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**::VOLUME 17, LESSON 2::**

***Radiopharmaceuticals for Planar and SPECT Brain  
Imaging***

Continuing Education for Nuclear Pharmacists  
And  
Nuclear Medicine Professionals

By

Richard. J. Kowalsky, PharmD, FAPhA



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# ***Radiopharmaceuticals for Planar and SPECT Brain Imaging***

By  
R.J. Kowalsky

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# ***Radiopharmaceuticals for Planar and SPECT Brain Imaging***

## **STATEMENT OF LEARNING OBJECTIVES:**

Upon successful completion of this lesson, the reader should be able to:

### **Brain Death**

1. Describe the biologic properties of imaging agents employed in brain death evaluation and list their advantages and disadvantages.
2. Describe the physiologic alterations in the brain that occur during brain death.
3. Describe the patterns of distribution of SPECT imaging agents in normal brain and in brain death.
4. Explain what causes the “hot nose” sign in brain death imaging.

### **Epilepsy**

1. Describe the physiologic changes that occur at a seizure site in the brain over time during ictus, postictus, and interictus.
2. Describe the radiopharmaceuticals used, the reasons for their use, and time frame during which they should be administered to identify a seizure focus in the brain.
3. Describe the sensitivity for detecting seizure foci in the brain with nuclear medicine imaging studies.

### **Cerebrovascular Disease**

1. List the basic requirements for SPECT and PET radiotracers for assessing regional cerebral blood flow.
2. Describe the major causes of stroke and its diagnostic assessment.
3. Describe what is meant by cerebrovascular reserve (CVR) and list major causes for loss of CVR.
4. Describe the procedure, agents used, and outcome expected in patients with compliant CVR and in patients with noncompliant CVR.

### **Neuronal Function**

1. Describe the processing of dopamine in brain neurons.
2. Distinguish between the mechanisms of localization of 18F-fluorodopa and 123I-ioflupane in the brain for evaluating Parkinson’s disease.
3. Describe the principal indication for 123I-ioflupane, the potential drugs that interfere with its localization, and the regulatory requirements for its use.

### **CSF Dynamics**

1. Describe the radiopharmaceuticals used to evaluate CSF dynamics, listing their name, administered activity, route of administration, required properties, and clinical applications in nuclear medicine.

2. Describe the patterns of normal and abnormal radiopharmaceutical distribution in patients being evaluated for NPH, CSF leak, and shunt patency.

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# **Radiopharmaceuticals for Planar and SPECT Brain Imaging**

R.J. Kowalsky

## **INTRODUCTION**

Brain imaging in nuclear medicine provides functional diagnostic information of the central nervous system. Brain imaging is particularly useful when paired with information from a patient's clinical evaluation and other brain imaging studies, such as computerized tomography (CT) and magnetic resonance imaging (MRI). Present day brain imaging may involve radiopharmaceuticals for planar imaging, single-photon emission computed tomography (SPECT), positron emission tomography (PET), and PET-CT or SPECT-CT fusion imaging. PET-MRI fusion imaging is currently being developed for clinical application. Fusion imaging modalities offer the advantage of a direct comparison between anatomic structures and their associated function, which enhances the diagnostic power of the study.

Over the years brain imaging studies have evolved to include single photon-emitting and positron-emitting radiopharmaceuticals for planar, SPECT and PET imaging, with some emphasis now in the development of PET agents because they offer the promise of more selective targeting in the brain, particularly in the evaluation of brain tumors, cognitive disorders, and central motor disorders. However, routine planar, SPECT, and SPECT-CT imaging studies of the brain still play a primary role in patient diagnosis. This continuing education article will focus primarily on single-photon emitting brain imaging agents, with occasional reference to PET agents where appropriate. The principal application areas for brain imaging that involve single-photon emitting agents include evaluation of brain death, epilepsy, cerebrovascular disease, neuronal function, and cerebrospinal fluid (CSF) dynamics.

## **Brain Death**

Brain death is characterized by irreversible cessation of brain and brain stem function caused by significant reduction in cerebral blood flow.<sup>2,3</sup> A variety of events, such as head trauma, anoxia, and cerebrovascular accidents, can cause an accumulation of fluid in the confined space of the calvarium. The resulting elevation of intracranial pressure causes a cessation of blood flow to the brain, a predisposition for brain death. A diagnosis of brain death is substantiated by clinical evidence in the



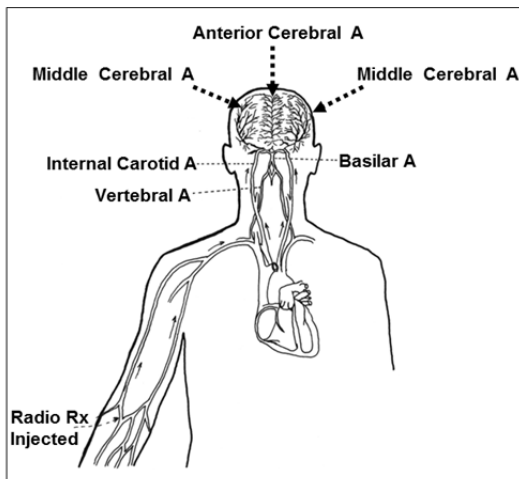
patient of absent brain stem reflexes, apnea, and a state of coma. Brain imaging is particularly helpful if any one of these conditions cannot be evaluated in a satisfactory manner by other means. Imaging may also be helpful in patients being considered for possible organ donation or when family members require further evidence to confirm brain death.<sup>3</sup> In these instances, a diagnosis of brain death may be substantiated by brain imaging to assess the absence of cerebral blood flow. It is important to note, however, that brain death scintigraphy is a confirmatory study only, not a primary diagnostic study.

Over the years imaging cerebral blood flow to assess brain function has employed primarily technetium agents, including both the nondiffusible tracers <sup>99m</sup>Tc-pertechnetate, <sup>99m</sup>Tc-pentetate (Tc-DTPA) and <sup>99m</sup>Tc-gluceptate (Tc-GH) and the diffusible tracers <sup>99m</sup>Tc-exametazime (Tc-HMPAO) and <sup>99m</sup>Tc-bicisate (Tc-ECD). Note that Tc-GH is currently available in Europe, but not in the United States. The properties of Tc-HMPAO and Tc-ECD are listed in Table 1.

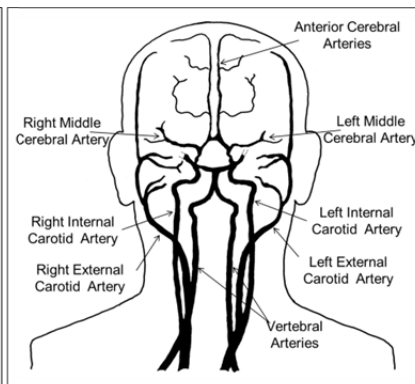
**Table 1**

<b>PROPERTIES OF SPECT BLOOD FLOW MARKERS FOR BRAIN IMAGING</b>		
<b>Property</b>	<b>Tc-HMPAO</b>	<b>Tc-ECD</b>
Molecular Charge/Lipophilicity	Neutral/Lipophilic	Neutral/Lipophilic
Brain Extraction Efficiency	72 – 80 %	47 – 60 %
Maximum Brain Uptake	4.1% (20 min)	6.5% (5 min)
Localization Mechanism	Glutathione reduction	Esterase hydrolysis
Brain Washout	15% over 2 min T <sub>1/2</sub> = 72 hr (slow component)	20% over 1 hr T <sub>1/2</sub> = 42.3 hr (slow component)
Blood Levels	12% ID (1 hr)	5% ID (1 hr)
Excretion	Urine (40% in 48 hr) Hepatobiliary (30% immediate)	Urine (72% in 24 hr) Hepatobiliary (12% in 48 hr)
Critical Organ	Lacrimal Glands 5.16 rad/20 mCi	Urinary Bladder Wall 5.6 rad/20 mCi

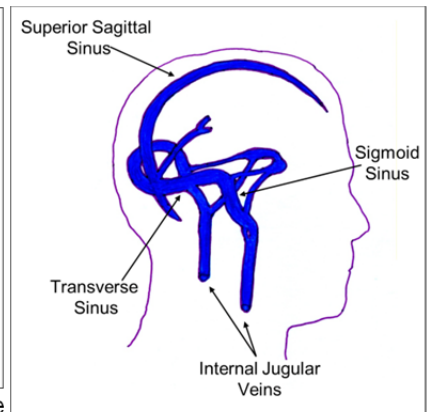
A typical nuclear medicine procedure for assessing cerebral blood flow in brain death assessment involves intravenous administration of either 15 to 30 mCi of Tc-DTPA or 10 to 30 mCi of Tc-HMPAO or Tc-ECD (Figures 1,2,3, and 4). Initially a dynamic flow study (radionuclide angiography) in the anterior position is obtained, which demonstrates arterial and venous blood flow in the brain. This is followed by static planar or SPECT brain imaging to assess activity distribution in the brain parenchyma. A small bolus of administered activity (typically ≤ 0.5 mL) is an important requirement for achieving a high quality image during the dynamic flow study. This is more important for nondiffusible tracers, such as Tc-DTPA, that are not retained in the brain, and less important for diffusible tracers that rely on retained parenchymal uptake during static image interpretation. Note that



**Figure 1.** Cerebral delivery of radiotracer to the brain after intravenous administration. (Reprinted with permission from [Kowalsky, R.J]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 414]. ©2011 by the American Pharmacists Association.)

