# Technetium-99m-HMPAO Cerebral Perfusion Scintigraphy: Considerations for Timely Brain Death Declaration

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The lipophilic cerebral perfusion agent $^{99m}$Tc-hexamethylpropylene amine oxime (HMPAO) is increasingly used to demonstrate the absence of blood flow for the declaration of brain death. We report a case that illustrates how the timing of such studies is important when organ harvesting is the underlying emergent indication. If performed too early, a study showing the presence of cerebral perfusion may not expedite the declaration of brain death, but instead may complicate patient assessment and unnecessarily delay the process.

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Scintigraphic demonstration of absent cerebral blood flow provides a confirmatory test in the diagnosis of brain death. The primary utility of the test is in both the mitigation of uncertainty due to factors interfering with the clinical examination and in expediting the correct diagnosis of brain death (*1*). The introduction of $^{99m}$Tc-labeled hexamethylpropylene amine oxime (HMPAO) as a cerebral perfusion agent, and its use in both planar and SPECT imaging, has facilitated the confirmatory process (*2–4*). The major advantage of this lipophilic radiopharmaceutical over the other commonly used intravascular agents (e.g., [$^{99m}$Tc]pertechnetate, $^{99m}$Tc-glucoheptonate, or $^{99m}$Tc-diethylenetriaminepentaacetic acid) is its ability to cross the intact blood-brain barrier and remain trapped within the brain with activity proportional to regional perfusion (*3*).

We report a case that illustrates how the featured characteristic of $^{99m}$Tc-HMPAO, persistent cerebral activity, may be disadvantageous in the timely declaration of brain death. Recommendations are then made for optimal use of this radiopharmaceutical given the timing concerns imposed by organ harvesting.

## CASE REPORT

A 48-yr-old previously healthy female abruptly collapsed while teaching at school. Physical examination on admission showed bilateral decerebrate posturing and no signs of head or body trauma. A CT scan of her head showed dilated ventricles and a large pontine hemorrhage with surrounding edema. After management in the ICU for one week, her mental status improved, she was alert and able to follow commands, and she was weaned off mechanical ventilation.

An MR scan of the brain during the second week of hospitalization showed a large vascular malformation in the midline of the cerebellar hemispheres (Fig. 1). There was also a large thrombosed fusiform aneurysm of the proximal basilar artery, a large subacute pontine hemorrhage and evidence of an acute left cerebellar hemorrhage.

Cerebral arteriography confirmed the diagnosis of a large arterial-venous malformation (AVM) involving the vermis and brain stem (Fig. 2). A large proximal basilar artery aneurysm, multiple aneurysms within the nidus of the AVM and narrowing of the distal internal carotid arteries were also demonstrated. Based on the CT, MR and angiographic findings, the patient was judged to be inoperable.

The patient's mental status abruptly deteriorated on hospital Day 14, and brain stem reflexes were absent within an hour. An emergency CT scan showed a large new bleed in the pons and midbrain. Careful examination of reflexes showed no brain stem or cortical function. Her pupils were fixed and dilated, there was no eye movement and the corneal, cough and gag reflexes were absent. There was no posturing in response to painful stimuli. An apnea test achieved a $PCO_2$ of 66 mmHg (abnormal above 60 mmHg) with an oxygen saturation of 99.9%.

Dynamic radionuclide angiographic images and multiple static images were obtained following the intravenous injection of 20 mCi of $^{99m}$Tc-HMPAO ($^{99m}$Tc-exametazine, or Ceretec™, Amersham, Arlington Heights, IL) (Fig. 3). The images showed decreased, but definite, cerebral perfusion. Twelve hours following the initial physical examination, brain stem and cortical reflexes remained absent and the patient again failed an apnea test, with the $PCO_2$ reaching 83 mmHg. Declaration of death by brain criteria was made following the second apnea test in accordance with our institution's set protocol. After discussion with the family, consent was given for the patient to become a multi-organ donor.

