

TRANSCRANIAL DOPPLER AS A CONFIRMATORY TEST IN BRAIN DEATH

Arijana Lovrenčić-Huzjan, Vlasta Vuković, Krešimir Jergović and Vida Demarin

University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic Croatia, Zagreb, Croatia

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 should be determined. In the Croatian legal acts on transplantation, repeated neurological examination must show the loss of brainstem reflexes, and one confirmation test has to be done. Several tests are available to show cessation of the brain or brainstem activity, or to confirm the cerebral circulatory arrest. Bedside evaluation is preferred, with the use of neurosonologic tests that show a high resistance pattern in hemodynamics, in parallel with the increase of intracranial pressure, eventually leading to cerebral circulatory arrest. Trained personnel and strict protocols are required. Bedside transcranial Doppler is presented along with the criteria and its value in brain death confirmation.

Key words: *Brain death – ultrasonography; Brain death – diagnosis; Brain death – physiopathology; Ultrasonography, Doppler – transcranial*

Introduction

Brain death in a normothermic, non-drug 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 ventilators and intensive care unit setting prevented respiratory arrest and transformed the course of terminal neurological disorder. Vital functions could since then be maintained artificially after the brain has ceased to function. The definition using neurological criteria was formally set upon the publication of a report by the Harvard Medical School Ad Hoc Committee in 1968². The definition of irreversible coma or brain death was defined as unresponsiveness and lack of receptivity, the absence of movement

and breathing, the absence of brainstem reflexes, and coma the cause of which has been identified. Throughout the years, the report of the Committee has been a target of criticism.

In 1971, Mohandas and Chou described damage to the brainstem as a critical component of severe brain damage³. The Conference of 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 and without its function, no life exists. 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 length of the observational period required 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 for

Correspondence to: *Arijana Lovrenčić-Huzjan, MD, PhD*, University Department of Neurology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: arijana.lovrencic-huzjan@zg.t-com.hr

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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 1976-1994 period, the Quality Standards Subcommittee of the American Academy of Neurology selected peer-reviewed articles with original work. Selection for this document was based on the quality of the original work. Textbooks and handbooks of neurology, medicine, intensive care, pulmonology and anesthesia 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. According to this document⁷, diagnostic criteria for 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 vary among different countries.

A survey on brain death criteria throughout the world revealed uniform agreement on the neurological examination with the exception of apnea test⁸. Major differences between countries were found in the existence of legal standards on organ transplantation, practice guidelines for brain death for adults, number of physicians required to declare brain death, observational period or required expertise of examining physicians. Only 28 of 70 (40%) national practice guidelines required confirmatory testing.

Legal Acts

In Croatian legislation, clinical neurological examination remains the standard for the determination of brain death⁹⁻¹². In patients presumed to be brain dead, clinical examination must be performed with due precision^{7,13}. The declaration of brain death requires not only a series of careful neurological tests but also identification of the cause of coma, ascertainment of irreversibility, resolution of any misleading clinical neurological signs, recognition of the possible confounding factors,

interpretation of neuroimaging findings, and performance of one confirmatory laboratory test which is mandatory. At least two physicians are involved in the clinical diagnosis, one should be an anesthesiologist and the other an 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 for brain death determination, clinical conditions that may confound clinical assessment should be ruled out. They are as follows: severe acid-base or endocrine disturbances, hypothermia defined as core temperature of 32 °C or lower, in Croatian legislation 35 °C or lower⁹, hypotension (systolic blood pressure <90 mm Hg), drug or alcohol intoxication, poisoning, or neuromuscular blocking agents.

Neuroimaging studies should provide evidence for 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. 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 (CSF) should reveal diagnostic findings in the circumstances of CNS infection.

Clinical Findings

A complete clinical neurological examination includes documentation of coma, absence of brain-stem reflexes, and apnea test^{6,7}. Neurological findings will show coma, absence of motor responses, absence of pupillary responses to light and pupils at midposition with respect to dilatation (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, and absence of respiratory drive at PaCO₂ that is 60 mm Hg or 20 mm Hg above the normal baseline values. The interval between two evaluations is at least 6 hours, or 24 hours in anoxic damage.

