

# *Brain death*

## History and controversies

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# Outlines

- History of the brain death concept and criteria
- Controversies:
  - Whole-brain death *vs.* brainstem death
  - Controversies in neurological determination of brain death
    - Clinical criteria and assessment
    - Subsequent clinical examinations and time intervals
    - Age-specific pediatric NDD guidelines
    - Other Confounding factors
  - Ancillary testing

# History of the brain death concept

## What is DEATH?

- Prior to the introduction of mechanical ventilators in the mid 20th century and the evolution of resuscitative measures:
  - The ***circulatory-respiratory formulation*** was used to determine death.

# Why a new concept?

- After that:
  - *neurological determination of death (NDD)* was considered.  
"the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions including the capacity to breathe".

## Why a new concept?

- Before transplantation concept:
  - To shorten the admission time of an artificially maintained patient in ICU.
- After transplantation concept:
  - To prevent wasting of time.

# History of the brain death criteria

- 1959:
  - Wertheimer P / Mollaret and Goulon
  - “coma dépassé” meaning “a state beyond coma”
  - 23 cases in which loss of consciousness, brain stem reflexes, and spontaneous respiration but with maintained circulation was associated with absent encephalographic activity.
  - In fact they described a condition from which they believed recovery was not possible.

*Mollaret P, Goulon M. Le coma dépassé. Rev Neurol (Paris). 1959; 101: 3–15*

Wertheimer P, Jouvet M, Descotes J. [Diagnosis of death of the nervous system in comas with respiratory arrest treated by artificial respiration]. *Presse Med* 1959;67:87–88.

# History of the brain death criteria

- 1963:
  - ‘brain dead’ was used by Guy Alexander, a Belgian surgeon, to describe a patient with heart beat from whom a kidney was procured for transplant into a non-related recipient.

# History of the brain death criteria

- 1968:

- The ad hoc Committee of the Harvard Medical School (Harvard criteria)

Unreceptivity and unresponsivity

No movements or breathing

No reflexes

Flat electroencephalogram

All repeated at, at least, 24 hr.

Exclusion of hypothermia (<32.2) or CNS depressants

- The committee deliberations focused on a whole-brain formulation to define brain death.
- It serves as the foundation of the brain death concept in the United States.

All subsequent criteria for brain death have been founded on this seminal work.

A definition of irreversible coma: Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain death. JAMA 1968; 205: 337–40.

# History of the brain death criteria

- 1971:
    - Mohandas and Chou emphasized the importance of irreversible loss of brainstem function in brain death.  
(Minnesota criteria)
      - Definition of the time of apnea( 4 min of disconnection)
      - Metabolic factors should be ruled out.
      - Shorter observation time to 12 hrs.
      - Irrelevance of EEG.
- Non of them with validating fact.



# History of the brain death criteria

- 1976:
  - The importance of brainstem function then became the focus of a published statement by the Conference of Medical Royal Colleges and Their Faculties in the United Kingdom.( Brain stem death)

Diagnosis of brain death: statement issued by the honorary secretary of the Conference of Medical Royal Colleges and Their Faculties in the United Kingdom on 11 October 1976. Br Med J 1976; 2: 1187–8.

- 1995:
  - Subsequently the brainstem formulation of brain death was formally adopted in the UK.

Criteria for the diagnosis of brain stem death: Conference of Medical Royal Colleges and their Faculties in the UK. Criteria for the diagnosis of brain stem death. Journal of the Royal College of Physicians of London 1995;29:381-2  
Pallis C, Harley DH. ABC of brainstem death, 2nd ed. London: BMJ Publishing Group; 1996: 8–12.

# History of the brain death criteria

- The medical consultants to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research detailed a comprehensive set of clinical circumstances and a battery of tests to identify brain death (1981):
  - 1) Cessation of brain function is recognized when evaluation discloses findings of (a) and (b):
    - (a) cerebral functions are absent,
    - (b) brain stem functions are absent.
  - 2) Irreversibility is recognized when evaluation discloses findings of :
    - (a) the cause of coma is established and is sufficient to account for the loss of brain functions,
    - (b) the possibility of any recovery of any brain function is excluded,
    - (c) cessation of all brain functions persists for an appropriate period of observation.

