Scintigraphy as a Confirmatory Test of Brain Death

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The concept of "brain death" was introduced to medicine in the second half of the 20th century, when technological advancements began to allow sustaining cardiorespiratory functioning of the body in the absence of brain function. Although physicians generally agree that a patient can be declared brain dead when the loss of brain function is total and irreversible, different approaches have been taken to define what constitutes brain death. A thorough clinical examination is essential to the diagnosis. The role of confirmatory tests differ among countries in the world but generally are indicated when a specific part of the clinical examination cannot be performed or is deemed unreliable. Under certain circumstances, confirmatory tests can be used to shorten the clinical observation. Of the confirmatory tests recommended by the American Academy of Neurology and the American Academy of Pediatrics, cerebral scintigraphy is a safe, reliable, and widely available alternative. Once the radiopharmaceutical is properly compounded, cerebral scintigraphy can be performed rapidly and can be interpreted in a straightforward manner. It is tolerant of metabolic aberrations and pharmacologic intoxicants. It is not affected by electrical interference, and the presence of skull defects or scalp trauma do not preclude its performance. The radiopharmaceuticals used in scintigraphy have no deleterious effects on potential donor organs. Cerebral radionuclide angiography has been highly sensitive. Either cerebral planar scintigraphy or cerebral scintitomography with Tc-99m hexamethylpropyleneamineoxime also are highly sensitive, but, in addition, appear to be 100% specific.

THE TERM "brain death" is used to signify the irreversible loss of function of the entire brain and, by general consensus, meets the criteria for human death. The determination of brain death has assumed importance in modern health care to prevent futile attempts to sustain ventilation and blood circulation artificially for prolonged periods, and to ensure the potential availability of organs for transplantation. Although the origin of the current scientific concept of brain death can be traced back to 1959,[1] considerable differences of opinion remain as to how to diagnose brain death. Current guidelines or requirements for the determination of brain death differ within the United States, as well as among countries worldwide.[2,3]

DEFINITION OF BRAIN DEATH

The Uniform Determination of Death Act (UDDA) forms the basis of brain death statutes for many states within the United States.[4] It declares "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards." The Act does not define these medical standards; rather, it leaves them open for refinement as medical technology advances. The recommendation by the UDDA that the entire brain must lose function to declare death is noteworthy. Of the states having relevant statutes, their language concerning brain death is broadly similar but contains specific differences.[2] For example, statutes in Virginia call for a specialist in neurology, neurosurgery, or electroencephalography to declare a patient brain dead,[5] but, in certain circumstances, they allow a registered nurse to declare a patient brain dead.[6] Alaska[7] and Georgia[8] also allow registered nurses to declare a patient brain dead. Although most states accept certification of brain death from one physician, others, like Kentucky, require two licensed physicians to make the determination of a "total and irreversible cessation of all brain function, including the brainstem."[9] Statutes in Florida require that "one physician shall be the treating physician, and the other physician shall be a board-eligible or board-certified neurologist, neurosurgeon, internist, pediatrician, surgeon, or anesthesiologist."[10] In New Jersey[11] and New York,[12] brain death cannot be declared against the patient's religious beliefs.

Over the years since the scientific description of brain death by Mollaret and Goulon,[1] several organizations have received widespread recognition for their formulation of specific diagnostic criteria. These organizations include the Ad Hoc Committee of the Harvard Medical School To Examine the Definition of Brain Death (1968),[13] the Ad Hoc Committee on Death of the Minnesota Medical Association (1976),[14,15] the conference of the Medical Royal Colleges (1976),[16] the United States Collaborative Study of Cerebral Death (1977),[17] and the President's Commission for the Study of Ethical Problems in Medicine and Biomedical And Behavioral Research (1981).[18] Differences among their criteria include (1) the regions of brain that must lose all function, (2) the extent and characteristics of areflexia, (3) the duration of the clinical observation, and (4) the role and category of confirmatory tests.

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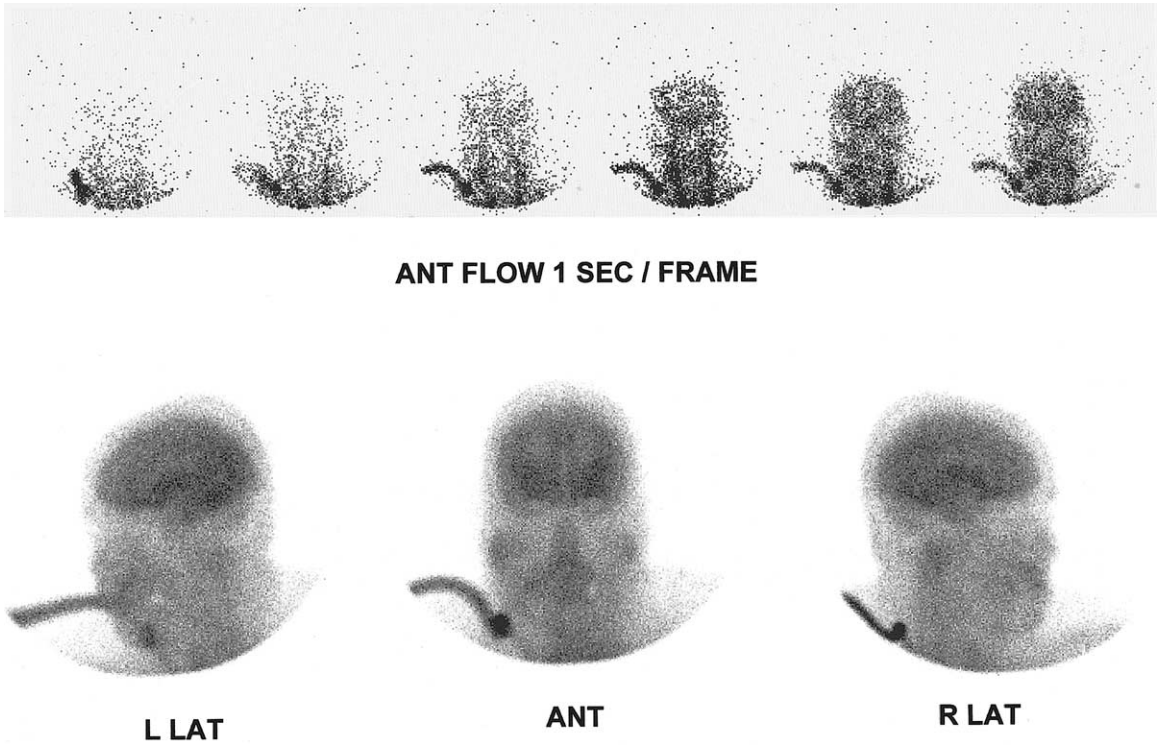