Diseases That May Mimic Brain Death

A number of neurological states may mimic brain death, so thorough history should be taken and careful examination should be performed, with relevant imag-

ing procedures. Still, these states should be kept in mind. A locked-in syndrome¹⁴, especially in the early phase, hypothermia or drug intoxication may be misdiagnosed. The locked-in syndrome is usually a consequence of the 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 the 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 may involve many peripheral and cranial nerves¹⁵. The progression usually occurs over a period of days, but may be fulminant developing in one day. Since this disease is curable in 90% of cases, it should be considered in the differential diagnosis of brain death.

Accidental hypothermia from prolonged environmental exposure may mimic the loss of brain function, and alcohol and drug intoxication as well as head injury are other major confounders¹⁶. Hypothermia causes a downward spiral 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 °C¹⁷. All these deficits are potentially reversible.

The effects of many sedative and anesthetic agents can closely mimic brain death, but the 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^{17,18}. An even 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 tests¹⁷. According to Croatian legislation, clinical diagnosis of brain death should not be started if drugs like sedatives, anesthetics, narcotics, muscle relaxants, antiepileptics and antidepressants are present⁹. Alcohol should not be present in the blood either. If a drug is suspected to be the cause of poisoning and traces are found in the blood

but the substance cannot be quantified, the observation time for fivefold elimination half-life of the substance would ensure its almost complete elimination.

Confirmatory Tests

Brain death is a clinical diagnosis. According to Croatian legislation, repeated clinical evaluation is required after a 6-hour observational period or after 24 hours in anoxic brain damage⁹. Also, according to the Croatian legislation, a confirmatory test is mandatory for confirmation of brain death. Tests that are accepted are conventional angiography, electroencephalography, evoked potentials, transcranial Doppler sonography, isotope angiography, and technetium-99m hexamethylpropylene-amineoxime brain scan (^{99m}Tc-HMPAO). Upon confirming the clinical diagnosis by one of the tests, the examined 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 electroencephalography tests are preferable, although technical or patient contraindications may present a problem. Conventional or isotope angiography and technetium-99m hexamethylpropylene-amineoxime ^{99m}Tc-HMPAO brain scan require special settings that are not available in all hospitals. The application of contrast medium in angiography is potentially harmful for the residual organ functions, so noninvasive tests are preferred.

Transcranial Doppler Sonography

Soon after Doppler sonography had been introduced for cerebrovascular evaluation, typical findings for cerebral circulatory arrest were described as oscillating flow or systolic spikes¹⁹⁻²¹. The reliability of the method increased with the introduction of transcranial Doppler sonography (TCD)²², and standardization of the insonating protocol²³. Extensive death of brain tissue causes an extreme increase in intracranial pressure (ICP). When the ICP equals diastolic arterial pressure, the brain is only perfused in the systole, and with further ICP increase over the systolic arterial pressure, cerebral perfusion will cease²⁴. Due to the arterial wall elasticity and 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

