Cerebral Perfusion Imaging with Technetium-99m HM-PAO in Brain Death and Severe Central Nervous System Injury

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We performed 38 cerebral perfusion studies in 33 patients with brain death or with severe central nervous system injury using technetium-99m hexamethyl-propyleneamine oxime ([^{99m}Tc]HM-PAO). Uptake by the cerebrum and/or cerebellum was present in all patients who were not clinically brain dead (ten studies) although the study was often abnormal. In those patients who were brain dead, 16/17 studies demonstrated no uptake in either the cerebrum or cerebellum. In patients suspected of brain death, but who had conditions interfering with the diagnosis, the test demonstrated no uptake in 9/11 studies, confirming brain death. A radionuclide angiogram (RNA) of the head was also performed in 33/38 studies and showed complete agreement with the [^{99m}Tc]HM-PAO uptake, except in one case. We conclude that cerebral perfusion imaging with [^{99m}Tc]HM-PAO is a simple, noninvasive and reliable test to confirm brain death. By comparison with conventional technetium agents, [^{99m}Tc]HM-PAO is not dependent on the quality of the bolus injection, is easier to interpret and allows evaluation of posterior fossa blood flow.

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Radionuclide angiography with technetium-labeled radiopharmaceuticals plays an important ancillary role in the diagnosis of brain death (*1–4*) because of its reliability, noninvasive nature, and portability. The currently favored techniques employ agents [^{99m}Tc-labeled gluconate, diethylenetriaminepentaacetic acid (DTPA), or pertechnetate] which do not cross the intact blood-brain barrier and brain death is confirmed by the absence of intracranial flow in the large cerebral arteries after a rapid i.v. bolus injection (*5–7*). Although the definition of brain death must include characteristic findings on physical examination, there are differing opinions concerning the need for confirmatory tests, the interval required for observation, and application of the diagnostic criteria in children. Radionuclide angiography is of particular value when interfering factors, including drugs, metabolic disturbances, and trauma prevent adequate diagnosis based on physical examination.

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Alternative modalities, including contrast cerebral angiography (*8,9*), evoked potential studies (*10*), contrast-enhanced computed tomography (*11*), and xenon-enhanced computed tomography (*12*), have also been proposed as confirmatory tests.

Technetium-99m hexamethyl-propyleneamine oxime ([^{99m}Tc]HM-PAO) is a new radiopharmaceutical which crosses the intact blood-brain barrier in proportion to tissue perfusion and is retained by the brain parenchyma (*13,14*). It has been used extensively as a cerebral perfusion agent in the evaluation of cerebral vascular disease, dementia and epilepsy (*15–19*). The purpose of this article is to review our experience with [^{99m}Tc]HM-PAO for the diagnosis of brain death.

PATIENTS AND METHODS

Patients

This was a retrospective chart review. Thirty-three patients presenting with suspected brain death or with severe central nervous system injury between January 1987 and September 1988 at participating hospitals form the basis of this study. The study included all [^{99m}Tc]HM-PAO brain scans per-

formed in severely brain-injured patients during this interval. Most of the patients came from the Critical Care/Trauma Centre at Victoria Hospital. Five of the 33 patients were studied twice for a total of 38 studies. Only one patient was < 1 yr old. The remainder varied between 2 and 73 yr of age.

Radionuclide Studies

The examination was performed at the bedside in the critical care/trauma center using a small field-of-view mobile scintillation camera or in the nuclear medicine department using a large field-of-view camera. Using a fresh generator eluate, 740 MBq of [^{99m}Tc]HM-PAO (synthesis by the London Regional Nuclear Pharmacy) were reconstituted in 5 ml of NaCl 0.9% and injected within 30 min. Radionuclide angiography (RNA) was performed in the anterior projection and recorded by computer for 60 sec following the i.v. bolus injection of the 740 MBq of [^{99m}Tc]HM-PAO. A head tourniquet was not used. The injection was made by a physician via the most central access available, typically the atrial port of a Swan-Ganz catheter.

Five to fifteen min after injection, anterior, right lateral and left lateral planar images of the head were obtained on film. Tomography was not performed. An anterior or posterior lower chest-upper abdomen image was obtained in 10 out of 33 patients to observe the biodistribution. The normal biodistribution image shows activity in both kidneys, in bladder, liver and both lungs, often more intense in the lower thirds.