Fig 1. Preservation of cerebral flow and metabolism. Radionuclide cerebral angiogram (above) following the intravenous bolus injection of 25 mCi (950 MBq) Tc-99m HMPAO shows flow within the anterior and middle cerebral artery distributions. Planar 500K "static" images (below) performed immediately thereafter show localization of the radiopharmaceutical within both cerebral hemispheres. Cerebellar hemispheric metabolism also is preserved but appears decreased (compare with Figs 2 and 5).

CLINICAL CRITERIA

The American Academy of Neurology (AAN), in its summary statement, lists the following prerequisites for the diagnosis of brain death in adults (1) clinical or neuroimaging evidence of acute central nervous system catastrophe; (2) exclusion of complicating medical conditions, such as severe electrolytic, acid-base, or endocrine disturbance; (3) absence of drug intoxication; and (4) core body temperature of at least 32°C (90°F).[19] These prerequisites are followed by a clinical examination to document 3 cardinal signs of brain death: (1) coma or unresponsiveness, (2) absence of all brain stem reflexes, (3) and apnea. A repeat clinical examination is recommended after 6 hours, although the AAN considers this interval to be arbitrary.

Commentary within the medical literature concerning the qualifications of practitioners for the appropriate diagnosis of brain death is sparse. Beyond statutory requirements, Baumgartner and Gerstanbrand believe that neurologic experts should be involved with brain death examinations whenever available.[20] Except for the purposes of transplantation, their recommendations do not preclude the practitioner from making the diagnosis when neurologic experts are unavailable. For transplantation purposes, they believe that the diagnosis should always involve a neurologic expert and never a member of the transplant team. Interestingly, Wang et al performed a retrospective review of the quality and completeness of brain death notes at a major medical center.[21] They suggest a need to increase quality assurance activities regarding these declarations.

CONFIRMATORY TESTS

Although several countries mandate the use of confirmatory tests in specific circumstances, they remain optional in the United States.[2,3] For adults, the AAN summary suggests a confirmatory test be performed when specific components of the clinical examination cannot be performed or are unreliable. The AAN summary lists the following confirmatory tests in their specified order of decreasing sensitivity: conventional contrast angiography, electroencephalography, transcranial Doppler ultrasonography, Tc-99m hexamethylpropyleneamineoxime (HMPAO; exametazime) brain scan, and somatosensory evoked potentials.[19] The Tc-99m HMPAO (Ceretec, Amersham Health, Arlington Heights, IL) brain scan is the only radionuclidic method specified within the AAN summary.

For children, the recommendations of the Task Force of the American Academy of Pediatrics (AAP) depend on age.[22] In the group of children 7 days to 2 months old brain

