A number of techniques have been developed during the past four decades to evaluate cerebral perfusion. The oldest used $^{133}$Xe, a lipophilic radioactive tracer that easily diffuses through the blood-brain barrier (BBB). It was either injected or inhaled, and probes placed over the scalp were used to measure perfusion to the cerebral cortex. In the mid-1970s, the development of a scanner to detect the emission of positrons led to positron emission tomography (PET) in humans. Using a number of radioisotopes, this technology can measure cerebral blood flow (CBF) and various metabolic processes, but until recently it has been primarily used as a research tool. Stable (“cold”) xenon was found to attenuate x-rays in a manner similar to iodine, and there were a number of projects in the 1970s to use this gas as a contrast agent for the rapidly emerging technology of computed tomography (CT), particularly as a perfusion tracer. This resulted in the development of the xenon-enhanced CT (XeCT) technique to calculate CBF in patients. With improvements in single photon emission CT (SPECT) during the 1980s, a number of compounds that are metabolized in the central nervous system (CNS) were found to be appropriate for perfusion imaging. Perfusion-weighted and diffusion-weighted magnetic resonance (MR) imaging (PWI and DWI) were developed in the late 1980s and that technology has continued to improve. Finally, with the evolution of helical and spiral multislice CT technology, CT perfusion (CTP) imaging is becoming a potentially important clinical technique.

Although the development of these technologies has been fascinating, their role in evaluating a variety of diseases of the CNS is controversial. It might seem obvious that a disorder of blood flow, such as acute stroke or chronic vascular occlusive disease, should be studied with a perfusion imaging technique. The accuracy, reproducibility, and reliability of the data from these techniques have been evaluated in animal models and in general have been found to be of very high quality. Their roles in predicting patient outcome and their use in planning treatment have received varying levels of scientific scrutiny. One of the purposes of this report is to assess the quality of such studies to determine the grade of recommendation that can be made for their use today and to guide the direction of future research. The rules of evidence for evaluating the quality and reliability of diagnostic tests such as perfusion imaging must obviously differ from those used to evaluate clinical studies. A committee of the American Academy of Neurology developed a scheme of evidence classification for diagnostic testing to evaluate reports of techniques that test the vestibular system. However, imaging studies differ from other types of diagnostic tests in important ways, because the data must often be interpreted by subjective rather than purely objective criteria. In addition, adequate clinical history is often necessary for an appropriate interpretation to be made. One way to assess the accuracy of an imaging study such as perfusion imaging is to gauge its ability to predict outcome, with or without subsequent treatment. This outcome may not be actual patient outcome but may be an outcome related to the tissue in question, such as the development of infarction. Another method of evaluation, possibly of even more importance, is an assessment of the ability of the information derived from the imaging test to influence the selection of subsequent medical management. For perfusion imaging, the ideal impartial assessment of the...
Quality of Evidence Ratings for Perfusion Imaging

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Evidence provided by a prospective study in a broad spectrum of subjects with the suspected condition, using a “gold standard” for case definition. The interpreters of the test and those providing treatment decisions and assessing outcome are each blinded to any data from the other, enabling assessment of the diagnostic accuracy of the test.</td>
</tr>
<tr>
<td>Class II</td>
<td>Evidence provided by a prospective study in a narrow spectrum of subjects with the suspected condition, or a well-designed retrospective study of a broad spectrum of subjects with an established condition (using a “gold standard”) compared with a broad spectrum of control subjects. The interpreters of the test and those providing treatment decisions and assessing outcome are each blinded to any data from the other, enabling assessment of the diagnostic accuracy of the test.</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence supplied by a retrospective study in which either the subjects with an established condition or the controls are of a narrow spectrum. The interpreters of the test and those providing treatment decisions and assessing outcome are each blinded to any data from the other, enabling assessment of the diagnostic accuracy of the test.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Any study design in which the interpretation of the test is not blinded relative to any treatment decision or outcome assessment, the treatment decision or outcome assessment is not blinded to the test interpretation, the evidence is provided by “expert opinion” alone, or there is only a descriptive series without controls.</td>
</tr>
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</table>

Strength of recommendation:

| Grade A           | Established as a useful/predictive or not useful/predictive test for the given condition in the specified population. Requires at least one class I study or two class II studies. |
| Grade B           | Probably useful/predictive or not useful/predictive test for the given condition in the specified population. Requires at least one class II study or three class III studies. |
| Grade C           | Possibly useful/predictive or not useful/predictive test for the given condition in the specified population. Requires at least two class III studies. |
| Grade D           | Data are inadequate or conflicting. Given current knowledge, the test is unproven. |

This report is intended to summarize what is known about the clinically available perfusion technologies, specifically XeCT, CTP, SPECT, and PWI (and the associated DWI), in their role of evaluating acute and chronic cerebral ischemic conditions. Major goals are to indicate the strengths and weaknesses of each technique, make recommendations as to the use of each, and indicate the need for future research. PET scanning is excluded because it is primarily a research tool in academic institutions. Traumatic head injury is included because of its close relationship to ischemic injury, but the use of perfusion imaging in other diseases, such as neoplasms and inflammatory conditions, has not been evaluated. This review should give impetus to the improvement and perfection of these techniques, the direct comparison of their ability to provide significant information, and the formation of studies to prove that perfusion imaging has a role in improving patient outcomes.

Roles of Perfusion Imaging

Acute Stroke

Therapy for acute stroke depends on ensuring the diagnosis and excluding diseases that mimic cerebral ischemia, such as hypoglycemia, hyponatremia, a seizure, or a mass lesion such as a tumor or subdural hematoma. The exclusion of a hemorrhagic rather than ischemic stroke can be determined rapidly and accurately with CT or MR imaging. The differentiation of a transient ischemic attack (TIA) from ischemia potentially producing infarction often can be made clinically, with the former lasting only a matter of minutes. It is more difficult to clinically differentiate those neurological deficits due to ischemia that are likely to improve or reverse spontaneously from those that are likely to persist or worsen, and this is a significant value of perfusion imaging.12–17 The demonstration of a normal level of CBF suggests that reperfusion has occurred spontaneously and that no acute vascular thrombosis or flow augmentation is necessary.18–20 The level of perfusion to the ischemic tissues may help to determine the relative benefits and risks of a given therapy. Neurological dysfunction occurs in a tissue after CBF falls below approximately 18 to 20 mL/100 g of tissue per minute. Given this dysfunction, it is impossible to determine by clinical examination alone the level of the persisting perfusion. CBF of less than 10 mL/100 g of tissue per minute cannot be tolerated beyond a few minutes before infarction occurs, but between 10 and 20 mL/100 g · min⁻¹, cell death requires many minutes to hours.21–30 Theoretically, tissues with flow values in this intermediate zone might be salvaged if flow restoration occurred quickly, either spontaneously by clot fragmentation and dissolution31,32 or by therapeutic means such as arterial thrombolysis. While some tissues might be dead at the core of the ischemic process, the more peripheral tissues (the “penumbra”) might still be salvageable.33–42 However, recanalization of arteries serving tissues that are severely ischemic or infarcted may increase the risk of edema and hemorrhage, which can produce enough mass effect that herniation and death ensue.42,43–47 Hence, the potential benefits of recanalization of arteries supplying injured but viable tissue must be weighed against the potentially increased morbidity and mortality.
The risks of recanalization might be based on the relative volume of dead versus injured but viable tissue and the degree of that injury. Unfortunately, a precise relationship of CBF level to the time available for tissue salvage has not been determined, and so the benefit of quantification of CBF in acute stroke has not been proven.48 In a given case, this “therapeutic window” depends to a large degree on the amount of collateral circulation beyond the primary occlusion providing enough perfusion to keep the tissue viable.22.41 However, because the neurological examination cannot fully differentiate the status of the tissue, some type of rapid and accurate technique may help to distinguish potentially reversible from irreversible ischemia, which, in turn, may aid in the decision to undertake risky but potentially life-saving therapies.22.36.44.49–51

Other benefits of perfusion imaging in acute stroke are the determination of the volume of tissue at risk and the vascular distribution of the ischemia.14,16,17,52–60 Anatomic imaging provided by CT and MR demonstrates the changes in tissue density or intensity based on the presence of cytotoxic and vasogenic edema after the onset of ischemia.61 However, these tissue changes require hours to fully develop, and hence it is difficult or impossible to adequately determine the volume of tissue at risk on the initial CT or MR. This volume has a substantial effect on the morbidity and mortality of therapy using thrombolytic drugs.37,43,44 The specific vascular distribution of ischemia cannot always be determined with accuracy from the clinical presentation alone. In addition, the prognosis and outcome of ischemia in one vascular distribution differ from those of another. Unfortunately, the large multi-center trials of tissue plasminogen activator (tPA) did not include any vascular imaging to accurately determine whether arterial obstruction persisted or define the site of that arterial obstruction prior to thrombolysis, so that the relative risks of the therapy and the outcome of the disease could not be stratified on the basis of the site and extent of the vascular occlusive disease.62.63

Chronic Ischemia
Stenoses and occlusions may lead to intermittent neurological symptoms, either because of hypoperfusion secondary to inadequate collateral circulation or because of emboli from the affected arteries. Cerebral angiography demonstrates a potential embolic source and the presence of the collateral circulation but cannot reliably determine whether that collateral is “adequate.” Perfusion imaging permits a rapid differentiation of these conditions so that a decision can be made to eliminate an embolic source or augment a low-flow condition. A rough comparison of the perfusion to part or all of a hemisphere relative to other parts or to the opposite hemisphere can be obtained at angiography by comparing the time of appearance of the capillary phase.64 Improvements in this “poor man’s blood flow study” are provided by the dedicated perfusion imaging methodologies discussed in this report.

