

# Radiographic assessment of vasospasm after aneurysmal subarachnoid hemorrhage: the physiological perspective

Andrew P. Carlson and Howard Yonas

Department of Neurosurgery, University of New Mexico, Albuquerque, NM, USA

**Objectives:** Vasospasm following aneurysmal subarachnoid hemorrhage is ascribed to be the cause of morbidity and mortality in 10–30% of patients. Vascular narrowing following SAH defined by angiography (along with non-invasive vascular imaging such as CT angiography) is, however, present in most patients. We seek to describe the need for understanding the clinically relevant syndrome of delayed ischemic neurological deficit (DIND) and to describe various perfusion techniques which in addition to vascular imaging studies, are needed to fully understand when delayed neurological deficits are due to vasospasm induced ischemia.

**Methods:** The literature regarding various perfusion techniques as they relate to vasospasm and DIND was reviewed.

**Results:** There are many techniques which offer some data regarding cerebral blood flow in the setting of DIND. Truly quantitative techniques such as positron emission tomography and xenon CT offer powerful tools to identify areas at increased risk for infarction. Xenon CT is a practical technique which may be performed at the bedside and may be used to assess cerebral blood flow response to a changing variable.

**Discussion:** Perfusion techniques offer clinical data which may be applied to the care of an individual patient so that treatment may be tailored to that patient's physiological needs. This allows the clinician to pursue a rational strategy for diagnosis and treatment of a patient with a delayed neurological deficit following aneurysmal SAH [Neurol Res 2009; 31: 593–604]

**Keywords:** Cerebral angiography; cerebrovascular circulation; perfusion; subarachnoid hemorrhage; vasospasm; intracranial

## INTRODUCTION: HISTORICAL PERSPECTIVE

The first angiographic demonstration of cerebral vasospasm after subarachnoid hemorrhage (SAH) was achieved in 1951<sup>1</sup>. Since that point, catheter angiography has formed the backbone of the anatomic assessment of the common phenomenon of vasospasm after SAH. Computed tomography (CT) has also been used in the identification of aneurysmal SAH since the 1970s. A key contribution has been the development of a reliable grading scale to predict the risk for angiographic vasospasm based on the amount and pattern of CT defined hemorrhage<sup>2</sup>. This scale, proposed by Fisher *et al.* in 1980, has become part of the standard neurosurgical assessment and has proven to be clinically useful and predictive of poor outcome in difficult situations.

The 1980s and 1990s saw the beginning of interventional techniques for the treatment of vasospasm offering new therapeutic options besides the standard 'triple H' medical management. The first balloon angioplasty was reported in 1984<sup>3</sup>. This has proven to

be a useful technique to reverse the appearance of vasospasm in large vessels accessible to microcatheters. The technique is not without risk and fatal results have been reported<sup>4</sup>. As technical advances such as digital subtraction and three-dimensional rotational angiography continue to improve, the resolution of vascular anatomy by angiography has become more precise.

There is a standard risk for each procedure of around 0.5–2% risk of stroke with diagnostic angiography. Furthermore, there are additional problems with iodinated contrast and radiation exposure. Angiography also requires an experienced practitioner and a radiographic team to be assembled and coordinated. Balancing the need for repeated angiography in patients with SAH involves understanding the need for these detailed images. Given that only a minority of the large number of patients with radiographic vasospasm will develop symptoms due to ischemia<sup>5</sup>, there is a need to find less invasive alternatives for defining not only vascular anatomy, but more importantly, the physiological compromise that cannot be determined by angiography alone.

## ALTERNATIVES TO ANGIOGRAPHY FOR ANATOMICALLY DEFINING VASOSPASM

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) have been evaluated for

Correspondence and reprint requests to: Howard Yonas, MD, Chairman and Professor of Neurosurgery, Department of Neurosurgery, University of New Mexico, MSC10-5615, 1 University of New Mexico, Albuquerque, NM 87131-0001, USA. [hyonas@salud.unm.edu] Accepted for publication May 2009.

their possible central role for the study of cerebral vasospasm; however, there are technical and practical limitations to their routine use. Their advantages include a lack of radiation and contrast exposure. In addition, some functional data regarding ischemia may be gathered at the same time as will be discussed later. Limitations include problems with transport for the more extended study, reliance on patient cooperation or sedation for optimal study, and technical problems such as metal artifact and subarachnoid methemoglobin interfering with the vessel examination.

Standard technique for MRA involves a time of flight sequence where the blood is excited in the neck, and signal acquisition is then obtained in the brain. The timing can be adjusted to capture the primarily arterial or venous phase. As the data acquisition sequence is heavily T1 weighted, any tissue with high T1 signal may cause artifact (intracellular methemoglobin, fat, contrast, etc.) Spatial resolution is around 1 mm. When compared to angiography, Grandin and colleagues<sup>6</sup> have shown fairly good correlation regarding evaluation of vasospasm in the 83% of cases where good quality MRA images were obtained. Sensitivity when compared to angiography was reported as 92%. They noted significant limitation in sensitivity, particularly of the internal carotid artery (ICA) of 25% and the middle cerebral artery (MCA) of 56%. Degree of stenosis was more difficult to accurately assess using this technique due to signal loss created by laminar flow. Other MRA techniques such as phase contrast or intravascular gadolinium contrasted MR are used occasionally. Phase contrast involves overlaying sequential images with subtraction of the moving blood signal. This avoids the problem of T1 artifact, but has much longer acquisition time and lower spatial resolution<sup>6</sup>. Other MR techniques addressing brain physiology including perfusion imaging will be discussed in a later section.

As imaging resolution improves with new generation CT scanners, the ability to detect narrowing of cerebral vessels is approaching that of formal angiography without the clinical risks and technical barriers. Recent studies using multislice (4–16 channel) CT angiography (CTA) suggest that there is very high concordance with angiography. There are several commonly used techniques for three-dimensional reconstruction of the vasculature, and neuroradiologists often use a combination of techniques to obtain relevant information. The maximum intensity projection is used commonly and relies on attenuation thresholding and manual removal of bones at the skull base. Otawara and colleagues<sup>7</sup> showed quite good correlation with angiography using this technique (90.8–92.3% agreement with angiography with  $p < 0.0001$ ). Volume rendered imaging is often faster and requires less operator experience, but may be limited by inability to distinguish partial vessel calcification. Yoon and colleagues<sup>8</sup> evaluated the use of this technique and found 96.1–97.3% correlation with angiography ( $p < 0.001$ ). There were no cases in this series in which calcifications were thought to interfere with results. Both of these studies compared both proximal and distal vessels, finding

