

European Association of Nuclear Medicine Procedure Guidelines for Brain Perfusion SPET using ^{99m}Tc-labelled Radiopharmaceuticals

Tatsch K (Coordinator), Asenbaum S, Bartenstein P, Catafau A, Halldin C, Pilowsky LS, Pupi A

I. Purpose

These guidelines summarize the views of the European Association of Nuclear Medicine Neuroimaging Committee (ENC). The purpose of the guidelines is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of brain perfusion SPET studies using ^{99m}Tc-labelled radiopharmaceuticals. The aim is to achieve a high quality standard of brain perfusion SPET imaging, which can increase the diagnostic impact of this technique in neurological and psychiatric practice.

The present document has been inspired by the Society of Nuclear Medicine Procedure Guideline for Brain Perfusion SPECT [1], by the views of the Society of Nuclear Medicine Brain Imaging Council [2], the sights of the Task group Neuro-Nuclear-Medicine of the German Society of Nuclear Medicine [3, 4], and the individual experience of experts in European countries. The guidelines intend to present information specifically adapted to the European practice. The information provided should be taken in the context of local conditions and regulations.

II. Background information and definitions

Single photon emission tomography (SPET) is a technique to obtain tomographic images of the 3-dimensional distribution of a radiopharmaceutical. Applied to the brain, SPET imaging can be used to assess various functions, among those cerebral perfusion plays a predominant role. This information is often complementary to the anatomic detail provided by structural neuroimaging techniques such as CT or MRI. However, brain perfusion SPET has clinical value itself, because functional impairment in cerebral diseases often precedes structural changes. Further, functional abnormalities can be present in several neurologic and psychiatric disorders without the presence of a structural defect. SPET images are often useful in the clinical management of patients providing new and additional information that cannot be obtained from other techniques. Brain perfusion SPET has a role in the diagnosis, therapeutic management, and follow-up of patients. In addition it is a useful tool for research, because it is widely available and provides non invasive in vivo assessment of human brain function [5, 6].

Several radiopharmaceuticals are commercially available for brain perfusion SPET. Even though for quantification (ml/min/100g tissue) of regional cerebral blood flow (rCBF) ¹³³Xe-SPET may be the method of choice, it has some major limitations that have restricted its use in clinical practice. Today the most widely used radiopharmaceuticals for rCBF SPET are ^{99m}Tc-labelled compounds. After intravenous injection these lipophilic compounds cross the intact blood brain barrier, distribute in the brain proportional to local blood flow and are retained in the brain with a fixed regional distribution for a sufficient time period to permit image acquisition. The peak brain activity is reached within 2 min post-injection. Since there is no redistribution, the initial tracer uptake and distribution remains almost unchanged for several hours and is independent of rCBF variations occurring after the fixation time (frozen images, which represent the rCBF at the time of injection). Differences between the two commercially available radiopharmaceuticals, ECD (Neurolite; DuPont Pharma) and HMPAO (Ceretek; Nycomed Amersham) include in vitro stability, uptake mechanism and dosimetry. In normal brain tissue, however, the kinetic properties are very similar for both agents. They enter the brain cells due to their lipophilic nature and remain there due to

conversion into hydrophilic compounds. While de-esterification accounts for ECD retention, hydrophilic conversion, instability of the lipophilic form and glutation interaction have been proposed for HMPAO retention. Differences in the retention mechanisms may account for some different behavior of the tracers in specific disorders (e.g. subacute stroke, inflammation). It has to be kept in mind that with the techniques used in clinical practice ECD and HMPAO SPET do not provide absolute quantitative flow values but rather estimate relative regional flow differences based on the comparison of count density ratios between various regions (e.g. right/left, reference regions etc.).

This guideline deals with the indications, assessment, processing, interpretation and reporting of brain perfusion SPET using the commercially available ^{99m}Tc -labelled radiopharmaceuticals ECD and HMPAO.

