

CONSENSUS OPINION ON DIAGNOSING BRAIN DEATH – GUIDELINES FOR USE OF CONFIRMATORY TESTS

Report of Croatian Neurovascular Society and University Department of Neurology,
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SUMMARY – Brain death is defined as the irreversible loss of all brain functions, including the brainstem. The diagnosis of brain death allows organ donation or withdrawal of support. Therefore the exact criteria for the diagnosis of brain death must be determined. In the Croatian Act on Transplantation, repeated neurologic examination must show loss of brainstem reflexes, and one confirmation test must be done. Several tests are available, showing the cessation of brain or brainstem activity, or confirming the cerebral circulatory arrest. Bedside evaluation is possible through electroencephalographic and neurosonologic tests. Conventional or digital subtraction angiography is done in radiology suite, and isotope angiography and technetium-99m hexamethylpropyleneamine oxime (99Tc-HMPAO) at the Department of Nuclear Medicine. Such tests require special settings, therefore bedside test like electroencephalography, evoked potentials and neurosonology tests are preferred. All tests require trained personnel and strict protocols, which differ from routine investigations. The confirmatory tests used in brain death confirmation, the techniques, criteria, results and validity of the tests are presented.

Key words: Brain Death – diagnosis; Brain Death – ultrasonography; Severity of Illness; Predictive Value of Tests; Guidelines; Brain death – legislation and jurisprudence; Croatia

Introduction

Brain death in a normothermic, nondrug comatose patient with a known irreversible massive brain lesion and no contributing metabolic or hormonal derangements, is declared when brainstem reflexes, motor responses and respiratory drive are absent. The first observation was documented in 1959 by Mollaret and Goulon¹. The use of mechanical ventilation and intensive care unit setting have

prevented respiratory arrest and transformed the course of terminal neurologic disorder. Vital functions could since then be maintained artificially after the brain has ceased to function. The definition using neurologic criteria became formalized after a report of the Harvard Medical School Ad Hoc Committee in 1968². The definition of irreversible coma or brain death was defined as unresponsiveness and lack of reactivity, the absence of movement and breathing, the absence of brainstem reflexes, and coma, the cause of which was identified. Over years, the Committee has been a target of criticism.

In 1971, Mohandas and Chou³ described damage to the brainstem as a critical component of severe brain damage.

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The Conference of the Medical Royal Colleges and their faculties in the United Kingdom published a statement on the diagnosis of brain death in 1976⁴. Brain death was defined as complete, irreversible loss of brainstem function. This statement provided guidelines that included a refinement of apnea testing and pointed to the brainstem as the center of brain function, with no life existing without its function. In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research published its guidelines⁵. This document recommended the use of confirmatory tests to shorten the duration of the required observational period and recommended a period of 24 hours for patients with anoxic damage. It ruled out shock as a requirement for determination of brain death.

In 1995, brain death was selected as a topic for practice parameters⁶ because of the perceived need of standardized clinical examination criteria for the diagnosis of brain death in adults, large differences in practice in performing the apnea test, and controversies over appropriate utilization of confirmatory tests. According to MEDLINE search for the years 1976-1994, Quality Standards Subcommittee of the American Academy of Neurology selected peer-reviewed articles with original work. Selection for this document was based on the original work quality. Textbooks and handbooks of neurology, medicine, intensive care, pulmonology and anesthesiology were reviewed for opinion. Since no class I studies (randomized clinical trials) were available, references were categorized as class II (well-designed clinical studies) or class III (case reports, uncontrolled studies and expert opinion). The Committee defined practice parameters that should serve as guidelines in the management of patients with brain death⁷. For the first time brain death patients were separated from persisting vegetative state. With this document⁷, diagnostic criteria for the clinical diagnosis of brain death were defined, as well as pitfalls in its diagnosis and clinical observations compatible with the diagnosis of brain death. A practical description of apnea testing was addressed. Optional confirmatory laboratory tests and standard medical record documentation were listed. Despite such definition, the criteria varied between countries.

A survey on brain death criteria⁸ throughout the world revealed uniform agreement on the neurologic examination with the exception of apnea test. Major differences between countries were related to the presence of legal standards on organ transplantation, presence of practice guidelines for brain death in adults, number of physicians required to declare brain death, observational period, or presence of required expertise of examining physicians.

Only 28 of 70 (40%) national practice guidelines require confirmatory testing.

Legal Acts

In Croatian legislature⁹⁻¹², clinical neurologic examination remains the standard for the determination of brain death. Clinical examination of patients who are presumed to be brain dead must be performed with precision^{7,13}. To declare brain death requires not only a series of careful neurologic tests but also the establishment of the cause of coma, the ascertainment of irreversibility, the resolution of any misleading clinical neurologic signs, the recognition of possible confounding factors, the interpretation of the findings on neuroimaging, and the performance of one confirmatory laboratory test are mandatory. At least two physicians are involved in the clinical diagnosis, one should be anesthesiologist and the other anesthesiologist, neurologist or neurosurgeon. The observational period is at least 6 hours, and in anoxic brain damage 24 hours or 48 hours in children.

Before clinical examination in brain death determination, clinical conditions that may confound clinical assessment must be ruled out. These include severe acid-base or endocrine disturbances, hypothermia defined as core temperature of 32 °C or lower, and according to Croatian legislature 35°C or lower⁹, hypotension (systolic blood pressure <90 mm Hg), drug or alcohol intoxication, poisoning or neuromuscular blocking agents.

Neuroimaging must show evidence of an acute central nervous system (CNS) catastrophe that is compatible with the clinical diagnosis of brain death. Usually, computed tomography (CT) scanning documents a mass or massive hemorrhage with brain herniation, multiple hemispheric lesions with edema, or edema alone. The confounders must be carefully searched for. The CT scan can be normal in the early period after cardiorespiratory arrest and in patients with fulminant meningitis or encephalitis. Examination of the cerebrospinal fluid should reveal diagnostic findings in circumstances of CNS infection.

