DIAGNOSIS OF BRAIN DEATH: USE OF COMPUTED TOMOGRAPHY ANGIOGRAPHY AS A NON-INVASIVE DIAGNOSTIC TOOL AVAILABLE TO EVERYONE

Diagnóstico de muerte cerebral: Uso de la angiografía por tomografía axial computarizada como herramienta diagnóstica no invasiva al alcance de todos

Jorge Humberto Marín Muñoz[1]
Juliana Andrea Echeverri Gómez[2]
Édgar Gerardo Ordóñez Rubiano[3]
Adriana Lucía Posso Murcia[2]
Juan Pablo Dávila Montecino[2]
Nadia Vanessa Ziade Sierra[2]
Nelson Oswaldo Lobelo García[4]

Key words (MeSH)
Brain death
Computed tomography angiography
Cerebral angiography
Computed tomography

Palabras clave (DeCS)
Muerte encefálica
Angiografía por Tomografía Axial computarizada
Angiografía cerebral
Tomografía Computarizada

Summary

*Objective:*To describe the brain CT angiography findings in patients with clinical signs of brain death (BD) and to evaluate its applicability as a diagnostic method of BD as well. *Methods:* A retrospective study was performed in one center, between September 2013 and April 2015, which included patients between 21 and 60 years, who underwent CT angiography with BD protocol. The clinical diagnosis of BD was made by neurological examination and with a positive apnea test. Additionally, a multi-slice CT angiography was performed with a 4-detectors tomograph, with three acquisitions, with 2mm axial slices from the vertebral body of C6 to 5 cm above in a caudo-cephalic fashion, showing complete absence of intracranial circulation. The BDscan diagnostic criteria was based on a 6-point scale. *Results:* 12 patients that met the inclusion criteria (5 males and 7 females), with a mean age of 46.6 years (21-60) were identified. The initial diagnosis of the patients were neurovascular (n = 8), head trauma (n = 2), meningioma (n = 1) and cardiopulmonary arrest (n = 1). Only one patient did not meet the 6 points of the proposed criteria for the evaluation with CT angiography. *Conclusions:* CT angiography could provide enough information to perform confirmatory diagnostic imaging of BD in patients with clinicaldoubtsof diagnosis of BD, however it is necessary in the future to compare it with catheter angiography.

Resumen

Introducción: Muerte cerebral (MC) se define como la pérdida irreversible de la función cerebral, ausencia de reflejos del tallo cerebral y de movimientos respiratorios. *Objetivo:* Describir los hallazgos en la angioTAC cerebral en pacientes con signos clínicos de MC, para evaluar su aplicabilidad como método diagnóstico. *Métodos:* Se realizó un estudio retrospectivo, entre septiembre de 2013 y abril de 2015; se incluyeron pacientes entre 21 y 60 años, a quienes se les practicó angioTAC para verificar MC. El diagnóstico clínico de MC se realizó mediante el examen neurológico y el test de

[1]Radiologis, neuroradiologist, Hospital Infantil de San José. Bogotá, Colombia.

[2]Radiologist resident, Hospital Infantil de San José. Bogotá, Colombia.

[3]Neurosurgery resident, Hospital Infantil de San José. Bogotá, Colombia.

[4]Radiologist, neurointerventionist, Hospital Infantil de San José. Bogotá, Colombia.

apnea. Adicionalmente se realizó una angioTAC con tomógrafo multicorte de 4 detectores, con tres adquisiciones, mediante cortes axiales de 2mm desde el cuerpo vertebral de C6 hasta 5 cm arriba. El diagnóstico escanográfico de MC se hizo basado en criterios de ausencia completa de circulación intracraneal con una escala de 6 puntos. *Resultados:* Se identificaron 12 pacientes que cumplían con los criterios de inclusión (5 hombres y 7 mujeres), con edad media 46,6 años (21-60). Los diagnósticos de base fueron: neurovascular (n = 8), trauma craneoencefálico (n = 2), meningioma (n = 1) y paro cardiorrespiratorio (n = 1). Solo un paciente no cumplió con los 6 puntos de los criterios propuestos para la evaluación con angioTAC. *Conclusiones:* La angioTAC puede suministrar información suficiente para realizar el diagnóstico confirmatorio imaginológico de MC en los pacientes con duda diagnóstica clínica; sin embargo, es necesario compararlo en el futuro con la angiografía por catéter.