This criteria reaffirmed the application of a whole-brain definition for brain death in the USA.

Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. JAMA 1981; 246: 2184–6.

# History of the brain death criteria

- The Uniform Determination of Death Act (UDDA - the United States Federal Legislation accepted by most State Legislatures which legally defines death) used the recommendation of the President's Commission as the basis for the statute.

Uniform Determination of Death Act, 12 Uniform Laws Annotated (U.L.A.) 589 (West 1993 and West Supp.1997).

- 1995:

## American academy of neurology guide line

Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995; 45:1012.

# Outlines

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    - Age-specific pediatric NDD guidelines
    - Other Confounding factors
  - Ancillary testing

# Controversies

- Despite general worldwide acceptance of the concept of (NDD), inconsistencies in clinical criteria and ancillary testing requirements remain.
- Scientific rationale for specific guideline recommendations often remains unclear. In fact there is a paucity of evidence-based literature to support many current practices related to brain death determination.
- In the USA in accordance with the Uniform Determination of Death Act, guidelines for brain death determination are developed at an institutional level, so that major differences exist in brain death guidelines among the leading neurologic hospitals in the United States.

Powner DJ, Hernandez M, Rives TE. Variability among hospital policies for determining brain death in adults. *Crit Care Med* 2004; 32: 1284–8.

Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology* 2002; 58: 20–5.

Greer, David M. MD, MA; Varelas, Panayiotis N. MD, PhD; Haque, Shamael DO, MPH; Wijdicks, Eelco F.M. MD, PhD: Variability of brain death determination guidelines in leading US neurologic institutions; *Neurology* 70(4), 22 January 2008, pp 284-289

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# Whole-brain death vs. brainstem death

- In the United States, the UDDA codifies the whole-brain formulation of brain death.  
*Uniform Determination of Death Act, 12 Uniform Laws Annotated (U.L.A.) 589 (West 1993 and West Supp.1997).*
- This formulation is the one most commonly applied worldwide, and forms the foundation for legal codification in many Western nations.
- A notable exception exists in the United Kingdom where the brainstem formulation of brain death is applied.

Pallis C, Harley DH. ABC of brainstem death, 2nd ed. London: BMJ Publishing Group; 1996: 8–12.  
Criteria for the diagnosis of brain stem death. Review by a working group convened by the Royal College of Physicians and endorsed by the Conference of Medical Royal Colleges and their Faculties in the United Kingdom. J R Coll Physicians Lond 1995; 29: 381–2.

# Whole-brain death vs. brainstem death

- Inconsistencies with the whole-brain formulation:
  - Anterior pituitary neuroendocrine function as well as hypothalamic mediated thermoregulatory control, and autonomic function may be preserved in patients who otherwise fulfill all clinical criteria for brain death
  - Perfusion to these structures arises from extracranial vessels. Continued cellular activity may be a manifestation of retained blood flow to these nests of cells despite total intracranial cerebral circulatory arrest.

Powner DJ, Hendrich A, Lagler RJ, Ng RH, Madden RL. Hormonal changes in brain dead patients. Crit Care Med 1990; 18: 702–8.

- Some retained rudimentary EEG activity has been reported in some brain dead patients.

Grigg MM, Kelly MA, Celesia GG, Ghobrial MW, Ross ER. Electroencephalographic activity after brain death. Arch Neurol 1987; 44: 948–54.



# Whole-brain death vs. brainstem death

- whole-brain formulation response:  
Whole brain criterion does not require the loss of all neuronal activities.  
Instead all clinical brain function measurable at bedside must be lost.  
In fact some neurons may survive and contribute to recordable brain activities but not to clinical functions.

