Department of Radiology
Division of Nuclear Medicine
Didactic
3 approaches can be used in the evaluation of patients with cerebrovascular disease:

1. measurement of the cerebral blood volume (CBV) /cerebral blood flow ratio, mathematically equivalent to the mean transit time (MTT)
2. degree of cerebral flow reserve; comparing CBF under baseline conditions and after a vasodilator stimulus such as ACZ
3. direct measurements of OEF to identify patients with increased oxygen extraction (currently performed by using positron-emission tomography [PET])
• clinical value of resting rCBF is of questionable significance in the assessment of cerebrovascular disease, due to a strong coupling of flow and metabolism within the brain.

• regions of decreased flow do not necessarily indicate a primary vascular supply problem, but may be seen in areas of decreased metabolic demand-deafferentation (diaschisis), selective neuronal loss and chronic ischemia.

• normal CBF at rest need not indicate an adequate vascular supply since local vasodilation may exist distal to vascular compromise. Such areas should potentially, however, have a decreased vascular reserve.
Assessment of cerebral vascular reserve

• assess the circulation at rest and after a vasodilatory stimulus (stress) to access flow reserve
• Areas of decreased flow reserve should not manifest an increase in vascular flow to the same extent as regions of normal vascular supply
• Areas of loss of selective neurons or deafferentation have normal vascular supply and although they have decreased rCBF at rest they should respond normally after a vasodilatory stimulus
• evaluation of rest along with stress images, increase the specificity for the detection of cerebral vascular disease of rest-stress imaging over rest alone
Assessment of cerebral vascular reserve

- The vascular response of the brain is very sensitive to the CO$_2$ level with hypercapnia inducing vasodilation and an associated increase in rCBF while flow is decreased with hyperventilation and resultant hypocapnia and alkalosis.
- Hypercapnia sufficient to induce flow changes that are measurable by PET or SPECT can be induced by breathing an enriched gas mixture containing 5% to 7% CO$_2$.
- A more convenient and less cumbersome method of inducing vasodilatation than CO$_2$ inhalation is by the IV administration of acetazolamide (Diamox).
ACZ- mechanism of action

• Acetazolamide is a carbonic anhydrase inhibitor that causes an increase in CO$_2$ in red blood cells, brain parenchyma, or cerebral vasculature.

• Direct effect of ACZ, independent of carbonic anhydrase inhibition, on the smooth muscle of the cerebral vasculature is another possible mechanism.

• Rapid onset of vasodilation with maximal response at approximately 25 minutes and a half-time of 90 minutes.

• The dosage administered ranges from 500 to 1000 mg with the 1-g dose being most common. No additional increase in rCBF has been noted when increasing the ACZ dosage from 1 to 2 g.
Contraindications

- cardiovascular instability
- renal or hepatic insufficiency
- history of allergy to sulfa drugs

The use of vasodilators in patients with acute strokes should be approached with caution.
Adverse effects (generally self-limited)

Side effects - occur in about 50% of patients & last for about 15 minutes
- a) numbness around mouth or fingers
- b) lightheadedness or blurred vision
- c) flushed feeling around face and neck
- d) Mild vertigo, tinnitus, paresthesias
- e) Nausea

- Reversible pontine ischemia caused by ACZ challenge has been discussed in a case report
- no acute ischemic sequelae in more than 1000 studies with the use of ACZ (Piepgras et al)
rCBF response to ACZ

• range of increase of rCBF of 5% to 70%, usually 30-50%
• response to ACZ has been described as independent of baseline flow and inversely related to age with decreasing response associated with increasing age.

• a decrease of 10 to 20% in activity on the Diamox exam compared to baseline is considered abnormal.
Dosage:

- Adults 1000 mg by slow iv push for typical patient.
- Children 14 mg/kg.
Protocol

• An I.V. line should be started 15-20 minutes before the tracer is administered.
• Patients should be injected with their eyes open and their ears unplugged (blood flow is increased by 30% in the occipital lobes when the eyes are open compared to closed).
• Inject 1 gm of acetazolamide intravenously over 5 minutes slowly.
• Check blood pressure and monitor blood pressure for 25 minutes.
• Wait 25 minutes and then inject the radiopharmaceutical.
• Wait 30 minutes (Tc99m-HMPAO or Tc99m-ECD) and acquire images in the usual manner.

• A baseline brain perfusion study without acetazolamide may be performed after a 1 day delay.
• exam has also been performed using both Tc99m-HMPAO and I-123 IMP
Limitations of the Diamox test

- Due to the nonlinear uptake properties of HMPAO and ECD, which underestimate perfusion in regions of increased flow, there can be limited contrast for flow differentiation.

- Acetazolamide has been shown to increase cerebral blood flow by only about 30% to 50% above baseline in normal older patients (range 5 to 70%). This is in contrast to coronary pharmacologic stress examinations in which coronary blood flow is increased by 300-400%.
Cerebral perfusion agents

(lipophilic agents that are transported from the arterial vascular compartment to the normal brain tissue compartment by diffusion and distributed proportional to rCBF)

- Tc99m-HMPAO and Tc99m-ECD T99m-labelled tracers are essentially irreversibly trapped in the tissue compartment
- Xe 133- freely diffusible not trapped in tissue (used in determination of clearance rate)
- I123-IMP unique properties of redistribution can be used in low flow state.
133-Xenon

- T1/2: 126 hours
- Low-energy gamma rays: 81 keV
- intra-arterial, intravenous, or by inhalation routes
- inert, lipid soluble gas which does not undergo any chemical transformation in the brain
- the best agent for determination of absolute quantitative blood flow (rCBF in mL/min/100 gm tissue)
- by measuring cerebral washout of the inhaled gas, an absolute rCBF can be obtained (washout is directly proportional to blood flow)

- Clinical use is limited:
  1. rapid transit and short biologic half-life in the brain
  2. low gamma energy of Xe-133 results in marked attenuation of deep structures which results in less than optimal SPECT images
Xe CBF rest/Xe CBF after ACZ; CPR is defined as percentage increase in CBF after ACZ enhancement, or CPR = [(CBF [ACZ] - CBF [rest])/CBF (rest)] x 100 (%).

http://jnm.snmjournals.org/cgi/content/full/43/12/1616
a. Tc99m-HMPAO unstabilized  
b. Tc99m-HMPAO stabilized  
c. Tc99m-ECD

2. Radiopharmaceutical Preparation  
   • a. Use fresh generator eluate (<2 hr old) for optimal results with Tc99m-HMPAO.  
   • b. Do not use peretechnetate obtained from a generator which has not been eluted for 24 hr or more.

3. Radiopharmaceutical Injection  
   • a. Tc99m-HMPAO (unstabilized): Inject tracer no sooner than 10 min pre- and no more than 30 min post-reconstitution  
   • b. Tc99m-HMPAO (stabilized): Tracer should be injected no sooner than 10 min pre and no more than four hr post-reconstitution.  
   • c. Tc99m-Bicisate (ECD): Inject tracer no sooner than 10 min pre- and no more than 6 hr post-reconstitution.
Tc99m-HMPAO

- HMPAO is a lipophilic compound which is chemically unstable in-vitro (it undergoes oxidation).
- It has a first pass extraction of about 80%.
- The distribution of the tracer is proportional to the regional cerebral blood flow, however,
  
  the ratio of gray to white matter activity is about 2.5:1 compared to the 4:1 with Tc99m-ECD.
- Activity parallels cerebral blood flow up to 200 ml/min/100 gm of tissue (normal gray matter blood flow is about 80 ml/min/100 gm). HMPAO appears to overestimate low flow slightly, while underestimating areas of high flow.
• Due to rapid decomposition of the compound in vitro to a hydrophilic compound which will not cross the blood brain barrier, the agent must be used within 20-30 minutes of its preparation.

• A radiochemical purity of less than 85% or mixing the sample with blood in the syringe prior to injection results in poor image quality (the lipophilic agent will enter the RBC's).

• Stabilized forms of HMPAO using either methylene blue or cobalt chloride are available and allow easier labeling and improved image quality with reduced background activity.

• Luxury perfusion which can result in an inability to properly identify areas of nonviable brain
Normal distribution

- Normally the frontal lobes, thalamus and cerebellum accumulates more radiotracer. Midline structures including the basal ganglia and thalami should be clearly evident and relatively symmetric. Eyes open or closed may increase or decrease, respectively, the visual cortex activity by 30%
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<th>Transaxial</th>
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<td><strong>Normal images in different color scales: Mid-Thalamic plane</strong></td>
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**Brigham & Women's Hospital**

**Harvard Medical School**
Tc99m-ECD

• stable in-vitro (4 to 6 hours after reconstitution, as compared to less than 30 minutes for Tc99m-HMPAO)
• freshly eluted Tc-99m is not required for its preparation
• higher gray-to-white matter ratio
• In subacute infarcts, during the period of luxury perfusion, persistent defect due to altered esterase function in hypoxia (hypometabolism) which results in an inability to fix the agent intracellularly
• In other words, Tc-ECD is considered to be a perfusion marker of viable brain tissue
### Radiation Dosimetry in Adults

<table>
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<tr>
<th>Radiopharmaceutical</th>
<th>Administered Activity</th>
<th>Organ Receiving the Largest Radiation Dose*</th>
<th>Effective Dose*</th>
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</thead>
<tbody>
<tr>
<td>Tc-99m HMPAO¹</td>
<td>555 – 1110 i.v. (15 – 30)</td>
<td>0.034 kidneys (0.126)</td>
<td>0.0093</td>
</tr>
<tr>
<td>Tc-99m ECD</td>
<td>555 – 1110 i.v. (15 – 30)</td>
<td>0.073 bladder wall (0.27)</td>
<td>0.011</td>
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Children
7.4–11.1 MBq/kg (0.2–0.3 mCi/kg). Minimum dose is 3–5 mCi.
I-123 IMP (d, l-N-isopropyl-p-iodoamphetamine hydrochloride):

- IMP has a high first pass extraction fraction of greater than 95% with a linear relationship between tissue activity and cerebral blood flow up to the high flow range.

- Peak brain activity is reached within 20 minutes. The remainder of the tracer predominantly localizes to the lungs (33%), liver (45%), and kidney.

- Imaging must be done promptly as IMP metabolites will washout and redistribute over time.

- In subacute strokes, during the period of luxury perfusion, in contrast to Tc99mHMPAO, IMP studies will still demonstrate a perfusion defect as the associated local acidosis decreases IMP uptake.
Indication of the test

• Assessment of vascular reserve in patients with
  1. Carotid stenosis
  2. TIA
  3. Cerebrovascular disease
  4. Diabetes
  5. Prior ECD-ICD by pass
  6. Moya-Moya disease
  7. Complementary method in determining selective carotid shunting during CEA
Complementary method in determining selective carotid shunting during carotid endarterectomy
ACZ – Tc99m-HMPAO
Moya-Moya disease ACZ/postsurgery STA-MCA
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