Aneurysmal subarachnoid hemorrhage (A-SAH) has potentially devastating consequences acutely, sub-acutely and long term. The incidence of A-SAH varies widely among populations with up to a tenfold difference. Incidence ranges from 2.0 per 100,000 per year in China to 22.5 per 100,000 per year in Finland.1 One of the most feared complications in patients who survive the acute A-SAH is cerebral vasospasm (CV). The peak incidence of CV is between 5 and 14 days after A-SAH. Cerebral vasospasm may occur angiographically in up to two-thirds of A-SAH patients, however this is only symptomatic in about one-third of them. Delayed neurologic defects or delayed cerebral ischemia (DCI) occurs in approximately half of patients with angiographic CV.2,3 Early diagnosis and treatment of CV can reduce morbidity and mortality.4 Therefore, it is important to diagnose and thereafter treat CV as early as possible in order to avoid permanent neurologic deficit.

The pathogenesis of CV is a poorly understood, although it can be thought of as an abnormal and prolonged contraction of vascular smooth muscle due to the presence of subarachnoid blood. Breakdown products of blood in the subarachnoid space appear to be involved in the development of CV after SAH. In a canine model, a relationship between the volume of blood in the subarachnoid space and the severity of CV was demonstrated.5 In humans, the amount of blood on computed tomogram (CT) in patients with SAH has been shown to correlate with the severity of CV.6

There is some evidence that oxyhemoglobin may be the primary blood product causing CV. Oxyhemoglobin has been shown to be present in high concentrations in cerebrospinal fluid during CV and has been shown to be the most vasoactive substance within blood.7 There is also some evidence that free radicals play a role in the pathogenesis of CV, in that antioxidants have shown some ability to improve vasospasm.2

DEFINITIONS

There is considerable inconsistency and overlap in terminology surrounding cerebral vasospasm and delayed cerebral ischemia. Some authors use the term CV to refer to the clinical finding of delayed onset neurologic deficit after A-SAH and some use the term purely to refer to radiographic evidence
of vessel narrowing. Relatively recently, a multidisciplinary expert panel recommended that future clinical trials and observational studies use a uniform definition of these terms to make future comparison among studies easier. The term DCI should refer to two main outcomes: [1] new neurologic deficit that was not present immediately after aneurysm occlusion and cannot be attributed to other causes, and [2] cerebral infarction on computed tomogram (CT) or magnetic resonance imaging (MR) that was not present immediately after aneurysm occlusion and not attributable to other causes. They recommend that the use of the words “vasospasm” or “arterial narrowing” be restricted to descriptions of a radiological test.8

The terms CV and DCI are related. Delayed cerebral ischemia is often the consequence of CV and CV is often the cause of DCI. The goal is to diagnose CV early enough and accurately enough to initiate appropriate therapy and avoid progression to DCI.

Modals for Assessment of Vasospasm

Digital subtraction angiography (DSA) is considered the gold standard method for the assessment of CV. Other methods that have been used in the evaluation of CV include transcranial Doppler ultrasound, CT angiography (CTA), CT perfusion (CTP) and MRI. The following sections will review the use of CTA and CTP in the diagnosis of vasospasm and/or DCI.

CT Angiography in the Diagnosis of Vasospasm

Computed tomogram angiography is a non-invasive technique which, compared to DSA, requires considerably less manpower and is much more readily available. As with DSA, CTA is able to directly visualize arterial narrowing related to cerebral vasospasm. There have been several studies published assessing the diagnostic potential of CTA for CV after A-SAH. The data is summarized in the Table. Figures 1a and 1b demonstrate the CTA findings of CV.

A study by Anderson et al compared CTA with DSA and found high sensitivity and specificity for CTA in the detection of CV. This was particularly evident in cases where there was no CV, with sensitivity of 92% and specificity of 80%, as well as in cases of severe CV, with sensitivity of 100% and specificity of 100%.9 Goldsher et al specifically looked at the use of CTA in diagnosing CV involving the vertebrobasilar system and showed that CTA was also accurate in this situation.10 Wintemark et al also compared CTA with DSA and found a slightly lower sensitivity for CTA detection of CV of 75.6%, but maintained a high specificity of 95.3%.11 Yoon et al found a very high sensitivity and specificity of 97.5 and 98.1% respectively when comparing CTA with DSA.12 Binaghi et al had similar results comparing CTA with DSA finding sensitivity and specificity of 87.7% and 99.2% respectively.13 Chaudhary et al prospectively compared CTA with DSA and demonstrated sensitivity of 63% and specificity of 90% for CV.14

Several of the above-mentioned studies were included in the meta-analysis by Greenberg et al that estimated 79.6% sensitivity and 93.1% specificity for the diagnosis of CV using CTA. They were able to perform a sub-analysis on several of the papers that included data on proximal and distal segments. Proximal segments were considered to be the internal carotid artery (ICA), the A1 segment of the anterior cerebral artery, the M1 segment of the middle cerebral artery, the anterior communicating artery, the vertebral artery, the basilar artery, the P1 segment of the posterior cerebral artery, and the posterior communicating artery. The pooled estimates for proximal vasospasm found an 81.7% sensitivity and 93.7% specificity.