The computer acquisition and the films were reviewed for the presence of intracranial flow on the RNA, for the intracranial distribution of [^{99m}Tc]HM-PAO on the 5- to 15-min images and for the presence of sagittal and/or transverse sinus activity on the 5- to 15-min images. The chest-abdominal images were also reviewed to confirm that the radiopharmaceutical biodistribution was that of [^{99m}Tc]HM-PAO. The RNA was judged consistent with brain death if no arterial flow was observed in the major intracranial arteries. The planar images were interpreted as consistent with brain death if *no* uptake of [^{99m}Tc]HM-PAO was seen in either the cerebrum *and* the cerebellum. The presence or absence of activity in the sagittal and/or transverse sinus was recorded but not used in the interpretation criteria.

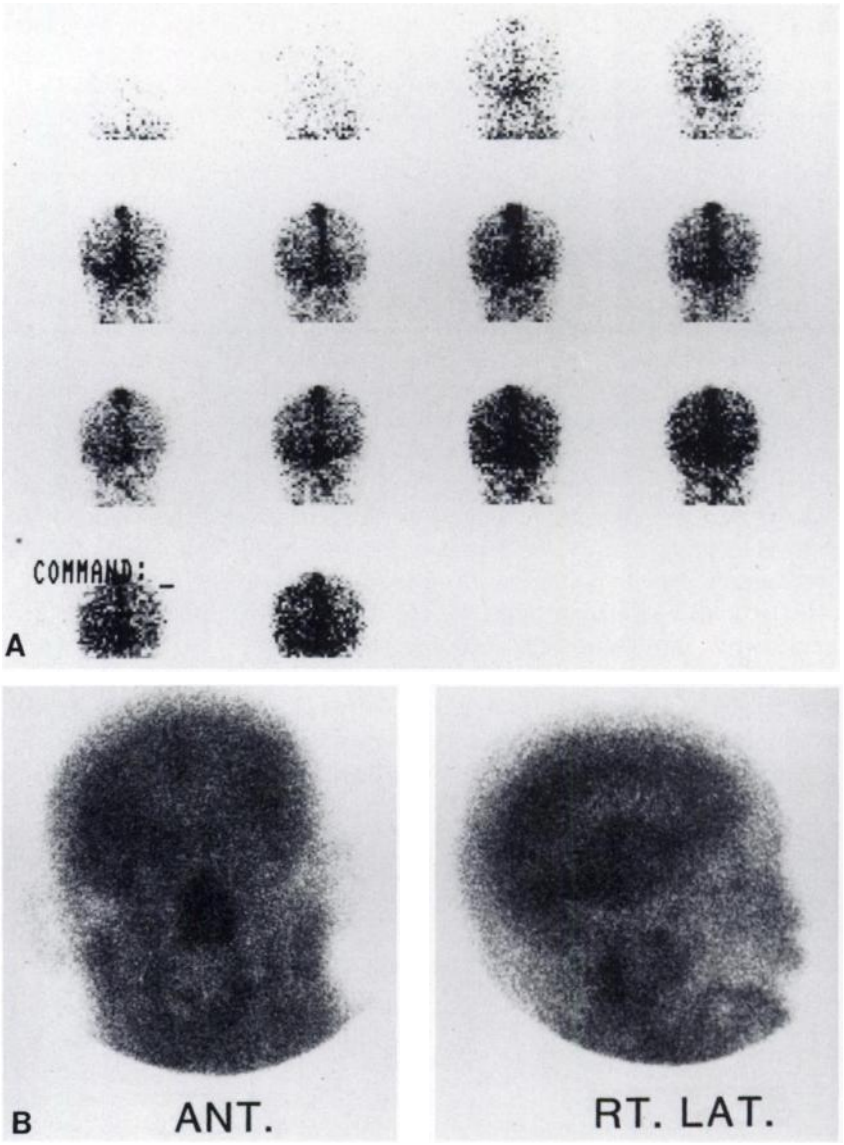

FIGURE 1
A: Normal RNA with [^{99m}Tc]HM-PAO. It is similar to the RNA obtained with conventional agents except for the early and marked uptake by the brain parenchyma. B: The normal distribution in the cerebrum and cerebellum.

Data Analysis

All records were reviewed by a single nuclear medicine physician (NL) but the results did not differ from the original report. The charts were reviewed with respect to: (a) the cause of the central nervous system (CNS) insult; (b) whether the patient was clinically brain dead at the time of the [^{99m}Tc] HM-PAO brain scan; (c) the presence of any interfering condition to the clinical diagnosis of brain death; (d) the use of other diagnostic tests (EEG, evoked potentials, apnea test); (e) organ donation; and (f) the patient's eventual outcome.