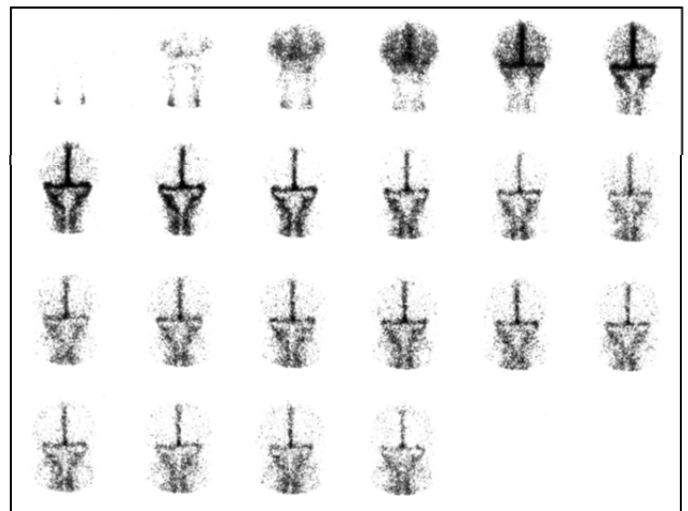


**Figure 2.** Major arteries that distribute blood in the brain.

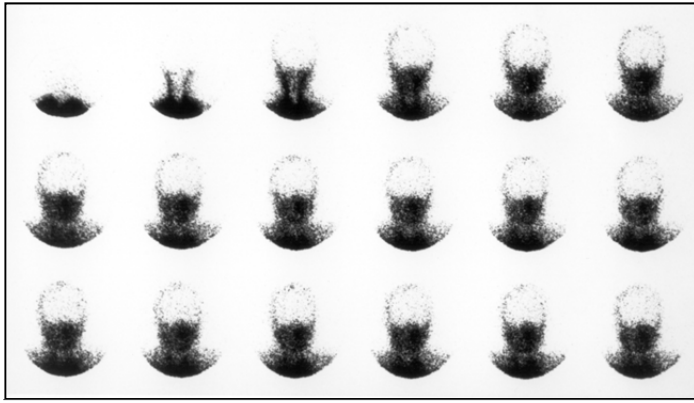


**Figure 3.** Major veins that drain blood from the brain.

nondiffusible tracers are ionized hydrophilic molecules that are excluded from entering normal brain parenchyma, whereas diffusible tracers are neutral lipophilic molecules that readily cross the blood-brain-barrier (BBB) and diffuse into neuronal cells in proportion to regional cerebral blood flow (rCBF), being trapped there following metabolic conversion to a nondiffusible form (see Table 1). Because diffusible tracers are retained they offer the advantage of assessing regional brain perfusion and viability, and are less disadvantaged by a poor quality flow study. Nondiffusible tracers do not normally cross the BBB and therefore evaluation of brain death relies primarily on the quality of a dynamic flow study. Consequently, diffusible tracers appear to be more commonly used to substantiate brain death than nondiffusible tracers.



**Figure 4.** Normal posterior radionuclide cerebral angiogram (flow study). Images shown are acquired at 2 second intervals after IV injection of 20 mCi (740 MBq) of <sup>99m</sup>Tc-gluceptate (<sup>99m</sup>Tc-GH). The arterial phase (first 2 to 6 seconds) is characterized by visualization of the two internal carotid, the two middle cerebral, and the anterior cerebral arteries. This is followed by a capillary “blush” phase leading quickly to the venous phase, which is recognized by the appearance of activity in the superior sagittal sinus (midline). Subsequent images show venous drainage through the lateral (transverse) venous sinuses and the jugular veins, which return blood to the heart. (Reprinted with permission from [Kowalsky, R.J]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 429]. ©2011 by the American Pharmacists Association.)

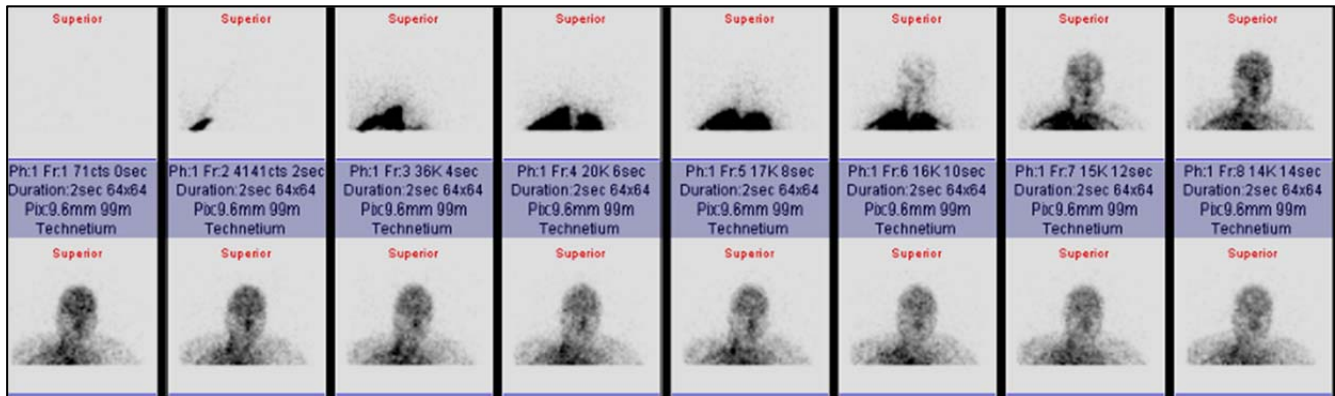


**Figure 5.** Brain death. Absence of cerebral perfusion after intravenous injection of  $^{99m}\text{Tc}$ -glucoptate ( $^{99m}\text{Tc}$ -GH) is seen in this 11 month old child, a victim of smoke inhalation in a house fire. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 430]. ©2011 by the American Pharmacists Association.)

A normal brain flow study with a nondiffusible tracer is described in Figure 4, which can be compared to a brain death study shown in Figure 5. In the case of brain death, there is typically evidence of activity in the carotid arteries, but blood flow from the carotid arteries to the brain ceases because of increased intracranial pressure or clotting (Figure 5). Thus, radiotracer activity is not seen in the anterior and middle cerebral artery territories. After a flow study, static images in brain death fail to demonstrate radiotracer

activity in the sagittal or transverse venous sinuses as well. If there is activity seen in the region of the venous sinuses, however, this does not necessarily imply that intracranial blood flow is present because activity in these regions may occur from flow of collateral blood vessels, and visualization does not preclude brain death.<sup>2</sup> With nondiffusible tracers, such as Tc-DTPA or Tc-GH, activity does not localize in the brain parenchyma in normal patients or in patients who are brain dead. The study relies principally on arterial activity distribution seen in the flow phase.

Figure 6 demonstrates a dynamic flow study and static image following administration of a diffusible tracer (Tc-HMPAO) in a patient suspected of brain death by clinical signs. If cerebral circulation is intact, Tc-HMPAO activity will enter into the brain parenchyma and be evident on static images. Since blood flow is blocked in the internal carotid arteries in brain death, blood is shunted to the external carotid arteries (see Figure 2), where it may cause increased accumulation of activity in the nasopharynx. This is called the “hot nose” sign (Figure 6).<sup>4</sup> On occasion, a patient with a clinical determination of brain death will exhibit some blood flow to the brain with a diffusible tracer, as with the case shown in Figure 6, and a diagnosis of brain death needs to carefully consider potential confounding factors in the clinical diagnosis and image interpretation. In some cases, the diagnosis of brain death must rely on clinical evaluation alone.<sup>5</sup> However, in most cases, if brain death is suspected by clinical neurologic signs, and there is no evidence of cerebral perfusion on the brain flow study with a nondiffusible tracer, or there is absent parenchymal retention with a diffusible tracer, the diagnosis is confirmed.<sup>3</sup>



**Figure 6.** Anterior brain images obtained in a 22 year old man with a shotgun wound to the neck. Images were obtained following intravenous administration of 22 mCi (888 MBq) of  $^{99m}\text{Tc}$ -HMPAO. Upper images show a normal brain flow study with evidence of flow to the carotid, anterior, and middle cerebral arteries. Static image in the lower panel shows accumulation of radiotracer in the cerebrum with a “hot nose” sign due to shunting of blood flow to the nasopharynx via the external carotid arteries. Although there is evidence of brain flow in this study the patient was declared brain dead from all other clinical signs. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 431]. ©2011 by the American Pharmacists Association.)

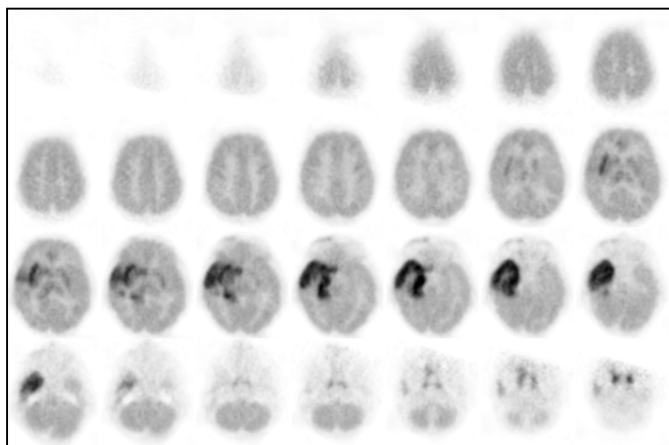


There are some considerations to keep in mind regarding radiopharmaceuticals used for brain death scintigraphy.<sup>3</sup> Nondiffusible tracers, such as Tc-DTPA, undergo rapid renal excretion, and this facilitates repeat examinations if necessary. A repeat study on the same day is often not possible following use of a diffusible tracer because of its parenchymal retention, and may require reexamination on another day to allow for decay of technetium-99m activity. Infiltration of the dose or a prolonged infusion will compromise evaluation of the dynamic flow phase of the study. Additionally, in rare instances, absence of activity in carotid vessels on the flow phase suggests complete infiltration of the dose. Finally, it is important to confirm acceptable radiochemical purity of a diffusible tracer because insufficient amount of the lipophilic form of the tracer may result in a reduced amount of brain uptake, which could be falsely interpreted as a lack of cerebral perfusion.

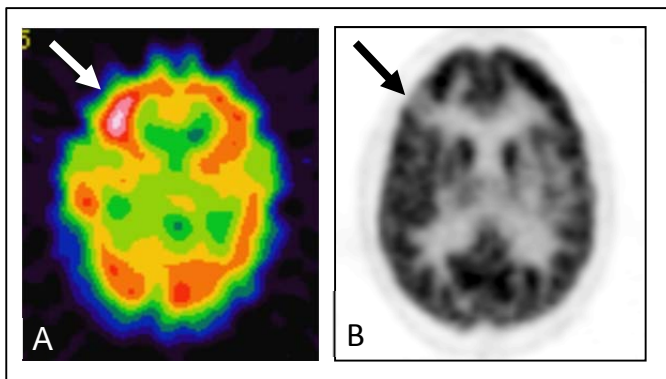
## Epilepsy

Epilepsy is a neurologic disorder of the brain that causes recurring excessive neuronal discharge resulting in repeated episodes of seizure. About 3% of the population experience seizures in their lifetime, of which, about 65% are partial seizures and 35% generalized seizures.<sup>6</sup> Seizures are controlled with medication in about 70% of patients. Those patients with partial seizure, who are not controlled by medication, are possible candidates for surgical resection of the neuronal epileptic focus

in the brain. Resection is 60 to 90% effective in temporal lobe epilepsy and is considered the treatment of choice for people with medically refractory partial seizures.



**Figure 7.** Rare ictal FDG PET brain study. The patient had a seizure just after being injected with FDG. Contiguous axial PET images of the brain show prominent uptake in the right temporal lobe, consistent with the seizure focus. If this had been an interictal study, the same region in the right temporal lobe would have demonstrated decreased uptake (relative hypometabolism) compared to the left temporal lobe. (Reprinted with permission from [Kowalsky, RJ]. [Clinical PET Procedures]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 650]. ©2011 by the American Pharmacists Association.)