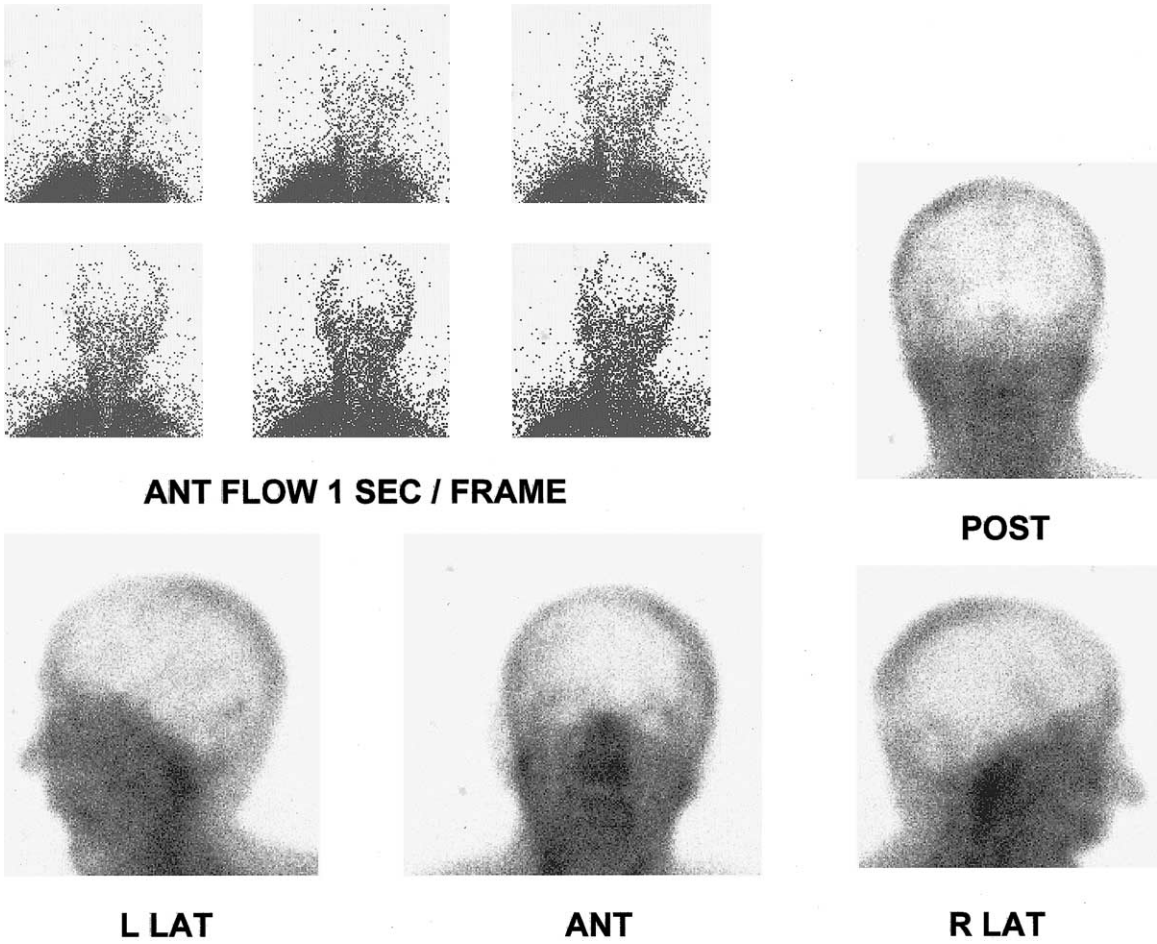

Fig 2. Brain death in a 58-year-old who had massive subdural hematoma. First pass radionuclide cerebral angiogram with intravenous bolus of Tc-99m HMPAO (upper left) shows flow in the common carotids, as well as flow within the external carotid artery distributions. The anterior and middle cerebral artery complexes were not visualized out to 1 minute. Subsequent planar imaging (below and right) show no radiopharmaceutical localization within the cerebral cortices, basal ganglia, thalami, or cerebellar hemispheres. The sagittal and transverse venous sinuses can be identified on the posterior projection images, and the sigmoid sinuses are just discernable on the lateral projection images.

death is diagnosed by clinical examination and an electroencephalogram (EEG) both of which are to be repeated after at least 48 hours. In the group of children 2 months to 1 year old, the separation between the 2 sets of examinations has to be at least 24 hours. The second clinical examination and the EEG are not necessary if a concomitant radionuclide cerebral angiogram fails to visualize the cerebral arteries. For children older than 1 year and when an irreversible cause can be identified, the Task Force recommends at least 12 hours of observation, with confirmatory testing optional. Under conditions such as hypoxic-ischemic encephalopathy, the Task Force recommends an observation period of at least 24 hours. This observation period may be reduced either by the showing of electrical silence on EEG, or the lack of visualization of cerebral blood flow by radionuclide by angiography. These AAP recommendations do not mention a specific tracer for use with radionuclide angiography.

SCINTIGRAPHY AS A CONFIRMATORY TEST

A comparison of the guidelines published by the American College of Radiology (ACR)[23] and the Society of Nuclear Medicine (SNM),[24] with the summary statement published by the AAN,[19] reveals a few interesting differences. The approach of the ACR is "to determine if there is cerebral blood flow," and that of the SNM is "to assess brain blood flow." Therefore, they list radiotracers excluded by the blood-brain barrier, such as Tc-99m pertechnetate, Tc-99m pentetic acid (DTPA) and Tc-99m gluceptate, as potential agents to be used for cerebral flow studies, in addition to the brain-avid agents Tc-99m HMPAO and Tc-99m N, N′-1,2-ethylenediylbis-L-cysteine diethyl ester

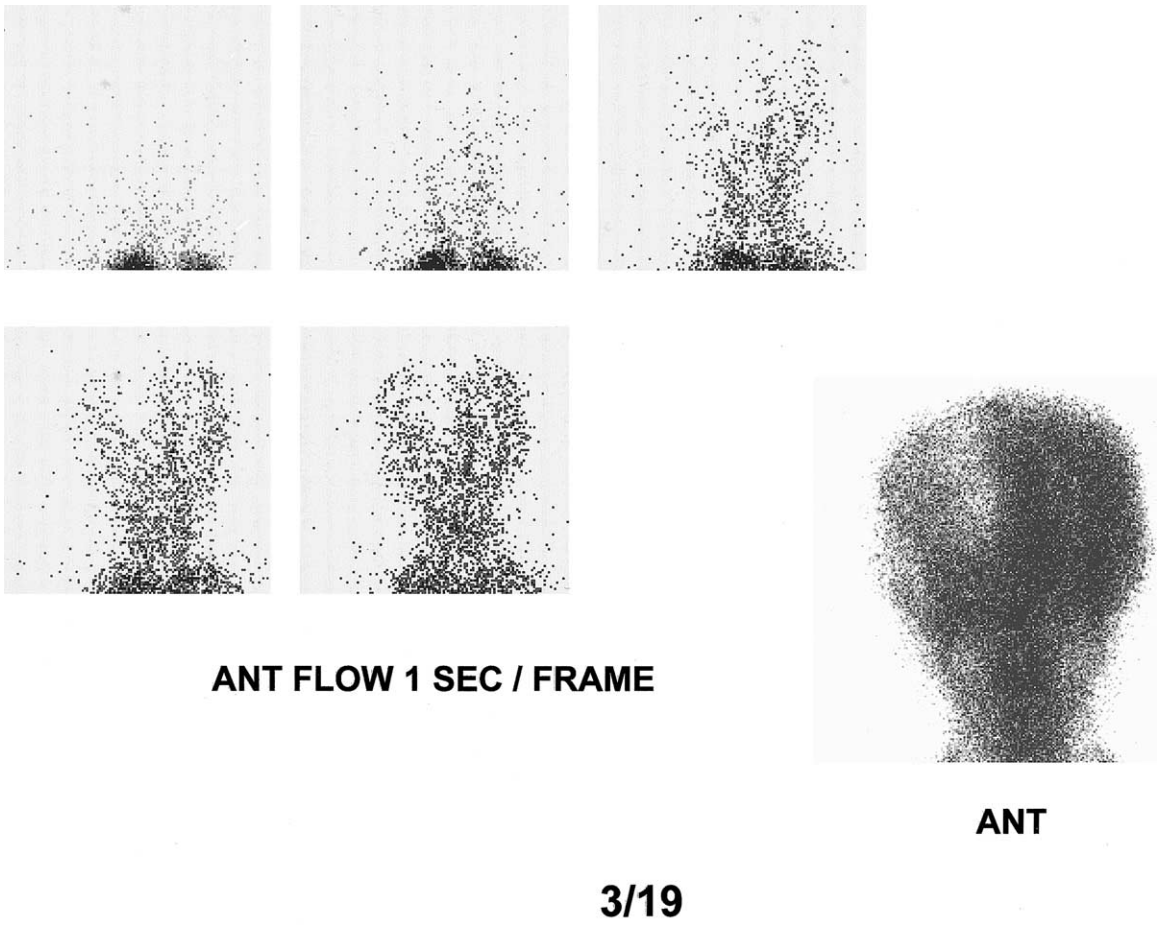

Fig 3. Brain death evaluation in a 15-month old who had a closed head injury. Radionuclide cerebral angiogram with 10 mCi (370 MBq) Tc-99m HMPAO (upper left) shows flow within a left-shifted anterior cerebral artery as well as flow within the left middle cerebral artery complex. Right middle cerebral flow is compromised due to subdural hematoma, right hemispheric infarction, and massive cerebral edema. Head CT disclosed transfalcine herniation. Yet the radionuclide angiogram and the immediate scintigraphic image (lower right) show perfusion of the left hemisphere.