The patients were considered *clinically* brain dead at the time of the scan if, they met the clinical criteria outlined in the Uniform Determination of Death Act from the President's Commission (*1*) and the Canadian Medical Association Guidelines for the diagnosis of brain death (*2*). Irreversible cessation of all functions of the entire brain, including the brainstem was defined by: (a) deep unresponsive coma, (b) no brainstem function; that is, absence of pupillary light, corneal, oculocephalic, oculovestibular, gag and tracheal reflexes, (c) no respiratory (apnea) reflex defined by apnea despite arterial $PCO_2 > 60$ mmHg (the Canadian guidelines actually specify a PCO_2 of > 50–55 mmHg but all patients tested achieved $PCO_2 > 60$). Unfortunately, apnea test was not obtained in all patients for reasons which will be discussed later.

RESULTS

There were 38 studies performed on 33 patients (five patients were studied twice). The studies were divided according to whether or not the patient was clinically brain dead at the time of the scan. Figures 1 and 2 show the appearance of the scan with normal cerebral blood flow and with brain death, respectively. Group I was composed of ten studies (nine patients) who were not clinically brain dead having some residual brainstem function. However, they were all in a deep coma and all but one had no response to central pain. They all exhibited some uptake of [^{99m}Tc]HM-PAO which varied from a normal pattern to minimal uptake in the cerebrum with good uptake in the cerebellum. The RNA was performed in 8/10 studies and showed intracranial flow in all, varying from normal to flow limited to one cerebral hemisphere. Only one patient survived but was in a persistent vegatative state at discharge. Three patients had a second [^{99m}Tc]HM-PAO study performed following clinical diagnosis of brain death (Fig. 3).

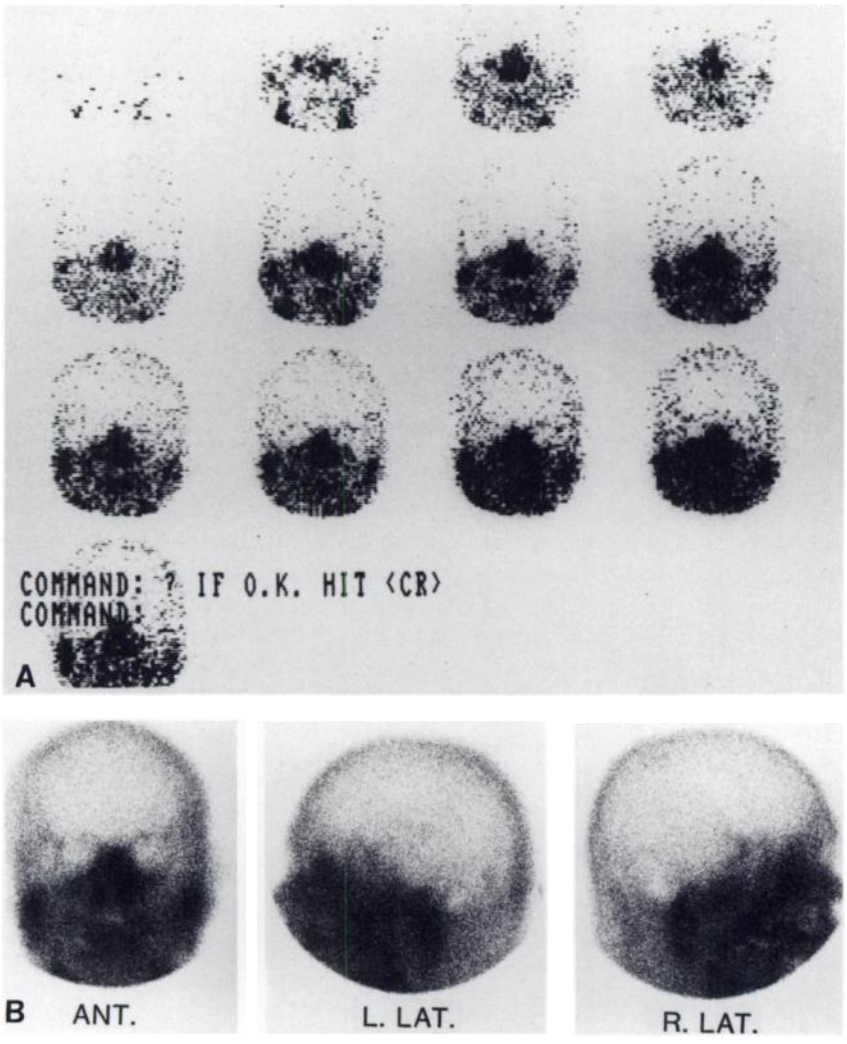

FIGURE 2
A,B: Absent intracranial flow on the RNA and no uptake of [^{99m}Tc]HM-PAO in both the cerebrum and the cerebellum consistent with brain death.