**Figure 8.** (A) <sup>99m</sup>Tc-HMPAO ictal brain SPECT axial image showing a focal area of increased uptake in the right inferior frontal lobe in a patient with complex partial seizures. (B) <sup>18</sup>F-FDG interictal PET brain study in the same patient showing a focal area of hypometabolism in the inferior right frontal lobe which corresponds to the focus of increased uptake on the ictal SPECT image. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 432]. ©2011 by the American Pharmacists Association.)

accumulate in the brain over 30 to 40 minutes, which is typically much longer than the duration of a complex partial seizure. Thus, FDG does not have the high first-pass extraction that <sup>99m</sup>Tc diffusible

Nuclear medicine imaging following radiopharmaceutical administration has been an effective method for identifying partial seizure foci. Foci can be imaged with SPECT during a seizure (ictally) following administration of an adult dose of 15 to 30 mCi of a blood flow marker such as Tc-HMPAO or Tc-ECD, because of increased blood flow to the seizure focus during ictus and the rapid first-pass uptake of these tracers relative to rCBF. Since blood flow can be normal between seizures (interictally), ictal SPECT is more sensitive for detecting the seizure focus. However, interictal SPECT is also performed in some patients for comparison to ictal SPECT to improve diagnostic sensitivity, as discussed later on. Perfusion and metabolism are normally coupled in the brain and therefore PET imaging with <sup>18</sup>F-fludeoxyglucose (FDG) could also be used to localize a seizure focus because of increased glucose metabolism at the focus and the trapping of FDG following intracellular phosphorylation to FDG-phosphate.<sup>7</sup> However, because <sup>18</sup>F has a physical half-life of only 110 minutes, it is difficult to have a dose ready and immediately available for an ictal study. Also, FDG uptake occurs by a slower process of facilitated diffusion and continues to

tracers have. However, despite its first-pass extraction limitation, FDG can identify an ictal focus if it is administered while a seizure is occurring (Figure 7). Typically, if it is done, metabolic brain imaging with FDG is usually performed during the interictal period because glucose metabolism is reduced at this time in the seizure region relative to normal brain after the seizure has occurred, seen as reduced FDG uptake in the seizure region. Sometimes an ictal SPECT study with either Tc-HMPAO or Tc-ECD is compared with an interictal FDG PET study (Figure 8).

Because SPECT agents are fixed in brain cells by metabolic conversion to nondiffusible forms, imaging can be performed after the patient has become stabilized. SPECT imaging can begin within 30 to 60 minutes and up to 4 hours post seizure. Ictal imaging with SPECT can effectively localize the seizure focus, but requires vigilant video-EEG monitoring of the patient to indicate when a seizure is about to occur. This is necessary because the radiopharmaceutical must be administered during the seizure when hyperperfusion to the ictal zone occurs.

Success of surgical resection of a seizure focus with minimal complications, such as loss of memory function, relies on identifying its exact location in the brain. Since it requires 15 to 20 seconds for the radiotracer to reach the brain after injection and a seizure may propagate from the region of onset, it is important to have knowledge of the time of tracer injection relative to seizure onset, the type of seizure, and the ictal EEG recording in order to best locate the seizure focus.<sup>6</sup> Ictal scans have been shown to be most closely correlated with the results of intracranial EEG electrodes in identifying a seizure focus.<sup>8</sup> The time of tracer injection relative to seizure onset is critical. Less interference from seizure propagation and more accurate location of the site of onset is achieved when radiotracer is injected within the first 20 seconds following onset.<sup>9</sup> However, it may not be possible to meet this ideal early time frame for tracer injection. Studies have shown that hyperperfusion to the onset zone may still persist after the end of the seizure in what is called the postictal period.<sup>8,10</sup> It has been shown that this occurs in about 60% of patients when tracer is injected within the first 100 seconds of seizure termination.<sup>11</sup> Hypoperfusion to the seizure focus is more prevalent interictally and this change in perfusion can be evaluated better if tracer is injected after 100 seconds of seizure termination, where all patients show hypoperfusion.

A meta-analysis of ictal, interictal, and postictal SPECT brain imaging with Tc-HMPAO relative to standard diagnostic evaluation and postsurgical outcome in patients with refractory partial seizures has been conducted.<sup>12</sup> For this meta-analysis, ictal SPECT was defined as tracer injection during a seizure

or within 30 seconds of seizure completion. Postictal SPECT was defined as tracer injection later than 30 seconds following seizure termination but not later than 5 minutes. It was found that interictal scans alone had a sensitivity of 44% and ictal scans a sensitivity of 97%. If a postictal scan was substituted for an ictal scan the sensitivity dropped to 75%. While ictal imaging yields the highest sensitivity of localizing a seizure focus, true ictal imaging is often difficult to achieve logistically. Therefore, it was concluded from the meta-analysis study that in institutions using SPECT imaging in epilepsy it is important to combine interictal (between seizures) with either ictal (during seizure) or postictal (after seizure) imaging because an ictal or postictal image could appear normal if read independently, but may show increased perfusion at the seizure focus relative to interictal hypoperfusion at the same site.

In institutions using FDG-PET imaging to localize an epileptogenic focus it has been shown that identifying an interictal focus of hypometabolism in the temporal lobe with FDG is associated with marked improvement of seizure control after surgery in 94% of patients.<sup>13</sup> In summary, FDG appears to be more sensitive in identifying a seizure focus during the interictal state, whereas Tc-HMPAO or Tc-ECD are more sensitive during the ictal state. A combination of these studies has the most accuracy in localizing a seizure focus in temporal lobe epilepsy.

### **Cerebrovascular Disease**

Cerebrovascular disease (CVD) can be caused by a variety of conditions, such as hypertension, diabetes mellitus, carotid artery stenosis, arteriovenous malformations, aneurysm, and thromboembolism. CVD can lead to hemorrhagic or ischemic consequences. Cerebral ischemia is the result of a reduction in rCBF below that required for normal neurologic function and can range from transient ischemic attacks or TIAs that produce a temporary (5 – 60 min) neurologic deficit to acute cerebrovascular ischemia or stroke that, if unresolved, leads to cessation of blood flow (completed stroke), producing a permanent neurologic deficit.<sup>14</sup>

There are three basic requirements for SPECT and PET radiotracers for assessing rCBF: (1) ability to cross the BBB, (2) brain retention long enough to acquire images, and (3) lack of redistribution in the brain.<sup>15</sup> A variety of radiopharmaceuticals have been employed over the years to study rCBF in CVD. The two most widely used SPECT agents are Tc-HMPAO and Tc-ECD.

## Stroke

Two major types of stroke are ischemic and hemorrhagic. Ischemic stroke results from sudden occlusion of arterial blood flow due to thromboembolism. Hemorrhagic stroke is the result of blood vessel rupture, such as from an aneurysm. Tc-HMPAO and Tc-ECD both have approved indications for evaluating patients with stroke. Diagnostic studies in stroke assessment have shown SPECT diffusible tracers to have high sensitivity for detecting an acute ischemic event within a few hours after the stroke has occurred, but sensitivity drops off at later times due to a variety of factors. Often it is evident from clinical signs that a patient has had a stroke and the most important consideration is determining the cause in order to begin appropriate therapy. A standard approach is to obtain a CT or MRI scan to determine the nature of the stroke, e.g. hemorrhagic vs ischemic. If the latter, tPA therapy may be started if it is < 4.5 hr from stroke onset and the patient's blood pressure is less than 185 systolic and 110 diastolic (Guideline and Treatment of Ischemic Stroke, <http://guideline.gov/content.aspx?id=23856>). Otherwise, heparin or aspirin therapy may be considered. Thus, in current practice, anatomic imaging can provide the required diagnostic information for decisions made in patient care and a nuclear medicine brain scan with a diffusible tracer may be supportive, but is not a first choice diagnostic procedure in stroke.

## Cerebrovascular Reserve

Progressive narrowing of the large vessels in the brain, such as the internal carotids or anterior and middle cerebral arteries, can produce chronic hypoperfusion and decreased perfusion pressure over time. The key issue in patients with ischemia is determining its extent and the risk of developing a stroke.<sup>16</sup> Conditions that cause regional ischemia in the brain create an oxygen and nutrient deficiency. Consequently, significant amounts of carbon dioxide and hydrogen ion accumulate in the ischemic region triggering an autoregulatory vasodilation to improve blood flow.<sup>16,17</sup> The ability of the brain to produce a maximal vasodilatory response via autoregulation is called the cerebrovascular reserve (CVR). If the autoregulatory response becomes exhausted (non-compliant) and collateral circulation is inadequate, patients may be unable to maintain sufficient blood flow against any further decreases in perfusion pressure, and be at risk of a cerebrovascular accident. Non-compliant regions with reduced CVR often exhibit normal blood flow under resting conditions, but demonstrate reduced flow, compared to normally perfused areas, when challenged by a vasodilator.



CVR can be assessed in nuclear medicine by the acetazolamide stress test. Acetazolamide is a carbonic anhydrase inhibitor that is believed to elevate carbon dioxide levels in the blood inducing hypercapnic vasodilation. The stress study involves intravenous injection of 1 gram of acetazolamide over 2 minutes. After a 15 to 20 minute wait, 30 mCi (1110 MBq) of Tc-HMPAO is administered and imaging is begun in 15 minutes to assess regional blood flow in the brain. A separate baseline rest study with Tc-HMPAO is done for comparison to the stress study, usually on the day following the stress study. Regions of the brain with compromised CVR will be unable to produce a normal vasodilatory response with increased blood flow following the acetazolamide challenge, evidenced by reduced radioactivity compared to the baseline rest study (Figure 9).<sup>18</sup> The procedure provides objective evidence of reduced CVR in patients being considered for carotid endarterectomy to improve cerebral blood flow.<sup>19</sup> It has also been shown to be useful in identifying patients at risk for ischemic stroke during endarterectomy, who may need carotid shunting during the procedure.<sup>20</sup>

The acetazolamide stress test is indicated for the evaluation of CVR in TIA, completed stroke, or vascular anomalies (e.g. arteriovenous malformation) and for distinguishing vascular from neuronal causes of dementia.<sup>21</sup> The test is contraindicated in patients who are allergic to sulfa drugs, or prone to migraine headaches, or within 3 days of acute stroke.

