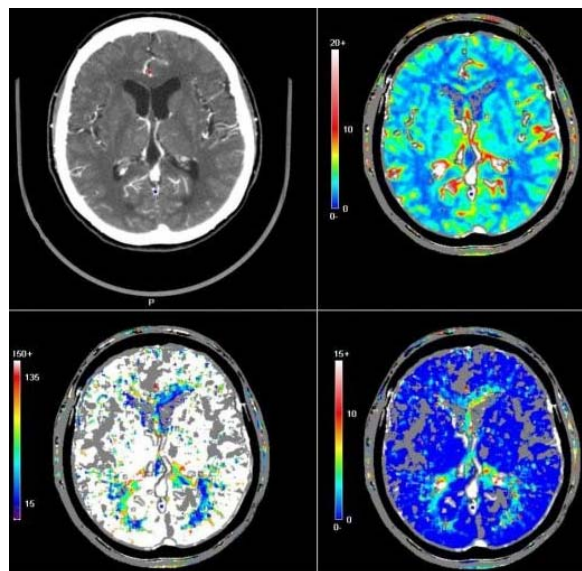


Figure 3. Example of Color enhanced CT perfusion study showing alterations in flow consistent with MCA distribution vasospasm.

As MRI technology continues to become more available its role in the evaluation of the SAH patient will continue to evolve and become a more utilized modality.

6.8. Single photon emission computed tomography

Single Photon Emission Computed Tomography (SPECT) scanning uses a gamma-emitting tracer used in brain imaging to detect alterations in cerebral blood flow. The tracer molecule is attached to bioactive molecule that is incorporated into brain tissue in a manner proportional to brain blood flow, in turn allowing brain blood flow to be assessed with the nuclear gamma camera. These gamma rays can then be detected by a gamma camera and quantitative information on blood flow can be determined.

SPECT scans have been shown to correlate with TCD (54) and clinical findings in the cases of cerebral vasospasm in one study while another study showed a poor correlation in a similar patient population.(55) More recent investigations have used three-dimensional (3D) reconstructions of SPECT images to more accurately show vasospasm-induced decreased cortical regional CBF (rCBF).(56) Areas of decreased cortical rCBF on the 3D SPECT was most likely to be present in three patient populations; those who developed DIND, patients who would go on to develop a large vasospasm induced infarction and in those patients who clinically did very poorly.(56)

Angiographically, cerebral vasospasm can be divided into peripheral, proximal or combined types depending on vascular distribution. 3D SPECT has correlated with DSA for the combined type of vasospasm that exhibits the most reduction in cerebral blood flow.(56) Correlation to vasospasm on angiographic studies have not been as readily available from two-dimensional or mean hemispheric analysis of CBF.(55).

The method of 3D SPECT appears to provide valuable information on rCBF in the SAH patient correlation to DSA needs to be demonstrated before a definitive conclusion about clinical utility can be drawn.

6.9. CT Angiography and CT Perfusion

The detection of vasospasm by non-enhanced CT often is too late to offer treatment. In the 6 to 12 hours that it can take for ischemia to become evident on the CT scans irreversible damage likely has occurred. In one study it was shown that CT defined cerebral ischemia could take as long as 24 hours to become fully evident.(57)

The use of CT angiography (CTA) and CT perfusion (PCT) studies to allow for early detection alterations in CBF that are present in the cerebral vasospasm patient. The recent widespread use of multi-slice CTA seems to have alleviated some of the early concerns of conventional CTA. The accuracy and prognostic values for the non-invasive imaging techniques such as these CT modalities must in the very least approach that of DSA to be considered appropriate screening tests.

Multi-slice CTA has been shown to detect cerebral vasospasm after SAH with an accuracy similar to that of DSA.(58,59) In one study however it was shown to be less accurate for detecting the extremes with no vasospasm and marked vasospasm correlating less frequently with DSA.(59) The anterior and middle cerebral arteries were shown to correlate most frequently with DSA with the abnormal vessel section, proximal or distal, being identified 90% of the time.(58) The location of vasospasm does matter though as sensitivity, specificity, and accuracy at the level of the A2 and M2 are the most consistent with DSA.(60) In contrast the carotid siphon shows the least concordance of intracranial vasospasm with DSA.(60) Multi-slice CTA provides a valuable tool for diagnostic evaluation and monitoring progression of cerebral vasospasm. Care must be taken in the routine use of CTA until further studies are completed as significant location specific differences do remain in comparison of DSA and CTA.