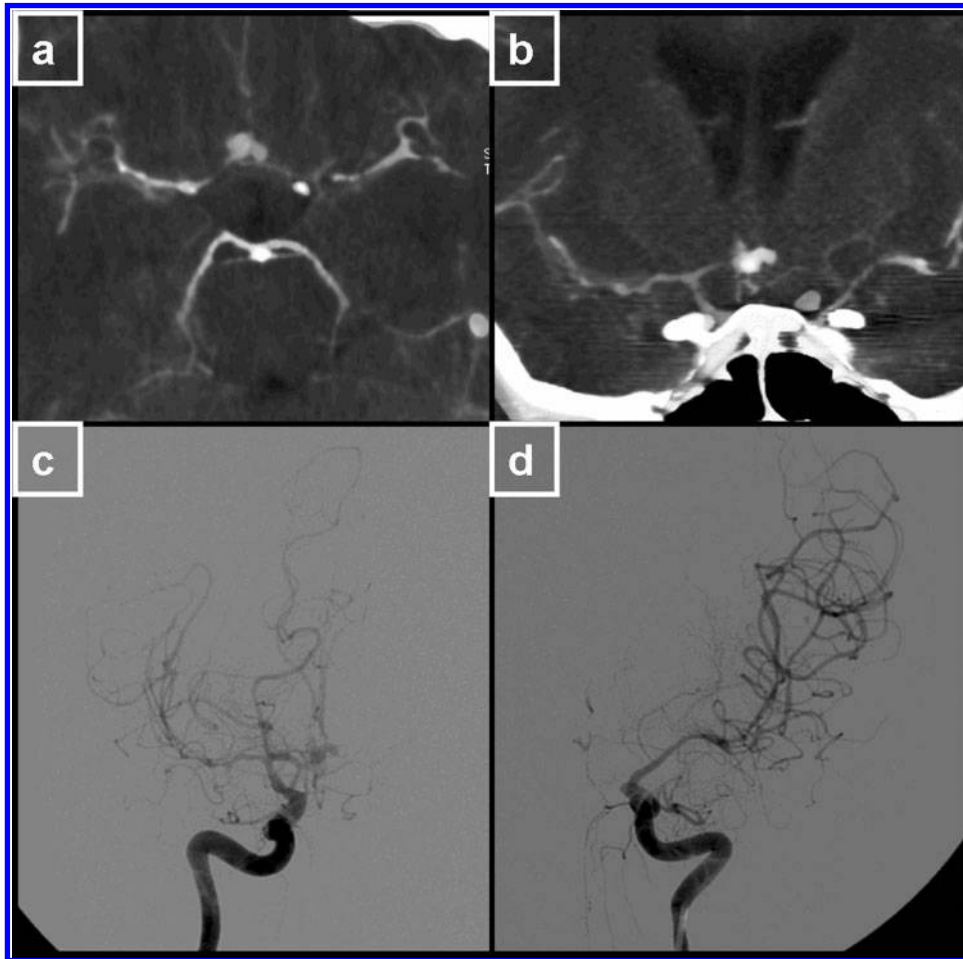
similar rate of agreement. Overall, the accuracy of CTA compared with angiography is probably practically equivalent, especially given that general practice is to use multiple reconstruction methods including those listed above as well as multiplanar reconstruction and the source axial images (Figures 1a,b, 2b,c and 3d). Limitations of CTA include poor visualization of the most distal vessels, and reliance on operator technique for bolus timing in order to ensure an adequate study. In addition, the inherent risks of radiation and iodinated contrast exposure remain.

### VASOSPASM: WHAT IS IT?

Although imaging techniques have allowed the visualization of vessel narrowing following SAH, this has been found to have poor clinical correlation. The majority of patients (~70%) with SAH develop radiographic vasospasm<sup>9,10</sup>; however, only a small minority (about 30–40%) develop ischemia in the form of clinical deterioration or eventual infarction<sup>5,10</sup>. A review of all articles mentioning vasospasm from 1975–2001 identified that there is a wide variety of how vasospasm is defined, from purely angiographic definitions, to TCD (Transcranial Doppler) parameter definitions, to purely clinical definitions (Kerr *et al.*, Definition of delayed cerebral vasospasm after subarachnoid hemorrhage: a need for clarification and standardization of terminology, 2002, unpublished work). The authors identified several key concepts encountered frequently in the literature: delayed, neurological deficit, vascular narrowing, and ischemia. These elements all seem to be important in the definition of the clinico-radiographic syndrome of vasospasm. The problem is delayed, suggesting that it is not due to the initial or perioperative insult. There is a neurological deficit present, and other causes such as hydrocephalus, new hemorrhage, and metabolic causes have been excluded. There is typically evidence of vascular narrowing (as discussed above) and the final critical element is that this is an ischemic process. Ischemia by definition is inadequate tissue blood flow to maintain viability, and the threshold for ischemia and infarction has been evaluated and found to be in the range of 8–20 cc/100 g/min depending on the time course and metabolic state of the tissue<sup>11–14</sup>. This concept has become more widely accepted as the clinical syndrome of vasospasm is becoming widely termed delayed ischemic neurological deficit (DIND)<sup>15,16</sup>. This paradigm shift allows an important change in our understanding of vasospasm treatment. Quantitative cerebral blood flow (CBF) techniques can allow for identification of specific at risk territories in a given patient and assessment of efficacy of specific interventions (medical therapy, angioplasty, intra-arterial papaverine, etc.) The following section discusses the relative merits of CBF techniques as they relate to vasospasm and DIND.

### MEASURING ISCHEMIA

There are many imaging modalities used to assess perfusion. A few are quantitative while the majority are