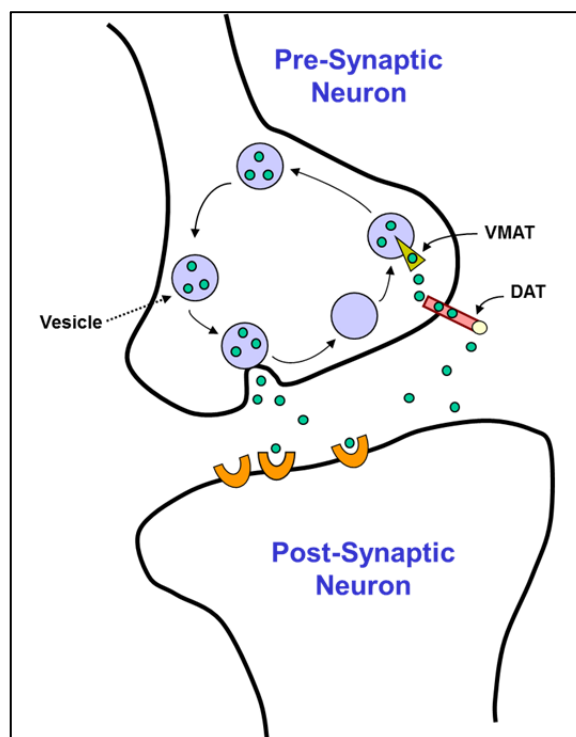


**Figure 9.** A patient with an old infarct (CT image on left) showed a corresponding small area of right parietal hypoperfusion (arrow) on routine <sup>99m</sup>Tc-HMPAO SPECT scan (center). The acetazolamide stress study (right) revealed a much larger area of reduced vascular reserve in the right middle cerebral artery territory, reflecting the area at risk for further vascular compromise that is not apparent on the baseline SPECT or CT study. (Reprinted by permission of Elsevier from Leung DK, Van Heertum RL. *Interventional Nuclear Brain Imaging. Semin Nucl Med* 2009;39:195-203.)

## Neuronal Function

The principal areas of the brain being investigated with neuroimaging agents are the dopamine system, serotonin system, cholinergic system,  $\gamma$ -aminobutyric acid (GABA) system, and opioid receptors.<sup>22-24</sup>

The area most thoroughly investigated is the dopamine system and its association with Parkinson's syndrome (PS), which includes idiopathic Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Parkinson's disease is characterized by a progressive degeneration and loss of dopamine-containing nerve cells in the substantia nigra. The substantia nigra is an important region of the midbrain associated with motor function. Some of the cells of the substantia nigra project to the caudate and putamen, two nuclei of the basal ganglia that together comprise what is called the striatum. Cells of the striatum utilize the neurotransmitter dopamine. Figure 10 illustrates the significant processes involved with dopamine storage, release, and reuptake in presynaptic neurons in the brain. Dopamine is synthesized in the presynaptic neuron from the amino acid tyrosine via a series of biochemical steps and is stored in presynaptic vesicles. During neuronal activation dopamine is released from storage vesicles into the synaptic cleft where it interacts with receptors on postsynaptic neurons. Excess dopamine is taken back up into presynaptic neurons via the dopamine transporter (DAT) and into vesicles via type 2 vesicular monoamine transporter (VMAT 2).



**Figure 10.** Presynaptic neuron with neurotransmitter (dopamine) in storage vesicles. Signal transmission releases neurotransmitter into the synaptic cleft where it activates receptor sites on the postsynaptic neuron. Excess neurotransmitter is returned to the presynaptic neuronal cytoplasm via the dopamine transporter (DAT) and taken back up into storage vesicles via the vesicular monoamine transporter (VMAT). (Reprinted with permission from [Kowalsky, R.J. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington

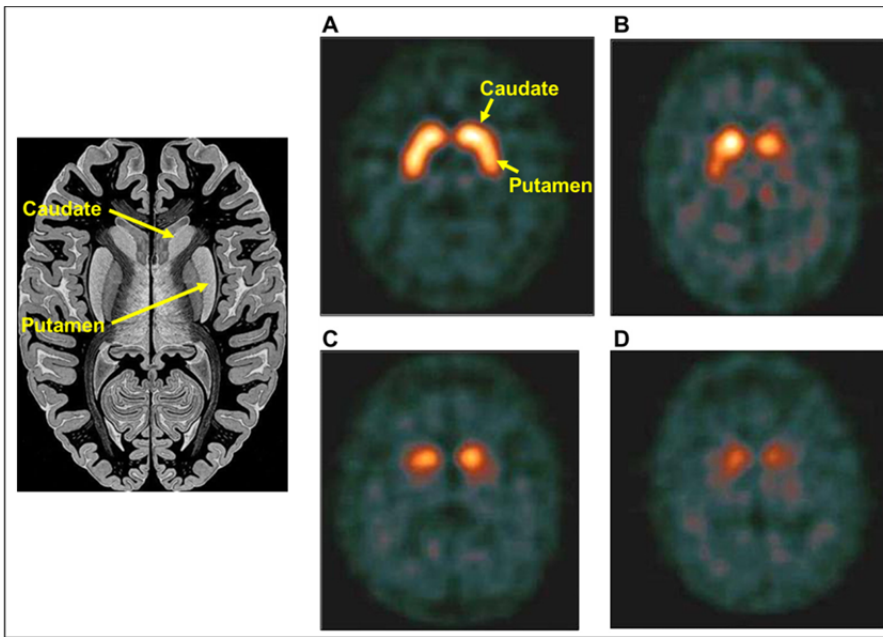
Table 2 lists several radiotracers that have been investigated to measure different aspects of dopaminergic function, notably presynaptic dopamine synthesis, the DAT, and VMAT2. The major tracers that have been used in nuclear medicine are <sup>18</sup>F-6-fluorodopa (FD) for PET imaging and <sup>123</sup>I-ioflupane (DaTscan) for SPECT imaging. FD assesses dopamine synthesis and DaTscan assesses DAT function.

**Table 2**

<b>RADIOPHARMACEUTICALS FOR EVALUATION OF PRESYNAPTIC NEURONAL FUNCTION IN PARKINSON'S DISEASE</b>	
<b>Radiotracer</b>	<b>Site of Action</b>
<sup>18</sup> F-FD, or <sup>18</sup> F-6-fluorodopa	Dopamine synthesis
<sup>123</sup> I-βCIT, or <sup>123</sup> I-2β-carbomethyl-3β-(4-iodophenyl)tropane	Dopamine transporter
<sup>123</sup> I-FP-CIT, or <sup>123</sup> I-ioflupane, or <sup>123</sup> I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane	Dopamine transporter
<sup>11</sup> C-DTBZ, or <sup>11</sup> C-dihydrotetrabenazine	Vesicular monoamine transporter 2
<sup>18</sup> F-FP-DTBZ, or 9-[ <sup>18</sup> F]-fluoropropyl-9- <i>O</i> -desmethyldihydrotetrabenazine	Vesicular monoamine transporter 2
<sup>18</sup> F-AV-133, or <sup>18</sup> F-(+)fluoropropylidihydrotetrabenazine	Vesicular monoamine transporter 2
<sup>99m</sup> Tc-TRODAT-1, or <sup>99m</sup> Tc-[2-[[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo [3.2.1]oct-2-yl]methyl](2-mercaptoethyl)amino]ethyl]amino] ethanethiolato(3-)-N2,N2'S2,S2']oxo-[1R-(exo-exo)]	Dopamine transporter
<sup>123</sup> I-altropane, or <sup>123</sup> I-2β-carbomethoxy-3β-(4-fluorophenyl)- <i>N</i> -(1-iodoprop-1-en-3-yl)nortropane	Dopamine transporter

FD is a fluorinated analogue of 3,4-dihydroxyphenylalanine (DOPA). It is a marker of presynaptic nerve terminal function because it traces dopamine synthesis. FD readily crosses the BBB by the neutral amino acid transporter into the brain ECF. It is then actively transported into dopaminergic neurons similar to DOPA, where it is decarboxylated to <sup>18</sup>F-fluorodopamine by the aromatic amino acid decarboxylase (AADC) enzyme. FD is therefore useful in assessing a deficiency in dopamine synthesis and storage in presynaptic nerve terminals. A decrease in FD localization has been shown to correlate with severity of disease. It has been investigated in the diagnostic workup of PD to evaluate the effects of PD therapy with dopamine agonists and to help differentiate PD from other neurodegenerative diseases that involve the dopaminergic system.<sup>25,26</sup> At present, there is no NDA-approved FD product and FD is used under expanded access IND or other research IND.

DaTscan binds to a transport protein located on the presynaptic membrane and can provide a measure of transporter density as an indirect measure of nerve terminal integrity.<sup>24</sup> DaTscan is available commercially as Ioflupane I 123 Injection in single-use vials containing 5 mCi (185 MBq) in 2.5 mL at calibration time. The usual adult dosage of Datscan is 5 mCi by slow intravenous administration over 15 to 20 seconds, followed by SPECT imaging in 3 to 6 hours. <sup>123</sup>I-ioflupane (DaTscan) is also known as <sup>123</sup>I-FP-CIT or <sup>123</sup>I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane.



**Figure 11.** Normal and abnormal DaTscan SPECT Images. (A) Normal DaTscan SPECT image: characterized by uptake of the tracer in both right and left putamen and caudate nuclei. The image was largely symmetrical with approximately equal levels of uptake on both left and right sides. Activity was contained close to the center of the image, forming two crescent-shaped areas of uptake. Abnormal DaTscan images fall into at least one of the following three categories (all are considered abnormal). (B) Abnormal DaTscan SPECT image type 1: included asymmetrical uptake with almost normal or reduced putamen activity in one hemisphere and a more marked change on the other side, likely on the side opposite the patient's first clinically affected side, and characterized by a significantly lower or no uptake in the putamen. The uptake was limited to a roughly circular area. (C) Abnormal DaTscan SPECT image type 2: included significantly reduced putamen uptake on both sides. Activity was confined to the caudate nuclei and formed two roughly circular areas. (D) Abnormal DaTscan SPECT image type 3: had virtually no uptake from both the putamen and caudate nuclei on both sides of the brain, resulting in a significant reduction in contrast and the visualization of background activity throughout the rest of the image. ("Reproduced from: Kupsch AR, Bajaj N, Weiland F, et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study. *J Neurol Neurosurg Psychiatry*. 2012;83:620-8, with permission from BMJ Publishing Group Ltd.")