Introduction

The term brain death (BD) was first introduced in 1960 by the committee of the Harvard Medical School (1). It is defined as the irreversible loss of brain function, where there is deep coma, absence of brain stem reflexes and of respiratory movements (1,2). In Colombia, BD was first legislated in 1989, with the issuance of decree-Law 1172 of June 6, 1989 on BD and organ donation (3), which was modified by the Law 454 of August 4 of 1998, (decree number 1546 of 1998) (4); in the legislation, some medical-legal guidelines on BD and organ donation are described, but it is not established any way to diagnose BD.

The diagnosis of BD is of medical, ethical and legal importance, since it serves the purpose of identifying at an early stage, the candidate patients for organ donation, in order to proceed to withdraw the artificial measures of invasive support.

When there is clinical diagnostic difficulty, as in the cases in which sedative drugs are used and there are metabolic alterations that invalidate the exploration and the realization of the electroencephalogram (EEG), current world legislation and clinical practice guidelines require the use of additional diagnostic methods for detection of brain flow, such as cerebral catheter angiography, which in the majority of centers in the world is considered the gold standard for the complementary diagnosis, since it has been the most studied For BD. The Colombian legislation, in Decree 2493 of 2014, Chapter 3, Article 14, proposes the possibility of carrying out certainty tests that evaluate the cerebral blood flow in the centers that count on this. Therefore, we propose the CAT angiography criteria as confirmatory evidence and, for greater accessibility, with a CT scanner Of 4 detectors.

In a hospital in Colombia a guide has previously been proposed for the diagnosis of BD, using the following parameters, based on In the legal conditions and in the clinical experience of professionals from the country; This guide is updated according to the latest revision of the American Academy of Neurology, which are also governed by institutional protocols in different entities (4-7):

Pre-requisites

- Hemodynamic stability systolic pressure ≥ 100 mmHg with vasopressor or inotropic, if necessary.
- Adequate oxygenation and ventilation: normal PaO_2 and $PaCO_2$ between 35 and 45 mmHg in controlled mechanical ventilation.
- Central body temperature greater than 36°C with the use of a thermal blanket if necessary: > 32°C for children under two years of age.
- Absence of metabolic alterations.
- Absence of substances or drugs depressants of the nervous system that could be responsible for the coma: 40 mg of ethanol / 100 ml of whole blood are interpreted as a negative state of inebriation, suspended sodium thiopental during a period equivalent to five half-lives or 58 hours before or barbiturates serum concentrations of less than 10 µg/ml.
- Absence of neuromuscular blockers.
- Sodium, potassium, calcium electrolytes near normal limits and acid base pH between 7.35 and 7.45.

Clinical exam

1. Absence of spontaneous breathing (apnea test):
   - Hemodynamically stable patient.
   - Ventilator adjusted to normocapnia ($PaCO_2$ between 35 and 45 mmHg).
   - Pre-oxygenated patient with 100% FiO_2 for 10 minutes to reach a PaO_2 of 200 mmHg. Provide oxygen through a catheter of suction in the carina to 6 L / min or place a T-tube with CPAP at 10 cm H_2O.
   - When the fan is switched off:
     - Absence of spontaneous breathing.
     - Take blood gases within 8 to 10 minutes; the patient is reconnected to the fan.
     - A PCO_2 of 60 mmHg or 20 mmHg increase of the normal baseline value is considered as a positive apnea test for absence of spontaneous breathing.
     - In case of inconclusive results or suspension for any reason, it can be repeated in 15 min if the hemodynamic conditions allow it.
2. Persistently dilated pupils.
3. Absence of pupillary reflexes to light.
4. Absence of corneal reflex.
5. Absence of oculovestibular reflexes. Each auditory canal is irrigated (one ear at a time) with approximately 50 ml of ice water. The movement of the eyes must be absent during one minute of observation. Both sides are tested, with an interval of a few minutes.

6. Absence of nauseous reflex.
7. Absence of cough reflex.

In some hospitals in Colombia and according to availability, non-standardized diagnostic methods are used such as:

1. Cerebral angiography.
2. Electroencephalography.
3. Transcranial doppler ultrasonography.
4. Brain scintigraphy with Tec99 HMPAO.

In our protocol, in cases where clinical doubt persists CAT angiography is used as an non-invasive, easily available confirmatory test with good diagnostic performance when interpreted by an expert in neuroimaging.