## DISCUSSION

Guidelines for the declaration of brain death at our institution include a known cause of coma, exclusion of

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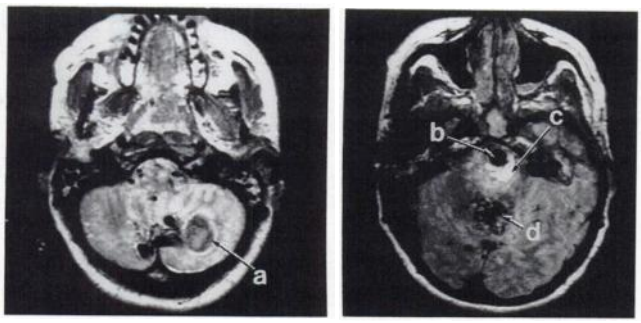


**FIGURE 1.** MR scan showing an acute left cerebellar hemorrhage (a), an aneurysm of the proximal basilar artery (b), a subacute pontine hemorrhage (c) and an AVM in the cerebellar vermis (d).

drug intoxication, maintenance of body temperature and blood pressure, absent pupillary, corneal, oculovestibular, gag, or cough reflexes, lack of spontaneous respiratory effort and no posturing in response to noxious stimuli. These criteria must be met and the absence of brain stem or cortical function must again be demonstrated after 12 hr. According to protocol, the time interval before reexamination halves to 6 hr if a cerebral flow study demonstrates absent perfusion following the initial neurological examination (*5*).

With organ harvesting as the impetus for prompt declaration of brain death, a radionuclide cerebral perfusion study was performed on our patient 1.5 hr after the first apnea test. The immediate angiographic images showed activity along the course of the anterior and middle cerebral arteries, and the static planar images demonstrated moderate diffuse intracranial uptake (Fig. 3). Although the intensity of uptake was decreased from normal, the findings were nonetheless consistent with maintained cerebral perfusion. This result was not expected (or readily accepted by the referring physician), given the unequivocal clinical evaluation and the radiographic studies demonstrating irreversible damage incompatible with sustained cerebral function.

The likely explanation for the discrepant findings is areflexia secondary to locally increased intracranial pressure (ICP) around the brain stem. This can result in "brain stem death", which may not be clinically distinguishable

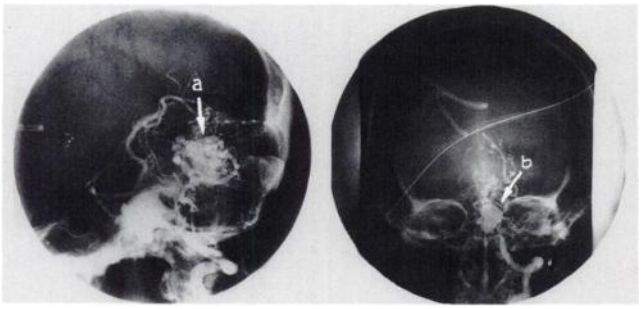


**FIGURE 2.** Cerebral arteriogram confirming the AVM (a) and basilar artery aneurysm (b) identified by MR imaging.

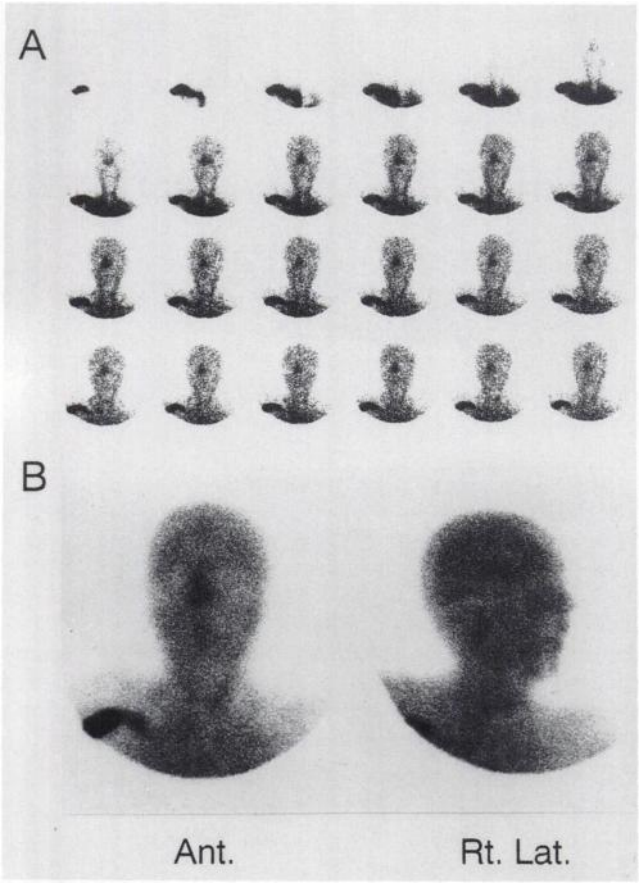


**FIGURE 3.** Technetium-99m-HMPAO cerebral blood flow scintigraphy showing reduced, but definite intracranial perfusion. (A) Dynamic angiography and (B) static images.

from "total" brain death (*6,7*). Until the ICP exceeds the systolic pressure, cerebral perfusion will persist in the carotid distribution along with approximately proportional cerebral uptake of radiotracer (*3*).