PCT imaging is a technique for the measurement of CBF, cerebral blood volume, mean transit time, and time to peak. (Figure 3) It is an inexpensive and fast imaging modality that may offer an additional tool for the management of patients with SAH. Abnormalities in mean transit time values have been shown to be more valuable detectors of cerebral ischemia than CBF or cerebral blood volume values as detected by PCT.(61) The presence of vasospasm on CT perfusion images can be determined by qualitative readings using color maps of mean transit time, cerebral blood flow, and cerebral blood volume.(62) A 91% concordance with angiographic findings in predicting the presence or absence of vasospasm has been shown.(62) PCT has the potential to provide real time evaluation of alterations in CBF and metabolism in the vasospasm patient and has recently been shown to be useful tool in evaluating the effect of treatment on cerebral vasospasm.(63).

A qualitative interpretation of CTA in combination with PCT-derived mean transit time (MTT) with a threshold at 6.4 seconds has been shown to accurately diagnose cerebral vasospasm in greater than 95% of patients in one study.(64) Providing evidence that the combination of CTA and PCT provide a more accurate screening test in patients with suspected vasospasm than each test used alone.

7. BIOMARKERS OF CEREBRAL VASOSPASM

The biochemical cascade from SAH to vasospasm is highly studied but as of yet not completely understood. The cerebral spinal fluid from SAH patients has been studied and a few target metabolites have been identified. Nitric oxide,(65) endothelins,(66) ATP,(67) and the breakdown products of oxyhemoglobin(68) are among the products that have been implicated in the development of vasospasm. The use of NMR-based examination of CSF from SAH patients has identified possibly 60 different metabolic compounds in their CSF that is absent in the CSF in control patients.(69)

Nitric Oxide (NO) is well described vasodilator and natural target for investigation in regards to metabolites involved in development of cerebral vasospasm. Pluta(70) has summarized one vasospasm hypothesis from work using a primate model of SAH developed at Vascular Laboratory of Surgical Neurology Branch of the National Institute of Neurological Disorders. In this model NO-releasing neurons are destroyed by oxy-hemoglobin leading to diminished availability of NO in the vessel wall and constriction of the vessels. Increased shear stress stimulated by narrowing of the arterial lumen should increase release of NO by endothelial nitric oxide synthase (eNOS). But further metabolism of hemoglobin to bilirubin oxidized fragments (BOXes) increases asymmetric dimethylarginine (ADMA), an inhibitor of eNOS, further decreasing the availability of NO and leading to vasospasm. With the resolution of vasospasm, the elimination of BOXes increases NO production by eNOS resulting ability of endothelium to dilate in response to increase shear stress.

Evidence that inflammatory and immune mechanisms may have a critical role in the development of vasospasm after subarachnoid hemorrhage is accumulating. Adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin, are important mediators of inflammation, and their levels are elevated in the serum of patients following aneurysmal subarachnoid hemorrhage (SAH). ICAM-1 may play a role in mediating SAH-induced vasospasm and that a reduction of ICAM-1 levels after SAH may partly contribute to the antispastic effect of CGS 26303, an anti-vasospasm drug that is in development.(71) E-selectin a molecule expressed by inflamed endothelial cells may play a role in the cellular development of vasospasm, as anti-E-selectin antibody was effective in prevention of SAH-induced vasospasm and imply a possible role of E selectin in the pathogenesis of vasospasm after SAH.(72).

Endothelin-1 (ET-1) is known to be a potent vasoconstrictor peptide. Numerous reports have suggested its roles in various neurologic and vascular disorders. There is evidence establishing the relationship between ET-1 and cerebral vasospasm in animals. The role of ET-1 in humans is still under investigation. Human studies have shown that concentrations of ET-1 in the CSF of SAH patients increased prior to the onset of cerebral vasospasm. With this information and the above suggested time course, ET-1 concentration in the CSF could be a useful early marker to detect cerebral vasospasm after subarachnoid hemorrhage.(73) An additional study examined ET-1 levels and time course in three different sources: CSF, plasma and microdialysate. It was shown that only elevated ET-1 in CSF seemed to be associated with development of cerebral vasospasm.(74)