The principal application for Datscan is in distinguishing patients with essential tremor from patients with tremor associated with dopaminergic deficit related to PS. Several studies have shown that patients with essential tremor have a greater likelihood of DaTscan uptake and localization in the striatum (normal Datscan images) compared with PS patients who show a greater likelihood of decreased localization in the striatum (abnormal Datscan images) (Figure 11). DaTscan is particularly useful when patient clinical data poses significant uncertainty in establishing a clinical diagnosis of parkinsonism and in assessing clinical management. DaTscan is also

helpful in assessing clinical management of patients suspected of PS. A study, differentiating patients with PD-associated tremor from those with non-PD-associated tremor, demonstrated in a 1-year follow-up assessment that a modification in diagnosis was made in 54% of patients who were scanned with DaTscan, compared to only 23% of patients who were not scanned.<sup>27</sup> Similarly, 41% of patients who were scanned had at least one change in clinical management in 12 months compared with only 22% of patients who were not scanned. Another study showed that combining clinical assessment with DaTscan imaging could reduce overdiagnosis of PD based on clinical assessment alone, which could result in inappropriate therapy.<sup>28</sup>

Datscan binds reversibly to the DAT located on presynaptic neurons in the striatum (caudate nucleus and putamen). Thus, drugs that bind to the DAT may interfere with the binding of Datscan in the striatum. Potentially interfering drugs include amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine, selegiline, and sertraline. However, the impact of such drugs on the results of Datscan imaging has not been established.

The presence of up to 6% free radioiodide ( $^{123}\text{I}$ ) in DaTscan requires thyroid gland protection. An oral thyroid blocking dose of potassium iodide, equivalent to 100 mg of iodide, should be administered at least one hour prior to the DaTscan dose, either as potassium iodide solution or Lugol's solution. Alternatively, 400 mg of potassium perchlorate orally may be administered to patients where there is a concern regarding iodine hypersensitivity.

DaTscan is structurally related to cocaine, which makes it a federally controlled substance (Schedule II), requiring a Drug Enforcement Administration (DEA) license for handling and administration. In order to use DaTscan, licensing and shipping requirements must be coordinated through GE Healthcare to establish the nuclear medicine department as a DaTscan Imaging Center of Excellence. The general requirements are having DEA and radioactive materials (RAM) licenses with the same address to which the product will be shipped and a secured storage location for the DaTscan product that complies with DEA requirements for Schedule II substances. The requirements for registration and DaTscan purchase can be performed online through the Controlled Substance Ordering System (CSOS), which can be accessed at <http://www.orderdatscan.com>. Below is a summary of what is required.

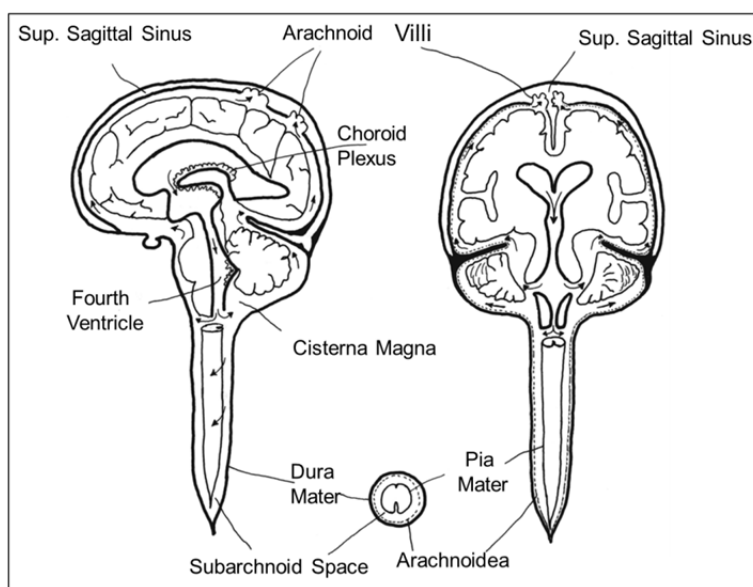
1. Obtaining a DEA-issued CSOS Digital Certificate. This involves completion of three possible downloadable forms depending on how many people are involved in the ordering and handling of DaTscan. Following is an example of the process involving several individuals, which may be altered to meet the specific needs of a facility. The registrant, who is typically a nuclear medicine physician will complete Form 251 with his/her DEA number; a coordinator, who might be a department administrative assistant and main DEA contact person, will complete Form 252; and each person who orders DaTscan electronically, such as nurses or others as allowed by state law and institutional policy, must complete Form 253. All forms will be under one DEA license number. The registration process will take 4 to 6 weeks, whereupon the facility will receive a certificate with access code and password.

2. Activation of Digital Certificate. The digital certificate must be activated online at <http://www.deacom.gov> within 60 days of its receipt using the access code, password, and web login. This will permit downloading of digital certificates of all individuals who are part of the DEA submission noted in step 1 above, to a computer that will be used to order DaTscan electronically.
3. DatScan Order Placement. A personal sign on account will be established by the GE Healthcare customer service once the CSOS digital certificate is issued. This will permit ordering DatScan by accessing the <http://www.orderdatscan.com> webpage using a login and password to access the CSOS system.

Details for obtaining digital DEA certificates and placing DatScan orders can be obtained via the GE Healthcare CSOS tutorial accessed online at [http://us.datscan.com/CSOS\\_tutorial/](http://us.datscan.com/CSOS_tutorial/).

## CSF Studies

Most of the CSF is formed by active secretion of ependymal cells of the choroid plexuses of the lateral, third, and fourth ventricles. CSF produced in the lateral ventricles flows through the interventricular foramina into the third ventricle, through the cerebral aqueduct into the fourth ventricle, and from there into the subarachnoid space around the brain and spinal cord (Figure 12).<sup>29</sup> A portion of CSF flow emerging from the ventricles occurs in a caudal direction toward the spinal canal, but the majority of flow occurs cephalad around the cerebral convexities toward the superior sagittal sinus. CSF is absorbed into the venous system through the arachnoid villi in the superior sagittal sinus.

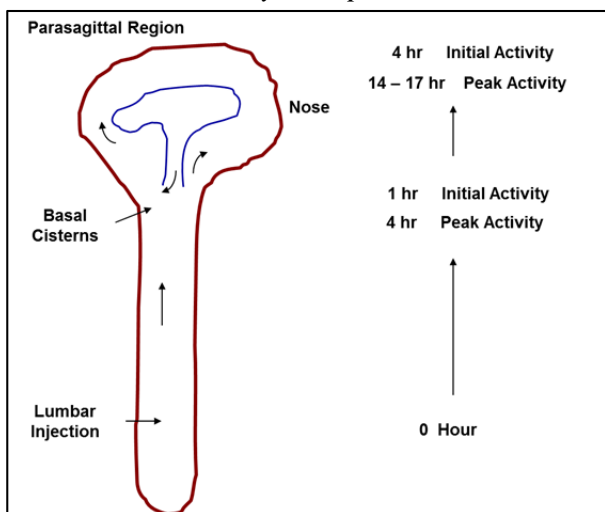


**Figure 12.** The brain and CSF space showing the site of CSF production (choroid plexus) in the lateral, third, and fourth ventricles. CSF flow proceeds out of the ventricles in a caudal direction around the spinal cord and cephalad over the cerebral hemispheres and is absorbed at the arachnoid villi into the superior sagittal sinus. The cord cross-section demonstrates the meninges and subarachnoid space. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine. 3rd ed. Washington, DC: American Pharmacists Association; 2011; [page 415]. ©2011 by the American Pharmacists Association.)

CSF imaging is often used to assess patients with normal pressure hydrocephalus (NPH), particularly in differentiating NPH from other forms of degenerative brain disease that is not treatable by surgically placed ventricular shunts. Imaging is also useful for evaluating shunt function and detecting suspected CSF leaks.

Evaluation of CSF flow is usually accomplished by gamma camera imaging following intrathecal administration of a radiopharmaceutical. The radiotracer must remain confined in the CSF space until it is removed through the arachnoid villi. Therefore it must not be lipid soluble, which would allow it to diffuse out through the meninges. Technetium-99m pertechnetate is not useful because it is actively transported from the CSF into the blood at the choroid plexuses. Additionally, pertechnetate is a small molecule with a molecular weight of 163, allowing it to readily escape from the CSF through the meninges. Both  $^{99m}\text{Tc}$ -DTPA and  $^{111}\text{In}$ -DTPA have physical properties that limit their removal from the CSF space except at the arachnoid villi. These hydrophilic complexes do not undergo choroid transport, and have limited diffusion through the meninges because of their larger molecular weights. Both agents are therefore useful for cisternographic procedures, however  $^{99m}\text{Tc}$ -DTPA is limited to short-term studies up to 24 hours because of its half-life.

### Normal-Pressure Hydrocephalus

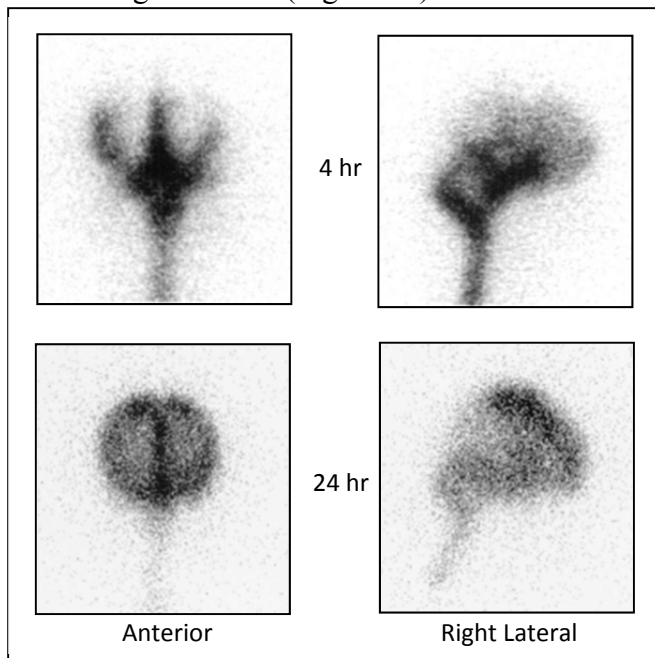


**Figure 13.** Right lateral view diagram of the brain and spinal canal illustrating the temporal movement of radiotracer from the lumbar injection site to the parasagittal region of the brain. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 426]. ©2011 by the American Pharmacists Association.)

