When Are Ancillary Tests Recommended In Brain Death Confirmation?

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Abstract

It is widely accepted that brain death (BD) is a clinical diagnosis, although ancillary tests are recommended when specific components of the clinical testing cannot reliably be evaluated. The therapeutic use of barbiturates in patients with severe intracranial hypertension or other forms of drug intoxication, hypothermia, and other metabolic disturbances, can prevent determination of BD by clinical criteria. We present a review here about the use of ancillary tests in BD confirmation. Confirmatory tests in BD can be divided in those proving absent cerebral blood flow (CBF) and those that demonstrate loss of bioelectrical activity. We recommend assessing circulatory arrest by transcranial Doppler (TCD), and neuronal function by a neurophysiologic test battery. If TCD fails to validate the absence of CBF, computer tomography angiography can be used to confirm BD diagnosis.

It is widely accepted that brain death (BD) is a clinical diagnosis, and it is currently defined as a complete and irreversible loss of brain function. Confirmatory laboratory tests are recommended when specific components of the clinical testing cannot reliably be evaluated [1-3] In certain European, Central and South American, and Asian countries, law requires confirmatory tests.[4,5] The diagnosis of BD in children and neonates is more complicated and ancillary tests are usually advocated. [6-12]

According to Wijdicks, “a confirmatory test is needed for patients in whom specific components of clinical testing cannot be reliably evaluated.”[13] An ideal confirmatory study for BD should be safe, extremely accurate and reliable, available, quick and inexpensive.[8,14-20] Heran et al. also affirmed that an ideal confirmatory study for BD should be “readily available, rapid, safe, portable, non-invasive, inexpensive, independently sufficient to establish brain death, not susceptible to external/internal confounding factors”.

The therapeutic use of barbiturates in patients with severe intracranial hypertension or other forms of drug intoxication, hypothermia, and other metabolic disturbances, can prevent determination of BD by clinical criteria.[21-33]

Confirmatory tests in BD can be divided in those proving absent cerebral blood flow (CBF) and those that demonstrate loss of bioelectrical activity.[2,34-37] In fact, confirmatory tests that are widely accepted are conventional angiography and EEG.[13,16,17,38]

We review here when ancillary tests are recommended in BD confirmation.

TESTS TO DEMONSTRATE ABSENT CEREBRAL BLOOD FLOW

Several authors have defended that the only reliable test to prove irreversibility in BD is showing the complete absence of intracranial circulation. [1,3]

During the 1950s and 1960s the phenomenon of 'cerebral circulatory arrest' (or 'blocked cerebral circulation') was repeatedly demonstrated.[39] Bernat recently emphasized that “the most confident way to demonstrate that the global loss of clinical brain functions is irreversible is to show the complete absence of intracranial blood flow.”[40] It is well established that brain neurons are irreversible damaged after a few minutes of complete cessation of CBF, and are globally destroyed when blood flow completely ceases for about 20-30 minutes.[40-43] Ingvar defended that the permanent cessation of CBF produces the total brain infarction.[44,45]

Although the absence of CBF is deemed as a precise indicator of BD, a patient may be brain-dead regardless CBF preservation.[4,5] According to Palmer and Bader, there are

two patterns of BD.[46,47] The most common pattern is characterized by an increase of intracranial pressure (ICP) to a point which goes above the mean arterial pressure (MAP), resulting in no net CBF. Of course, tests proving absent cerebral blood flow (CBF) are appropriate for this pattern. The second pattern is typified by ICP not exceeding MAP, but as there is an inherent pathology which affects brain tissue on a cellular level, BD may occurs. Hence, in this BD pattern CBF is preserved, and ancillary tests relying on its lack would result in false negative. Hence, ancillary tests in this situation should evaluate neuronal function and viability.[34,37,48,49]

Several tests have been developed in the last decades that can accurately and validly measure CBF in suspected brain-dead patients. The first technique used to demonstrate absence of intracranial circulation in BD distal to the intracranial portions of the internal carotid and vertebral arteries was the cerebral angiography.[50-52] Other techniques used to determine absent CBF have been: Cerebral intravenous digital subtraction angiography, Intravenous radionuclide angiography, single photon emission tomography (SPECT). echoencephalography, measurement of arm to retina circulation time, ophthalmic artery pressure, rheoencephalography, xenon-enhanced computed tomography, MRI angiography, CT angiography and CT perfusion, and transcranial Doppler (TCD). We will concentrate our review on TCD in BD confirmation.

