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Diagnosis of Brain Death by Orbital Doppler Ultrasound: A Comparative Research Study

Orbital Doppler Ultrasonografi ile Beyin Ölümü Tanısı: Karşılaştırmalı Araştırma

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ABSTRACT

AIM: It remains unknown whether orbital Doppler-ultrasound (ODUS) could be an alternative to other established ancillary tests for the diagnosis of brain death. We investigated the effectiveness of ODUS in the diagnosis of brain death and compared data obtained from ODUS with transcranial Doppler-ultrasound (TDUS) and carotid Doppler-ultrasound (CDUS) findings.

MATERIAL and METHODS: ODUS, CDUS and TDUS examinations were performed on 22 consecutive patients who had clinical examination and confirmatory test findings consistent with brain death. The compatibility of resistive indices (RI) from ODUS, TDUS and CDUS examinations were analyzed.

RESULTS: In ODUS examinations, the RI values were equal to or greater than one in 15 patients (68%). In the remaining 7 patients, the RI values were ≥0.75. RI values were ≥ 1 in 16 (72%) and 18 (82%) patients in CDUS and TDUS examinations, respectively. RI values of CDUS and TDUS were ≥0.76 in the remaining patients.

CONCLUSION: ODUS is an easily applicable technique that is safer, cheaper and faster when compared with the other confirmatory tests. False results could be prevented by evaluating patients with an ODUS RI value of <1 together with the TDUS and/or CDUS results.

KEYWORDS: Brain death, Cerebral blood flow, Transcranial Doppler sonography, Orbital Doppler-ultrasound

ÖZ

AMAÇ: Orbital Doppler-ultrasonografi (ODUS)'un; beyin ölümü tanısında, diğer doğrulayıcı testlere alternatif bir yöntem olup olamayacağı henüz bilinmemektedir. Çalışmanın amacı beyin ölümü tanısında ODUS'un etkinliğini araştırmak ve transkraniyal Doppler-ultrasonografi (TDUS) ve karotid Doppler-ultrasonografi (CDUS) bulgularıyla karşılaştırmaktır.

YÖNTEM ve GEREÇLER: Klinik muayene ve doğrulayıcı testler ile beyin ölümü tanısı alan ardışık 22 hastaya ODUS, CDUS ve TDUS uygulandı. ODUS, CDUS ve TDUS rezistif indeks (RI) değerlerinin beyin ölümü tanısı ile uyumluluğu analiz edildi.

BULGULAR: Çalışmadaki hastalardan on beşinin (%68) ODUS incelemesinde; RI değeri 1'den büyük ya da eşit, geriye kalan 7 hastada ise 0,75 veya üstüydü. CDUS ve TDUS değerlendirmelerinde RI değerleri; CDUS incelemelerinde 16 hastada (%72) RI değeri 1'den büyük veya eşit iken TDUS incelemelerin de ise 18 hastada (%82) RI 1'den büyük ya da eşitti. Geriye kalan hastaların tümünün CDUS ve TDUS incelemelerinde RI değeri 0,75'ten büyüktü.

SONUÇ: ODUS; anjiyografi gibi diğer doğrulayıcı testler ile karşılaştırıldığında kolay uygulanabilinen, zararsız, güvenli ve hızlı bir tekniktir. ODUS incelemede RI değeri 1 ve üstü ise beyin ölümü tanısı güvenle konulabilir. ODUS'ta RI<1 ise TDUS ve/veya CDUS ile tanının kesinleştirilmesi gerekmektedir. Hatalı sonuçlar, ODUS, TDUS ve/veya CDUS sonuçlarının birlikte değerlendirilmesi ile engellenebilir.