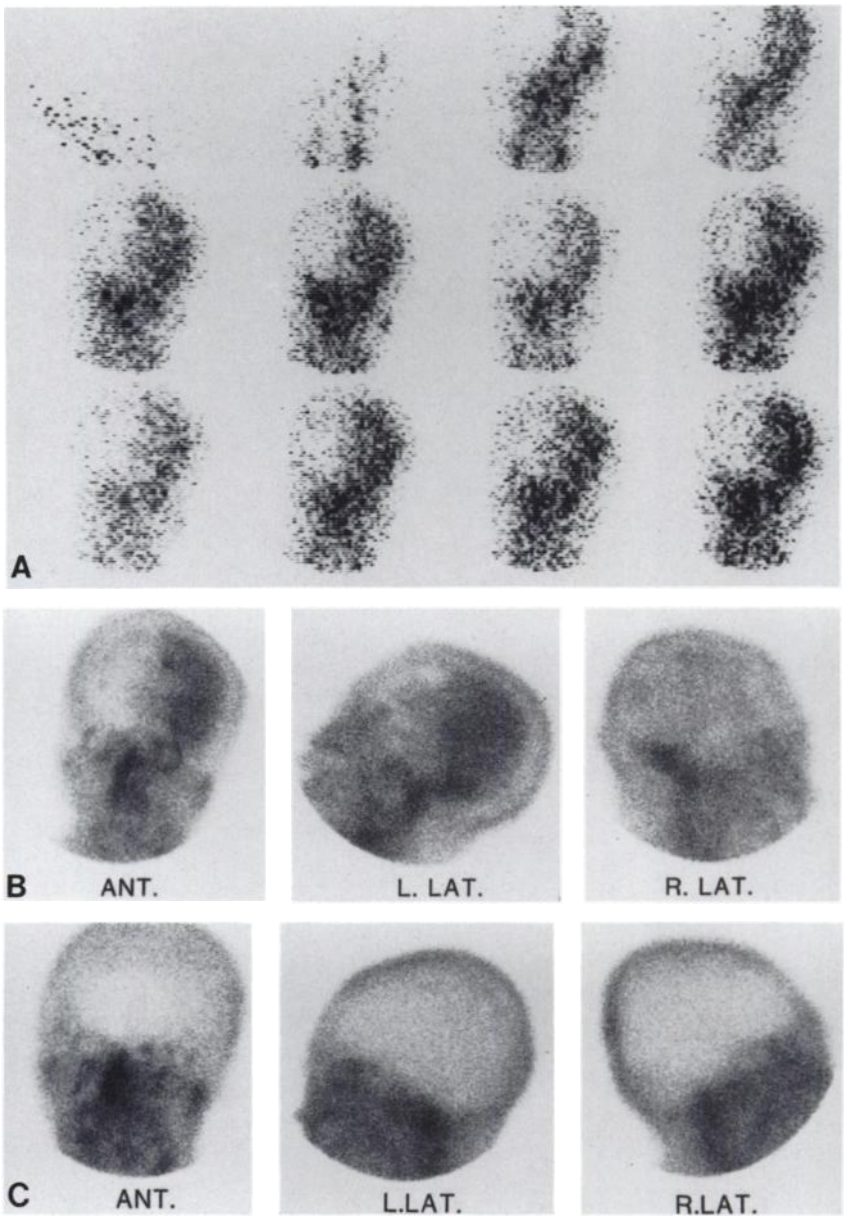

FIGURE 3
An example of an abnormal scan with absent flow in the right hemisphere on the RNA (A). There is evidence of [^{99m}Tc]HM-PAO uptake in the left parietal and occipital part of the cerebrum and good uptake in the posterior fossa (B). The patient had severe CNS injury but residual brainstem function. He later became clinically brain dead and a repeat scan showed no uptake of [^{99m}Tc]HM-PAO (C).