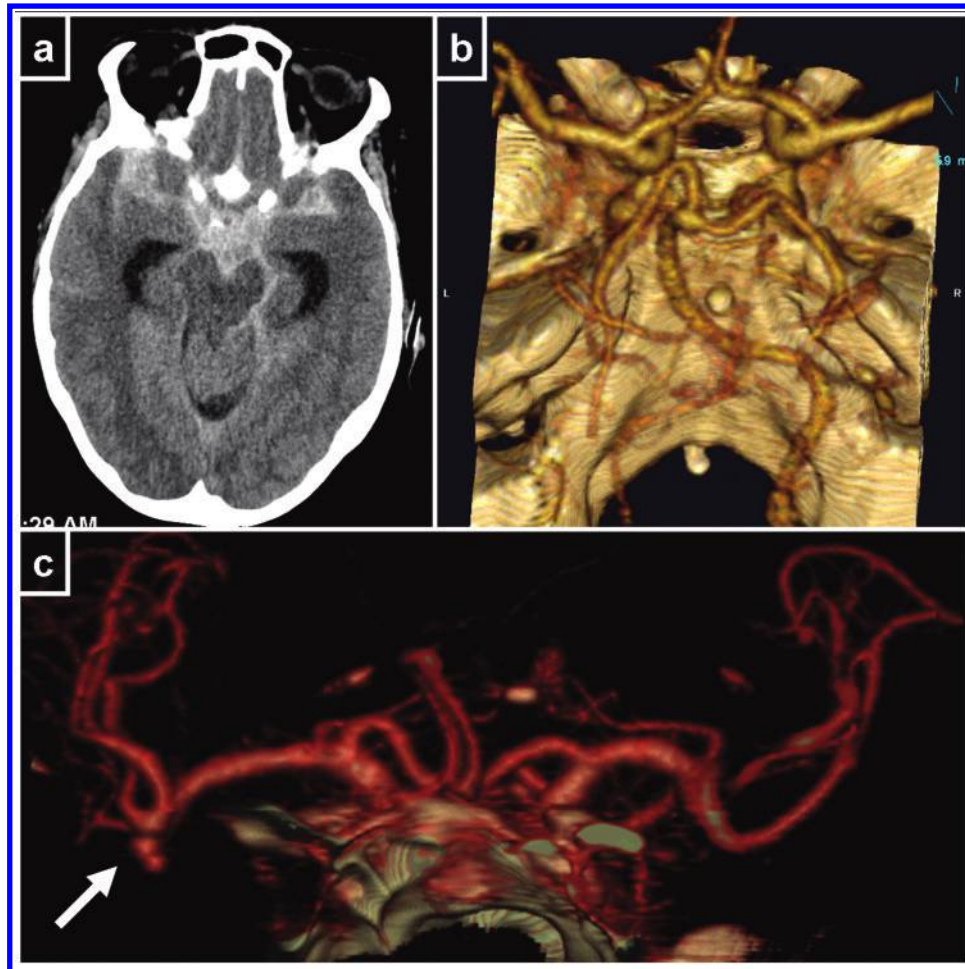
**Figure 1:** Initial imaging studies of patient no. 1. Axial (a) and coronal (b) multislice three-dimensional reconstruction of computed tomography angiography (CTA), demonstrating severe bilateral vasospasm (white arrowheads) as well as a bilobed anterior communicating artery aneurysm (white arrows). Right (c) and left (d) internal carotid artery angiograms with straight anterior posterior projection again showing severe bilateral vasospasm (white arrowheads) and the anterior communicating artery aneurysm (white arrow). Note that the left A1 segment is very hypoplastic with minimal filling of the A2 branches

qualitative. Quantitative techniques provide a measure of flow that provides an insight to when tissue is not threatened by ischemia as well as where it is on the continuum from oligemia to reversible and irreversible ischemia. Qualitative studies are instead utilized by making assumptions about internal ratios of flow from one brain region to another that one has to assume is normal. These types of assumptions are rarely valid in clinical practice<sup>17</sup>. For a complete overview of perfusion techniques, the reader is referred to a recent excellent compilation of the strengths and benefits of each<sup>18</sup>. The following attempts to provide a brief overview of each technique and its utility in the diagnosis and treatment of DIND.

### Positron emission tomography

Positron emission tomography (PET) offers a powerful tool for understanding multiple variables relevant to CBF and metabolism in a quantitative manner. This technique is accepted as the radiographic gold standard

technique for determination of CBF, cerebral blood volume (CBV), oxygen extraction fraction (OEF), and cerebral metabolic rate for oxygen (CMRO<sub>2</sub>). Although these values offer a great deal of insight into both blood flow and metabolism of brain, there are several features of the technique that limit its use to research purposes. All of the values require either intravenous injection or inhalation of radiolabeled <sup>15</sup>O. The half life of this isotope is only 122.1 seconds, making performing repeat examinations feasible; however, it also necessitates the use of an on-site cyclotron for production of the isotope. After injection (for CBF) or inhalation (for CBV and OEF) of the <sup>15</sup>O in the form of H<sub>2</sub><sup>15</sup>O or C<sup>15</sup>O, the radioactive signal is detected by the PET scanner at several brain levels correlated to CT levels for anatomic detail. Regional data along each slice can then be calculated and correlated with the anatomic region of interest on the CT scan<sup>19,20</sup>. Despite the above widely accepted statement, the fact that clinically available PET CBF techniques utilize a non-lipid soluble tracer (H<sub>2</sub><sup>15</sup>O) means that flow values derived by PET are



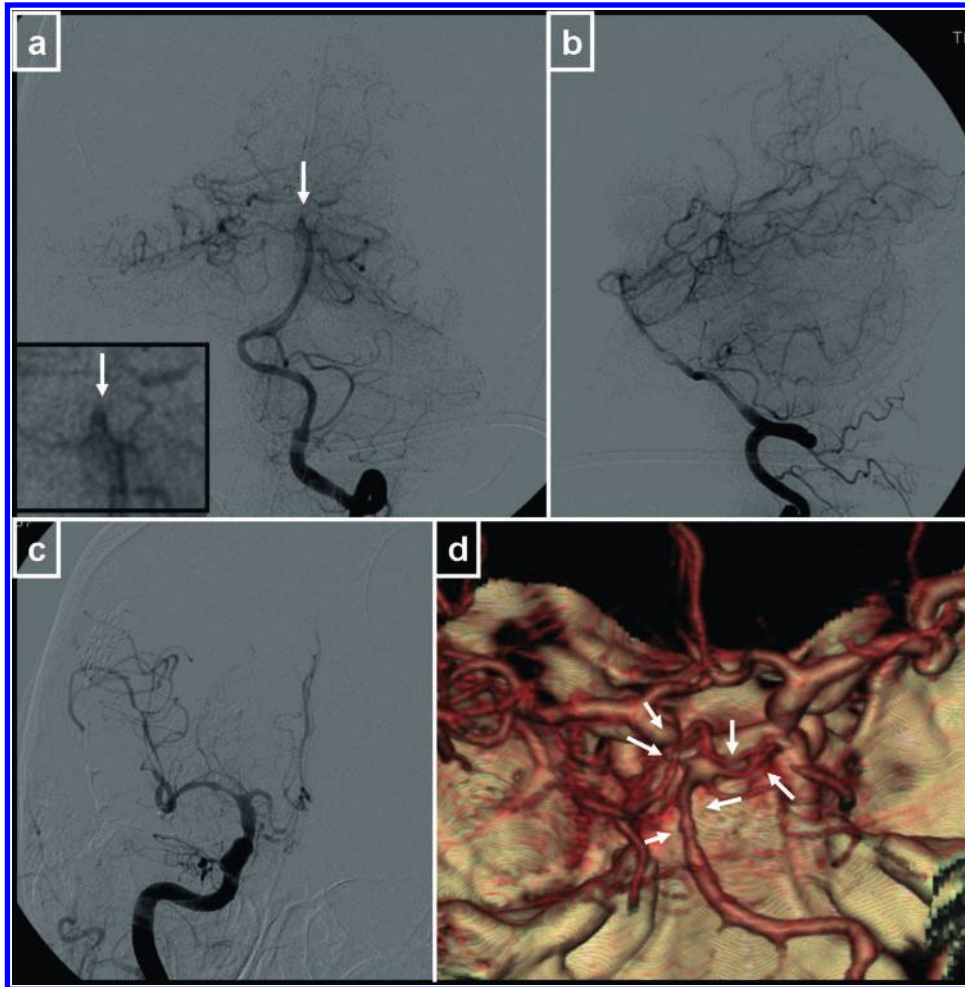
**Figure 2:** Initial presentation of patient no. 2. (a) Non-contrast axial head CT at the level of the midbrain, showing the focal blood clot in the temporal lobe as well as thickly layered subarachnoid hemorrhage in both sylvian fissures and the basilar cisterns. (b) CT angiogram three-dimensional reconstruction (volume rendered imaging) showing the initial wide patency of the large cerebral vessels, particularly the posterior cerebral arteries. (c) CT angiogram three-dimensional reconstruction (volume rendered imaging using slightly different software) showing the aneurysm at the bifurcation of the right middle cerebral artery (white arrow)

inherently inaccurate especially as flow increases above 20 cc/100 g/min.

