Diagnostic and Functional Neuroimaging

Early Diagnostics

*Roentgenography (aka. X-rays)

*Intracranial Pneumography

Intracranial pneumography was once one of the most valuable diagnostic aids at the disposal of the neurologist or neurosurgeon. Its purpose was is to localized intracranial pathology. The procedure is based upon the principle that a gaseous replacement of the fluid within the ventricular and subarachnoid systems offers a contrast medium, air being much less dense than fluid to x-rays. In this manner the convolutions and ventricles can be visualized.

Encephalogram: An encephalogram is carried out by the removal of cerebrospinal fluid and the injection of an equivalent amount of air through a lumbar puncture needle. The procedure is extremely painful and often disables patients for several days due to severe headache. By the introduction of air the cerebral ventricles, subarchnoid spaces, and basilar cisterns are clearly outlined. Abnormal variations in the appearance of the ventricles or sub-arachnoid channels are readily detected.

Ventriculogram: This is carried out by the injection of air directly into the ventricles through trephine openings in the skull. By means of this method, the ventricles are clearly outlined but the subarachnoid pathwas are visualized. The method was used as a "first-line" diagnostic in cases of brain tumor in which localization of the tumor was impossible by traditional means. Like encephalography it depends upon deformities of the ventricular system for its efficacy. Ventriculography was always used in preference to encephalography in cases of increased intracranial pressure.

Myelography: Air myelography is a method of air injection into the spinal canal in order to outline the spinal subarachnoid space. Its greatest field of usefulness was as an aid in the diagnosis of spinal-cord tumors or of other obstructions of the spinal subarachnoid space.

*Arteriography

This technique was sometimes used in the diagnosis of brain tumor and aneurysms. The technique invloves the injection of 10 cc. Of thorotrast into the carotid artery, followed immediately by x-ray exposure and again two seconds later. The first films outline the arterial trunks (arteriograms), the second the veins (phlebogram). The method reveals the presence of tumor, aneurysm, or vascular deformities by the distortion of the normal vascular outline.

*CT Scan

CT images are computer-generated images of tissue density, produced by tomographically measuring the attentuation of tissue to x-rays passed through the body at different angles. CT scans, almost overnight, replaced the need for the rather unpleasant diagnostics listed above. The benefit to patients has been substantial through increased safety, accuracy, and promptness of diagnosis. The revolutionary nature of this type of imaging was recognized when the Nobel prize for physiology and medicine was awarded to A.M. Cormack and G.N. Hounsfield for work leading the the development of the x-ray CT.

The primary contribution of x-ray CT to our understanding of human brain function has been to provide highly accurate ante-mortem data on the location of specific areas of injury affecting human brain function. This has permitted accurate correlations to be made between the signs and smptoms of an illness and the specific brain structures involved.

MRI (Magnetic Resonance Imaging)

How it Works:

MRI depends on the action of spinning atomic nuclei when exposed to a magnetic field and radiowaves. The spinning atomic nucleus imaged is almost always hydrogen, a solitary proton, for two reasons: (1) High abundance in the human body (70% of the body is H20) and (2) high MR sensitivity for signal detection. The nucleus of the hydrogen atom, a single spinning proton, is positively charged. It, therefore, behaves like a small bar magnet and aligns with a strong external magnetic field (actually it behaves like a wobbling child's top, precessing about the axis of the external magnetic field depending on the field's strength). If a short burst of radiowaves (RF energy) at exactly the same frequency as the precessing proton is applied, the nuclei start precessing in phase and emit a coherent signal (MR signal). This phenomenon called resonance adds energy and the excess energy must be dissipated. The time required for dissipation is indicated by the magnetic relaxation time and depends on the molecular environment of the tissue. Every tissue in the body can be characterized by its normal relaxation values. When tissue is altered by disease, the relaxation values may change. Since these relaxation values affect the intensity and duration of the RF signal emitted by the protons, the changes can be interpreted as pathological alterations.