There were 17 studies (17 patients) in group II. The patients were clinically brain dead and there was no condition interfering with the clinical diagnosis. Sixteen of seventeen studies demonstrated absent uptake of [^{99m}Tc]HM-PAO; the remaining study showed uptake in the right parietal region and in the cerebellum: this patient was a 53-yr-old woman with intracranial bleeding. A RNA was not performed. Twenty-four hours later she had persistent apnea despite $PCO_2 > 60$ mmHg. She was eventually declared dead and became an organ donor. RNA was performed in 14/17 studies and showed no intracranial arterial flow in all cases. No patient survived. Nine patients were withdrawn from life support and eight became multiple organ donors. Unfortunately, the apnea test was performed in only 7/17 studies (for reasons which will be discussed later) and confirmed brain death in all cases. EEG was performed in one case and showed no brain waves.

There were 11 studies (ten patients) in group III; the patients appeared clinically brain dead but interfering conditions were present and were preventing a firm diagnosis (Table 1). Nine of eleven studies showed no

TABLE 1
Interfering Conditions

Basal skull fracture with hemotympanum preventing oculovestibular testing
Barbiturate coma
Hypothermia
High doses pancuronium
High doses fentanyl
Pregnancy preventing apnea testing

uptake of [^{99m}Tc]HM-PAO and no intracranial blood flow on the RNA, confirming the diagnosis of brain death. Two studies that showed HM-PAO uptake were abnormal. In one, the uptake was limited to the cerebellum with no evidence of intracranial flow on the RNA. This patient was a 16-yr-old male victim of a car accident and was maintained in barbiturate coma. A repeat scan performed 18 hr later showed complete absence of HM-PAO uptake (Fig. 4). The second study was performed in a 68-yr-old male, also victim of a car accident, having basal skull fractures with right hemotympanum preventing oculovestibular testing in the right ear. He was otherwise clinically brain dead. The scan showed [^{99m}Tc]HM-PAO uptake in the left cerebral hemisphere laterally and good uptake in the cerebellum. The RNA showed minimal flow in the left hemisphere laterally. No patient in this group survived. Eight were withdrawn from life support and two became organ donors. No EEG were performed. Only 2/10 patients had had an apnea test which showed persistent apnea in both.