Although impractical for guiding individual patient management, important physiological information regarding the underlying pathology in vasospasm has been elucidated. Early studies helped to define CBF values below which irreversible ischemia will occur<sup>20</sup>. Applying the physiological variables which can be measured, it has been shown that there is a general transient reduction in  $CMRO_2$  in SAH even without radiographically defined vasospasm<sup>19,21</sup>. This may be due to a generalized toxic reaction of the brain to blood products<sup>19</sup>; however, it may be related to the permissive hemodilution and subsequent relative anemia which is part of standard therapy for SAH<sup>22</sup>. Even without vasospasm, patients with SAH tend to have globally decreased CBF,  $CMRO_2$ , and CBV with normal OEF. This suggests metabolic depression with decreased demand. In patients with symptomatic vasospasm, the CBF and  $CMRO_2$  can decrease further, with eventual

tissue infarction. In normal brain, when perfusion is decreased, the arterioles dilate in order to compensate (and preserve cellular metabolism); however, this ability seems to be lost following SAH. In this setting, the arteries seem to be unable to dilate, and OEF acts as an adaptive variable, increasing in response to decreased CBF. This has been confirmed with PET studies obtained post-SAH in which CBF is decreased, OEF is increased, and CBV is decreased (indicating a lack of the vasodilatory response<sup>19</sup>). This probably reflects inability of the distal vasculature to normally dilate due to the remote vascular effects that can occur as part of 'vasospasm'.

Because the immediate response to SAH is complex including often a profound disturbance of perfusion and a suppression of metabolism, the delayed responses of the vasculature require careful study in order to understand how best to treat each patient. It is clear that patients may respond to interventions differently due to differing degrees of tissue dysfunction. Therefore, it is



**Figure 3:** Severe multiple vessel vasospasm in patient no. 2. Anterior–posterior (a) and lateral left (b) vertebral artery injection. Inset magnifies the basilar apex, where there is a near complete absence of filling of the posterior cerebral arteries. (c) Anterior–posterior view of right internal carotid injection showing severe spasm of multiple vessels. (d) Computed tomography (CT) angiography demonstrates the patency of the posterior cerebral arteries, but confirms the severe spasm of the distal basilar artery and posterior cerebral arteries (white arrows)

important to find technologies which can reliably predict tissues at increased ischemic risk as well as tissues that are reversibly or irreversibly ischemic.

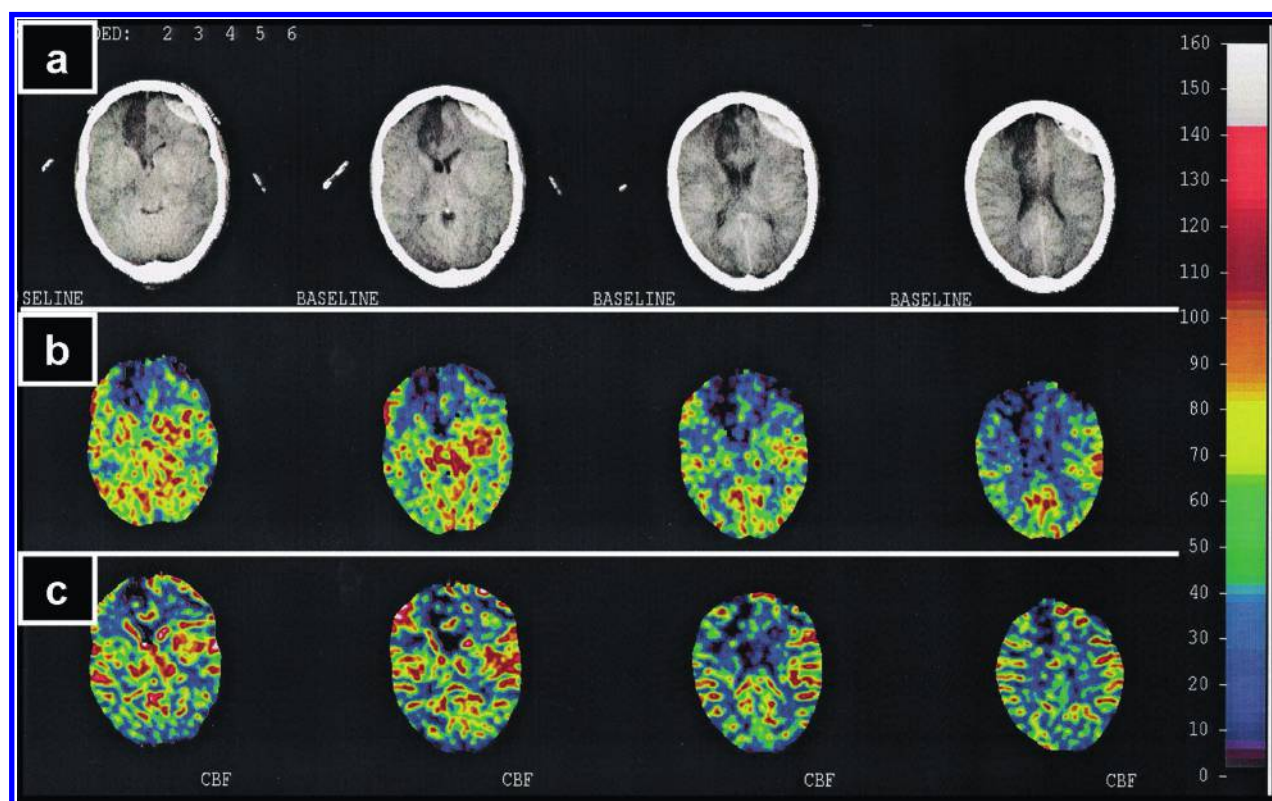
### Xenon CT

Xenon has been used as a quantitative measure of CBF due to its properties as a radio-opaque gas which is readily diffusible into brain tissue. Early work measured hemispheric washout of xenon by applying the Fick principle; however, with refinements in CT technology, it is possible to directly serially measure CBF via measuring the changes of the concentration of xenon for each of the 24,000 pixels of a CT slice<sup>23</sup>. Stable xenon (28%) is inhaled by the patient, while in the CT scanner and the end tidal CO<sub>2</sub>, end tidal xenon, and other clinical variables are monitored, either in an awake, cooperative patient or a mechanically ventilated, chemically relaxed patient. The calculation of CBF relies on a modification of the Kety–Schmidt equation which relates the concentration of such an inert, diffusible agent measured over time. The two