ANAHTAR SÖZCÜKLER: Beyin ölümü, Beyin kan akımı, Transkraniyal Doppler-ultrasonografi, Orbital Doppler- ultrasonografi

INTRODUCTION

The simplest definition of brain death is failure to provide effective cerebral circulation (12). This irreversible condition leads to complete termination or impairment of brain function, including the brainstem, whereas the blood continues to circulate in other parts of the body (1, 6). Correct and quick diagnosis of brain death is very important and plays an essential role in the decision making of organ donation for transplantation or withdrawal of life-support (11). Although guidelines and/or standards vary from country to country, diagnostic criteria are usually determined by various committees in each country (1, 11).

The diagnosis of brain death is often made by a multidisciplinary team consisting of neurosurgeons, neurologists and intensivists who frequently care for patients devastated by neurological disorders. Neurological examination is quite important for the determination of brain death, and, is usually performed by a neurologist or a neurosurgeon. The patients are in a deeply comatose state and brain stem reflexes are absent (6). Nevertheless, in many countries, the diagnosis of brain death necessitates confirmatory tests (11). Four vessel digital subtraction angiography (DSA), radionuclide cerebral angiography (RCA), computed tomographic cerebral angiography (CTA), transcranial Doppler ultrasonography (TDUS), carotid Doppler ultrasonography (CDUS), serial electroencephalograms (EEG), and brainstem auditory evoked potentials (BAEP) are among these tests (1). The last two tests can be used to detect loss of electrical activity of the brain (electrocerebral silence) and the others are used to evaluate cerebral blood flow (6, 11). These confirmatory tests, however, have many limitations and disadvantages.

Orbital Doppler ultrasound (ODUS) is a relatively new technique that can be used in evaluating changes in cerebral blood flow (11). The primary aim of the present study was to investigate the effectiveness of ODUS in the diagnosis of brain death in patients in whom brain death had been diagnosed based on clinical findings and other confirmatory tests. The second aim of this study was to compare data obtained from ODUS with TDUS and CDUS, and to detect the most effective Doppler ultrasound technique in patients with possible brain death. To the best of our knowledge, there is no original study in the literature that compares the efficiency of ODUS data obtained from central retinal or ophthalmic artery (OA) with other Doppler ultrasound methods.

MATERIAL and METHODS

Between January 2010 and May 2012, ODUS, CDUS and TDUS examinations were performed on 22 consecutive patients (14 men and 8 women) who had clinical examination findings consistent with brain death (Glasgow coma scale < 7). Patients ranged in age from 34 to 79 years (mean age 58 years). Written informed consent was obtained from each subject's family. The internal review board of our institution approved the methodology of this study.

Patients with drug intoxication, hypothermia or hypotension (systolic pressure < 100 mm Hg), patients who were followed due to endocrine-metabolic induced coma and pediatric patients were excluded. In addition, 9 patients who did not have at least one confirmatory test, e.g., CTA; DSA, or the apnea test, were excluded. As a result, 22 patients with the precise diagnosis of brain death confirmed by the Brain Death Committee of our hospital were studied and TDUS, ODUS and CDUS were performed on all patients. Patients' demographic data and the causes of brain death are presented in Table I.

Arterial blood pressure and pulse velocity were measured during the Doppler ultrasound (DUS) examinations. All patients were under mechanical ventilation. A cardiopressor agent, i.e., dobutamine, was administered intravenously if the arterial systolic pressure decreased to below 100 mmHg.

All DUS examinations were performed with a Siemens, Sonoline G-40 device (Siemens Medical solutions, Erlangen, Germany). ODUS and CDUS were done with a 9-MHz linear probe. TDUS was performed with 2 MHz convex-array probe. In all patients, Doppler settings of the ultrasound machine were calibrated to low-flow determination (11) and the smallest available Doppler gate was used for all ODUS and TDUS exams.