Clinical Findings

Complete clinical neurologic examination includes documentation of coma, absence of brainstem reflexes, and apnea test^{6,7} (Table 1). As brain death occurs, patients lose their reflexes in a rostral to caudal direction. Therefore, the cessation of medulla oblongata reflexes occurs last. The brainstem destruction may last for hours to be complete,

*Table 1. Clinical criteria for brain death in adults***Coma**

Absence of motor responses
 Absence of pupillary responses to light and pupils at mid-position with respect to dilation (4-6 mm)
 Absence of corneal reflexes
 Absence of caloric responses
 Absence of gag reflex
 Absence of coughing in response to tracheal suctioning
 Absence of sucking and rooting reflexes
 Absence of respiratory drive at a PaCO₂ that is 60 mm Hg or 20 mm Hg above normal baseline values
 Interval between two evaluations is at least 6 hours, or 24 hours in anoxic damage

and during that period medullary functions are present¹⁴, so normal blood pressure is obtained as well as cough response after tracheal suctioning and tachycardia after the administration of 1 mg of atropine.

Coma or unresponsiveness*Testing motor responses of the limbs*

The depth of coma is assessed by documentation of the presence or absence of motor responses to a standardized painful stimulus such as nail-bed pressure or pressing on the supraorbital nerve or temporomandibular joint (Table 2). Motor response known as Lazarus sign¹⁵ may occur spontaneously during apnea testing, often during hypoxic or hypotensive episodes, and is of spinal origin. Neuromuscular blocking agents can produce prolonged weakness. If neuromuscular blocking agents have recently been administered, examination with a bedside peripheral nerve stimulator is needed.

Absence of brainstem reflexes

A) Pupils may be round, oval or irregularly shaped. Most pupils in brain death are in midline position (4-6 mm), but the size of the pupils may vary from 4-9 mm. Dilated pupils are compatible with brain death because intact sympathetic cervical pathways connected with the radially arranged fibers of the dilator muscle may remain intact. The response to bright light should be absent in both eyes. Many drugs can influence pupil size, but response to light remains intact. In conventional doses, atropine given intravenously has no marked influence on pupillary response. Topical ocular instillation of drugs and trauma to the cornea or bulbus oculi may cause abnormalities in pupil size and

can produce nonreactive pupils. Pre-existing anatomic abnormalities of the iris or effects of previous surgery should be excluded.

B) Ocular movements are absent after head-turning and caloric testing with ice water¹⁶. The testing is done only when no fracture or instability of the cervical spine is apparent. In patients with head injury, the cervical spine must be imaged to exclude potential fractures or instability or both.

Oculocephalic reflex is elicited by fast and vigorous turning of the head from middle position to 90° on both sides and normally results in eye deviation to the opposite side of the head turning. Vertical eye movements should be tested with brisk neck flexion. Eyelid opening and vertical and horizontal eye movements must be absent in brain death.

Caloric testing should be done with the head elevated to 30° during irrigation of the tympanum on each side with 50 ml of ice water (4 °C). A prior examination of auditory canal is required. Tympanum irrigation is accomplished by inserting a small suction catheter into the external auditory canal and connecting it to a 50-ml syringe filled with ice water. Tonic deviation of the eyes directed to the cold caloric stimulus is absent. The investigator should allow up to 1 minute after injection, and the time between stimulation on each side should be at least 5 minutes.

Drugs that can diminish or completely abolish the caloric response are sedatives, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic and chemotherapeutic agents. After closed head injury or facial trauma, lid edema and chemosis of the conjunctiva may restrict movement of the globes. Clotted blood or cerumen may diminish caloric response and repeat testing is required after direct inspection of the tympanum. Basal fracture of the petrous bone abolishes the caloric response only unilaterally and may be identified by an ecchymotic mastoid process.

C) Facial sensation and facial motor response are tested through corneal reflexes and grimacing to pain. Corneal reflexes should be tested with a throat swab, and corneal reflex and jaw reflex should be absent. Grimacing to pain is tested by applying deep pressure with a blunt object on the nail beds, pressure on the supraorbital ridge, or deep pressure on both condyles at the level of the temporomandibular joint.

Severe facial trauma may limit interpretation of all brainstem reflexes.

D) Pharyngeal reflexes are tested by stimulation of the posterior pharynx with a tongue blade, and the gag

response should be absent. Absence of tracheal reflexes is demonstrated by the lack of cough response to bronchial suctioning.

The gag response may be difficult to interpret in orally intubated patients.

Table 2. Diagnostic procedure for clinical diagnosis of brain death

A. Diagnostic criteria for clinical diagnosis of brain death

Prerequisites. Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible:

- presence of clinical or neuroimaging evidence of an acute central nervous system catastrophe that is compatible with the clinical diagnosis of brain death
- exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base or endocrine disturbance)
- no drug intoxication or poisoning
- core temperature ≥ 32 °C

B. Clinical findings

1) coma or unresponsiveness: absent motor response to pain in all extremities (nail-bed pressure and supraorbital pressure)

2) absence of brainstem reflexes

Pupils:

- midposition (4 mm) to dilated (9 mm)
- no response to bright light

Ocular movement:

- no oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent)
- no deviation of the eyes to irrigation in each ear with 50 ml of cold water (allow 1 minute after injection and at least 5 minutes between testing on each side)

Facial sensation and facial motor response:

- no corneal reflex to touch with a throat swab
- no jaw reflex
- no grimacing to deep pressure on nail bed, supraorbital ridge or temporomandibular joint

Pharyngeal and tracheal reflexes:

- no response after stimulation of the posterior pharynx with tongue blade
- no cough response to bronchial suctioning

3) Apnea testing performed as follows

Prerequisites:

