# Single photon emission computed tomography (SPECT)

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*Journal of the Ceylon College of Physicians,* 1995, **28**, 74-78

The introduction of Single Photon Emission Computerised Tomography has markedly enhanced study of brain function. The development of SPECT was a culmination of a series of investigations of cerebral blood flow pioneered by Kety and Schmidt in the late 1940's, combined with the introduction of transmission computerised tomography in the early 1960's in which three dimenional images are derived from two dimensional data[1].

Positron emission tomography (PET) in addition to providing information on cerebral blood flow, also allows the evaluation of brain metbolism and neuro transmitter receptor function[1].

However, the technology required for PET is expensive and sophisticated with little prospect for general clinical application. Fortunately, SPECT is relatively cheap and widely available for clinical use.

**Evolution of SPECT**

Kety and Schmidt in 1948[2] pioneered CBF studies in man using nitrous oxide as a diffusible agent. This required inhalation of nitrous oxide and sampling of arterial and internal jugular venous blood and could only provide a measure of whole brain blood flow.

Next, techniques to measure Regional Blood Flow followed and used freely diffusible radio nuclides such as:

- Krypton - 85
- Xenon - 133

which were injected into the carotid artery.

Xenon-133 emits gamma radiation which can be detected through the intact skull and multiple scintillation probes allow the measurement of CBF in specific regions of the brain.

Recently new radio tracers labelled with iodine 123 and Technetium 99M have been introduced. These lipophilic radio pharmaceuticals cross the blood brain barrier and distribute in proportion to the regional cerebral blood flow shortly after intravenous injection. They are trapped in the brain and have a stable or static distribution over time, unlike freely diffusible dynamic radio traces, such as Xenon, enabling images of higher resolution to be obtained.

These agents can be used with the conventional rotating gamma cameras that are widely available in most nuclear medicine departments, whereas Xenon labelled agents cannot.

The most advanced SPECT systems are now capable of resolution of 8 mm and imaging times as short as two — three minutes for regional cerebral blood flow.

Further technological advances in detector sensitivity and data analysis allowed the replacement of intra-arterial injections by intra venous infusions or inhalations of gaseous Xenon so that the measure of regional cerebral blood flow became a non invasive procedure.

The regional cerebral blood flow data were initially presented in two dimensions and essentially reflected cortical flow, but with the development of the tomographic technology for SPECT a three dimensional cerebral blood flow could be obtained.

Radio tracers used in SPECT emit a single gamma ray (or Photon) as opposed to the dual simultaneous gamma rays of PET radio tracers and hence the term "single photon".

Unlike PET, there is no current propect of SPECT being able to provide a direct measure of regional cerebral metabolism but its use to measure neuro transmitter receptors is an evolving technique.

The radio ligand iodine[1,2,3] — 3 Quinuclidinyl 4 iodobenzylate has been developed for the measure of muscarinic acetyl choline receptors and has been applied in the study of Alzheimer's disease.

**Normal subjects and normal aging**

The pattern of regional cerebral blood flow reported in normal subjects reflects, at least in part, the conditions of the subjects at the time.

For example, if subjects are studied with eyes open the visual cortex has the highest individual regional cerebral blood flow but if the eyes are closed the regional cerebral blood flow is reduced.

Presently there are no generally accepted standards for the control or resting state, but it is clear that these should be standardised for any individual study.

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Initial studies of the whole brain found a reduction in cerebral blood flow and cerebral metabolic rate of oxygen with age (Kety 1956). Subsequent studies have however, generally confirmed that cerebral blood flow does fall slightly with age[4].

Also, asymptomatic elderly patients with atherosclerosis or hypertension have significantly reduced cerebral blood flow, although the cerebral metabolic rate of oxygen was not reduced to a similar level. Reduced cerebral blood flow occurs in relation to both advancing age and progressive cerebral vascular disease.

The researchers concluded that hypertension was the most important predisposing factor for a significant reduction in cerebral blood flow.

**Activation studies**

Two dimensional and tomographic techniques to study regional cerebral blood flow and regional metabolism have been used to study brain function in relation to:

1. Sensory
2. Motor
3. Congitive
4. Pharmacological Activation

A number of PET studies have demonstrated that sensory stimulation is associated with increased regional cerebral blood flow or metabolism with area specific activation depending on the sensory modality stimulated[6]. For example SPECT has demonstrated increased regional cerebral blood flow in the visual cortex in response to visual stimulation.

The left posterior, inferior frontal region (Broca's area) has increased flow during speech while the posterior region of the right hemisphere has increased flow during visuo-spatial problem solving[7].

In the normal brain under resting conditions energy is provided almost entirely by the oxidative metabolism of glucose, and over 90% of glucose metabolism occurs by oxidation. Thus in the normal individual at rest, the regional cerebral blood flow is closely coupled to the regional metabolism of glucose and oxygen and is felt to reflect underlying cerebral function.