For ODUS examinations, sterile coupling gel was applied on closed eyelids. During the ODUS examination, we were cautious to avoid excessive pressure on the globe. Central retinal and ophthalmic arteries were found in the retrobulbar area. Doppler parameters including peak-systolic velocities (PSVs), end-diastolic velocities (EDVs), systole/diastole (S/D) ratios, and resistive indices (RIs) were obtained. Following these measurements, average values of all parameters were calculated for both arteries. In cases where the central retinal artery could not be demonstrated, 2 measurements were obtained from the OA and the average of these values was accepted as the final value.

For TDUS examinations, a convex probe was placed on the central part of the line connecting the lateral palpebral fissure to the meatus acusticus externus, and 1 cm superior to the

Table I: Age, Gender, and Causes of Brain Death (BD)

No	Sex	Age	Cause of BD
1	M	38	TBI
2	M	75	TBI
3	M	64	TBI
4	F	74	Aneurysmal SAH
5	M	46	Aneurysmal SAH
6	M	68	Cerebrovascular accident
7	M	59	Aneurysmal SAH
8	M	37	TBI
9	M	52	Operated intracranial tumor
10	M	71	TBI
11	F	51	Operated intracranial tumor
12	F	48	Aneurysmal SAH
13	F	34	TBI
14	M	70	Aneurysmal SAH
15	F	68	ICA occlusion
16	M	41	Operated intracranial tumor
17	M	77	TBI
18	F	46	Aneurysmal SAH
19	M	67	TBI
20	M	58	Aneurysmal SAH
21	F	79	Operated intracranial tumor
22	F	54	TBI

***SAH:** subarachnoid hemorrhage; **TBI:** traumatic brain injury; **ICA:** internal carotid artery.*

zygomatic arc. Doppler parameters were obtained from the middle cerebral artery (MCA). For CDUS examination, a linear probe was placed over the internal carotid artery (ICA). The PSV, EDV, S/D ratio and RI values were obtained from each ICA and MCA, similar to ODUS examinations. Two measurements were obtained from ICA and MCA and their average was calculated. The average value was accepted as the final value.

All ODUS, TDUS and CDUS examinations were performed bilaterally except for patients in whom bilateral measurements could not be done due to an open sore, dressing or postoperative changes. Doppler images obtained from all patients were recorded in real time on the sonography device. All DUS examinations were performed by the same experienced radiologist. The average DUS examination duration for each patient was approximately 20 minutes.

The same procedure was applied to the seven volunteers (4 men and 3 women, mean age: 34, range 26-49) before the Doppler examinations of the study patients. The purpose of these examinations was to improve the DUS experience of the radiologist.

Statistical Analysis

Following data acquisition, all DUS results were analyzed. Mean bilateral measurements were calculated. In cases that could not be evaluated bilaterally, the average of 2 measurements from only one side were obtained and recorded directly to the study table. Similar to previous Doppler studies, brain death was confirmed in cases with an RI ≥ 1 (1, 6, 12).

RESULTS

An apnea test was performed on 20 (91%) patients, EEG was applied to 9 (41%) patients, DSA was done on 12 (55%) patients, and CTA was performed on 8 (36%) patients. The overall results of these tests were compatible with brain death (Figure 1A-D). During DUS examinations, the mean systolic/diastolic arterial pressure and mean pulse rate of patients were 126/78 mm Hg (range: 100-178/54-120) and 112/min (range: 80-145) respectively.

In ODUS examinations, RI values were ≥ 1 in 15 patients (68%). RI values were greater or equal than 0.75 in the other 7 patients (Table II, Figure 2A-D). RIs were ≥ 1 in 16 (72%) and 18 (82%) patients in CDUS and TDUS examinations, respectively. RI values of CDUS and TDUS were greater than 0.76 in the remaining patients (Table II, Figure 3A-F). The PSV, S/D, and EDV values from ODUS, CDUS, and TDUS exams from patient and control groups are summarized in Table III.

