

CT angiography as a confirmatory test in diagnosis of brain death: comparison between three scoring systems

Hilal Şahin, Yeliz Pekçevik

PURPOSE

Computed tomography (CT) angiography emerges as a viable alternative technique for confirmation of brain death. However, evaluation criteria are not well established for demonstration of cerebral circulatory arrest. This retrospective study aimed to evaluate CT angiography scoring systems in diagnosis of brain death, review the literature, and compare interobserver agreement between different scales for the diagnosis of brain death.

METHODS

CT angiography examinations of 25 patients with a clinical diagnosis of brain death were reevaluated according to 10-, 7-, and 4-point scales. Exams were performed with a 64-slice CT scanner including unenhanced, arterial (20 s) and venous phase (60 s) scans. Subtraction images of both phases were obtained. Interobserver agreement was evaluated for the assessment of vessel opacification and diagnosis of brain death.

RESULTS

According to 10-, 7-, and 4-point scales; 13, 16, and 22 of 25 patients had full score, respectively. Using the clinical exam as the reference standard, sensitivities obtained for 10-, 7-, and 4-point scales were 52%, 64%, and 88%, respectively. Percent agreement between readers was 100% for 10- and 7-point scales and 88% for 4-point scale. Percent agreement for opacification of scale vessels was equally high for all three scales (93.6%, 93.7%, 91% for 10-, 7-, and 4-point scales, respectively).

CONCLUSION

The 4-point scale appears to be more sensitive than the 10- and 7-point scales in CT angiography evaluation for brain death. Interobserver agreement is high for all three scales when subtraction images are used.

Clinical diagnosis of brain death is established by national guidelines and laws in many countries. Deep unresponsive coma, absence of brain stem functions and spontaneous ventilation are principal requisites for diagnosis (1). Guidelines are revised by New York Task Forces in 2011 for determining brain death and represent a broad consensus on clinical evaluation (2). Although clinical criteria are well established, considerable practice variations are found between countries or leading hospitals of the countries such as the number of staff responsible from diagnosis, number of required examinations, observation period between examinations, application of apnea test, and confirmatory tests (3).

Confirmatory tests are required in the presence of confounding factors that could influence the exam (e.g., sedative medications, electrolyte disturbances, acid-base disorders) or make the examination severely difficult to test (e.g., severe facial or orbital trauma) (4). In neonates and children, diagnosis of brain death is more complicated and ancillary tests are usually advocated (5–7). On the other hand, a confirmatory test demonstrating lack of cerebral function or circulation is obligatory after clinical evaluation in some countries. Among the ancillary tests demonstrating absence of cerebral blood flow, multidetector computed tomography (CT) angiography emerges as a viable alternative to other tests due to its noninvasiveness, ease of access, lower operator dependence, and greater rapidity (8). However, an international consensus about application and parameters of this technique is currently not established.

The CT angiography protocols for diagnosis of brain death differ between studies in the literature. Scanning time of arterial or venous phase is the major difference in applied protocols. Beside this, disparities in scoring systems, evaluation of blood flow phases, specific vessels, and number of vessels may constitute confusing points for radiologists. Also, CT angiography findings in patients with open skull or anoxia following cardiac arrest may cause false negative interpretation (9). In the context of those diversities, diagnosis of brain death by CT angiography may become quite complicated.

In the present study, we aimed to retrospectively evaluate CT angiograms of patients with a clinical diagnosis of brain death according to 10-, 7- and 4-point score systems, review the literature, and emphasize the difficulties and confusing points of the diagnosis by previous methods. Interobserver agreement was evaluated for the diagnosis of brain death and opacification of scale vessels by CT angiography.

Methods

Diagnosis of brain death

Brain death was diagnosed when unresponsive coma, absence of brain stem reflexes, and positive apnea test (no spontaneous ventilation at

From the Department of Radiology (H.Ş. ✉ hilalcimen@gmail.com), Tepecik Training and Research Hospital, Izmir, Turkey.