The concepts of tissue demand, “autoregulation,” and “vascular reserves” must be understood to appreciate the complexities in the interpretation of perfusion images, particularly in patients who have chronic cerebrovascular disease with previous infarction. A patient may present with an old vascular occlusion and new symptoms of transient neurological deficit. Progressive occlusive disease increases the risk of major stroke in the distribution of the marginal perfusion. However, if the previous ischemic process has led to tissue injury, the demand for blood flow to the territory in question may be diminished, and a single measurement of CBF will be misleading.65–69 Conversely, CBF may normalize in a region distal to the occlusive disease because of both collateral flow and dilatation of regional arteries to increase blood volume (autoregulation), both of which contribute to the vascular reserves.68–73 However, maximally dilated arteries are unable to increase their capacity from a stress such as hypotension or decreased cardiac output, and acute stroke may occur. A single perfusion study at rest is insufficient to evaluate the tissue need and ability of the vascular reserves to respond to that need, particularly during an additional stress.72,73 Therefore, “challenge tests” to determine the ability of the vascular bed to respond to a stress must be an integral part of any perfusion imaging methodology that seeks to evaluate chronic cerebral ischemia.68–70,72–75 Perfusion imaging with a challenge test may help to identify those patients with chronic ischemia who are at high risk for future stroke.69

These challenge tests include the intravenous injection of 1 g of the vasodilating agent acetazolamide (Diamox).70,72–75 This produces an increase in CBF of 50% to 100% within 20 to 30 minutes. The lack of such flow augmentation indicates a loss of autoregulation and inadequate vascular reserves.68 Other types of challenge tests include the measurement of CBF at 2 levels of blood pressure or at 2 tissue pH levels; the latter can be achieved by altering the ventilation rate of the intubated patient.76–78

Perfusion imaging with a challenge test may be able to select those patients who would benefit from an extracranial-to-intracranial (EC-IC) bypass to augment CBF. A new national trial using the oxygen extraction fraction (OEF) as measured with PET scanning will attempt to define the patient population with occlusive vascular disease at risk for stroke and the potential of an EC-IC bypass to decrease that risk.79–81 Other types of perfusion imaging with challenge tests may act as surrogate techniques for the more elaborate and expensive PET-OEF technique; the Xe/CT method with an acetazolamide challenge has already demonstrated its ability to detect such patients.70 Perfusion imaging might be used to determine when a patient with moyamoya disease or syndrome should undergo a procedure to augment flow.82,83 Conceivably, such tests could be used to select those patients for carotid endarterectomy or angioplasty and stenting who have multiple vascular stenoses and occlusions but who do not now qualify for such procedures by demonstrating focal neurological symptoms and a 70% or greater stenosis. However, this will take large, well-planned studies utilizing control groups to compare natural history data with postprocedural outcomes.

Ischemia From Vasospasm
Subarachnoid hemorrhage (SAH) leads to vasospasm, which is a major determinant of morbidity and mortality in those patients who survive the initial event. Vasospasm produces ischemia and infarction in the territory distal to the involved
vessels because of low flow. Perfusion imaging helps to establish the diagnosis of ischemia and differentiate it from other complications that produce neurological deficits, such as recurrent hemorrhage or metabolic disorders. The initial treatment of vasospasm is by medical means, including systemic hypertension, hemodilution, and hypervolemia (“triple-H therapy”). If not successful, endovascular methods may be employed, including intracranial angioplasty and the infusion of vasodilators. It appears that outcomes are improved if these treatments are instituted as early as possible. Perfusion imaging may aid in this early diagnosis and therapeutic intervention.18,68,90

**Prevention of Stroke Following Therapeutic Carotid Occlusion**

Approximately 10% of patients cannot tolerate carotid occlusion because of inadequate collateral circulation to the affected hemisphere. There is another large group of patients who will have a low-flow state after vascular sacrifice, leading to ischemia and possibly infarction unless adequate blood pressure is maintained to permit perfusion through collateral channels. By identifying those patients at risk preoperatively, decisions can be made to augment cerebral perfusion before vascular sacrifice using a bypass graft or to avoid the vascular occlusion.88

Temporary occlusion of the vessel to be sacrificed with an inflatable balloon for a number of minutes, during which neurological examinations are performed (the balloon occlusion test [BOT]), is the traditional method to identify the at-risk patient. However, the lack of neurological symptoms during temporary arterial occlusion only means that CBF to the cerebral tissue distal to the occluded vessel is >20 mL · 100 g−1 · min−1. An assessment of the actual CBF to the tissues may help to determine the relative risk of vascular occlusion, especially if postoperative hypotension or decreased cardiac output were to occur. Performing a CBF test during carotid occlusion, assuming the BOT with neurological examination has not produced symptoms of ischemia, can provide objective data.88 The CBF in the distribution of the temporarily occluded vessel is compared with that of the “normal” contralateral hemisphere.99 Although a ratio of flows can be calculated, the degree of asymmetry that indicates the need for preoperative flow augmentation is a matter of continuing research.18,68,90

**Aid in Patient Management Following Head Trauma**

Management of significant head trauma frequently involves hyperventilation to decrease the small intracranial volume required for the blood volume (approximately 4%) to an attempt to provide more space for the swelling brain. However, when autoregulation of the arterial supply to the injured tissue is lost, hyperventilation leads to vasoconstriction of the normal vessels and potential ischemia of normal brain, with a paradoxical increased flow in those arteries feeding the injured tissues, followed by increased swelling.91,92 Hence, perfusion imaging may provide information on appropriate ventilation management.76,92,93 In addition, significant loss of this chemoregulation is indicative of irreversible tissue injury.76–78 Therefore, perfusion imaging with tests of vascular and tissue response provides important information on potential patient outcome.

**Determination of Brain Death**

A surrogate of clinical brain death determination is the demonstration of inadequate cerebral perfusion to maintain tissue viability. Perfusion imaging may be of aid in cases in which the clinical determination cannot be made; eg, when an accurate clinical examination is hampered by the presence of hypnotics or sedatives.94,95

**Perfusion Technologies**

There are 2 major classes of perfusion techniques: those that utilize a diffusible tracer and those that rely on a nondiffusible agent. The physiological principles underlying these 2 classes of techniques and the mathematical models used to attempt quantification of their data are different.

A diffusible tracer technique relies on the ability of a lipophilic molecule to rapidly pass the BBB and pass into the cerebral parenchyma. The measurement of CBF is a determination of both the amount of agent in the feeding arteries and the uptake of that agent by the tissues. Quantification of CBF requires knowledge of the arterial (arterial input function [AIF]) and tissue concentrations of the agent, or the partition coefficient between these spaces at equilibrium.