(ECD). However, the approach given by the AAN summary statement is based on a lack of tracer uptake in the brain parenchyma on "static" Tc-99m HMPAO images (ie, "hollow skull" phenomenon[25]). A background article to the AAN summary statement,[26] which appears separately from the summary statement itself, actually does mention dynamic imaging with Tc-99m human serum albumin. However, regarding the validity of dynamic imaging, this background article mentions that "the sensitivity and specificity of lack of intracranial radioisotopes have not been defined in adults." These different definitions and recommendations underscore the notion that scintigraphy, as a confirmatory test, can be separated into two general approaches.

Scintigraphy With Hydrophilic Agents

Nondiffusible radioisotopes have been used for the determination of brain death as early as the late 1960s, and their use has been well documented and accepted.[27-32] Confirmation of brain death with this method relies primarily on the absence of cerebral flow on anterior-projection rapid-sequence angiography obtained for up to 1 minute following intravenous bolus injection of the radiopharmaceutical. Flowers and Patel reported 98.5% sensitivity for confirmation of clinical brain death in 203 patients using this technique.[33] They did have 5 false-positive studies, of which 3 showed superior sagittal sinus activity. Although the dynamic imaging technique is technically demanding, it has the advantages of speed, noninvasiveness, performance without moving the patient from the bed, freedom from electrical interference, and the avoidance of iodinated contrast. The potential effects of modern non-ionic agents on donor organs are not well established. However, data obtained using traditional contrast media suggest a decrease in cadaver renal allograft survival when angiography is performed within 2 hours of explantation.[34]

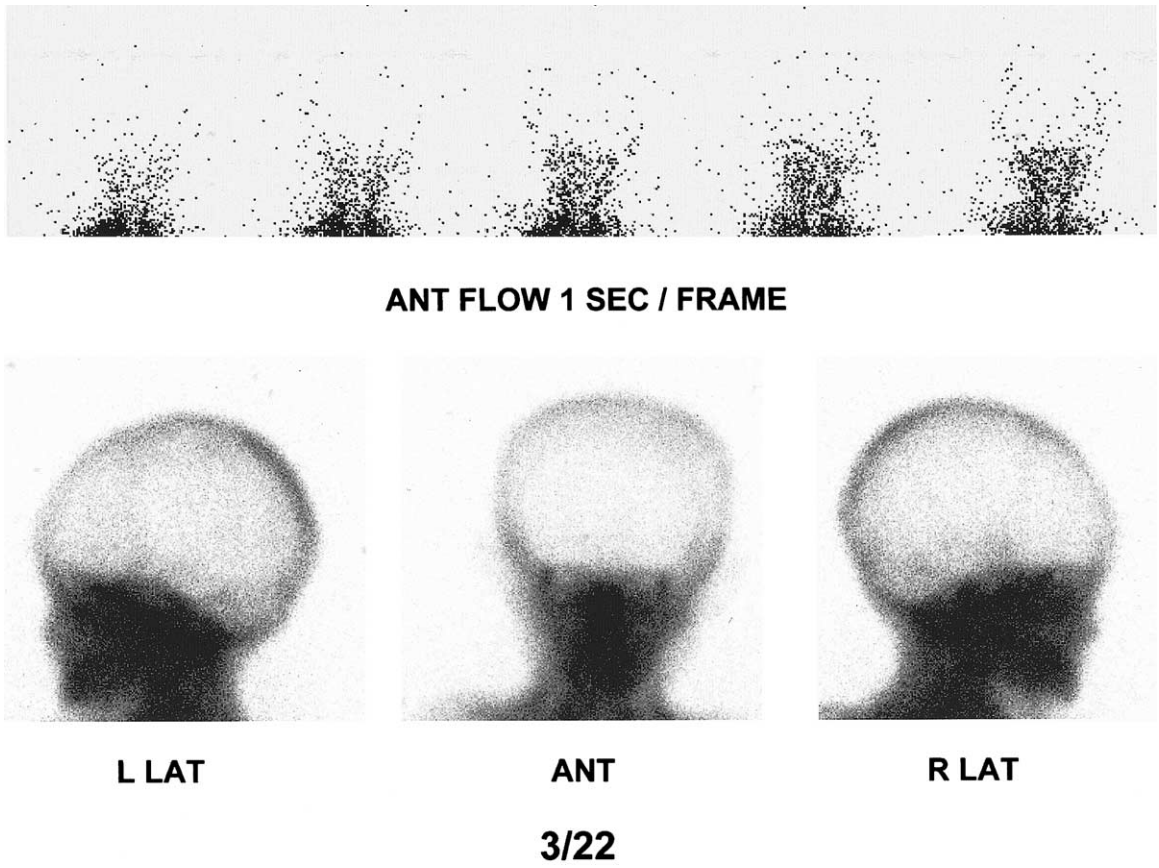

Fig 4. Brain death evaluation in a child (continued from Fig 3). Radionuclide angiogram (above) and static images (below) repeated 2.5 days later, with reinjection of (HMPAO) show absent flow and metabolism within the cerebral hemispheres, basal ganglia, thalami, and cerebellar hemispheres.