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Pa CO₂ 60 mm Hg) were confirmed by a council of physicians specialized in neurology, neurosurgery, anesthesia, and cardiology. Atropine test (no tachycardia after 2 mg atropine injection) was performed by a staff cardiologist during the clinical evaluation. Patients with reversible pathologies such as metabolic and endocrine disorders, hypothermia, and intoxication were excluded from the study. None of the patients were under sedation.

Study population

Patients who were diagnosed to have brain death by a council of physicians in our institution between June 2011 and December 2013 were retrospectively evaluated. This study was approved by the institutional review board. Inclusion criteria were clinical diagnosis of brain death by a clinical council and unenhanced and biphasic (arterial and venous phases) contrast-enhanced multidetector CT angiography as a confirmatory test after clinical diagnosis. The study included 25 patients who fulfilled the inclusion criteria. Mean interval between clinical examination and CT angiography was six to 24 hours.

Imaging protocol

All examinations were performed by a 64-slice CT scanner (Aquilion 64, Toshiba Medical Systems). All patients had a systolic blood pressure greater than 90 mm Hg just before the exam. Multidetector CT scans were acquired according to the protocol outlined by Frampas et al. (8). After a lateral topography, three similar acquisitions with same section thickness (0.5 mm) were planned starting at the C1–C2 level to the convexity. Following precontrast images, a total of 80–85 mL of contrast media with high iodine concentration (370–400 mg/mL) was injected at a flow rate of 3 mL/s, followed by a 20 mL saline chaser using an 18-gauge catheter. The second and third scans were acquired at 20 s and 60 s after the contrast medium injection, respectively. The scanning parameters included 120 kV, 225 mAs, section thickness of 0.5 mm, reconstruction interval of 0.3 mm, pitch 0.641, 220 mm FOV, and 512×512 matrix. The scan revolution time was 0.4 s. CT angiography data

were obtained in a caudocranial direction without gantry angulation.

Image analysis

All multidetector CT data were transferred to a workstation (Aquarius workstation, TeraRecon), via internal network connections, providing 3D post-processing options, multiplanar image reformatting and maximum intensity projections (MIP). Axial plane subtraction images of both arterial and venous phases were obtained; coronal and sagittal reformatted images and MIP images with thickness of 5 mm were acquired in the workstation for reevaluation. Technical success of the study was confirmed by opacification of the superficial temporal artery in the arterial phase at 20 s. Opacification of ophthalmic arteries, cervical, petrous, cavernous, and supraclinoid parts of the internal carotid arteries, M1 and M4 segments of the middle cerebral arteries (MCA), A3 segments of the anterior cerebral arteries, P2 segments of the posterior cerebral arteries (PCA), V4 segments of the vertebral arteries, basilar artery (BA), internal cerebral veins (ICV), great cerebral vein (GCV), straight sinus, superior sagittal sinus, transverse sinuses, and ophthalmic veins were independently evaluated in both arterial and venous phases by two radiologists (H.S. and Y.P.) with three and five years of CT angiography experience, respectively. Diagnosis of brain death was assessed according to the previously established 10-, 7-, and 4-point scoring systems in CT angiography. Lack of opacification in peri-

callosal arteries (A3 segment), cortical branches of MCA (M4 segment), ICV, and GCV were considered in 7-point scale, while only M4 segments and ICV were evaluated in 4-point scale (Table 1). PCA-P2 segments and BA were added for the evaluation of the 10-point scale. After those assessments, both radiologists determined a final score by consensus by reevaluating all subtraction images. Interobserver agreement was evaluated for assessment of vessel opacification and diagnosis of brain death according to 10-, 7-, and 4-point scoring systems. Sensitivities of the scoring systems were calculated according to consensus scores.