The nondiffusible tracer technique uses an agent that remains within the vasculature. The central volume principle states that CBF is the ratio of the blood volume within all blood vessels in a given volume of tissue (cerebral blood volume [CBV]) to the mean transit time (MTT, in seconds) of the agent from the arterial input to the venous drainage within the volume being evaluated (CBF=CBV:MTT).96–98 After intravenous contrast injection, a time-density curve is constructed that indicates the change in CT density or MR intensity of the imaged tissues as the agent passes through the vasculature, and the area under that curve is the CBV.99–101 Calculation of MTT and CBF requires knowledge of the agent concentration in the feeding arteries (AIF) and draining veins related to the volume of tissue. Using mathematical models—“deconvolution” techniques—the MTT and CBF can be approximated. These models assume an intact BBB, so that the agent stays in the vasculature.102–107

**Diffusible Tracer Techniques**

**Xenon-Enhanced CT**

**Rationale of Technique**

Xenon is a small, biologically inert molecule that is soluble in both lipid and water and is freely diffusible. These attributes make it an ideal tracer for evaluation of cerebral perfusion, because the gas dissolves in blood after inhalation and freely crosses the lipid-rich BBB. A measure of its tissue concentration reflects both arterial input to and uptake by the target tissue. The radioactive form ($^{133}$Xe) has been used for cerebral perfusion evaluation for over 40 years.1 Because x-ray attenuation by xenon is similar to that by iodine, it can be used as a contrast agent for a sensitive x-ray-based technology such as CT.4 Therefore, the nonradioactive form is used
as an inhaled diffusible tracer during CT scanning to measure tissue perfusion in patients.\(^5\)

**Method of Performance**

The technique requires the inhalation of a mixture of stable xenon gas and oxygen. With improvements in CT scanner technology, including both speed and contrast resolution, the amount of xenon required for an adequate contrast-to-noise ratio has decreased, which also decreases the neurological effects of the gas. Currently, a mixture of 28% xenon and 72% oxygen is most commonly used, with inhalation over a period of 4.33 minutes. Following the acquisition of a non-enhanced baseline scan of the entire head, 6 contiguous 10-mm-thick levels are selected for study. Each level is scanned 6 times during the inhalation period, requiring exact table relocation. As the xenon accumulates in the cerebral tissues, the patient experiences a sedative effect, which is relatively mild given the percentage of xenon used today. After gas inhalation ceases, a few minutes are required for the gas to be washed out of the cerebral tissues and the patient to return to baseline attentiveness. This test is easily performed in an outpatient setting.\(^{108}\)

**Quantification, Accuracy, and Reproducibility**

The CT scanner measures the x-ray attenuation coefficient (Hounsfield units) of every voxel during each acquisition period. By subtracting the baseline values from those acquired during xenon inhalation, a build-up curve of tracer accumulation over time is calculated for each voxel. The AIF is estimated by measuring the xenon concentration during expiration. The Kety-Schmidt equation for perfusion is solved in an iterative manner for each of the 24,000 voxels in each CT slice, yielding both CBF in mL · 100 g tissue \(^{-1}\) · min \(^{-1}\) and the partition coefficient, lambda, between blood and tissue.\(^{109}\) The integration of the partition coefficient to the flow data adds another parameter to ensure accuracy, even in disease states. Superimposition of the numerical data on the anatomic image yields a high-resolution (Full Width Half Maximum [FWHM] <4 mm) map of quantitative flow data that is tightly coupled to cerebral anatomy.\(^{109}\) With the addition of a gray or color scale, the data are converted to a map for visual inspection (Figure 1), on which regions of interest (ROIs) can be drawn for regional quantitative assessment. A confidence map is also produced to demonstrate the effects of any patient motion and other artifacts on the data. The data processing requires approximately 10 minutes before the flow maps are available for inspection and analysis.

There is a high degree of correlation between CBF values acquired with the XeCT technique and \(^{131}\)Xe,\(^{110}\) iodoantipyrine,\(^{111}\) and microsphere embolization\(^{112-114}\) in prospective, comparative studies using animal models in tightly controlled laboratory experiments. Although the stability of the flow value in a single voxel of 10 mm\(^3\) is poor, the reliability of the data from an ROI of >100 voxels is approximately 12%.\(^{115}\) This reliability in spite of the pharmacological property of xenon to directly increase CBF by 20% to 30% is explained by the fact that nearly all of the important flow data are acquired prior to this flow activation, which does not become significant until after 2.5 minutes of inhalation.\(^{116}\) The use of a flow phantom not only allows each scanner to be calibrated between studies, but its universal use by all sites performing XeCT examinations permits standardization of the data between scanners of different manufacturers and the potential integration and comparison of the data for multi-institutional studies.

**Significant Issues in Study Performance**

Head motion is the major problem, because each voxel in a slice that is studied must remain in its location throughout the 4 minutes of scanning. Head stabilization with inflatable restraints is necessary. The sedative effect, particularly in a neurologically impaired patient, can lead to increased motion.
Lowering the xenon concentration to 28% has lessened the incidence of significant patient agitation and sedation to <5%. Interpretable studies have been obtained in 87% of nonintubated acute stroke victims in whom the xenon/oxygen mixture was delivered with a tightly fitting face mask, although 30% did require intravenous sedation (class IV). In more impaired patients, intubation is required, which yields diagnostic studies in 100% of patients.102 Adverse reactions to a 32% concentration of xenon have been reported in <0.1% of cases117 (class II).

Diversity of Data and Ability to Perform Challenge Tests

Acute Stroke

It has been demonstrated in numerous studies using both animal and human subjects, and both normal controls and subjects with ischemia, that CBF values attained with this technique are accurate, especially in the flow ranges that distinguish low but nonischemic territories from reversibly and irreversibly ischemic areas (Figure 1).110,114,118,119 (class I). In acute ischemia, flow values above 20 mL · 100 g⁻¹ · min⁻¹ have been consistent with sustained viability and reversible neurological deficits without the immediate need for vascular recanalization or augmentation.18–20 CBF in the range of 10 to 20 mL · 100 g⁻¹ · min⁻¹ has been consistent with the onset of neurological deficits that have been reversible using aggressive revascularization techniques, or with infarction if there is no revascularization, depending on the duration of the ischemia.19,20,33–37 Flow values below 10 mL · 100 g⁻¹ · min⁻¹ within a major vascular territory have correlated with the volume of eventual infarction,35–37 and global flow values near zero have been utilized for the diagnosis of brain death.94,95 Of particular note are the multiple retrospective studies that have demonstrated an increased risk of hemorrhage, edema formation, and herniation due to massive edema with CBF values below 15 and especially below 10 mL · 100 g⁻¹ · min⁻¹, in spite of or due to reperfusion.43,44 These clinical studies with a data quality of class II–III, because of their retrospective nature, demonstrate the value of highly accurate quantification of CBF within a narrow range.

Chronic Ischemia

In chronic vascular occlusive disease, the XeCT technique yields quantitative CBF data but does not measure directly any metabolic functions, such as oxygen and glucose utilization, which are important to understand both the arterial supply of oxygen and nutrients, and the demand of the tissues for them. However, because of the coupling of blood flow and metabolism in chronic ischemia, measuring the ability to maintain or augment vascular reserves allows an assessment of the underlying tissue metabolism and the risk of subsequent infarction.68,69 Performance of 2 XeCT studies with different blood pressures following pharmacologic manipulation has defined an important subset of patients who develop a paradoxical lowering of flow to blood pressure elevation, an indication of the loss of autoregulation.120,121 The Pco₂ levels can be manipulated by changing the ventilation rate in an intubated patient,76–78 or by injecting acetazolamide intravenously. The resulting vasodilatation produces an increased CBF of 50% to 100% in normal tissues.73 The lack of flow augmentation is indicative of maximal vasodilatation and a lack of vascular reserves.69,73 A paradoxical decrease of regional CBF has proven to be diagnostic of a subgroup at high risk for future infarction69 (class I). No prospective study has been undertaken to determine whether that risk can be minimized by a flow augmentation procedure, such as an EC-IC bypass.

Vasospasm

The XeCT method has been used to determine which patients developing neurological deficits after SAH are suffering from vasospasm-induced slow flow and cerebral ischemia and to differentiate this condition from other causes of deterioration33,34,84 (class IV). If vasospasm is present, medical therapy can be instituted initially, and, if this fails, intracranial angioplasty and/or the infusion of a vasodilator can be performed with a higher risk of vascular and neurological injury. XeCT can establish the presence of ischemia,33,34,84 and both medical and endovascular techniques can be used to increase CBF, as demonstrated on subsequent XeCT studies33,34 (class IV). However, it has not been proven that such treatments improve patient outcome.

Head Injury

The XeCT technique can be used in the intubated head injury patient to determine the appropriate rate of assisted ventilation that seeks to balance the need to lower intracranial vascular volume while maintaining adequate blood flow.91–93 The loss of normal chemoregulation (a 3% lowering of CBF in response to a 1-mm Hg lowering of Pco₂ during a double XeCT study) is a significant indicator of irreversible cerebral injury, and the level and pattern of CBF reduction in the injured tissues have been prognostic of poor outcome81–83 (class II).

Balloon Occlusion Test

CBF maps can be made before and after temporary occlusion of a carotid or vertebral artery with an inflatable balloon during a XeCT test if no neurological deficit has occurred during prolonged balloon inflation under fluoroscopic control.88 Such flow studies provide assessment of the potential for collateral circulation, and of the potential risk of arterial sacrifice, possibly much better than just the neurological examination90 (class IV).

Marker of Seizure Focus

XeCT CBF has also been used to demonstrate a region of increased flow as a marker for the site of seizure activity in patients with chronic epilepsy122,123 (class IV).

Availability of the System, Cost, and Reimbursement

There are only 30 systems in the United States at this time, and 40 in Europe, but there are more than 700 in Japan. Although there has been a hiatus in the supply of medical-grade xenon in the US, the agent is currently available under an Investigational New Drug (IND) authorization until the Food and Drug Administration reviews a new NDA application for safety and efficacy.

