Variability Across Countries for Brain Death Determination in Adults

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Research

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Abstract

Background: Currently there is variability in diagnostic procedures across countries. Our aim was to compare guidelines of brain death determination in adults among five countries: China, UK, US, France, and Germany.

Method: This is a retrospective study based on a prospective database of consecutive coma patients who received brain death determination. The technical specifications, completion rates, and positive rates of brain death determination according to criteria of different countries were compared. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each ancillary test for the identification of brain death diagnosed according to different criteria were investigated.

Results: One hundred and ninety-nine patients who received brain death determination from June 2018 to June 2020 were included in this study. One hundred and thirty-one (65.8%) patients were diagnosed with brain death according to French criteria, 132 (66.3%) according to Chinese criteria, and 135 (67.7%) according to criteria of US, UK, and Germany. The sensitivity and PPV of EEG (92.2% - 92.3%) and SLSEP (95.5% - 98.5%) were higher than TCD (84.3% - 86.0%), and all these three tests have a very low specificity and NPV.

Conclusions: The duration of apnea test and requirements of ancillary tests vary among countries. The discrepancy in brain death determination between clinical assessments and additional confirmation of ancillary tests is small.

Background

The concept of death has been a philosophical debate as well as a medical controversy for millennia. The rapid development of technology in life support continues to blur the line between life and death. A major confusion among the public is the difference between death of the person and death of the human organs. In 1968, the Harvard Ad Hoc Committee proposed that death of the individual could be determined as the cessation of brain function (irreversible coma), despite the persistent respiration and circulation supported by mechanical ventilation¹. This visionary widely accepted concept opened up the avenue for exploring criteria and tools for brain death determination.

Most countries have implemented laws giving a legal definition of brain death, however, the legalization of brain death is still on the way in China². Medical consensuses have been reached across countries that the determination of brain death is to diagnose the irreversible cessation of the entire brain function by confirming the absence of consciousness due to a known cause, brainstem reflexes, and spontaneous breath. Only in the United Kingdom, brain death was defined as the irreversible cessation of brain-stem function^{3,4}. On the operational level, there are still a few disparities in the diagnostic procedures across countries. In this study, we compared national guidelines of brain death in adults among five countries with different criteria: China, United Kingdom (UK), United States (US), France, and Germany.

Methods

Study design

This retrospective study was based on a prospective database of consecutive coma patients received brain death determination in the Second Affiliated Hospital of Guangzhou University of Chinese Medicine, China. This study was approved by the Ethics Committee of The Second Affiliated Hospital of Guangzhou University of Chinese Medicine. All the procedures in brain death determination were based on the Chinese guidelines^{5,6}, and all the data in this study have been de-identified, the informed consent was waived therefore. This study was conducted in compliance with Chinese laws and the Declaration of Helsinki.

Patients

Consecutive patients received brain death determination from June 2018 to June 2020 were included in this study. The criteria for conducting brain death determination are: (1) age ≥ 18 ; (2) Glasgow Coma Scale (GCS): 2T (no opening of the eye, intubated, no motor response); (3) coma with a known and irreversible cause; (4) body temperature $> 36^{\circ}\text{C}$; (5) mean arterial pressure ≥ 65 mm Hg.

Brain death determination

Based on Chinese guidelines for the diagnosis and confirmation of brain death in adults^{5,6}, the determination of brain death contains three steps. The first step is the determination of testing prerequisites which includes: (1) the confirmation of a known cause for coma; (2) the exclusion of any reversible coma. The second step is the clinical assessment which includes three parts: (1) deep coma (GCS 2T; all the stimuli should be given above the neck); (2) absence of brainstem reflexes including direct and indirect pupillary light reflexes, corneal reflex, oculoccephalic reflex, oculovestibular reflex (using iced saline), and cough reflex; (3) apnea test. All these five reflexes should be absent after multiple repetitions. The third step is the confirmatory examinations consisting of electroencephalogram (EEG), short-latency somatosensory evoked potential (SLSEP), and transcranial Doppler (TCD). Two of the three confirmatory tests should be fulfilled. If any of the above brainstem reflexes cannot be tested, all the three confirmatory tests should be fulfilled. Apnea test was conducted after the fulfillment of all the other assessments in order to avoid any potential adverse event. All the assessments were conducted by neurologists with more than five years of clinical experience and with a certificate in national standard training of brain death determination. All the evaluations for one patient were given independently by two neurologists, and consensuses should be reached. For patients who admitted to our hospital before May 2019, the brain death determination was conducted according to Chinese guidelines in 2013⁵: brain death determination should be conducted twice at least 12 hours apart, only the patients who fulfilled both sets of examinations can be diagnosed as brain death. For patients who admitted to our hospital after May 2019, the brain death