Interpreting Images:

Signal in MR images is high or low (bright or dark), depending on the pulse sequence used, and the type of tissue in the image. The following tables are a general guide to how tissue appears on T1- or T2- weighted images (which refers to the pulse sequence type).

Dark on T1-weighted image:
increased water, as in edema, tumor, infarction, inflammation, infection,
hemorrhage (hyperacute or chronic)
low proton density, calcification
flow void

Bright on T1-weighted image:
fat
subacute hemorrhage
melanin
protein-rich fluid
slowly flowing blood
paramagnetic substances: gadolinium, manganese, copper
calcification (rarely)
laminar necrosis of cerebral infarction

Bright on T2-weighted image:
increased water, as in edema, tumor, infarction, inflammation, infection,
subdural collection
methemoglobin (extracellular) in subacute hemorrhage

Dark on T2-weighted image:
low proton density, calcification, fibrous tissue
paramagnetic substances: deoxyhemoglobin, methemoglobin
(intracellular), iron, ferritin, hemosiderin, melanin
protein-rich fluid
flow void

Contrast agents in MRI:

Contrast agents generally serve the same purpose as the iodine-containing materials used in x-ray: They increase the sensitivity, conspicuity, and accuracy of an exam. The agent most commonly used is Gadolinium-DTPA (Gd-DTPA), also called Magnevist. If the hospital is thorough it will perform an MRI w/ or w/out contrast to detect any interscan descrepancies.

Contrast Agents are indicated for the following neurological illnesses or syndromes:

A. Central Nervous System
1. Primary brain tumors
2. Metastatic disease
3. Seizures
4. Inflammatory disease
5. Postoperative brain
6. Recurrent tumor vs. scar
7. Acoustic neuroma (also evaluation of deafness)
8. Pituitary adenoma
9. Differentiation of microvascular from macrovascular infarction
10. Selected cases of complex vascular disease

B. Spine
1. Differentiation of recurrent disc vs. scar or granulation tissue
2. Spinal cord neoplasm
3. Any case of myelopathy
4. Inflammatory cord disease, particularly myelitis or multiple sclerosis

MRI Neurological Indications:

A. Malignancy

B. Metastatic

Application: Procedure of Choice

With an accuracy rate approaching 100%, MRI discloses areas, such as the cerebellar and brain stem regions, that are "hidden" from CT. It is estimated that CT may miss up to 15.5% of hemispheric tumors.

C. Intracranial Vascular Lesions
1. Vascular Malformations
   Arteriovenous: Serpiginous, multiloculated flow void
   Venous angioma: Parallel line sign of misregistered slow flow
   Cavernous Hemangioma: Calcification with hyperintense center and hypointense hemosiderin ring (T2)
   Telangiectatic or Capillary Hemangioma: Thin spiderlike foci of flow void or increased signal
2. Aneurysms: Lamellated foci of alternating signal void, bright signal (clot of slow flow) and hypointense signal (hemosiderin and vessel wall)
3. Dolichoectasia: Basivertebral > carotid, flow void without clot, thrombus, or hemorrhage (may produce mass effect on brain stem)
4. Moyamoya Collaterals: Punctate foci of signal void (fast flow), frontal, subfrontal, and centrosylvian distribution.
5. Hemangiopericytoma: Dural based, homogeneous enhancement, mixed hyperintense T2 signal (resembles angioblastic meningioma on histology)

D. Multiple Sclerosis

Vascular White Matter Disease vs. MS

Application: Procedure of choice

CT has no more than a 50% success rate in diagnosing MS plaques. MRI is more sensitive and replaces the need for CT, CSF studies, and urinary dynamics.