Immediate "static" scans have been used as an adjunct to radionuclide cerebral angiography to improve the distinction between internal and external circulation.[35] The lack of dural venous sinus visualization on these images, in combination with absent cerebral radioisotopic flow, strongly confirms a clinical diagnosis of brain death. Several investigators using Tc-99m glucoheptonate,[36] Tc-99m pertechnetate,[37] and Tc-99m DTPA[38] have reported faint visualization of the dural sinuses in small numbers of their patients who otherwise had no evidence of cerebral flow on the dynamic images. Each patient died within 48 hours of the study, and in a few patients, a repeat study showed no tracer in the venous sinuses. Coker and Dillehay also reported dural sinus activity in 14 of 55 children who were brain dead.[39] In a series of 53 patients, Lee et al concluded that the mere presence of tracer in the superior sagittal sinus in Tc-99m glucoheptonate studies does not contradict the diagnosis of brain death.[40] They cite angiographic studies showing external carotid filling of intracranial venous sinuses via emissary veins, or supplying vessels to the falx and tentorium.[41,42] To reduce external carotid circulation to the scalp, Goodman and Heck described the placement of a tourniquet around the head during the radionuclide angiogram.[30] With experience, these same investigators later concluded that head tourniquets are unnecessary.[31] The SNM guidelines state that a tourniquet should not be used unless there is "adequate monitoring of intracranial pressure or there is little reason to expect an elevation of intracranial pressure".[24]

Scintigraphy With Lipophilic Agents

Concerns over the significance of sinus activity can be mitigated by agents that cross the blood-brain barrier.[43,44] Studies with Tc-99m HMPAO permit immediate and delayed "static" images. They are insensitive to intravenous bolus techniques. They allow the assessment of individual brain regions, and they readily distinguish between low and absent flow (Figs 1-8).[43,48,49] They do not appear to be affected by metabolic disturbances, including hypothermia to 30°C.[43]

The ACR and SNM guidelines mention the use of Tc-99m ECD for brain death, while the AAN summary statement and its background article do not. With this

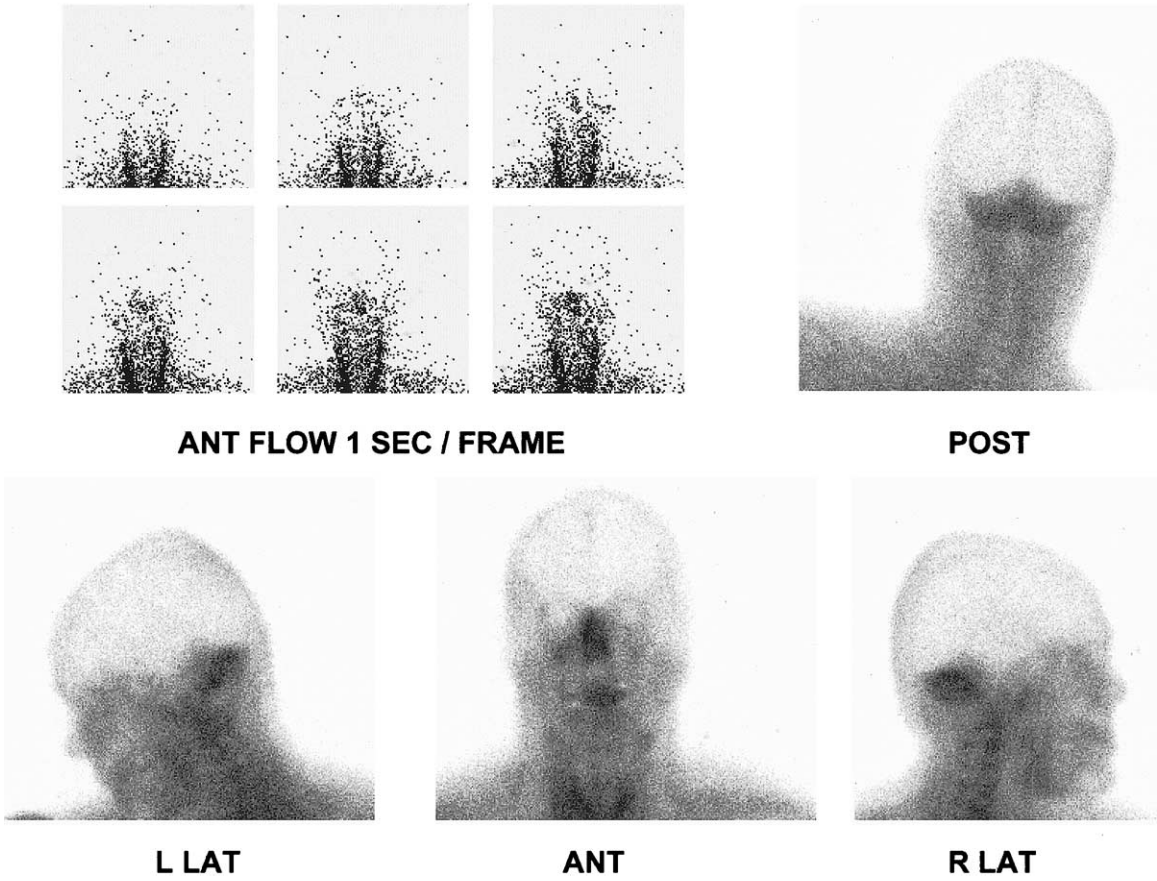

Fig 5. Isolated preservation of cerebellar metabolism in a 37 year-old who had a gun shot wound to the head. The radionuclide angiogram following intravenous Tc-99m HMPAO showed no convincing evidence of intracranial flow. The lateral and posterior projection "static" images show cerebellar hemispheric metabolism, despite the absence of metabolic activity within cerebral hemispheres and basal ganglia. This cerebellar uptake cannot be identified on the anterior projection images alone. The tentorium cerebelli is shifted caudally.

difference in mind, one notes that the US package insert of Tc-99m bicisate (ECD), marketed as Neurolite (Bristol-Myers Squibb Medical Imaging, Inc., N. Billerica, MA) states. "The relevance of the Neurolite scan results to the prediction of neurological function or brain cell viability is not known. . . . Neurolite is not indicated for assessment of functional viability of brain tissue."[50] The context of this statement suggests simply a disclosure of the unknown ability of bicisate to predict recovery of ischemic neural tissue, rather than a specific exclusion for use in brain death. However, the package insert of Ceretec makes no similar declaration.[51] On the other hand, neither the Ceretec nor the Neurolite insert list brain death as indications. So, presumably, neither agent has been specifically approved by the US Food and Drug Administration for determination of brain death.