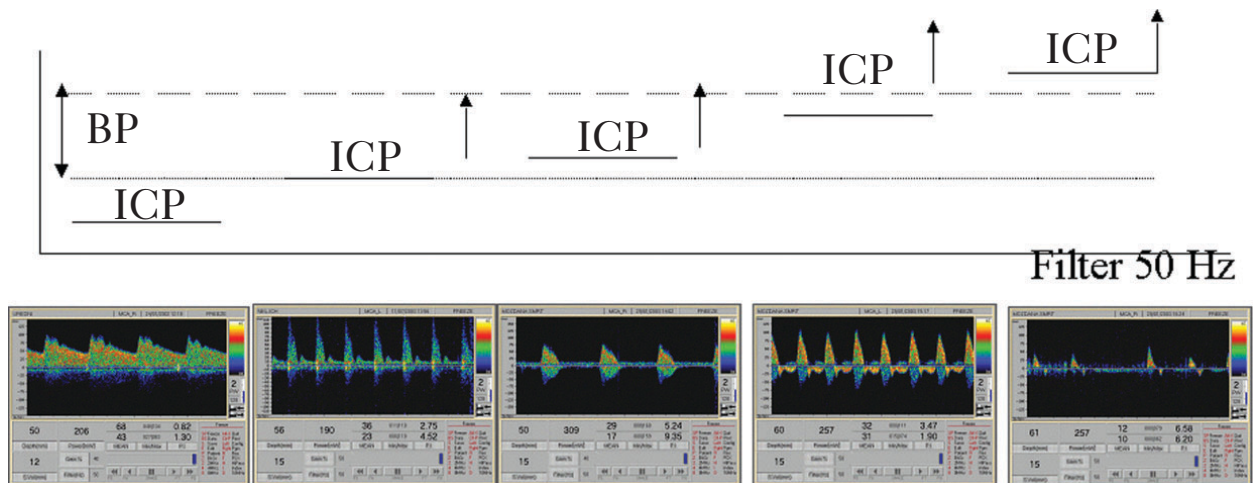


Fig. 1. Time course of flow velocities in middle cerebral artery from normal condition to cerebral circulatory arrest.

IREVERSIBLE

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 arrest²⁵. At the time of angiographic flow arrest at the internal carotid artery, Doppler sonography shows an oscillating flow pattern in the middle cerebral artery (MCA) because the contrast medium progresses slowly toward the brain. Clinical experience with cardiac arrest indicates that such cerebral ischemia of about 10-15 minutes *in vivo* at normal body temperature leads to the irreversible total loss of brain function²⁶.

TCD is actually evaluating blood flow velocities from the 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 ICP increase, higher pulsatility is recorded in basal cerebral arteries, and with further ICP increase over diastolic BP only forward flow persists in the systole. With further increase of ICP that equals systolic BP, the reverberating flow with forward and reverse flow is nearly equal and cerebral perfusion ceases. The net flow is zero when both flow components equalize and if the area under the envelope of positive and negative deflection is the same. This finding correlates with the angiographic appearance of cerebral circulatory arrest²⁵. With further ICP increase over systolic BP, only systolic spikes can be recorded and the amplitudes become ever lower. Such systolic spikes are a characteristic pattern of cerebral circulatory arrest but may resem-

ble the high resistance pattern with diastolic flow reduction, i.e. the phase before the development of reverberating flow. Due to the usage of high pass filters for elimination of artifacts from wall movement, the reverberating flow may be missed. Therefore, the filters must be set at the lowest level, at 50 Hz.

With further reduction of blood movement, further amplitude reduction is recorded until complete cessation of signals. A failure to detect flow signals alone as the first finding may also result from ultrasonic transmission problems. In such cases, the extracranial findings showing typical hemodynamic spectra in common carotid arteries (CCA), internal carotid arteries (ICA) and vertebral arteries (VA) represent an important criterion (Figs 2, 3 and 4). At the same time, the flow in the external carotid arteries remains patent, with normal hemodynamic spectrum. The flow in the ICA can be influenced by the flow through the ophthalmic artery, although the volume of the ophthalmic artery flow plays a minor portion of the ICA flow.

The Neurosonology Research Group (NSRG) of the World Federation of Neurology (WFN) has established a Task Force Group to evaluate the role of Doppler sonography as a confirmatory test for determining brain death, and has developed defined criteria and guidelines for the use of Doppler sonography in this setting²⁰. These guidelines have been adopted and endorsed by the Croatian Neurovascular Society and University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Ministry of Health of the Republic Croatia²⁶.

According to the aforementioned findings, the WFN NSRG Task Force Group has set guidelines for the use of Doppler sonography as a confirmatory test for cerebral circulatory arrest as follows²⁰ (Table 1):

Table 1. Guidelines for the use of Doppler sonography as a confirmatory test for cerebral circulatory arrest

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.
2. Other conditions such as intoxication, hypothermia, severe arterial hypotension, metabolic disorders and others have been excluded.
3. 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 sonography findings have been recorded and documented both intra- and extracranially and bilaterally on two examinations at an interval of at least 30 min:

1. 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 waveform (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.
2. The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the CCA, ICA and VA.
3. The lack of signal during transcranial insonation of the basal cerebral arteries is not a reliable finding