# Whole-brain death vs. brainstem death

- Inconsistency with the brain stem formulation:
  - The possibility of a “profound locked-in syndrome” in which awareness might be retained in the absence of all other signs of brainstem activity.

# Whole-brain death vs. brainstem death

- There is even a third formulation: “higher brain formulation”
  - It is related to a small group of scholars, but not jurisdictions anywhere in the world.
  - It is based on another definition of death: “the irreversible loss of that which is considered to be essentially significant to the nature of man.”
  - According to this definition PVS and anencephalic neonates are brain dead.

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# Clinical assessment

- Clinical assessment to determine brain death is remarkably similar in all guidelines
- All guidelines require an absence of centrally mediated response to pain. A proportion of patients may continue to display some reflex spinal activity which may range from subtle twitches to the more complex "Lazarus sign".

# Clinical assessment: guideline performance

- There was marked variability in the types of physicians who could perform the examinations, and the waiting periods between examinations.
  - Critical care physicians, neuroscience specialists, anesthesiologists, trauma surgeons and emergency medicine physicians are frequently involved in the care of critically brain injured patients.
  - In a study in the USA a neurologist or neurosurgeon was required to be involved in only 42% of guidelines, and of these, only 35% required that an attending neurologist or neurosurgeon be involved.
  - Some states (eg, Virginia) specifically require the physician to be a specialist in the neurosciences, while others (Alaska, Georgia) give authority to nurses with subsequent certification by a physician.

Greer, David M. MD, MA; Varelas, Panayiotis N. MD, PhD; Hague, Shamael DO, MPH; Wijdicks, Eelco F.M. MD, PhD: Variability of brain death determination guidelines in leading US neurologic institutions; *Neurology* 70(4), 22 January 2008, pp 284-289

- Number of physicians range between 1 to 3 or more in Europe.

Haupt WF, Rudolf J. European brain death codes: a comparison of national guidelines. *J Neurol* 1999;246:432-437.

# Clinical assessment: Pupillary reflex

- There are subtle differences in many guidelines regarding assessment of pupillary response to light and degree of dilatation, but no scientific basis for these differences has been clearly identified.

Leonard Baron, MD\*, Sam D. Shemie, MD , Jeannie Teitelbaum, MD and Christopher James Doig, MD MSc: Brief review: History, concept and controversies in the neurological determination of death; Canadian Journal of Anesthesia 53:602-608 (2006)

# Clinical assessment: oculocephalic reflex

- Most guidelines make no mention of the oculocephalic or doll's eye reflex.

- Pallis and Harley recommend the inclusion of doll's eye response even though it is not required by the United Kingdom code for brain death determination.

*Pallis C, Harley DH. ABC of brainstem death, 2nd ed. London: BMJ Publishing Group; 1996: 8–12.*

- Wijdicks does not include the oculocephalic reflex in his guidelines, arguing that this reflex lacks sensitivity in adult brain injured patients.

*Wijdicks EF. Brain Death. Philadelphia: Lippincott Williams & Wilkins; 2000: 29–43*

- Ashwal recommends that the reflex be evaluated and documented in neonates and infants in whom the vestibulo-ocular reflex may be more difficult to determine.

*Ashwal S. Clinical diagnosis and confirmatory testing of brain death in children. In: Wijdicks EF (Ed.). Brain Death. Lippincott Williams & Wilkins; 2000: 91–114*

- the Canadian guidelines do not require the testing of the oculocephalic reflex, but The American criteria do require this testing.

*Canadian Neurocritical Care Group: Guidelines for the Diagnosis of Death. Can J Neurol Sci 1999; 26: 64–6.*

*Practice parameters for determining brain death in adults (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995; 45: 1012–4.*



# Clinical assessment: Persistent apnea

Determination of persistent apnea is required in almost all guidelines although specific endpoints for evaluation are inconsistent.

- In less technically advanced nations apnea determined by ventilator disconnection may be sufficient. Apnea testing, using a PCO<sub>2</sub> target, was recommended in 59% of the surveyed countries.

*Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 2002; 58: 20–5.*

- Most Western guidelines require documentation of apneic threshold as determined by arterial blood gas analysis,
  - in the United Kingdom a threshold PaCO<sub>2</sub> more than 50 mm Hg is required.
  - Most North American guidelines recommend an apneic threshold PaCO<sub>2</sub> more than 60 mm Hg or 20 mm above normal baseline.
  - Some guidelines also require documentation of an acidemic pH < 7.28.

An evidence base for these thresholds could not be identified.

Leonard Baron, MD\*, Sam D. Shemie, MD, Jeannie Teitelbaum, MD and Christopher James Doig, MD MSc: Brief review: History, concept and controversies in the neurological determination of death; *Canadian Journal of Anesthesia* 53:602-608 (2006)

# Clinical assessment: Persistent apnea

- In the Greer's study in different centers of the USA:
  - in only one guideline was an apnea test not required.
  - Only 66% of guidelines specified that an arterial blood gas (ABG) be drawn prior to testing, and a normal pCO<sub>2</sub> level was specified in only 39%.
  - Other areas of particular deviation include Preoxygenation, the acceptable final values for pCO<sub>2</sub>, reasons to stop the test due to instability, and how and when to repeat the test if inconclusive.

## Subsequent clinical examinations and time intervals

- Most clinical guidelines require two clinical examinations within a predetermined time. it was presumably introduced to minimize the likelihood of technical errors in examination.
  - interval depending upon the etiology of brain injury.
    - A 24-hr observation period between examinations be observed in hypoxic-ischemic brain injury.
    - Guidelines, however, tend to be less specific regarding appropriate interval times in all other clinical circumstances.
  - Interval waiting times have progressively diminished since the earliest guidelines of the ad hoc Committee of the Harvard Medical School.

There is no scientific evidence to support any of these positions in the medical literature.

## Subsequent clinical examinations and time intervals

- In the Greer's study in different centers of the USA:
  - Multiple examinations were required in 71% of guidelines, and 3% required greater than two.
  - Forty-four percent stipulated that two separate physicians perform the examination, rather than the same physician twice.
  - Some (3%) guidelines permitted the omission of one of the two clinical examinations if neuroimaging was consistent with a neurologic catastrophe.
  - For institutions that did require multiple examinations, the time required between examinations varied widely, from 1 to 24 hours. The most commonly stipulated waiting period was 6 hours (80%), but this interval could be shortened if there was supportive ancillary testing (14%), or lengthened for children (24%), for patients with brain death of unknown cause (10%), or for patients with a non-structural cause (5%).
  - Sixteen percent mentioned a specific waiting period for cardiac arrest patients, but the waiting period varied from 24 hours (66%) to 12 or 6 hours (17% for each).

# Subsequent clinical examinations and time intervals

- In the Europe hours to repeat testing is not defined in some countries. In others its range is between 2 to 24 hours

Haupt WF, Rudolf J. European brain death codes: a comparison of national guidelines. *J Neurol* 1999;246:432-437

- the Canadian guidelines allow an interval between examinations as short as two hours( 24 hr if due to anoxic-ischemic insult).

Canadian Neurocritical Care Group: Guidelines for the Diagnosis of Death. *Can J Neurol Sci* 1999; 26: 64–6.

- Some guidelines (ANZICS) mandate that two different physicians determine brain death when organ transplantation is being considered.

*Pearson IY.* Australia and New Zealand Intensive Care Society Statement and Guidelines on Brain Death and Model Policy on Organ Donation. *Anaesth Intensive Care* 1995; 23: 104–8

- Some believe that in experienced hands, the second examination for brain death is invariably consistent with the first, and that an apnea test need not be repeated during the second evaluation.

*Wijdicks EF.* Brain Death. Philadelphia: Lippincott Williams & Wilkins; 2000: 29–43.