To elaborate further this issue, Léveillé et al showed that, in neurologically normal subjects, Tc-99m HMPAO and Tc-99m ECD have similar cerebral kinetics and initial distribution.[52] Both agents are rapidly assimilated by gray matter, both have cerebral distributions that correlate with brain perfusion, and, once trapped, both have distributions that change little regarding time. A rare dissociation between HMPAO and ECD in cerebral disease (ie, encephalitis) has been reported.[53] The current authors observe that in essentially all published studies in which a lipophilic agent was prescribed for brain death, HMPAO has been used.

Successful reconstitution of Tc-99m HMPAO requires strict adherence to the instructions of the manufacturer.[51] One salient point is that the Mo-99/Tc-99m generator must have been eluted within 24 hours preceding the current elution for the reconstitution of Ceretec. If methylene blue stabilization is used, the methylene blue must be used within 30 minutes of formulation. The stabilized and radionuclidic pure Tc-99m HMPAO can be used within the subsequent 4 hours. If methylene blue stabilization is not used, then the Tc-99m HMPAO must be administered within 30 minutes of reconstitution.

The relative merits of radionuclide cerebral angiography,

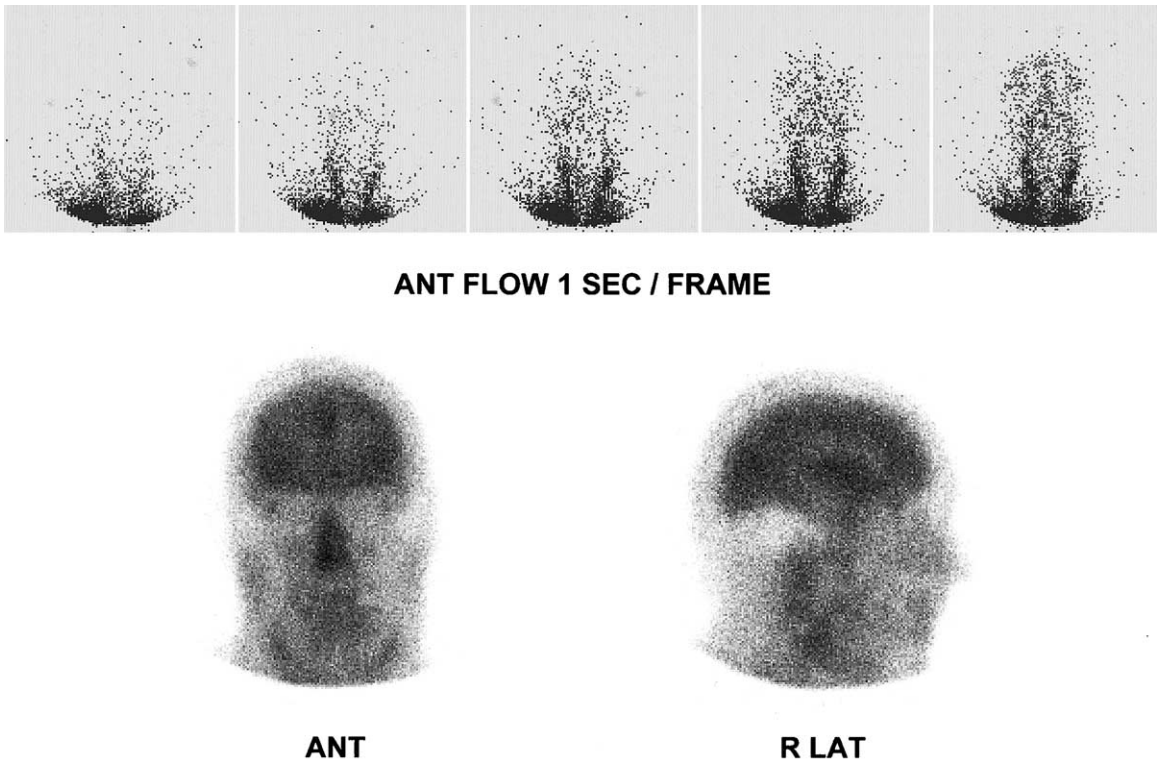

Fig 6. Isolated cerebellar death. The potential disassociation between cerebral and cerebellar flow is further illustrated in this (HMPAO) study showing cerebellar hemispheric infarction at the brain death evaluation. This 39-year-old had vertebral occlusions from dissection. Frontal, parietal, temporal, and occipital cortices show substantial metabolic activity.

planar imaging, or SPECT, all using HMPAO, have been discussed.[25,43,54-59] Although some investigators consider cerebral angiography with HMPAO an optional procedure, others believe that it provides supportive information and quality assurance.[55,58,60] Some investigators recommend SPECT for a more accurate evaluation of the cerebellum and potentially for the brain stem.[57,61,62] These advantages of SPECT are partially offset by the requirement that the patient be moved to the imaging table. Interestingly, both the ACR and SNM guidelines mention the potential use of SPECT for confirming brain death, while the AAN summary statement does not. Furthermore, the static imaging approach of Tc-99m HMPAO described by the AAN has been expanded by Wijdicks to consist of 500,000-count static images obtained immediately, between 30 and 60 minutes, and at 2 hours.[63] The origin of this latter recommendation is uncertain. Wilson et al found that immediate statics in 17 patients suspected of brain death to be of equal value to those performed between 30 and 60 minutes, and those at 2 hours.[56]