E. Parkinson's Disease

1.Generalized atrophy
2.Alteration in brain iron stores with exaggerated putaminal hypointensity
3.Loss of normal signal hypointensity in the dorsal lateral sub stantia nigra on T2 (40%)
4.Narrowing of the normal hyperintense signal of the zona compacta of substantia nigra on T2 (10%)

Value-added MRI Factoids:

***Potential risks** of MRI fall into four categories:

1.)*Those caused by static magnetic fields:*
Static magnetic fields generate electric current across moving blood; therefore, EKG changes have been observed in patients exposed to these fields. It has been shown that intracranial aneurysm clips having high nickle content may experience torque when placed in a static magnetic field, separating the clip from the vessel (gross, hunh).
2.)*Those caused by rapidly changing magnetic fields (the gradients):*
For varying magnetic fields (gradients), the potential problem is posed as a consequence of Faraday's Law (a changing magnetic field induces a voltage in a conductor. If the conductor is a closed circuit, a current will flow). Patients with pacemakers are not candidates for MRI since currents will be induced in the pacemaker leads. In addition, pacemakers may switch from the demand to asynchronous mode when exposed to the magnetic field. Currents induced in surgical clips may cause local heating (these effects have been examined in detail and found to be nonsignificant). Physiological effects of induced electric currents range from benign visual light flashes (magnetophosphenes) to platelet activation, skin sensations, muscle contractions, and ventricular fibrillation as the gradients are changed rapidly. The threshold for visual phenomenon is 4.4 Tesla per second at repetition rates of 30 per second (pretty cool…magnetically-induced visual hallucinations).
3.)*Those caused by the RF magnetic fields:*
The only potential hazard attributable to RF magnetic fields are tissue heating and heating of metallic implants. Heating of metallic implants has been found to be insignificant for surgical clips and possibly insignificant for larger prostheses. Tissue heating can be compared to the heat generated by the human body at the basal metabolic rate and during heavy exercise.
4.)*Acceleration of Ferromagnetic objects:*
Ferromagnetic objects can be accelerated to potentially lethal velocities by the static magnetic field. For this reason, such objects should be strictly excluded from the MRI magnet room (the watch or pen that became a bullet…).

***MRI Imaging Terminology:**
Tesla: a measure of magnetic strength
Gauss: a measure of magnetic strength
Exclusion Zone: the point at which the magnetic field becomes 5 gauss in strength
Security Zone: the magnet room
Magnetic Susceptibility: refers to how easily a material becomes magnetized when placed in

a magnetic field
Ferrous: material that has a high positive magnetic susceptibility
Nonferrous: material that has no magnetic susceptibility
Diamagnetic: material that has small negative magnetic susceptibility
Paramagnetic: material that has positive magnetic susceptibility

Positron Emission Tomography (PET)

Introduction:

Emission tomography is a nuclear medicine technique that produces an image of the distribution of radioactivity in the human body, resulting from the administration of a substance containing radioactive atoms. PET uses the unique properties of radioactive atoms, that decay by the release of positively charged particles called positrons, to provide an image that is a highly faithful representation of the spatial distribution of radioactivity in selected planes through the tissue. The radioactive atoms most frequently employed in PET are atoms with very short half-lives that are commonly utilized in the body's physiological processes, such as oxygen-15 (122 seconds), nitrogen-13 (10 minutes), and carbon-11 (20 minutes). Because of the development of ingenious labelling techniques, radio-chemists can incorporate these atoms into compounds utilized normally by the body, such as glucose or oxygen, permitting clinical investigators to monitor safely and accurately such important physiological processes as brain metabolism and blood-flow with PET.

Positron emission tomography (PET) has enhanced our understanding of the biochemical basis of normal and abnormal functions within the body, and permitted biochemical examination of patients as part of their clinical care. These capabilities are important because:

1. The basis of all tissue function is chemical.
2. Diseases result from errors introduced into its chemical systems by viruses, bacteria, genetic abnormalities, drugs, environmental factors, aging, and behavior.
3. The most selective, specific, and appropriate therapy is one chosen from a diagnostic measure of the basic chemical abnormality.
4. Detection of chemical abnormalities provides the earliest identification of disease, even in the presymptomatic stages before the disease process has exhausted the chemical reserves or overridden the compensatory mechanisms of the brain.
5. Assessment of restoration of chemical function provides an objective means for determining the efficacy of therapeutic interventions in the individual patient.
6. The best way to judge whether tissue is normal is by determining its biochemical function.