determination was conducted according to Chinese guidelines in 2019⁶: brain death can be diagnosed after fulfilling one set of brain death determination tests.

Diagnostic standards of confirmatory tests

A continuous EEG is conducted for more than 30 min with eight scalp electrodes arranged according to the international 10–20 system (Fp1, Fp2, C3, C4, O1, O2, T3, and T4, referred to A1 and A2). The complete electrocerebral silence is defined as EEG activity $\leq 2 \mu\text{V}$ and is considered as brain death. SLSEP includes the following obligate components: N9, N13, P14, N18, and N20. Electrical stimulation was given at a rate of 1–5 Hz, with a pulse width of 0.1–0.2 ms (up to 0.5 ms, if necessary) and an intensity of 5–25 mA. Brain death in SLSEP is defined as the existence of bilateral N9 and / or N13 and the absence of bilateral P14, N18, and N20. Bilateral middle cerebral arteries are used to assess anterior circulation (alternative arteries: bilateral terminal internal carotid arteries or carotid siphons), and basilar artery for posterior circulation (alternative arteries: bilateral intracranial vertebral arteries). TCD should be performed twice at intervals of ≥ 30 min. Brain death in TCD is defined as the cerebral circulatory arrest presented with the following presence of the following flow patterns: reverberating flow, small systolic peaks in early systole, and disappearance of flow signals.

Statistical analysis

Demographics, etiology, history of cardiopulmonary resuscitation (CPR) before brain death evaluation, use of vasopressors and continuous renal replacement therapy (CRRT) before or during brain death evaluation, and results of all the tests of brain death determination were collected for analysis. The Chinese criteria of brain death were compared with national criteria of US⁷, UK³, Germany⁸, and France⁹. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each ancillary test for the identification of brain death confirmed according to different criteria were calculated. All the statistical analyses were performed with SPSS version 22 software (SPSS Inc., Chicago, IL, United States).

Results

Clinical profiles

From June 2018 to June 2020, a total of 199 patients received brain death evaluations in our hospital (Table 1). The median age was 44 years old, and the majority was male (81.9%). Intracranial hemorrhage (ICH), brain trauma, and subarachnoid hemorrhage (SAH) were the most common etiologies in our cohort. Almost all the patients (97.5%) were given vasopressors to maintain blood pressure at a normal level, and more than half of patients (54.3%) received CRRT to maintain homeostasis.

Table 1
Clinical features of patients who received brain death determination

	Patients (n = 199)
Age (IQR, years)	44 (33–50)
Male (%)	163 (81.9)
Etiology (%)	
ICH	95 (47.7)
Ischemic stroke	8 (4.0)
Trauma	62 (31.2)
SAH	25 (12.6)
HIE	8 (4.0)
Other	1 (0.5)
CPR before BD evaluation (%)	24 (12.1)
Use of vasopressors (%)	194 (97.5)
Use of CRRT (%)	108 (54.3)
<i>BD</i> brain death; <i>CPR</i> cardiopulmonary resuscitation; <i>CRRT</i> continuous renal replacement therapy; <i>HIE</i> hypoxic ischemic encephalopathy; <i>ICH</i> intracranial hemorrhage; <i>SAH</i> subarachnoid hemorrhage	

Brain death determination

All the patients met testing prerequisites and did not have any brainstem reflexes (Table 2). Most patients received EEG and SLSEP, and less than half of patients were evaluated by TCD. The apnea test was not conducted in 44 patients who did not meet the prerequisites of apnea test and in 8 patients died of cardiac arrest before the test. Apnea test was aborted in four patients due to arrhythmia or significant decrease of oxygen saturation, or blood pressure. 48 patients admitted to our hospital before May 2019 received two sets of brain death assessments according to Chinese guidelines in 2013⁵. The positive rates of repetitive apnea tests and ancillary tests increased.