# Age-specific pediatric NDD guidelines

- There is little scientific basis for published age-related guidelines. Most authorities agree that adult clinical criteria may be applied in children with a post-conceptual age of 52 weeks.
- In spite of this, virtually every guideline acknowledges that protocol changes in evaluating neonates and infants are required.
- However, clinical examination alone is generally thought to be insufficient in children less than one year of age.

# Age-specific pediatric NDD guidelines

- Observation period in children according to AAN guideline:
  - Infants between 7 days and 2 months must have 2 examinations, separated by 48 hours and 2 confirmatory ancillary tests (EEGs) consistent with brain death.
  - Infants between 2 months and 1 year must have
    - 2 examinations separated by 24 hours and 2 confirmatory ancillary tests (EEGs) consistent with brain death.
    - Or 1 examination and an initial EEG showing ECS combined with a radionuclide angiogram showing no CBF
  - Children less than 18 years must have 2 examinations separated by 12 hours. EEG or other ancillary tests are optional.
- These are all controversial in different guidelines.

## Other confounding factors: hypothermia

- It is well recognized that hypothermia, defined as core temperature  $< 32^{\circ}\text{C}$ , induces hyporeflexia and that at temperatures  $< 28^{\circ}\text{C}$  areflexia may ensue.
- Many guidelines include specific core temperature thresholds for clinical determination of brain death, but recommended thresholds range from  $32.2^{\circ}\text{C}$  to  $36.0^{\circ}\text{C}$  *without clear evidence base for any of these limits.*

*Danzl DR, Pozos RD. Accidental hypothermia. N Engl J Med 1994; 331: 1756–60.*



# Other confounding factors: hypothermia

- the Canadian guidelines permit a core temperature as low as 32.2°C during the apnea test, The American require a core temperature of more than 36.5°C.

Canadian Neurocritical Care Group: Guidelines for the Diagnosis of Death. Can J Neurol Sci 1999; 26: 64–6.  
Practice parameters for determining brain death in adults (summary statement). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995; 45: 1012–4

- In the Greer's study in different centers of the USA:
  - A specific lowest acceptable temperature for apnea testing was required in 26%, and that temperature varied from 36.5 °C (70%) to 35 °C (10%) and 32 °C (20%).
  - 11 different minimum temperatures were mentioned across the country: 32.0 °C, 32.2 °C, or 90.0 °F was mentioned in the majority (74%); other temperatures that were mentioned include 35 °C (6%), 36 °C (6%), 36.5 °C (6%), 35.5 to 36.5 °C (3%), 97 °F (6%), and 96.5 °F (3%).

Greer, David M. MD, MA; Varelas, Panayiotis N. MD, PhD; Haque, Shamael DO, MPH; Wijdicks, Eelco F.M. MD, PhD:  
Variability of brain death determination guidelines in leading US neurologic institutions; Neurology 70(4), 22 January 2008, pp 284-289

# Other confounding factors

- Also in the Greer's study in different centers of the USA:
  - An absence of shock was required in the majority (71%), but the definition of shock varied widely, and 24% of guidelines did not specify an acceptable blood pressure.
  - The most commonly specified was a systolic blood pressure (SBP)  $\geq 90$  mm Hg (45%), but others mentioned included an SBP  $> 80$  mm Hg (6%) or 100 mm Hg (3%), a mean arterial pressure  $> 55$  mm Hg (12%), an SBP no less than 10 mm Hg below the patient's baseline (3%), within 20% of the baseline (3%), and "normal blood pressure for age" (3%).

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# Ancillary testing

1. Cerebral angiography
2. Electroencephalography
3. Transcranial doppler
4. Cerebral scintigraphy

- Although the reliability of somatosensory evoked potentials has been drawn into question, they remain an acceptable technique in a large number of guidelines.
- Promising tests such as CT angiography, CT perfusion, and MR angiography have permeated some of the guidelines, but these tests, although interesting, have shown questionable value in comparison to conventional angiography (the gold standard), and have not been validated or recommended by a governing committee.

