Clinical Experience with Transcranial Doppler Ultrasonography as a Confirmatory Test for Brain Death: A Retrospective Analysis

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Abstract

Background Transcranial Doppler (TCD) ultrasonography to demonstrate cerebral circulatory arrest (CCA) is a confirmatory test for brain death (BD). The primary aim of this retrospective study was to evaluate the practical utility of TCD to confirm BD when clinical diagnosis was not feasible due to confounding factors. Secondary aims were to evaluate the reasons for inability of TCD to confirm BD and to assess the outcome of patients not brain dead according to the TCD criteria.

Methods TCD waveforms and medical records of all the patients examined to confirm suspected BD between 2001 and 2007, where clinical diagnosis was not possible, were analyzed. BD was diagnosed based on CCA criteria recommended by the Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology. Final outcome of patients and the use of other ancillary tests were noted.

Results Ninety patients (61 males), aged 40 ± 21 (range 3–84) years underwent TCD examination for confirmation of suspected BD. TCD confirmed BD in 51 (57%) patients and was inconclusive in 38 (43%), with no flow signals on the first examination in 7 (8%) patients and the waveform patterns in 31 (35%) being inconsistent with BD. Fourteen of the 19 patients who had CCA pattern in at least one artery but did not meet all the criteria for BD were subsequently found brain dead according to SPECT/clinical criteria or suffered cardiovascular death.

Conclusion Using the conventional criteria, TCD confirmed BD in a large proportion, of patients where clinical diagnosis could not be made. The presence of CCA pattern in one or more major cerebral artery may be prognostic of unfavorable outcome, even when BD criteria are not satisfied.

Keywords Transcranial Doppler ultrasonography · Brain death · Cerebral circulatory arrest

Introduction

The importance of diagnosing brain death (BD) timely and accurately cannot be overemphasized. The diagnosis of BD is primarily clinical, and practice parameters for the same have been published by the American Academy of Neurology [1]. However, when clinical tests of brain stem function cannot be performed reliably due to the presence of confounding factors, a confirmatory test is required. These might include hemodynamically unstable patients (excluding systemic hypotension) or patients who could not be subjected to the apnea test because of hypoxemia. Transcranial Doppler (TCD) ultrasonographic examination of major cerebral arteries to demonstrate cerebral circulatory arrest (CCA) is a well-known method to confirm BD [2]. A number of studies have evaluated the sensitivity and specificity of TCD to diagnose BD by conducting the TCD exam in patients clinically diagnosed brain dead [3–8]. However, the practical utility of TCD is in the scenario where it is not possible to
make a clinical diagnosis. To this end, there is no previous report of clinical experience with TCD to diagnose BD. The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has stated that TCD can provide useful information in diagnosing BD (Type A, Class II evidence), but its clinical utility remains to be determined [9].

Our hospital (Harborview Medical Center) is a level-1 trauma center serving five states and a tertiary level neurosurgical service center with a dedicated cerebrovascular laboratory. TCD ultrasonography is performed in our hospital as a confirmatory test in most patients suspected to be brain dead when the diagnosis cannot be made clinically. The primary aim of this retrospective study was to evaluate the practical utility of TCD in a setting where clinical diagnosis of BD was not feasible due to the presence of confounding factors. Secondary aims were to evaluate the reasons for inability of TCD to confirm BD in this setting and to assess the outcome of patients who were not brain dead according to the existing TCD criteria so as to evaluate the prognostic utility of TCD when the waveform pattern does not satisfy BD criteria.

Materials and Methods

Following Institutional Review Board (IRB) approval, we used the cerebrovascular laboratory registry to identify all patients who underwent TCD examination to confirm suspected BD at our hospital between 2001 and 2007. Printouts of TCD examinations for all patients were retrieved and analyzed to categorize the waveform patterns in bilateral middle cerebral arteries (MCA) and the basilar artery (BA) of each patient as oscillating, short systolic spikes, and disappearance consistent with CCA (IPA) along with extracranial bilateral recording of the common carotid artery (COCA), internal carotid artery (ICA), and vertebral artery (VA). BD is diagnosed if findings consistent with CCA are obtained on two examinations at an interval of at least 30 min as recommended by the Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology [2].