Core temperature ≥ 36 °C

Systolic blood pressure ≥ 90 mm Hg

Euolemia. Option: positive fluid balance in the previous 6 hours

Normal PCO₂. Option: arterial PCO₂ ≥ 40 mm Hg

Normal PO₂. Option: preoxygenation to obtain arterial PO₂ ≥ 200 mm Hg

- connect pulse oximeter and disconnect the ventilator
- deliver 100% O₂, 6 L/min, into the trachea. Option: place a cannula at the level of the carina
- look closely for respiratory movements (abdominal or chest excursions that produce adequate tidal volumes)
- measure arterial PO₂, PCO₂ and pH after approximately 8 minutes and reconnect the ventilator
- if respiratory movements are absent and arterial PCO₂ is ≥ 60 mm Hg (option: 20 mm Hg increase in PCO₂ over a baseline normal PCO₂), the apnea test result is positive (i.e. it supports the diagnosis of brain death)
- if respiratory movements are observed, the apnea test result is negative (i.e. it does not support the clinical diagnosis of brain death), and the test should be repeated

- connect the ventilator if, during testing, the systolic blood pressure becomes ≤ 90 mm Hg or the pulse oximeter indicates significant oxygen desaturation and cardiac arrhythmias are present; immediately draw an arterial blood sample and analyze arterial blood gas. If PCO_2 is ≥ 60 mm Hg or PCO_2 increase is ≥ 20 mm Hg over baseline normal PCO_2 , the apnea test result is positive (it supports the clinical diagnosis of brain death); if PCO_2 is ≤ 60 mm Hg or PCO_2 increase is ≤ 20 mm Hg over baseline normal PCO_2 , the result is indeterminate
- 4) Clinical conditions that may interfere with the clinical diagnosis of brain death, and the diagnosis cannot be made with certainty on clinical grounds alone

Severe facial trauma

Pre-existing pupillary abnormalities

Toxic levels of any sedative drugs, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, chemotherapeutic agents or neuromuscular blocking agents

Sleep apnea or severe pulmonary disease resulting in chronic retention of CO_2

5) Confirmatory laboratory tests

After repeat clinical evaluation of 6 hours or 24 hours after anoxic injury, the confirmatory test must be done. It should be emphasized that any of the suggested confirmatory tests may produce similar results in patients with catastrophic brain damage who do not (yet) fulfill the clinical criteria of brain death.

- conventional or digital subtraction angiography: no intracerebral filling at the level of carotid bifurcation or circle of Willis, patent external carotid circulation
- electroencephalography: electrical silence during at least 30 min of recording in 16-channel EEG instruments
- transcranial Doppler ultrasonography: two times performed, recording reverberating flow pattern or one reverberating flow pattern followed by small systolic spikes, at least one arterial segment *per* window through three bone windows, documentation of similar flow patterns in both common and internal carotid and vertebral arteries extracranially
- $^{99\text{m}}\text{Tc}$ -HMPAO: no uptake of isotope in brain parenchyma (“hollow skull phenomenon”)
- isotope angiography with the injection of serum albumin labeled with technetium 99m is followed by bedside imaging with a portable gamma camera, and intracranial radioisotope activity is absent
- evoked potentials: bilateral absence of N20-P22 response with median nerve stimulation in somatosensory evoked potential
- CT or MRI absence of brain blood flow

Apnea test

Prerequisites: since important changes in vital signs as marked hypotension or severe cardiac arrhythmias may be related to the lack of adequate precautions but may also occur spontaneously during increasing acidosis, the following prerequisites are suggested: core temperature of at least 36°C , systolic blood pressure greater or equal to 90 mm Hg, euolemia or optional positive fluid balance in the previous 6 hours, eucapnia or optional arterial PCO_2 greater or equal to 40 mm Hg, normoxemia or optional preoxygenation to obtain arterial PO_2 greater or equal to 200 mm Hg. A pulse oximeter is connected to the patient.

Testing is performed by disconnecting the ventilator, thereafter, 100% O_2 , 6 L/min, is delivered into the trachea or a cannula is placed at the level of the carina.

Respiratory movements should be closely looked for. Respiration is defined as abdominal or chest excursions

that produce adequate tidal volumes. If present, respiration can be expected early in the apnea test. When respiratory-like movements occur, they can be expected at the end of the apnea test, when oxygenation may become marginal. When the result is in doubt, a spirometer can be connected to the patient to confirm that the tidal volumes are absent.

Arterial PO_2 , PCO_2 and pH are measured after approximately 8 minutes and the ventilator is reconnected. If respiratory movements are absent and arterial PCO_2 is ≥ 60 mm Hg or optional 20 mm Hg increase in PCO_2 over a baseline normal PCO_2 , the apnea test result is positive (i.e. it supports the diagnosis of brain death).

If respiratory movements are observed, the apnea test result is negative (i.e. it does not support the clinical diagnosis of brain death), and the test should be repeated.

If during testing, the systolic blood pressure becomes ≤ 90 mm Hg or the pulse oximeter indicates significant

oxygen desaturation and cardiac arrhythmias are present, an arterial blood sample should be immediately obtained, the ventilator connected and arterial blood gas analyzed. The apnea test result is positive if PCO_2 is greater or equal to 60 mm Hg or PCO_2 increase is equal to greater than 20 mm Hg over baseline normal PCO_2 . The result is indeterminate if PCO_2 is less than 60 mm Hg or PCO_2 increase is less than 20 mmHg over baseline normal PCO_2 .

If no respiratory movements are observed, PCO_2 is less than 60 mm Hg, and no significant cardiac arrhythmia or hypotension is observed, the test may be repeated with 10 minutes of apnea.

