Comparison Between Transcranial Color Doppler Ultrasonography and Angiography in the Confirmation of Brain Death


ABSTRACT

Objective. Cerebral blood flow tests have increasingly been advocated for the confirmation of brain death (BD). Angiography has been considered the gold standard in the diagnosis of BD but is invasive. We validated transcranial color Doppler ultrasonography (TCD) to confirm BD by comparing it to angiography.

Patients and methods. Forty patients experienced the clinical diagnosis of brain death due to head injury in 19 cases (47.5%), cerebral hemorrhage in 11 (27.5%), subarachnoid hemorrhage in 7 (17.5%), and cerebral infarction in 3 (7.5%). Blood pressure, heart rate, SPO2, and P CO2 were monitored throughout the study. Patients were excluded if episodes of hypoxia, arrhythmia, and hypotension occurred during examinations, or if the TCD was not technically feasible.

Results. Both angiography and TCD confirmed BD in all patients. The agreement between the above methods to confirm BD was 100%. Angiography showed the absence of filling of intracranial arteries, while TCD revealed: (1) brief systolic forward flow or systolic spikes and diastolic reversed flow (50%); (2) brief systolic forward flow or systolic spikes and no diastolic flow (25%); (3) no demonstrable flow in a patient in whom flow had been clearly documented on a previous TCD examination (12.5%). Five patients required repeated TCD examinations, because of initial detection of a diastolic to-and-fro flow pattern. BD was confirmed by TCD in the above patients after 30 hours of clinical BD.

Conclusion. TCD was a sensitive tool to diagnose BD, affording a reliable alternative examination to standard angiography.

SINCE THE FIRST REPORTS describing irreversible coma and brain death (BD),1,2 both the definition of BD and its diagnostic criteria have evolved considerably3,4 mainly due to the advent of cardiopulmonary support for severely brain-injured patients. BD is defined as the irreversible cessation of all hemispheric, cerebellar, and brain stem neurological functions. In addition, an essential feature of BD is “brain tamponade,” that is, the arrest of brain circulation caused by increased intracranial pressure.5 As a result, cerebral blood flow (CBF) tests have increasingly been advocated for confirmation and/or estimation of cessation of cerebral circulation.6–10 Such tests include (1) four vessel angiography, which has been considered the gold standard for the diagnosis of BD but is invasive; (2) electroencephalography, which is noninvasive, however is time-consuming and unreliable in the presence of sedatives8; and (3) transcranial doppler ultrasonography (TCD), a noninvasive and inexpensive examination, which has been used for the confirmation of cessation of cerebral circulation in brain-dead patients.11

Previous studies have shown the accuracy of transcranial color-coded duplex ultrasound to estimate stenosis of...
intracranial vessels to be similar to that of contrast angiography. In this study, we compared TCD with contrast angiography to validate the former method in the confirmation of BD diagnosis. Furthermore, we have described a novel color Doppler sonographic pattern observed in brain-dead patients.

**PATIENTS AND METHODS**

**Patients**

From the 70 consecutive patients with Glasgow coma scale score less than 5 who were included in the study, 50 were diagnosed as clinically brain dead. All patients were continuously monitored for systemic blood pressure, heart rate, intracranial pressure, PaO2, and PaCO2 to maintain steady-state conditions and prevent hypotension (systolic blood pressure > 110 mm Hg, bradycardia (heart rate > 60 beats/min), and hypoxia (SpO2 < 95%). For all patients, the PaCO2 was maintained at 33 to 35 mm Hg throughout the study. Any episode of hypoxia or hypotension during angiography or TCD resulted in exclusion of the patient from the study.