Table 2
Results of each section of brain death determination

Evaluations	Performed	Completed	Positive	Negative
Irreversible coma with a known cause, %	100 (199/199)	100 (199/199)	100 (199/199)	0 (0/199)
Deep coma, %	100 (199/199)	100 (199/199)	100 (199/199)	0 (199/199)
Brainstem reflexes, %	100 (199/199)	100 (199/199)	100 (199/199)	0 (199/199)
EEG, %	96.5 (192/199)	96.5 (192/199)	94.8 (185/192)	3.6 (7/192)
SLSEP, %	95.5 (190/199)	95.5 (190/199)	95.3 (183/190)	3.7 (7/190)
TCD, %	43.2 (86/199)	43.2 (86/199)	88.4 (76/86)	11.6 (10/86)
Apnea test, %	73.9 (147/199)	71.9 (143/199)	91.8 (135/147)	5.4 (8/147)
Repeat brain stem reflexes, %	100 (48/48)	100 (48/48)	100 (48/48)	0 (48/48)
Repeat EEG, %	97.9 (47/48)	97.9 (47/48)	97.9 (46/47)	2.1 (1/47)
Repeat SLSEP, %	97.9 (47/48)	97.9 (47/48)	100 (47/47)	100 (47/47)
Repeat TCD, %	8.3 (4/48)	8.3 (4/48)	100 (4/4)	0 (0/4)
Repeat apnea test*, %	100 (48/48)	97.9 (47/48)	85.1 (40/47)	14.9 (7/47)
<i>EEG</i> electroencephalogram; <i>SLSEP</i> short latency somatosensory evoked potentials; TCD transcranial doppler.				

Comparisons of determination criteria among five countries

The general criteria of brain death determination in China, US, UK, Germany, and France were presented in Table 3. Irreversible coma with a known etiology, absence of brainstem reflexes, and cessation of spontaneous respiration are mandatory in criteria of all the countries. The duration of apnea test is five mins in British criteria, eight to ten mins in American and Chinese criteria, and unspecified in German and French criteria. For patients who fulfil clinical criteria of brain death, confirmatory tests are not mandatory in US, UK, and Germany. Chinese criteria stipulate that two of the three confirmatory tests (EEG, TCD, and SLSEP) must be fulfilled, and French criteria require at least one confirmatory test for the diagnosis of brain death.

Table 3
The criteria of brain death determination in five countries.

Country	Known etiology	Irreversible coma	Absent brainstem reflexes	Repetition of brainstem reflexes tests	Apnea test	Repetition of apnea test	Duration of apnea test (min)	Confirmatory tests	Accepted confirmatory Tests	Number of raters for one patient	Qualificati of raters
China (2019) ⁶	Yes	Yes	Yes	Yes	Yes	No	8–10	Mandatory (two of three)	EEG, SLSEP, TCD	2	National standard training
US (2010) ⁷	Yes	Yes	Yes	Yes	Yes	No	8–10	Optional	EEG, nuclear scan, cerebral angiogram	Not specified	Not specified
UK (2008) ³	Yes	Yes	Yes	Yes	Yes	No	5	Optional	4 vessel angiography, TCD, HMPAO SPECT, PET, EEG, EP	2	Not specified
Germany (1998) ⁸	Yes	Yes	Yes	Yes	Yes	No	Not specified	Optional	EEG, EP Scintigraphy, TCD, angiography	2	Not specified
France (1996) ⁹	Yes	Yes	Yes	Yes	Yes	No	Not specified	Mandatory (one of two)	EEG*, angiography	2	Not specified

EEG electroencephalogram; *EP* evoked potential; *HMPAO SPECT* 99mTc-HMPAO single proton emission tomography; *PET* proton emission tomography; *SEP* somatosensory evoked potential; *SLSEP* short latency somatosensory evoked potentials; *TCD* transcranial doppler. *EEG should be performed twice at intervals of ≥ 4 hours.