The significant amount of $^{99m}$Tc-HMPAO that remains trapped in the brain for more than 24 hr following administration (*2,3*) is the feature of the radiopharmaceutical that allows static planar or SPECT images to be obtained. However, the persistence of cerebral activity with the typical 20-mCi dose prohibits repeat scintigraphic examination with adequate sensitivity before three to four half-lives have elapsed (18 to 24 hr; $T_{eff} \sim T_{phys}$ for $T_{biol} \gg T_{phys}$ = 6.03 hr). Without demonstration of absent cerebral flow, brain death cannot be declared for 12 hr (per protocol) and the window of opportunity for organ harvesting may be missed if the patient decompensates.

The declaration of brain death was made in our case after the confirmatory 12-hr repeat physical examination and apnea test. The scintigraphic results did not delay the process beyond 12 hr since brain death was felt to be imminent and no repeat attempt was made to scintigraphically demonstrate the absence of cerebral perfusion. With rapidly progressing cerebral edema, a $^{99m}$Tc-HMPAO flow study closer to the 6-hr point following the initial neuro-

logical examination may have shown no cerebral uptake and therefore expedited the declaration of death by brain criteria.

In other cases where there was an early $^{99m}$Tc-HMPAO study showing cerebral uptake of radiotracer, repeat scans were not consistently performed (*8–10*). When scans were repeated, the motivation was more than just because the previous scan had demonstrated cerebral perfusion; all patients either had interfering factors associated with the first clinical examination (e.g., hypothermia, barbiturate coma or high dose of a paralytic agent), or the patient was simply found not to be clinically brain dead.

Our case is notable for the fact that the patient was unequivocally brain dead in the absence of interfering factors and had failed an apnea test. If no flow was present, the clinical diagnosis of brain death would have been confirmed. Laurin et al. (*8*) recognized a tendency not to perform apnea tests given a flow study and clinical examination consistent with brain death. This was viewed as a bias introduced by the scan results. Our experience suggests the clinician appears unduly biased by the neurological examination; when a patient is found to be convincingly brain dead, the flow study can then only serve to expedite the declaration process.

Because clinically brain dead trauma patients with cerebral uptake of $^{99m}$Tc-HMPAO may survive (*9*), the judgement of imminence of brain death can be dangerous. Consideration should be given to repeat scintigraphy. An alternative approach that we suggest is to study the patient as late as possible in the brain death declaration protocol. At our institution, this means just before the repeat neurological examination and apnea test at 6 hr. Absent intracranial uptake would obviate the need for repeated study of those patients for whom brain death was truly imminent, and who may have had cerebral perfusion 4–6 hr earlier. Injection of radiopharmaceutical in the ICU followed by imaging at a later time (*11*) is not recommended since only the state of cerebral perfusion at the earlier point in time will be assessed.

Since certain situations, including persistent perfusion, may still necessitate a repeat study, we also recommend administration of a smaller initial dose of $^{99m}$Tc-HMPAO (<10 mCi). This would allow subsequent study at a shorter time interval with a higher dose (20 mCi) of the same agent, or with an intravascular agent for radionuclide angiographic images.

In conclusion, we have presented a case that illustrates how the persistence of cerebral activity following $^{99m}$Tc-HMPAO uptake—one attribute responsible for the popularity of this radiopharmaceutical—may potentially impede the timely declaration of brain death. To best utilize this cerebral perfusion agent, we suggest that it only be used: (1) after unequivocal brain death has been established clinically, (2) with the minimum dosage for adequate imaging (<10 mCi) and (3) as late as possible in the sequence of clinical events prior to declaration of death by brain criteria in order to increase the likelihood of demonstrating absent cerebral uptake.

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**EDITORIAL**

# Brain Death: A Diagnostic Dilemma

The diagnosis of death has generated extensive multicultural debate. The results of this debate necessarily influence medical concepts about death and also our efforts to develop and choose between appropriate diagnostic methods. The discussion by Larar and Nagel (this volume) represents one step in a much needed effort to clarify the use of a relatively new diagnostic approach to brain death. These data, and more, are imperative for the medical credibility and social acceptance of the diagnostic technique.

The accurate and timely determination of the death of an individual

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