DISCUSSION

Quick and effective diagnosis of brain death is of critical importance in terms of social, legal, medical, and financial aspects (5). In recent years, with the expansion of organ transplantation, rapid and accurate diagnosis of brain death has gained more importance. Neurological examination and apnea test are the most important tools for diagnosis (11). However, it is mandatory in many countries to perform at least one confirmatory test (10). These confirmatory tests include EEG and BAEP, which evaluate neuronal activity, and other tests, e.g., DSA, CTA or RCA that show the absence of cerebral blood flow (11). Each of these confirmatory tests,

Table II: Resistive Indexes (RIs) of the Patient Group

No	RI-ODUS	RI-CDUS	RI-TDUS
1	>1	0.88	>1
2	1	>1	>1
3	0.83	0.89	1
4	0.78	>1	>1
5	0.75	>1	0.84
6	1	>1	1
7	1	>1	0.96
8	0.95	>1	0.92
9	1	>1	>1
10	>1	>1	>1
11	>1	>1	1
12	>1	>1	>1
13	1	>1	1
14	0.75	0.84	>1
15	>1	>1	>1
16	>1	>1	>1
17	1	0.81	>1
18	>1	0.82	0.92
19	1	1	1
20	1	1	1
21	0.83	0.76	>1
22	0.8	>1	>1

ODUS: *orbital Doppler ultrasound;* ***CDUS:*** *carotid Doppler ultrasound;* ***TDUS:*** *transcranial Doppler ultrasound.*

Table III: The PSV, S/D, and EDV Values from ODUS, CDUS, and TDUS Exams from the Patient and Control Groups

	Patients Mean (range)	Controls Mean (range)
PSV-ODUS	45 (7-90) cm/s	63 (34-97) cm/s
S/D-ODUS	10 (3-30)	4 (1-4)
EDV-ODUS	9 (0.3-26) cm/s	16 (4.5-26) cm/s
PSV-CDUS	70 (33-107) cm/s	42 (27-84) cm/s
S/D-CDUS	10 (2-18)	3 (2-4)
EDV-CDUS	11 (1-18) cm/s	26 (14-36) cm/s
PSV-TDUS	26 (9-43) cm/s	67 (28-121) cm/s
S/D-TDUS	18 (2-42)	2 (1.8-2.5)
EDV-TDUS	6 (0-8.3) cm/s	32 (13-49) cm/s

ODUS: *orbital Doppler ultrasound;* ***CDUS:*** *carotid Doppler ultrasound;* ***TDUS:*** *transcranial Doppler ultrasound;* ***PSV:*** *peak-systolic velocity;* ***S/D:*** *systole/diastole;* ***EDV:*** *end-diastolic velocity.*

Figure 1: Cerebral angiography of a 41-year old male with brain death (Glasgow Coma Scale Score: 3; patient no: 16). **A)** Bilateral common carotid arteries and vertebral arteries are patent on arcus aortography. **B)** On anterior-posterior images obtained after left vertebral artery catheterization, the basilar artery is not filled. **C)** Anterior-posterior images obtained after contrast administration from left and **D)** right carotid bulbs show the thin caliber of both internal carotid arteries, the absence of cerebral circulation and the transition of most of the contrast material to the external carotid system. Note: Carotid angiograms are obtained by administration of contrast material from the carotid bulb in order to prevent internal carotid artery spasm.

however, has certain limitations and disadvantages (6). DSA is a time-consuming and highly invasive procedure that requires experience. CTA and DSA require application of a nephrotoxic contrast media that can cause damage to the donor's kidneys (4, 10). In addition, it has been reported that iodinated contrast media may increase pre-existing brain edema (1). CTA, DSA and RCA require transportation of the patients to another unit, which may cause problems for intensive care unit patients, e.g., cardiac arrest in hemodynamically unstable patients (7, 10). In addition, the medical devices required to perform CTA, DSA and RCA are not always readily available. The apnea test cannot be applied in patients with progressive hypotension, hypoxemia, or drug intoxication (11). EEG and BAEP are time consuming tests that cannot be performed easily, and also require experience. Furthermore, all of these tests may have false results (10).