Results

Ninety patients (61 males), aged 40 ± 21 (range 3–84) years underwent TCD examination for confirmation of suspected BD during the study period (Fig. 1). There was one missing record. Most patients were Caucasians (n = 58), followed by Asians (n = 19), Hispanics (n = 7) and African Americans (n = 5). BD was suspected owing to the following causes: traumatic brain injury (n = 37),

Hospital Policy for Diagnosing BD

Our hospital is a level-1 trauma center and a tertiary level neurosurgical service center. We frequently receive severely head-injured patients and patients with intracranial hemorrhage of diverse etiologies. Some of these patients end up in a clinical condition consistent with BD despite optimal medical and surgical treatment. Every effort is made to make timely and accurate diagnosis of BD in such patients in accordance with state laws to avoid inappropriate care and to provide correct information to the families. TCD ultrasonography is performed as a confirmatory test in all the patients suspected to be brain dead when clinical diagnosis is not feasible. Single Photon Emission-Computed Tomography (SPECT) is performed in some of these patients, especially when insonation of cerebral vessels is not possible with TCD. Angiography is rarely performed to confirm BD, given the risk of transporting critically ill patients, invasive nature of the procedure, and radiation exposure.

The TCD confirmation is requested by the clinical care team on suspicion of BD, and the results of the examination are reported by an independent attending physician. At the time of TCD examination, the neurocritical care team ensures the maintenance of adequate systemic blood pressure in keeping with prevalent guidelines for the determination of brain death. Mean arterial pressure is maintained ≥60 mmHg. We use either the DWL (Multidop, Sipplingen, Germany) or Viasys (Madison, Wisconsin, USA) machine with a 2-MHz standard transcranial probe for the test, which involves insonation of bilateral MCAs and the BA along with extracranial bilateral recording of the common carotid artery (COCA), internal carotid artery (ICA), and vertebral artery (VA). BD is diagnosed if findings consistent with CCA are obtained on two examinations at an interval of at least 30 min as recommended by the Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology [2].
hypoxic/ischemic brain injury \((n = 26)\), spontaneous intracranial hemorrhage \((n = 25,\) including ten due to aneurysmal rupture), and massive ischemic stroke \((n = 1)\). Clinical assessment was insufficient to diagnose BD, necessitating TCD examination most often because of the inability to perform apnea test or abandoned/inconclusive apnea test due to hemodynamic instability or oxygen desaturation \((n = 46)\). Other causes included intoxication with alcohol/use of sedative medications or neuromuscular blocking agents \((n = 18)\), and severe facial trauma \((n = 3)\). In the remaining patients, no clear reason for inability to clinically diagnose BD was documented. Fifty-two \((58\%)\) patients were on one or more vasopressors to maintain cerebral perfusion at the time of TCD ultrasonography.

The TCD confirmed BD in 51 \((57\%)\) patients, leading to organ donation in 27 cases. It was inconclusive in 38 \((43\%)\) patients, with no flow signals seen on the first examination in 7 \((8\%)\) patients and the waveform patterns in remaining 31 \((35\%)\) patients being inconsistent with standard BD criteria for CCA (Fig. 2). The inconsistent findings included the presence of normal waveforms in any one, two, or three of the major cerebral arteries (bilateral MCAs and the BA) in 11, 6, and 12 patients, respectively (Fig. 3). In two cases, bilateral MCAs could not be insonated despite the presence of oscillating flow/systolic spike in the BA.

None of the patients with inconclusive TCD findings had a good outcome despite not meeting TCD criteria for BD (Fig. 4). While the majority of them \((n = 17)\) received comfort care subsequently in view of the lack of clinical improvement in their condition, others were either declared brain dead based on subsequent SPECT study or clinical criteria \((n = 12 \text{ and } n = 5, \text{ respectively})\) or suffered cardiac arrest \((n = 4)\). Of the five patients who were diagnosed brain dead later by clinical criteria, TCD was requested initially due to high blood levels of alcohol or sedative and neuromuscular blocking medications in four cases and due to inability to perform apnea test in one case. Clinical diagnosis was possible later in these cases subsequent to wearing off of the neuromuscular blocking agents and sedative medications/alcohol levels in four patients and positive apnea test in the fifth. In one of these five patients, flow signal could not be obtained from any window, whereas normal flow pattern was observed in two
of the three major vessels in three patients. In the fifth case, only BA showed normal flow while bilateral MCAs were consistent with CCA. These can be considered false negatives.

The SPECT confirmed BD in 12 patients not identified by TCD. However, it was performed on an average, 6.5 h after the TCD exam. Out of these 12 patients, three had no flow signals in any major artery on TCD while normal flow pattern was seen in 1, 2 and 3 arteries in five, one and three patients, respectively. Cardiac arrest ensued in four patients. One of them had no flow on bilateral MCAs while BA demonstrated BD, another patient had normal flow pattern in one major artery while remaining two had normal waveforms in two major arteries. Of the 17 patients who received comfort care subsequently, no flow signal could be detected in any artery in three patients whereas in one patient, bilateral MCAs could not be insonated despite the presence of short systolic spikes on BA. Nine patients receiving comfort care had normal flow pattern in all three arteries while four patients had normal pattern in one artery. The different waveform patterns negating the diagnosis of BD in these 38 patients and their subsequent outcome are summarized in Fig. 5. In all, among the 38 patients found not brain dead based on existing TCD criteria, 21 were either brain dead later based on SPECT/clinical criteria or suffered cardiovascular death. Eighteen of these 21 patients had TCD waveform patterns consistent with CCA on at least one major cerebral artery (but not all arteries so as to meet BD criteria).