variables required to solve the equation accurately include the arterial concentration curve of the agent as well as the tissue arrival time (which is dependent upon the blood–brain partition coefficient or lambda). The arterial concentration is measured in real time as the end tidal xenon concentration (a very good approximation with such a highly diffusible gas). In addition, the brain partition coefficient is measured for each CT pixel by measuring increasing Hounsfield enhancement units, giving a tissue arrival curve for each pixel. Quantitative CBF can then be calculated by the simultaneous solving of both variables using integral math (equation (1)). This calculation is performed for each CT pixel, typically at four CT levels

$$C_{Xe_{br}}(t) = \lambda k_0 \int^t C_{Xe_{Ar}}(u) e^{-k(t-u)} du \quad (1)$$

where  $C_{Xe_{br}}(t)$  is the time dependent brain xenon concentration,  $\lambda$  is the brain–blood partition coefficient,  $k$  is the brain uptake flow rate constant and  $C_{Xe_{Ar}}(u)$  is the time dependent arterial xenon concentration.



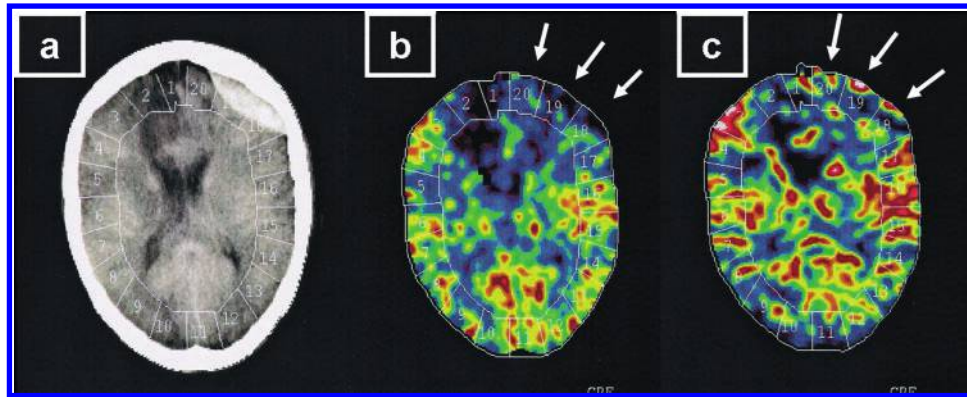
**Figure 4:** Xenon computed tomography (CT) study of patient no. 1. The scale on the right of the image represents absolute values for cerebral blood flow in cc/100 g/min. (a) Baseline CT images reveal a hypodense area from a peri-procedural right anterior cerebral artery stroke. There is also an epidural hematoma which occurred during placement of an intracranial pressure monitor. (b) The first xenon study with induced hypertension to systolic blood pressure 190–200 mmHg shows quantitative CBF at each of the four CT levels. The right medial frontal region is expectedly low in CBF; however, there is also a region in the left frontal area underlying the epidural hematoma with very low flow values. (c) After pressors are withdrawn and systolic blood pressure returns to the range of 160 mmHg, the study is repeated, showing return of CBF to non-ischemic values, particularly in the left frontal region

The flow values are represented graphically in a standardized color coded fashion for each pixel after the calculation is complete. In order to obtain useful regional values, the cortical mantle may be divided into 20 two cm deep regions of interest (ROIs), and the average for each ROI is displayed. Alternatively, any ROI can be selected on either the CT or the CBF image for mixed cortical sources. CBF in the range of  $54 \pm 10$  cc/100 g/min is normal, and values less than 15–20 cc/100 g/min represent ischemia and correlate closely with neurological deficit and infarction<sup>24–26</sup>. The study can then be repeated nearly immediately with an altered physiological parameter, as the half life of arterial xenon concentration is ~90 seconds with 99% of the agent being washed out of the body within 5 minutes (Figure 4–6). The xenon unit itself is small enough that it can be used effectively even at the bedside using a portable CT scanner<sup>27</sup>.

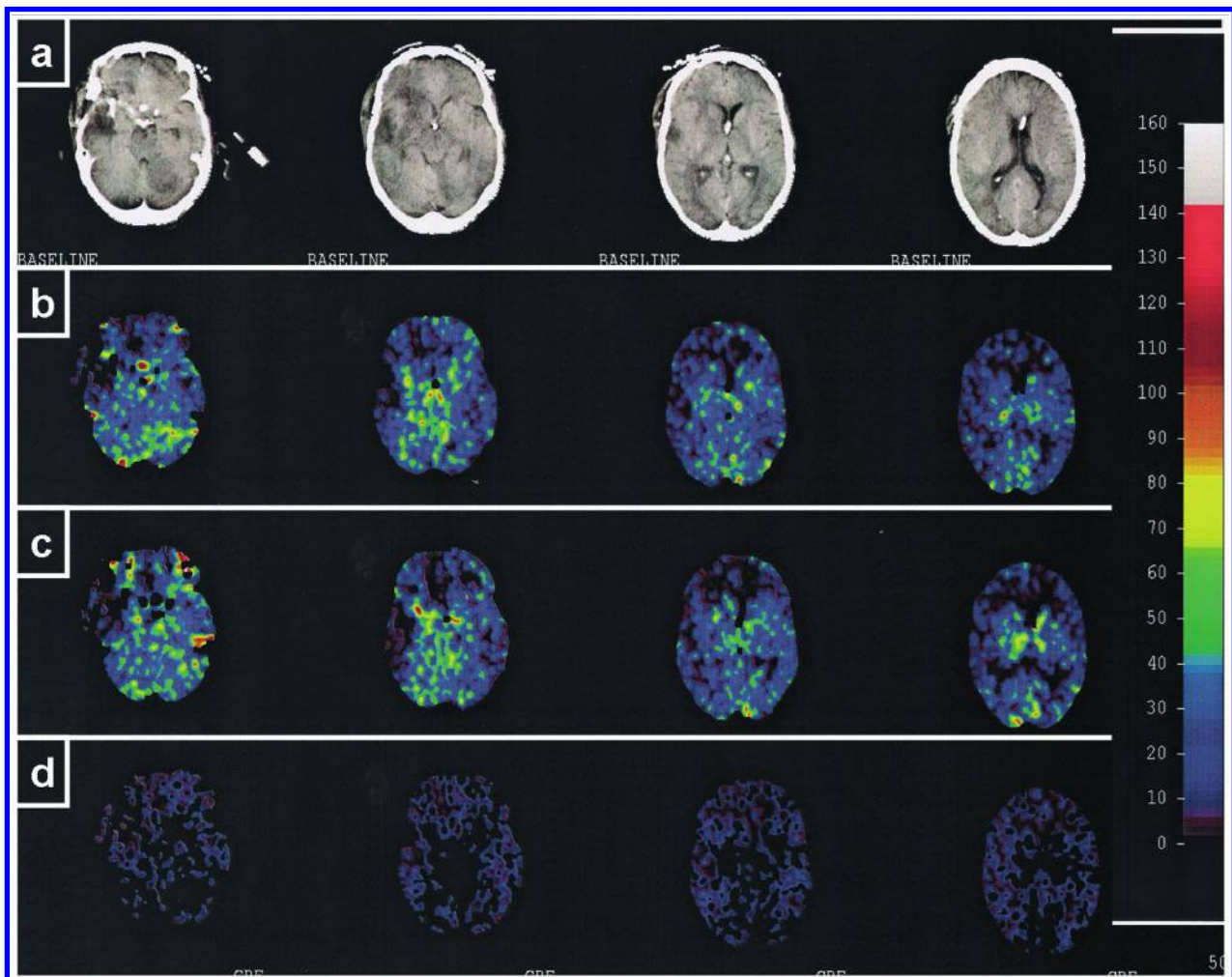
The utility of such a technique allows accurate measurement of ischemia in patients with DIND. Decreased CBF is correlated closely with neurological deficits in these patients, and it is found that the blood flow remains significantly lower than control groups even after the 21 day period of greatest risk for DIND<sup>26</sup>. CBF less than 15 cc/100 g/min was highly predictive of development of infarct, while CBF greater than 19 cc/100 g/min did not go on to infarction<sup>26</sup>. These values