Statistical analysis

Degree of interobserver agreement was determined for each analyzed vessel by using weighted-kappa statistics. Kappa coefficients were calculated for each vessel and mean kappa values were obtained for vessels with right and left side. In evaluating agreement of score point scales, percentage agreement and kappa values were calculated according to individual diagnosis of brain death (with fulfilled specific score system) or not brain death (with less than full score). Kappa values normally lie between 0 and 1, with 0 indicating agreement purely by chance and 1 indicating perfect agreement (10). Calculated kappa values were interpreted as follows; <0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; 0.81–1.00, very good agreement (11). Statistical analysis was

Table 1. Summary of radiological scores for determination of circulatory arrest^a

Vessel	10-point scale	7-point scale	4-point scale
MCA-M4 (R and L)	2	2	2
ACA-A3 (R and L)	2	2	
PCA- P2 (R and L)	2		
BA	1		
ICV (R and L)	2	2	2
GCV	1	1	
Sum of scores	10	7	4

MCA, middle cerebral artery; R, right; L, left; ACA, anterior cerebral artery; PCA, posterior cerebral artery; BA, basilar artery; ICV, internal cerebral vein; GCV, great cerebral vein.

^aOne point is given for nonopacification of each vessel.

performed using SPSS software version 20.0 (IBM Corp).

Results

There were four women and 21 men, aged 8–80 years (mean±SD, 41.9±19.8 years; median, 37 years) in the study. Two patients were in the pediatric group, aged 8 and 14 years. The cause of coma was intracranial hemorrhage in 19 patients (11 traumatic and 8 nontraumatic hemorrhage), ischemic events in six patients. Following the diagnosis of brain death only three patients became organ donors, because family members of the other patients did not give consent for organ donation.

All 25 CT angiograms were technically adequate with opacification of both superficial temporal arteries in the arterial phase indicating sufficient intravenous bolus injection of the contrast, sufficient cardiac output, and correct timing of the exam. In consensus analysis of subtraction images of the arterial phase CT angiograms, the cortical segment of the MCA (12%) and P2 segment of the PCA (12%) were the least opacified arteries. In venous phase, ICV and GCV were the least opacified veins (2% and 4%, respectively). The number and percentages of all opacified vessels are shown in Table 2.

According to the 10-point scale, 13 patients (52%) had a score of 10 (Fig. 1). A complementary exam was proposed for the remaining 12 patients (48%), since their score was less than 10. According to the 7-point scale, 16 patients (64%) had score of 7 (Fig. 1), while on the 4-point scale, 22 patients (88%) had a score of 4. Using the clinical exam as the reference standard, the most sensitive scoring system was the 4-point scale with a sensitivity of 88%. The sensitivity obtained for 10- and 7-point scales was 52% and 64%, respectively.

There were four patients (16%) with open skull defects (one craniectomy, three craniotomies). By consensus, none of them had a diagnosis of brain death when the 7- or 10-point scales were used. Only one of them had a diagnosis of brain death when the 4-point scale was used.

In evaluation of the arterial phase, degree of interobserver agreement

Table 2. Number and percentage of opacified vessels in arterial and venous CT scans

	Arterial phase n (%)		Venous phase n (%)	
STA	R: 25 (100)	L: 25 (100)	R: 25 (100)	L: 25 (100)
ICA-cervical	R: 13 (52)	L: 15 (60)	R: 20 (80)	L: 20 (80)
ICA-petrous	R: 13 (52)	L: 15 (60)	R: 20 (80)	L: 20 (80)
ICA-cavernous	R: 12 (48)	L: 14 (56)	R: 19 (76)	L: 19 (76)
ICA-supraclinoid	R: 11 (44)	L: 11 (44)	R: 15 (60)	L: 14 (56)
Ophthalmic artery	R: 20 (80)	L: 20 (80)	R: 21 (84)	L: 22 (88)
MCA-M1	R: 11 (44)	L: 10 (40)	R: 15 (60)	L: 13 (52)
MCA-M4	R: 3 (12)	L: 3 (12)	R: 4 (16)	L: 4 (16)
ACA-A3	R: 9 (36)	L: 9 (36)	R: 13 (52)	L: 13 (52)
PCA-P2	R: 3 (12)	L: 3 (12)	R: 7 (28)	L: 7 (28)
VA-V4	R: 7 (28)	L: 7 (28)	R: 8 (32)	L: 8 (32)
BA	7 (28)		9 (36)	
ICV	R: 0 (0)	L: 0 (0)	R: 0 (0)	L: 1 (4)
GCV	0 (0)		1 (4)	
SS	0 (0)		2 (8)	
SSS	0 (0)		2 (8)	
TS	R: 0 (0)	L: 0 (0)	R: 4 (16)	L: 4 (16)
Ophthalmic vein	R: 16 (64)	L: 19 (76)	R: 23 (92)	L: 24 (96)