Clinical Observations Compatible with the Diagnosis of Brain Death

Certain clinical observations are compatible with the diagnosis of brain death. Respiratory acidosis, hypoxia or brisk neck flexion may generate spinal cord responses^{15,17,18}. Spontaneous movements of the limbs from spinal mechanisms can occasionally occur and are more frequent in young adults. These spinal reflexes include rapid flexion in arms, raising of all limbs off the bed, grasping movements, spontaneous jerking of one leg, walking-like movements, and movements of the arms up to the point of reaching the endotracheal tube¹⁵. Respiratory-like movements may also occur and are typical agonal breathing patterns. They are characterized by shoulder elevation and adduction, back arching and intercostal expansion without any significant tidal volume. Profuse sweating, blushing, tachycardia and sudden increases in blood pressure may be observed, but are compatible with the diagnosis of brain death¹⁹. Such observations may be elicited by brain death testing or apnea testing. Normal blood pressure and absence of diabetes insipidus without pharmacologic support are also compatible with brain death. Muscle stretch reflexes, superficial abdominal reflexes and Babinski reflexes are of spinal origin and do not invalidate the diagnosis of brain death. Patients may have initial plantar flexion of the great toe followed by sequential brief plantar flexion of the second, third, fourth and fifth toes after snapping off one of the toes (“undulating toe flexion sign”)¹⁷.

Diseases That Can Mimic Brain Death

There are several neurologic states that can mimic brain death, so careful history should be taken and thorough examination should be performed, with relevant imaging procedures. Still, these states should be kept in mind. A locked-in syndrome²⁰, especially in early phase,

hypothermia or drug intoxication may be misdiagnosed. The locked-in syndrome is usually a consequence of destruction of the base of the pons. The patient cannot move the limbs, grimace, or swallow, but the upper rostral mesencephalic structures involved in voluntary blinking and vertical eye movements remain intact. During the early phase patient may be comatose due to edema, and later is conscious because the tegmentum with the reticular formation is not affected. This condition is most often caused by an acute embolus to the basilar artery. Even more dramatic is the Guillain-Barre syndrome, which involves all the peripheral and cranial nerves²¹. The progression usually occurs over a period of days, but may be fulminant developing in one day. The precise history should prevent this reversible disease. Accidental hypothermia from prolonged environmental exposure may mimic loss of brain function, and alcohol and drug intoxication and head injury are often major confounders²². Hypothermia causes a downward spiral of loss of brainstem reflexes and pupillary dilatation. The response to light is lost at core temperatures of 28 °C to 32 °C, and brainstem reflexes disappear when the core temperature drops below 28 °C²². These deficits are all potentially reversible.

The effects of many sedative and anesthetic agents can closely mimic brain death, but aspects of brainstem function, particularly the pupillary responses to light, remain intact. In large quantities ingested, many drugs can cause partial loss of brainstem reflexes. Formal determinations of brain death documenting conditions that are entirely similar to those caused by structural lesions are exceptional but have been reported in cases of intoxication with tricyclic antidepressants and barbiturates^{23,24}. Even a more complex problem is the possible confounding of the clinical determination of brain death by metabolites or traces of circulating pharmaceutical agents. Screening test for drugs may be helpful but some toxins like cyanide, lithium or fentanyl may not be detected by routine screening tests²³. According to Croatian legislature⁹, the clinical diagnosis of brain death should not be started before drugs like sedatives, anesthetics, narcotics, muscle relaxants, antiepileptics, or antidepressants are present. Alcohol should not be present in the blood. If the drug of poisoning is known but the substance cannot be quantified, the observation time for five elimination half-life of the substance would ensure its almost complete elimination.

Confirmatory Tests

Brain death is a clinical diagnosis. According to Croatian legislature⁹, repeat clinical evaluation after a 6-hour

Table 3. Clinical observations compatible with the diagnosis of brain death that should not be misinterpreted as evidence for brainstem function

- Spontaneous movements of limbs other than pathologic flexion or extension response
- Respiratory-like movements (shoulder elevation and adduction, back arching, intercostal expansion without significant tidal volumes)
- Sweating, blushing, tachycardia
- Normal blood pressure without pharmacologic support or sudden increases in blood pressure
- Absence of diabetes insipidus
- Deep tendon reflexes; superficial abdominal reflexes; triple flexion response
- Babinski reflex

observational period, or after 24 hours in anoxic brain damage, is required. Also, according to Croatian legal provisions, a confirmatory test is mandatory for confirmation of brain death. The tests that are accepted are conventional angiography, electroencephalography, evoked potentials, transcranial Doppler sonography, isotope angiography, and technetium-99m hexamethylpropyleneamine oxime brain scan (^{99m}Tc -HMPAO) (Table 5). After confirming the clinical diagnosis with one of the tests, the examined brain death person is declared dead.

Some of the tests are more convenient to use for technical reasons such as bedside evaluation of unstable brain death patients. Therefore, transcranial Doppler and elec-

troencephalographic tests are preferable, although technical or patient contraindications may present a problem. Conventional or isotope angiography or ^{99m}Tc -HMPAO brain scan require special settings that are not available in all hospitals, although they have little technical or patient contraindications. The application of contrast medium in angiography is potentially harmful for the residual organ functions, so noninvasive tests are preferred.

Transcranial Doppler sonography

Oscillating flow or systolic spikes are typical Doppler sonography flow signals found in the presence of cerebral circulatory arrest, which results in brain death²⁵. The Neurosonology Research Group (NSRG) of the World Federation of Neurology (WFN) has established a Task Force Group in order to evaluate the role of Doppler sonography as a confirmatory test for determining brain death, and has defined criteria and guidelines for the use of Doppler sonography in this setting²⁶.