To assess CBF in suspected brain-dead patients we recommended the use of transcranial Doppler ultrasonography (TCD).[53-56] Transcranial Doppler ultrasonography (TCD) is a noninvasive technique that measures local blood flow velocity and direction in the proximal portions of large intracranial arteries. TCD requires training and experience to perform it and interpret results; hence it is typified as operator-dependent.[57,58]In the ICU setting intensivists or neurologists usually receive training to apply this technique using portable Doppler devices in suspected brain-dead cases.[54,56,59-61]

Immediately after Doppler-sonography had been introduced in clinical practice, typical findings for brain circulatory arrest were described.[62-65] In general, the principal advantages of TCD are: it is noninvasive, it can be carried out at the bedside, it can repeated as needed or in continuous monitoring, it is less expensive than other techniques, and dye contrast agents are not needed. Its main chief disadvantages are: it can only study CBF velocities in certain segments of large intracranial vessels, it is operator-dependent requiring training and experience to perform it and interpret results, and, up to 20% of studies may be unsuccessful because some patients have cranial vaults too thick impeding a proper visualization of intracranial arteries.[54,57,61,66] Nonetheless, Conti et al. have recently recommended serial TCD examinations using trancervical and transorbital carotid Insonation for improving TCD sensitivity in BD confirmation.

The American Academy of Neurology Therapeutics and Technology Assessment Subcommittee presented a remarkable report on the transcranial Doppler ultrasonography (TCD) clinical applications. The use of TCD to diagnose cerebral circulatory arrest and brain death (BD) was fully analyzed. The Subcommittee reviewed a number of high quality articles that also discuss some caveats with an important impact upon the diagnosis of BD by TCD, concluding with strict criteria, that TCD is highly sensitive and specific for the diagnosis of BD.[58]

Oscillating flow and systolic spikes patterns are typical Doppler-sonographic flow signals found in the presence of cerebral circulatory arrest, which if irreversible, results in BD. The pathophysiology to explain these findings is the following. In comatose patients, the earliest sign of an ICP augmentation is an increased pulsatilty followed by progressive decrease in diastolic flow velocities and reduction in mean flow velocities. If the velocity at the end of diastole becomes zero, then the ICP has reached the diastolic blood pressure. Forward flow continues in systole, and hence in this phase it can't be diagnosed a brain circulatory arrest. When the ICP the ICP equals or exceeds the systolic blood pressure forward and reverse flow are nearly identical, and in this stage a cessation of cerebral perfusion has been reached. It is characterized by a pattern known as oscillating flow, biphasic flow, net zero flow, etc. Equality of forward and reverse flows can be demonstrated calculating the area under the envelope of the positive and negative deflection in the velocity waveforms. As an additional reduction of the blood movement occurs, systolic spikes appear, which very short velocity peaks are. The systolic spike is a distinctly pattern for diagnosing brain circulatory arrest. Finally, when ICP augments further and flow hitch becomes more proximal, no flow signals in the basal cerebral arteries are identified. It is important to stress that a failure to detect flow signals can be due to ultrasonic transmission problems. To face this controversy and confirm diagnosis, it is necessary to perform extracranial bilateral

recording of the common carotid, internal carotid, and vertebral arteries.[55,56,58,61,62,67-85]

The Neurosonology Research Group of the World Federation of Neurology created a Task Force Group in order to evaluate the role of Doppler-sonography as a confirmatory test for determining brain death, concluding that "extra- and intracranial Doppler-sonography is a useful confirmatory test to establish irreversibility of cerebral circulatory arrest as optional part of a brain death protocol. Moreover, this Task Force Group specially recommended TCD in patients when the therapeutic use of sedative drugs causes to be electroencephalography unreliable. This Group proposed a series of guidelines for the use of Doppler-sonography for detecting brain circulatory arrest:[86]

- 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 or oscillating flow 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).
- The diagnosis established by the intracranial examination must be confirmed by the extracranial bilateral recording of the common carotid, internal carotid, and vertebral arteries.
- The lack of a 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 with typical extracranial signals can be accepted as proof of circulatory arrest.
- Ventricular drains or large openings of the skull like in decompressive craniectomy possibly interfering with the development of the ICP are not present.

CT angiography (CTA) seem to be promising exam to confirm BD.[87] The recent development of a new generation of multirow CT allowing reconstructions of intracranial vessels have lead several teams to change the use of conventional digitized angiography to CTA and CTP. However, few studies have evaluated the efficacy of both CTA and CTP to diagnose BD.[88-92] These tests can be easily and rapidly carried out and they are robust against confounding factors that mimic BD. Its main disadvantages are: its lack of portability and that requires the use of iodinated contrast.[87,91,93-98]

TESTS TO DEMONSTRATE LOSS OF BIOELECTRICAL ACTIVITY

Multimodality evoked potentials (MEP) and electroretinography (ERG) are highly resistant to drug intoxication, hypothermia, and have been shown to be reliable in the intensive care unit environment.[49,99-106] Due to these features, a substantial interest has grown over the past two decades on multimodality evoked potentials (MEPs) in BD, and a wealth of data are now available in the literature.[49,99,103,104,104,106,106-114] Nonetheless, considered as single tests, they have their limitations and they are not routinely included as confirmatory tests for BD diagnosis.[4,8,16-18,20,115] Hence, we have proposed to combine MEP and ERG in a test battery to study brain-dead patients in order to increase diagnostic reliability. The use of each modality, singly and in combination, in the diagnosis of BD will now be briefly reviewed.