III. Common indications

Indications

- A. Acute and chronic cerebrovascular disease. Perfusion SPET provides valuable information in acute stroke with respect to complications [7, 8], outcome [9-11] or choice of treatment strategy [12]. In chronic cerebrovascular disease rCBF SPET with assessment of functional reserve capacity may guide decisions regarding vascular surgery [13-16].
- B. Presurgical lateralisation and localisation of epileptogenic foci. Ictal SPET studies (eventually complemented by interictal investigations) are indicated in temporal and extratemporal focal epilepsies for localisation of foci prior to epileptic surgery [17, 18].
- C. Evaluation of suspected dementia. Indications include the early detection and differential diagnosis of dementia [19, 20].
- D. Evaluation of traumatic brain injury. SPET has shown perfusion abnormalities in traumatic brain injury despite normal morphology and results are considered to have a prognostic value [21, 22].
- E. Evaluation of suspected inflammation. Perfusion SPET may be indicated and provide helpful information in viral encephalitis (e.g. herpes simplex encephalitis) [23], vasculitis (e.g. systemic lupus erythematosus) [24], and HIV-encephalopathy [25].
- F. Assessment of brain death. Scintigraphic assessment of arrest of cerebral perfusion (even in planar technique; specific acquisition modes may apply) is a safe technique to confirm brain death [26].

Besides the common indications mentioned here, brain perfusion SPET appears to be promising in a variety of additional indications which are currently under further evaluation.

Contraindications

- A. Pregnancy (mothers should interrupt breast feeding for 24 hrs if SPET is indicated)
- B. Evident lack/unability of cooperation

IV. Procedure

A. Patient preparation

A.1. Pre-arrival

Prior to the investigation patients should in general avoid excessive caffeine, cola (energy) drinks, alcohol, smoking, and any drugs known to affect cerebral blood flow. It may be necessary to discuss drug withdrawal with the clinician in care of the patient.

A.2. Pre-injection

A.2.1. Check and ensure that the patient is able to cooperate during the investigation

A.2.2. Achieve a stable environment at the time of injection and the uptake period

- place the patient in a quiet, dimly-lit room
- place an i.v. cannula 10 to 15 min prior to injection
- position the patient in a comfortable (preferably supine) position
- instruct the patient to keep the eyes open (or use a mask) and keep the ears unplugged
- instruct the patient not to speak, read, or move from at least 5 min prior to 5 min post injection
- do not interact with the patient from at least 5 min prior to 5 min post injection
- record carefully any event that might influence rCBF during drug delivery (e.g. patient's motion, talk etc.)
- it may be helpful to maintain the same environment for all perfusion studies in your center

B. Information pertinent to performing rCBF SPET studies

- Patient history with particular focus on neurological and psychiatric disorders, current neurological and psychiatric status, previous surgery, radiation, or trauma of the brain.
- Patients ability to lie still for approx. 30 to max. 60 min. If sedation is necessary, it should be given at least 5 min after injection of the radiopharmaceutical.
- Information about (recent) morphologic imaging studies (CT, MRI).
- Current medication, and when last taken.

C. Precautions

Continuous supervision of the patients during the whole scanning procedure is necessary. This is especially important for patients with epilepsy and dementing disorders.

D. Radiopharmaceutical

D.1. Radionuclide

Technetium-99m (^{99m}Tc)

D.2. Pharmaceutical

- ECD (ethyl cysteinate dimer)

- HMPAO (hexamethyl propylene amine oxime) stabilized or, if not available, unstabilized
- D.3. Preparation of the radiopharmaceutical
- Use pertechnetate from generators which have been eluted within the last 24 hours
 - Use fresh generator eluates not older than 2 hours, particularly for HMPAO
 - For HMPAO be certain that the mixed vial is given at least 10 min prior to dose withdrawal
- D.4. Quality control
Radiochemical purity should be determined on each vial prior to injection using the methods outlined in the package inserts. It should be >90% for ECD and >80% for HMPAO.
- D.5. Time interval for injection
Inject the radiopharmaceuticals after quality control check not later than 30min (^{99m}Tc-HMPAO, unstabilized), 4h (^{99m}Tc-HMPAO, stabilized), and 6h (^{99m}Tc-ECD) post-reconstitution.
- D.6. Dose
Adults: 555 – 1110 MBq (typically 740 MBq) of either radiopharmaceutical
Children: 7.4 – 11.1 MBq/kg; minimum dose 110 MBq
- D.7. Radiation dosimetry

	Organ receiving the largest radiation dose mGy/MBq	Effective dose equivalent mSv/MBq
Adults ^{99m} Tc-ECD ^{99m} Tc-HMPAO	0.073; bladder wall 0.034; kidney	0.011 0.0093
Children (5 yrs) ^{99m} Tc-ECD ^{99m} Tc-HMPAO	0.083; bladder wall 0.14; thyroid	0.023 0.026

Calculations based on: ICRP 62, page 13

- E. Data acquisition
- E.1. Time delay from injection to beginning of data acquisition
- Try to keep always the same time delay from injection to beginning of data acquisition.
 - ^{99m}Tc-ECD: For best image quality allow for a delay of 45-60 min. Images obtained after a delay of 20 – 30 min will be interpretable.
 - ^{99m}Tc-HMPAO: For best image quality allow for a delay of 90 min. Images obtained after a delay of 20 – 30 min will be interpretable.
 - Imaging should be completed within 4 hr post injection if possible. Excessive delay should be avoided.