Another principle relates to the value of examining these biochemical processes with an imaging technology. Because in most cases the location and extent of a disease is unknown, the first objective is an efficient means of searching throughout the body to determine its location. Imaging is an extremely efficient process for accomplishing this aim, because data are presented in pictorial form to the most efficient human sensory system for search, identification, and interpretation‹the visual system. Recognition depends upon the type of information in the image, both in terms of interpreting what it means and how sensitive it is to identifying the presence of disease.

How it works:

PET images are based on the *in vivo* detection of two high-energy, annihilation radiation photons (511 kilo electron volts) that simultaneously emerge from tissue, after the local interaction of a positron with an electron. Detection of the annihilation radiation is based on the use of the coincidence circuits, in which two oposing radiation detectors record an event in the tissue between them only when two annihilation photons strike the detector coincidentially. To optimize the efficiency of such a system, detectors are usually arrayed about the head

in a circular fashion (hence, the donut looking apparatus). The use of several rings of detectors permits the simultaneous measurement of radioactivity in several tomography slices of the tissue.

Radiolabeled tracers are employed throughout the biological sciences to measure such processes as blood flow, membrane transport, metabolism, synthesis, and ligand-receptor Interactions; for mapping axonal projection fields through anterograde and retrograde diffusion; measurement of cell birth dates; marker assays using recombinant DNA techniques; radioimmunoassays; and the study of drug Interactions with chemical systems of the body. The tracer technique continues to be one of the most sensitive and widely used methodologies for performing assays of biological systems. PET allows the transfer of the tracer assay methodology to the living subject, particularly humans. PET builds a bridge of communication and investigation between the basic and clinical sciences, based upon a commonality of methods used and problems studied.

The transfer of tracer methods from the basic biological sciences to humans with PET is made possible by the unique nature detection. Natural substrates, substrate analogs, and drugs can be labeled with these radio isotopes without altering their chemical or biological properties. This allows the methods, knowledge, and interpretation of results from tracer kinetic assays used in the basic biological sciences to be applied to humans by the quantitative measurement abilities of the PET scanner.

PET Tracers:

I. **Oxygen** - Oxygen-15 has a half-life of 2.1 minutes.

- Radiolabeled water and carbon dioxide have both been used to study local cerebral blood flow
- Oxygen extraction fraction. [15O]-labeled oxygen can be used to measure tumor necrosis.

II. **Nitrogen** - Nitrogen-13 has a half-life of 10.0 minutes.

- [13N]-labeled ammonia can be used to measure blood flow. This tracer moves from the vascular space to tissue by both active transport (sodium-potassium pump) as well as by passive diffusion. Once inside cells, this tracer is primarily metabolized by the glutamic acid-glutamine pathway. [13N]-ammonia has been found to be an excellent measure of regional myocardial perfusion in both normal and diseased states.