Discussion

In summary, the results of this study indicate that in patients suspected to be brain dead, where the diagnosis could not be made solely on clinical criteria due to the presence of confounding factors, TCD was useful as a first line confirmatory test or as a specific prognosticator in the majority of the cases.

The accurate and timely diagnosis of BD is important for guiding decision making in the critically ill patients, including assessing the need for continued mechanical support and identifying candidates for organ donation. In addition, the advent of DCD (Donation after Cardiac Death) has necessitated the establishment of a specific prognostic test that can reliably predict unfavorable outcome. Although the diagnosis of BD is primarily clinical, it cannot be diagnosed with certainty on clinical grounds alone in some conditions. These include severe facial trauma, preexisting pupillary abnormalities, toxic levels of sedative drugs, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptics, chemotherapeutic agents,
or neuromuscular blocking agents, and conditions like sleep apnea or severe lung disease or inability to correctly perform the apnea test as well as metabolic disturbances and hypothermia [1]. Under such circumstances, ancillary tests are required which include cerebral angiography (showing no intracranial filling), electroencephalography (showing the absence of electrical activity for 30 min), Tc99 HMPAO SPECT scan (showing an absence of brain uptake of tracer), SSEP (with bilateral absence of the N20-P22 response to median nerve stimulation) and TCD ultrasonography [1]. Recognizing this importance, The American Academy of Neurology (AAN) recently updated the 1995 Guidelines, with the specific purpose of answering five important questions regarding the diagnosis of BD. Two out of the five questions asked have relevance to the current study: (1) What is an adequate observation period to ensure that cessation of neurologic function is permanent? and (2) Are there new ancillary tests that accurately identify patients with brain death? AAN concluded that there is insufficient evidence to provide answers to either question [10]. Although our study does not directly address either question, the results provide useful information regarding the use of TCD as an ancillary test for the determination of BD.

The TCD ultrasonography has the unique advantages of being a non-invasive, non-radioactive and relatively inexpensive bedside technique, and one that can be repeated readily. A number of studies have evaluated the sensitivity and specificity of TCD in diagnosing BD contemporaneously with clinical testing [3–8]. The ultimate goal of establishing such data is to facilitate the use of TCD in situations where BD cannot be diagnosed on the basis of clinical criteria due to one or more confounding factors. However, there is no previous report of practical experience with TCD to diagnose BD in situations where clinical diagnosis is not feasible. Our study for the first time, presents the clinical experience with this technique and its practical utility in a neurointensive care unit.

We observed that in a significant proportion of suspected BDs, the diagnosis could be readily confirmed with TCD leading to organ donation for subsequent transplantation in 27 patients and avoidance of inappropriate care in the rest without further delays. In the absence of TCD, the diagnosis could have been delayed for numerous hours/days, and in the meantime, some patients may have suffered cardiac arrest or received comfort care precluding organ donation for transplantations; or else the patients would have to be transported for a SPECT study or angiography, which have their own inherent disadvantages. Previous studies have shown that TCD can both increase and decrease the delay in diagnosis of BD [7]. In one series, the reduction of diagnostic delay was by 85%, and, in this respect, TCD examination was superior to Tc 99 m HMPAO brain scintigraphy [11].

Although TCD was beneficial in most cases, it was inconclusive in a significant proportion. In seven instances, no flow signal could be obtained and in two other patients, bilateral MCAs could not be insonated while BA showed flow patterns consistent with BD. Although this may be due to failure of insonation which is an inherent limitation of TCD [12, 13], it could also be a late stage of CCA with complete loss of flow. The inability to differentiate loss of flow from absent acoustic window on first exam potentially reduces the sensitivity of TCD to diagnose BD. In addition to transtemporal and suboccipital insonation, a transorbital approach has been shown to increase the diagnosis rate of BD [14], although it is not generally accepted in clinical practice. It is possible that TCD performed at an earlier stage may have picked up diagnostic patterns in our patients and earlier deployment of TCD may increase its utility. SPECT confirmed BD in three of these patients. Early use of alternative ancillary test to confirm BD may be

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**Fig. 5** Outcome of patients with inconclusive TCD examination for BD. MCA Middle cerebral artery, BA basilar artery
warranted if no flow signals can be seen on the first TCD since it may be late stage of CCA.