E.2. Set up for data acquisition

E.2.1. Positioning of the patient

- Patient should void prior to acquisition for maximum comfort during the study. Advise the patient to void again after the acquisition has been completed which may help to reduce radiation exposure.
- Patient should be informed about the total acquisition time and positioned for maximum comfort. Since postprocessing routines allow one to correct for minor obliquities of head orientation, patient's comfort (which reduces the probability of motion during acquisition) is more important than perfect alignment of the head. The patient has to be informed about the necessity to avoid (voluntary) movements of the head and has to be asked for her/his active cooperation. If cooperation is poor, sedation may be used. The patient's head should be only lightly restrained. It is not recommended to rigidly fix the head in place.

E.2.2. Imaging device

- Multiple detector (triple or dual head) or other dedicated SPET cameras for brain imaging should be used for acquisition since these devices generally produce results superior to those obtained with single headed cameras.
- Single detector units may only be used if the scan time is prolonged appropriately (> 5 million total cts) and meticulous care is taken to produce high-quality images.
- LEHR or LEUHR parallel-hole collimators are the mostly available collimator sets for brain imaging. They may be used if acceptable count rates are obtained. All purpose collimators are not suitable. Fan-beam collimators may be generally preferred over parallel-hole collimators due to the advantageous trade-off between resolution and count rate capability.
- Acquisition parameters
 - Rotational radius: smallest possible with appropriate patient safeguard
 - Matrix: 128 x 128 (or higher)
 - Angular sampling: $\leq 3^\circ$ (360 ° rotation)
 - Zoom: acquisition pixel size should be 1/3 – 1/2 of the expected resolution therefore it may be necessary to use a hardware zoom to achieve an appropriate pixel size
 - Acquisition mode: Step and shoot mode is predominantly used. Continuous mode acquisition may provide shorter total scan times and reduce mechanical wear to the system
 - Total counts: > 5 million
 - Total scan time: depending on the imaging device, typical scan time for triple head cameras is around 20-30 min (e.g. 120 projections; 40 projections per head; 25-30 sec/projection)
- Segmentation of data acquisition into multiple sequential acquisitions may permit exclusion of bad data, e.g. remove segments of projection data with patient motion

F. Interventions

F.1. Vasodilatory challenge

It may be performed with acetazolamide (Diamox) or other pharmacological stressors (e.g. adenosine or low concentrations of carbon dioxide).

The following recommendations are focused on Diamox, which has been widely used in the past. Diamox is a carboanhydrase-inhibitor and leads in normal cerebral vessels via dilatation to an increase in rCBF.

F.1.1. Indications

Evaluation of cerebrovascular reserve in TIA, completed stroke, carotid artery stenosis or occlusion, vascular anomalies, and monitoring the results of carotid surgery. Furthermore it may be used to aid in distinguishing vascular from neuronal causes of dementia.

F.1.2. Contraindication

- known sulfa allergy
- use of acetazolamide is not recommended within 3 days of an acute stroke
- use of acetazolamide may provoke migraine in patients with migraine history
- be cautious in renal and hepatic insufficiency

F.1.3. Diamox

- Dosage: 1000 mg by slow i.v. push in adults, children 14 mg/kg.
- Adverse effects: mild vertigo, tinnitus, (perioral) paresthesia and, rarely, nausea. In general these effects are self-limited and do not require specific treatment. Postural hypotension may occur.
- Acetazolamide is a diuretic (patients should void prior to acquisition).
- Since the diagnostic use as vasodilatory challenge for SPET is not reported in the information sheet of Diamox, according to local laws it may be necessary to obtain a specific consent to perform the Diamox test.