STA, superficial temporal artery; R, right; L, left; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; VA, vertebral artery; BA, basilar artery; ICV, internal cerebral vein; GCV, great cerebral vein; SS, straight sinus; SSS, superior sagittal sinus; TS, transverse sinus.

was highest for superficial temporal artery and cervical ICA with perfect agreement of 100%, while it was lowest for M4 segment of the MCA with 86% agreement and $\kappa=0.407$ (Table 3, Fig. 2). Other arteries with low agreement were the V4 segment of the vertebral artery and the ophthalmic artery ($\kappa=0.677$ and $\kappa=0.598$; 88% agreement). For MCA-M4, agreement decreased 2% in the venous phase. In evaluation of the other arteries, agreement changed between 88% and 98% with lower agreement in the venous phase and in lower vessel calibration.

In venous phase assessment, agreement between readers was highest for the ophthalmic vein and lowest for the transverse sinuses (100% and 92% agreement, respectively) (Table 3). Percent agreement was similar for ICV, GCV, straight sinus, and superior sagittal sinus (96%). When veins were evaluated in the arterial phase, agreement was perfect since none of them opacified. However, evaluation in the venous phase resulted in lower agree-

ment, though it remained above 90% (Fig. 3).

In evaluation of scoring systems for the diagnosis of brain death, agreement between readers was excellent for the 10- and 7-point scales (100%), and very good for the 4-point scale (88%). Percent agreement for opacification of scale vessels was equally high for all three scales (93.6%, 93.7%, 91% for 10-, 7-, and 4-point scales, respectively; Table 4).

Discussion

Our results suggest that the sensitivity of CT angiography in the diagnosis of brain death is higher when a 4-point evaluation scale is used rather than a larger scale. In our study, sensitivity of 10-, 7-, and 4-point scales were 52%, 64%, and 88%, respectively. In CT angiograms, the least opacified vessels were cortical branches of MCA and P2 segment of PCA in the arterial phase, and ICV and Galen vein in the venous phase. Interobserver agreement was sufficiently high for all three scales.

Table 3. Interobserver agreement results and kappa values for vessel opacification in CT angiography

	Arterial phase		Venous phase	
	κ	Interobserver agreement n (%) ^a	κ	Interobserver agreement n (%) ^a
STA	1.000	50 (100)	1.000	50 (100)
ICA-cervical	1.000	50 (100)	0.788	47 (94)
ICA-petrous	0.960	49 (98)	0.875	48 (96)
ICA-cavernous	0.960	49 (98)	0.944	49 (98)
ICA-supraclinoid	0.920	48 (96)	0.917	48 (96)
Ophthalmic artery	0.598	44 (88)	-0.068 ^b	40 (80)
MCA-M1	0.959	49 (98)	0.919	48 (96)
MCA-M4	0.407	43 (86)	0.471	42 (84)
ACA-A3	0.956	49 (98)	0.880	47 (94)
PCA-P2	0.623	46 (92)	0.653	43 (86)
VA-V4	0.677	44 (88)	0.729	44 (88)
BA	0.905	24 (96)	0.749	22 (88)
ICV	N/A	50 (100)	0.000	48 (96)
GCV	N/A	25 (100)	0.000	24 (96)
SS	N/A	25 (100)	0.648	24 (96)
SSS	N/A	25 (100)	0.779	24 (96)
TS	N/A	50 (100)	0.752	46 (92)
Ophthalmic vein	1.000	50 (100)	1.000	50 (100)

STA, superficial temporal artery; ICA, internal carotid artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; VA, vertebral artery; BA, basilar artery; ICV, internal cerebral vein; N/A, not available (Kappa could not be calculated); GCV, great cerebral vein; SS, straight sinus; SSS, superior sagittal sinus; TS, transverse sinus.