III. **Carbon** - Carbon-11 has a half-life of 20.4 minutes.

- Carfentanil is a mu-opiate receptor agonist that is approximately 8000 times more potent than morphine.
- [11C]-labeled carfentanil is use with PET to study opiate receptors in the brain (Dannals, et al., 1985, 1993).
- PET can be utilized for the identification and characterization of drug binding sites in the brain. [11C] labeled cocaine has been utilized in human and monkey brain to study the distribution and pharmokinetics of this agent. For example, it was demonstrated that cocaine is rapidly taken up and cleared from the striatum, and the time course of this parallels the temporal pattern of the "high" experienced with cocaine. PET has also been used to study the biochemical effects of cocaine. It has been demonstrated that while acute doses of cocaine have little, if any, effect on dopamine D2 receptor availability (measured with [11C]N-methylspiroperidol), chronic cocaine results in a down regulation of D2 receptors. Dopamine metabolism is also reduced in chronic cocaine abusers (measured with 6-[18F]fluoro-L-DOPA).
- The distribution of monoamine oxidase (MAO) type B, the isoenzyme that catabolizes dopamine, has been monitored in the human brain by PET following injection of radioactive [11C]-deprenyl (Fowler, et al., 1987). Deprenyl is a potent MAO B inhibitor and has been shown to be effective in the treatment of early Parkinson's disease.
- [11C]-labeled methionine and leucine can be used to evaluate amino acid uptake and protein synthesis, providing an indicator of tumor viability.
- N-methylspiperone (N-methylspiroperidol) binds to dopaminergic D2 receptors. [11C]-labeled N-methylspiperone has been used to study the neurochemical effects of various substances on dopaminergic function.

- [11C]-labeled raclopride is used in PET to study the function of dopaminergic synapses. Raclopride binds to dopamine D2 receptors and is a selective, reversible inhibitor of dopaminergic D2 receptor function.

IV. **Fluorine** - Fluorine-18 has a half-life of 109 minutes.

- PET has been used to study the binding sites of haloperidol, a widely used antipsychotic and anxiety reducing drug. Haloperidol is a potent antagonist of the neurotransmitter dopamine, and acts on dopamine D2 receptors. Recent evidence suggests that haloperidol may also act on other types of dopamine receptors, since [18F]-haloperidol binding is seen in the cerebellum, a structure devoid of D2 receptors (Fowler, et al., 1990).
- Fluorodopa - 18F-labeled PET tracers are used in neurology to study metabolism, neurotransmission, and cell processes. L-[18F]DOPA can be used to examine the presynaptic distribution of stored neurotransmitter. L-DOPA is the precursor for the neurotransmitter dopamine and radiolabeled L-DOPA is taken up by dopaminergic terminals and becomes incorporated into the neurotransmitter. L-[18F]DOPA has been used clinically in the study of Parkinson's disease.
- Fluoroethylspiperone - 18F-labeled PET tracers are used in neurology to study metabolism, neurotransmission, and cell processes. [18F]-labeled fluoroethylspiperone is a radioligand used to probe dopamine D2 recepors. [18F]-FESP binds to D2 receptors with high affinity; up to 10x higher than raclopride, for example. PET studies of dopaminergic function have been used to monitor hormonal effects (Wong, et al., 1988), aging (Iyo, et al., 1989), and neuropathological conditions such as Parkinson's disease and Schizophrenia.

Single Photon Emission Computed Tomography (SPECT)

Equipment:

Single Photon Emission Computed Tomography (SPECT) images of the brain can be performed using either multidetector or rotating gamma camera systems. Each imaging system has its own advantages; the choice of equipment depends on the level of utilization and on the purposes for which the technique will be applied.

SPECT images are generated using gamma cameras or ring-type imaging systems that record photons emitted by tracers trapped in the brain. SPECT results in better image quality than planar (2-D) imaging because focal sources of activity are not superimposed upon each other; hence the signal-to-noise-ratio (i.e. the contrast between the target and the background activity) becomes greatly increased.

The high collection efficiency of the multidetector system makes rapid scanning of an entire slice possible. The primary advantage of this system is its high sensitivity, resulting in high spatial resolution and rapid imaging of the organ. As a result, SPECT perfusion images of the brain can be obtained with a spatial resolution of 10 mm FWHM (full width at half maximum) in the plane of the slice. The multidetector system would, therefore, be the preferred instrument for studies requiring high spatial resolution, regional quantification, or rapid sequential imaging.

