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Benefits of combination of electroencephalography, short latency somatosensory evoked potentials, and transcranial Doppler techniques for confirming brain death

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Abstract: Objective: Optimization of combining electroencephalography (EEG), short latency somatosensory evoked potentials (SLSEP) and transcranial Doppler (TCD) techniques to diagnose brain death. Methods: One hundred and eleven patients (69 males, 42 females) from the major hospitals of Zhejiang Province were examined with portable EEG, SLSEP and TCD devices. Re-examinations occurred ≤12 h later. Results: The first examination revealed that the combination of SLSEP and EEG led to more sensitive diagnoses than the combination of SLSEP and TCD. Re-examination confirmed this and also revealed that the combination of TCD and EEG was the most sensitive. Conclusion: The results show that using multiple techniques to diagnose brain death is superior to using single method, and that the combination of SLSEP and EEG is better than other combinations.

Key words: Brain death, Electroencephalography (EEG), Short latency somatosensory evoked potentials (SLSEP), Transcranial Doppler (TCD)

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INTRODUCTION

While the concept of brain death was introduced in 1959 (Wjdicks, 2001), diagnostic criteria were not established until 1968 (Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death, 1968). Since then, many countries, including China, have established diagnostic criteria based on clinical assessment, and also on electroencephalography (EEG), short latency somatosensory evoked potentials (SLSEP), and transcranial Doppler (TCD) examinations. Although the diagnosis of brain death is clinical, investigative techniques have an important role to confirm the diagnosis. Previous research has demonstrated that these three methods (EEG, SLSEP, and TCD) may not be ideal when used individually (Grigg *et al*., 1987; Facco *et al*., 1990; 2002; Kuo *et al*., 2006). Here, we examined the combinatory benefits of EEG, SLSEP, and TCD to most reliably and accurately diagnose brain death in the clinical setting.

PATIENTS AND METHODS

Patients

All the irreversibly comatose patients came from big hospitals in Zhejiang Province, China. A total of 111 patients (69 males, 42 females; age range 9~85 years, average age 43.5 years) were included in the present study. Patients with reversible factors of coma (e.g., sedative administration, toxic or metabolic components) were not included. Major causes of brain death included cerebral trauma, cerebral hemorrhage, cerebral infarcts, intoxation, drowning,

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encephalitis, and acquired brain damage (Table 1). There were also single cases of viral encephalitis, suppurative encephalitis, carbon monoxide poisoning and gas poisoning, and two cases of organophosphate poisoning.

Table 1 Breakdown of patients in the study

Diagnosis	Number	Percentage (%)
Cerebral trauma	57	51.35
Cerebral hemorrhage	20	18.02
Cerebral infarcts	6	5.41
Intoxication	4	3.60
Drowning	4	3.60
Encephalitis	2	1.80
Acquired brain damage	14	12.61
Others	4	3.60
Total	111	100

Clinical methods

The concept of brain death and the criteria published in China (The National Ministry of Health's Drafting Group of the Standard Judgment of Brain Death, 2003) were adopted. Clinical assessment of brain function included conscious state, Glasgow coma scale (GCS), corneal reflex, light reflex, cough reflex, oculocephalic reflex, vestibulo-ocular reflex, and the apnoea test. Seven patients died before the second examination and 104 died within 85 d of the second examination.

Laboratory techniques

1. Electroencephalography (EEG)

EEG recordings were performed on a portable EEG machine (Italian EB Neuro Belight) using needle electrodes. The frontal central zero (Fz) electrode pole was used as ground. Two electrodes at the mastoid process were used as references and were >10 mm apart. The electrode resistance at the skin ranged from 0.1 Ω to 10 kΩ. The high-frequency smoothing wave was 70 Hz and the time constant was 0.3 ms. The sensitivity was 2 μV/mm. EEG waves at all electrodes were monitored for 30 min as both arms and pupils were stimulated. The EEG criterion of brain death's wave amplitude is <2 μV.

2. Short latency somatosensory evoked potentials (SLSEP)

SLSEP recordings were performed on a Keypoint-4 electromyogram (EMG) machine (Medtronic Co., Denmark). Disposable electrodes were adopted. The SLSEP criterion of brain death is devoid of a potential behind the P13. Square waves (1~3 Hz) stimulated bilateral medianus nerves at the wrists at different time. Thumb movement (~1 cm) was the standard stimulus strength. The record reference of wave N20 was Cc' and the reference electrode was Fz. When recording the far-field wave of the N18, the non-cephalic reference electrode of N18 was located at the second cervical spine (Cv2) and the recording electrode placed at Ci'. The record reference of wave N13 was Cv7 and the reference electrode was the Fz. The one side wave overlaid 500~2000 times, and the record repeated 2 to 3 times.

3. Transcranial Doppler (TCD)

TCD recordings were performed on a TC2021-III TCD machine (EME Co., Germany). Both middle cerebral arteries (MCAs) were insolated through the temporal window. The depth of the Doppler transducer was 40~65 mm. At the systolic phase, the Doppler transducer faced the direction of blood flow. If necessary, we compressed the carotid artery to make sure that the arterial flow was coming from the MCAs. The filter was set at its lowest level. The TCD pattern of brain death is systolic peaks, an oscillating or reverberating flow pattern, or an absence of systolic flow in the TCD.

All the EEG, SLSEP, and TCD examinations, including the first time and the repetition after 12 h, were performed by the same investigators.

Data analysis

Statistical analyses were done using the 2-related samples (matched) test, and $P<0.05$ was considered significantly different.

RESULTS

Clinical assessments

All patients (n=111) showed no corneal reflex, light reflex, cough reflex, oculocephalic reflex, vestibulo-ocular reflex, or a GCS grade of 3. None had voluntary breathing and all were in irreversible comas.

EEG examinations

At the first EEG examination, 92.79% (103/111) of the patients were considered to have brain death

according to the above criteria, while 8 patients had discrepancy results, of which 7 had waveforms of 2~40 μV and 1 had uncertain waveform. Patients (94.59%; 105/111) were re-examined 12 h later and 97.14% (102/105) still met the criteria for brain death, while the remaining 3 had 2~40 μV waveforms. EEG data are summarized in Table 2.

SLSEP examinations

At the first examination, 87.39% (97/111) of patients were considered to have brain death by the above pattern, while 14 were undetermined, including 7 who lacked periphery potentials, 6 with discrepancy results, 1 uncertain. Patients (94.59%; 105/111) were re-examined 12 h later and 92.38% (97/105) still met the pattern for brain death. One patient had inconsistent pattern and 7 lacked periphery potentials. SLSEP data are summarized in Table 2.

TCD examinations

At the first examination, 82.88% (92/111) of the patients were considered to have brain death using the above criteria, while 19 were undecided, including 1 with low velocity flow, 1 with quick velocity flow, 2 with normal wave, and 15 with asymmetry spectrum (8 presented in both the right and left middle cerebral arteries (RMCA and LMCA), 1 in RMCA and 6 in LMCA). Patients (94.59%; 105/111) were re-examined 12 h later and 82.86% (87/105) still met the criteria for brain death, while 3 patents had low velocity flow, 1 had normal wave, and 14 had asymmetry spectrum (9 presented in both RMCA and LMCA, 1 in RMCA, and 5 in LMCA). Four patients who did not present with asymmetry spectrum at the first examination did so at the second examination, and 1 patient who had quick velocity flow at the first examination changed to have asymmetry spectrum at the second examination. TCD data are summarized in Table 2.

Combinatory effects

To get the combinatory effects of TCD, SLSEP, and EEG, we used the rank sum test (2 related samples). For the first examination, EEG+SLSEP was better than TCD+SLSEP (Z=2.837, P=0.007; Table 3). For the second examination, EEG+SLSEP was still better than TCD+SLSEP (Z=3.638, P<0.001; Table 3). Additionally, TCD+EEG was better than TCD+SLSEP combination (Z=2.333, P=0.020; Table 3), making that combination of EEG+SLSEP the most sensitive combination of techniques when compared with other combinations. To reduce the possible bias, we analyzed the effects of cerebral trauma on the different methods and found that at the first examination EEG+SLSEP was better than TCD+SLSEP (Z=2.714, P=0.007), and at the second examination TCD+EEG was better than TCD+SLSEP (Z=2.333, P=0.020; Table 3).

DISCUSSION AND CONCLUSION

Since brain death was first described in the 1950's, there has been debate over the best way to accurately confirm brain death. EEG, evoked potentials, SLSEP, and TCD have been used as diagnostic techniques; however, results have been variable. The sensitivity of EEG in diagnosis of brain death ranges from 69.6% (Grigg *et al*., 1987) to 92.04% (Luo *et al*., 2006a; 2006b), the sensitivity of SLSEP ranges from 97.3% to 100% (Facco *et al*., 1990; 2002), and the sensitivity of TCD ranges from 70.5% to 100% (Kuo

Table 2 EEG, SLSEP and TCD examination results of patients

Examination	Number of patients									
	Positive	Uncertainty	Negative	Low voltage	No periphery potential	Low velocity	Quick velocity	Asymmetry spectrum	Normal wave	Total
Examination 1										
EEG	103	1		7						111
SLSEP	97	1	6		7					111
TCD	92					1	1	15	2	111
Examination 2										
EEG	102	0		3						105
SLSEP	97	0	1		7					105
TCD	87					3	0	14	1	105