Of the total 38 studies performed, 25 showed no

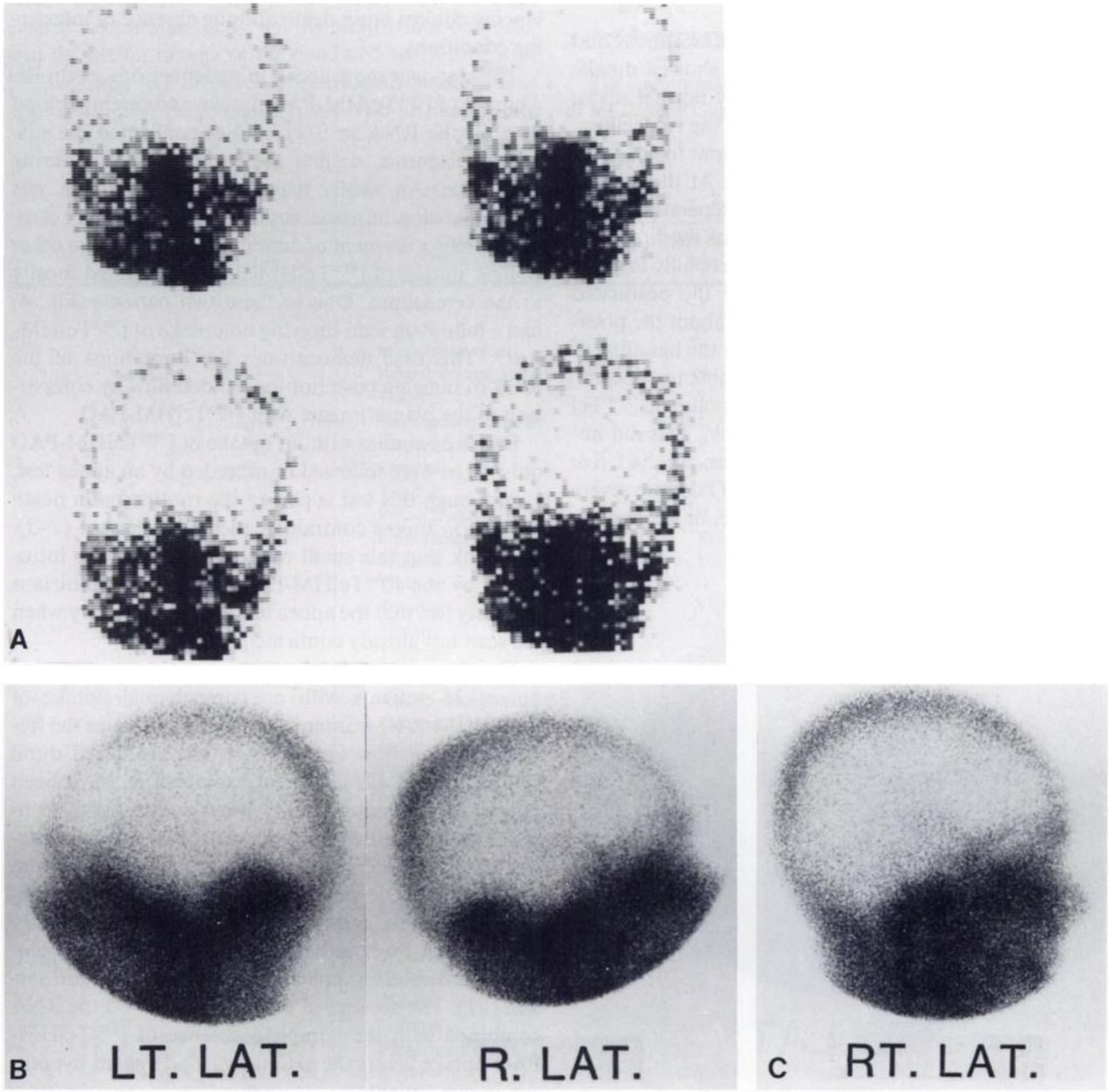

FIGURE 4
This car accident victim with severe CNS injury was clinically brain dead but was being treated with high doses of barbiturates. Figure 4A shows absent intracranial flow on the RNA. B shows no uptake of [^{99m}Tc]HM-PAO in the cerebrum. However there is good uptake in both cerebellar hemispheres. A follow-up study 18 hr later (C) shows completely absent uptake. This 16-yr-old male became a multiple organ donor.

uptake of [^{99m}Tc]HM-PAO in cerebrum and cerebellum. However, sagittal and/or transverse sinus activity was present in nine of these 25 studies (Fig. 5). Despite the presence of severe head trauma with soft-tissue edema and hematoma in several patients, this did not interfere with interpretation of the RNA or planar images since the soft-tissue injuries did not accumulate [^{99m}Tc]HM-PAO. Biodistribution images were available in ten studies. They were all consistent with the expected biodistribution of the [^{99m}Tc]HM-PAO.

DISCUSSION

As expected, all patients with severe CNS injury and residual brainstem function (Group I) showed uptake of [^{99m}Tc]HM-PAO. Some had entirely normal scans, but some had uptake mostly limited to the cerebellum. The RNA also showed intracranial flow in all cases when it was performed (8/10 studies). At the cellular level, uptake of [^{99m}Tc]HM-PAO is dependent upon delivery (blood flow) and conversion of the lipophilic ^{99m}Tc complex to poorly diffusible hydrophilic form(s). Interaction with glutathione is one of the postulated mechanisms (*20*). We were concerned about the possible effects of metabolic disturbances on the handling of [^{99m}Tc]HM-PAO by the cells. Is it possible to "poison" the cellular metabolism and inhibit uptake of [^{99m}Tc]HM-PAO while maintaining blood flow? This did not occur in our experience. In our series, we had five patients with uptake of [^{99m}Tc]HM-PAO despite severe metabolic disturbances (anoxic, uremic, or hepatic encephalopathy; severe sepsis; high doses of fentanyl, diazepam or barbiturates; hypothermia of 30°C). In addition, there were no cases of preserved blood flow on the RNA without uptake of [^{99m}Tc]HM-PAO.

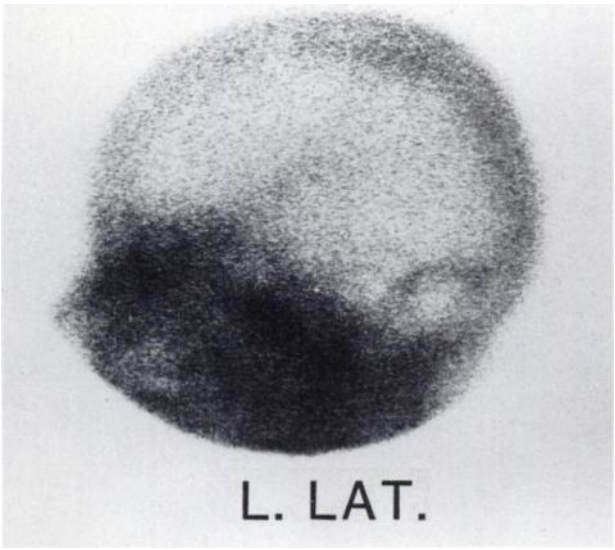

FIGURE 5
This patient was brain dead clinically and had no intracranial flow on the RNA. This figure shows definite sagittal and transverse sinus activity despite absent uptake in the cerebrum and cerebellum.