In normal resting individuals regional cerebral blood flow and the regional cerebral metabolic rate of oxygen on glucose will provide similar information about underlying cerebral function but when physiologically (or perhaps pharmacologically) stimulated then they convey information about different aspects of cerebral function, with none being automatically considered to be the most relevant index of cerebral function. Similarly, in pathological cerebral conditions, close coupling of regional cerebral blood flow and cerebral metabolic rates of glucose and oxygen cannot be automatically presumed to be retained[8].

**Studies in dementia**

In addition to the effects of normal ageing, functional imageing studies in dementia have three further problems:

1. Normal variation in measures of cerebral blood flow or metabolism
2. Uncertainty of diagnosis of type of dementia; i.e. Alzheimer's disease or multi infarct dementia.
3. Presence of cerebral atrophy.

Brain atrophy occurs with ageing in normal individuals and with greater severity in patients with dementia than age matched controls.

However, some demented individuals have little atrophy while some normals show considerable atrophy.

Consequently, areas of apparently reduced regional cerebral blood flow in patients with dementia may be due to:

1. Reduced flow to a normal volume of brain.
2. Normal flow to a reduced volume of brain.
3. Reduced flow to a reduced volume of brain.

The studies of Kety and Schmidt have shown lower rates of mean cerebral blood flow in patients with dementia than in normal subjects and more subsequent studies have confirmed these findings.

**PET studies**

Studies using PET have been able to make regional measurements of oxygen and glucose metabolism in addition to regional cerebral blood flow in dementia.

In Alzheimers disease, whichever index of cerebral activity is measured, the studies demonstrate a similar pattern of regional pathology which is characteristically bilateral in posterior temporal and parietal regions in the early stages and later affects the frontal lobes.

White matter as well as grey matter is affected but the primary motor, sensory and visual cortices are unaffected.

The PET studies have confirmed that the reduction

in mean cerebral flow and oxygen and glucose metabolic rates are correlated with a degree of dementia.

Severe language impairments show a focal left hemisphere hypometabolism.

Marked personality changes or attentional deficits have promitnent frontal hypometabolism.

**SPECT**

The use of SPECT to study dementia has been reported since the mid 1980's.

Bonte et al (1986)[12] used Xenon 133 and found that of 24 patients with probable Alzheimer's disease, 19 had perfusion deficits which were most commonly found in the parieto-temporal region bilaterally and less frequently in the frontal lobes. Patients with multi infarct dementia had a patchy distribution pattern.

Xenon 133 SPECT — involves measuring temporal variation in activity. Image characteristics are relatively poor because of the scatter of low energy gamma rays.

Iodine 123 Iodoamphetamine — does not have these technical problems and its initial cerebral uptake is proportionate to regional cerebral blood flow[13].

It was the first tracer to be used in static SPECT studies of dementia.

Patients with Alzheimer's disease have deficits in flow which are maximal bilaterally in the parieto-temporal cortex while patients with multi infarct dementia vary from having a normal pattern to marked asymmetric focal deficits anywhere in the cortex[14].

Despite having regional abnormalities on SPECT the majority of patients had a normal appearance in those regions on MRI. The use of iodine 123 Iodoamphetamine is restricted because:

1. Redistribution of tracer occurs one hour after injection.
2. Half life of iodine 123 is 1 hour (long) and is costly to produce and requires a cyclotron.

**$^{99}$ Technetium hexa methyl propylene amine oxime SPECT — 'CERETEC'**

1. Readily available from commercial generators in nuclear medicine departments.
2. Inexpensive.
3. Shorter half life (six hours) than iodine 123.

However, labelling with Technetium is a much more complex procedure and the development of a technetium labelled compound to provide a measure of regional cerebral blood flow was a major advance in SPECT technology resulting in a joint research programme between.

1. Amersham International and
2. The University of Missouri.

Technetium labelled Hexa Methyl Propylene Amine Oxime is a lipophic tracer which comes in a freeze dried kit which after intravenous administration crosses the blood brain barrier with high extraction and is retained in the brain in hydrophilic form. The brain uptake occurs over the first two minutes and has a stable distribution for many hours[15].

This enables conventional equipment to be used to detect the radiation emitted from the brain.

Comparative studies in PET in humans reveal a tendency to:

> Under estimate areas of increased regional cerebral blood flow but a good correlation exists between areas of low and medium cerebral blood flow[16].

$^{99}$Technetium HMPAO cannot at present be used to quantify regional cerebral blood flow absolutely, the results however can be expressed semi quantitively by comparing the counts in each brain region of interest (ROI) to a reference area such as the whole brain or cerebellum.

The early studies used qualitive assessment of the images and found that most patients with Alzheimer's disease had a bilateral parieto-temporal deficit.

Those who did not tended to be less impaired cognitively[17]. Frontal deficits were also seen in Alzheimer's disease in the more severely impaired patients.

The later studies have generally been semi quantitative. When a rotating gamma camera is used the whole brain is scanned and the cerebellum has been used as the reference area as it is relatively unaffected by the pathology of Alzheimer's disease[18].

Studies have consistently shown the patients of Alzheimer's disease have a bilateral decrease in cerebral blood flow in:

- posterior temporal
- parietal regions adjacent to the occipital lobes. Sometimes the frontal lobes are affected.

**Activation studies**

Pharmacological activation studies of the effect of central cholinergic stimulation upon regional cerebral

blood flow in Alzheimer's disease have recently been reported. Paired SPECT studies, firstly basal, (after saline infusion) was compared with activated (after infusion of cholinergic agents; e.g. Physostigmine).

In patients with Alzheimer's disease the reduced cerebral blood flow in posterior parieto-temporal region in the basal scan was focally increased after the cholinergic agent[19].

The effect of cholinergic stimulation did not occur in control subjects. The regional cerebral blood flow response to cholinergic stimulation is interpreted as evidence of a functional cholinergic deficit that is at least partly reversible.

**Discussion**

Studies employing SPECT or PET can reveal cerebral abnormalities when C.T. and M.R.I. do not, because the latter are measures of cerebral structure while the former are measures of function.

SPECT is likely to remain much more generally available than PET, but is not currently capable of absolute quantification. This has been regarded as a deficiency but the normal individual variation in the absolute values of regional cerebral blood flow and metabolic rate is such that absolute measurements are of limited value.

The characteristic SPECT findings of Alzheimer's disease are bilaterally decreased regional cerebral blood flow in the parietal and temporal lobes adjacent to the occipital lobes. Sometimes involving the frontal lobes especially in late (advanced) cases.

The primary motor sensory visual cortices and basal ganglia are relatively unaffected.

This contrasts with the typical C.T. findings of diffuse cerebral atrophy though the C.T. scans were not orientated along an axis that obtains optimal views of any focal atrophy in the hippocampus or temporal lobe.

The extent of focal C.T. abnormalities is less than that seen on SPECT and it appears that structural atrophy lags behind clinical deficit[20].

**The appropriate role of SPECT in current clinical practice in the assessment of dementia**

1. If the clinical diagnosis of dementia is made in an individual patient and it appears to be a primary degenerative dementia, the SPECT can add weight to the clinical impression that the underlying diagnosis is that of Alzheimer's disease or a dementia of the frontal lobe type (D.F.T.) or a progressive supranuclear palsy (P.S.P.).

   Alzheimer's disease is most characteristically associated with posterior regional cerebral blood flow deficits.

   D.F.T. and P.S.P. are associated with anterior regional cerebral blood flow deficits[21].

   C.T. scans are not particularly helpful.

2. SPECT can help in the clinical assessment in the differentiation of Alzheimer's disease from multi infarct dementia.

   Bilateral parieto-temporal deficits are strongly suggestive (but not diagnostic) of Alzheimer's disease though it must be remembered that multi infarct dementia and Alzheimer's may co-exist.

   There is no particular single pattern for regional cerebral blood flow deficits in multi infarct dementia.

   SPECT findings vary from normal to asymmetric deficits and theoretically, multi infarct dementia could mimic any other pattern.

   Multi infarct dementia is likely if the regional cerebral blood flow deficits coincide with cerebral infarct seen on structural imaging on C.T. or M.R.I.

   If a patient with a relatively advanced dementia has a normal SPECT scan it is unlikely to be Alzheimer's disease and may be consistent with multi infarct dementia.

   All these conclusions however, must be tempered with the knowledge that our present association of the SPECT (and PET) patterns with specific conditions is based on studies where clinical diagnoses of patients are made initially and then correlated with SPECT findings. These have not been compared with postmortem diagnoses. Therefore we need further follow up studies and pathological findings postmortem to make more definite assessments of the significance of specific SPECT patterns.

3. We could learn whether the SPECT studies could help predict clinical outcome in individual cases.

   SPECT may have different predictive power in comparison with PET in early Alzheimer's disease.

4. It is possible that patients at risk of Alzheimer's disease may be diagnosed in the pre-symptomatic phase by the SPECT findings of reduced regional cerebral blood flow in the parieto-temporal regions.

   It is clear that SPECT will be used substantially in further research in Alzheimer's disease.

Most significant advances in our knowledge are likely to come from activation studies.

Pharmacological activation studies would enable direct measurements of specific neuro transmitter function to be made and hence the pharmacological characterisation of disease in an individual with implications for treatment and prognosis.

5. Another promising direction of SPECT is a study of neuro transmitter receptors.

The radio ligand 123 iodine quinuclidinyl iodobenzylate has been developed for the measurement of muscarinic cholinergic receptors and it has been used in the study of Alzheimer's disease.

Currently it requires a radio chemist on site to produce 123 quinuclidinyl iodbenzylate so it is not commercially available, but the development of radio ligands for general use in receptor studies is likely to continue and therefore to extend the role of SPECT

I wish to acknowledge the secretarial assistance of Dorothy Johnson.

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