^aNumber of times the readers agreed between themselves. For vessels with right and left side, both sides are evaluated and mean kappa value is calculated.

^bThe strength of agreement is worse than expected by chance alone.

Table 4. Interobserver agreement results for CT angiography confirmation of brain death by 10-, 7-, and 4-point score systems

	Agreement for diagnosis of brain death		Agreement for opacification of scale vessels	
	κ	%	κ	%
10-point	1.000	100	0.757	93.6
7-point	1.000	100	0.748	93.7
4-point	0.519	88	0.357	91.0

Recently, Cochrane collaboration performed a comprehensive literature search to assess the diagnostic accuracy of CT angiography in cohorts of adult patients using the diagnosis of brain death according to neurological criteria as a target condition (12). After analyzing 10 studies including 366 patients,

they proposed that CT angiography may be useful as a confirmatory or an add-on test following the clinical diagnosis of brain death. However, specificity could not be estimated in those studies due to lack of true negatives and false positives. According to available published data, the use of CT angiography as a man-

datory test or a complete replacement for neurological testing was not recommended. On the other hand, it is important for clinicians to know the utility of CT angiography when added to usual clinical tests. This fact increases the necessity for standard radiological interpretation protocol for future studies.

Dupas et al. (1) published the first paper on CT angiography for detecting cerebral circulatory arrest in 1998. They performed CT angiography in two stages (20 s and 54 s after contrast injection). Most of the other studies in the literature are also based on arterial and venous scanning with unenhanced scan for comparison. However, Berenguer et al. (13) established that delayed venous blood flow was from collaterals and this phase of the scan could be omitted. Furthermore, some authors evaluated intracranial circulatory arrest in arterial series (1, 9, 13–15), while others studied it in venous series (8, 16–18). Recently, Welschehold et al. (19, 20) proposed that analysis of arterial vasculature should be carried out in the arterial scanning phase and that of deep venous system in the venous phase, as employed in our study. Besides those disparities, scanning time of arterial and venous phases also differ between studies. Most studies initiated the arterial phase scan 20 s after contrast injection (1, 8, 18), while bolus triggering technique was used in others (9, 21). Timing of the venous phase also ranged between 54 s and 80 s after contrast injection (1, 21). Therefore, various CT angiography scanning parameters from different studies make the comparison of the data difficult.

Following the introduction of 7-point scale by Dupas et al. (1) in 1998 and 4-point scale by Leclerc et al. (18) in 2006, some studies compared the 7- and 4-point scoring systems. Frampas et al. (8) established the sensitivity of CT angiography as 62.8% according to the 7-point scale and 85.7% according to the 4-point scale, whereas Rieke et al. (21) proposed a sensitivity of 75.9%. Shankar and Vandorpe (22) reported the sensitivity of CT perfusion and CT angiography as 72.7% for 7- and 4-point scales. In our study, the sensitivity of 7- and 4-point scales was determined as 64% and 88%, respectively, which is slightly higher than the sensitivity rates of Frampas et