The hardware and software cost approximately $150 000. Reimbursement in the United States is currently for a CT scan with and without contrast enhancement, and a charge for...
computer manipulation of the data might be added. The consistency of this reimbursement in each state is unknown.

Advantages and Disadvantages Relative to Other Techniques

The advantages are the following:

1. The technique is based on CT, which is a ubiquitous technology.
2. CBF analysis can be added to other CT studies, such as nonenhanced CT and CT angiography (CTA), in the same imaging session.
3. This is a quantitative technique, with CBF given in absolute values.
4. The hardware and software are relatively inexpensive in relation to other types of imaging equipment.
5. The examinations are standardized for a given CT system and between different systems.
6. Challenge tests can be performed to study cerebrovascular physiology.
7. The literature describes numerous studies ranging from class I to IV in quality that used the technique in both animals and humans for diversity of diseases.

The disadvantages are the following:

1. Patient motion can produce artifacts, making interpretation difficult and inaccurate.
2. It directly measures only one parameter, CBF (with the exception of the partition coefficient). Other vascular and tissue parameters must be evaluated by performing challenge tests to derive surrogate endpoints.
3. There is no ability to evaluate cell viability or function-ality, such as with diffusion-weighted MR; these parameters are assumed, given the level of CBF and the duration of the insult. Concurrent changes in CT images do provide the ability to integrate CBF data with CT-defined evidence of infarction.

Recommendations

1. With increased availability of stable xenon gas, it is imperative that more centers evaluate the utility of this technology in numerous clinical conditions.
2. Quantitative data, especially absolute values of perfusion, may be helpful as an aid in determining the risks and benefits of revascularization of the acute stroke patient, including post-thrombolysis hemorrhage, and XeCT can be used to acquire such information (grade A).
3. Prospective controlled outcome studies of acute stroke patients treated with revascularization after XeCT studies, with blinding of their CBF values, must be undertaken in order to prove the predictability of the quantitative data.
4. Prospective outcome studies following the recanalization of acute stroke patients, with and without XeCT perfusion imaging and blinded to specific CBF levels if acquired, must be undertaken to evaluate the relative benefits of earlier treatment versus the time-consuming acquisition of physiological data that may predict outcome and risk.
5. XeCT perfusion imaging with an acetazolamide challenge test can be used to define a group of patients with chronic ischemia who are at significant risk for infarction (grade A). Larger prospective studies are necessary, along with prospective comparative studies, to determine whether a flow augmentation bypass can reduce the risk predicted by XeCT.
6. CBF levels obtained with XeCT, combined with studies of autoregulation and the responses to physiological challenges, can probably be used to accurately predict outcome following head trauma (grade B). Larger prospective and comparative studies should be undertaken to prove the validity of this utilization.

Single Photon Emission CT

Rationale of Technique

A radioisotope such as technitium-99m (99mTc) is attached to a delivery compound that passes through the BBB after intravenous injection and is metabolized by neuronal and glial cells. Hence, this radioactive compound “sticks” during first passage, with uptake proportional to CBF at the moment of passage, rather than the progressive tissue uptake that is characteristic of the xenon methods. Imaging can be performed anytime within a few hours after injection.

Method of Performance

The radioisotope, 99mTc, must be attached to the delivery compound, hexamethylpropyleneamine oxime (HMPAO) or ethyl cysteinate dimer (ECD), before injection. Combining 99mTc and HMPAO can be done in-house, using a commercially available kit, and requires approximately 20 to 30 minutes.

Once the compound is injected, circulation to and localization within the cerebral tissues occurs within 1 minute. Scanning of the head can be performed within the next few hours, preferably using a system that provides maximum spatial resolution, such as a 2-headed or, even better, a 3-headed SPECT imaging system. Data acquisition starts 5 to 10 minutes after injection and is acquired in a 64×64 or 128×128 matrix through a 360-degree rotation that requires approximately 5 minutes to complete. Reconstruction is by standard filtered back-projection techniques using a 2D Butterworth filter.

Quantification, Accuracy, and Reproducibility

Absolute quantification of the flow kinetics requires knowing the AIF, but this requires an indwelling arterial line. However, an alternative method that obviates the need for arterial blood sampling uses graphical analysis of the time-activity curves between the aortic arch and the brain. Usually a semiquantitative approach is taken by comparing the counts in a given ROI with those in a comparable ROI (grade B).

For example, in a case of acute embolus to a middle cerebral artery (MCA), the relative perfusion in the frontotemporal region distal to the embolus can be determined by drawing an elliptical ROI in the ROL measuring the counts in that region, moving the ROI to a control area and determining those counts, then dividing the former number by the latter to obtain the ratio (relative cerebral blood flow [rCBF]). Of course, this assumes that the CBF to the unaffected hemisphere is normal, which is frequently not the case. This assumption is obviously fallacious for patients with chronic
cerebrovascular disease, which is usually multifocal, or with vasospasm. Even in acute stroke, there are complicated alterations of CBF in distant territories, even in the presumably unaffected hemisphere, which will produce errors when such ratios are calculated.\textsuperscript{133,134}

The accuracy and reliability of SPECT CBF determination are indicated by comparisons to other techniques. There is a linear relationship between rCBF measured by ECD-SPECT and that measured with PWI, which has a linear relationship with absolute CBF measured with PET. The volume of hypoperfusion detected by HMPAO-SPECT has been shown to correlate significantly with that demonstrated by PWI\textsuperscript{130,135,136} (class II).

This is a relatively low-resolution method for imaging cerebral perfusion (Figure 2), without the inherently high spatial resolution of CT or MR. However, the counts in a given region are very high, so that a large amount of data are provided rapidly, obviating the effects of minor head motion.

**Significant Issues in Study Performance**

Preparation of the compound is rapid and can be done while the patient is undergoing a CT scan to exclude hemorrhage. The only problem may be the availability of the kit to make the compound. The ratio of the counts of uptake to background is so high that data acquisition is rapid, head motion is not an issue, and sedation is not necessary. The semiquantitative method is extremely simple; ratios of counts in the ROIs, indicative of relative blood flow, are determined with a calculator, and no special software is required.

**Availability of the System, Cost, and Reimbursement**

Essentially all radiology departments in hospitals of 250 beds or more in the United States have 2- and 3-headed SPECT imaging systems that are used for a variety of procedures. No special software is needed for CBF analysis. There is no problem with reimbursement, which is sufficient to cover the cost of the procedure, including multiplanar reformations.

**Diversity of the Data and Ability to Perform Challenge Tests**

**Acute Stroke**

*No treatment:* Numerous reports demonstrate the ability of HMPAO-\textsuperscript{99m}Tc SPECT imaging to detect hypoperfusion after the onset of acute stroke symptoms.\textsuperscript{31,38,45,54–59,135–144} Two prospective, blinded, controlled trials demonstrated a sensitivity of the technique to abnormal perfusion in acute stroke ranging from 61\% to 74\%, with a specificity of 88\% to 98\%.\textsuperscript{140} (class I). Of course, focal or regional ischemia of gray matter supplied by the larger pial vessels with more rapid flow was much more apparent than decreased flow to white matter supplied by the smaller perforating vessels at a slower rate. Findings on these studies have been shown to correlate with the severity of neurological deficit, infarct size, and clinical outcome in untreated patients without evidence of spontaneous recanalization\textsuperscript{54–59,135,136,143,144} (class I-III). Early severe hypoperfusion within 6 hours after onset of symptoms was highly predictive (up to 92\%) of poor neurological outcome.\textsuperscript{54–58,145} (class I). SPECT imaging is better than the neurological deficit score at predicting short-term outcome if performed within 72 hours of symptom onset; if performed later, the improved flow after spontaneous recanalization gives false-negative information.\textsuperscript{54} The size of the infarct predicted by SPECT has been shown to correlate significantly with that measured by CT.\textsuperscript{59} The threshold of rCBF on SPECT imaging between infarction and sustained viability over time without thrombolyis has been shown to be 0.52.\textsuperscript{136} Improvement in the perfusion abnormality due to spontaneous recanalization has been shown to correlate with improved clinical outcome\textsuperscript{31,32} (class II).

*With thrombolytic treatment:* Based on 42 lesions in 30 patients, Ueda et al\textsuperscript{22} reported that the rCBF threshold for reversibility of the ischemic process with intra-arterial thrombolysis was 0.55, and the threshold for hemorrhage following this thrombolytic treatment was 0.35 (Figure 2).\textsuperscript{22} These imaging parameters predicted the treatment outcome, which was not influenced by the duration of the ischemic process, the location of the vascular occlusion, the sex of the patient, or the dosage of thrombolytic drug (class I). Relative CBF on SPECT imaging has also been shown to correlate with response to intravenous tPA therapy and clinical outcome.\textsuperscript{38,143} These studies provide strong evidence for the role of collateral circulation in maintaining viability until treatment can be performed. Like the studies using the XeCT technique, they demonstrate the value of determining the degree of perfusion to the ischemic tissue in making treatment decisions rather than simply using the time between symptom onset and potential treatment. Demonstrating the degree of tissue viability may allow a prediction of the response to treatment, no matter the time from symptom onset. Again as in the XeCT studies, the degree of pretreatment perfusion predicts the potential for hemorrhage after thrombolytic treatment, thereby aiding in the decision to undertake the risk of chemical recanalization\textsuperscript{2,38,45,143} (class I).