are similar to the range for reversible ischemia and infarction reported with the use of xenon CT in myriad situations<sup>11</sup>. Thus xenon CT provides the ability to accurately predict tissue at risk for infarction and need for and response to clinical interventions.

Several large centers, particularly in Japan and at the University of Pittsburgh (where the technique has undergone significant development and validation over several decades), have used xenon CT to address common problems in the management of vasospasm. One landmark study evaluated the ability of TCD to predict ischemia. A common neurosurgical practice has been to follow daily TCD measurements for changes in velocity and plasticity which are presumed to reflect vasospasm. When these readings are compared with xenon CT measurements of ischemia, it was found that increased velocity correlates greater than 50% of the time with increased local CBF, not with ischemia, pointing out the insensitivity of TCD for distinguishing clinically relevant vasospasm from hyperemia or other blood flow changes<sup>28</sup>. The authors concluded that clinical decisions should not be made of TCD data alone. These results have been recently confirmed, showing that neither TCD velocity nor Lindegaard index is useful at detecting ischemia in sedated or comatose patients where clinical exam is not reliable<sup>29</sup>.



**Figure 5:** Xenon computed tomography (CT) data for one level of patient no. 1 demonstrating quantitative regional cerebral blood flow data. (a) Non-enhanced axial CT (once again, the epidural hematoma from ICP monitor placement is noted). (b) CBF map using pressors and induced hypertension. The blue and indigo values represent  $\text{CBF} < 20 \text{ cc}/100 \text{ g}/\text{min}$ . Averages are reported for each region of interest (ROI). Areas 1 and 2 can be seen to cover the area of the previous right anterior cerebral artery stroke and are therefore clearly ischemic. Areas 18, 19 and 20 (white arrows) show average CBF of 22.5, 15.3 and 24.8  $\text{cc}/100 \text{ g}/\text{min}$  averaged over the hundreds of pixels in each ROI. (c) These CBF values improve to 37.7, 44.2 and 48.3  $\text{cc}/100 \text{ g}/\text{min}$  respectively after stopping pressors, and allowing normotension (color coded scale is the same as in the previous figure)



**Figure 6:** Xenon computed tomography (CT) study of patient no. 2. The scale on the right of the image represents absolute values for cerebral blood flow in  $\text{cc}/100 \text{ g}/\text{min}$ . (a) Baseline non-enhanced axial CT. There are several hypodense lesions in the right temporal lobe, frontal lobe and left cerebellum. (b) Initial study with systolic blood pressure in the range of 140 mmHg and end tidal  $\text{CO}_2$  around 30 mmHg. (c)  $\text{CO}_2$  stable on this study with systolic blood pressure elevation to 190 mmHg using pressors. (d) Using thresholding, only the areas of CBF less than 20  $\text{cc}/100 \text{ g}/\text{min}$  are shown in blue and purple

As medical management for SAH and vasospasm has improved, morbidity from DIND has significantly lessened<sup>30,31</sup>. Xenon CBF technology has been used to evaluate when and to what degree medical therapy can be safely used. Lennihan *et al.*<sup>32</sup> showed (using xenon washout) that the widely used practice of hypervolemia is no more effective than aggressive normovolemia for preservation of CBF even when patients have DIND due to vasospasm. More recent xenon CT data suggest that augmentation of cardiac output is effective similarly to the commonly used hypertensive therapy, and confirms that elevation of volume status alone does not improve regional CBF<sup>10</sup>.

Various endovascular techniques have been developed for treatment of vasospasm. CBF measurements with xenon CT can delineate the small number of patients with angiographic vasospasm who are suffering from medically intractable ischemia. This allows for not only a more rational treatment of patients with these endovascular methods but also the ability to examine the efficacy of treatment. The use of intra-arterial papaverine has been shown to reverse angiographic vasospasm, though this only led to improvement in blood flow in 46% of patients<sup>24</sup>. Occasionally, the ischemia is even worsened<sup>33</sup>, leading to the possibility that though effective for large vessel vasospasm, papaverine may actually exacerbate the small vessel vasospasm not easily seen on angiography<sup>24</sup>. Xenon CT has also been used to evaluate the efficacy of balloon angioplasty for vasospasm. Murai *et al.*<sup>34</sup> showed return of normal CBF and vascular reactivity to acetazolamide of the angioplastied vessel after 3 weeks, indicating long term safety. Firlik *et al.*<sup>35</sup> showed that angioplasty is effective not only at improving CBF, but at returning CBF in ischemic territories to non-ischemic levels.

### Single photon emission computed tomography

Single photon emission computed tomography (SPECT) CBF techniques involve the use of various radio-isotopes which are taken up and retained in brain tissue in a flow dependent fashion<sup>36,37</sup>. The most commonly used isotope is technetium-99m coupled to hexa-methyl propyleneamine oxime (<sup>99m</sup>Tc-HMPAO.) The HMPAO is taken up into cells and converted into a hydrophilic form which it is retained for an extended period, allowing delayed imaging. Measuring the concentration of the isotope tracer using a collimator after intravenous injection allows conclusions to be drawn regarding the relative blood flow in various brain regions. The collimator data are formatted into slices and coupled to tomographic data for anatomic reference. The data are represented visually for interpretation or alternatively, ROIs can be constructed where flow is expressed as a percentage of a ROI where CBF is arbitrarily defined as 100% (often the cerebellum<sup>38</sup> or the contralateral hemisphere<sup>39</sup>). Repeated studies may be necessary to determine trends in the pattern<sup>40</sup>.