Normal anterograde waveforms were observed in one, two and three of the major cerebral arteries (12, 7, and 12% patients, respectively) where CCA could not be demonstrated. Although some of these may be false negative for BD, it is probable that TCD was performed too early, and the patients were actually not brain dead (especially those with anterograde flow in all three arteries). Persistent flow in the intracranial arteries has been reported in as many as 17.4% of clinically BD patients [4]. In 20% of the cases, persistent flow in the ICA may be found despite CCA due to shunting of blood from the ICA into the external carotid system or the arrest of blood flow at a higher level than the carotid siphon [15]. Signals may also be normal in patients with anoxic brain injury after cardiac arrest [16]. Moreover, initial false negative results have been associated with the timing of TCD exam in relation to the clinical diagnosis of BD, female gender, and the absence of sympathomimetic drug use [4]. Confirmatory findings on TCD might have been detected if it was repeated later (when BD was confirmed by SPECT or clinical criteria). While it is important for an ancillary test to be sensitive enough to diagnose all BDs, it is absolutely crucial that it be highly specific, especially in the scenario of organ retrieval. The sensitivity of TCD in the diagnosis of brain death has been reported as 70–100% and specificity as 97–100% [4–8].

Majority of the 19 patients who had CCA pattern in at least one artery but did not meet all the criteria for BD were found brain dead according to SPECT (n = 6) or clinical criteria (n = 4); or suffered cardiovascular death (n = 4). Remaining patients (n = 5) underwent withdrawal of support by family instruction. On the other hand, majority of patients with anterograde waveforms in all the three major arteries, proceeded to withdrawal of support (75%) with only 25% being diagnosed brain dead. Eighty-six percent (18/21) of the patients who were not brain dead based on existing TCD criteria, but were either brain dead later based on SPECT/clinical criteria or suffered cardiovascular death, had waveform patterns consistent with CCA in at least one major cerebral artery. These findings suggest that the appearance of CCA pattern in any one major cerebral artery may be a poor prognostic sign and may herald the onset of eventual CCA. Repeated TCD exam may be warranted in patients with CCA pattern in either MCA or BA.

The absence of radionuclide activity of Tc-99 m-HMPAO on SPECT images (“hollow skull” appearance) is indicative of BD [1]. SPECT confirmed BD in 12 patients not identified by TCD. However, on average, it was performed 6.5 h after the TCD exam in our series. Repeat TCD performed at the same time as SPECT might have been positive, but was not possible for logistic reasons, and performance of both tests was not required for clinical decision making. Whether SPECT performed earlier at the time of initial TCD would have diagnosed BD is difficult to speculate because it tends to be negative early on in the setting of brain death. Moreover, SPECT findings may be discordant with clinical exam of confirmed BD in 17–38% cases [17, 18].

Our study is not without limitations, and these include both technical and design considerations. From the technical point of view, for the TCD test to be useful, trained personnel must be available round the clock, as brain death can occur at anytime, and for trauma victims, more likely to occur in after hours and weekends than otherwise. Furthermore, good quality control must be established, as the technique is somewhat operator dependent, although the wave pattern is likely more reliable than measurement of absolute velocity, which is more insonation angle dependent. Finally, not all the patients have ultrasonic temporal windows for insonation, and without prior insonation waveforms, no flow pattern cannot be distinguished from lack of ultrasonic window. However, as shown in our study, these factors do not significantly impact the potential utility of this test.

From a study design point of view, although the TCD exams were prospectively ordered, this is a retrospective analysis. Second, the use of TCD as an ancillary test for diagnosing BD was variable with preference of individual attending neurointensivist. Hence, TCD was not ordered uniformly in all the patients, and in some cases the test might have been performed earlier than others, which may affect the patterns observed. Third, in most patients with inconclusive first TCD, a subsequent repeat examination was frequently not performed due to logistic issues. Repeated TCDs in these patients might have enhanced the diagnosis rate. Finally, the clinical exams and confirmatory tests were not performed at the same time in all the patients. Despite these limitations, our study, for the first time, presents the clinical experience with the use of TCD as a diagnostic modality for BD when other tests are not feasible and its practical utility to this end. Furthermore, it suggests that the presence of CCA pattern in one major cerebral artery in suspected BD may have prognostic value, although this utility remains to be confirmed.

In conclusion, TCD ultrasonography is a useful first line ancillary test to confirm suspected BD when clinical examination is not conclusive. The utility of TCD in this respect may be further enhanced by early and repetitive exams, particularly in patients with CCA pattern in any major cerebral artery. The poor prognostic value of appearance CCA pattern in one or more major cerebral arteries may be helpful for the family and clinicians in decision making regarding subsequent care, and needs further evaluation.
References