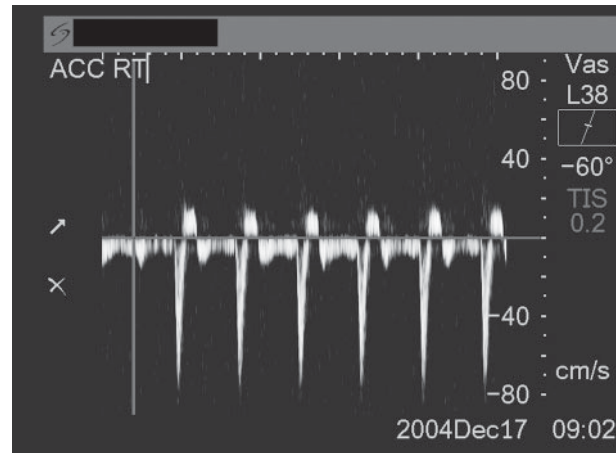


Fig. 2. Reverberating flow pattern in common carotid artery.

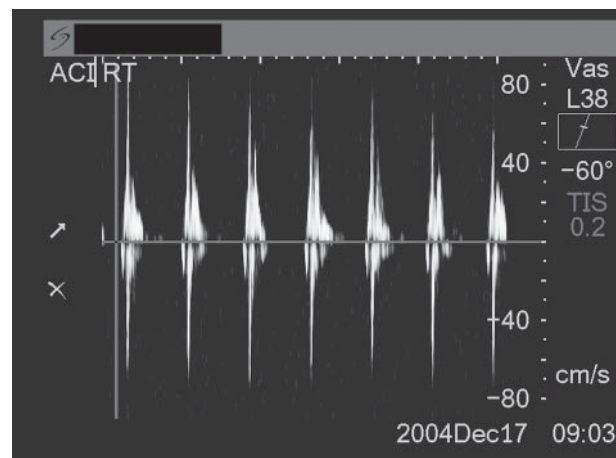


Fig. 3. Reverberating flow pattern in internal carotid artery.

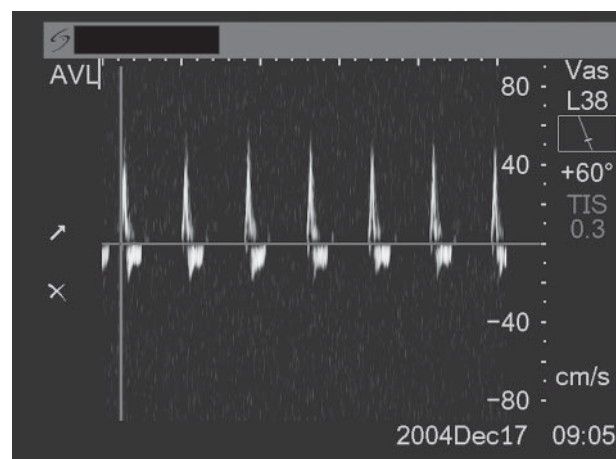


Fig. 4. Reverberating flow pattern in vertebral artery.

because this can be due to transmission problems. But, the disappearance of intracranial flow signals in conjunction with typical extracranial signals can be accepted as a proof of circulatory arrest.

- Ventricular drains or large openings of the skull as 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,

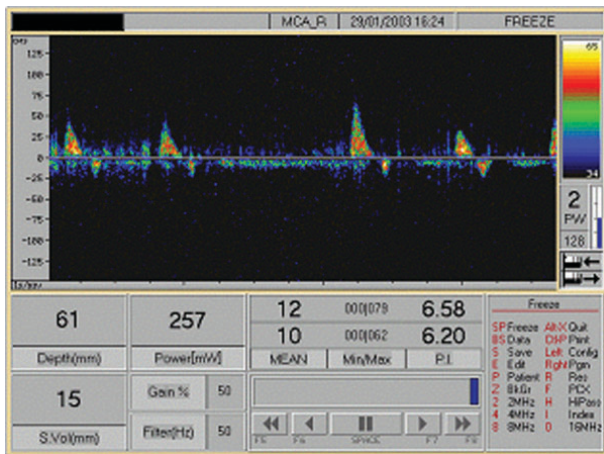


Fig. 5. Systolic spikes – sharp unidirectional velocity signals in early systole of less than 20 ms duration, less than 50 cm/s peak systolic velocity, and without a flow signal during the remaining cardiac cycle.

