PAPER

Time dependent validity in the diagnosis of brain death using transcranial Doppler sonography

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J Neurol Neurosurg Psychiatry 2006;**77**:646–649. doi: 10.1136/jnnp.2005.076406

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Received 20 July 2005
In revised form 26 December 2005
Accepted 5 January 2006

Objective: To evaluate the validity of transcranial Doppler (TCD) in confirming brain death from various pathological conditions.
Methods: An observational case–control study over a 2.5 year period, in which transcranial Doppler (TCD) examinations were done on 101 comatose patients for confirmation of brain death. Between October 2002 to May 2005, 44 clinically diagnosed brain death cases (29 male, 15 female; mean (SD) age, 46.5 (19.5) years; Glasgow Coma Scale (GCS) score, 3.0 (0.0)) and 57 controls (36 male, 21 female; age 48.1 (16.5) years; mean GCS, 4.9 (1.7)) were examined. Reverse diastolic flow, very small systolic spikes, or no signals were considered characteristic of cerebral circulatory arrest.
Results: The sensitivity and specificity of TCD examination of both the basilar artery and the middle cerebral arteries (MCAs) in confirming brain death were 77.2% and 100%, respectively. The sensitivity of TCD-diagnosed brain death increased with elapsed time. There was a trend for the basilar artery to have greater sensitivity (86.4% *v* 77.2%), higher positive predictive value (90.5% *v* 85.1%), and fewer false negatives (14% *v* 23.7%) than the MCAs for diagnosing brain death (all NS). The consistency of the basilar artery and the MCAs for diagnosing brain death was significant ($\kappa = 0.877$, $p < 0.001$ and $\kappa = 0.793$, $p < 0.001$, respectively).
Conclusions: TCD can be a confirmatory tool for diagnosing brain death. The validity of TCD diagnosed brain death depends on the time lapse between brain death and the performance of TCD. TCD of both the basilar artery and the MCAs showed significant consistency in brain death diagnosis.

The diagnosis of brain death can be made on the basis of a neurological examination. Clinically, there is deep coma, but brain stem reflexes—such as papillary light, corneal, oculocephalic, oropharyngeal, and respiratory reflexes—are absent.[1] However, subsidiary investigations, such as electroencephalography (EEG), arteriography, and radionuclide scan, have been used either to determine the arrest of the cerebral circulation or to confirm the diagnosis of brain death. These criteria vary from country to country.[2–5]

Transcranial Doppler (TCD) is a non-invasive ultrasonic technique that measures local blood velocity and direction in the proximal portions of large intracranial arteries.[6] It is convenient and inexpensive, and can be used repeatedly in the detection of cerebral collateralisation or the arrest of the flow pattern. The TCD findings indicative of brain death have been confirmed by four vessel angiography[7] and Tc-99m radionuclide scanning.[8] The potential limitations to its clinical use in the diagnosis of brain death are transmission problems or false positive interpretations.[6 9] TCD diagnostic criteria for cerebral circulatory arrest in brain death have been published, with sensitivity ranging from 70.5% to 100%, and specificity from 97.4% to 100%.[9–14] The discrepancies in sensitivity rates between various series can be attributed to the number of vessels examined, the numbers of patients, and the time lapse from clinical brain death to the performance of TCD. However, the predictive values between the middle cerebral arteries (MCAs) and the basilar artery, and the relation between the time lapse from clinical brain death to the performance of TCD, have rarely been investigated. In this study our aim was to evaluate the validity of TCD in confirming brain death from various pathological conditions.

METHODS

From October 2002 to May 2005, 101 patients with intracranial hypertension caused by various underlying diagnoses (table 1), who had been admitted to the neurosurgical intensive care unit of a tertiary medical centre in southern Taiwan, were included in the study. All patients had isolated brain lesions and a measured Glasgow Coma Scale (GCS) score of less than 7 during the TCD examination. The hospital is a full facility, 1200 bed regional teaching hospital, which is responsible for the health care of 900 000 residents and serves as a referral centre for the care of severely ill and organ transplantation patients from neighbouring satellite hospitals and outpatient clinics in southern Taiwan. In all, about 120 to 150 patients undergo TCD each month. The clinical diagnosis of brain death included unresponsive deep coma, an absence of brain stem reflex (no pupillary response to light, no corneal reflex, no vestibulo-ocular reflex, no gag reflex, and no oculocephalic reflexes), an absence of limb movement, and a lack of spontaneous respiration.[9 15] The subjects were divided into brain death and non-brain-death groups when TCD was undertaken. A Multidop X_2 TCD probe (DWL, Elektronische Systeme GmbH, Germany) with a 2 MHz transducer was placed on the temporal bone window to detect the middle cerebral arteries, and on the suboccipital window to detect the basilar artery, was used.

A stable arterial blood pressure of no less than 90/50 mm Hg was maintained, even with the vasopressive agents used throughout the study. The presence of a specific TCD flow pattern—such as a reverse diastolic flow, a very small systolic spike, or no signal, as described by Ducrocq *et al*[16]—in both the MCAs and basilar artery, was considered to be characteristic of cerebral circulatory arrest. The TCD data were obtained at various times to meet the clinical criteria of brain death. On admission and before the TCD examination,

Abbreviations: MCA, middle cerebral artery; ROC, receiver-operating characteristic; TCD, transcranial Doppler

Table 1 The demographic data of the clinically dead (cases) and non-dead deep coma subjects (controls)

Variable	Clinical brain death (cases)	Clinically not brain death (controls)
Number of patients	44	57
Age (years) (mean (SD))	46.5 (19.5)	48.1 (16.5)
Sex (male:female)	29:14	36:21
GCS when TCD done (mean (SD))	3.0 (0.0)	4.9 (1.7)
Time lapse to TCD (h) (mean (SD))*	15.2 (14.1)	21.5 (12.3)
Diagnosis		
Head trauma	26	39
Cerebral haemorrhage	11	6
Subarachnoid haemorrhage	6	7
Cerebral infarct	0	3
Coagulopathy	1	1
Hypoxia	0	1

*From clinical brain death to TCD.
GCS, Glasgow coma scale; TCD, transcranial Doppler sonography.

all patients underwent neuroimaging studies to define the irreversible changes. Data were analysed using qualified SPSS software, version 12.0. The validity, sensitivity, specificity, positive predictive value, negative predictive value, and false positive and false negative values were all determined. Consistency between clinically diagnosed brain death and TCD diagnosed brain death was compared by kappa (κ) statistics. A null hypothesis of a p value less than 0.05 was considered statistically significant. We also used the receiver-operating characteristic curve (ROC)[17] to determine the appropriate cut off point of the time lapse from clinical brain death to the performance of TCD. The theoretical point of each independent axis would meet on a soothing curve at the farthest point from the diagonal. This time point and the ROC area could be estimated if the curved line was ideal.

RESULTS

One hundred and one patients were included in this observational case–control study. Forty four individuals (29 male; 15 female) were clinically brain dead, while 57 were in a deep coma but did not initially fulfil the criteria of brain death (36 male; 21 female) when TCD examinations were undertaken. The aetiologies of the 101 patients with intracranial hypertension are listed in table 1. The mean (SD) age was 46.5 (19.5) years among the brain dead individuals, compared with 48.1 (16.5) years in the control group.

Overall, we evaluated 132 vessels in 44 dead individuals, including 88 MCAs and 44 basilar arteries. Five patterns of TCD signals were recorded after the diagnosis of brain death and are shown in table 2. In all, 23 vessels (17.4%) did not fulfil the arrest flow pattern, while 109 (82.6%) vessels had a reverberating diastolic flow, very small systolic spikes, or no signals at all. Reverberating diastole was the most common flow pattern (52.3%) in the MCAs, followed by very small systolic spikes (34.1%) in the basilar artery. In one patient, no signal was detected in one MCA, while the opposite MCA was easily identified. No basilar artery signals were recorded in nine patients.

Table 2 The Doppler waveform patterns by transcranial Doppler sonography in 44 brain dead individuals

TCD signal waveform	MCA (n = 88)	BA (n = 44)
Normal	6	3
Decreased diastole	11	3
Diastolic reverse flow	46	14
Very small systolic spikes	24	15
Undetectable flow	1	9

BA, basilar artery; MCA, middle cerebral artery.

Table 3 The time lapse from clinical diagnosis to transcranial Doppler sonography examination in 44 brain death cases

Time lapse (h)	Number and percentage of: Brain deaths in a TCD diagnosed specific pattern	Brain deaths in a TCD diagnosed non-specific pattern
0–6	7 (58.3%)	5 (41.7%)
6–12	10 (76.9%)	3(23.1%)
12–24	10 (83.3%)	2 (16.7%)
24–36	7 (100%)	0 (0%)

TCD, transcranial Doppler sonography.

Table 3 shows the time lapse from the clinical diagnosis of brain death to the TCD examination. TCD was carried out in 37 cases (84.1 %) within 24 hours of the clinical diagnosis of brain death. From these, 27 of 37 (61.3%) were clearly correlated with the specific TCD waveforms. These specific patterns increased to 77.3% if the time lapse was greater than 24 hours, and reached a plateau by 36 hours.

The overall validity tests of the intracranial vessels in the diagnosis of brain death are shown in table 4. They revealed that both the MCAs and the basilar artery have a specificity and positive predictive value of 100%. They also disclosed that the basilar artery had a higher sensitivity rate (86.4%), a higher negative predictive value (90.5%), and a lower false negative value (14%) statistically, and that the basilar artery was also highly consistent with clinically diagnosed brain death ($\kappa = 0.877$, $p<0.001$). The correlated consistency between clinically diagnosed brain death and TCD diagnosed brain death was higher than for the basilar artery ($\kappa = 0.877$) than for either the right MCA ($\kappa = 0.793$), or the left MCA ($\kappa = 0.856$), or both ($\kappa = 0.793$). However, these differences were not statistically significant.

DISCUSSION

The sensitivity and specificity of different studies (table 5) has ranged from 70.5% to 100%, and from 97.4% to 100%, respectively. The specific waveform pattern would seem inconsistent with the clinically diagnosed brain death in our study if the TCD had been carried out earlier, as reported by others.[14 15] This indicated that there must be a time lag between the cerebral circulatory arrest and the total loss of brain function.[18] Thus the timing of the clinical diagnosis of brain death in relation to the timing of the TCD being performed may be a crucial factor affecting sensitivity. We attempted to demonstrate this phenomenon using the ROC curve. The curve was jagged and a clear cut off point was difficult to find. The curve is not shown here owing to the small sample size; however, it reached a plateau after the time lapse. In this study, we confirmed the 100% specificity of TCD (no false positives in 57 non-clinically-diagnosed dead subjects) in the diagnosis of brain death, and showed a sensitivity of 77.2% (10 false negatives out of 44 clinically brain dead individuals). This outcome was similar to the results of Dosemeci *et al* in that the flow arrest pattern is additively useful in confirming brain death if the clinical diagnosis is made. In a large scale, evidence based analysis, the specific waveform was identical to the cerebral flow arrest in clinical practice,[19] and the arrest flow pattern was equal to the diagnosis of brain death. The saving of time is important for transplantation once brain death is established. In some cases, confirmation by the conventional procedure of an apnoea test would delay the declaration of brain death. Based

Table 4 The validity of transcranial Doppler sonography studies in the diagnosis of brain death of the middle cerebral arteries, basilar artery, or both

Validity (%)	Right MCA	Left MCA	Both MCAs	BA	BA + left MCA	Both MCAs + BA
Sensitivity	77.2	84.1	77.2	86.4	84.1	77.2
Specificity	100	100	100	100	100	100
PPV	100	100	100	100	100	100
NPV	85.1	89.1	85.1	90.5	89.1	85.1
FP	0	0	0	0	0	0
FN	23.7	16.0	23.7	14	16.0	23.7
Consistency	$\kappa = 0.793$ $P<0.001$	$\kappa = 0.856$ $p<0.001$	$\kappa = 0.793$ $p<0.001$	$\kappa = 0.877$ $p<0.001$	$\kappa = 0.856$ $p<0.001$	$\kappa = 0.793$ $p<0.001$

BA, basilar artery; FN, false negative; FP, false positive; MCA, middle cerebral artery; NPV, negative predictive value; PPV, positive predictive value; TCD, transcranial Doppler sonography.

on our findings (the high accuracy of TCD for the diagnosis of brain death), we considered that TCD is a useful complementary tool to confirm the diagnosis of brain death in special situations, when a complete neurological examinations cannot be carried out, or even when results are dubious. The value of TCD for confirming brain death has varied widely in different countries, and its use is not officially sanctioned in Taiwan yet.

The sequence of the cerebral circulatory arrest waveform changed from a decreasing diastole, to a reverse diastole, to the appearance of small systolic spikes, and eventually to no signal with increasing intracranial pressure and decreasing cerebral perfusion pressure. In the series by Ducrocq *et al*[16] and Hassler *et al*,[20] the progress from a diastolic reverse flow to very small systolic spikes and then to no signals was evidence of no surviving neurones. Ropper *et al*[10] and Powers *et al*[11] also reported that a normal TCD flow signal did not mean the neurones were adequately perfused. Our study (table 2) showed that reverse diastole is the most frequent pattern in both MCAs (52.3 %), followed by very small systolic spikes in the basilar artery (34.1%). In all, 23 vessels (17%) with either normal flow or a decreased diastole were detected in the MCAs or basilar artery. All these waveforms can be seen in brain death. Therefore, a single TCD interpretation without a clinically based correlation can lead to a diagnosed error.

We detected no MCA flow in one subject and no basilar artery flow in nine dead individuals. The lack of a flow signal may be caused by transmission problems or a true cessation of cerebral flow.[20 21] In our series, no flow was detected in 10 dead individuals (7.8%), but in only two members of the control group (1.9%). The differences between the cessation of cerebral flow and transmission problems can be detected by an experienced technician. However, if the subjects with no flow were excluded based on presumed faults, the sensitivity would fall to 73.5% (nine false negatives out of 34 clinically dead individuals). This emphasises the importance of technique in determining sensitivity. In published reports, the accuracy rate was more affected in MCAs scanned through the temporal window because of the bony limitation, but not in the freely penetrated suboccipital window through the foramen magnum. This also highlights the fact that zero flow signals in the basilar artery indicate a TCD diagnosis of brain death rather than artificial technical problems.

One of our patients, who had undergone a suboccipital craniectomy and ventricular drain for cerebellar haemorrhage, and who fitted the criteria for a clinical diagnosis of brain death, had false negative TCD studies. The preservation of the forward flow signal resulted from a skull defect with ventricular drainage, permitting relief of the markedly increased intracranial pressure. This result was similar to that of a previously published report[12] showing that a brain dead individual could have a forward or even normal TCD flow pattern in the earlier stages. In all these observations and reports, time dependent specific flow patterns were a factor leading to the TCD diagnosis of brain death.

The basilar artery has a higher sensitivity than the MCAs in the TCD diagnosis of brain death, and the left MCA has a higher sensitivity than the right, but with no statistically significant difference. The basilar artery is the major vessel supplying the brain stem, and we found that if circulatory arrest appeared in the basilar artery, brain stem function would immediately cease. Hence, basilar artery dynamics seem more directly involved than the MCAs in the time lapse of brain death. Furthermore, the left hemisphere is dominant in the majority of people. Taken together, we stress that a complete Willis circle survey, or both the MCAs and the basilar artery, or at least the left MCA and basilar artery, should be the minimum requirement for a confirmatory diagnosis of brain death in patients who meet the established clinical criteria.

Conclusions

From our experience with TCD in comatose patients and brain dead subjects, we found first, that TCD can be a confirmatory tool in the diagnosis of brain death; second, that the validity of TCD depends on the time lapse from

Table 5 The validity of transcranial Doppler sonography in the diagnosis of brain death in other studies

		No of patients who were:					
Reference	Vessels surveyed	Clinically brain dead	Clinically not brain dead	TCD FP	TCD FN	Sensitivity (%)	Specificity (%)
Ropper[9]	Unilateral or bilateral MCAs	24	–	0	3	87.5%	–
Powers[10]	Both MCAs	18	6	0	1	94.5	100
Petty[11]	At least 2 vessels	23	26	0	2	91.3	100
Feri[12]	Both MCAs	22	15	0	0	100	100
Hadani[13]	Both ICA MCAs, VAs and BA	84	53	0	1	96.5	100
Dosemeci[14]	At least any 3 vessels	61	39	1	22	70.5	97.4
This study	Both MCAs+BA	44	57	0	10	77.2	100

BA, basilar artery; FN, false negative; FP, false positive; MCA, middle cerebral artery; TCD, transcranial Doppler sonography.

clinical brain death to the TCD examination; and third, that there was satisfactory consistency between clinically diagnosed brain death and TCD diagnosed brain death for both the basilar artery and the MCAs.

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Competing interests: none declared

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