Doppler ultrasound is a non-invasive technique that has no known side effect (1). TDUS has been used as a bedside test in the diagnosis of brain death to overcome the limitations mentioned above (4). Detection of reverberating-oscillating (reverse) flow or the absence of diastolic flow while there is systolic flow (systolic spikes, diastolic stopping-leakage) on TDUS examination is meaningful in terms of brain death (7, 12). The Doppler patterns mentioned above (RI≥1) represent a stop in cerebral perfusion that develops secondary to the very high distal brain resistance that is often seen in individuals with brain death (2, 4, 7, 10).

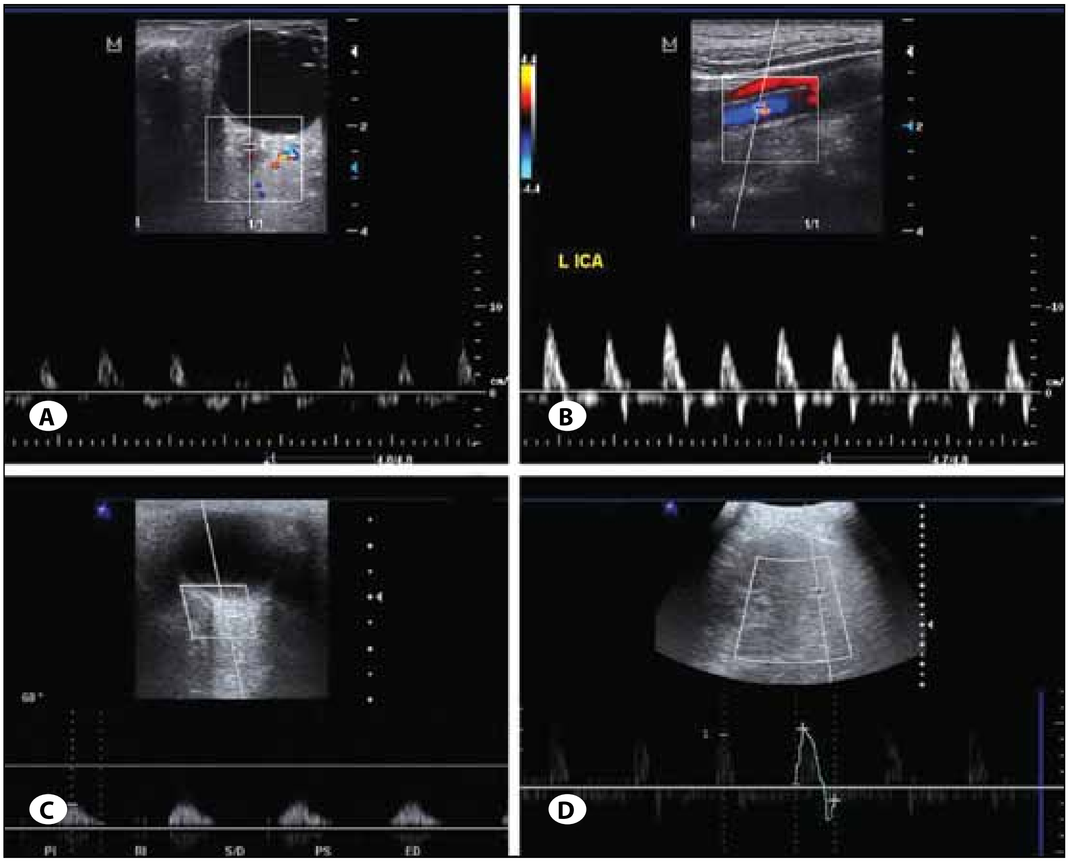

Figure 2: Doppler ultrasound (DUS) images of a 68-year old female patient with right ICA occlusion (patient no: 15). **A)** DUS examinations performed from the central retinal, **B)** left internal carotid, **C)** ophthalmic, and **D)** middle cerebral arteries revealed high RI values (RI≥1) which were compatible with brain death. Cessation of the flow (RI=1) during systole in the ophthalmic artery and presence of reverse flow (RI>1) in other arteries are observed.

However, due to certain limitations, TCD examinations cannot take place in daily routine practice (7). The most important limitation is failure to perform an appropriate TDUS exam due to an inadequate temporal window. Ultrasound waves cannot penetrate the skull of adults, thus the Doppler signal cannot be received and TDUS cannot be performed (1, 3). The transorbital approach may increase the efficacy of TDUS (8). TDUS also requires dedicated Doppler probes and experienced practitioners. Another limitation of TDUS is that it cannot be performed in patients who have a large wound or major fracture at the temporal area, which was the case in 3 of our patients that were not included in the study.

CDUS is also reported to be useful in the diagnosis of brain death (9). Similar to TDUS, an RI value of greater than 1 in CDUS is reported to be a reliable finding for brain death (6, 9). However, CDUS measurements of intracranial circulation can be misleading. Hadani et al showed that extra-cranial ICA flow was maintained in 9 patients with brain death (4). Direct shunting from ICA branches to the external carotid system is said to be responsible for this condition (1, 4). Therefore, presence of pseudoperfusion limits the reliability of CDUS and necessitates other confirmatory tests (such as TDUS) when cerebral perfusion is detected by CDUS in brain death patients (4).

ODUS is a relatively new method that has been used to evaluate orbital flow changes in various diseases (6). OA is the first intracranial branch of the ICA, and arises from within the subarachnoid space after the ICA has emerged from the cavernous sinus. Once the OA crosses over the optic nerve, it branches, and the first branch is usually the central retinal artery (CRA). DUS parameters obtained from CRA and OA can be useful for the evaluation of intracranial blood flow changes (6). The most important advantages of ODUS include no need for a special probe, the possibility of bedside application, its ease of use and non-invasiveness. ODUS could be used either alone or in conjunction with other Doppler methods in patients in whom TDUS or CDUS would be inappropriate due to poor acoustic window, presence of a short neck, severe ICA calcification, surgical wounds, cervical large hematomas, or vascular catheters (6).

To the best of our knowledge, there is only one study in the literature in which ODUS examination was used for the diagnosis of brain death (6). In this study with 8 patients, RI values were equal to or greater than 1 on Doppler measurements of OA and CRA in all patients with brain death. Nevertheless the ODUS parameters were not compared with TDUS or CDUS in this study.

In our study, ODUS examinations of 22 patients with a diagnosis of brain death revealed an RI value equal or greater than 1 in 15 patients (68%). RI values were equal or greater than 0.75 in the remaining 7 patients. In these 7 patients, RI values of TDUS or CDUS were ≥1. These results suggest that

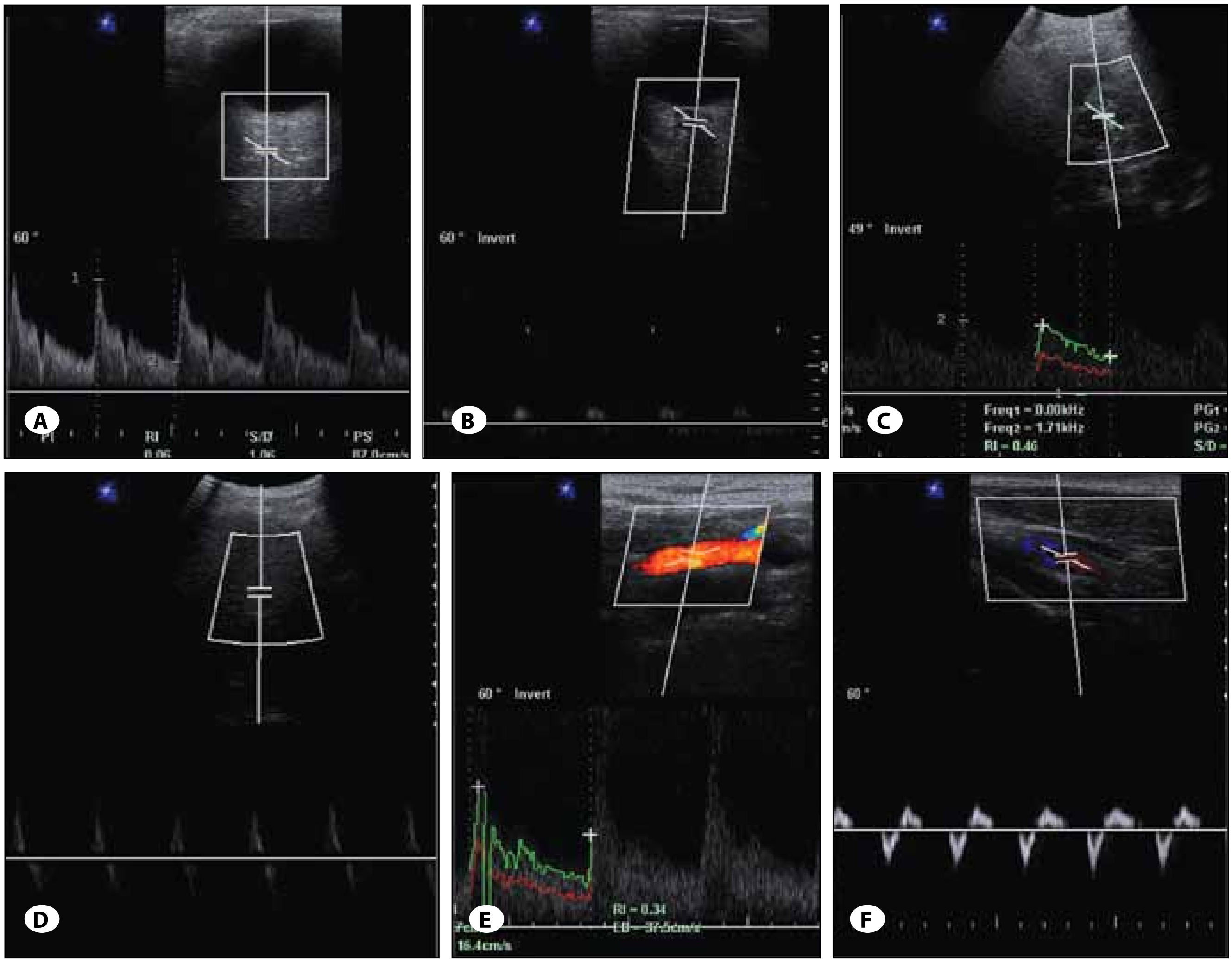

Figure 3: The control Doppler ultrasound (DUS) images of a 49-year old male volunteer and DUS images of the patient in figure 1 who had postoperative brain death following tumor surgery. The **A)** orbital, **C)** transcranial, and **E)** internal carotid DUS examinations of the control patient show arterial flow with low resistance (RI values: 0.06, 0.46, 0.34; respectively). In the patient with a diagnosis of brain death, **B)** cessation of flow (RI^{ODUS}=1) during diastole on orbital DUS examination, and **D)** presence of reverse flow on transcranial and **F)** internal carotid DUS examinations are shown (RI^{TDUS} and RI^{CDUS}=1). The flow pattern in Figure 3B, Figure 3D, and Figure 3F are compatible with brain death (RI≥1).

ODUS may be sufficient in the majority of patients for the diagnosis of brain death. In patients with an RI value of <1 on ODUS examination, brain death may be diagnosed by adding TDUS and/or CDUS examinations to ODUS.