Another target of exploration is the role of oxygen free radicals and their ability to produce cellular inflammation. Reduced glutathione (tau-glutamylcysteinylglycine, GSH) is an oxygen radical scavenger and plays an important role in protection of cells from ischemia and from the harmful effects of free oxygen radicals. Free oxygen radicals in the vasospasm patient have been shown to increase both the rate of vasospasm and development of proliferative vasculopathy.(75) The administration of GSH intra-arterially to SAH patients provided protection against the development of symptomatic vasospasm, suggesting that free oxygen radicals play a role in the development of vasospasm.(75)

The role of calcium as a mediator in the determination of vascular smooth muscle tone has been well described. S100-B and neuron specific enolase (NSE) are known predictors of outcome in head injured and stroke patients. S100-B refers to members of a multigenic family of calcium-modulated proteins. S100-B and NSE have been shown to predict the development of vasospasm and outcome if identified within the first 3 days after subarachnoid hemorrhage (SAH).(76) S100-B values were significantly higher in those patients who died than in those with unfavorable or favorable outcome.(76) The role of S100-B in the development of vasospasm is not yet clear. S100-B has been shown to have effects on downstream proteins including neuromodulin and p53.(77) The mechanism of action of S100-B in response to the vasospasm patient however remains unclear.

Recent studies have indicated that arachidonic acid (AA) is metabolized by the cytochrome P450 4A (CYP4A) enzymes in cerebral arteries to produce 20-hydroxyeicosatetraenoic acid (20-HETE). 20-HETE is a potent vasoconstrictor of cerebral microvessels. In laboratory models 20-HETE has effects on cerebral vascular tone that closely replicate those seen following SAH. Inhibiting formation of 20-HETE serves to block the myogenic response of cerebral arterioles to elevations in transmural pressure thus disrupting one facet of cerebral autoregulation.(78) 20-HETE also plays an important role in modulating the cerebral vascular responses to vasodilating compounds (NO and CO) and vasoconstrictors (angiotensin II, endothelin, serotonin). Recent studies have

indicated that the levels of 20-HETE in CSF increase in rats, dogs and human patients following SAH and that inhibitors of the synthesis of 20-HETE prevent the acute fall in CBF and reverse delayed vasospasm in animal models.(78) 20-HETE is present in the CSF of SAH patients at physiologically relevant concentrations(79), future prospective studies are needed to delineate the role of this metabolite as it relates to the pathogenesis of SAH in the human SAH patient.

8. SUMMARY

It is impossible to know where the future investigation of cerebral vasospasm will lead. The quantification of blood on initial HCT currently provides the only way to "predict" who will go on to develop cerebral vasospasm.(80) In the nearly 30 years since this article has been published, the use of the initial HCT for prediction of cerebral vasospasm remains an imperfect science at best.

With the recent explosion of genomics it is natural to wonder what role genetics play in the development of cerebral vasospasm. A genetic predisposition for coronary vasospasm has been documented for decades.(81) The role genetics play in development of cerebral vasospasm is yet to be determined but is under intensive study. Polymorphisms in the *eNOS* gene have been identified as a possible target in the development of cerebral vasospasm given its role as a vasodilator, inhibitor of inflammation and role in aggregation of platelets.(82) Genetic variations in APOE and haptoglobin, two proteins associated to this point with atherosclerotic disease, also are being studied to further determine their role in the development of cerebral vasospasm.(82) The ability to identify those patients with the genetic susceptibility towards cerebral vasospasm would provide an additional non-invasive study that could be conducted upon hospital admission, long before any signs or symptoms of vasospasm have had a chance to develop.

Alterations in cerebral blood flow and metabolism after subarachnoid hemorrhage are well known and many modalities exist in the intensive care setting to monitor for changes. Ranging from classic neurological exam to novel imaging studies a variety of modalities is available for neurological monitoring. In the last two decades the introduction of cerebral perfusion imaging has provided much information on alterations in cerebral blood flow and metabolism and their relationship to cerebral ischemia. Utilizing this information to guide clinical management however remains up for much discussion as few randomized clinical trials exist. The dynamics of cerebral blood flow and metabolism following SAH are unique and require additional studies before any monitoring technique can be used as stand alone modality and supplant the DSA as the gold standard for detection of cerebral vasospasm.

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Key Words: Cerebral Vasospasm, Subarachnoid Hemorrhage, Cerebral Blood Flow, and Cerebral Metabolism, Review

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