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Table: Summary of CTA and CTP studies which investigated the diagnosis of CV or DCI

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Authors</th>
<th>N patients</th>
<th>Diagnosis</th>
<th>Gold Standard</th>
<th>CT Scanner</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA</td>
<td>Anderson et al.</td>
<td>17</td>
<td>CV</td>
<td>DSA</td>
<td>Not reported</td>
<td>57 - 100</td>
<td>80 - 100</td>
</tr>
<tr>
<td>CTA</td>
<td>Goldsher et al.</td>
<td>36</td>
<td>CV</td>
<td>Transcranial Doppler</td>
<td>Phillips MX 8000 (16 slice)</td>
<td>Not reported</td>
<td>Not Reported</td>
</tr>
<tr>
<td>CTA</td>
<td>Wintermark et al.</td>
<td>27</td>
<td>CV</td>
<td>DSA</td>
<td>8 or 16 slice</td>
<td>75.6</td>
<td>95.3</td>
</tr>
<tr>
<td>CTA</td>
<td>Yoon et al.</td>
<td>17</td>
<td>CV</td>
<td>DSA</td>
<td>Phillips MX 8000 (16 slice)</td>
<td>97.5</td>
<td>98.1</td>
</tr>
<tr>
<td>CTA</td>
<td>Binaghi et al.</td>
<td>22</td>
<td>CV</td>
<td>DSA</td>
<td>16 slice</td>
<td>87.7</td>
<td>99.2</td>
</tr>
<tr>
<td>CTA</td>
<td>Chaudhary et al.</td>
<td>33</td>
<td>CV</td>
<td>DSA</td>
<td>16 slice</td>
<td>63</td>
<td>90</td>
</tr>
<tr>
<td>CTA</td>
<td>Shankar et al.</td>
<td>34</td>
<td>CV</td>
<td>DSA</td>
<td>Toshiba Aquilion 64 (64 slice)</td>
<td>82 - 92</td>
<td>50 - 90</td>
</tr>
<tr>
<td>CTA</td>
<td>Dankbaar et al.</td>
<td>39</td>
<td>DCI</td>
<td>Clinical (DCI)</td>
<td>Philips Mx8000 LDT (64 slice)</td>
<td>64</td>
<td>50</td>
</tr>
<tr>
<td>CTP</td>
<td>Binaghi et al.</td>
<td>23</td>
<td>CV</td>
<td>DSA</td>
<td>16 slice</td>
<td>20 - 90</td>
<td>100</td>
</tr>
<tr>
<td>CTP</td>
<td>Dankbaar et al.</td>
<td>39</td>
<td>DCI</td>
<td>Clinical (DCI)</td>
<td>Philips Mx8000 LDT (64 slice)</td>
<td>84</td>
<td>79</td>
</tr>
<tr>
<td>CTP</td>
<td>Mofidkhar et al.</td>
<td>14</td>
<td>CV</td>
<td>DSA</td>
<td>GE 8 or 16 slice</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>CTP</td>
<td>Killeen et al.</td>
<td>57</td>
<td>DCI</td>
<td>Clinical (DCI)</td>
<td>GE Lightspeed or Pro-16 (16 Slice)</td>
<td>80</td>
<td>67</td>
</tr>
</tbody>
</table>
The pooled estimates for distal vasospasm were not statistically different with 85.5% sensitivity and 92.3% specificity. Yoon et al also specifically evaluated proximal and distal CV and found no statistically significant difference in sensitivity of specificity between proximal or distal CV. A more recent study by Shankar et al once again demonstrated high sensitivity and specificity using the CTA to diagnose CV. The sensitivity and specificity were found to be slightly lower in the assessment of peripheral CV versus central CV. The sensitivity and specificity for central CV was 91 - 92% and 73 - 90% respectively. This dropped to 82 - 90% sensitivity and 50 - 69% specificity in the assessment of peripheral vasospasm.

The majority of the literature suggests that CTA has a high sensitivity and specificity in the diagnosis of CV. There is some evidence that CTA may be less accurate in the assessment of peripheral vessels compared with central vessels.

Dankbaar et al specifically looked at the diagnosis of DCI with different CT modalities and showed that CTA had sensitivity and specificity of 64% and 50% respectively. This study was not a comparison with DSA as a gold standard, but used the clinical diagnosis of DCI as the gold standard. This data does not contradict the higher sensitivities and specificities previously reported, it just reaffirms that not all CV will result in DCI.