# Ancillary testing

- Cerebral angiography:
  - The contrast should be injected with high pressure in both ant and post circulation.
  - Arrest of flow is found at the foramen magnum in the posterior circulation and at the petrosal portion of the carotid artery in the anterior circulation.
  - The external carotid should be patent

# Ancillary testing

- Electroencephalography with a minimum of 8 scalp electrodes
  - The distance of the electrodes should be at least 10 cm.
  - The sensitivity should be increased to at least 2 mic.v. for 30 min.
  - The high and low frequency filter should not be set below 30 and above 1Hz respectively.
  - EEG should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.
  - EEG examination is limited by an inability to detect activity in deep brain structures and electrical interference in the intensive care environment when high gain examinations are performed.
  - This testing may also be adversely affected by conditions such as hypothermia and pharmacotherapeutic agents used in the management of brain injured patients.

# Ancillary testing

- Transcranial doppler should be done bilaterally with the zygomatic and suboccipital window.
  - There should be a lack of diastolic flow and documentation of a small systolic peak in early systole
  - A finding of a complete absence of flow may not be reliable owing to inadequate transtemporal window.

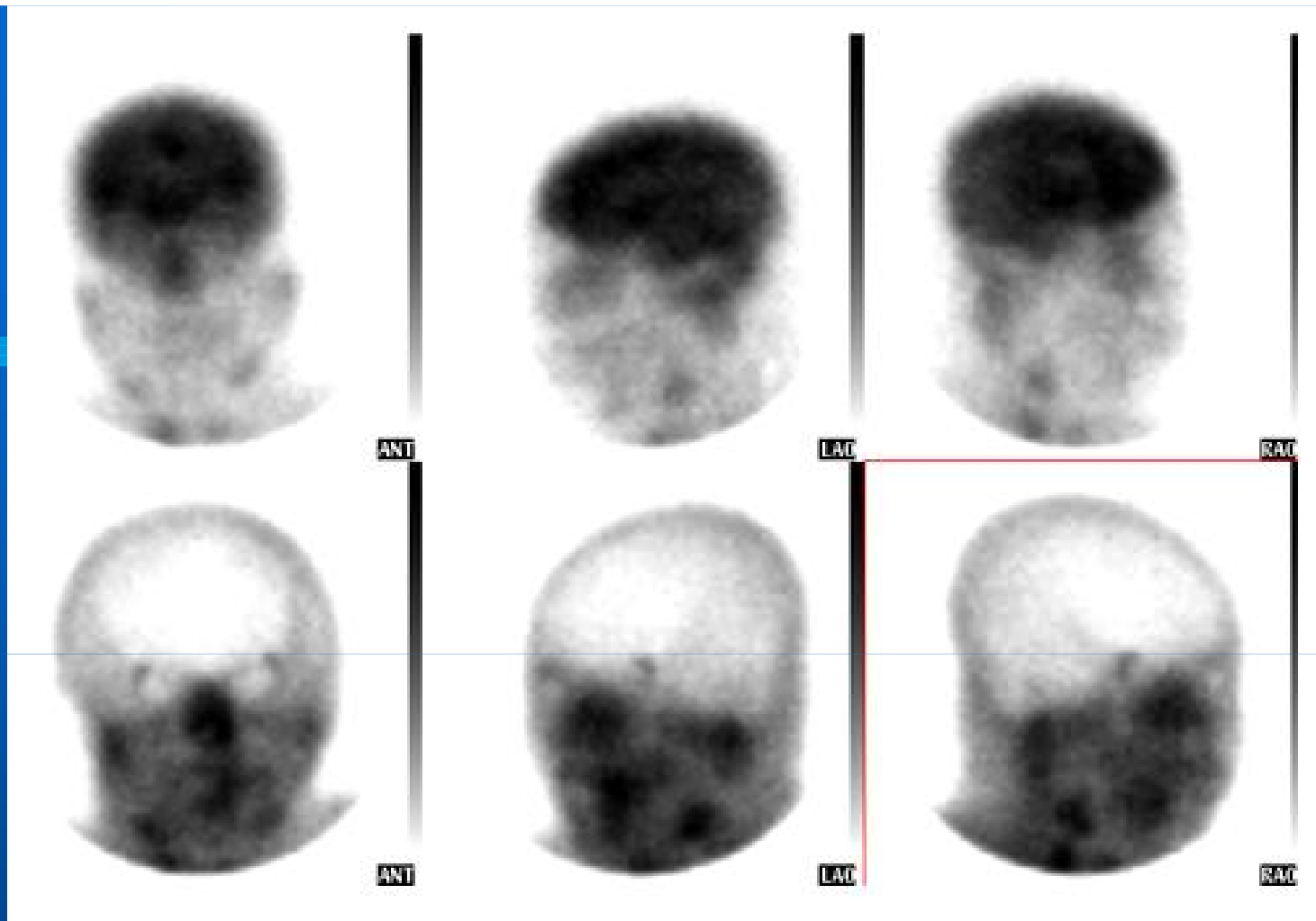
# Ancillary testing

- Cerebral scintigraphy should be done with radioisotope (Tc-99m hexamethylpropylene - amine oxime (Tc -HMPAO) radionuclide) injected within 30 min after its reconstitution.
  - A static images of 500,000 counts should be obtained immediately, between 30 and 60 min later and at 2 hrs.
  - A correct IV injection may be confirmed with additional images of the liver.

Eelco F.M. Wijdevicks, M.D. The Diagnosis of Brain Death: NEJM 344:1215-1221

*Schlake HP, Böttger IG, Grotemeyer KH, Husstedt IW, Brandau W, Schober O.* Determination of cerebral perfusion by means of planar brain scintigraphy and 99m Tc-HMPAO in brain death, persistent vegetative state and severe coma. Intensive Care Med 1992; 18: 76-81





- Two-planar imaging with HMPAO-Tc99m:
  - The top figures show anterior posterior and lateral views of a normal scan with uptake in the brain.
  - The bottom figures (same sequence) show lack of brain perfusion and the "empty light bulb" and "hot nose" signs.