Not only does SPECT perfusion imaging help to determine the relative risks and benefits of treatment, these studies demonstrate the value of data that are semiquantitative, in contradistinction to the more quantitative approach that is...
provided by the XeCT method. Whether such semiquantification is sufficient to make difficult clinical decisions, or a more quantitative approach is necessary is a significant focus of clinical research in perfusion imaging.

**Chronic Ischemia**

SPECT imaging has been used to evaluate rCBF in patients with symptoms of chronic cerebral ischemia. As previously discussed, a single measurement of rCBF may be misleading. Determining the ratio of CBF in the symptomatic region relative to a control area may also be misleading, because the latter values are considered to be normal, which may not be correct. In addition, such a test does not provide data regarding tissue demand, autoregulation, and vascular reserves. Therefore, the need for a challenge test to provide data points under different physiological conditions is apparent.

SPECT imaging before and after the administration of acetazolamide has been used to demonstrate impaired vascular reserves and maximum vasodilation in a territory referable to the presenting symptoms. This challenge test requires the performance of 2 procedures separated by 1 or more days and assumes that CBF does not change substantially between tests. The ratio of CBF values before and after acetazolamide is obtained in the ROI and also between the area in question and that in the control area. A lack of significant change in CBF after acetazolamide within tissues having low flows on the pre-acetazolamide test is indicative of a low-flow state with maximum vasodilation. Tissue demand is present, autoregulatory mechanisms have been exhausted, and there are no vascular reserves (class III and IV data). However, such ratios assume a normal state in the comparative tissues. Validation of this qualitative methodology relative to more quantitative techniques is currently lacking. The precise ratios of rCBF that suggest an increased risk for future stroke and the potential need for surgical flow augmentation have not been determined.

**Vasospasm**

Regional hypoperfusion on SPECT due to vasospasm after SAH correlates with the presence and severity of delayed neurological deficits. SPECT can provide the early evidence of vasospasm-induced hypoperfusion and may help to differentiate this hypoperfusion from other causes of neurological deterioration, such as edema, hydrocephalus, elevated intracranial pressure, and metabolic etiologies. SPECT combined with transcranial Doppler may prove to be sensitive enough for the early detection of vasospasm and delayed ischemic deficits to obviate other more invasive techniques (class IV).

**Potential Ischemia Following Carotid Artery Sacrifice**

During temporary carotid occlusion with a balloon, HMPAO is injected intravenously in order for the distribution of CBF at the time of occlusion to be documented. After the balloon has been deflated, the patient can be scanned within the succeeding few hours, and the images will demonstrate the CBF at the time of occlusion. Ratios of the counts in an ROI of the cerebral hemisphere supplied by the temporarily occluded ICA relative to an ROI in a control area can be calculated, similar to the method for the acute stroke patient. However, the threshold of lowered CBF that indicates the collateral circulation is inadequate to prevent cerebral ischemia after permanent ICA occlusion has not been determined (class IV).

**Evaluation After Head Trauma**

SPECT scanning is used following head trauma, especially in patients with persistent neurobehavioral abnormalities after mild degrees of trauma when the CT and MR studies are normal. Areas of hypoperfusion may be seen in patients who have abnormal neuropsychological tests (class IV). However, the pathophysiology of these abnormalities and their role in predicting patient outcome and patient management remain elusive.

**Advantages and Disadvantages Relative to Other Techniques**

The advantages are the following:

1. The SPECT imaging is easy to perform, requiring only an intravenous injection.
2. Most large radiology departments have adequate hardware and software.
3. The software provides 3 orthogonal views of CBF in color.
4. Semiquantitative measurements can be obtained rapidly, requiring only a calculator.

The disadvantages are the following:

1. Acquisition of the kit to make the injected compound may be difficult on short notice.
2. The data are nonanatomic, so that correlation must be made with either a CT or MR scan acquired at another time. Coregistration with a CT or MR scan can be performed, overlaying the SPECT data on the anatomical substrate, but this is a tedious, time-consuming procedure.
3. The technique has low spatial resolution compared with CT and MR scans.
4. Because the arterial concentration of the isotope is usually not known, only semiquantitative analysis can be made, such as the comparison of counts in analogous ROIs.
5. There is no standard with which to compare the counts in a given ROI. Comparison to the uptake in another region assumes that the CBF in the comparison ROI is normal.
6. Comparison of studies performed on different days assumes that CBF does not change. Comparison of studies in different patients and between institutions requires many assumptions and may be misleading.
7. The ability to perform challenge tests is limited because the baseline examination and the study during the challenge usually must be performed on different days, and stable CBF must be assumed. Hence, the acquisition of accurate data that may act as surrogates for cerebral metabolism or physiology is very difficult.

**Recommendations**

1. SPECT CBF studies can be used to determine the relative risks of hemorrhage following thrombolysis of
acute stroke patients, whatever the time after onset of symptoms (grade A).
2. Because both the quantitative (XeCT) and semiquantitative (SPECT) methods provide class I data regarding the risks of hemorrhage following thrombolysis, and both may be helpful in identifying patients at greater risk of hemorrhage after thrombolysis, comparative studies must be undertaken to determine the relative merits of the 2 methodologies. Studies should also be performed to determine the value of the time expenditure in obtaining such data.
3. Because the SPECT data obtained with challenge tests cannot be controlled, the reliability of this technique to evaluate patients with chronic ischemia is unproven (grade D). These techniques should be compared with more stable, quantitative methodologies to determine their role in such assessment.
4. The SPECT CBF technique is unproven (class IV data) in determining the presence of clinically significant vasospasm and for predicting infarction following carotid artery sacrifice (grade D). These techniques should be compared with more rigorous, quantitative methodologies.
5. The value of SPECT CBF in head-injured patients is unproven (grade D).

**Nondiffusible Tracer Techniques**

**CT Perfusion**

**Rationale of Technique**

The Central Volume Principle relates CBV, MTT, and CBF.96–98 CT can measure the integrated change in tissue density following the intravascular injection of a contrast agent to calculate CBV.147 MTT and CBF are time-related values and require rapid imaging of a limited volume of imaged slices to determine the density change over time, arterial input and venous outflow values, and the use of mathematical models that assume that the contrast stays within the vasculature.102–107 Although the concept of perfusion CT is not new,148 the ability to measure these perfusion parameters with accuracy has been made possible with the development of high-speed helical/spiral CT scanners having solid-state detectors and a gantry design to contain the very high gravitational forces generated by high-speed rotation of the x-ray tube.169 Software development has been a crucial part of this development, allowing rapid electronic transfer of data from the detector arrays and rapid image reconstruction for perfusion analysis.39,85,100,149–164

**Methods of Performance**

There are 2 methods of CTP, which differ in the amount of brain that can be imaged, the rate and volume of contrast injected, the type of data that are acquired, and the degree of quantification that is possible.

**Slow-Infusion/Whole-Brain Technique**

**Technique:** First, a nonenhanced CT of the head is obtained. Then, a typical intravenous iodinated contrast infusion protocol is 3 mL/s of a nonionic agent over 40 seconds, for a total of 120 mL. A delay of 25 seconds permits a peak of contrast enhancement of the entire brain and vasculature to be achieved before the start of scanning. The CT table movement and scanner rotation speed are adjusted so that scan thickness is 1 to 1.25 mm from vertex to skull base. Image reconstruction yields 3- to 5-mm-thick images of the entire brain parenchyma for the determination of relative CBV, and 1- to 1.25-mm-thick images for the simultaneous reconstruction of a CTA of the vessels at the skull base.39,53,101,154

**Relative quantification:** Pixel-by-pixel subtraction of the unenhanced from the enhanced scans is performed to yield maps of contrast concentrations only, minus the underlying brain density. Normalization of brain values with density measurements in a large vein such as the superior sagittal sinus yields relative “perfused CBV” maps.166 MTT and CBF cannot be determined with this method because there are no timed data and no AIF. Low-density changes on the nonenhanced CT are assumed to represent infarction, and changes on the CBV map are correlated with these parenchymal abnormalities to differentiate reversible from nonreversible ischemia. In addition, it may be possible to generate maps of the risks of infarction using CBV values only.165

**Utilization, accuracy, and reproducibility:** Recent papers suggest that the combination of CTA and the relatively simple CTP CBV maps is a fast and effective way of evaluating the acute stroke patient. The CTA can demonstrate a clot in a large vessel that might respond better to IA than IV thrombolysis. The combination of the nonenhanced CT showing the parenchymal changes that have already occurred, the CBV map showing the tissue at risk, and the location and length of the vascular obstruction is used to make the determination to undertake thrombolysis39,53,100,101,161 (class III and IV data). However, the actual level of ischemia and a better distinction between reversible and nonreversible ischemia may not be possible without the use of a more rigorous, time-dependent quantitative method.166 In addition, evaluation of physiological parameters such as vascular reserves in a patient with chronic ischemia is probably not possible with this limited technique.

**First-Pass Bolus-Tracking Methodology**

**Technique:** The requirement for multiple data points from a given volume of tissue and the limited ability of current scanners to move quickly back and forth from one slice to the next mean that at this time, only a limited amount of the brain can be imaged during a CTP study, usually 2 sections up to 10 mm in thickness each, covering 2 to 3 cm of the brain. This requires the physician to determine the most likely location of the ischemic process, either on the basis of the initial nonenhanced CT scan or on clinical grounds. Usually one of the slices passes through the basal ganglia, so that portions of the middle, anterior, and posterior cerebral distributions are evaluated.40,100,167–170 The advent of multislice scanners has permitted the acquisition of 2 contiguous 10-mm slices, 0.5- to 0.8-mm slices, or even 0.25-mm slices, but no significant increase in the overall volume of scanned tissue. Although it is possible to move (“toggle”) the scanner between 2 more separated locations during the scanning protocol,135 fewer data points are acquired at each location, leading to signal-to-noise limitations and lower-quality, less-accurate perfusion maps.

An indwelling catheter of at least 18-gauge is inserted into the brachial or cephalic vein, preferably on the right. A precontrast scan provides the baseline of attenuation values that will be subtracted, voxel by voxel, from the enhanced scan. An injection of a contrast agent is performed, usually a non-ionic agent to minimize any sensations that might result in movement. From 3 to 10 mL/s, for a total of 40 to 80 mL, has been reported. A 40-mL injection delivered at 5 mL/s will yield a “bolus width” in the brain of 16 to 20 seconds. An
Obviously, this type of analysis does not address the slice can be quickly constructed from the time-density data.

The complexity of the deconvolution method. Maps of the relative complexity of the deconvolution method. Relative CBV, rCBF, and rMTT. The color scale can be used to determine relative flow values, which can be compared with those of the contralateral hemisphere.

An analysis of the "time to peak" does not require the complexity of the deconvolution method. Maps of the relative speed of the contrast agent reaching each voxel of the single slice can be quickly constructed from the time-density data. Obviously, this type of analysis does not address the volume of blood that reaches the destination, whether by direct or collateral channels, just the relative speed. A vascular distribution far from the ICA, fed primarily by collateral channels, would have a significantly delayed time-to-peak value yet might be adequately perfused. The role of this method in triaging patients with acute ischemia for treatment is under investigation.

A recent article suggests that truly quantitative CBV and CBF values can be obtained with CTP and that they may differentiate reversible from non-reversible ischemia. The underlying concept is that as CBF falls, CBV is initially unchanged or increases slightly, reflecting vasodilation, as part of the autoregulatory process. As CBF continues to fall to levels of irreversible ischemia, CBV drops, too. The authors used a CBV level of <2.5 mL/100 g to define infarcted tissue and CBF <34% of the analogous tissues in the opposite hemisphere to define the combined reversible and irreversible ischemic tissues (infarct plus penumbra). Some of the patients underwent thrombolysis with salvage of tissue. There was a highly significant correlation between the defined values and the outcome of the at-risk tissues on subsequent CT and diffusion-weighted MR studies. The authors’ use of "prognostic maps," with the very low CBV map analogous to the MR DWI map, parallels the MR perfusion/diffusion mismatch concept. There are no data as to how knowledge of the perfusion as demonstrated with CTP may aid in the assessment of the risk of hemorrhage following thrombolysis.

Issues regarding accuracy and reproducibility: The accuracy of the Central Volume Principle has been validated many times over the past 100 years since its proposal (class I). The accuracy of the deconvolution method of quantification of CTP has been validated relative to other methods of blood flow analysis, including injected microspheres in the experimental animal and the diffusible tracer, xenon (class I). However, there are significant issues regarding the quantification of CTP as used clinically with a CT scanner. Many problems exist with the accuracy of measuring the AIF. First, the horizontal portion of the MCA is only 3 mm in diameter and the ACA 2 mm, which permits partial volume effects in their density measurements. Second, which MCA should be chosen for the AIF? That on the side of the ischemia will probably have a slower flow rate than the normal, contralateral one. Third, a significant problem occurs if the slice of interest is higher than the usual one through the basal ganglia and a smaller vessel must be chosen for the AIF measurement. The AIF measurement, so that the accuracy in density measurement is even less than for the MCA or ACA. Fourth, the desired MTT parameter is transit time through the same volume in which the CBV is determined, not between the MCA and a venous sinus, but transit time to and from that tissue volume cannot be determined with current methodology. Finally, the presence of large vessels in the analyzed volume overestimates CBF.

Diversity of Data From Both Methods and Ability to Perform Challenge Tests

Diversity of Data From Both Methods and Ability to Perform Challenge Tests

Most of the reports discussing this new and evolving technology deal with evaluating the acute stroke patient. The slow infusion method provides both CBV maps and a high-resolution CTA of the large vessels at the skull base (class III and IV data). However, there is a question whether this technique provides the ability to distinguish reversible from non-reversible ischemia. The bolus-tracking method seeks to provide such discrimination by acquiring quantifiable data, albeit in a limited volume of tissue (class III and IV). A combination of these
2 techniques may be necessary to determine the correct level from which to obtain quantified data, or the approach of 2 or more injections may suffice. Whether the extra time for performing these studies leads to better decision-making for therapy and better patient outcomes will be determined by future research.53,101,171,175

For the study of chronic ischemic disease, there are few articles evaluating cerebrovascular reserves,71 such as with an acetazolamide challenge test75,176,177 or by varying Po2 levels in the intubated subject160 (class IV). Performance of 2 studies during the same imaging session requires more contrast material, but the use of non-ionic agents decreases the risk of a contrast reaction significantly.176–183 Study of the patient with vasospasm using CTP has been limited85 (class IV). There are no data on its use in head injury, as part of the BOT, or as an aid in brain death determination.

Availability of the System, Cost, and Reimbursement

The use of helical and spiral CT scanners is increasing rapidly in the United States, and most urban hospitals and imaging centers now have such equipment for many other uses. Multi-detector systems are becoming common, and the newest scanners have 16 detector arrays. Thus, the performance and the cost of CTP are limited only by the purchase of an independent workstation, which can be used for many software processing applications, and appropriate CTP software (≈$60 000 to $80 000). Reimbursement for CTA exists, and should be forthcoming for CTP as the necessary codes evolve to cover complex data processing applications for both CT and MR.

Advantages and Disadvantages Relative to Other Techniques

The advantages are the following:

1. The technique is based on the use of helical and spiral CT scanners, the numbers and scanning capabilities of which are rapidly increasing.
2. Because the technique is CT-based, any other CT technique, such as nonenhanced CT and CTA, can be performed during the same imaging session.
3. The method of performance is rapid, requiring only 60 seconds or less of contrast infusion.
4. The slow-infusion CBV technique is very easy, requiring a minimum of software.
5. The slow-infusion technique also provides a CTA to visualize the obstructed artery.
6. Perfusion parameters can be quantified to characterize various degrees of tissue ischemia.
7. Maps of probably irreversible ischemia (very low CBV) and tissue at risk (lowered CBF, reflecting both infarct and penumbra) may improve analysis of a large amount of complex data.
8. A combination of both the qualitative slow infusion CBV method to demonstrate the area of ischemia and the status of the vasculature and the quantitative technique to more fully characterize the tissue could be performed without an overdose of injected contrast material.

The disadvantages are the following:

1. The amount of brain that is imaged with the bolus-tracking method is limited, and the newest multislice CT systems do not improve this volume of coverage.
2. Even with a multislice CT system, the speed of image acquisition is significantly slower than with echoplanar MR. This may directly affect the number of slices that can be studied, the amount of data per slice, and, therefore, the accuracy of the data.
3. The radiation dose to the volume of tissue studied with the bolus-tracking method is relatively high compared with other perfusion techniques.
4. Although the slow-infusion technique can demonstrate decreased blood volume in the ischemic tissue, the ability to differentiate between reversible and irreversible ischemia is probably not as great as with the quantifiable techniques.
5. The accuracy and reproducibility of the quantifiable bolus-tracking method requires a more robust way to measure the AIF.
6. The ability to assess the risk of hemorrhage following thrombolysis, as demonstrated with both the XeCT and SPECT methods, has not been demonstrated by acquiring quantified CTP perfusion parameters.
7. The accuracy of the quantified data depends on an intact BBB, which is frequently not the case if the ischemic event has been ongoing for a few days.
8. The role of quantitative CTP in patients with chronic cerebral ischemia, vasospasm, or head injury as part of the BOT and as a surrogate for brain death determination has not been demonstrated.
9. The number of repeated examinations, including those for challenge tests, is limited by the amount of contrast that can be tolerated systemically.

Recommendations

1. Quantitative CTP may possibly be useful to differentiate between reversibly and irreversibly ischemic tissues in the acute stroke patient (grade C). Large prospective and appropriately blinded studies will be necessary to determine the value of this technique. There are no data regarding the ability of this technique to predict the potential for hemorrhage following thrombolysis, as there is for the diffusible tracer techniques.
2. Qualitative mapping of CBV with the slow-infusion method, in combination with the acquisition of CTA, may possibly be of value to determine emergent forms of therapy for the acute stroke patient (grade C). Again, larger prospective studies are needed.
3. No recommendation can be made for the use of this technique in patients with chronic cerebral ischemia, vasospasm, head trauma, or as part of the BOT (grade D).

Perfusion and Diffusion MR

Although PWI and DWI are distinctly different techniques, they will be considered together in this section because they are interrelated physiological parameters, and both are usually performed during the same imaging examination.

Rationales of the Techniques

Perfusion MR

There are 2 types of perfusion MR, the First Pass Bolus Tracking technique (also called dynamic susceptibility contrast [DSC] imaging), analogous to CTP, and the arterial
spin-labeling (ASL) method. In DSC imaging, a paramagnetic contrast agent produces dephasing of protons in an area equal to the radius of the blood vessel as the agent moves through the vasculature, leading to an alteration of $T_1^*$ relaxation in the adjoining tissues. The degree of $T_1^*$ effect is proportional to the perfusion.$^{9,12,14,60,99,184–187}$

In the ASL method, water proton spins in the extracranial blood are saturated and inverted electromagnetically, and these labeled protons mix with extravascular water in the brain. Intracranial imaging before and after spin inversion detects the difference in tissue magnetization, which is proportional to local perfusion.$^{188–191}$ The method suffers from a relatively low signal-to-noise ratio, requiring long imaging times as compensation, but may provide quantifiable data.$^{192}$ However, because this is an experimental method with few data regarding its utilization in acute or chronic ischemia, there will be no further discussion of this technique.

**Diffusion MR**

The ability of water molecules to diffuse can be evaluated by the use of powerful gradient coils that undergo rapid switching in polarity on either side of a 180-degree excitation pulse. The random motion of diffusion leads to phase shifts and relative signal loss, whereas decreased or no motion produces little or no signal loss and a relatively bright appearance on the diffusion-weighted image. The degree of diffusion weighting can be varied, with different values applied so that an apparent diffusion coefficient (ADC) can be calculated. Because the actual route of the diffusing molecule is not measured, only its origin and final destination, and because there are unmeasured variables that influence the rate of diffusion, such as the temperature of the tissue, the ADC value is only “apparent” or “relative,” not absolute, and must be compared with those obtained in other areas during that DWI sequence. Diffusion is normally altered by the presence of membranes or the increased concentration of large molecules. In acute ischemia, the bulk movement of water into the intracellular environment, containing many membranes and macromolecules, is a major reason for the observed decrease in the rate of diffusion. Another is cell swelling, which increases the tortuosity of the path that extracellular water protons must traverse and therefore increases the diffusion time. After the dead tissue has been absorbed, fewer obstructing membranes are present, and the diffusion coefficient increases.$^{8,193–196}$

**Method of Performance of DSC**

Ten to 13 brain slices are usually imaged, using a $T_1^*$-weighted pulse sequence. Ten to 15 images per slice are obtained before contrast injection and averaged to provide a baseline intensity of each pixel in that slice. A gadolinium-containing contrast agent is injected into a peripheral vein, usually at 5 mL/sec. If the gradient-echo echoplanar imaging (EPI) technique is used for image acquisition, a dose similar to $T_1$ contrast enhancement (ie, 0.1 mmol/kg body weight) is used. If the spin-echo EPI technique is used, that concentration is doubled. Imaging of the 10 to 13 brain slices is repeated for 70 to 80 seconds after contrast injection, with 20 to 40 images per slice obtained. Rapid imaging methods such as EPI permit tracking of the bolus through the entire brain. The alterations of the signal intensity (SI) of the tissues are measured, and a time-SI curve is calculated for each voxel. The information provided by the gradient-echo technique relates more to the magnetic susceptibility effects from the contrast agent within large blood vessels, whereas the spin-echo technique provides more information regarding signal alterations from small vessels, which is more important when studying tissue perfusion and metabolism.$^{14,185}$

**Quantification**

Quantification depends on measuring the signal intensity change within the tissues, which is a function of the susceptibility effect of the contrast agent rather than directly related to the contrast concentration in the tissues, as it is with CTP.$^{175}$ Relative quantification of CBV is straightforward, because it represents a simple change of intensity relative to the nonenhanced images. The multiple images per voxel are used to calculate the time-intensity curve for that voxel, with the area under the curve approximating the CBV of that voxel (rCBV).$^{184–187}$ Quantification of MTT and CBF, which are time-dependent parameters, is much more complex. The highest degree of quantification utilizes the deconvolution method, similar to CTP, and requires knowledge of an AIF. This is obtained by highlighting a few voxels near but not in a well-visualized major artery at the skull base, such as an MCA. A relative value of CBF is calculated; then, rMTT=rCBV/rCBF. Unfortunately, these are still relative values. Absolute values cannot be calculated because there are variables such as the dispersion of the contrast material following IV injection, cardiac output, and the precise amount of contrast entering and leaving an ROI at a given point in time that cannot be measured.$^{185,197–201}$

Because the deconvolution method is computationally intensive, a simpler, more approximate method can be used. Once the time-SI kinetic curve has been calculated for each voxel, the value of the width of the curve when it reaches one half of its maximum value (full width-half maximum) is proportional to the rMTT, whereas the slope of the increase in SI after contrast arrival is proportional to rCBF.$^{185}$

**Accuracy and Reproducibility of PWI Perfusion Parameters**

There are significant issues regarding the ability to obtain an AIF. The measurements of SI around an artery at the skull base may be even less accurate than simply measuring arterial density as in the CTP methodology. In addition, tissue SI is not in a direct linear relationship to tissue contrast concentration, as in CTP.$^{175}$

There are a few reports comparing the perfusion parameters obtained with PWI to those acquired with PET scanning in both animals and humans that demonstrate the positive correlation between the 2 techniques.$^{202–204}$ A few demonstrate the positive correlation between PWI and SPECT in human acute cerebral ischemia.$^{135,143,205}$ One shows the positive correlation between PWI and the XeCT technique.$^{206}$

**Interrelationship With DWI**

Most reports focus on the perfusion/diffusion “mismatch.” The areas of DWI abnormalities with decreased ADCs are assumed to have suffered irreversible injury, at least by the time the patient is scanned. The area of lowered perfusion values is usually larger than the DWI abnormality (Figure 4), and it has been shown that unless there is an increase in flow to this tissue in jeopardy, the DWI abnormality increases to
match the perfusion abnormality. Hence, this area of lowered PWI and normal DWI is an index of the penumbra, or tissue that has potentially reversible ischemia (Figure 4). PWI-DWI mismatch does not precisely correlate with the physiological penumbra. The DWI lesion overestimates the volume of the irreversibly ischemic tissue—the infarct—early after the onset of ischemia. The rMTT map appears to overestimate the size of the penumbra, but whether rCBF also overestimates or is an accurate predictor of the tissue in jeopardy differs among reports. CBV varies during the ischemic process. It is increased initially after vascular occlusion via vasodilation and collateral flow, in conjunction with a prolonged rMTT, but a decreased rCBV probably indicates that these autoregulatory mechanisms are exhausted and are inadequate to prevent infarction, and may be the best predictor of the size of the eventual infarct in the untreated patient. Despite these complexities, diffusion-perfusion mismatch does appear to provide a good indication of the presence of salvageable penumbral tissue. Conversely, a pattern in which the diffusion abnormality is equal to or larger than that for perfusion indicates that there is no penumbra to salvage.8,14,16,17,41,42,60,185,201,207–210

It must be stressed that all perfusion and diffusion parameters are relative, and no specific thresholds between reversible and irreversible ischemia have been defined. In addition, the validity of “irreversibility” can only be determined by measuring these parameters in a large group of patients before and after some form of treatment, such as thrombolysis, or in patients who undergo early spontaneous recanalization.40,41,211–213

Diversity of Data and Ability to Perform Challenge Tests

Acute Stroke

Many controlled trials of perfusion and diffusion MR in the experimental animal with induced ischemia have demonstrated the ability of these techniques to define ischemic tissue (class I data). Numerous retrospective trials in humans have demonstrated the ability of these methods not only to define ischemic tissue but also to predict its death if no treatment is possible or successful.12–16,184–196,201,206–210 (class II).