Patients with NPH characteristically exhibit dementia, incontinence, and ataxia with ventricular enlargement and normal CSF pressure, measured by lumbar puncture. Enlargement of the ventricles may be caused by overproduction of CSF by the choroid plexus, obstruction of CSF flow within the ventricles, or obstruction of CSF absorption at the arachnoid villi. In a typical procedure for evaluating NPH, 500  $\mu\text{Ci}$  (18.5 MBq) of  $^{111}\text{In}$ -DTPA is administered intrathecally into the lumbar subarachnoid space, whereupon the radiopharmaceutical begins to ascend in the spinal canal by bulk flow and diffusion (Figure 13). Initial anterior images of the head are obtained 6 hours after administration of the radiopharmaceutical. Sometimes, posterior images of

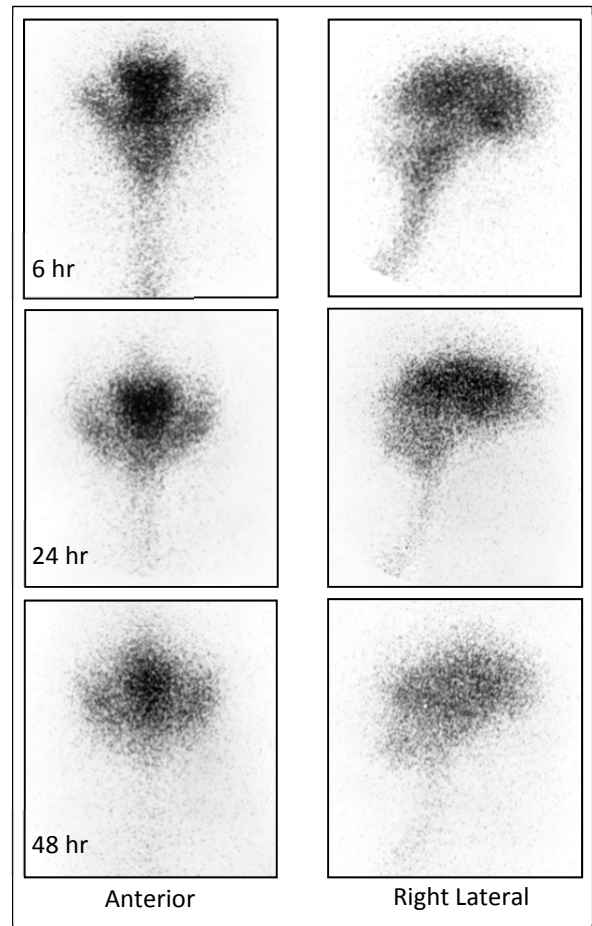
the lumbar region of the back are obtained to evaluate whether the injection was successful. Anterior images of the head are obtained at 24 hours and 48 hours after injection. Sometimes images are also obtained at 72 hours, which is an advantage of  $^{111}\text{In}$ , which has a 2.8 day half-life.

In normal adult patients, activity can be seen accumulating in the basal cisterns by 2 to 4 hours. Activity can also be seen in the interhemispheric and sylvian fissures at this time. Normally, radiotracer is not seen entering the lateral ventricles at any time. Over the next 24 hours, radiotracer should ascend over the cerebral convexities to the sagittal sinus, and activity in the basal cisterns should begin to clear (Figure 14).



**Figure 14.** Normal CSF cisternogram.  $^{111}\text{In}$ -DTPA study showing normal radiotracer accumulation in the basal cisterns, interhemispheric and sylvian fissures on the 4 hour images (trident appearance). Images at 24 hours demonstrate normal ascent of the radiotracer over the convexities to the superior sagittal sinus. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 437]. ©2011 by the American Pharmacists Association.)

In patients with NPH a different CSF flow pattern occurs. Early on, there is reflux of radiotracer into the lateral ventricles. This will persist on the delayed images. In addition, ascent over the cerebral convexities is usually markedly delayed (Figure 15).



**Figure 15.** Normal-pressure hydrocephalus. The 6 hour images demonstrate  $^{111}\text{In}$ -DTPA activity in the spinal subarachnoid space, basal cisterns, and lateral ventricles. At 24 hours the activity persists in the lateral ventricles and in this patient there is very slow progression over the hemispheres. This pattern is essentially the same at 48 hours and indicates extraventricular obstruction and normal-pressure hydrocephalus. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 437]. ©2011 by the American Pharmacists Association.)

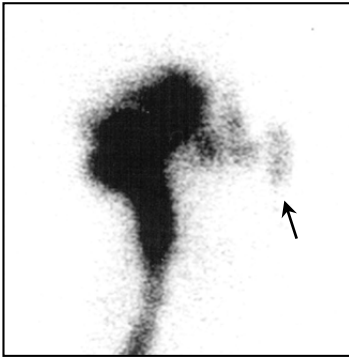


### CSF Leak

The most common cause of CSF leaks is trauma. Most CSF leaks are located in the skull base between the region of the sphenoid sinus and temporal bone. CT imaging is most often used to evaluate a CSF leak. However, when this is nondiagnostic, nuclear imaging can be useful in helping to confirm and localize the leak site.

Both  $^{111}\text{In}$ -DTPA and  $^{99\text{m}}\text{Tc}$ -DTPA have been used for CSF studies.  $^{111}\text{In}$ -DTPA is approved for intrathecal injection at a maximum dose of 0.5 mCi (18.5 MBq).  $^{99\text{m}}\text{Tc}$ -DTPA has also been used off-label at a dose of 1 to 2 mCi (37–74 MBq) for CSF leak studies or the evaluation of ventriculoperitoneal shunt patency.<sup>30</sup> Workers should be aware that kits with DTPA as the free acid or trisodium salt have the potential to chelate  $\text{Ca}^{2+}$  and  $\text{Mg}^{2++}$  in the spinal fluid and may cause an adverse reaction in the patient. Therefore, if  $^{99\text{m}}\text{Tc}$ -DTPA is used in a CSF procedure, a kit that contains  $\text{Ca}^{2+}$  is preferred. Additionally, since  $^{99\text{m}}\text{Tc}$ -DTPA kits intended for intravenous administration are permitted a higher endotoxin limit (175 EU per maximum patient dose) compared with  $^{111}\text{In}$ -DTPA (14 EU per patient dose for intrathecal administration), it is advisable to prepare a DTPA kit with a high specific activity to limit the amount of DTPA and endotoxin administered. Endotoxin testing of the end product could also be performed before intrathecal administration so that the acceptable number of EUs per administered dose is not exceeded. Currently, the only DTPA kit available for purchase in the U.S. is that produced by DraxImage, which contains DTPA, stannous ion, calcium chloride, and para-aminobenzoic acid. An alternative off-label Tc-99m radiopharmaceutical to consider for CSF leak studies is  $^{99\text{m}}\text{Tc}$ -pyrophosphate, which has been shown to be effective in the evaluation of spontaneous spinal fluid leaks.<sup>31</sup>

To evaluate a possible CSF leak in the skull region, pledgets are typically placed at the suspected leak site prior to intrathecal administration of the radiopharmaceutical. If the suspected leak is from the nose, pledgets are placed in locations near the sphenoidal recess, the cribriform plate, and the middle meatus, bilaterally. If the suspected leak is from the ear, a pledget is placed in the ear canal. As in the evaluation of normal-pressure hydrocephalus, a lumbar puncture is then performed and the radiopharmaceutical is administered intrathecally. The patient is placed in the prone position or a position that most exacerbates the leak. Anterior, posterior, and lateral imaging of the head is performed, usually 2 to 4 hours later as radiotracer arrives in the basal cisterns. It is important to continue imaging until the radiotracer accumulates in the suspected site of the leak before removing the pledgets. Normally, there should be no evidence of radiotracer accumulation outside the cranial



**Figure 16.** CSF Leak in a patient with rhinorrhea after motor vehicle accident. Lateral image of the head taken 1 hour after a lumbar intrathecal injection of 2 mCi (74 MBq) of <sup>99m</sup>Tc-DTPA demonstrates activity in the nose consistent with a CSF leak. Pledget-to-plasma ratios (Table 3) demonstrate the main area of the leak to be in the left cribriform/middle meatus region. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 438]. ©2011 by the American Pharmacists Association.)

vault. Images positive for CSF leak demonstrate focal accumulations of radiotracer outside the cranium (Figure 16). A sample of the patient's blood is then collected to measure activity in the plasma. The pledgets are also collected. The pledget volume and plasma sample should be equal, about 0.5 mL each.<sup>32</sup> Saline is added to pledget samples to equal the plasma volume and weight. Pledget and plasma sample activities are then measured in a well counter and recorded as counts per minute per gram. Pledget-to-plasma activity ratios are then calculated. An evaluation of the pledget-to-plasma activity ratio in 16 normal subjects was reported to not exceed 1.3 to 1, while a patient with an occult leak had a ratio of 6.2 to 1.<sup>32</sup>

Radiotracer activity should not be seen in the systemic circulation until the radiotracer is absorbed into the venous system at the arachnoid villi. Thus, there should be no appreciable activity in the blood at 4 hours. Likewise, if there is no CSF leak, there should be no appreciable activity in the pledgets, and the pledget-to-plasma activity ratio should be 1 to 1. A pledget-to-plasma ratio greater than 1.5 to 1 is considered positive for CSF leak.<sup>32,33</sup> In the nasal sinus region, the pledgets with the highest ratios suggests the location of the leak (Table 3).

**Table 3**

<b>NASAL PLEDGET-TO-PLASMA ACTIVITY RATIOS IN THE ASSESSMENT OF A POSITIVE CSF LEAK WITH <sup>99m</sup>Tc-DTPA (SEE FIGURE 14)<sup>a</sup></b>		
<b>Pledget Placement</b>	<b>Net Counts per Minute</b>	<b>Pledget-to-Plasma Ratio</b>
Right Cribriform	84	0.24
Right Middle Meatus	590	1.7
Right Sphenoid	2627	7.5
Left Cribriform	126,169	360
Left Middle Meatus	111,795	319
Right Sphenoid	53,881	154
Plasma	350	1

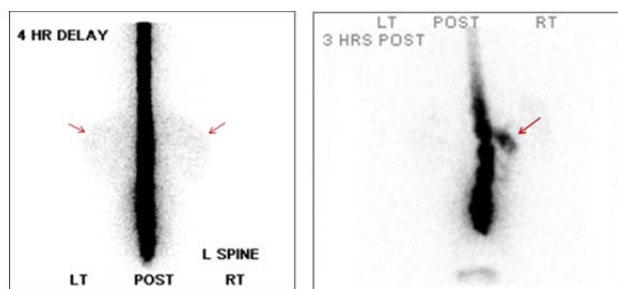
<sup>a</sup> 0.5 mL of plasma, obtained at the end of procedure, is counted along with each nasal pledget suspended in 0.5 mL of saline.

A less common occurrence seen in nuclear medicine practice is a CSF leak caused by small tears in the spinal meninges that can lead to a condition known as spontaneous intracranial hypotension.<sup>34</sup>

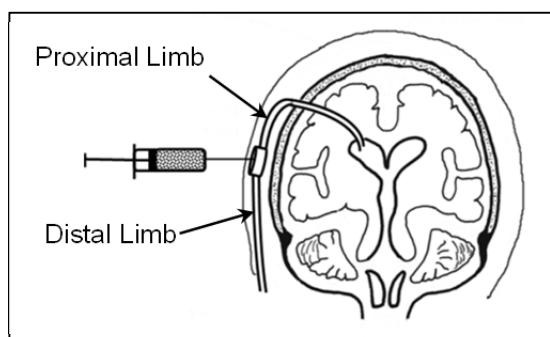
Detection of this type of CSF leak requires imaging. An example is shown in Figure 17.