CT Perfusion in Vasospasm

Computed tomogram perfusion is often used in the assessment of embolic stroke. It involves CT imaging repeatedly obtained through a region of the brain during the administration of a small bolus of intravenous contrast. After administration of intravenous contrast, there is a transient increase in the attenuation of the brain parenchyma. This is proportional to the amount of contrast material within the brain parenchyma and this data can be plotted versus time for arterial, venous and parenchymal regions of interest. Post-processing can provide several different parameters with this data. The most commonly acquired data are cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and time to peak (TTP). The CT perfusion does not directly visualize areas of arterial narrowing as CTA and DSA do, but instead detects areas of altered perfusion, which will often be due to CV in A-SAH patients. Figures 1c and 1d demonstrate abnormal TTP and CBF related to CV.

There have been several studies assessing the use of CTP in the evaluation of CV and/or DCI after A-SAH. Although CTP does not directly visualize cerebral arteries, several studies have compared CTP with DSA to determine if perfusion abnormalities are accurate in the diagnosis of CV. This data is summarized in the Table. Several groups have evaluated CTP for the diagnosis of DCI at the time of clinical worsening and some have evaluated the use of CTP to predict which patients are at increased risk of progressing to DCI, even if they do not have clinical worsening at the time of the CTP study.

A study by Moftakhar et al compared CTP with DSA and found a 91% concordance rate in predicting the presence or absence of CV. Binaghi et al also compared CTP with DSA to diagnose CV and showed a high sensitivity and specificity of 90% and 100% respectively for severe vasospasm, but only 20% sensitivity and 100% specificity for mild - moderate vasospasm. A meta-analysis by Greenberg et al that compared CTP with DSA showed 74.1% sensitivity and 93% specificity for CTP in diagnosing CV.

Dankbaar et al assessed CTP for the diagnosis of DCI and showed an 84% sensitivity and 79% specificity. A study by Killeen et al compared CTP with DSA in diagnosing DCI. They found similar characteristics for the two tests with sensitivity and specificity of 80% and 67% respectively for CTP compared with 73% and 75% respectively for DSA. They also found a
significant difference in CBF values between DCI and non-DCI patients with 29.4 mL/100g/min for the DCI group and 40.5 mL/100g/min for the non-DCI group. Another study by Dankbaar et al examined threshold values for CTP in diagnosing DCI and found a significant difference in CBF, MTT and perfusion asymmetry between patients with DCI and those without. An MTT threshold of 5.9 seconds optimized sensitivity and specificity, however this cutoff time will vary with each CT scanner and CTP protocol. Lefournier et al were not able to determine a threshold value for MTT that could predict patients with vasospasm. Sanelli et al evaluated quantitative CTP for the diagnosis of DCI and were able to determine a threshold level of 35 mL/100g/min for CBF had a sensitivity of 90% and specificity of 68% while a threshold of 5.5 seconds for MTT had a sensitivity of 73% and specificity of 79%. They also performed a subanalysis for the diagnosis of CV on the patients who underwent DSA. They found similar thresholds of 36.5 mL/100g/min for CBF had a sensitivity of 95% and specificity of 70%. and 5.4 seconds for MTT had a sensitivity of 78% and specificity of 70%. Wintemberg et al compared CTP with DSA in an attempt to determine threshold values for CBF, CBV and MTT for the diagnosis of CV. They showed high sensitivity of 95.1% using an MTT threshold value of greater than 6.4 seconds.

In terms of predicting which patients will proceed to DCI, van der Schaaf et al performed CTP in patients within 72 hours of aneurysm hemorrhage and assessed the CBF ratio (a ratio of CBF values from the same region in each hemisphere) as a predictor for the development of DCI. They showed that CBF ratio in the acute phase was an independent predictor for the development of DCI. Pham et al assessed the predictive value of CTP for later acquiring a secondary cerebral infarction and found that visual assessment of TTP maps were most sensitive at 93%, but only demonstrated 67% specificity. Dankbaar et al showed that patients that are going to progress to DCI already have abnormal CBF and MTT values before any focal clinical worsening. Sanelli et al performed CTP early after A-SAH and found that CBF reduction and MTT prolongation demonstrated high specificity for later development of CV. The standard to determine if CV developed was a multi-stage process with DSA at the primary level. A CBF threshold value of 24-25 mL/100g/min showed 91% specificity for patients going on to have CV. Sanelli et al were also able to determine that CTP had a sensitivity of 78% and specificity of 66% for patients who would develop permanent neurologic deficits and sensitivity of 88% and specificity of 59% for patients who would later develop an infarct. Their quantitative analysis showed that a CBF of 30.5 mL/100g/min and an MTT of 5.0 seconds were optimal threshold values.