The ability to use these data to guide the use of intraarterial41 and intravenous42 thrombolytic therapy was reported in 1999. Recent reports suggest that a significant portion of the abnormal DWI signal may normalize with flow restoration, indicating that this DWI abnormality is a combination of both reversible and nonreversible ischemia.40,212 Although “pseudo-normalization” of the DWI parameter may occur during the process of infarction and tissue absorption,214 recent observations suggest that patients with a significant true normalization of their pretreatment DWI abnormality demonstrate significant clinical improvement.212,215 One report demonstrates the use of perfusion MR to monitor the effects of hypertensive therapy to augment blood flow after an acute stroke, improving the language deficits (all class IV data).

The ability of perfusion and diffusion MR to be as accurate in their predictive ability when treatment is a possibility and to guide those patient management decisions appears to be less clear than in the studies in which no treatment was possible. Quantitative threshold values of DWI and PWI parameters differentiating reversible and irreversible ischemia have not been determined. The fate of cerebral tissue subjected to ischemia is a complex, multifactorial process, which includes factors of time from occlusion, hemodynamics, tissue susceptibility, and types of intervention. It may be difficult to determine which of the perfusion and diffusion parameters, or a combination of them, adequately predict the potential success of treatment strategies to salvage tissue in jeopardy.213 In addition, there are no data at this time on threshold values or even patterns of perfusion and diffusion parameters that would define the risk of inducing hemorrhage with thrombolysis, as with both the XeCT and SPECT techniques.22,43

Other Uses

There are a few reports regarding the use of PWI in chronic ischemia,65,66,217 and some demonstrating the use of acetazolamide and DSC scanning to evaluate vascular reserves.218 There is no substantial experience with the use of PWI to determine the relative degree of ischemia from vasospasm or its use after head injury, to supplement the BOT, or to aid in brain death determination.

Difficulties in Study Performance

Although the perfusion and diffusion MR sequences are relatively short, they are usually combined with other sequences, making for a lengthy examination (30 to 45 minutes) on a sick patient. However, many institutions have developed limited, stroke-specific protocols that can be accomplished within 15 to 20 minutes of actual “in-room” time.

MR studies are performed in a relatively “closed” scanning environment, where it is difficult to monitor the patient. In addition, with the relative lack of MR scanning resources compared with those of CT, many institutions are reluctant to insert an acute stroke patient into the already-busy MR schedule.

Finally, manufacturers have not made the calculations of the parametric perfusion maps as easy or rapid as necessary to make them an integral part of the MR examination. Rather, the imager frequently must download the scanning data to a separate console to obtain the maps. The diffusion images, however, are obtained quickly and easily and have become routine in most institutions. Because of this, DWI scans are frequently obtained without PWI maps. If the DWI scan is normal, an inexperienced observer may make a diagnosis of “no stroke,” even when there is a neurological deficit, only to find that the DWI scan becomes abnormal at a later time, beyond the window for thrombolytic treatment (Figure 4).209,219,220 It is not appreciated that collateral circulation or other factors may prevent the DWI image from becoming abnormal as quickly as expected but that ADC mapping may have demonstrated an abnormality, and PWI would show focally abnormal perfusion. The best patient to treat with thrombolysis has normal DWI and abnormal PWI, ie, decreased perfusion without irreversible injury.211 Making the parametric perfusion and ADC maps readily accessible and “user-friendly” will decrease this source of confusion.

Availability of the System, Cost, and Reimbursement

PWI currently requires a 1.5T system and expensive modifications of both hardware (especially high-performance gradient coils) and software to permit EPI scanning.
field strength is not an issue for the performance of DWI, it requires expensive gradient coils. Diffusion and perfusion MR are usually added together to a 1.5T system. The cost of these MR modifications is in the hundreds of thousands of dollars and is significantly greater than with any of the other perfusion technologies. Even so, PWI is the most frequently used perfusion technology in the United States today. Reimbursement for DWI is not an issue in most states, but payment for PWI is variable.

Advantages and Disadvantages Relative to Other Techniques

The advantages are the following:

1. The ability to image not only cerebral perfusion, but also the status of the tissue (diffusion), the patency of the vasculature (MR angiography), and the anatomical substrate during the same imaging session.
2. The potential for differentiating reversibly and irreversibly ischemic tissue by defining the status of the tissue via DWI relative to its perfusion.
3. The rapidity of imaging the entire brain during the perfusion study, rather than a limited volume of brain tissue.
4. The acquisition of many data points per voxel, increasing the quality of the time-dependent calculations.

The disadvantages are the following:

1. The expense of the equipment
2. The time of the examination
3. The inhospitable MR scanning environment
4. It is not clear that using only relative parametric maps of the various forms of perfusion, in combination with diffusion and ADC maps, provides enough predictive value regarding the ability to reverse the ischemic process.
5. The accuracy of the quantification of DSC imaging is extremely difficult and requires a far more robust method of determining the AIF.
6. The assumptions underlying the mismatch method of defining the amount of salvageable tissue are still being investigated.
7. There is no information regarding the potential for hemorrhage following thrombolysis using either perfusion maps alone or the combination of diffusion and perfusion mapping, as there is with the diffusible tracer techniques.
8. There is no standardization between MR machines, even those of the same field strength. Thus, there is no ability to compare any objective parameters between sites, only relative data.
9. The ability to perform challenge tests to study cerebrovascular physiology has not been defined. Using DSC imaging, challenge tests may be limited by the volume of contrast material that can be injected. However, they may be possible using the ASL technique.

Recommendations

1. Perfusion and diffusion MR can be recommended as techniques that have been proven capable of demonstrating severely ischemic tissue in the acute stroke

Figure 4. MR Perfusion and Diffusion Studies. This 70-year-old man presented with acute onset of right leg weakness. An emergency MR study was performed, with a normal DWI sequence (A), especially in the left ACA distribution. However, the MTT map of the perfusion study demonstrated markedly slow flow in the medial left posterior frontal and anterior parietal lobes (B). It was elected not to perform thrombolysis. The DWI study the next day (C) demonstrated infarction in the same distribution as the MTT abnormality.
patient. These techniques are probably useful at differentiating between reversibly and irreversibly ischemic tissues (grade B), although the issue of reversibility of a diffusion abnormality, especially in the early stages of ischemia, requires more study.

2. No recommendation can be given for the ability of these techniques to guide the use of treatment modalities such as thrombolysis in the acute stroke patient, nor in their use to predict complications from that treatment, such as postthrombolytic hemorrhage (grade D).

3. No recommendation can be made regarding the ability of these techniques to provide accurate information on the status of vascular reserves in patients with chronic ischemia or in patients with vasospasm or head trauma. No information is available regarding their use as part of the BOT (grade D).

Summary Statement

1. More comparison testing of the different techniques must be performed in experimental ischemia models and in humans to determine the relative abilities of these technologies to differentiate tissues having normal perfusion, reversibly ischemic, and irreversible ischemia/infarction.

2. Quantifiable data are a laudable goal. Although the XeCT technique provides such data, and CTP may, obtaining such quantification with SPECT and Perfusion/Diffusion MR is much more complex. More research must be conducted to make these techniques, especially the MR-based methods, quantifiable. In addition, the accuracy of the quantification must be improved for all methods.

3. Outcome studies must determine not only the ability of each technology to predict the potential for infarction and for reversibility but also the need for quantifiable data to make those predictions. The use of perfusion patterns, mismatches, and multi-parametric maps of relative data may be appropriate surrogates and much more rapid to acquire than quantified data.

4. Controlled outcome studies must determine whether perfusion data help to define the risks and benefits of treatment for acute ischemia and the ability to triage patients into treatment groups. Are the data worth the delay in time to treatment and the expense of the technology?

5. Are physiological challenge tests of vascular reserves in patients with chronic ischemia an adequate surrogate for tissue metabolic data, like that derived from PET? Can such tests adequately predict potential infarction unless flow augmentation is undertaken?

6. Reproducibility of the data is essential if patients with chronic ischemia are to be followed and if data between centers are to be compared. Scanning of a standard phantom has permitted reproducibility for the XeCT technique, and the reproducibility of the other methods must also be ensured.

References


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Guidelines and Recommendations for Perfusion Imaging in Cerebral Ischemia: A Scientific Statement for Healthcare Professionals by the Writing Group on Perfusion Imaging, From the Council on Cardiovascular Radiology of the American Heart Association

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