Positive rates of each item of criteria of different countries were presented in Table 4. The results of apnea tests at eight mins were used in the determination of brain death based on criteria of these five countries, therefore the positive rate of apnea test might be slightly overestimated in UK criteria group. Among 199 patient who received brain death determination, 131 (65.8%) patients were diagnosed with brain death according to French criteria, 132 (66.3%) according to Chinese criteria, and 135 (67.7%) according to criteria of US, UK, and Germany.

Table 4
Positive cases determined by criteria of different countries.

Evaluations	China	US	UK	Germany	France
Irreversible coma with a known cause	100 (199/199)	100 (199/199)	100 (199/199)	100 (199/199)	100 (199/199)
Deep coma	100 (199/199)	100 (199/199)	100 (199/199)	100 (199/199)	100 (199/199)
Absence of brain stem reflexes	100 (199/199)	100 (199/199)	100 (199/199)	100 (199/199)	100 (199/199)
Apnea test*	91.8 (135/147)	91.8 (135/147)	91.8 (135/147)	91.8 (135/147)	91.8 (135/147)
EEG	94.8 (185/192)	-	-	-	94.8 (185/192)
SLSEP	95.3 (183/190)	-	-	-	-
TCD	88.4 (76/86)	-	-	-	-
Confirmed cases	66.3 (132/199)	67.8 (135/199)	67.8 (135/199)	67.8 (135/199)	65.8 (131/199)
*Tested at 8 min.					
EEG electroencephalogram; SLSEP short latency somatosensory evoked potentials; TCD transcranial doppler.					

Performance of confirmatory tests

Diagnostic performance of EEG, SLSEP, and TCD was analyzed for the identification of confirmed cases according to criteria of US, France, and China (Table 5). Among these three tests, EEG has the highest accuracy according to all the criteria (92.2%-92.3%). The sensitivity and PPV of EEG and SLSEP were higher than TCD. All these three tests have a very low specificity and NPV.

Table 5
Diagnostic performance of ancillary tests in brain death determination.

Test	Accuracy	Sensitivity	Specificity	PPV	NPV
US standard (n = 143)					
EEG (n = 142)	92.2%	97.8%	0.0%	94.2%	0.0%
SLSEP (n = 141)	92.9%	98.5%	0.0%	94.2%	0.0%
TCD (n = 54)	79.6%	84.3%	0.0%	93.5%	0.0%
French standard (n = 142)*					
EEG (n = 142)	-	-	-	-	-
SLSEP (n = 141)	90.8%	95.5%	0.0%	92.1%	0.0%
TCD (n = 54)	77.8%	85.4%	16.7%	89.1%	12.5%
Chinese standard (n = 143)					
EEG (n = 142)	92.3%	98.5%	10.0%	93.5%	33.3%
SLSEP (n = 141)	92.2%	98.5%	0.0%	93.5%	0.0%
TCD (n = 54)	81.5%	86.0%	25.0%	93.5%	12.5%
*EEG was used as the only ancillary test.					
EEG electroencephalogram; SLSEP short latency somatosensory evoked potentials; TCD transcranial doppler.					

Discussion

The determination of brain death is essential for medical decision making in comatose patients. However, how to determinate brain death accurately with appropriate tests has been an ethical and academical focus for long time. Currently, there are some disconformities across countries on the procedures of brain death determination. Our study reported the variability on criteria of brain death in China, US, UK, Germany, and France, and investigated the diagnostic performance of ancillary tests according to criteria of different countries.

Apnea test is a mandatory technique to confirm the absence of spontaneous respiration in criteria of all the countries. The positive result of apnea test is arterial $P_{CO_2} \geq 60$ mm Hg (or 20 mm Hg increase from the baseline level) and the absent respiratory movements^{6,7}. However, the duration of apnea test was not the same across countries. Short duration may lead to false negative, whereas long duration may induce hypotension, severe hypoxemia, and serious arrhythmia which cause secondary insults¹⁰. The duration of apnea test is five minutes in UK, eight to ten minutes in US and China, and unspecified in German and French criteria. Identifying the optimum duration of apnea test is a crucial issue that should be investigated in future studies. Moreover, apnea test with continuous positive airway pressure was proposed to be a safer method than the classic oxygen insufflation method^{11–13}. More related evidence may lead to revisions in criteria of brain death determination in the future.