There are case reports in patients with CV that demonstrate improvement or resolution of CTP abnormalities after intervention, indicating CTP may be an accurate way to assess intervention success. Majoie et al report a case of using CTP before and after intraarterial intervention with abnormal CBV and MTT prior to intervention which then normalized on the post procedure CTP study. A similar result was reported by Shankar et al.

The literature generally suggests that perfusion abnormalities on CTP are accurate in the diagnosis of CV when compared with DSA. It also performs well in the diagnosis of DCI. There is also evidence that CTP abnormalities present before clinical worsening signify an increased risk of progressing to DCI.

CTA and CTP in Treatment Decisions

Due to the fact that not all radiographically evident vasospasm will result in clinical deterioration and/or development of an infarct, the decision whether or not to treat vasospasm is often a difficult one. The fact that many of these patients will be in an ICU setting and sedated makes evaluation of clinical symptoms difficult and makes treatment decisions even more difficult. Several of the studies in the preceding sections specifically evaluated CTA and/or CTP with respect to treatment decisions. Wintemberg et al performed a sub-analysis on patients who required treatment for CV and showed that CTA only had a sensitivity of 53.3% for patients requiring treatment, but maintained a high specificity of 96.3%. They also did the same with CTP data and showed that an abnormal MTT with cutoff of greater than 7.6 seconds had a sensitivity of 70.0% and specificity of 87.5% and that an abnormal CBF with cutoff of less than 39.3 ml/100g/min had a sensitivity of 61.7% and very high specificity of 98.2%. Shankar et al compared a treatment recommendation based on CTA findings with actual treatment received and found good agreement for patients who would receive endovascular treatment, but not for patients who would only receive medical treatment (triple H therapy). Binaghi et al found that the addition of CTP data “strongly influenced” the decision to treat in 9/27 patients when CTP was added to CTA.

There is not a large amount of published data with respect to...
using results from CTA or CTP in terms of how it affects treatment. There is some evidence that CTP may provide more information than CTA alone in terms of guiding treatment decisions. CTP with abnormal MTT and CBF values has higher sensitivity for patients who require endovascular treatment compared with CTA and is still able to maintain a high specificity. It is likely that patients with abnormal CTA and CTP would require endovascular treatment, but it is not clear whether patients with abnormal CTA, but normal CTP also require endovascular treatment. Figure 2 demonstrates evidence of CV on CTA without evidence of CTP abnormality in a patient who recovered without endovascular treatment and had no stroke on follow-up MRI (Figure 3).

The CTP parameters are dependent on various hemodynamic parameters and hence are dynamic. It is important to have a protocol for regular monitoring of these changes. Outside the ICU setting, this monitoring is usually done using frequent clinical examinations. For patients in ICU, where clinical examination is extremely limited, these imaging tools play a significant role in management decisions. Future studies are required to come up with an acceptable guideline for perhaps a combination of both CTA and CTP in these patients.

Limitations of CTA and CTP

A limitation of CTA and CTP is radiation exposure. However, compared with DSA, the radiation dose from CTA and CTP is generally lower. A recent study by Manninen et al showed that the effective radiation dose of CTA in the assessment of cerebral vessels was approximately 20% that of DSA.30 In terms of CTP, there are multiple factors that can be altered to attempt to minimize the radiation exposure, including tube voltage,31 tube current,32 scan duration,33 pitch and sampling interval.34 Another limitation of CTA and CTP is the placement of an IV catheter and the administration of iodinated contrast material. There are multiple studies that have shown that injection of contrast media for CTA and CTP in acute stroke setting does not cause renal failure (REF). However in cases of CV, where multiple CTP/CTA studies may be required in any given patient, the effect is yet to be reported. In terms of CTP, there is also limitation with respect to quantitative analysis. CBF, CBV, MTT and TTP values will vary between based on equipment and technique, therefore quantitative threshold values are not immediately transferable between different institutions.

Until recently, CT scanners were unable to provide whole brain coverage with CTP protocols. The majority of the published literature using CTP in CV has been done using older 16 or 64 slice CT scanners, which only provide a thin slab of brain coverage. With modern CT scanners, this is no longer the case, and some scanners are able to provide whole brain coverage using a CTP protocol.29

CONCLUSIONS

Cerebral vasospasm is an important and potentially devastating complication after A-SAH. The ultimate goal is the early diagnosis of patients that will progress to DCI in order to enact treatment and halt the progression.

The gold standard for the diagnosis of CV is considered to be DSA, however the non-invasive technique of CTA and functional technique of CTP demonstrate significantly high sensitivity and specificity both for the diagnosis of CV and prediction of progression to DCI. Functional information on CTP is more promising for guiding the treatment decision. Due to significant radiation dose, there is no consensus on what should be the proper monitoring protocol for CV using CTA and CTP.

REFERENCES