Table 3 Statistical analyses of the combinatory effects

Combination effects	*n*	*Z*	*P*
The first combination effects			
TCD+EEG vs TCD+SLSEP	111	0.622	0.481
EEG+SLSEP vs TCD+SLSEP	111	2.837	0.007
TCD+EEG vs EEG+SLSEP	111	−1.576	0.137
The second combinatory effects			
EEG+SLSEP vs TCD+SLSEP	105	3.638[a]	<0.001
TCD+SLSEP vs TCD+EEG	105	−2.333[b]	0.020
EEG+SLSEP vs TCD+EEG	105	1.633[a]	0.102
Effects of cerebral trauma on combinatory effects			
EEG+SLSEP vs TCD+EEG	111	0.500[a]	0.617
TCD+SLSEP vs EEG+SLSEP	111	−2.714[b]	0.007
TCD+SLSEP vs TCD+EEG	111	−2.333[b]	0.020

[a]Based on negative ranks; [b]Based on positive ranks; "+" stands for combinatory

et al., 2006). The sensitivity of these methods has some variability, for example, in one study, the sensitivity changed from 73.91% to 80.43% during two examinations (Luo *et al*., 2006a; 2006b). Ultimately, the technique used to confirm brain death should meet the following criteria: (1) there should be no "false positive" results; (2) it should be sufficient on its own to establish a diagnosis; (3) it should not be susceptible to "confounders" such as drug effects or metabolic disturbances; (4) it should be standardized in technology, technique, and classification of results; and (5) it should be safe and available (Young *et al*., 2006; Cheng and Lin, 2008). Currently, EEG, SLSEP, and TCD are insufficient to satisfy these criteria, when used to diagnose brain death. In the current study, the single test sensitivity of EEG, SLSEP, and TCD was 92.79%, 87.39% and 82.88% at the first examination and 97.14%, 92.38% and 82.86% at the second examination, respectively.

The accuracy of EEG in diagnosing brain death is limited by the following factors: (1) it does not provide information on the brain stem; (2) it may be flat in patients with preserved subcortical function (e.g., comatose or vegetative patients following prolonged cardiac arrest); (3) it is unreliable in the case of sedation, hypothermia, or presence of toxic or metabolic factors; and (4) there is the constant risk of mistaking artifacts for residual cortical activity, thus yielding uncertainty about the presence or absence of electrocerebral activity.

Unlike EEG signals, the early components of SLSEP are minimally affected by sedative drugs and anesthetics. SLSEP is also ineffective for patients who have suffered from the high transverse cervical diseases (Waters *et al*., 2004). However, drugs and metabolic derangements affect far-field components of SLSEP waves. In our research, we recorded waves N18 and N20-P25. Wave N18 reflects the electric activity of the brain stem, while wave N20-P25 may reflect the function of the cortex. This may explain why the single test sensitivity of SLSEP is superior to those of the EEG and the TCD.

TCD is a noninvasive way to study intracranial basal artery blood flow velocity in real time and at the patient's bedside. One of the TCD applications concerns the evaluation of cerebral blood flow under different conditions of intracranial focus, which, in extreme, can lead to cerebral circulatory asymmetry. Therefore, TCD is prone to false negative results when the subject has had craniotomy decompression or cerebral ventricle drainage, catholicity cranium fractures or serious posterior cranial fossa trauma, and when an infant's bony sutures have not closed up (Cabrer *et al*., 2003).

Thus, a combination of these methods may be a key for diagnosing brain death. Here, we used EEG, SLSEP and TCD in combination and analyzed the sensitivity in confirming brain death. Our results show that the combination of SLSEP and EEG was better than the combination of SLSEP and TCD in the diagnosis of brain death, which was confirmed by re-examination 12 h later. However, the fact that the majority of our brain death patients suffered trauma may have affected our results. For example,

the sensitivity of TCD was lower than what has been reported in studies involving intracranial hypertension patients. Additionally, during SLSEP examinations, 7 patients had no periphery potential, which could be due to trauma destroying the peripheral nerve and obstructing signal conduction. EEG has a very high positive rate, which may be due to medicinal and metabolic factors leading to false positive results.

In summary, we conclude that when combining EEG, SLSEP and TCD to diagnose brain death, the combination of EEG and SLSEP was more sensitive than that of SLSEP and TCD, and the combination of TCD and EEG is more sensitive than that of SLSEP and TCD. Future studies should examine the combinatory effects of these techniques in a population of patients with more varied causes of brain death.

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