The rotating gamma camera approach is preferable for routine clinical imaging because of its availibility and because it can be used for other types of the tomographic and nontomographic imaging. The major constraint on rotating tomographic gamma camera tomography is sensitivity. The low sensitivity on each tomographic slice is compensated for by the fact that the gamma camera collects volumetric information obtained with multidetector system. With the rotating gamma camera, data is collected from multiple views obtained as the sodium iodide detector rotates about the patient's head. Since spatial resolution and image quality are dependant on the total number of primary, unscattered photons recorded by the detector, gamma cameras have been designed with multiple detectors to improve instrument sensitivity.

Special purpose ring-type imaging systems are also designed to maximize the amount of detector recording activity from the brain. They use multiple detectors or a single sodium iodide ring and collect activity simultaneously from either a single or multiple slices (multidetector systems) or from all regions of the brain (annular detectors). Special purpose systems produce high quality images with a spatial resolution of 5 to 6 mm FWHM.

The volume imaging capacity of most SPECT systems permits reconstruction at any angle, including the axial, coronal and sagittal planes, or at the same angle of imaging obtained with CT or MRI to facilitate image comparisons. SPECT images can be merged with MRI and CT, creating a single image that combines anatomy and physiology (morphological and functional correlation). three dimentional surface and volume rendered images add perspective and facilitate the localization and sizing of lesions.

What is "NORMAL"

A clear and unequivocal knowledge of what represents normal brain perfusion is a prerequisite to objective interpretation of scans. The extent of anatomic variability must be recognized and accounted for. Normal perfusion and the acceptable limits of variability in each region must be recognized.

Patients without central nervous system disease and with normal X-Ray/ CT examination demonstrate bilaterally symmetrical activity on the SPECT perfusion images. Activity is greatest along the convexity of the frontal, temporal, parietal and occipital lobes -corresponding anatomically to cortical gray matter. Activity is also high in the regions corresponding to the basal ganglia and thalamus. Regions between the basal ganglia and the convexity corresponding anatomically to cortical white matter and the ventricles have less activity.

Cerebral perfusion tracers

A number of commercially available and experimental pharmaceuticals have been applied to SPECT studies of cerebral perfusion. The radiotracer accumulates in different areas of the brain proportional to the rate of delivery of the blood to that volume of brain tissue. Accumulation is described in units of ml/min/100 g (differing from the flow of blood in vessels, which is described in units of ml/min).

Perfusion may also be referred to as regional blood flow or, in the brain, regional cerebral blood flow (rCBF)". Implicit in the use of those tracers that remain in the brain is the notion of a multicompartment clearance (the microsphere model). This model assumes that : injected isotope is freely diffusible from the blood pool into the brain the brain extracts all or nearly all of the available isotope by the blood once in the brain tissue, the isotope is fixed, or "trapped", or that backflux from the brain into the blood can be accounted for, and following initial tracer uptake, its initial redistribution is nil.

This approach also assumes that all compartments --including the blood pool and the brain tissue --are accounted for in the model and that forward (and reverse) transport of the tracer are predictable throughout the brain, as are potentially confounding influences such as inhomogenecities in flow, extraction, and potential receptor binding. Many if not all of these assumptions are violated to greater or lesser degrees by virtually all available flow tracers. Despite these caveats, work in animals and humans has demonstrated that, under properly controlled conditions, SPECT data obtained with perfusion agents approximates perfusion closely enough to be meaningful in clinical and research studies.

Furthermore, most routine clinical applications of brain-perfusion SPECT do not require quantitation of rCBF and rely exclusively on the generation of images that reflect tracer uptake and retention only. Tracer activity in the brain correlates well with independent measures of rCBF over a wide range of flow, but achieving this determination requires arterial sampling, scrupulous technique and highly accurate instrumentation.

Regional blood flow measurement (functional brain imaging)

Functional brain imaging requires radiotracers that cross the blood brain barrier, distribute proportionally to regional cerebral blood flow, and remain fixed in the brain for a sufficient time to permit SPECT imaging. For radiotracers that have a very slow clearance from the brain, estimates of regional cerebral blood flow (rCBF) are based on the microsphere model, which assumes that:

- the radiotracer is freely diffusible from the blood pool,
- it is completely extracted from the blood into the blood brain barrier, and
- it remains fixed within the brain without redistribution.

Only microspheres injected directly into the carotid artery can satisfy these requirements completely, however radiotracers that are available for brain perfusion imaging follow rCBF closely enough to be clinically useful.

Quantitative blood flow measurment

Blood flow can also be measured quantitatively from the clearance of the inert blood gas Xenon-133 with highly sensitive instrumentation that can image its distribution repeatedly during its rapid clearance from the brain. Most routine clinical applications of brain perfusion SPECT do not require quantitation of rCBF and rely on the generation of images which reflect tracer uptake and retention only. Quantitation of regional cerebral blood flow using these radiotracers requires arterial sampling and careful modeling to account for incomplete extraction, back flux from the brain and other deviations from the theoretical model. Despite such constraints, intravenous injection of brain perfusion radiotracers results in regional brain activity which correlates well with independant measures of rCBF over a wide range of flows.

The following are the chief radiotracers employed for brain-SPECT imaging:

Iodine-123 ligands - I-123-IMP is highly lipophilic, and moves across the blood brain barrier with almost complete extraction during a single passage through the cerebral circulation. Even though the amine has a low affinity for blood brain barrier transport sites, the speed of uptake is very fast compared to glucose. It distributes proportionally to rCBF under normal physiologic conditions and over a wide range of flow, but may be decreased with low plasma pH as in respiratory acidosis, metabolic acidosis or cerebral ischemia. In the human, brain uptake of IMP is rapid, reaching 45% of the maximum brain activity by 2 minutes and 6-9% of the injected dose by 30 minutes. The clearance of the tracer from the brain is balanced by slow release of IMP from the lungs. Thus brain activity remains constant from 20 minutes to at least 60 minutes after injection. The gray to white activity ratio remains almost constant during that time. By 24 hours, the gray/ white matter activity ratio has reversed, and activity is higher in the white matter. IMP concentration in brain tissue immediately after an intravenous bolus injection is a reflection of blood flow. As the distribution of the tracer equilibrates between brain and blood over time, the brain concentration becomes a function of the partition coefficient. IMP washes out of the brain relatively slowly.

99m-Technitium ligands - Technetium-99m-hexamethyl propylamine oxime (Tc-99m-HMPAO, Ceretec, Amersham Ltd., U.K.), now known as Tc-99m-exametazime, is a lipid soluble macrocyclic amine. Brain uptake of the radiotracer is rapid and reaches its maximum within 10 minutes post-injection time. Its first-pass extraction into the brain is less than that of I-123-IMP, and it underestimates rCBF. However, this underestimation can be corrected by accounting for the freely exchangeable component of HMPAO. The distribution of the radiotracer remains constant for many hours post-injection. Once it crosses the blood brain barrier, 99m-Tc-HMPAO is converted into a hydrophilic compound in the presence of intracellular glutathione and is trapped, with slow blood clearance.

Limitations:

- Perfusion defects are not seen as sharply as with I-123-IMP.
- Tc-99m-HMPAO may also mask ischemic lesions in subacute stroke because of hyperemia resulting in normal or increased tracer uptake.
- The radiopharmaceutical is chemically unstable in vitro by 30 minutes after preparation.

Xenon-133 - The inert gas Xenon-133 has long been used to study rCBF by clearance techniques that relate the change in radiotracer activity over time to blood flow. A number of centers have used SPECT to measure perfusion following the inhalation of Xe-133.

Advantages

1. rCBF can be measured quantitatively without arterial sampling
2. Owing to its rapid clearance from the brain, multiple studies can be performed

Limitations

1. It has a low photon energy (80 KeV) which is (a) difficult to image and (b) cause photon attenuation by brain structures.
2. Its rapid clearance from brain (a) causes poor spatial resolution and (b) requires very sensitive instrumentation to capture photons.
3. The inhalation technique is technically more difficult than giving an intravenous injection.

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