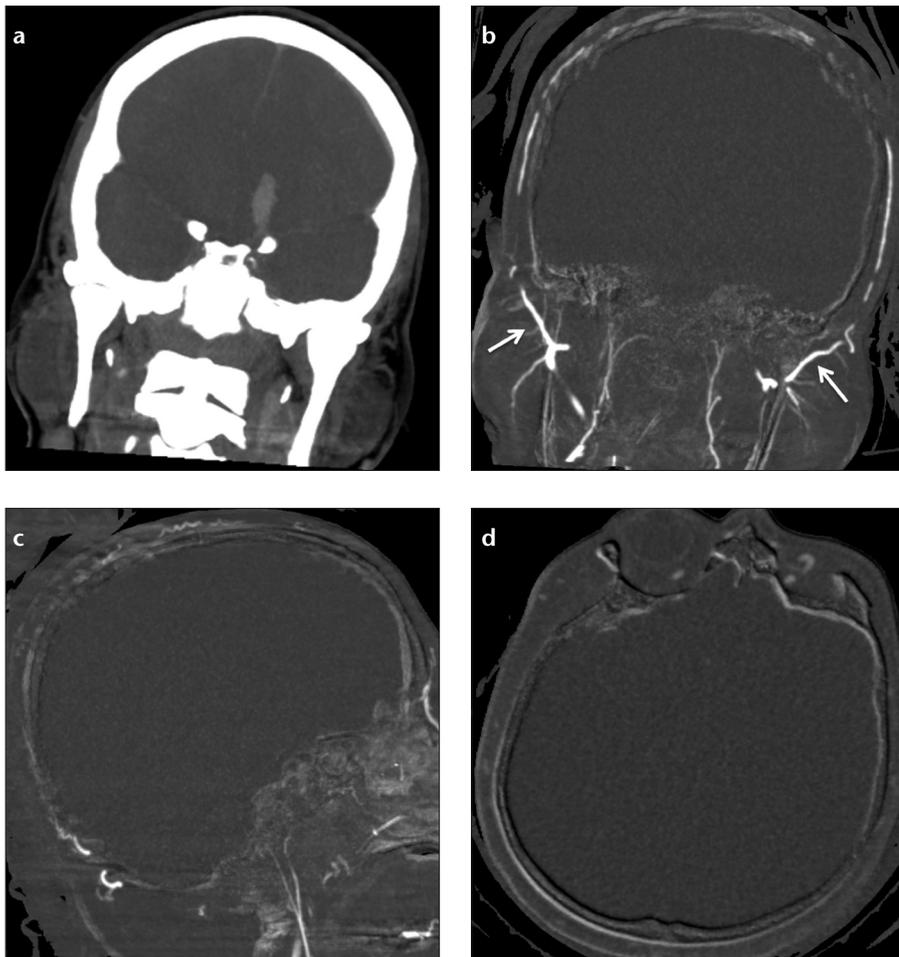


Figure 1. a–d. A 42-year-old female patient. Unenhanced coronal reformatted image (a) shows hematoma in the left inferior frontal lobe. Arterial phase 5 mm coronal maximum intensity projection (MIP) subtraction image (b) shows absence of opacification of the middle cerebral arteries and branches. Both superficial temporal arteries have intense opacification indicating adequate technique (*arrows*). Arterial phase 5 mm sagittal MIP subtraction image (c) shows no enhancement in pericallosal arteries. Venous phase 5 mm axial MIP subtraction image (d) shows absence of opacification of the internal cerebral veins and great cerebral vein. Note that both ophthalmic veins are enhancing. This patient was diagnosed to have brain death both clinically and radiologically.

al. (8). Sensitivity of our 4-point scale was close to the results of two recent meta-analyses (12, 23). According to a meta-analysis of twelve studies involving 541 patients, the pooled sensitivity was 62% for venous phase and 84% for arterial phase, when complete lack of opacification of intracranial vessels was taken as the CT angiography criterion for brain death (23). Sensitivity was 85% (77%–93%) when the CT angiography criterion involved the lack of opacification of ICVs and distal MCA branches using the 4-point scale. Cochrane analysis (12) also reported the sensitivity of CT angiography as 85% after retrospective reanalysis of eight studies including a total of 344

patients by the four-vessel radiological review methodology.