In 3 patients, RI values of CDUS examinations were 0.88, 0.81, and 0.82 (patients no: 1, 17, and 18) as RI values were ≥1 in ODUS examinations. Similarly RI values of ODUS examinations were ≥1 in two patients in whom the RI values of TDUS were 0.96 and 0.92 (patient no: 7 and 18). Therefore ODUS can be used in the diagnosis of brain death whenever TDUS and CDUS are inadequate.

The first limitation of our study was the small number of cases. Secondly, the intra-observer and inter-observer variability were not evaluated for DUS examinations. Assessment of these variations will be necessary in further studies. Finally, we were unable to determine whether patients enrolled in the study had significant anatomical variations in their OA and/or CRA.

CONCLUSION

ODUS is an easily applicable technique that is safer, cheaper and faster when compared with other confirmatory tests used in the assessment of brain death. Frequently, ODUS alone is sufficient to confirm the diagnosis in patients who have a prediagnosis of brain death based on clinical findings. However, false results may be prevented by evaluating those patients with an RI value of <1 in ODUS, with additional TDUS and/or CDUS examinations.

REFERENCES

1. Bode H, Sauer M, Pringsheim W: Diagnosis of brain death by transcranial Doppler sonography. Archives of Disease in Childhood 63: 1474-1478, 1988
2. Bor-Seng-Shu E, Teixeira MJ, Hirsch R, Andrade AF, Marino R Jr: Transcranial doppler sonography in two patients who underwent decompressive craniectomy for traumatic brain swelling: report of two cases. Arq Neuropsiquiatr 62: 715-721, 2004
3. Dominguez-Roldan JM, Jimenez-Gonzalez PI, Garcia-Alfaro C, Rivera-Fernandez V, Hernandez-Hazañas F: Diagnosis of brain death by transcranial Doppler sonography: Solutions for cases of difficult sonic windows. Transplantation Proceedings 36: 2896-2997, 2004
4. Hadani M, Bruk B, Ram Z, Knoller N, Spiegelmann R, Segal E: Application of transcranial Doppler ultrasonography for the diagnosis of brain death. Intensive Care Med 25: 822-828, 1999
5. Idea RJ, Lewis DH: Timely diagnosis of brain death in an emergency trauma center. AJR Am J Roentgenol 163:927-928, 1994
6. Karaali K, Cevikol C, Senol U, Arici G, Kabaalioğlu A, Ramazanoğlu A, Bircan O: Orbital Doppler sonography findings in cases of brain death. AJNR Am J Neuroradiol 21: 945-947, 2000
7. Kassab MY, Majid A, Farooq MU, Azhary H, Hershey LA, Bednarczyk EM, Graybeal DF, Johnson MD: Transcranial Doppler: An introduction for primary care physicians. J Am Board Fam Med 20: 65-71, 2007
8. Lampl Y, Gilad R, Eschel Y, Boaz M, Rapoport A, Sadeh M: Diagnosing brain death using the transcranial Doppler with a transorbital approach. Arch Neurol 59: 58-60, 2002
9. Payen DM, Lamer C, Pilorget A, Moreau T, Beloucif S, Echter E: Evaluation of pulsed Doppler common carotid blood flow as a noninvasive method for brain death diagnosis: A prospective study. Anesthesiology 72: 222-229, 1990
10. Quesnel C, Fulgencio JP, Adrie C, Marro B, Payen L, Lembert N, El Metaoua S, Bonnet F: Limitations of computed tomographic angiography in the diagnosis of brain death. Intensive Care Med 33: 2129-2135, 2007
11. van der Lugt A: Imaging tests in determination of brain death. Neuroradiology 52: 945-947, 2010
12. Yoneda S, Nishimoto A, Nukada T, Kuriyama Y, Katsurada K: To-and-fro movement and external escape of carotid arterial blood in brain death cases. A Doppler ultrasonic study. Stroke 5: 707-713, 1974