Soon after Doppler sonography had been introduced for cerebrovascular evaluation, typical findings for cerebral circulatory arrest were described²⁷. The reliability of the method increased with the introduction of transcranial Doppler sonography (TCD)²⁸ and standardization of the insonating protocol²⁹. Extensive death of brain tissue causes extreme increase of intracranial pressure (ICP). When the ICP equals the diastolic arterial pressure, the brain is perfused only in the systole and with further increase of ICP over the systolic arterial pressure cerebral perfusion will cease³⁰. Due to elasticity of the arterial wall and the

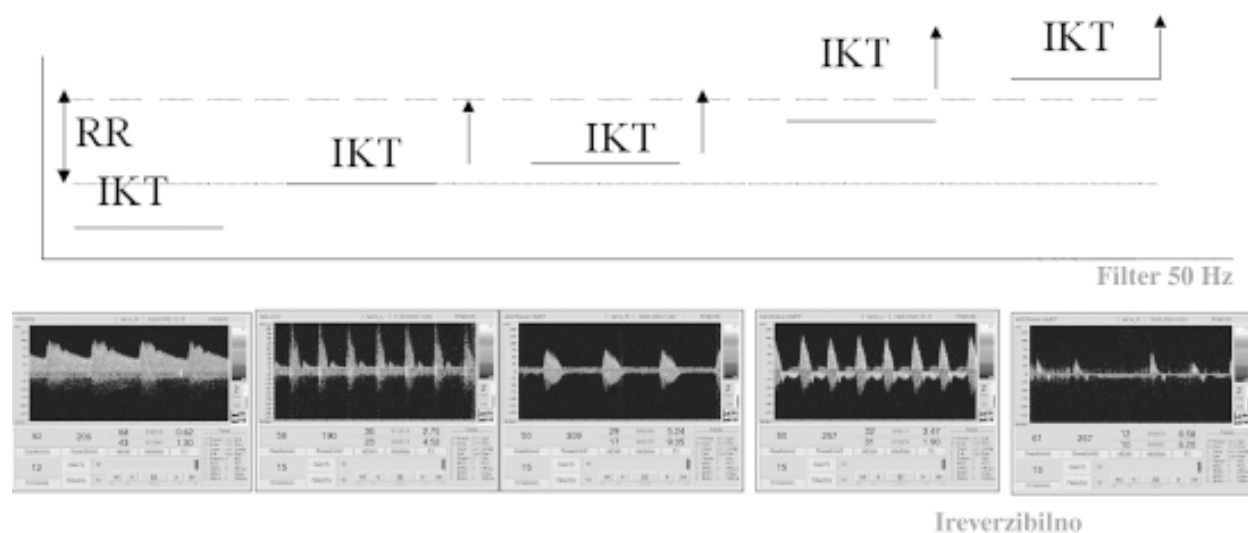


Fig. 1. Time course of flow velocities in middle cerebral artery from normal condition up to cerebral circulatory arrest

compliance of the vasculature distal to the recording site, such cerebral circulatory arrest is associated with Doppler evidence of oscillatory movement of blood in the large arteries at the base of the brain. However, the net forward flow volume is zero. With time the oscillations become low amplitude spectral spikes until no pulsations are detectable. This development correlates with a more proximal demonstration of the angiographic flow arrest³¹. At the time of angiographic flow arrest at the internal carotid artery (ICA), Doppler sonography shows an oscillating flow pattern in the middle cerebral artery (MCA), because the contrast medium progresses slowly toward the brain. From the clinical experience in cardiac arrest, such cerebral ischemia of about 10-15 minutes *in vivo* at normal body temperature leads to irreversible total loss of brain function³².

TCD actually evaluates blood flow velocities from basal cerebral arteries, depending on the systemic blood pressure (BP) and ICP. Figure 1 shows time course of flow velocities in MCA from normal condition up to cerebral circulatory arrest. The relation of ICP with BP is presented. With the increase of ICP, a higher pulsatility in basal cerebral arteries can be recorded, and with further increase of ICP over diastolic BP only forward flow persists in the systole. With further increase of ICP that equals systolic BP, reverberating flow with forward and reverse flow are nearly equal and cerebral perfusion ceases. Net flow is zero when the equality of both flow components is present and if the area under the envelope of the positive and negative deflection is the same. This finding correlates with the angiographic appearance of cerebral circulatory arrest³¹.

With further increase of ICP over systolic BP, only systolic spikes can be recorded, and the amplitude becomes

ever lower. Such systolic spikes are a characteristic pattern for cerebral circulatory arrest, but may resemble high resistance pattern with reduction of diastolic flow, a phase before the development of reverberating flow. Due to the usage of high pass filters for elimination of artifacts from wall movement, reverberating flow can be missed. Therefore, the filters must be set at lowest level, i.e. 50 Hz. With further reduction of blood movement, further reduction of amplitude is recorded until complete cessation of signals occurs. A failure to detect flow signals alone as the first finding may also result from ultrasonic transmission problems. In such cases, extracranial findings show typical hemodynamic spectra in common carotid arteries, ICAs and vertebral arteries (VA), representing an important criterion (Figs. 2, 3 and 4). At the same time, the flow in the external carotid arteries remain patent, with normal hemodynamic spectrum. The flow in the ICA can be influenced by flow through the ophthalmic artery, although the volume of the ophthalmic artery flow plays a minor portion of the ICA flow.

According to the aforementioned findings, the Task Force Group of the NSRG WFN²⁶ has set guidelines for the use of Doppler sonography as a confirmatory test for cerebral circulatory arrest, as follows (Table 4):

Prerequisites

Doppler sonography can be used to confirm cerebral circulatory arrest thus confirming brain death only if the following diagnostic prerequisites are fulfilled:

1. The cause of coma has been established and is sufficient to account for a permanent loss of brain function.

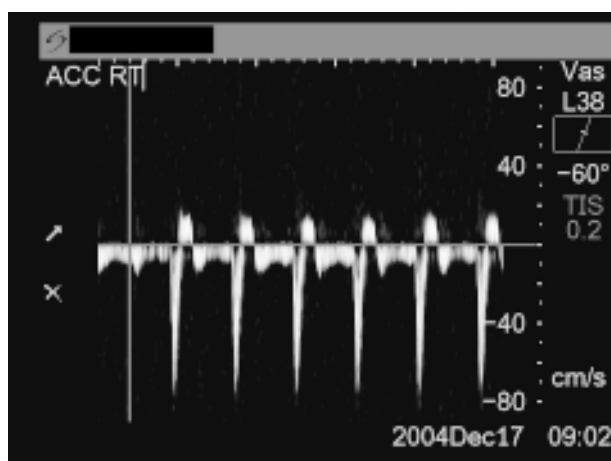


Fig. 2. Reverberating flow pattern in common carotid artery

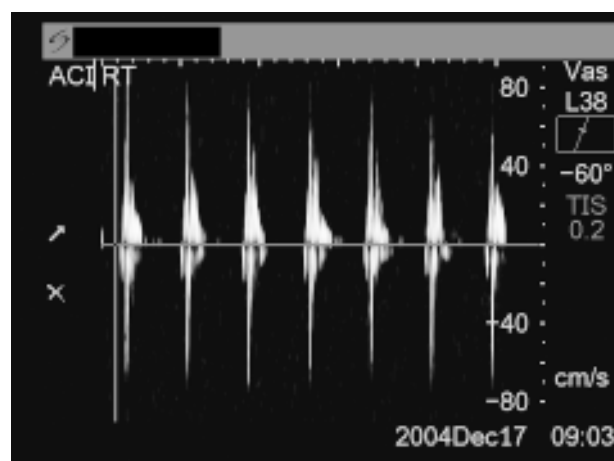


Fig. 3. Reverberating flow pattern in internal carotid artery

- Other conditions such as intoxication, hypothermia, severe arterial hypotension, metabolic disorders, and others have been excluded.
- Clinical evaluation by two experienced examiners shows no evidence of cerebral and brainstem function.

Criteria

Cerebral circulatory arrest can be confirmed if the following extra- and intracranial Doppler sonographic findings have been recorded and documented both intra- and extracranially and bilaterally on two examinations at an interval of at least 30 min:

- Systolic spikes (Fig. 5) or oscillating flow (Fig. 6) in any cerebral artery which can be recorded by bilateral transcranial insonation of the ICA and MCA, respectively, any branch or other artery which can be recorded (anterior and posterior circulation). Oscillating flow is defined by signals with forward and reverse flow components in one cardiac cycle exhibiting almost the same area under the envelope of the wave form (to and fro movement). Systolic spikes are sharp unidirectional velocity signals in early systole of less than 200 ms duration, less than 50 cm/s peak systolic velocity, and without a flow signal during the remaining cardiac cycle. Transitory patterns between oscillating flow and systolic spikes may be seen.
- The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the CCA, ICA and VA.
- The lack of signal during transcranial insonation of the basal cerebral arteries is not a reliable finding because this can be due to transmission problems. But the disappearance of intracranial flow signals in conjunction

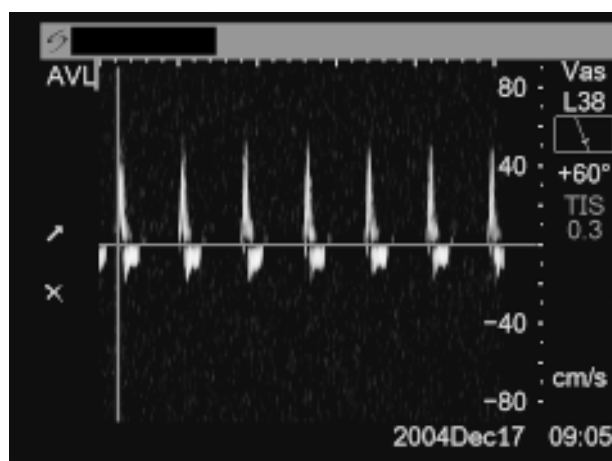


Fig. 4. Reverberating flow pattern in vertebral artery

Table 4. Guidelines for use of Doppler sonography as a confirmatory test for cerebral circulatory arrest

Prerequisites

- The cause of coma has been established and is sufficient to account for a permanent loss of brain function
- Other conditions such as intoxication, hypothermia, severe arterial hypotension, metabolic disorders and others have been excluded
- Clinical evaluation by two experienced examiners shows no evidence of cerebral and brainstem function

Criteria

- TCD: systolic spikes or oscillating flow in any cerebral artery by bilateral transcranial insonation and in any artery of the vertebrobasilar system
- Confirmation by extracranial examination: bilateral recording of the CCA, ICA and VA
- The lack of signal during transcranial insonation can be accepted as a finding only if the extracranial findings support the diagnosis of cerebral circulatory arrest, and hemodynamic spectra suggesting development of cerebral circulatory arrest were previously recorded
- Absence of ventricular drains or large opening of the skull
If the clinical prerequisites are fulfilled and documented by Doppler sonography in two recordings one following the other after at least half an hour, according to the above mentioned criteria, the diagnosis of cerebral circulatory arrest can be set, thus confirming brain death.

with typical extracranial signals can be accepted as a proof of circulatory arrest.

- Ventricular drains or large openings of the skull like in decompressive craniectomy possibly interfering with the development of the ICP is not present.

If the clinical prerequisites are fulfilled and cerebral circulatory arrest has been documented by Doppler sonography according to the above mentioned criteria, the diagnosis of brain death may be confirmed without further observation time²⁶. There are no reports of previously published literature of a child or adult patient “surviving” who demonstrated bilateral signals or oscillating flow or systolic spikes in the MCA and ICA for at least half an hour. Only false positive reports with “some flow” in MCA or basilar



Fig. 5. Systolic spikes: sharp unidirectional velocity signals in early systole of less than 200 ms duration, less than 50 cm/s peak systolic velocity, and without a flow signal during the remaining cardiac cycle

artery were the result of skull defects³³. Since TCD records BFV in relation to ICP, skull defects are contraindications for examination (Fig. 1). Due to the relation of BFV to BP, hypotension should be corrected before starting the examination (Fig. 1).