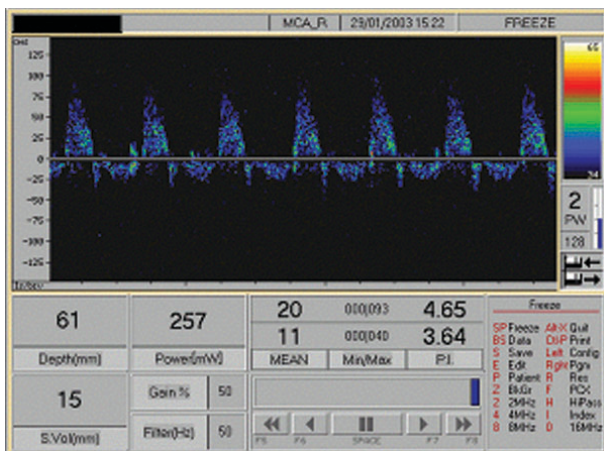


Fig. 6. Reverberating flow – signals with forward and reverse flow components in one cardiac cycle exhibiting almost the same area under the envelope of the waveform (to and fro movement).

the diagnosis of brain death may be confirmed without further observation time^{20,26}.

There are no reports on previously published literature data on 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 on “some flow” in the MCA or basilar artery were the result of skull defects²⁸. Since TCD records BFV in relation to ICP, skull defects are a contraindication for examination (Fig. 1). Due to the BFV relation to BP, hypotension should be corrected before starting the examination (Fig. 1).

Sonographic condition in which false positive findings can be detected

A high resistance pattern that is similar, although not identical to that of complete flow arrest can occur shortly after cardiac arrest in the “no reflow phase”²⁹. Acutely raised ICP due to bleeding from an aneurysm was observed with transient flow patterns similar to those in cerebral circulatory arrest^{30,31}. 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 not brain dead. A proportion of these patients may later deteriorate to brain death.

Since brain death is a clinical condition, clinical findings must first be fulfilled. 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 the CCA and

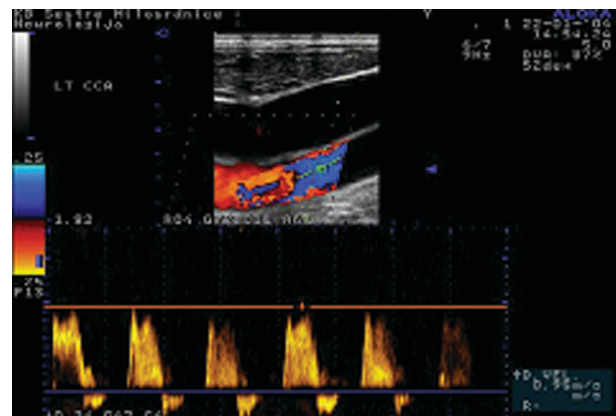


Fig. 7. Flow in common carotid artery: aortic insufficiency due to aortic arch dissection.

ICA (Figs. 7 and 8). The reverse component, if present, is smaller than the forward component of the flow signals. If the flow signals cannot be transtemporally recorded, transmission problems should be suspected. Up to 20% of individuals have strong ossification of the temporal bones making the insonation impossible.