F.1.4. Study protocols

- Since the vasodilatory effect is most pronounced around 15 to 20 min p.i. of acetazolamide, the radiopharmaceutical should be injected within this narrow time frame.
- Various protocols have been used to study rCBF under baseline condition and acetazolamide provocation. The two-day repeat study technique is simplest and therefore preferable (allow sufficient time between the investigations for residual activity to clear, e.g. 24 hrs). Either test, baseline or challenge, may be performed first. A „challenge first“ approach may have the advantage that if it is normal it may be considered to omit the baseline scan. On the other hand, performing the baseline prior to the challenge study can be advantageous if large perfusion defects are present, suggesting caution during the challenge procedure. One day protocols using split-dose techniques (2nd dose at least 2x 1st dose) require more sophisticated evaluation and data processing, and are therefore less favourable in general practice.

F.2. Focal epilepsy

- Ictal SPET studies

The tracer should be injected as soon as possible after seizure onset (preferably via an i.v. line placed previously). It is recommended to store prepared syringes in the epilepsy monitoring unit to assure the quickest possible injection time (in case of using unstabilized HMPAO mix with freshly eluted ^{99m}Tc-pertechnetate).

Patients should have continuous video-EEG-monitoring in order to relate the injection time exactly to the time point of behavioral and electrical seizure onset and end.

- Interictal SPET studies

Tracer injection under conditions as outlined before, however, additionally continuous EEG monitoring should be performed at least from 2 hrs prior to injection until 15 min p.i. to exclude that seizures occurred shortly before and during the uptake period of the radiopharmaceuticals. Interictal studies may add useful information to ictal studies. However, these cannot be recommended as a sole diagnostic procedure for focus detection.

G. Image processing

G.1. Review of projection data

Unprocessed projection data should be reviewed in cinematic display prior to filtering to assess presence and degree of motion artifacts, target-to-background ratios and other potential artifacts. Inspection of projection data in sinogram form may also be useful.

G.2. Reconstruction

- methods: filtered backprojection
 iterative reconstruction
- make sure to reconstruct the entire brain volume
- reconstruct data at highest pixel resolution, i.e. one pixel thick

G.3. Filtering

- Data should be filtered in all 3 dimension (x,y,z). This can be achieved either by two-dimensional prefiltering the projection data or by applying a 3-dimensional postfilter to the reconstructed data.
- Low-Pass (e.g. Butterworth) filters should generally be used. Resolution recovery or spatially varying filters have to be used with caution, as they may produce artifacts. Therefore the latter cannot be recommended for general use.

G.4. Attenuation correction

- Attenuation correction is recommended and should be performed in all cases unless specific circumstances would dictate otherwise.
- Methods
 - Use of a calculated homogenous correction matrix according to Chang (correction coefficient for ^{99m}Tc : $\mu = 0.12\text{-}0.14 \text{ cm}^{-1}$). If fan beam collimators are used adapt μ appropriately to avoid overcorrection.
Shape contouring should be used if available. Contours should include scalp and not just grey matter. Contours should be defined for each individual transaxial slice. Correct shape and position of the contours should be reviewed prior to calculation of the corrected slices.
 - Use of a measured correction matrix e.g. from a simultaneously assessed transmission scan or from a CT scan

G.5. Reformatting

- Transaxial slices have to be reformatted into at least 3 orthogonal planes. Generate transverse sections parallel to a given anatomic orientation (e.g. AC-PC line)

assuring a high degree of standardization in plane orientation. Create coronal and sagittal sections orthogonal to the transverse sections.

- Depending on the indication, views other than standard reorientation may be helpful e.g. sections parallel to the long axis of the temporal lobe in the evaluation of epilepsy.
- Three-dimensional display of the dataset (e.g. by volume rendering) can be helpful for more accurate topographic orientation in some clinical questions and to appreciate overall patterns of disease. However, such displays are subject to considerable artifact and must be used with caution.

G.6. Comparative evaluation

- ROI techniques may be used to compare regional blood flow abnormalities with the rCBF of corresponding structures in the contralateral hemisphere or other reference regions (e.g. cerebellum, hemisphere, total brain).
- ROI size should be at least twice FWHM.
- If intra-individual comparison is performed (i.e. ictal vs. interictal, baseline vs. acetazolamide, baseline vs. follow-up for therapy control or assessment of disease progression) standardized evaluation using approaches based on techniques such as stereotactic normalisation are most useful. They guarantee that exactly same structures are compared and allow one to more reliably verify even subtle changes.
- If data from age matched normal controls are available for comparison it is recommendable to use analytical approaches based on stereotactic normalisation and statistical subtraction in order to determine abnormalities of rCBF in an observer independent way [27-28].

H. Interpretation criteria

H.1. Visual interpretation

- Images should be read on the computer screen rather than from hard copies, because this allows variation in colour table and adjustments of background subtraction or contrast.
- For comparison it is desirable to have a normal (preferably age matched) database available, studied with the same type of camera and processed in the same way as patient studies (reconstruction, filtering, attenuation correction). This allows for assessment of normal variability of rCBF and may help to avoid overinterpretation of the patient data.
- Data interpretation must consider relevant structural information (CT, MRI). Specific attention should be paid to the extent of perfusion abnormalities relative to the observed morphological defects and take into account possible effects of atrophy and partial-volume. When available, image fusion may be helpful to further substantiate rCBF changes in relationship to structural observations.
- Pitfalls/sources of error

- Normal variability
The extent of substantial variability between subjects and between scans of a single subject obtained at different times has to be appreciated to avoid overinterpretation.
- Level of contrast and background subtraction
Inappropriate thresholding may result in artifacts. Thresholding, if used, must be based upon knowledge of a normal database for specific radiopharmaceuticals and set-up.
- Color table
Use of non-continuous color tables may overestimate findings due to abrupt color changes.
- Technical artifacts
The images should be critically examined during interpretation for presence of head motion- or attenuation-artifacts or other technical artifacts due to gamma camera problems (center of rotation, inhomogeneity).
- Medication
Possible interaction of concomitant medication has to be taken into account.

H.2. Quantification

- Quantification is helpful in assisting visual interpretation and to objectively assess changes in interventional or follow up studies.
- Quantification can be performed with anatomically adjusted ROI or on a pixel-wise basis (see above). In general the results should only be considered as abnormal if they are outside of two standard deviations of normal data.

I. Reporting

I.1. General

Reports should include all pertinent information, including name of patient and other identifiers, such as birthdate; name of the referring physician(s); type and date of examination; radiopharmaceutical including the administered activity; patient history, including the reason for requesting the study.

I.2. Body of the report

I.2.1. Procedures and materials

- Include in the report a brief description of the imaging procedure, and assessment of scan quality (if compromised give the reason, e.g. motion artifacts etc.)
- If sedation is performed, briefly describe the procedure including type and time of medication given in relation to the radiotracer injection.
- If interventions are performed briefly describe the protocol applied.

I.2.2. Findings

Describe if the SPET pattern is normal or not. If not, describe the location and intensity of abnormal rCBF findings. Functional topography (i.e. based on Brodmann areas) as well as anatomic descriptions can be used to precisely describe the location. Vascular topography (e.g. use of CT vascular atlases) may be appropriate in assessment of vascular disease. State what criteria were used for interpretation (visual

assessment, quantitative or semiquantitative measures, comparison to normal data base etc.).

I.2.3. Limitations

Where appropriate, identify factors that can limit the sensitivity and specificity of the result of the examination (i.e. movement, small lesions).

I.2.4. Clinical issues

The report should address or answer any pertinent clinical issues raised in the request for the imaging examination.

I.2.5. Comparative data

Comparisons with previous examinations and reports, if available, have to be part of the report, furthermore results of morphological imaging modalities (CT, MRI) and, if available, image fusion, should also be taken into account for interpretation.

I.3. Interpretation and conclusions

I.3.1. Precise diagnosis should be given whenever possible. It should be based on generally accepted disease-specific patterns. Any (subjective) interpretation not based on such criteria has to be explicitly stated and considered as hypothetical.

I.3.2. The full spectrum of differential diagnosis should be given when appropriate.

I.3.3. When appropriate, follow-up or additional studies should be recommended to clarify or confirm the suspected diagnosis.

J. Quality control

See procedure guidelines of the TG QA&C of the EANM.

K. Sources of error

Not intended cerebral activation

Artifacts (patient movement, camera related, induced by inappropriate processing)

Interference with drugs acting on cerebral blood flow

V. Issues requiring further clarification

Value of quantification techniques providing results in physiologic units (ml/min/100g)

Value of iterative reconstruction

Measured transmission scans for attenuation correction

VI. Concise bibliography

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VII. Disclaimer

The European Association has written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These general recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be different than a spectrum usually seen in a more general setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition resources available to care for patients may vary greatly from one European country or one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

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