Brain death is rapidly followed by cerebral edema and increased intracranial pressure. The intracranial pressure eventually exceeds the arterial pressure and cerebral perfusion ceases. The finding of absent [^{99m}Tc]HM-PAO uptake by the cerebrum and the cerebellum in 16/17 studies from group II is therefore not surprising. The one study showing [^{99m}Tc]HM-PAO uptake was more remarkable. Apparently some cerebral and/or cerebellar blood flow may be present despite convincing clinical brain death and the absence of interfering conditions.

The scan was most useful in patients from group III. Absence of [^{99m}Tc]HM-PAO uptake and cerebral blood flow on the RNA in 9/11 studies confirmed the suspected diagnosis, despite the presence of interfering conditions. An earlier diagnosis of brain death was made allowing humane withdrawal of respirator support and procurement of donor organs. In the two other studies, uptake of [^{99m}Tc]HM-PAO was limited mostly to the cerebellum. One of these two patients (Fig. 4) had a follow-up scan showing no uptake of [^{99m}Tc]HM-PAO. This case demonstrates the limitations of the RNA in imaging posterior fossa blood flow by comparison to the planar images with [^{99m}Tc]HM-PAO.

Of the 25 studies without uptake of [^{99m}Tc]HM-PAO only seven were followed or preceded by an apnea test, even though this test is part of the routine brain death evaluation unless contraindications are present (*1–3*). We think that this small number reflects a bias introduced by the [^{99m}Tc]HM-PAO scan. Some clinicians probably feel that the apnea test is not mandatory when the scan has already confirmed brain death.

The presence of dural venous sinus activity in nine out of 25 patients with no parenchymal uptake of [^{99m}Tc]HM-PAO is interesting. It approximates the frequency of no flow on the RNA but visualized dural venous sinuses (*21*). Several explanations have been offered for the sinus activity when conventional technetium agents which do not cross the blood-brain barrier are used (*5,7,21*). It could result from persistent intracranial tissue perfusion (*22*); from blood coming from the external carotid artery circulation via emissary veins (*8*); or from activity in the falx cerebri and tentorium which are supplied by the external carotid system (*21*). The absence of intracranial flow on the RNA combined with the complete absence of [^{99m}Tc]HM-PAO uptake favors the external carotid system hypothesis in our patients.

What are the advantages of [^{99m}Tc]HM-PAO over conventional agents such as [^{99m}Tc]glucoheptonate or DTPA? First, it does not depend upon the adequacy of the bolus injection to determine brain death. Although

these radiopharmaceuticals are adequate in the vast majority of patients, the quality of the bolus is critical and more difficult to achieve in small children. Second, there is no complete agreement about the significance of persisting dural venous sinus activity. This ceases to be a consideration if [^{99m}Tc]HM-PAO is used. Third, [^{99m}Tc]HM-PAO allows visualization of the posterior fossa perfusion which may be present in the absence of supratentorial cerebral blood flow. Fourth, the test is easier to interpret in patients with severely decreased but not absent blood flow. Finally, it displays regional blood flow in much better detail. The only disadvantage is the higher cost of the [^{99m}Tc]HM-PAO. We have elected to combine the RNA, the biodistribution image and the planar images of the head at 5 to 15 min with [^{99m}Tc]HM-PAO in all our brain death studies. This approach offers protection against both an inadequate bolus and erroneous or poor quality radiopharmaceutical.

In both Canada and the United States, confirmatory tests such as radionuclide cerebral angiography or EEG are not necessary to confirm brain death unless there is a condition interfering with the clinical diagnosis or one wishes to shorten the observation period (*1,2*). Under such circumstances cerebral perfusion imaging with [^{99m}Tc]HM-PAO is a simple, noninvasive and reliable test which is applicable both to adults and children (*23*).