EEG is used to confirm the electrical inactivity of cortical layers in brain death determination. Very few studies investigated the validity of EEG in determination of brain death. A study¹⁴ in 1995 (n = 15) showed that EEG only had a sensitivity of 53%, and another study¹⁵ in 1987 (n = 56) reported a sensitivity of 80.6%. These two early studies compared the EEG with clinical criteria of brain death and used paper EEG recordings which might contain substantial artifacts. A recent German study¹⁶ (n = 67) and a Chinese study (n = 37)¹⁷ indicated that EEG had a high sensitivity of 94%-100% which was consistent with our findings.

Somatosensory evoked potentials (SEPs) examines lemniscal pathways in the hemispheres and brainstem, and was reported to be a reliable test for brain death determination with a sensitivity of 87.4%-100%^{18–20}. The examination of cerebral circulation provides an alternative evaluation of brain function. TCD is recognized as one of the three confirmatory tests in Chinese criteria of brain death. However, TCD has a lower sensitivity (73%-78%) than EEG and SEPs^{19,21}. Therefore, TCD was used less often than the other two ancillary tests in our study and was confirmed to have a medium sensitivity (84.3%-86.0%). Besides, TCD is limited by the penetrability of transtemporal windows and interexaminer variability. MR and CT angiography were proposed to assist brain death determination^{22,23}. However, angiography requires higher cost and the transfer of patients out of intensive care unit which generates potential safety hazards.

Among patients who had negative results of confirmatory tests (3 in EEG, 2 in SLSEP, and 8 in TCD), few were not diagnosed as brain death. Therefore, the specificity and NPV of confirmatory tests were very low in our study. The positive results of confirmatory tests suggest a high likelihood of brain death, whereas the negative results do not necessarily mean not of brain death. Among 135 (67.8%) patients who met the clinical criteria of brain death in our study, there were three patients who did not reach the brain death criteria of confirmatory tests, and they were not diagnosed as brain death in China. These three patients had no recovery of consciousness until the withdrawal of medical support. So far there are no reports of neurologic function recovery in patients who met clinical diagnosis of brain death. The routine and repeat use of ancillary tests in brain death determination need to be further justified. However, the confirmation of ancillary tests may avoid some possible human errors in clinical evaluations of brain death. Moreover, the raters of brain death should be trained and certified by national medical societies in order to minimize potential variability in the practice.

There are some limitations in this study. Apnea tests were conducted for eight minutes in our patients according to Chinese criteria. Therefore, we are unable to investigate the positive rate and safety of different test durations. There is a possibility that the positive rate of apnea test was slightly overestimated and the completion rate was mildly underestimated in patients evaluated according to UK criteria. Moreover, as EEG, SLSEP, and TCD are the only ancillary tests recognized in China, other ancillary tests, such as angiography, bispectral index, and positron emission tomography, were not conducted and investigated in this study.

Conclusions

Diagnostic procedures of brain death vary among countries. The criteria of brain death in China and France are comparatively stricter than in US, UK, and Germany. The discrepancy in brain death determination between clinical assessments and additional confirmation of ancillary tests is small. The optimum duration of apnea test and routine use of ancillary tests need to be further justified.

Declarations

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Conflicts of interest

There are no conflicts of interest.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Second Affiliated Hospital of Guangzhou University of Chinese Medicine. The requirement for informed consent for each patient was waived based on the use of anonymized patient and hospital data.

Consent for publication

Not applicable.

Data availability

By request to the corresponding author.

Author contributions

Study concept and design: FY, LW, SW; data acquisition: WZ, WW, HL; analysis and interpretation of data: WZ, WW, HL; drafting of the manuscript: FY and SW; study supervision: LW, SW; critical revision: FY, LW, SW. All authors read and approved the final manuscript.

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