Sonographic conditions in which false positive findings can be detected

A high resistance pattern that is similar yet not identical to that of complete flow arrest can occur shortly after cardiac arrest in the “no reflow phase”³⁴. Acutely raised ICP due to bleeding from an aneurysm has been observed with transient flow patterns similar to those in cerebral circulatory arrest^{35,36}. Both conditions are transient and the flow abnormalities will reverse at least partially within less than 30 minutes. During this initial phase, patients are clinically



Fig. 6. Reverberating flow: signals with forward and reverse flow components in one cardiac cycle exhibiting almost the same area under the envelope of the wave form (to and fro movement)

not brain dead. A proportion of these patients may later deteriorate to brain death.

Since brain death is a clinical condition, the clinical findings must be met first. In patients with both ICA distal occlusion, only systolic spikes in both ICAs would be detected. These patients would be mistaken if examination of the posterior circulation is not part of the protocol. Aortic insufficiency may also pose problems for interpretation of the flow pattern of CCA and ICA (Figs. 7 and 8). The reverse component, if present, is smaller than the forward component of the flow signals. If the flow signals transtemporally cannot be recorded, transmission problems can be suspected. Up to 20% of individuals have strong ossification of temporal bones making the insonation impossible.

An experienced investigator is required. During the development of cerebral circulatory arrest, marked changes of hemodynamic spectra develop. Therefore, an unexperienced examiner may mistake ECA for ICA, due to patent flow in extracranial circulation, with normal spectrum and therefore lower pulsatility than in intracranial circulation (which is contrary to normal situation).

Recently, a report of false negative results due to the presence of diastolic flow in intracranial ICA obtained through orbital window in clinically brain dead patients have been described³⁷. Although not specifically stated in the article, presumably all patients who had ICA flow consistent with cerebral circulatory arrest also had other intracranial arteries demonstrating a similar flow pattern. The authors propose that the ICA should not be routinely studied for confirmation of brain death, except in patients whose transtemporal windows are inadequate, leading to the inability to insonate the MCA. In the editorial

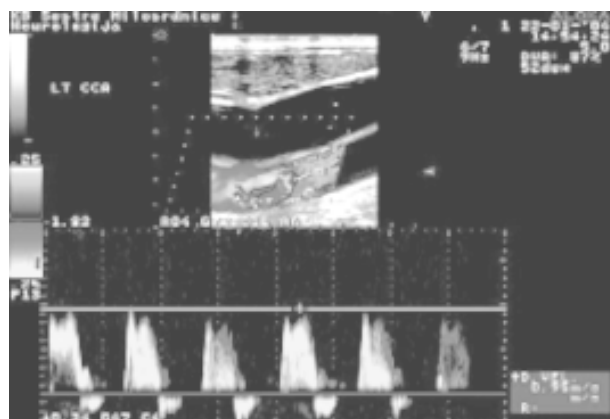


Fig. 7. Flow in common carotid artery: aortic insufficiency due to aortic arch dissection

to the article³⁸, reasons for reviewing current criteria for TCD diagnosis of brain death²⁶ are presented. Besides de Freitas' reasons for exclusion of the intracranial ICA insonation³⁷, there is a suggestion for exclusion examination of extracranial arteries, which was reviewed and refuted by a recent study³⁹. The suggestion³⁸ was to be less conservative in brain death confirmation. Since no new statement of the NSRG WFN has been published, the confirmation of cerebral circulatory arrest using Doppler sonography should be done according to the aforementioned criteria²⁶.

Advantages and disadvantages of Doppler sonographic evaluation

The greatest advantage of Doppler sonography is the possibility of bedside evaluation, which enables close monitoring and intervention in unstable patient. No contrast agents are applied, preserving the residual organ function.

A disadvantage of TCD is that in up to 20% of individuals the insonation is not possible due to bone hyperostosis. In patients with skull defects or drainage, false results can be produced due to inappropriate ICP recording, and therefore TCD is not the method of choice for brain death confirmation. The blood flow velocities can be affected by marked changes in PCO₂, hematocrit and cardiac output. It cannot be performed in hypotensive patients. TCD ultrasonography requires considerable practice and skill.

Conventional angiography or digital subtraction angiography

A selective four-vessel angiogram is done in the radiology suite. Iodinated contrast medium is injected under

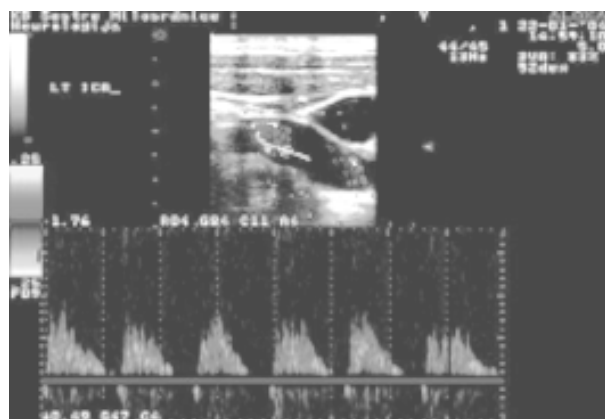


Fig. 8. Flow in internal carotid artery: aortic insufficiency due to aortic arch dissection

high pressure in both the anterior and posterior circulation. Intracerebral filling is absent at the level of carotid bifurcation or circle of Willis^{40,41}. The external carotid circulation is patent, and time delayed filling of the superior longitudinal sinus may be seen. Interobserver studies have not been published, and no guidelines for interpretation have been developed. Repeat contrast injections may increase the risk of nephrotoxicity and decrease the acceptance rate in organ recipients.