As mentioned above, a cited advantage of the brain-avid agents over the blood-pool agents is the ability of the former to assess the posterior fossa.[43,48,64] Given the appropriate prerequisites, the presence of cardinal signs, and proper quality assurance, a Tc-99m HMPAO study showing no flow on the cerebral angiogram and no brain uptake on multiprojection early static images provides a straightforward confirmation of brain death (Figs 2, 4, 7, and 8). In contradistinction, preservation of flow and metabolism of HMPAO by the cerebrum and cerebellum precludes this confirmation (Fig 1). Other patterns on HMPAO have been described in the literature, and the current authors have observed 2 additional cases (Figs 5 and 6). One pattern is the occasional preservation of cerebellar perfusion in the absence of cerebral perfusion (Fig 5).[43,49,55,59,61,64-66] Valle et al suggest this pattern is a "step in the brain death phenomenon."[61] Indeed, in the current study and those published in which follow-up has been provided, the patients died from hours to days later. Nevertheless, Valle et al and others appear to share in the belief that brain death cannot be confirmed by brain scintigraphy under this latter circumstance.[55,58,61]

In a rare fourth pattern, cerebellar uptake of Tc-99m HMPAO is absent, yet cerebral perfusion is substantially preserved.[58,59,67] This article adds a fourth case of this type to the literature (Fig 6). Of the 4 cases, one was associated with posterior fossa hemorrhage,[67] while another revealed necrosis at autopsy.[58] The authors' patient had massive

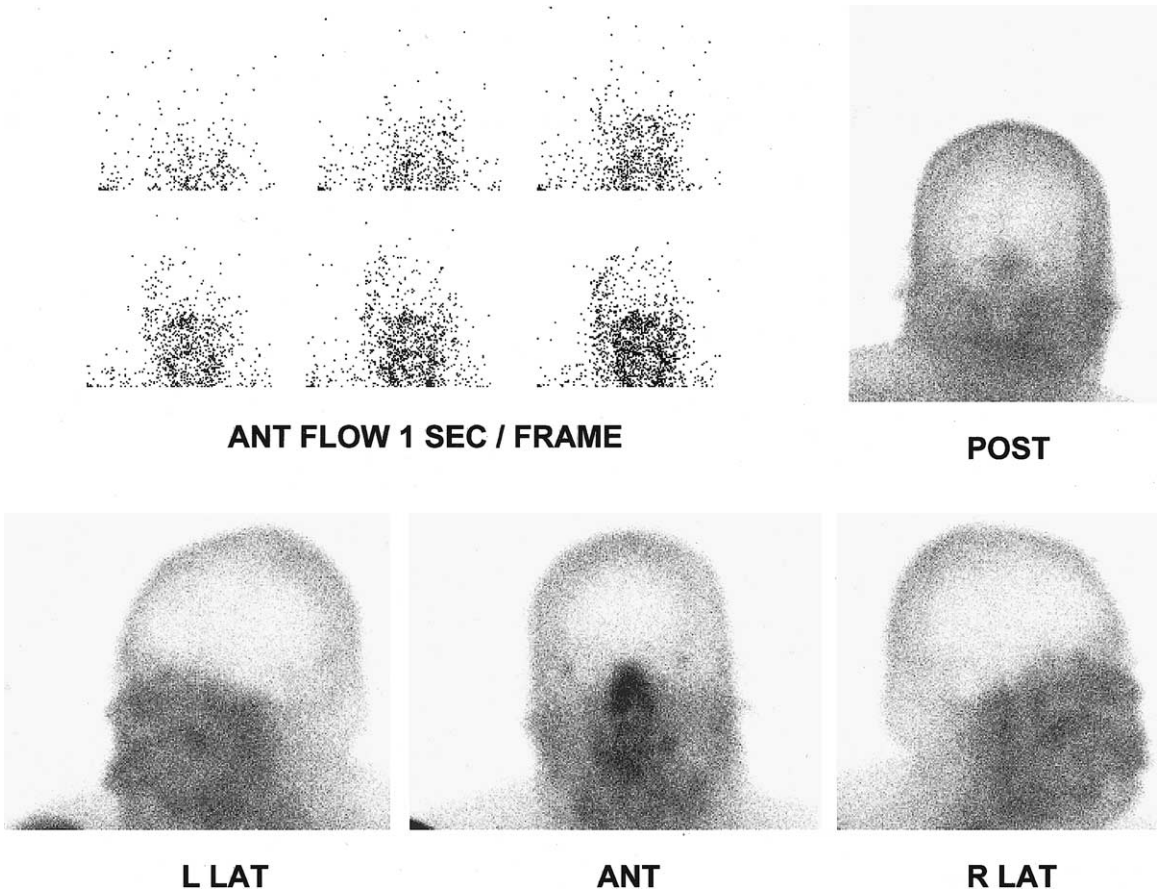

Fig 7. Technical considerations in the evaluation of whole brain death. This 44-year-old had subarachnoid hemorrhage and vasospasm associated with cerebral aneurysms. Redundant neck soft tissues make difficult evaluation of the occipital cortices and posterior fossa. Either planar imaging in the posterior projection (shown here) or SPECT[58] can be helpful in these cases. Unlike radionuclide studies with blood-pool agents, evaluation with (HMPAO) is assisted when low-grade activity is present in the dural sinuses. In this case, the intravenous bolus was prolonged (upper left), but because HMPAO was used, the diagnosis is not diminished. The "hot nose sign" is supportive, but not diagnostic of death.[45-47]

cerebellar infarction (Fig 6). These scintigraphic patterns of dissociation between cerebral and cerebellar flow do appear to fit current concepts. Balslev-Jorgensen et al proposed the presence of intracranial pressure gradients early in the course of brain death, and cite data supporting the existence of these gradients across the tentorium.[68] In transcranial Doppler examinations, ultrasonographic patterns occurring from the middle cerebral arteries do not always match those from the basilar artery.[69,70] However, these evolutionary patterns of brain injury do challenge our commitment to the concept of "whole brain" death (ie, death of the cerebrum, cerebellum, and brain stem). As technology advances, the extent of brain damage that must occur before a patient can be declared dead will continue to be a topic of debate.[71,72] In the meantime, further understanding of the appropriate timing for confirmatory tests might help to reduce the frequency of negative examinations.[73]

Scintigraphic Evaluation of Brain Death in Childhood

From a technical standpoint, scintigraphic examinations are feasible for the assessment of brain death in children and, in certain instances, have clear advantages over EEG or extended neurologic examinations.[36,74-79] However, studies published to date suggest a higher false-negative rate for children when compared with adults.[57,77,80-82] Therefore, discordance between clinical and scintigraphic findings will require follow-up neurologic or confirmatory examinations (Figs 2 and 3). As mentioned previously, the AAP Guidelines propose scintigraphy in 2 to 12-month-old infants to shorten the clinical observation. Practitioners who prefer Tc-99m HMPAO for brain death should be aware that the

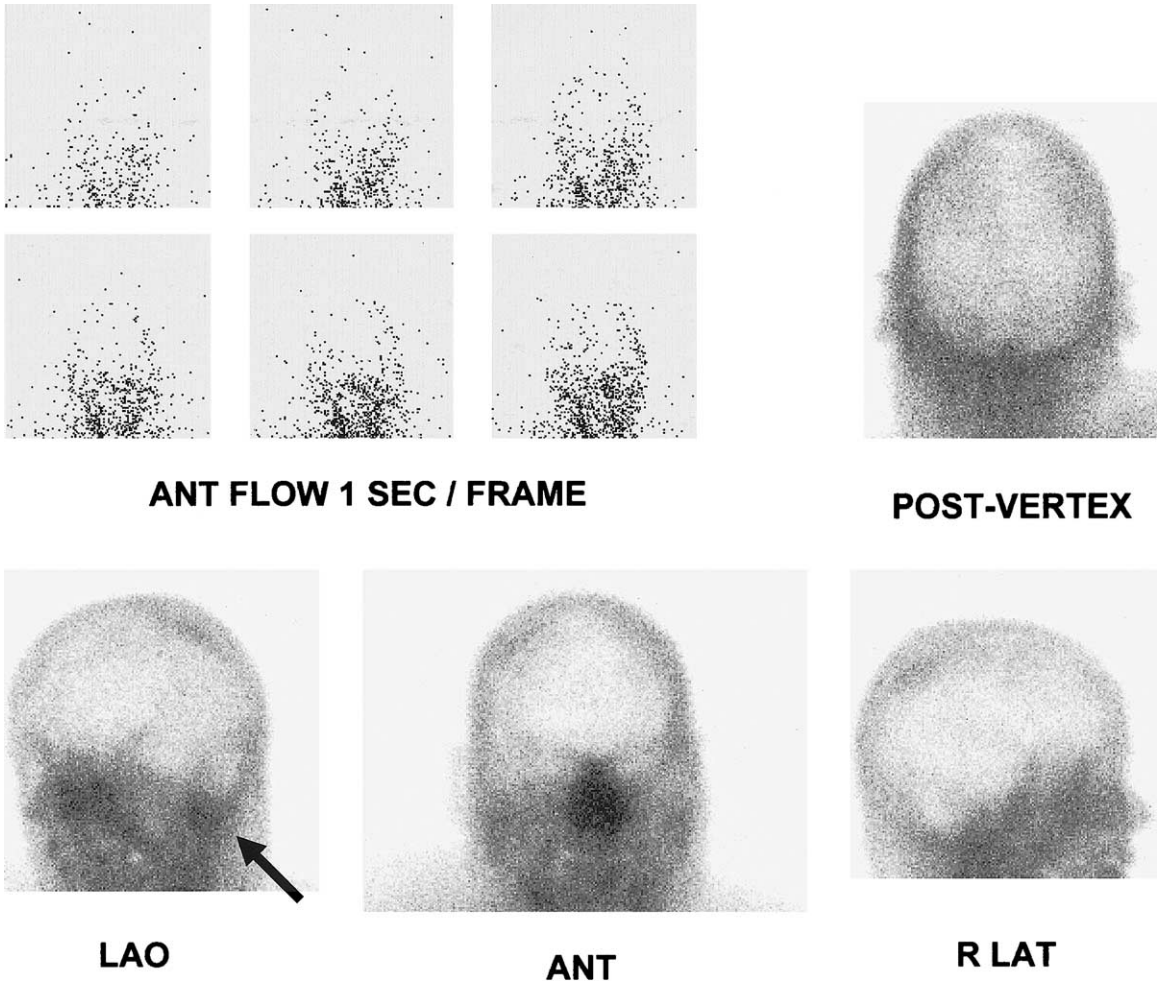

Fig 8. Technical considerations in the evaluation of whole brain death. This 52-year-old had a large frontal hemorrhage. The radionuclide angiogram plus the anterior and left anterior oblique "statics" were initially performed following intravenous (HMPAO). They might have been sufficient for confirmation of brain death, given the appropriate clinical criteria were met, which included absent brain stem reflexes. However, supplemental right lateral and posterior projection images secure the diagnosis. Parotid salivary gland activity (arrow) can mimic isolated preservation of cerebellar metabolism on shallow anterior obliques (compare with Fig 5, and see Fig 1b in Weckesser and Schober[58]).

number of cases currently published with this agent and for this particular age group is relatively small. An understanding of the rate of telencephalic maturity in this latter group also will help to avoid errors of interpretation.[83]

SUMMARY

Cerebral scintigraphy is a safe, reliable, and widely available confirmatory examination to the clinical diagnosis of brain death. Once the radiopharmaceutical is properly compounded, cerebral scintigraphy can be performed rapidly, and its interpretation will be relatively straightforward. Metabolic aberrations, pharmacologic intoxicants, electrical interference, and the presence of skull defects or scalp trauma do not preclude its performance. Cerebral radionuclide angiography has been highly sensitive, while either cerebral planar scintigraphy or cerebral scintitomography with Tc-99m HMPAO appears to be 100% specific.[58] One of the ethical concerns in cadaveric transplantation is how to achieve the appropriate balance between the desire to minimize the interval between the clinical appearance and the declaration of brain death on the one hand, and the need to meet all legal, moral, and potentially religious concerns on the other. Tc-99m HMPAO scinti-

graphy should excel in this regard, not only because it is without deleterious effects on donor organs, but because it shows metabolically functioning brain tissue, and it has very high specificity. Further study is desirable to help optimize the timing of cerebral scintigraphy relative to the various clinical parameters of suspected brain death.

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