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APPENDIX 1

Patient no.	Age (yr)	Cause of CNS injury	Brain dead Y/N	Interfering condition Y/N
1	19	Trauma	Y	Y;pancuronium
2	0.22	Trauma	N	N
3	59	Intracranial bleed	Y	Y;high Na
4	73	Anoxic encephalopathy	N	Y;metabolic enc.
5	33	Trauma	Y	N
6	26	Meningoencephalitis	Y	N
7	53	Intracranial bleed	Y	N
8	55	Trauma	Y	N
9	23	Trauma	Y	N
10	19	Intracranial bleed	N	Y;metabolic enc.
10	19	Intracranial bleed	Y	Y;fentanyl
11	54	Trauma	Y	Y;skull Fx
12	8	Trauma	N	Y;barb;hypothermia
12	8	Trauma	Y	Y;barbiturate
13	10	Trauma	Y	N
14	16	Trauma	Y	Y;barbiturate
14	16	Trauma	Y	Y;barbiturate
15	11	Anoxic encephalopathy	Y	N
16	9	Trauma	Y	N
17	8	Multif. encephalopathy	N	N
18	58	Trauma	Y	Y;skull Fx;hypother
19	35	Anoxic encephalopathy	N	Y;diazepam
19	35	Anoxic encephalopathy	N	N
20	15	Anoxic encephalopathy	N	Y;head burns
21	56	Intracranial bleed	Y	N
22	44	Intracranial bleed	Y	N
23	50	Intracranial bleed	Y	N
24	26	Anoxic encephalopathy	Y	N
25	65	Trauma	N	N
26	20	Trauma	N	N
26	20	Trauma	Y	N
27	2	Trauma	Y	Y;barb;hypother
28	50	Intracranial bleed	Y	N
29	56	CVA (infarct)	Y	N
30	69	Intracranial bleed	Y	N
31	68	Trauma	Y	Y;skull Fx
32	30	Intracranial bleed	Y	Y;pregnancy
33	35	Intracranial bleed	Y	N

(Appendix 1 continued on next page)

(*Appendix 1 continued*)

Patient no.	RNA detail	Uptake Y/N	Outcome	Time lapsed*
1	No flow	N	WLS	6 hr
2	Normal	Y;L cerebrum <R	WLS	9 days
3	No flow	N	WLS	6 hr
4	Not done	Y;normal	Died of ARF	1 mo
5	No flow	N	Organ donor	17 hr
6	No flow	N	WLS	18 hr
7	Not done	Y;R pariet;cerebellum	Organ donor	24 hr
8	No flow	N	Organ donor	13 hr
9	No flow	N	Organ donor	12 hr (approx)
10	Normal	Y;normal		
10	No flow	N	WLS	6 hr (approx)
11	No flow	N	WLS	6 hr (approx)
12	Not done	Y;normal		
12	No flow	N	WLS	24 hr
13	No flow	N	Organ donor	12 hr
14	No flow	Y;normal		
14	No flow	N	Organ donor	6 hr
15	No flow	N	WLS	18 hr
16	No flow	N	Organ donor	2 hr
17	Normal	Y;normal	Survived; veg. state	
18	No flow	N	WLS	6 hr
19	Normal	Y;normal		
19	Normal	Y;normal	WLS	8 hr
20	Normal	Y;normal	Died on ward	3 mo
21	Not done	N	WLS	1 hr
22	No flow	N	WLS	8 hr
23	No flow	N	WLS	4 hr
24	No flow	N	Organ donor	24 hr
25	Flow R hemisph	Y;R cerebrum;cerebel	WLS	48 hr
26	Flow L hemisph	Y;L parietal;cerebel		
26	No flow	N	Organ donor	5 hr
27	No flow	N	Organ donor	6 hr
28	Not done	N	WLS	6 hr
29	No flow	N	WLS	8 hr
30	No flow	N	WLS	6 hr
31	Flow L hemisph	Y;L parietal;cerebel	WLS	24 hr
32	No flow	N	C-Sec; organ donor	4 hr
33	No flow	N	WLS	4 hr

* Time lapsed between scan and WLS, organ harvesting or spontaneous death.

Index of abbreviations: Enc: encephalopathy; Barb: barbiturates; WLS: withdrawal from life support; CVA: cerebrovascular accident; L: left; R: right; Veg state: vegetative state; Fx: fracture; C-sec: cesarean section; Hypother: hypothermia; Cerebel: cerebellum; Y: Yes; N: No; ARF: acute renal failure; Multif: multifactorial; Pariet: parietal; Hemisph: hemisphere.

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