In 2007, Combes et al. (17) included the vessels of the posterior circulation (PCA-P2 and BA) into the scoring system in their study, creating the 10-point scale. Welchhold et al. (19) also used this scoring system excluding GCV. Combes et al. (17) proposed a sensitivity of 69.7%, while Welchhold et al. (19) estimated a sensitivity of 95%. According to our results, sensitivity for the 10-point score was 52%. A possible explanation for this difference may be the shorter mean interval between the clinical exam and CT angiography, as the intracranial perfusion pressure might not have been suf-

ficiently high. Up to now, published meta-analyses have not evaluated the sensitivity of the 10-point scale. A recent article compared three scoring systems and recorded the sensitivity using the 10-, 7- and 4-point scales as 67.1%, 74.4%, and 96.3%, respectively (24). Our study has some technical differences from that study. First, we obtained arterial and venous phases at 20 s and 60 s rather than a single contrast-enhanced phase at 40 s. Second, subtraction images of both phases were obtained in our study to avoid interpretation mistakes due to subarachnoid hemorrhage, pseudo-subarachnoid hemorrhage, or cranial shift and to increase interobserver concordance. As expected, in both studies, sensitivity decreased as the number of evaluated vessels increased. When posterior circulation arteries were included in the diagnostic scale, sensitivity decreased even more, as also established in our study. Sawicki et al. (24) explained this statement by the protective role of the cerebellar tentorium. They also proposed that, in up to 17% of brain death patients, BA may enhance, which does not preclude a diagnosis of brain death. According to our results, 28% of BAs enhanced. This result may represent the disparity between the sensitivity of the 10-point scale and others. On the other hand, PCA-P2 was the least enhanced artery (12%) as MCA-M4 in our study. Therefore, we believe that analysis of posterior cranial circulation might also be performed by CT angiography including only PCA-P2 which is closer to the capillary bed. In this way, sensitivity of the 10-point scale may be improved by excluding BA.

Frampas et al. (8) established that the absence of internal cerebral veins and bilateral cortical branches of the MCAs were the best criteria of brain death diagnosis by CT angiography. In addition to MCA-M4 and ICVs, PCA-P2 and GCV were the most sensitive vessels for diagnosis of cerebral circulatory arrest in our study. Both ICVs and GCV were absent in 96% of the patients and this was the most sensitive and earliest sign. Frampas et al. (8), and Quesnel et al. (16) also found similar results; 98.1% and 85.7% of patients lacked deep venous return relatively in their studies, respectively.