The difficulty of comparing blood flow in brain regions in a relative fashion is that an assumption is

made that the reference area has normal flow. This has been shown to be a poor assumption in many situations. Even in the situation of carotid occlusion (where it should be straightforward to compare blood flow in the affected to non-affected hemisphere), it has been found that relative values have a very poor correlation when compared to quantitative xenon CT data<sup>17,41</sup>. This situation is further complicated in the far more variable situation of vasospasm, where multiple vessels may be affected and even if large vessel spasm is not seen on angiography, small vessel spasm may alter flow to the presumed normal region. This is evidenced by studies which show only moderate correlation of SPECT changes with even clinical signs of DIND<sup>37,42,43</sup>. Lewis *et al.*<sup>38</sup> suggested that relatively decreased <sup>99m</sup>Tc-HMPAO uptake improved when the study was repeated after angioplasty if patients improved clinically.

An emerging SPECT technology may offer calculation of somewhat quantitative CBF values; however, there are inconsistencies with established data and prospective validation is still in progress. The use of N-isopropyl-p-[<sup>123</sup>I] iodoamphetamine (<sup>123</sup>I-IMP) by the autoradiographic method has yielded quantitative reproducible results<sup>44</sup>. The technique involves a timed injection of the tracer which as above, is taken into cells due to the hydrophilic conversion of the IMP in cells. By sampling the tracer radioactivity in arterial blood and the lipophilic fraction of IMP at 10 minutes, the arterial input function can be calibrated. This assumes that the arterial concentration curve is normal, and the curve must be inferred from a single arterial sample. In addition, lambda cannot be measured and so is assumed to be 1.0. The CBF is then calculated for each pixel after the SPECT scan is performed at a mid-scan time of 40 minutes from the injection. Although quantitative values are obtained, they are significantly lower than obtained by other modalities (mean CBF: 33 cc/100 g/min<sup>44</sup>). Despite the difference in absolute values, the measurements have been shown to correlate with PET data<sup>44</sup>. A number of factors may contribute to these differences including the assumptions regarding the normal arterial curve, the lack of ability to solve for lambda, and limited spatial resolution of the SPECT scanner. A fixed volume of distribution of the IMP is assumed which may or may not be accurate in pathological states, resulting in some over- and under-estimations of CBF<sup>44</sup>. Only small patient series have yet been published evaluating the predictive value, though preliminary data suggest that the threshold for irreversible ischemia may be around 20 cc/100 g/min and for reversible ischemia around 30 cc/100 g/min<sup>44,45</sup> (significantly higher than with the above quantitative methods). Despite the mathematical and technical limitations, emerging data suggest that the technique is sensitive for changes in CBF and may be predictive of infarction and clinical outcome in vasospasm<sup>44,45</sup>. One study using the technique found improved correlation with clinical outcome with the area of presumed marginal CBF (<30 cc/100 g/min) as measured by a three-dimensional reconstruction technique. This



technique may offer an additional semi-quantitative technique for assessing CBF and directing patient care if the above inconsistencies can be understood.

### CT perfusion

CT perfusion provides a powerful glimpse into several elements of cerebral vascular physiology; however, it has several important limitations, especially in the setting of vasospasm and interpretation of DIND. CT perfusion measures the increased attenuation after injection of an iodinated contrast bolus. This is an intravascular bolus and so an average of large vessel and capillary flow is measured, leading to higher CBF values than with diffusible tracers such as with PET or xenon (which measures capillary tissue flow only). In order to perform the mathematic functions (based once again on the Fick principle as described above), arterial and venous input functions are required, and typically a large anterior cerebral artery vessel and the superior sagittal sinus are analysed tomographically to determine iodine concentration. The contrast bolus must be injected quickly, or the slope for CBF may be artificially lowered. Some mathematical techniques use a 'leveling function' to avoid the problem of recirculation, which may cause an overestimation of CBF, especially in marginally ischemic tissue, where delayed flow via collateral pathways may be an important source of perfusion. For these reasons, it is frequently called a 'semi-quantitative' technique<sup>46</sup>. Many authors use a relative or even qualitative analysis of the results<sup>46</sup> of these studies, a problem when attempting to assess response to an intervention, and especially problematic in a potentially bilateral problem such as vasospasm. A specific concern in the clinical situation of vasospasm and DIND is the fact that the technique assumes intact blood-brain barrier. This is often not true in vasospasm, and the iodinated contrast agent may be taken up into the tissue, making CBF values in these critical locations suspect<sup>46,47</sup>. The three primary parameters measured are CBF, CBV and mean transit time (MTT). The MTT is probably the most useful because it is the least noise-sensitive parameter<sup>48</sup> and it is not degraded by contrast in larger vessels as with CBV and CBF<sup>46</sup>.

Despite these limitations, several studies have shown that this technique may have a role in overall decision making regarding DIND if interpreted within this context. Nabavi *et al.*<sup>48</sup> showed significantly lower CBF in patients with infarcts than those without, though commented on the lack of a clear-cut threshold for ischemia. Similarly, Sviri *et al.*<sup>47</sup> showed a high degree of concordance of CT perfusion values with clinical deterioration, suggesting that regional CBF less than 25 cm<sup>3</sup>/100 g/min and regional MTT greater than 6.5 seconds increases risk for ischemic deficit. They further contribute that normal CBF and MTT values may obviate the need for formal angiography in a patient with suspected DIND. The technique has also shown restoration of normal perfusion parameters after angioplasty<sup>49</sup>. These techniques should be understood and interpreted with understanding of these limitations

because the availability and relative simplicity of administration have made this technique increasingly popular for evaluation of DIND.

A final observation is that due to the contrast load which must be renally excreted, there are a limited number of exams that can be safely performed and more importantly, the test cannot be repeated at brief intervals to determine the efficacy of an intervention due to the interference of the previous contrast bolus. This makes CT perfusion less useful in answering specific questions regarding individual patient management.

### Magnetic resonance technologies

MRI is an attractive alternative in some respects for imaging in DIND; besides the ability to suggest the presence of vasospasm (as discussed above), there are several additional useful features of various MRI techniques. Diffusion-weighted and apparent diffusion coefficient (ADC) techniques are very sensitive sequences for infarction. It is thought that the technique measures cytotoxic edema due to proton pump failure, which is an irreversible process<sup>50</sup>. One series of patients with vasospasm evaluated by MRI, however, noted that loss of ADC signal was occasionally reversible without infarct<sup>50</sup>, though there is currently no quantitative threshold for reversible ischemia. In addition, there are several technical limitations of this technique. ADC is quite variable depending on the region considered due to tissue anisotropy. Analysis is often limited to comparison to 'normal' appearing tissue, yielding only relative values. Although it is possible that there may be a reversible level of loss of ADC signal, there are no studies showing any predictive value of diffusion or ADC for reversible ischemia.

Perfusion-weighted MRI, like CT perfusion, measures the time dependent concentration of a bolus of contrast to the tissue. Gadolinium is an intravascular contrast agent, like iodine, allowing only the measurement of contrast within the vasculature. In addition, as with CT perfusion, the technique is not able to assess tissue which may be perfused in a delayed fashion via collateral vessels. Similar parameters as CT perfusion are obtained. Areas of restricted perfusion may represent tissue at risk for infarction, but may or may not progress. The limitations are the same with this technique to CT perfusion as described above. Several studies have used perfusion MR in patients with vasospasm and DIND, but the limitations of the technique have not allowed for assessment that is predictive of ischemia or infarct or with which to guide patient care<sup>51,52</sup>.

A final MRI technique which has been used in evaluation of these patients is MR spectroscopy. This technique allows spectral measurement of lactate (a marker of tissue ischemia), N-acetyl aspartate (a neuronal marker) and other molecules in a given region of interest. The utility appears only to serve as a surrogate for ischemia and neuronal loss, and levels are predictably correlated with more severe infarct and worse clinical grade<sup>51</sup>. Regarding MRI techniques overall, though useful for documenting ischemia, MRI

has little utility in directing patient care in DIND due to inherent limitations of the technology. MR perfusion techniques share the same limitations as CT perfusion.

### MEASURING EFFICACY OF INTERVENTIONS: PATIENT DIRECTED CARE

Current care of SAH from aneurysm rupture has dramatically reduced early morbidity and mortality associated with vasospasm and DIND. Nonetheless, the treatments used are not without risk and in some cases, may harm the patient. Furthermore, the treatment of patients with the most severe forms of DIND is often frustrated not only by lack of understanding of the efficacy of interventions, but regarding the prognosis and when care is becoming futile. We assert that there is a strong role for radiographic assessment with quantitative CBF analysis in guiding clinical care for these patients. The following are two illustrative cases related to these points:

Case 1: this is a 45 years old female who presented with 7 day history of severe sudden onset headache, with a progressive deterioration of motor function. She was found to have a Fisher grade 2 SAH, primarily within the interhemispheric and right sylvian fissures from a ruptured bilobed anterior communicating artery aneurysm (*Figure 1*). Initial CT angiography revealed severe narrowing of bilateral ICAs, MCAs, and ACAs (*Figure 1*) with the right A1 being the primary blood supply to both A2s. The patient underwent endovascular coiling of the aneurysm.

Standard post-operative management including nimodipine and hypertensive therapy for the symptomatic vasospasm was initiated. In order to maintain hypertension, multiple vasopressor drugs were required, including levophed, dobutamine, and ultimately vasopressin. Serial CT scans showed developing right ACA territory infarct and her clinical exam continued to deteriorate with developing left hemiparesis and coma. This progressed despite increasing her blood pressure and cardiac output parameters to systolic blood pressures in the range of 160–200 mmHg. Two xenon CT studies (*Figure 4*) were performed on hospital day 8 (SAH, day 15.) The first study was performed with induced hypertension and the second after withdrawal of pressors with blood pressure returning to normotension. An area in the left frontal region was identified on the first study as ischemic, with CBF values less than 20 cc/100 g/min (*Figure 4b*). On the second study with withdrawal of vasopressors, the CBF in the left frontal lobe was no longer ischemic (*Figures 4c* and *5*). Vasopressor agents were thus stopped, and no further infarcts were noted. The patient clinically made a rapid and significant improvement to the point where she was awake and oriented, although she remained hemiparetic. She was subsequently discharged to a rehabilitation facility.

This case illustrates the point that despite the presumed efficacy of certain interventions, such as hypertensive therapy, for patients with DIND; some patients will have seemingly paradoxical reactions. We

postulate that the effect of induced hypertension in this patient constricted cerebral vasculature in the regions of disrupted blood–brain barrier, causing potentially reversible ischemia. The quantitative measurement of this ischemia with hypertensive therapy and the resolution with pressor withdrawal allowed medical management guided by patient specific information.

Case 2: this 58 years old female presented neurologically intact with 1 day history of sudden onset headache and vomiting and Fisher grade 4 SAH with focal clot in the region of the MCA bifurcation (*Figure 2a*). The CT angiogram revealed a right MCA aneurysm (*Figure 2b,c*) which was subsequently clipped. On post-operative day 5 (SAH, day 6), the patient became less responsive. A CT angiogram was performed, showing severe spasm, particularly of the posterior circulation (*Figure 3*). Hypertensive and hyperdynamic therapy were instituted more aggressively, but the clinical situation did not change. She eventually required re-intubation due to her decreasing arousability. The patient was then brought for angiography which showed near occlusion of both PCAs due to vasospasm (*Figure 3a,b*) and generalized vasospasm in the anterior circulation, particularly in the distal vasculature (*Figure 3c*). Angioplasty of the right ICA and MCA was performed, and verapamil was infused into the left vertebral artery and the right ICA. Areas of developing infarct began to be noted on serial CT scans. A xenon CT (*Figure 6*) was performed to determine the regions of brain that were at increased ischemic risk as well as the efficacy of therapy. The study showed multiple areas of ischemic flow which was unresponsive despite maximal blood pressure elevation. The study was then repeated the following day. Two studies were once again performed: the first was with end tidal CO<sub>2</sub> around 30 mmHg, and the second study was performed with hypoventilation for an end tidal CO<sub>2</sub> of around 40 mmHg in order to test the vasodilatory capability of the vasculature. Once again, no increase in CBF was noted. Aggressive supportive care was continued for several further days; however, widespread infarcts began to develop in the areas of decreased flow defined by the earlier xenon CT. These findings were discussed with the patient's family and the decision was made to withdraw care, after which the patient died within several days.

This case illustrates the problems often faced in severe vasospasm where patients are unresponsive to multiple treatment modalities. The xenon study helps to provide further information regarding the efficacy of ongoing aggressive treatment. The case also emphasizes a number of important points regarding monitoring for symptomatic vasospasm. First, the primarily affected vessels were in the posterior circulation rather than involving the vessel from which the ruptured aneurysm arose. TCD, which is most sensitive to velocity changes within the MCA, would have undoubtedly also failed to detect the problem. The data obtained with several xenon studies as well as clinical correlation provided more confidence in clinical decision making and family

discussions that the disease was so severe as to be unresponsive to maximal intervention.

## CONCLUSION

The word 'vasospasm' has been variably defined in the literature, forcing us to consider what the exact problem is that we are trying to define. It is clear from a clinical point of view that we are interested in the syndrome called delayed ischemic neurological deficit. This is the clinically relevant syndrome of vasospasm. Angiography remains the gold standard, though MRA and especially CTA may offer non-invasive alternatives for diagnosis of anatomic vascular narrowing. To assess the clinical and physiologically relevant syndrome, additional technologies must be used. Ischemia can be quantified as CBF is less than 8–20 cc/100 g/min. This can be measured using technologies such as xenon CT and PET. Other CBF technologies must be assessed with caution to avoid the inaccuracy inherent in semi-quantitative or relative values. Xenon CT may be used practically to direct patient care both in predicting tissue ischemia and in measuring efficacy of interventions. This ability potentially opens a new era of treatment of vasospasm where our treatment may be guided by the physiology of an individual patient.

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