Methodology

A retrospective study was conducted between September 2013 and April 2015, which included adult patients 18 years of age and onwards, who underwent CAT angiography with protocol for BD due to clinical suspicion of it. The cases were identified from the statistical records of the radiology service. The criteria for inclusion were: patients who were in the adult Intensive Care Unit (ICU), with clinical diagnostic criteria as candidates for organ donation, without taking into account the pathology.

The clinical diagnosis of BD, according to the institutional protocol, based on the guidelines of the Harvard Medical Committee (4) and the German guides of 1998 (8), confirmed the deep coma, absence of brain stem reflexes and positive apnea test (no spontaneous ventilation with PaCO2 greater than 60 mmHg), in the absence of depressant drugs of the central nervous system (CNS) for more than 72 hours.

All were submitted to CAT angiography protocol. They were no additional electrophysiological studies, such as electroencephalogram, performed.

The images of CAT angiography were analyzed at the time by a neuroradiologist and the following diagnostic criteria were used for evaluation:

Technical verification of the study: it was established as a requirement the complete distal opacification of terminal branches of the external carotid arteries: both superficial temporal arteries and both occipital arteries. For the diagnosis of positive BD by scenography, 6 possible points in the protocol outlined below were followed.

Protocol proposed for CAT angiography for BD

Given the lack of clinical certainty, in the event that a patient fulfilled out the prerequisites and partially met the clinical criteria for BD, the following steps were proposed for the realization of the CAT angiography protocol, using a Toshiba multi-slice® tomograph, Asteion model with 4 detectors.

- The venipuncture site: strictly in the middle third of the forearm with catheter number 16 or 18.
- Scout View images AP and lateral, to choose the acquisition volume: from C6 to 5 cm above the Turkish chair (caudal to cephalic) with axial cuts every 2 mm, with a reconstruction interval of 1 mm.
- Administration of intravenous, nonionic contrast medium, in an amount of 100 cm3, at an injection rate of 5 cm3 /sec and pressure of 300 psi. The Surestart program was used with a ROI (Region of Interest) in the cervical carotid artery at a height of C6 with an increase of 40 HU for automatic acquisition, or using manual Surestart, evaluating cervical carotid filling at the same height: C6.
- Acquisition of images in arterial phase with posterior multiplanar reconstructions and 3D with MIP (maximum intensity projection).
- Evaluation of the following imaging criteria in CAT angiography (6 points):
    - Absence of distal enhancement of both internal carotid arteries from its supraclinoid segment. (Two points).
    - Absence of distal enhancement of both vertebral arteries from the V4 segment. (Two points).
    - Absence of retrograde and/or antegrade enhancement (via collateral) of both middle cerebral arteries from the M1 segment. (Two points).

The CAT angiography is based on the following cerebral perfusion pressure formula (CPP):

CPP = Mean Arterial Pressure (MAP) – ICP

Where:
CPP: cerebral perfusion pressure
MAP: mean arterial pressure
ICP: intracranial pressure

Any change in the ICP or MAP may directly affect CPP, which is an indirect indicator of cerebral blood flow (CBF), represented in the following formula:

CBF = CPP/cerebrovascular resistance (CVR)

Therefore, if there is an increase in ICP, CPP decreases which shows in the CAT angiography as a decrease of the flow of all the intracranial vessels dependent on the internal carotid arteries and the vertebral arteries.

In addition, carotid artery-dependent perfusion is independent of ICP, which is why a satisfactory technical criterion of the test, is the opacification of distal vessels dependent of this artery.

CVR is determined, to a large extent, by arterioles. The dural venous sinuses, on the other hand, do not play an important role in the determination of these variables. For this reason, the opacification of these are not relevant for the diagnosis of BD.

Ethical Considerations: This study is governed by the ethics for research with humans guidelines from the declaration of Helsinki of the World Medical Association.

According to resolution 8430 of 1993 of the Ministry of Health of Colombia (9), this research is classified as safe because it is a retrospective study in which the data were obtained through the review of

medical records and no intervention was performed nor modification of biological, psychological or social variables of the participants. The radiological examinations that were done to the patients were indicated for their clinical conditions and were performed under prior consent of their family members. This consent included the authorization to use their data in academic publications protecting the identity of patients.

The investigators of this study declare no conflicts of interest.

Results

We identified 12 patients who met the inclusion criteria (5 men and 7 women), with a mean age of 46.6 years (range 21-60). The basic diagnoses of the patients were: subarachnoid haemorrhage (SAH) (n = 4), traumatic brain injury (TBI) (n = 2), cerebrovascular accident (stroke) (n = 1), cardiorespiratory arrest (N = 2), arteriovenous malformation (AVM) (n = 1), meningioma (N = 1) and dural fistula (DF) (n = 1). Only one patient did not meet the 6 Points of the proposed criteria for evaluation with CAT angiography, with a final score of 2/6 (due to lack of flow of both vertebral arteries); In view of the high clinical suspicion of BD, we tried applying an angiogram by catheter, without success because the patient suffered a cardiorespiratory arrest (Table 1). The patient with negative CAT angiography one day after the completion of the CAT angiography presented CRA and died (figures 1 and 2).

The CAT angiography registry demonstrates normal enhancement of carotid and vertebral vessels in their cervical portions and the registry of distal vessels from for both external carotid arteries (superficial temporal arteries) due to a satisfactory technique of the study. Absence of flow of all intracranial vessels, in a patient diagnosed with brain death (Figures 1 and 2).

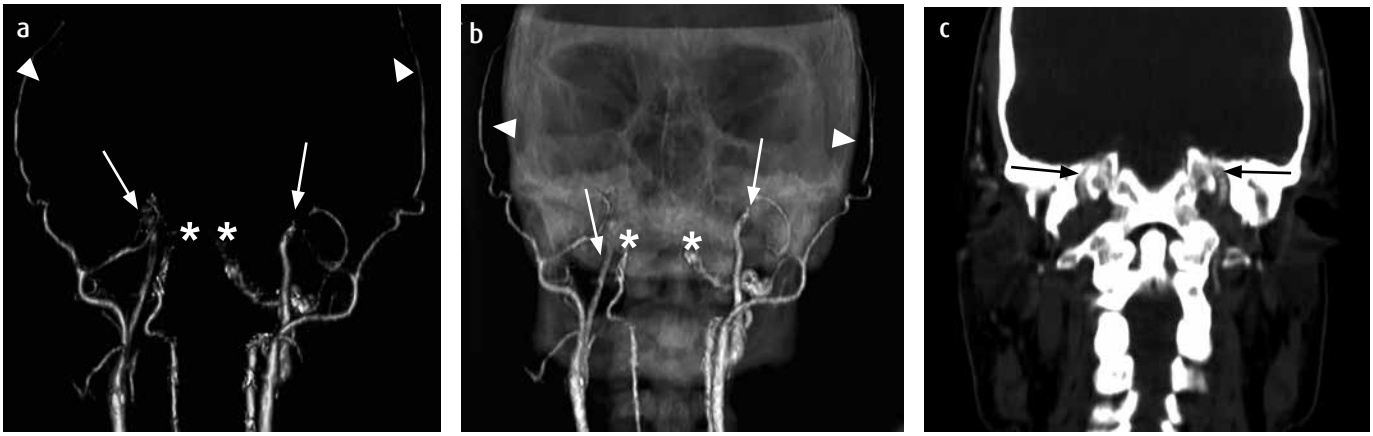

Figure 1. CAT angiography of one of the patients with clinical diagnosis of BD that add up to 6 of the 6 criteria proposed for diagnosis of BD. a and b) 3D Reconstruction of cerebral CAT angiography. Adequate distal flow is recorded in both superficial temporal arteries (white arrow heads), absence of flow of both internal carotid arteries from distal cervical portions (white arrows), absence of flow from both vertebral arteries (asterisks) and from both cerebral arteries socks. c) Coronal section of cerebral CAT angiography, both internal carotid arteries are identified without distal flow at the intracranial level (black arrows).

Figure 2. CAT angiography of the patient who did not meet the imaging criteria of BD. a) Flow is recorded in both supraclinoid carotids and in both M1 portions of the middle cerebral arteries (white arrows). b) Absence of flow from both vertebral arteries (arrowheads). c) 3D reconstruction of cerebral CAT angiography. Both temporal surface arteries and both middle meningeal arteries are identified by distal flow dependent on both external carotid arteries (white arrow heads), flow registry of polygon vessels by intracranial distal flow (white arrow). (Final score: Two positive points of six possible, negative for brain death).

Table 1. Clinical and radiological characteristics of the patients

Patient No.	Age	Sex	Diagnosis	BD CAT Angiography score	Arteriography by catheter	Stay in days	Stay in days	Stay in days	Other test	Donor
						ICU	Pre CAT angiography	Post CAT angiography		
1	55	F	SAH	6/6	No	5	4	1	No	Yes
2	21	F	TBI	6/6	No	6	5	1	No	Yes
3	32	F	SAH	6/6	No	6	5	1	No	Yes
4	60	F	SAH + TBI	6/6	Sí	14	13	1	Sí	Yes
5	45	M	CVA	6/6	No	4	4	0	No	Yes
6	28	F	CRA	6/6	No	4	3	1	No	Yes
7	46	F	SAH	6/6	Sí	16	14	2	SÍ	Yes
8	26	M	Meningioma	6/6	No	5	5	0	Sí	Yes
9	52	M	CRA	6/6	No	26	25	1	No	Yes
10	35	F	AVM	6/6	No	5	4	1	No	Yes
11	56	M	DF	6/6	No	12	12	0	No	Yes
12	31	M	TBI	2/6	No	8	5	3	No	Yes

Notes: F: Female. M: Male. TBI: Traumatic brain injury. SAH: Subarachnoid haemorrhage. CRA: Cardiorespiratory arrest. CVA: Cerebro-vascular accident. Other test, such as EEG: Electroencephalogram. ICP: Intracranial pressure monitoring. AVM: Arterio-venous malformation. DF: Dural fistula.

Discussion

Tests for BD are performed in patients with severe brain injury, who are mechanically ventilated and in coma. Establishing a correct and early BD diagnosis is very important from the clinical and medico-legal point of view, with high relevance for the possibility of organ donation. There are different studies that show the applicability of CAT angiography for BD diagnosis. However, they are all series with few patients. Most of these with applicability in patients with high levels of sedation, whose use is predictive, but not confirmatory (8,10-12). Nevertheless, the most important limitation is from the technical point of view for the use of contrast medium, which may affect the viability of the organs for donation, due to for example, nephrotoxicity, although in a small percentage (13).

In a Cochrane review, which included 10 studies with a total of 366 patients, it was shown that out of every 100 patients with brain death by clinical criteria, 85 were diagnosed in the same way with CAT angiography, which varies in studies between 77 and 91. Canadians in 2006 were the first to register the CAT angiography as well as scintigraphy for BD. However, it has not been universally standardized. That is why this study tries to make an approximation from the radiological point of view to show how with a 4-detector tomograph it is possible to obtain enough information with CAT angiography to make the diagnosis of BD by image. It is important to emphasize that CAT angiography is not enough to make a definitive diagnosis of BD, but indirectly demonstrates the flow of intracranial vessels through distal visualization of the contrast medium (11,14).

The major advantage of the present study is that it shows that CAT angiography could be used for BD confirmation. However, it has several limitations: the first of which is the reduced sample and the second is that it was not possible to compare the CAT angiography with catheter angiography, the latter being considered worldwide as the complementary diagnostic gold test, since according to hospital protocol, by having a negative apnea test in a patient with high BD suspicion, the procedure to follow is the realization of CAT angiography. Only in the case that this diagnostic test is negative and clinical diagnostic doubt persists, catheter angiography is performed (11, 14). In our study, the diagnostic yield of CAT angiography could not be established because it was not compared with catheter angiography. The only candidate patient to catheter angiography died before its completion.

Additionally, brain scintigraphy with SPECT and Transcranial Doppler (TCD) are non-invasive diagnostic tools that also exist to confirm the diagnosis of BD. Nevertheless, the SPECT scan represents a higher cost and has low availability in our environment. On the other hand the TCD is an inexpensive, non-invasive alternative, but with the disadvantage of being dependent on operator training.

Conclusion

The CAT angiography could provide enough information to perform the confirmatory diagnosis of BD in patients with clinical doubt diagnosis. However, in future studies CAT angiography scan should be compared to a control group of patients who underwent catheter angiography, the complementary diagnostic gold test for BD (11, 14).

In addition, it is necessary that these tests be done in series to establish it as a diagnostic protocol.

Acknowledgements

To Dr. Patricia Gallego Cruz, Radiologist, Coordinator of Radiology of the Children's Hospital of San José, Bogotá.

To the Group of the Intensive Care Unit, especially doctor Ronald Medina. Children's Hospital of San José, Bogotá.

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Correspondence

Jorge Humberto Marín Muñoz
Carrera 52 # 67A-71, of. 207
Bogotá, Colombia
jhmarinm@yahoo.es

Received for evaluation: December 1, 2015
Accepted for publication: June 24, 2016