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

Recently, false negative results due to the presence of diastolic flow in intracranial ICA obtained through orbital window in clinically brain dead patients have been reported³². 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 article editorial³³, reasons for reviewing the current criteria for TCD diagnosis of brain death²⁶ are presented. Beside de Freitas's³² reasons for exclusion of the intracranial ICA insonation, exclusion of the extracranial artery examination is suggested, which was reviewed and refuted by a recent study³⁴. The suggestion³⁴ was to be less conservative in the brain death confirmation. As no new statement of the WFN NSRG has been published,

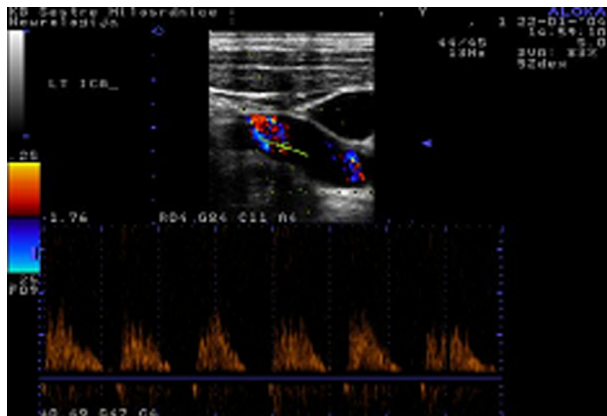


Fig. 8. Flow in internal carotid artery: aortic insufficiency due to aortic arch dissection.

confirmation of the cerebral circulatory arrest using Doppler sonography should be done according to the aforementioned criteria^{20,26}. Since the introduction of TCD in brain death confirmation is preferable, numerous clinicians have adopted its usage. It has resulted in a number of publications³⁵⁻³⁹, some of them³⁶ reporting lower sensitivity than previous reports, however, the specificity was 100%. Therefore, a meta-analysis of studies assessing the validity of TCD in confirming brain death was conducted, with systematic review of articles published in English on the diagnosis of brain death by TCD between 1980 and 2004⁴⁰. An oscillating or reverberating flow and systolic spikes were considered to be compatible with cerebral circulatory arrest. The quality of each study was assessed by use of standardized methodological criteria. The literature was searched for any article reporting a false-positive result. Two high-quality and eight low-quality studies were included. Meta-analysis of the two high-quality studies showed a sensitivity of 95% (95% CI 92-97%) and specificity of 99% (95% CI 97-100%) to detect brain death. Meta-analysis of all ten studies showed a sensitivity of 89% and specificity of 99%. In the literature, two false-positive results have been reported, however, brainstem function did show brain death shortly thereafter in both patients. The authors concluded that the anterior and posterior circulation TCD findings predicted fatal brain damage in all patients, therefore TCD could be used to determine the appropriate moment for angiography. Further research is needed to demonstrate that cerebral circulatory arrest by TCD on repeated examination can also predict brain death in all patients.

Advantages and disadvantages of Doppler sonography evaluation

The greatest advantage of Doppler sonography is the possibility of bedside evaluation, which enables close monitoring and intervention in unstable patients. It should be noted that the prerequisites should be fulfilled. No contrast agents are applied, preserving the residual organ function.

The 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 may be obtained due to inappropriate ICP recording, therefore TCD is not the method of choice for brain death confirmation. Blood flow velocities can be affected by marked changes in PCO₂, hematocrit and cardiac output. The examination should not be per-

formed in hypotensive patients. Transcranial Doppler ultrasonography requires considerable practice and skill.

Conclusion

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

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Sažetak

TRANSKRANIJSKI DOPPLER KAO POTVRDNA PRETRAGA KOD MOŽDANE SMRTI

A. Lovrenčić-Huzjan, V. Vuković, K. Jergović i V. Demarin

Definicija moždane smrti uključuje gubitak svih funkcija mozga, uključujući onu 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. Dostupno je nekoliko testova koji pokazuju prastanak funkcije mozga ili moždanog stabla ili daju potvrdu cerebralnog cirkulacijskog aresta. Prednost se daje primjeni uz krevet bolesnika neurosonoloških testova koji pokazuju porast rezistencije hemodinamskih krivulja usporedno s porastom intrakranijskog tlaka, što konačno dovodi do razvoja cerebralnog cirkulacijskog aresta. Za dijagnostiku je potrebno uvježbano osoblje i strogi protokoli. Prikazana je primjena transkranijskog Dopplera uz krevet bolesnika s kriterijima i vrijednosti testa u potvrdi moždane smrti.

Ključne riječi: Moždana smrt – ultrazvuk; Moždana smrt – dijagnostika; Moždana smrt – fiziopatologija; Ultrazvuk, Doppler – transkranijski