Electroencephalography

A 16- or 18-channel instrument is used with guidelines developed by the American Electroencephalographic Society for Recording Brain Death^{42,43}. No electrical activity occurs above 2 μ V at a sensitivity of 2 μ V/mm with filter setting at 0.1 or 0.3 s and 70 Hz. Recording should continue for at least 30 min. However, according to Croatian legislature⁴⁴, electroencephalography (EEG) must be performed three times for at least 15 min, and absent electrical activity must be recorded. Most patients meeting the clinical criteria for brain death have isoelectric EEGs. Nevertheless, in one consecutive series of patients fulfilling the clinical diagnosis of brain death, 20% of 56 patients had residual EEG activity that lasted up to 168 hours⁴⁵. Such activity may be the consequence of autolytic process. A major disadvantage are considerable artifacts in the intensive care unit settings that can limit interpretation⁴⁶.

Isotope angiography – radionuclide cerebral angiography

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 accepted⁴⁷⁻⁵¹. Any of hydrophilic radiopharmaceutical agents (^{99m}Tc-pertechnetate, ^{99m}Tc-glucoheptonate, ^{99m}Tc-DTPA) can be used and they are readily available at nuclear medicine departments. 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 min following intravenous bolus injection of the radiopharmaceutical. The method is highly sensitive (98%) and 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 avoidance of iodinated contrast media. A confounding finding is faint visualization of dural sinuses, reported in small numbers of patients, due to external carotid filling of intracranial

venous sinuses *via* supplying vessels to the falx and tentorium. Those patients otherwise had no evidence of cerebral flow on dynamic images, therefore it does not contradict the diagnosis of brain death.

Scintigraphy with lipophilic agents – ^{99m}Tc-HMPAO

Agents that cross the blood-brain barrier can overpass the concerns over the significance of sinus activity. Studies with ^{99m}Tc-HMPAO are insensitive to intravenous bolus techniques, allow for assessment of individual brain regions, and they readily distinguish between low and absent flow^{52,53}. Lipophilic tracers such as ^{99m}Tc-HMPAO cross the blood-brain barrier and after extraction by brain cells convert to hydrophilic form and remain trapped in cell. The accumulation is not affected by metabolic disturbances, pharmacologic intoxicants or hypothermia. Reconstitution of ^{99m}Tc-HMPAO within nuclear medicine “hot-labs” requires strict adherence to the instructions of the manufacturer. If stabilized with methylene blue it can be used within the subsequent 4 hours, otherwise ^{99m}Tc-HMPAO must be administered within 30 minutes of reconstitution. Planar static images obtained immediately and between 30-60 minutes show absence of brain uptake and provide straightforward confirmation of brain death, with nearly 100% sensitivity. Dynamic study is an optional procedure and absence of flow on cerebral angiogram is a supportive information.

Both cerebral scintigraphic methods are noninvasive, safe, rapid and highly sensitive confirmatory methods, without deleterious effects on donor organs. Metabolic aberrations, pharmacologic intoxicants, hypothermia, and the presence of skull defects or scalp trauma do not preclude its performance. The main disadvantage is inaccessibility and also dislocation of nuclear medicine departments, which requires transport of patients.

Somatosensory and brainstem evoked potentials

A portable instrument can be used at the bedside. According to the Croatian legislature⁹, somatosensory evoked potentials can be used. Cables and contacts should be shielded from the external electromagnetic influences. The results should be confirmed in at least two consequent testings.

In somatosensory evoked potentials testing, median nerve stimulation is performed on both sides. N13-P14 response (Fz-Pgz) or N18-20 response (Cz-NC or C2), with positivity measured at the peak, upwards from the baseline, is expected to be bilaterally absent^{54,55}.

In brainstem auditory evoked potential testing, both flat auditory responses (I-V) are expected⁵⁶. The major disadvantage of the technique is that it is nonspecific, so deaf patients may also have a flat auditory response.

Other Tests

CT or magnetic resonance imaging showing cessation of blood brain perfusion can be used⁵⁷. Contrast CT with a bolus of meglumine diatrizoate, 1 ml/kg body weight, followed by drip infusion of 0.02 ml/kg *per* minute, does not visualize intracranial vessels⁵⁸. A good correlation with cerebral angiography has been demonstrated.

Conclusion

In comatose patients with absent motor and brainstem reflexes, and evidence of brain damage compatible with the diagnosis, brain death is suspected. An observational period of at least 6 hours is mandatory according to the Croatian legislature, and repeat examination should be performed according to the protocol. Apnea testing and one of the confirmatory test should be performed. Noninvasive, bedside evaluation is preferable.

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Sažetak

KONSENZUS ZA DIJAGNOSTICIRANJE MOŽDANE SMRTI – SMJERNICE ZA PRIMJENU POTVRDNIH
PRETRAGA

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Definicija moždane smrti obuhvaća gubitak svih funkcija mozga, uključujući moždanog stabla. Dijagnostika moždane smrti omogućava donaciju organa ili prekid potpore. Stoga se moraju točno odrediti kriteriji dijagnoze. Prema Hrvatskom zakonu o transplantaciji, ponovljeni neurološki pregled mora pokazati gubitak refleksa moždanog stabla a obavezan je i jedan od testova potvrde. Nekoliko je testova dostupno, koji pokazuju prestanak aktivnosti mozga ili moždanog stabla ili potvrđuju nastup moždanog prekida cirkulacije. Procjena uz krevet bolesnika je moguća upotrebom elektrofizioloških i neurosonoloških testova. Konvencionalna ili digitalna subtrakcijska angiografija se izvodi na radiologiji, a izotopna angiografija i perfuzija mozga heksametil-propilen-amin-oksimom (^{99m}Tc-HMPAO) u Klinici za nuklearnu medicinu. Takvi testovi zahtijevaju posebne pogodnosti, stoga se preferiraju testovi koji se primjenjuju uz krevet bolesnika kao elektroencefalografija, evocirani potencijali i neurosonološki testovi. Svi testovi zahtijevaju uvježbano osoblje i striktno protokole koji se razlikuju od onih koji se upotrebljavaju u rutinskoj dijagnostici.

Prikazani su testovi koji se primjenjuju u potvrdi moždane smrti, tehnike, kriteriji, rezultati i vrijednosti testova.

Ključne riječi: