Transcranial Doppler Ultrasonography in the Assessment of Cerebral Circulation Arrest: Improving Sensitivity by Trancervical and Transorbital Carotid Insonation and Serial Examinations

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Abstract

Introduction Transcranial Doppler (TCD) can detect the cerebral circulation arrest (CCA) in brain death. TCD is highly specific, but less sensitive because of false-negatives accounting for up to 10%. The aim of the study was to explore the diagnostic accuracy of TCD and to determine whether it can be augmented by strategies such as the insonation of the extracranial internal carotid artery (ICA) and sequential examinations.

Methods Data of 184 patients, who met clinical criteria of brain death, observed from 1998 through 2006, were retrospectively reviewed. The study of cerebral arteries was performed through the transtemporal approach, suboccipital insonation of the vertebro-basilar system, transorbital insonation of the ICA and ophthalmic artery, and transcervical insonation of the extracranial ICA. Repeated exams were performed in cases of persistent diastolic flow.

Results The specificity of the testing was 100%, no false-positive cases were recorded. The sensitivity of conventional TCD examination was 82.1%. The insonation of the extracranial ICA increased sensitivity to 88% allowing the detection of CCA in those patients lacking temporal windows; serial examinations further increased sensitivity to 95.6%.

Conclusions The addition of insonation of the cervical ICA and of the siphon increased sensitivity of TCD. Nevertheless, a CCA flow patterns may appear later on those segments. Serial examinations, may be needed in those cases.

Keywords Transcranial Doppler ultrasonography · Cerebral circulatory arrest · Brain death · Specificity and sensitivity

Abbreviations

TCD	Transcranial Doppler
CCA	Cerebral circulation arrest
ICA	Internal carotid artery
CBF	Cerebral blood flow
HMPAO	Hexamethylpropyleneaminoxime
MCA	Middle cerebral artery
ACA	Anterior cerebral artery
BA	Basilar artery
ICP	Intracranial pressure
SPECT	Single photon emission computed tomography
ABP	Arterial blood pressure
CPP	Cerebral perfusion pressure

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Introduction

The condition defined as "brain death" is a neurologic condition engendered by technological advances of

contemporary medicine that allow to maintain the integrity of the cardiopulmonary system in patients with loss of every brain function. In many countries, physicians practice guidelines are available for the determination of brain death [1]. Those guidelines all specify a prerequisite (a known cause of persistent, irreversible, and totally unresponsive comatose state), and comprises a differential-diagnosis process to exclude states that may mimic brain death (hypothermia, metabolic disorders, drugs, neurologic diseases). Clinical criteria include: absent motor response, absent brainstem reflexes, and apnea testing, using a PCO_2 target [1–6].

Nevertheless, there are circumstances in which clinical criteria cannot be reliably applied, e.g., when cranial nerves cannot be adequately examined, neuromuscular paralysis or heavy sedation is present, or in some patients for whom the apnea test is precluded (respiratory instability or high cervical spine injury). In these situations, ancillary tests may support the diagnosis. Truly confirmatory ancillary tests for brain death should meet the following criteria: (1) There should be no "false positives", i.e., when the test confirms "brain death," there should be none who recover or who have the potential to recover. (2) The test should be sufficient on its own to establish that brain death is or is not present. (3) The test should not be susceptible to "confounders" such as drug effects or metabolic disturbances. (4) The test should be standardized in technology, technique, and classification of results. (5) The test should be available, safe, and readily applied [7].

Though a laboratory support to the clinical diagnosis can be valuable, a delay in the diagnosis of brain death can affect the quality of organs, or make them unsuitable to be transplanted by permitting the occurrence of events such as multiple organ failure of cardiac arrest. For this reason, ancillary tests should meet another criterion: they should not cause the delay of diagnosis.

Only 28 out of 70 (40%) national practice guidelines, actually, mandate confirmatory testing in patients who meet the neurological standards [1]. Those tests evaluate the electric activity of the brain, the cerebral metabolism or the cerebral blood flow (CBF). Testing modalities which demonstrate the absence of blood flow to the brain meet the above mentioned criteria. Among those tests, four-vessel contrast angiography remains the most reliable, but the method is invasive, expensive, and requires transporting critically ill patients. Radioisotope techniques are equally costly and require the use of radiopharmaceutical agents and cumbersome equipment.

Ultrasounds represent a relatively simple, non-invasive diagnostic tool to repeatedly determine the status of cerebral circulation. In many countries, transcranial Doppler (TCD) has been recommended by medical councils as one

of the methods, which can shorten the waiting time for fulfilling the criteria for diagnosis of cerebral death. The TCD turned out to be highly specific but not completely sensitive in detecting cerebral circulation arrest (CCA) [8]. In fact, when no signal is detected through the temporal window, it is impossible to distinguish a CCA detected in later stage from the absence of ultrasonic windows. Furthermore true false-negative cases, namely, patients in whom CBF persists despite cessation of brain activities, account for up to 10% of cases.

The aim of this study was to determine whether the diagnostic accuracy of TCD, in the standard approach, can be improved by the transcervical and transorbital study of the internal carotid artery (ICA) and by serial examinations.

Clinical Materials and Methods

Data concerning 184 patients admitted at the University Hospital of Messina during a nine-year period (1998–2006) were retrospectively reviewed. The patients aged from 3 months to 84 years (mean 52 ± 18 years). All the patients underwent TCD study before being officially declared dead according to criteria set by the Italian Medical Council and established by the Italian law.

Transcranial Doppler Study

The TCD examinations were performed (by AC, DGI, and MG) according to the method described by Aaslid et al. [9] using pulse-waved and range-gated TCD devices with a 2-MHz transmission frequency probe and fast Fourier frequency analysis (EME TC2000-S, Überlingen, Germany, and Explorer CVS, Perols, France, respectively). Routine procedure consisted of transtemporal detection of the middle cerebral artery (MCA) at a 45–60-mm depth, ICA (C6–C7 segments) at a 55–70-mm depth, and the anterior cerebral artery (ACA) at a 65–75-mm depth on both sides. The basilar artery (BA) was studied through a suboccipital approach at a depth of 75–90 mm. In all the patients, the study was completed with a transorbital study of the ICA siphon (C4–C6 segments) and ophthalmic artery (Fig. 1). Also, the examination of the extracranial ICA was added using both a 2- and 4-MHz pulsed Doppler probes. The extracranial ICA was insonated through a submandibular approach with beams directed slightly medially and posterior to the longitudinal axis of the body where the ICA could be tracked at depth of 40–65 mm. This allowed the insonation of the ICA from the carotid bifurcation to the origin of the petrosal segment (C1 segment). Whenever multiple examinations were needed, the same operator performed all the studies.
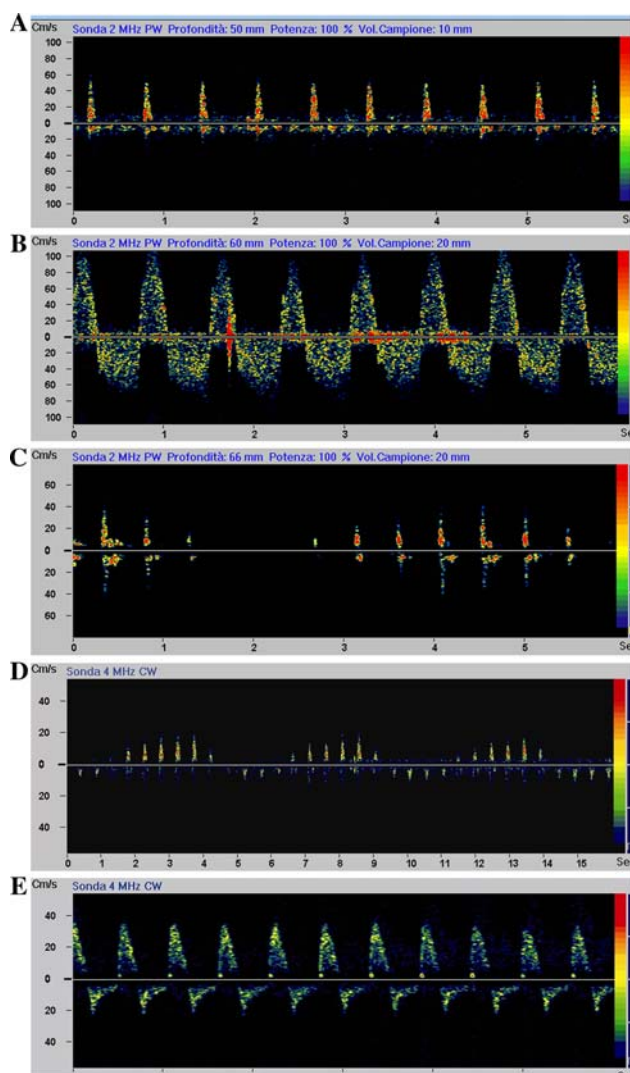
Fig. 1 a Insonation of the middle cerebral artery through the temporal window. The initial stage of cerebral circulation arrest has a typical pattern characterized by systolic peaks without diastolic spectrum. b As intracranial pressure increases, the small vessels collapse. In such a situation, a small degree of antegrade blood flow during systole is allowed: however, since forward flow is negated, blood reverberates backward. This produces a characteristic oscillating flow velocity wave form on TCD evaluation described as "To and Fro" movement. c The following stage is represented by the appearance of the "systolic spikes" characterized by sharp, narrow peaks at the beginning of the systole due to a short vibration of the vessel. Flow velocity during the rest of the cardiac cycle is zero. The systolic TCD spikes show a typical respiration-dependent fluctuation in amplitude. d Ophthalmic artery insonation through the orbital window. The basal arteries of cerebral circulation are still patent in the early stage, and blood may shunt into the extracranial vessels trough collaterals such as the ophthalmic arteries. Note the respiration-dependent change of flow direction indicating the patency of the collateral pathway and the correlation of flow with the respiration-dependent change of intracranial pressure. e Cervical insonation of the extracranial internal carotid artery (ICA). The final stage of cerebral circulation arrest is characterized by disappearance of diastolic flow in the extracranial segment of the ICA and tendency to evolve toward the oscillating flow

Clinical Criteria

The TCD study preceded other confirmatory studies and the official clinical evaluation for the declaration of brain death. During the procedure of brain death assessment, each operator was blinded to the results of the others. At the end, a medical college was devoted to collect and evaluate results from each testing before declaring the death.

Clinical and instrumental criteria set by Italian medical college to declare the death and used in this series were: (a) absence of brain stem reflexes and oculovestibular responses; (b) absence of motor responses following painful stimuli in trigeminal areas; (c) absence of oropharyngeal and respiratory reflexes, and apnea (with a Pa-CO$_2$ >60 mmHg); (d) flat EEG (three recordings, each lasting at least 30 min, at the beginning, in the middle, and at the end of the period of observation); (e) observation lasting 6 h in adults, 12 h in children below 5 years of age, and 24 h in newborns, and infants under 1 year of age; (f) demonstration of cerebral circulatory arrest in infants below 1 year of age. Also, all the included patients fulfilled the following pre-requisites: (1) the cause of coma was established and was sufficient to account for a permanent and irreversible loss of brain functions; (2) other conditions such as intoxication, hypothermia, severe arterial hypotension, metabolic disorders have been excluded; (3) clinical evidence of brain function loss was assessed by at least two experienced examiners.

According to the national guidelines for the determination of brain death, established in 1994, the study of CBF is compulsory in the following conditions: (1) infants below 1 year of age; (2) presence of factors that may interfere with the clinical picture (intoxication, hypothermia, neuromuscular paralysis, metabolic disorders not readily reversed); (3) uncertain etiology, or clinical situations preventing from an adequate exploration of brainstem reflexes (orbital or middle and inner ears trauma, cranial neuropathies). Precise criteria for the use of TCD were established in 2003 by a working group of the National Commission for Transplant. Accordingly, up to 2003, in all the patients in whom a study of flow was needed, alternative flow studies to supplement TCD findings were performed. Four-vessel cerebral angiography was performed in 39 cases (21%), and [99m]TC HMPAO-Single Photon Emission Computed Tomography (SPECT) in 53 patients (29%). Patients were examined in the absence of hypothermia, circulatory shock or metabolic disorders. Intoxication was ruled out by history, or in doubtful cases by appropriate urinary and blood analysis. Arterial blood pressure (ABP) and ventilation parameters were taken into account during TCD examination with mean ABP's extremes ranging between 70 and 100 mmHg.

Results

Clinical Data

All the patients underwent brain computerized tomography (CT). Intracranial pressure (ICP) was monitored in 64 of them (35%). Evidence of raised ICP was furnished either by CT alone or by CT and ICP monitoring. The causes of death were: traumatic brain injury (83 patients, 45%), subarachnoid hemorrhage (32 patients, 17%), non-traumatic intracerebral hematoma (29 patients, 16%), ischemic stroke (13 patients, 7%), anoxic encephalopathy (11 patients, 6%), brain tumor (8 patients, 4%), other causes (8 patients, 4%). Sixty-nine patients (37%) had craniotomy. Ten patients (5%) had a decompressive craniectomy. Twenty-eight patients (15%) had an external ventricular drainage.

Transcranial Doppler

Data on TCD examination are summarized in the diagram in Fig. 2. In 165 patients (90%), a flow signal could be detected through the temporal windows at the time of the first examination. In the remaining 19 patients (10%), no signal was detected by transtemporal approach mono- or bilaterally.

(A) In 101 patients (55%), a typical oscillating flow pattern was detected bilaterally on the MCAs, ICAs, and on the basilar artery. This pattern was a brief sharply contoured systolic envelope with reversal of flow during diastole. Antegrade flow occupied 15–50% of the cardiac cycle. Systolic orthograde flow velocity ranged from 7 to 65 cm/s (mean 28 cm/s). Diastolic retrograde flow occupied 50–85% of the cardiac cycle with a systolic flow velocity that ranged between 5 and 30 cm/s (mean 20 cm/s).

(B) In 41 patients (22%), systolic spikes were recorded on one side and oscillating flow in the contralateral side or on the BA.

(C) In nine patients (5%), TCD showed a pattern characterized by systolic spikes recorded bilaterally on the MCAs and ICAs. The flow pattern was represented by the presence of sharp narrow peak at the beginning of the systole, with no flow in the rest of the cardiac cycle. The velocity ranged from 13 cm/s to 45 cm/s (mean 26 cm/s).

(D) In 14 cases (8%), a persistent diastolic flow was recorded on intracranial vessels despite clinical evidence of brain death. Twelve of those patients had undergone surgical procedure: craniectomy (4 patients), craniotomy (5 patients), a ventriculostomy (3 patients). The remaining two patients had a large skull defect due to fractures of the cranial vault. By performing serial examinations, the persistent flow signal changed into a typical CCA pattern in 10 cases. The remaining four cases were regarded as true false-negatives. One of such cases is described below.

Transcervical and Transorbital Carotid Study and Serial Examinations

The addition of the study of extracranial ICA and carotid siphon in the 165 patients with detectable intracranial sonographic signal, a persistent diastolic flow was present in 37 patients (20%). In particular, TCD showed the presence of diastolic flow on the ICA through the temporal windows in 14 patients (7.6%), a residual diastolic flow attributable to the ICA siphon was detected in 15 patients (8%) through the transorbital window. A diastolic flow was present at the level of one or both ICAs at cervical level in all the 37 patients. In the remaining cases (80%), the study of the ICA showed an oscillating flow along the entire course. We noticed that characteristics of diastolic flow were correlated

Fig. 2 Diagram summarizing results of the study. Abbreviations: CCA: cerebral circulation arrest; eICA: extracranial internal carotid artery
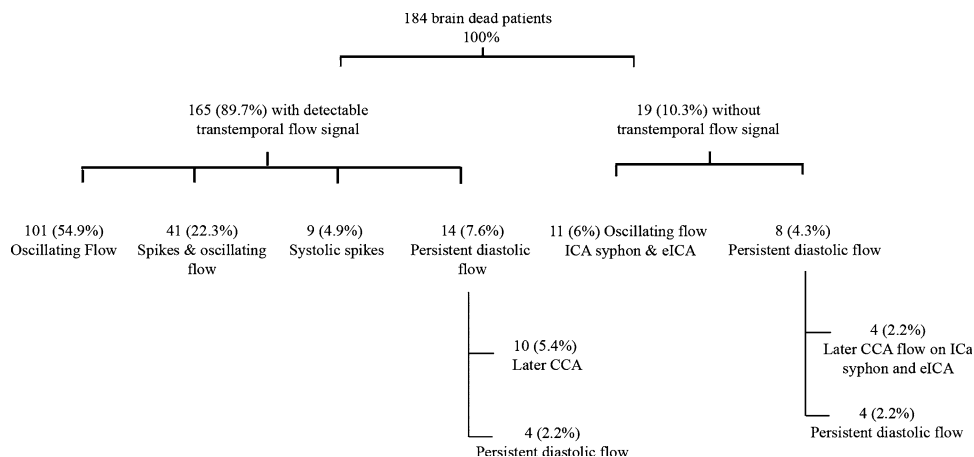
to the intracranial flow pattern and to the rate of ophthalmic collateralization.

In patients in whom no signal was detected through the temporal windows (19 out of 184, 10%), transcervical and transorbital insonation of the ICA revealed the presence of a bilateral oscillating flow in 11 out of 19 patients. In the remaining eight patients, a clear diastolic flow was still present on one side in four and bilaterally in four cases. Serial examinations showed the progressive disappearance of the diastolic component in four further cases, particularly in those with monolateral oscillating flow.

Specificity and Sensitivity

All the patients presenting a TCD pattern of cerebral circulation arrest turned out to fulfil clinical and EEG criteria of brain death; alternative flow studies, performed in 50% of cases, confirmed the status of CCA. No false-positive case was recorded. Accordingly, the specificity of the TCD examination was 100%. Table 1 summarizes data on sensitivity. The TCD detected a CCA flow pattern in 151 patients out of 184 brain dead patients using the standard approach (82.1%). In 19 out of 184 cases (10.3%), no signal was detectable through the conventional transtemporal approach. In 14 out of 184 cases (7.6%), a persistent diastolic flow was recorded on the intracranial vessels despite clinical and EEG evidence of brain death. Accordingly, sensitivity of the standard examination was 82.1% (151/184 Pts.) with 10.3% of undiagnosed patients, due to the lack of temporal windows, and the remaining 7.6% of false-negatives.

The transcervical and transorbital study of the ICA enabled the identification of a pattern of circulation arrest, at this level, in further 11 patients lacking temporal windows. This increased the sensitivity up to 88% (162/184 Pts.). Follow-up serial examinations allowed the detection of a circulation arrest in further 10 out of 14 patients with persistent intracranial flow, and by studying the extracranial ICA, in further four out of eight patients with previously persistent flow (Fig. 2). According to those

data, final sensitivity was 95.6% (165 patients with evidence of circulation arrest out of 184 brain dead patients).

Illustrative Case 1

In February 2005, a 74-year-old man was admitted because of diffuse cerebellar and brainstem non-traumatic hematoma. The patient was unresponsive and without brainstem reflexes on admission. The patient underwent posterior fossa surgery. Nevertheless, after surgery the CT scan showed diffuse brainstem ischemic damage (Fig. 3a). The TCD examination performed 12 h after admission showed waveforms with normal flow velocity and pulsatility parameters in the ICA, MCA bilaterally, while TCD examination of BA revealed the presence of reverberating flow (Fig. 3b). Only 3 days, later the patient fulfilled instrumental criteria for brain death with evidence of circulation arrest on supratentorial arteries (Fig. 3c) and isoelectric EEG activity.
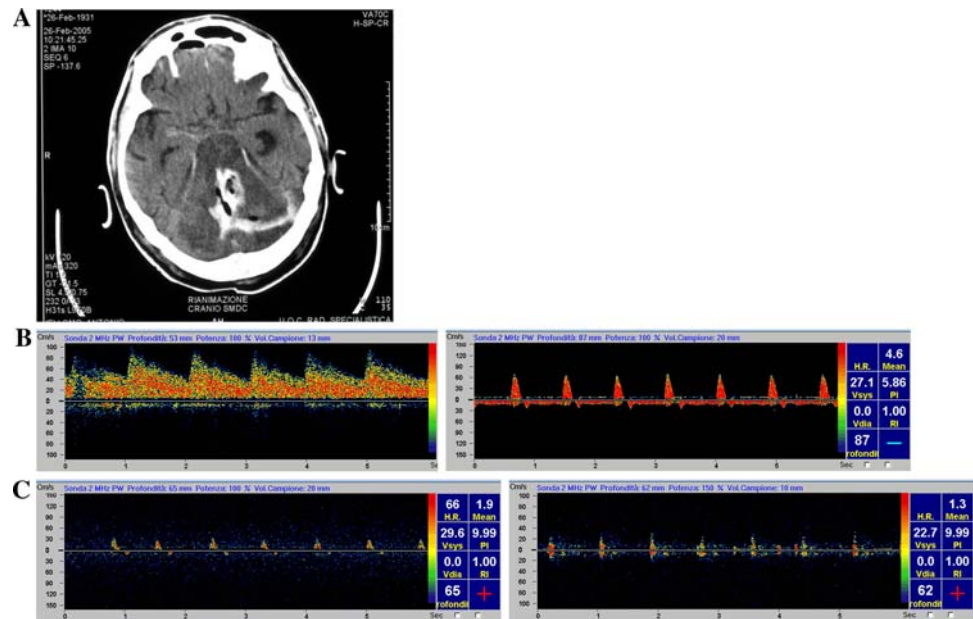
Illustrative Case 2

In May 2002, an 18-year-old woman was admitted to our department because of traumatic brain injury with diffuse axonal injury and a left-sided temporal epidural hematoma (Fig. 4a). Neurological examination showed a Glasgow coma score of 3, non-reagent midriasis, and absence of spinal reflexes. The patient was apnoeic and mechanically ventilated. The TCD showed a CCA pattern on MCAs, ICAs, and BA (Fig. 4b). The patient underwent surgical removal of the clot through a large fronto-temporal craniotomy. In order to achieve more space for the swollen brain, the bone flap was not repositioned. After the surgical treatment, a different flow pattern with a diastolic flow recovery was recorded bilaterally (Fig. 4c). Nevertheless, the neurologic status of the patients remained unchanged. The TCD was repeatedly performed in the following days, showing a progressively reduced, but persistent diastolic flow (Fig. 4d). On day 3 post-injury, the patient underwent radioisotope examination which showed a condition of CCA (Fig. 4e), and the death was declared.

Table 1 Summary of data on sensitivity of TCD

	CCA/Brain dead pts. (Sensitivity %)	No signal/Brain dead pts. (Lack of temporal window %)	Persistent Flow/Brain dead pts. (False-negatives %)	Total
Standard approach	151/184 (82.1%)	19/184 (10.3%)	14/184 (7.6%)	184 (100%)
Transcervical and transorbital ICA insonation	162/184 (88%)	–	22/184 (12%)	184 (100%)
Repeated TCD	176/184 (95.6%)	–	8/184 (4.4%)	184 (100%)

CCA Cerebral Circulation Arrest, ICA Internal Carotid Artery, TCD Transcranial Doppler

Discussion

After a brain injury causes total neuronal death, the physiologic cerebral circulation is progressively transformed into a high resistance and low-flow system, a process that culminates with the arrest of the CBF. The TCD is a valuable diagnostic tool in detecting those changes, its application in this field dates back to the late 80s, and the advantages of its use are widely recognized [10–15] (Fig. 1).

Nevertheless, the diagnostic accuracy of this technique still needs to be definitively determined. As regards the specificity, in most series the TCD was 100% specific in diagnosing the CCA (Table 2). Nevertheless, 12 false-positives have been reported to date [13–24]. Specifically, Kirkham et al. [18] and Newell et al. [13] reported a preserved weak spontaneous respiration for a short period of time (∼1 h) in patients with TCD evidence of CCA. In neither of those studies, the cases were regarded as false-positives by those authors, because the signs of circulatory arrest proved to be irreversible, and the patients soon became apnoeic. In fact, those and most of the other reported cases cannot be considered as true false-positives when currently accepted criteria to define the cerebral circulation arrest are applied. In only two of those 12 cases, actually, both the anterior and posterior circulation were studied [25]. In a study by Hadani and others [17] a patient with CCA demonstrated weak respiration, but brain death occurred few hours later. Van Velthoven et al. [14] reported a clinically brain dead patient with CCA, confirmed by angiography, in whom EEG became iso-electric only several hours later. Accordingly, to date none of patients with TCD evidence of circulation arrest survived

for a clinically relevant interval of time. Our study confirms this high specificity.

On the other hand, the sensitivity did not reach the 100% in most series (Table 2). In ours and other series, the sensitivity of TCD was limited by several factors, the failure of the temporal window to permit the insonation of cerebral arteries being the most frequent. This phenomenon is usually due to the coexistence of several factors: a weak sonographic signal due to low blood flow velocity; a small window, which is more frequent in elderly patients; a surgical wound in the temporal region. The other source of reduced sensitivity was represented by the presence of patients with persistent CBF, despite the clinical evidence of whole-brain death. Those cases, regarded as true false-negatives, are commonly associated with the presence of large craniotomies, bone defects, such as decompressive craniectomies or skull fractures, or external ventricular drainages. These conditions, in fact, may interfere with the mechanism of ICP rising and fall of cerebral perfusion pressure that characterizes the death of the brain, thus preventing from the arrest of cerebral circulation. In this setting, it is also possible for a recovery from CCA without changes of the clinical status. This phenomenon was described in cases of subarachnoid hemorrhage, where the transitory flow arrest is a consequence of an abrupt rise of the ICP [19, 21, 22]. We observed a case of recovery from CCA occurring after a decompressive craniectomy, and the details were reported in the illustrative case 2. The case described is worthy of note also because we recorded a discrepancy between the TCD and the radioisotope study performed on the same day. In fact, TCD showed a persistent diastolic flow whereas the ^{99m}Tc-HMPAO SPECT showed an "empty skull" (Fig. 4). This can be explained

Fig. 4 Illustrative case 2. **a** CT scan showing diffuse axonal injury, absent basal cisterns, and a left-sided temporal epidural hematoma. **b** Bilateral reverberating flow on MCA recorded before surgical treatment. **c** After a large left-sided fronto-temporal craniectomy, a new TCD examination was performed showing the recovery of diastolic flow. **d** TCD was repeatedly performed in the following days showing the progressive reduction of the diastolic flow, but no absent or negative diastolic flow re-appeared. **e** Three days later, the patient underwent [99m]TC HMPAO-Single Photon Emission Computed Tomography which showed a condition of CCA; the death was declared
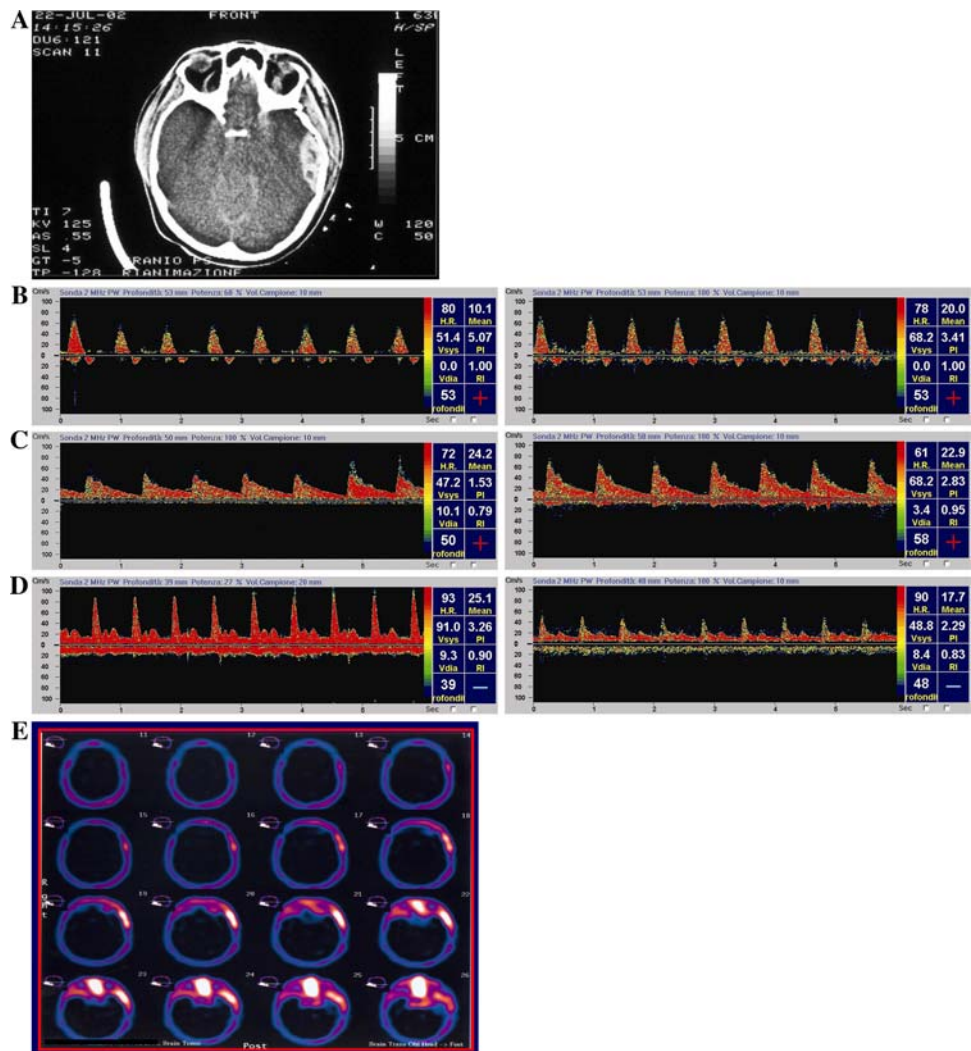
considering that ^{99m}Tc-HMPAO penetrates into the brain parenchyma in proportion to regional blood flow, but its cerebral uptake requires the persistence of viable brain. Accordingly, in particular circumstances, TCD may show the persistence of arterial circulation in brain dead patients, whereas ^{99m}Tc-HMPAO SPECT may demonstrate, in those same patients, the absence of brain perfusion. Accordingly, in patients who underwent decompressive craniectomies or ventriculostomies, it is advisable to use other tests to confirm the clinical diagnosis of BD. This holds true also for children below the age of 1 year who, because of immature skull, may present similar problems and in whom key Doppler alterations, such as absent or retrograde flow during diastole, are not uniquely associated with the diagnosis of brain death, particularly in the setting of congenital heart disease [26].

Another cause of persistent flow in patients with absence of brainstem activity is the dissociation between the carotid and the vertebro-basilar circulation [27]. As observed in a patient of this series (illustrative case 1), this is a

consequence of a primary injury to the brainstem. Nonetheless, similar cases can be regarded as false-negatives only if a brainstem formulation of death is applied. In most Western Countries, including Italy, a whole-brain formulation of brain death is adopted, and death is defined by the irreversible cessation of all functions of the entire brain. The TCD may assist the differential diagnosis between whole-brain death and brainstem death.

The question thus arises whether there are technical strategies that may increase sensitivity of the examination. It has been demonstrated that the insonation of the ICA at the level of the siphon and at the extracranial level, through transorbital and cervical insonation, may show a sonographic pattern of circulatory arrest [39, 40]. This gives evidence for the absence of flow in the whole anterior cerebral circulation, even in case of lack of temporal windows. Even though this concept is theoretically correct, the sensitivity of transorbital or cervical insonation of the ICA in the detection of CCA still needs to be determined. In this series, the CCA was diagnosed in 82.1% of patients

Table 2 Specificity and sensitivity of the TCD test for diagnosis of brain death in various studies

Ref. No.	Authors	Year	No. of Brain dead pts	Specificity (%)	Sensitivity (%)	Arteries examined
[10]	Ropper et al.	1987	24	100	100	MCA, ICA
[18]	Kirkham et al.	1987	13	100	92.3	MCA
[14]	Van Velthoven et al.	1988	29	96.6	89.7	MCA, ICA, VBA
[16]	Powers et al.	1989	18	100	94.5	MCA
[13]	Newell et al.	1989	12	100	90.9	MCA
[8]	Petty et al.	1990	25	100	91.3	MCA, VBA
[41]	Zurynski et al.	1991	111	100	87.4	MCA
[31]	Davalos et al.	1993	13	100	92	MCA, ICA, VBA
[27]	Feri et al.	1994	22	100	81.8	MCA
[32]	Dominguez–Roldan et al.	1995	26	100	84.6	MCA
[20]	Paolin et al.	1995	15	100	53.3	MCA
[15]	Ducrocq et al.	1998	135	100	91.1	MCA, ICA
[17]	Hadani et al.	1999	83	98.8	96.4	MCA, ICA, VBA
[33]	Azevedo et al.	2000	22	100	90.9	MCA, ICA, VBA
[34]	Nebra et al.	2001	25	100		MCA, ICA
[35]	Lample et al.	2002	57	100	78.9	MCA, ICA, VBA
[36]	Dosemeci et al.	2004	61	100	70.5 & 100*	MCA, ICA
[37]	Kuo et al.	2006	44	100	77.2 (MCA) 86.4 (VBA)	MCA, VBA
[28]	De Freitas et al.	2006	270	100	75.5	MCA, ICA, VBA
[38]	Poularas et al.	2006	40	100	87.5 & 100*	MCA, ICA, VBA
Present	Conti et al.	2009	184	100	95.6*	MCA, ICA, VBA, eICA

* After serial examinations

MCA middle cerebral artery, *VBA* vertebro-basilar arterial system, *eICA* extracranial internal carotid artery

using the standard transtemporal and suboccipital approach, that is apparently lower than 89% reported in a meta-analytic study by Monteiro et al. [25]. Nevertheless, this value was extrapolated from studies reporting data on sensitivity without taking into account those cases with lack of temporal windows. The inclusion of a transorbital and transcervical approach in our study protocol increased sensitivity from 82.1 to 88% (Table 1) allowing the diagnosis of CCA in further 11 patients lacking the temporal ultrasonic window. Nevertheless, 22 patients (11.9%) had weak persistent diastolic flow. This finding agrees with those of others. In fact, ICA diastolic flow could be present in up to 20% of patients with clinical evidence of brain death [28, 29]. Extracranial ICA diastolic flow has also been reported in 10.7% of patients with evidence of intracranial circulation arrest [27].

We observed that changes of flow pattern in the extracranial segment of the ICA were similar to those recorded in the intracranial vessels with progressive disappearance of the diastolic spectrum culminating in a reverberating flow. According to the angiographic observations of Hassler et al. [11, 12], the origin of the intracranial ICA remains patent during the early stage of intracranial circulation arrest. Persistent diastolic forward flow in the ICA

is therefore compatible with early intracranial CCA, in the hypothesis that basal arteries are still patent and blood shunts into the external carotid through collaterals, such as the ophthalmic arteries.

In those cases, the progressive passage toward a reverberating flow in the ICA could be recorded during serial examinations, with an earlier appearance on the side in which a greater ICP could be expected. This allowed to increase sensitivity from 88 to 95.6%. Of note, the presence of oscillating flow in the extracranial ICA corresponded in all cases to an intracranial circulation arrest demonstrating that the detection of circulation arrest on the extracranial ICA reliably reflects intracranial flow absence.

The results of our study need to be interpreted with caution. This study was based on a consecutive series of patients whose clinical and instrumental data were retrospectively reviewed. It has been suggested that this type of data collection may be associated with an overestimation of the diagnostic accuracy [30]. This for several reasons, in studies in which data collection is planned after all tests have been performed, the selection of inclusion criteria may be not sufficiently strict. We actually included all brain dead patients who underwent TCD examination; the results on accuracy may be different if measured only in

the subgroup of patients that are more suitable for TCD examination. In our practice, the TCD study preceded other confirmatory studies and the official clinical evaluation for the declaration of the brain death, and in general, each operator was unaware of the results of the others. Nevertheless, this was not a prospective study organized to blind operators. The interpretation of the index test (TCD) can be influenced by the knowledge of the gold standard; this being called "review bias", can result in overestimation of sensitivity and specificity.

Conclusions

The TCD is an effective technique, which can shorten the waiting time for fulfilling the criteria for diagnosis of brain death. This technique is, however, not completely sensitive. Further, in patients lacking the temporal windows, the transcervical and transorbital study of the ICA may increase the sensitivity of the exam. Nevertheless, there is a quota of patients in which diastolic flow is still present on the ICA despite clinical evidence of brain death. In those patients, awaiting for the later stages of CCA, when the process of CCA is completed and reverberating flow appears in the intra- and extracranial carotid artery may further increase sensitivity, but other instrumental techniques are required to arrive to an earlier diagnosis.

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