VISUAL EVOKED POTENTIALS (VEP) AND ELECTRORETINOGRAPHY (ERG)

We have found a characteristic pattern in all patients. When a cephalic reference was used for both VEPs and the ERG, the a- and b- waves of the ERG were recognized in all cases. The visual evoked responses consisted of waves with less amplitude but the same latency and morphologic features as in the ERG. When a noncephalic derivation was chosen for the ERG and VEPs, the ERG waves were the same in latency and morphologic characteristics, but the VEP channel showed no response.[49,116-121]

BRAIN STEM AUDITORY EVOKED POTENTIALS (BAEP)

We have reported the following BAEP patterns in BD.[122]

- No identifiable waves (73.34%)
- An isolated bilateral wave I (16.66 %)
- An isolated unilateral wave I (10.00 %)
- Waves II, III, IV and V were not observed in any

of the cases.

SHORT LATENCY SOMATOSENSORY EVOKED POTENTIALS (SEP)

The SEP patterns of BD are:[105,123-125,125-130]

- Absence of all components following N13/P13 components.
- The dissociation between N13/P13 and P14, that is, the persistence of cervical N13/P13 with absent P14.
- Regarding N18, considering the medullary origin of N18, this component helps to avoid premature apnea testing; in fact, the apnea test may be dangerous in comatose, non-brain-dead patients, and SEP recording may allow postponing it until the disappearance of N18.

Hence, the preservation of P14 or N18 SEP components could indicate that the lower part of the brainstem is still functioning, and that a definitive BD diagnosis must be postponed until future examinations.[49,131]

MULTIMODALITY EVOKED POTENTIALS (MEPS)

Apart from the specific advantages and limitations of each modality, it is obvious that MEPs provide a better assessment of BD compared to any single modality, allowing assessment of different nervous pathways with different anatomic locations of their generators: VEPs explore fronto-occipital hemispheric structures, BAEPs the pons and mesencephalon, and SEPs a long rostrocaudal path from parietal cortex to the cervical spinal cord (with relevant caudal generators in the medulla oblongata). Therefore, depending on the site and extent of primary and secondary lesions, a single modality might exclude BD. For example, VEPs might be preserved in brain-stem lesions that extinguish both BAEPs and SEPs; conversely, patients with medullary lesions may retain BAEPs, while in patients with hemispheric lesions and rostrocaudal evolution, SEPs alone may disclose a still viable brain stem with reserved P14 and/or N18.[106,108,115,118,132-136]

When VEPS and ERG are elicited and recorded simultaneously, using cephalic and non-cephalic references in BD, a clear is found confirming that in the visual pathways of brain-dead patients, electrical activity in confined to the retina.[48,116,118,121,122,134] Moreover, the detection of wave I, without any later components, is the most clear-cut BAEP finding compatible with BD.[108,137-143] However, a higher proportion of cases with bilateral absence of responses has been reported by most authors; This BAEP pattern, as a single test, can provide a false-positive BD diagnosis because when the history is incomplete it is not possible to exclude that the patients may have had a preexisting deafness.[122,144] As it has been previously remarked, In head trauma, transverse fracture of the temporal bone could damage the cochlea and/or the statoacoustic nerve or produce hemotympanum.[122,144,145]

Furthermore, MEPs enable the exclusion of BD in sedated patients, easily and noninvasively, therefore helping to optimize the timing of contrast angiography; in a few patients with a clinical and EEG picture of BD and no reversible factors MEPs may even show residual function in the brain stem, illustrating how MEPs may also improve diagnostic safety.[115]

Hence, we have proposed suing a test battery, including electroencephalography, brainstem auditory evoked potentials, short-latency somatosensory evoked potentials, VEPs and ERG to study brain dead patients. Such a test battery would permit the assessment of several sensory pathways and the evaluation of both brainstem and cerebral hemispheric functions. Thus, the reliability of the diagnosis of brain death could be considerably increased.[37,115,116,118]

CONCLUSION

In Cuba, we proposed using confirmatory tests (still optional): when clinical examination is not reliable, to shorten period of observation, and in primary brainstem lesions.[1,3,36,37,146]

Hence, an adequate medical practice would be to assess comatose patients by monitoring CBF by TCD, and neuronal function by the above mentioned neurophysiologic test battery. If TCD fails to validate the absence of CBF, CTA can be used to confirm BD diagnosis.

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