## Shunt Evaluation

Ventriculoperitoneal (VP) and ventriculoatrial (VA) shunts are used to relieve elevated CSF pressure associated with obstructive hydrocephalus. A VP shunt drains CSF from the ventricles to the peritoneal cavity where it is absorbed via the lymphatics back to the venous system. A VA shunt drains CSF directly to the systemic circulation via the right atrium of the heart. If a patient's clinical symptoms begin to return after shunt placement or interval enlargement of the ventricles is seen on MRI or CT, the shunt may be obstructed. Anatomic studies such as plain film x-rays can determine if the shunt tubing is broken or kinked. If there is no evidence of this, nuclear medicine techniques can examine shunt function.



**Figure 17.** Posterior gamma camera images of the lumbar-thoracic spine region in spontaneous intracranial hypotension CSF leak studies. Image on the left illustrates a normal study (no spinal leak) made after intrathecal administration of  $^{99m}\text{Tc}$ -pyrophosphate (PYP); note faint uptake in the kidneys (arrows). Image on the right following intrathecal administration of  $^{99m}\text{Tc}$ -pentetate (DTPA) illustrates a CSF leak at the right L2 nerve root (arrow). (Courtesy of James A. Ponto, University of Iowa Hospitals and Clinics, Iowa City, IA).



**Figure 18.** Diagram illustrating the injection port for radiotracer administration during ventriculoperitoneal shunt evaluation. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 439]. ©2011 by the American Pharmacists Association.)

To evaluate for shunt patency, radiotracer is injected into the shunt port using sterile technique (Figure 18).

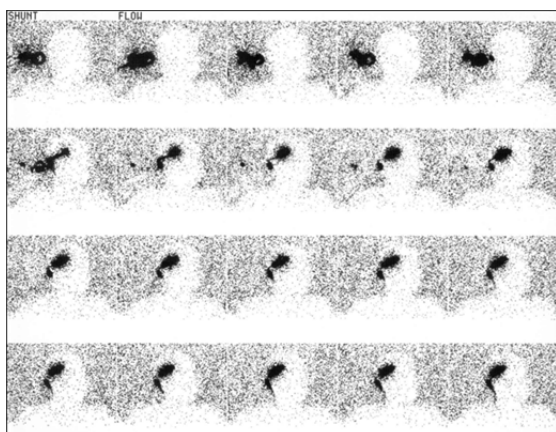
Typically, 1 to 2 mCi (37–74 MBq) of Tc-DTPA is used.

There are three parts to a VP or VA shunt: (1) the shunt port, (2) the proximal limb from the port to the ventricle, and (3) the distal limb from the port to either the cardiac atrium or the peritoneal cavity. To evaluate the proximal limb of the shunt, radiotracer is injected while manual compression is maintained on the distal limb near the port. With proper manual pressure on the distal limb of the shunt during tracer injection into the port, there should be prompt visualization of activity in the ventricle

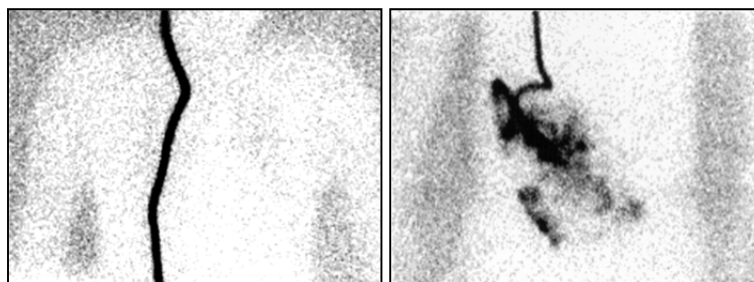
after injection. If the port is accessed properly and radiotracer fails to appear in the ventricle, this is evidence of a proximal limb obstruction. Dynamic images of the head during this procedure can be obtained by using a transmission source behind the patient to verify radiotracer accumulation in the ventricle. With proximal limb patency and radiotracer seen in the ventricle, pressure is released from the distal limb and serial images are obtained to follow the flow of radiotracer through the distal limb. There should be prompt passage of radiotracer through the distal limb. If the patient has a patent VP

shunt, activity should be seen spilling freely from the distal limb into the peritoneal cavity in a few minutes to an hour (Figures 19 and 20). There is evidence of obstruction if the radiotracer fails to advance through the shunt tubing or pools at the distal tip (Figure 21). If the patient has a patent VA shunt, radiotracer will reach the systemic circulation and will be seen in the kidneys.

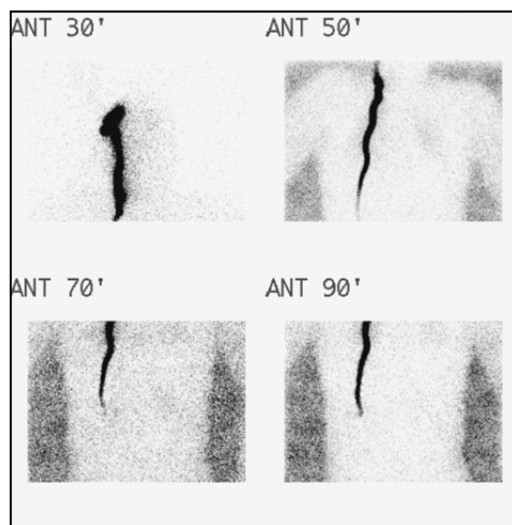
Radiopharmaceuticals, such as  $^{111}\text{In}$ -DTPA, have also been used to evaluate the function and patency of pumps employed for intraventricular and intrathecal administration of drugs, such as morphine for the treatment of pain associated with spinal tumors.<sup>35,36</sup>



**Figure 19.** Ventriculoperitoneal (VP) shunt evaluation.  $^{99\text{m}}\text{Tc}$ -DTPA study demonstrating patent VP shunt. With thumb pressure on the distal limb of the VP shunt, radiotracer is injected into the VP shunt port during the flow phase of the study. Once activity is seen in the lateral ventricle and obstruction of the proximal limb is ruled out, manual pressure is taken off the distal limb. Activity is seen to flow freely through the shunt toward the peritoneal cavity. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 439]. ©2011 by the American Pharmacists Association.)



**Figure 20.** Patent ventriculoperitoneal shunt. Abdominal view of the same patient as Figure 19 demonstrating movement of radiotracer down the patent distal limb and spilling into the peritoneal cavity. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 440]. ©2011 by the American Pharmacists Association.)



**Figure 21.** Obstructed ventriculoperitoneal shunt.  $^{99\text{m}}\text{Tc}$ -DTPA study demonstrating delayed progression of radiotracer through the distal limb of the shunt. There is no evidence of tracer in the peritoneal cavity after 90 minutes. (Reprinted with permission from [Kowalsky, RJ]. [Brain]. In: Kowalsky RJ, Falen SW, eds. *Radiopharmaceuticals in Nuclear Pharmacy and Nuclear Medicine*. 3<sup>rd</sup> ed. Washington, DC: American Pharmacists Association; 2011; [page 440]. ©2011 by the American Pharmacists Association.)

## REFERENCES

1. Kircher MR, de la Zerda A, Jokerst JV, et al. A brain tumor molecular imaging strategy using a new triple-modality MRI-photoacoustic-Raman nanoparticle. *Nature Medicine*, 15 April 2012, published online, <http://www.nature.com/nm/journal/vaop/ncurrent/full/nm.2721.html>
2. Zuckier LS, Kolano J. Radionuclide studies in the determination of brain death: Criteria, concepts, and controversies. *Semin Nucl Med*. 2008;38:262-73.
3. SNM Guidelines, Donohue KJ, Agrawal G, Frey KA, et al. SNM Practice Guideline for Brain Death Scintigraphy 2.0. Practice Management Procedure Guidelines. Reston, VA: Society of Nuclear Medicine; 2012.
4. Huang AH. The hot nose sign. *Radiology*. 2005;235:216-7.
5. Brill DR, Schwartz JA, Baxter JA. Variant flow patterns in radionuclide cerebral imaging performed for brain death. *Clin Nuc Med*. 1985;10:346-52.
6. Goffin K, Dedeurwaerdere S, Van Laere K, et al. Neuronuclear assessment of patients with epilepsy. *Semin Nucl Med*. 2008;38:227-39.
7. Kuhl D, Engel J, Phelps M, et al. Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of  $^{18}\text{F}$ FDG and  $^{13}\text{N}$  $\text{H}_3$ . *Ann Neurol*. 1980;8:47-60.
8. Devous MD Sr, Leroy RF, Homan RW. Single-photon emission tomography in epilepsy. *Semin Nucl Med*. 1990;20:325-41.
9. Lee SK, Lee SY, Yun CH, et al: Ictal SPECT in neocortical epilepsies: Clinical usefulness and factors affecting the pattern of hyperperfusion. *Neuroradiology*. 2006;48:678-84.
10. O'Brien TJ, Brinkmann BH, Mullan BP. Comparative study of  $^{99\text{m}}\text{Tc}$  ECD and  $^{99\text{m}}\text{Tc}$  HMPAO for peri-ictal SPECT: qualitative and quantitative analysis. *J Neurol Neurosurg Psychiatry*. 1999;66:331-9.
11. Avery RA, Spencer SS, Spanaki MV, et al: Effect of injection time on postictal SPECT perfusion changes in medically refractory epilepsy. *Eur J Nucl Med*. 1999;26:830-6.
12. Devous MD Sr, Thisted RA, Morgan GF, et al. SPECT brain imaging in epilepsy: A meta analysis. *J Nuc Med*. 1998;39:285-93.
13. Delbeke D, Lawrence SK, Abou-Khalil BW, et al. Postsurgical outcome of patients with uncontrolled complex partial seizures and temporal lobe hypometabolism on  $^{18}\text{F}$ FDG-positron emission tomography. *Invest Radiol*. 1996;31:261-5.
14. Hellman RS, Tikofsky RS. An overview of the contribution of regional cerebral blood flow studies in cerebrovascular disease: Is there a role for single photon emission computed tomography? *Semin Nucl Med*. 1990;20:303-24.

15. Kung HF. Brain radiopharmaceuticals, In: Fritzberg AR, ed. *Radiopharmaceuticals: Progress and Clinical Perspectives*. Vol II. Boca Raton, FL: CRC Press;1986:21-39.
16. Eskey CJ, Sanelli PC. Perfusion imaging of cerebrovascular reserve. *Neuroimag Clin N Am*. 2005;15:367-81.
17. Frenkel A, Front D. Clinical investigation of cerebral blood flow. In: Magistretti PL, ed. *Functional Radionuclide Imaging of the Brain*. Vol 5. New York: Raven Press; 1983:31–45.
18. Leung DK, Van Heertum RL. Interventional nuclear brain imaging. *Semin Nucl Med*. 2009;39:195–203.
19. Cikrit DF, Burt RW, Dalsing MC, et al. Acetazolamide enhanced single photon emission computed tomography (SPECT) evaluation of cerebral perfusion before and after carotid endarterectomy. *J Vasc Surg*. 1992;15:747–54.
20. Kim JS, Moon DH, Kim GE, et al. Acetazolamide stress brainperfusion SPECT predicts the need for carotid shunting during carotic endarterectomy. *J Nucl Med*. 2000;41:1836–41.
21. Juni JE, Waxman AD, Devous MD Sr, et al. Society of nuclear medicine procedure guideline for brain perfusion single photon computed tomography (SPECT) using Tc-99m radiopharmaceuticals. Version 3.0. *Practice Management Procedure Guidelines*. Reston VA: Society of Nuclear Medicine; 2009. ([www.snm.org/guidelines](http://www.snm.org/guidelines)). Accessed September 27, 2010.
22. Heiss WD, Herholz K. Brain receptor imaging. *J Nucl Med*. 2006; 47:302–12
23. Meyer JH. Applying neuroimaging ligands to study major depressive disorder. *Semin Nucl Med*. 2008;38:287–304.
24. Seibyl JP. Single-photon emission computed tomography and positron emission tomography evaluations of patients with central motor disorders. *Semin Nucl Med*. 2008;38:274–86.
25. Heiss W-D, Hilker R. The sensitivity of 18-fluorodopa positron emission tomography and magnetic resonance imaging in Parkinson's disease. *Eur J Neurol*. 2004;11:5–. 26. Ravina B, Eidelberg D, Ahlskog JE, et al. The role of radiotracer imaging in Parkinson's disease. *Neurology*. 2005;64:208–15.
27. Kupsch AR, Bajaj N, Weiland F, et al. Impact of DaTscan SPECT imaging on clinical management, diagnosis, confidence of diagnosis, quality of life, health resource use and safety in patients with clinically uncertain parkinsonian syndromes: a prospective 1-year follow-up of an open-label controlled study. *J Neurol Neurosurg Psychiatry*. 2012;83:620-8.
28. Marshall VL et al. Parkinson's Disease is Overdiagnosed Clinically at Baseline in Diagnostically Uncertain Cases: A 3-Year European Multicenter Study with Repeat [<sup>123</sup>I]FP-CIT SPECT. *Mov Disord*. 2009 24:500-8.
29. Moore KL. *Clinically Oriented Anatomy*. Baltimore: Williams & Wilkins;1980:941–6.

30. Curnes JT, Vincent LM, Kowalsky RJ, et al. CSF rhinorrhea: detection and localization using overpressure cisternography with Tc-99m DTPA. *Radiology*. 1985;154:795–9.
31. Ponto J, Graham M. Technetium-99m Pyrophosphate for Cerebrospinal Fluid Leaks: Pharmaceutical Considerations. *J Am Pharm Assoc* 2013; 53(2):e62.  
<http://www.aphameeting.org/files/content/docs/Abstracts.pdf>
32. McKusick KA, Malmud LS, Kordela PA, et al. Radionuclide cisternography: normal values for nasal secretion of intrathecally injected <sup>111</sup>In-DTPA. *J Nucl Med*. 1973;14:933–4.
33. Ommaya A, O'Tuama L, Lorenzo A. Hydrocephalus, shunts and cerebrospinal fluid leaks. In: Wagner H, Szabo Z, Buchanan J, eds. *Principles of Nuclear Medicine*. Philadelphia: WB Saunders; 1995:576–84.
34. Thomas DL, Menda Y, Graham MM. Radionuclide cisternography in detecting cerebrospinal fluid leak in spontaneous intracranial hypotension. *Clin Nucl Med*. 2009; 34: 410-416.
35. Schmidt E, Oates E. In-111 DTPA to evaluate the patency of an implanted intrathecal infusion pump. *Clin Nucl Med*. 1997; 22: 768-770.
36. Rosenson AS, Ali A, Fordham EW, et al. Indium-111 DTPA flow study to evaluate surgically implanted drug pump delivery system. *Clin Nucl Med*. 1990; 15: 154-156.

## ASSESSMENT QUESTIONS

1. Which one of the following agents is not a typical choice for the evaluation of patients suspected of brain death?
  - a. Tc-99m pentetate (DTPA)
  - b. Tc-99m pertechnetate
  - c. Tc-99m exametazime (HMPAO)
  - d. Tc-99m bicisate (ECD)
  
2. In a patient who is assessed clinically to be brain dead, Tc-HMPAO activity is expected to be seen in each of the following anatomic areas except the:
  - a. carotid arteries
  - b. nasopharynx
  - c. brain parenchyma
  - d. venous sinus region
  
3. A disadvantage of diffusible tracers for brain death evaluation is:
  - a. a flow study cannot be done
  - b. the static brain scan must be done within 1 hour of tracer administration
  - c. a repeat study may not be possible on the same day
  - d. interfering uptake in the nasopharynx
  
4. The major parameter evaluated to confirm brain death with a non-diffusible tracer is:
  - a. parenchymal uptake in the brain
  - b. lack of blood flow in the carotid arteries
  - c. the presence of the “hot nose” sign
  - d. lack of blood flow in the anterior and middle cerebral arteries
  
5. Which one of the following statements is false regarding diagnostic imaging in temporal lobe epilepsy?
  - a. The seizure focus with Tc-99m labeled HMPAO and ECD demonstrates increased uptake during ictus and decreased uptake interictally
  - b. The seizure focus demonstrates decreased uptake interictally with F-18 FDG
  - c. A desirable diagnostic procedure is to perform the ictal study with Tc-99m HMPAO and interictal study with F-18 FDG
  - d. F-18 FDG is the best agent to use for ictal imaging because it measures both blood flow and metabolism



6. Which one of the following statements is false regarding SPECT imaging with Tc-99m HMPAO in temporal lobe epilepsy?
- Imaging can begin within 30 to 60 minutes and up to 4 hours post seizure
  - Seizure focus identification is most accurate if the tracer is injected within 20 seconds of seizure onset
  - The order of sensitivity from highest to lowest for identifying a seizure focus is ictal imaging > postictal imaging > interictal imaging
  - Performing an independent ictal or postictal study is the most accurate procedure for identifying a seizure focus
7. The rationale for using Tc-99m labeled HMPAO or ECD for localizing seizure foci in the brain is their:
- ability to measure regional cerebral blood flow
  - ability to measure cellular metabolism
  - ability to measure blood flow and metabolism
  - hydrophilicity
8. The standard adult dose of administered activity for Tc-99m HMPAO or ECD SPECT tracers for localizing seizure foci in the brain is:
- 3 – 5 mCi
  - 5 – 10 mCi
  - 10 – 20 mCi
  - 15 – 30 mCi
9. All of the following are radiotracer requirements for assessing rCBF except:
- BBB penetration
  - brain retention
  - brain redistribution
  - lipophilicity
10. Which one of the following statements is false?
- CVR is mediated via autoregulatory control.
  - Loss of CVR is associated with chronic ischemia
  - A normal CVR response is triggered by reduced amounts of carbon dioxide and hydrogen ion
  - A normal CVR response maintains rCBF as perfusion pressure drops

11. During an acetazolamide stress test, which one of the following statements is true for a patient with non-compliant CVR?
- The brain region in question demonstrates decreased blood flow at stress compared to rest.
  - The brain region in question demonstrates no difference in blood flow at rest and stress
  - A patient with an infarct would have a blood flow as described in response “b” above
  - The patient is administered 30 mCi Tc-HMPAO followed by 1 gram of acetazolamide intravenously
12. Which one of the following statements is true?
- Dopamine is synthesized in postsynaptic neurons of the striatum
  - Dopamine is removed from the synaptic cleft by VMAT 2
  - Dopamine is stored in presynaptic neuronal vesicles
  - Dopamine stimulates presynaptic neuronal receptors on during neuronal transmission
13. Which one of the following statements is true?
- F-18 fluorodopa and I-123 ioflupane have similar patterns of distribution in the brain but different mechanisms of localization
  - I-123 ioflupane binds to VMAT 2 whereas F-18 fluorodopa binds to presynaptic DAT
  - I-123 ioflupane binds to presynaptic DAT whereas F-18 fluorodopa binds to VMAT 2
  - I-123 ioflupane uptake is a measure of dopamine synthesis
14. The pattern of I-123 ioflupane activity distribution in the right and left striatum of the brain as Parkinson’s disease progresses is best described as follows.
- Caudate and putamen show uniform declining activity with disease progression
  - Caudate activity only declines with disease progression
  - Putamen activity declines more so earlier with disease progression compared to the caudate
  - Putamen activity only declines with disease progression
15. Which one of the following statements regarding DaTscan imaging is false?
- DaTscan is classified as a Schedule 1 controlled substance
  - DaTscan imaging can reduce overdiagnosis of Parkinson’s disease
  - DaTscan imaging can help distinguish patients with essential tremor from Parkinson’s tremor
  - DaTscan is structurally related to cocaine
16. Each of the following is a requirement for purchase and receipt of DaTscan except:
- submission of a form with the nuclear medicine physician’s DEA number
  - submission of a form by each person who will place orders for DaTscan
  - submission of a form by a study coordinator DEA contact person
  - submission of DaTscan order forms must be made through a contract nuclear pharmacy

17. Which one of the following statements about radionuclide cisternography with In-111 pentetate (DTPA) is false?
- Choroid plexus activity will not be evident
  - Radioactivity will enter the ventricular system in patients with normal pressure hydrocephalus
  - Clearance of the radiotracer from the CSF space occurs by diffusion through the meningeal membranes of the spinal chord
  - It normally takes 2 to 3 days for most of the In-111 radioactivity to clear from the CSF space
18. The maximum approved dosage of In-111 DTPA for cisternography is:
- 50 microcuries
  - 250 microcuries
  - 500 microcuries
  - 2 millicuries
19. Regarding evaluation of CSF leak, the nasal pledget-to-plasma activity ratio must be greater than \_\_\_\_\_ for a leak to be present.
- 5-to-1
  - 3-to-1
  - 2.3-to-1
  - 1.5-to-1
20. Which one of the following statements is true regarding a CSF VP shunt evaluation following administration of Tc-DTPA?
- Evidence of ventricle activity indicates patency of the distal limb of the shunt
  - Evidence of ventricle activity indicates obstruction of the distal limb of the shunt
  - Evidence of peritoneal activity indicates patency of the proximal limb of the shunt
  - Evidence of peritoneal activity indicates patency of the distal limb of the shunt