# Ancillary testing

- An ideal ancillary test for brain death should meet all of the following criteria:
  - There should be no "false positives,"
  - The test should be sufficient on its own to establish that brain death is or is not present, ie, whether there is total and irreversible destruction of the brain stem or the entire brain.
  - The test should not be susceptible to "confounders" such as drug effects or metabolic disturbances.
  - The test should be standardized in technology, technique, and classification of results.
  - The test should be available, safe, and readily applied in all medical centers with ICUs.
- Unfortunately, no currently available test for brain death meets all of these criteria.

# Ancillary testing

- The use of ancillary diagnostic testing in the determination of brain death was addressed in the 1981 recommendations of the President's Commission, specially for confounding clinical conditions
- To this day many international guidelines mandate ancillary diagnostic testing to establish brain death. Confirmatory laboratory testing was mandatory in 28 of 70 practice guidelines (40%).

# Ancillary testing

- In the Greer's study in different centers of the USA:
  - Specific situations in which to procure ancillary testing were mentioned in 66% of guidelines. These situations included inability to complete the clinical examination (74%), toxic drug levels (56%), inconclusive apnea testing (44%), normal neuroimaging (16%), and chronic CO<sub>2</sub> retention (32%).

# Ancillary testing

- In the Europe:
  - Confirmatory testes is not necessary to do in UK, Poland, and Switzerland,
  - Is optional in some, e.g. Germany,
  - Is mandatory in others, e.g. France.

# Conclusions

- A number of clinical guidelines for NDD which share many common features have been published in the literature.
- However, variability and inconsistency within these guidelines does exist, particularly in regard to the thresholds applied to diagnostic tests and requirements for ancillary testing.
- These discrepancies appear to reflect the lack of scientific evidence in the literature and selected thresholds may represent the collaborative decision by various bodies and organizations developing guidelines.
- Because of existing variabilities and inconsistencies in neurological determination of death, it is necessary to generate and disseminate uniform criteria.