Five patients were excluded because no flow could be detected at the baseline TCD examination (absence of bone window), three other patients because apnea tests could not be performed due to desaturation and arrhythmia, and two patients due to hypoxia (SpO2 < 95%) during the TCD measurements. In total, the study population kept 40 patients with clinical brain death. Twenty patients were men and 20 were women of mean age 48 ± 18.5 years. Brain death was attributed to various pathological conditions (Table 1). The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

**Clinical Diagnosis of Brain Death and Confirmatory Tests**

Clinical BD was diagnosed according to the following criteria: deep irreversible coma, absence of brain stem reflexes, flat electroencephalogram, and a positive apnea test in a normothermic nondrugged patient. According to Hellenic State law, confirmatory tests (standard angiography) establishing cessation of CBF are required for documentary records and to declare a patient brain dead.

Following clinical diagnosis of BD by angiography and repeated bedside TCD evaluation, the family’s consent was obtained for organ donation by a committee consisting of an intensive care consultant, a neurologist, a cardiologist, a neurosurgeon, and an anesthesiologist. In this series, 20 patients became organ and tissue donors.

Four-vessel angiography was performed by femoral catheterization with selective injection of iodinated contrast medium into the common carotid artery and vertebral artery of each side. Iodinated nonionic medium (iodine concentration, 300 mg/mL) was injected using pump at a dose of 12 mL (rate, 6 mL/s) into the common carotid artery and at a dose of 8 mL (rate of 4 mL/s) into the vertebral artery. A Siemens DSA device (Angiotron) was used to obtain six images per second for 20 s. Two angiographic patterns were considered indicative of BD: (1) absent filling of the intracranial arteries at the entry into the skull (at the foramen magnum in the posterior circulation and at the petrosal portion of the carotid artery in the anterior circulation); and (2) minimal arterial opacification with absent parenchymal and venous phases.

TCD examinations were performed with an HDI 3500 (ATL, Philips, Bothell) equipped with a 2-MHz transducer. Bilateral middle cerebral arteries, anterior cerebral arteries, and basilar and internal carotid arteries were insulated. The following flow patterns were regarded as consistent with the TCD diagnosis of brain death: brief systolic forward flow or systolic spikes and diastolic reversed flow, brief systolic forward flow or systolic spikes and no diastolic flow, or no demonstrable flow in a patient in whom flow had been clearly documented in a previous TCD examination. The above TCD findings were accepted as confirmation of BD only when they were found bilaterally or in at least three different arteries and persisted for at least 3 minutes within the same examination. In patients with a unilateral absent temporal bone window, the finding of typical TCD signals in three different arterial segments on one side was considered as confirmation. In contrast, the finding of diastolic back-and-forward flow (to-and-fro flow) was not accepted as confirmation of BD. The examination was repeated until BD was confirmed ultrasonographically. Absence of flow in all arterial segments during the first TCD examination may be caused by total cerebral circulatory arrest or possibly by the absence of an adequate temporal bone window. All cases in which no flow was detected at the initial TCD examination were considered as having an “absent bone window.” In clinically brain-dead patients, the TCD was repeated if previous TCD examinations did not show a flow pattern consistent with BD. All patients were repeatedly evaluated more than twice during the study period. Furthermore, we recorded two-dimensional color mode patterns of interest during each TCD examination. All observers who performed the above confirmation tests were blinded to the patient’s identity. Statistical analysis was performed using Cohen’s k to verify agreement between TCD and angiography.

**RESULTS**

For all cases, angiographic recordings took approximately 20 minutes, while TCD recordings took approximately 30 minutes. Thus, the entire study was completed within 1 hour for all patients. Both angiography and TCD showed the arrest of brain perfusion in all patients (Fig 1).

The only observed angiographic pattern was the absence of filling of intracranial arteries. The agreement between angiography and TCD in our series was 100% (k = 1) with both investigations showing no CBF in all cases. In brain-dead patients, the average time from admission to the intensive care unit and clinical diagnosis of BD was 70.8 ± 110 hours. Initial TCD examination of the 40 patients clinically diagnosed as brain dead and having an adequate bone window revealed flow patterns confirming BD in 35 patients while forward systole-diastolic flow or a diastolic to-and-fro flow pattern was detected in four patients with head injuries and in one patient with brain infarcts and anoxie brain injury.

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<table>
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<th>Diagnosis</th>
<th>Total No. of Patients (%)</th>
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<tr>
<td>Head injury</td>
<td>19 (47.5%)</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>11 (27.5%)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Cerebral infarct</td>
<td>3 (7.5%)</td>
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<tr>
<td>Total</td>
<td>40 (100%)</td>
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TCD showed the following flow patterns: (1) brief systolic forward flow or systolic spikes and diastolic reversed flow (20 patients, 50%); (2) brief systolic forward flow or systolic spikes and no diastolic flow (10 patients, 25%); (3) no demonstrable flow in a patient in whom flow had been clearly documented in a previous TCD examination (five patients, 12.5%).

The mean duration between the clinical examination and the first TCD session was $3 \pm 1.5$ hours. The sensitivity and specificity of the first TCD examination were 87.5% and 100%, respectively. The five patients in whom initial TCD examination failed to confirm BD underwent a second TCD examination $10 \pm 5.5$ hours. Thereafter, clinical BD that showed confirmation of TCD signs was seen in three patients. The sensitivity after the second TCD examination was 95%. The remaining two patients underwent a third TCD examination 30 hours after clinical diagnosis of BD that showed confirmatory TCD signs of BD. The sensitivity after the third TCD examination was 100%.

With respect to our results, two-dimensional color mode recordings demonstrated an interesting pattern as systolic and diastolic flow coexisted simultaneously, resulting in a pulsating flashing signal akin to that of a beacon, the “beacon” signal. This signal was observed in all patients during the time of cessation of cerebral circulation according to synchronous Doppler signals in all studied intracranial vessels (Fig 2).

DISCUSSION

Previous studies have clearly demonstrated that cessation of CBF confirms BD. The above strategy has become more popular since the development of the modern intensive care for severely brain-injured patients and the growing demand for tissue and organ donors. In this study, we

**Fig 1.** Four-vessel angiography (top) and TCD (bottom) results for a brain-dead patient. Angiography shows no filling of the intracranial arteries at the entry into the skull, while TCD shows a pattern of brief systolic forward flow or systolic spikes and diastolic reverse flow.

**Fig 2.** Two-dimensional color Doppler sonography results, in the area of left middle cerebral artery, for a brain-dead patient showing that systolic flow (top) and diastolic flow (middle) coexisted simultaneously in time resulting in a pulsating flash (the “beacon” signal). TCD results for the same brain-dead patient during the same session showing a pattern of systolic spikes and diastolic reverse flow (bottom).
validated TCD to confirm BD compared with contrast angiography.

Angiography is invasive, which could result in severe complications, such as vasospasm, subintimal injection, and thrombosis, leading to a false image of absent flow and cerebral ischemia. As a result of its invasiveness, ethical questions arise pertaining to its use to diagnose BD, since the patient is exposed to possible complications with no potential benefits. Its invasiveness may also make test repetition troublesome in patients who are not brain dead during the first examination.

TCD confirmation of BD in children and adults has been considered operator-dependent, not 100% specific, and technically demanding. However, it is a noninvasive examination that is inexpensive and manageable when performed by experienced observers.

In this study, TCD was not technically feasible in approximately 10% of clinically brain-dead patients. Our results indicate that TCD specificity to confirm the diagnosis of BD was 100% similar to other reports. TCD sensitivity also increased after repeated examinations, which is in accordance with the findings of Dosemeci et al. Furthermore, our findings showed that diastolic to-and-fro flow pattern was detected in four patients with head injuries and one patient with anoxic brain injury. The preservation of forward flow during diastole may be partially due to the fact that decompressive surgical procedures and/or ventricular derivations were performed in these patients. Thus, skull hermetism was affected during the progression to BD. Hadani et al described the preservation of approximately normal flow in all major intracranial vessel in one case of BD resulting from anoxic brain damage. It is presumed that in some cases of anoxic injury, irreversible failure of all vital functions of the brain occurs without persistent elevation of intracranial pressure (ICP), causing total cerebral circulatory arrest. However, our results showed that all patients who had obvious flow, even at a time when they were clinically brain dead, eventually developed cerebral circulatory arrest. Finally, the TCD waveforms observed in our brain-dead patients were similar to those reported by other groups.

In this study, we also described a novel color Doppler sonographic pattern observed in brain-dead patients. Our two-dimensional color mode recordings demonstrated an interesting pattern as systolic and diastolic flow coexisted simultaneously in time, resulting in a pulsating flashing signal akin to that of a beacon. This signal was observed in all patients during the time of cessation of cerebral circulation according to synchronous Doppler signals in all intracranial vessels. Although cerebrovascular hemodynamics are complex, cerebral perfusion pressure (CPP) can be calculated as the difference between the mean arterial blood pressure (MABP) and the ICP. Furthermore, assessment of cerebral autoregulation using TCD depends on the assumption that relative changes in blood flow velocity (FV) correlate with relative changes in CBF. The value of CPP at which autoregulation fails and FV begins to fall is called the autoregulatory “threshold” or “break point.” Mathematical models have been generated to predict the CPP and cerebral autoregulatory status of the cerebral circulation from TCD FV waveform analysis. The intracranial vascular resistance (R) may be depicted from Hagen-Poiseuille’s law for steady laminar flow (F) in long cylindrical tubes: 

\[ F = \frac{P}{(8 \mu l)}(\pi r^4) = Pr \]  

where \( P \) = pressure; \( \mu \) = viscosity; \( l \) = length; \( r \) = radius; \( R \) = resistance. According to this concept, CBF at any time should be given by: 

\[ \text{CBF} = \frac{(\text{MABP} - \text{ICP})}{R} = \frac{\text{CPP}}{R}. \]  

Noninvasive calculation of CPP (nCPP) by means of TCD has previously been reported based on the formula

\[ \text{nCPP} = \frac{\text{MABP} \times \text{FVd}}{\text{FVm}} + 14 \text{ mm Hg} \]  

where \( FVd \) is diastolic flow and \( FVm \) is mean flow. According to the above equations as CPP falls \( FVd \) approaches zero and forward movement of blood only occurs during systole. When CPP falls further and vascular resistance increases, a state of reverberant flow can be seen, where reversed flow occurs during diastole. Once backflow during diastole equals forward flow during systole, no net flow of blood occurs and cerebral tamponade in the territory of the sonated vessel is completed.

Therefore, our color mode recordings may be an image of the transitory “flickering” of cerebral circulation observed as autoregulation fails and vascular resistance increases just before cessation of CBF becomes permanent and brain tamponade is complete.

Technical Considerations and Study Limitations

The major technical limitations of TCD include the examination of the posterior circulation, which can be extremely difficult in a bedridden patient who is intubated and an “absent bone window.” Furthermore, observers who are performing TCD in brain-dead patients must be well trained and adequately experienced. In many countries, an observation time between 6 and 72 hours is required after the first examination showing brain death to the declaration of the patient as brain dead. This time could be shortened in patients in whom both clinical evidence of brain death and TCD confirmation of cerebral circulatory arrest is demonstrated. Such patients may be declared brain dead without a second examination after a period of observation if appropriate legal measurements are taken. Only a few countries allow confirmatory tests to shorten the time to declaration. However, patients who are clinically brain dead and still have obvious CBF depicted by TCD pose a medicolegal problem. Moreover, no global consensus exists if confirmatory tests are really necessary in patients with the clinical diagnosis of BD.

In conclusion, our results showed perfect agreement between contrast angiography and TCD for the confirmation of intracranial circulatory arrest in BD. Although further studies are clearly required, we suggest that TCD was a sensitive noninvasive tool in the diagnosis of BD and a good candidate for the “gold standard” of diagnosis.
REFERENCES

2. Harvard Medical School Ad Hoc Committee to Examine the Definition of Brain Death: A definition of irreversible coma. JAMA 205:337, 1968