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Reliability in diagnosis of brain death

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Abstract *Objective:* To compare some of the confirmatory investigations of brain death with clinical criteria in order to achieve the most sensitive and accurate diagnosis of brain death.
Design: All patients with isolated brain lesions and Glasgow Coma Scale (GCS) = 3 were subjected to neurological examination after ruling out hypothermia, metabolic disorders and drug intoxications and diagnosed as clinically brain-dead when the brainstem reflexes were absent and the apnea test positive.
Patients: 15 patients with clinical diagnosis of brain death entered this study.
Measurements and results: The patients were submitted to the following investigations: electroencephalogram (EEG), transcranial Doppler (TCD) of the middle cerebral arteries (MCA), cerebral blood flow measurements with the i.v. Xe-133 method (CBF) and selective cerebral angiography (CA). EEG was isoelectric in 8 patients while the remaining 7 patients showed persistence of electrical activity. TCD was compatible with intracranial circulatory arrest in 18 MCA districts, compatible with normal flow in 2 and undetectable in 10 out of 30 districts insonated. In CBF examinations, however, all the patients showed a characteristic "plateau" of the desaturation curves lasting through the whole investigation and suggestive of absent cortical flow. CA showed circulatory arrest in both carotid and vertebral arteries.
Conclusions: Our study suggests that cerebral angiography and CBF studies are the most reliable investigations whereas the role of EEG and TCD remains to be determined because of the presence of false negatives and positives.

Key words Brain death · EEG · CBF · Transcranial Doppler · Cerebral angiography

Introduction

The diagnosis of cerebral death has become more and more important since it involves broad clinical and ethical aspects. Thus, this diagnosis must be precise and certain since this situation if often related with a possible organ transplantation or removal of "life-support" measures. Traditionally, the diagnosis of brain death has been done using clinical and/or instrumental criteria. These criteria vary widely from country to country; British [1] and the Australian legislations, for example rely only on the clinical confirmation of brain stem death without taking the function of the cortex into any consideration, and do not require any confirmatory test. In these countries, therefore, the clinical evaluation is accepted as probatory of cerebral death. In other countries including Germany and Italy, cerebral death means the death of the whole brain and an isoelectric electroencephalogram (EEG) as confirmatory test is mandatory. However, in cases in

which the clinical and the electroencephalographical examinations should result unreliable the lack of intracranial circulation documented by selective cerebral angiography is an accepted criterion of brain death, and is requested in countries such as Norway and Switzerland [2] as confirmatory test before organ removal. More recently, other techniques of cerebral blood flow measurements such as radionuclide brain scanning, radioisotope bolus technique, Transcranial Doppler, contrast enhanced CT and stable Xenon CT [3–13] have been employed in order to assess the cerebral death in a precocious and unequivocal way.

However, the validity of all these techniques remains to be determined. The purpose of this study is to compare some of the confirmatory investigations of brain death with clinical criteria in order to achieve the most sensitive and accurate diagnosis of brain death.

Materials and method

Fifteen patients (9 males and 6 females, mean age 49.7 ± 16.9) were studied in this protocol approved by the ethical committee of our hospital (see Table 1 for patients' clinical data). All patients with isolated brain lesions and Glasgow coma scale (GCS) = 3 at admission in intensive care unit or who became 3 on GCS during the hospitalization were included after ruling out hypothermia, metabolic disorders and drug intoxications. They were subjected to neurological examination in order to assess: i) brainstem reflexes (pupillary light, corneal, oculocephalic, spinociliar and oculovestibular reflexes and ii) the apnea test. This test was done as follows: every patient was previously ventilated with 100% oxygen for 15 min and ventilator indices modified to achieve an arterial $PCO_2 > 40$ mmHg. Upon disconnection from the ventilator an O_2 passive endotracheal flow of 6 l/min was maintained. The test was considered positive when no respiratory efforts occurred with an arterial carbon dioxide tension (PCO_2) above 60 mmHg verified with radial artery sampling at 1 min intervals in the following 10 min. When all the above mentioned brainstem reflexes were absent and the apnea test was positive the patient was considered clinically brain-dead, and then, submitted on chronological schedule to the following investigations:

i) Electroencephalogram (EEG);
ii) Transcranial Doppler (TCD);
iii) Cerebral blood flow (CBF) measurements;
iv) Cerebral angiography (CA).

Table 1 Patients' clinical data (*HI* head injury, *ICH* intracranial hemorrhage, *SAH* subarachnoid hemorrhage, *PECE* post-endocarditis cerebral embolia)

No.	Age (year)	Sex	Pathology
1	53	M	HI
2	52	M	ICH
3	41	M	HI
4	78	F	ICH
5	50	M	HI
6	79	F	ICH
7	44	M	ICH
8	43	F	SAH
9	49	M	SAH
10	69	F	SAH
11	34	F	HI
12	23	M	PECE
13	68	F	SAH
14	23	M	HI
15	49	M	HI

All patients were mechanically ventilated with a PCO_2 between 35–40 mmHg (Mean PCO_2 = 37.7 mmHg) and an arterial (radial) oxygen tension (PO_2) above 70 mmHg. The arterial blood pressure was constantly monitored by a radial artery catheter and sustained with infusion of dopamine at dosages between 10–14 μg/kg/min when it fell below 70 mmHg as mean blood pressure. All the patients after admission to the neurosurgical ICU underwent routine antiepileptic treatment with phenobarbital at dosage of 200 mg/day and this therapy was withdrawn when diagnosed clinically brain-dead.

EEG

EEG recordings were performed by 8 channels equipment (ESAOTE Biomedica, Florence, Italy) with a passband filter from 1 to 30 Hz, sensibility of 2 μv/mm and impedance of the electrodes under 10 KOhm. Electrodes were placed according to 10–20 International System and bipolar montage was employed (Left: F3-C3, C3-O1, F7-C3, T5-O1; Right: F4-C4, C4-O2, F8-C4, T6-O2). Each record was done in basal condition for 15 min followed by a second registration of same length after painful stimulation. To minimize environmental artifacts, electrical equipment was turned off and the nursing was suspended until the recording was terminated.

TCD

TCD was performed at the bedside with a 2 MHZ pulsed Doppler (Eden Medical Electronics, Uberlinger, Germany). Signals from the middle cerebral arteries (MCA) were obtained using the transtemporal approach and insonating to a depth of 45–58 mm from the surface. The following two types of TCD waveforms are considered compatible with the condition of cerebral death: i) the "oscillating flow" and ii) the "systolic spikes" [5]. These two types of TCD findings (Fig. 1) have been observed when intracranial pressure raises up to the arterial pressure level, and therefore the cerebral perfusion pressure becomes equal to zero with complete and irreversible cessation of cerebral perfusion.

CBF

CBF was evaluated by a 32 channel Cerebrograph (16 channels for each hemisphere) employing Xenon-133 intravenously injected. For this investigation a dose of 15 mCi of Xenon 133 in 2 cc was injected and gamma activity wash-out was recorded for 11 min after the injection. The initial slope index (ISI) as defined by Risberg [14] was adopted as flow variable since it is more reliable than are compartmental flows in pathological situations as intracranial lesions where shift between the gray and white matter flow may occurs making the two compartments (white and gray matter) not always separable and therefore the flow data unreliable.

CA

It was performed after CBF measurement as soon as possible. The four intracranial vessels (i.e. the two carotids and the two vertebral

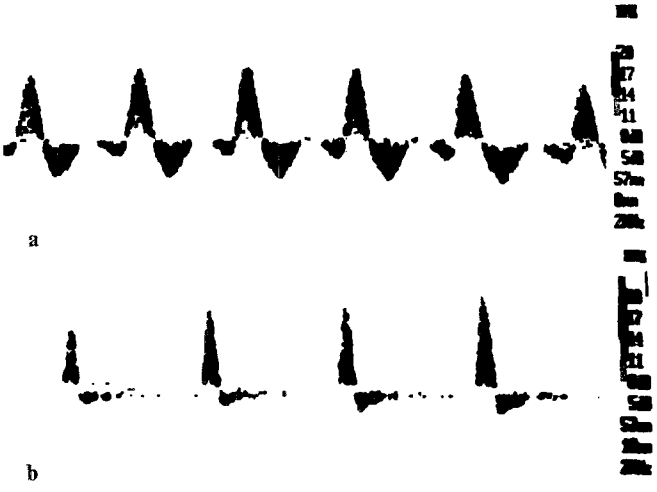

Fig. 1 Transcranial Doppler patterns in brain-dead patients. **a** Systolic peaks followed by retrograde flow during diastole ("oscillating flow"). **b** Sharp peaks at the beginning of the systole without backflow during diastole ("systolic spikes")

arteries) were catheterized by Seldinger's technique from the right femoral artery. Selective catheterisation of each vessel was preferred to the aortic arch angiography since with the last method there is an overlapping of different vessel fields and an optimal visualization of intracranial circulation is not always possible due to slowed circulation time. For the carotid study we employed 12 ml of non ionic contrast media while 8 cc were necessary for the vertebral investigation. The pictures have been detected in a digital way using Politron (Siemens) with a matrix of 1024×1024 with three images per second in the first 4 s followed by one image every second in the following 26 s.

Results

EEG

Eight cases presented electrocerebral silence. The remaining 7 patients showed persistence of low-voltage electrical activity. Two cases showed electrocerebral activity in one hemisphere only; in one of them the presence of such an activity was restricted to the frontal area. In both patients the electrocerebral activity was low-voltage (3–10 μv) monotonous and unreactive beta activity. The remaining five patients presented beta activity (3–10 μv) interposed to theta (7–10 μv) or delta activity (10–15 μv) as in one case. In all patients the electrocerebral activity was diffuse and unreactive (Table 2).

TCD

Nine patients presented the same TCD findings bilaterally; these were compatible with a TCD pattern of brain death in 8 cases (4 showing an "oscillating flow" and 4 "systolic spikes"). In one case a TCD spectra of normal morphology was observed bilaterally in the MCA district. Two patients (# 1, 3) had a TCD compatible with brain death on one side and "no signal" on the other side. The remaining 4 patients (# 5, 6, 9, 13) had "no signal" bilaterally (Table 2).

Table 2 Angiographic, TCD and EEG finding, **C* cervical level, *C2* clinoid process level, *C4* intracavernous level, *C5* intrapetrous level, *ss* subarachnoid arterial segments (A1, M1 and P1), ***TCD* transcranial Doppler, *MCA* middle cerebral artery, *os* oscillating flow, *ss* systolic spikes, ****EEG* electroencephalogram, + electrical activity, – no activity)

Angiographic arrest level*		TCD**		EEG***
Carotid artery		MCA		
Right	Left	Right	Left	
C2	C4	ss	ss	+
C5	C5	ss	ss	–
C4	C4	of	of	–
C2	C2	of	of	–
C	C	ns	ns	+
C	C	ns	ns	–
C5	C5	ss	ss	+
C2	C2	ss	ss	+
C	C	ns	ns	–
C4	C4	of	of	–
C4	C4	ss	ss	–
C4	C4	of	of	–
C4	C	ns	ns	+
C2	C2	of	of	+
SS	SS	nf	nf	+

CBF

On 32 examinations, all the patients showed a characteristic output of the desaturation curves. In fact, after a short initial spike following the injection of gamma-tracer, the head curves showed a "plateau" lasting through the whole investigation showing no tendency to zero as had been seen in patients with preserved cerebral circulation (Fig. 2). All the curves required monoexponential solutions and the peak counts were never above 1000 (a value observed in the tail part of head curves deriving from healthy subjects) making estimation of quantitative rCBF of no significance.

CA

At the angiography the stop point of contrast medium in 13 patients was at the same level in the internal carotid arteries and at a different level in the remaining 2 other cases. In one patient with MCA flow at TCD an opacity of middle cerebral arteries stem (M1 segment) and initial

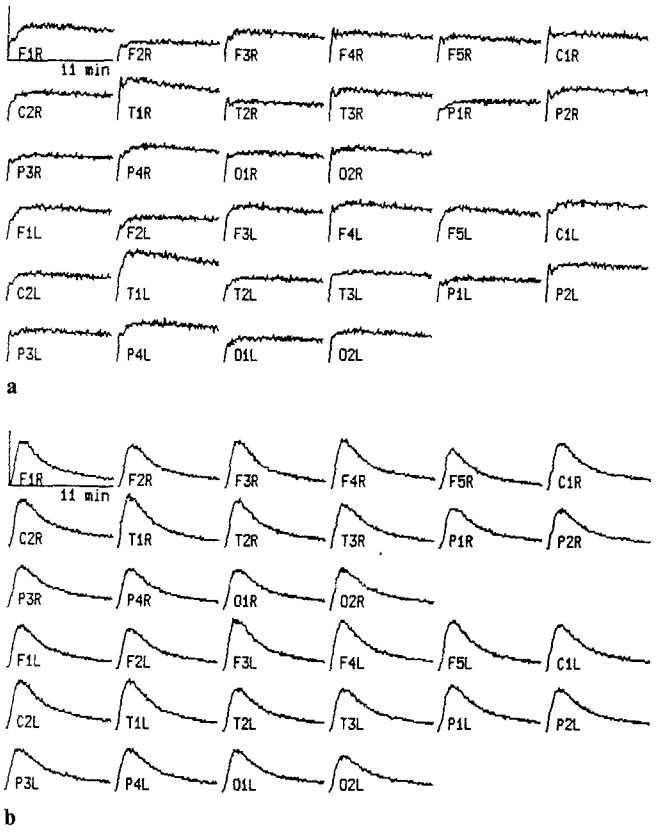

Fig. 2 **a** Xenon clearance curves for a brain-dead patient. **b** Xenon clearance curves for a patient with preserved cerebral circulation. *Note:* The number (11 min) under the first of the 32 head curves indicates the duration of the examination; *F* indicates frontal probes, *C* central (pararolandic), *T* temporal, *P* parietal and *O* occipital; *R* and *L* stand for right and left, respectively

tract of anterior and posterior cerebral arteries (A1, P1 segments) was detected without any evidence of venous drainage after 30 s from injection. In the vertebral arteries the stop was situated between C1–C3 on all cases (Table 2).

Discussion

There is no single definition of brain death. In fact, there are two main current opinions: one identifies cerebral death with brain stem death while the other correlates brain death with loss of any cortical activity and therefore the death of the whole brain. The actual legislations in Western countries reflect these two opinions; one requires only clinical criteria while the other always requires an isoelectric EEG as confirmatory test. Another important concept is that brain death is always associated to the absence of intracranial circulation [15–17]. From a practical point of view, the most important question is how the diagnosis of brain death can be made. The first criterion is certainly the clinical examination proving the absence of cortical and brain stem function. Any other criteria used are based upon neuroradiological or neurophysiological tests. The clinical examination, in our patients, appeared to be sensitive and specific enough to avoid any false-positive and/or false-negative, respectively. We also consider, as already sustained by others [18, 19] that brain death is clinically ascertained when a critical number of neurons have been damaged such as to cause an irreversible loss of all the integrative neuronal capacities. The loss of these capacities does not necessarily imply the death of all neurons, therefore the diagnosis of brain death based only on clinical criteria could in some cases preceed the same diagnosis carried out by the confirmatory investigations. The other test that, in our experience, resulted extremely accurate and has guided us in a confirmatory fashion to support the clinical diagnosis of brain death, was cerebral angiography (sensitivity of 100%). The fact that this test can visually show the absence of cerebral circulation constitutes a fundamental reason to be considered the most important "instrumental" test. The angiographic filling of basal subarachnoid segments without subsequent venous enhancement after 30 s, as seen in the patient no. 15, is considered an expression of intracranial circulatory arrest. This finding termed by Kricheff et al. [16] subarachnoid "stasis filling", has been reported as angiographic finding in 10 out of 65 clinically brain-dead patients by Hassler et al. [5]. Cerebral AGF is considered sensitive enough to be recommended as the ancillary confirmatory procedure when clinical criteria have not been met or when an early diagnosis of cerebral death is required [20]. The absence of cerebral circulation ascertained by angiography allows in some countries, such as Norway, to prove cerebral death diagnosis thereby abolishing the delay before organ removal. Unfortunately, cerebral angiography presents some drawbacks that make it almost unapplicable in the clinical practice. The cost is high because of the need of a specialized personnel and technology; the patients need to be transported out of the ICU with major medical risks; finally, the use of contrast media can be detrimental for the already compromised patient organs, such as kidneys. Because of such limitations a multiinstitutional protocol could be recommended in order to establish methodological criteria, advantages and disadvantages of cerebral angiography in diagnosis of brain death. At any rate the search of other equally accurate techniques capable of substituting the cerebral angiography is a great need.

In our study EEG was planned because it is a requisite of Italian law for diagnosis of brain death. In the series of patients here presented electrocerebral silence was observed in eight patients only, determining a low sensitivity (53.3%) of this examination in the diagnosis of brain death. The remaining seven patients presenting electrocerebral activity fulfilled the clinical criteria of brain

death and showed an absence of cerebral blood flow at the angiographic study. It is not possible to rule out that the electroencephalographic activity when only of minimal low-voltage could be artifactual in origin owing to interference of the electrical environment or muscles activity [21, 22]. In fact, many unsatisfactory recordings do not allow to establish with certainty if an EEG is isoelectric or not in a percentage between 6% to 20% [20, 23, 25]. Nevertheless all the seven patients with EEG activity after clinically determined brain death underwent daily EEG recordings till death. The EEG became isoelectric within 48 h following diagnosis of brain death in one patient who subsequently underwent surgery for organ removal. The remaining six patients died at different times due to cardiac arrest but all with EEG activity still present. Three patients died within 24 h after diagnosis of brain death, 1 patient 48 h after, 1 patient 4 days after and 1 patient 1 week after. The fact that in these same patients cerebral angiography demonstrated absent flow is a striking dissociation already reported in literature both in adults [26] and children [24]. The reason for the lack of correlation between the EEG and cerebral blood flow is unknown. In these patients the cardiac function and blood pressure are usually sustained with drugs and therefore the circulation in the external carotid artery is almost preserved. From this through leptomeningeal collaterals some cerebral perfusion, beyond the resolution of angiography, may persist and perfuse the cortical areas responsible for the EEG activity recorded after clinical diagnosis. Gaches et al. [27] in their sample of 71 cases of coma depasse' observed that residual low-voltage activity was common after structural brain disease but never persisted beyond 48 h. But two cases of our series showed an EEG activity lasting more than 48 h after the clinical diagnosis. These findings confirm the literature reports where an EEG showing electrocerebral activity persisting up to 14 days after brain death had been diagnosed [24, 28]. Therefore it seems that while the presence of electrocerebral activity in the clinically brain-dead patients does not change the outcome, the EEG, on the basis of the literature and our data, does not seem to be the most sensitive confirmatory examination.

TCD is another recently introduced technique, and is widely employed to make diagnosis of brain death [5–10]. In our series the sensitivity of TCD as one time test has been low (60%) and this is due to the fact that TCD signal was unobtainable bilaterally in 4 patients and monolaterally in two. The "no signal" finding might be due to lack of temporal window, displacement of the cerebral vessels, absence of cerebral circulation and probably also to the particular setting in which the investigation is carried out. In fact the ICU presents objective problems for all operators concerning the position of the patient, the presence of other apparatus connected to the patient, which altogether make the recording of the signals difficult. However the "no signal" cannot be considered an expression of circulatory arrest unless confirmed by cerebral angiography or be the end point of a deteriorating intracranial hemodynamics in patients submitted to serial TCD investigations. As regards the patient in which the TCD showed a preserved flow in both districts, it must be underlined that this patient was the particular case (# 15) where the initial segments of the basal arteries were visualized by angiography. This false negative finding as those described by Zurinsky et al. [9] does not question the clinical diagnosis of brain death but stresses how, as the vessels at the base of the skull are patent, it is possible to find a TCD spectra not consistent with brain death by insonating the MCA district. In our series the TCD pattern of "oscillating flow" and "systolic spikes" were supported by the cerebral angiography findings confirmatory of cerebral circulatory arrest. However, these TCD signals should be detected in more than 1 artery to be considered confirmatory of brain death without any other supportive test [10].

The last neurophysiological test we have used to establish the diagnosis of brain death is the CBF measurement. The determination of CBF by external detectors is not able to detect the presence of flow in the deep cerebral structures and in the brainstem and this is the reason why this method has never been used for diagnosing brain death. Nevertheless this technique in our study presented a sensitivity comparable to the clinical examination and to angiography. The characteristic "plateau" pattern of the curves is due to very slow xenon clearance in the extracranial circulation as demonstrated by the angiography. Analogous head curves were reported by others [29–31] in patients following severe head injuries with impending or actual brain death. The brief initial spike seen in some curves is a typical artifact of these examinations. The most probable interpretation is that these counts are filling the airway and are seen especially by probes oriented vertically. However, fast components of flow in the superficial circulation could account for this artifact, as recognized by Hadjidimos et al. [29] with the intracarotid injection method.

Our study suggests that the most reliable predictors in the diagnosis of brain death are: i) an accurate neurological evaluation showing neither cortical and brain stem activity nor spontaneous breathing; ii) cerebral angiography which is the most reliable confirmatory test to demonstrate the absence of cerebral circulation, which is aspected as synonym of cerebral death. However, this test is invasive, requests the presence of a skilled radiological team, and often requires to move a critical patient; iii) TCD in clinically brain-dead patients can have a substituting role to the angiography in confirming the absence of cerebral circulation in cases where the signals have "oscillating flow" or "systolic spikes" patterns; iv) CBF is as predictive as clinical evaluation and angiography when the head curves show the typical "plateau". Moreover, in this investigation only the inspective analysis of the

curves is sufficient to establish the absence of cerebral blood flow; v) the role of EEG remains to be determined because of the presence of electrocerebral activity even after the clinical diagnosis.

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