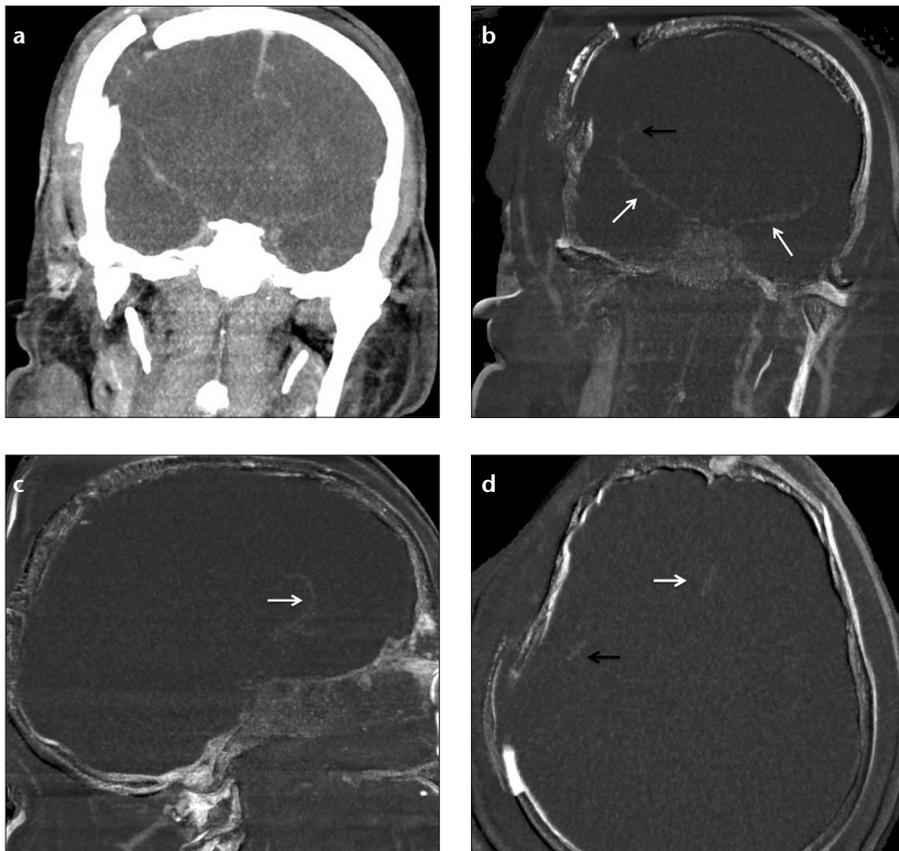


Figure 2. a-d. A 44-year-old male patient with traumatic subarachnoid hemorrhage and decompressive craniotomy. Unenhanced coronal reformatted CT scan (a) shows subarachnoid hemorrhage and low density brain parenchyma indicating diffuse brain ischemia. Arterial phase 5 mm coronal MIP subtraction image (b) shows enhancement in the horizontal part of the middle cerebral arteries (white arrows). Cortical branches of the right middle cerebral artery have slight opacification which caused disagreement between readers (black arrow). In consensus decision, the right M4 segment was accepted as opacified. Arterial phase 5 mm sagittal reformatted MIP subtraction image (c) shows slight opacification of A2 segment of the anterior cerebral artery (white arrow). Arterial phase 5 mm axial MIP subtraction image (d) shows slightly enhancing A2 segment of the anterior cerebral artery (white arrow) and cortical branch of the right middle cerebral artery (black arrow).

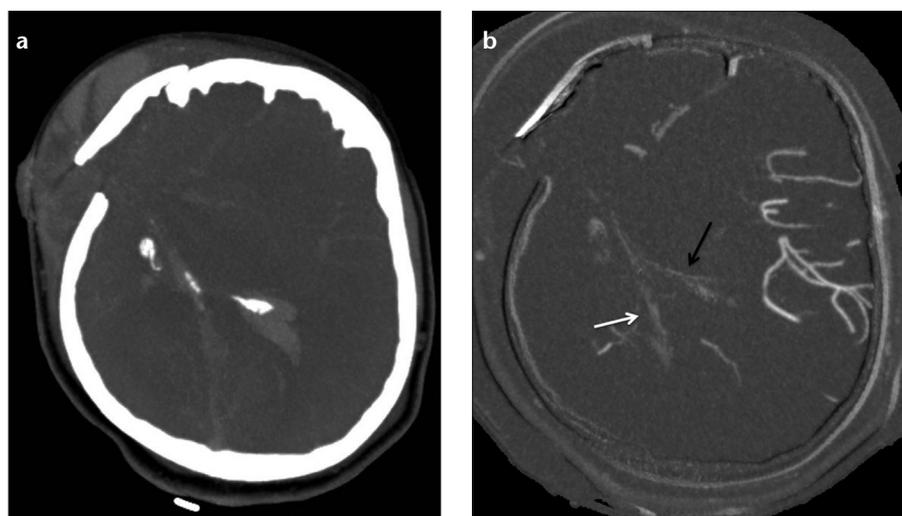


Figure 3. a, b. A 31-year-old female patient. Unenhanced axial CT scan (a) shows craniotomy defect, severe midline shift, and extra cerebral herniation. Venous phase 5 mm axial MIP subtraction image (b) shows slight opacification in the left internal cerebral vein (black arrow) and the great cerebral vein (white arrow). However, it is difficult to evaluate right internal cerebral vein due to hemorrhage and cranial shift. In this case, both readers agreed on nonopacification of the right internal cerebral vein. Note that the cortical branches of the left middle cerebral artery shows intense enhancement.

Preserved opacification of intracranial vessels in brain-dead patients with skull defects, such as craniectomy or skull fractures, is a known phenomenon which is reported by several authors previously (8, 9, 21, 24). In case of pressure relieving defect, intracranial pressure does not exceed the cerebral perfusion pressure (9). This can cause diagnostic problems in patients with skull defects, particularly craniectomy, leading to false negative results. In the literature, craniectomy frequencies of 19%–32% were reported (9, 21, 24). Frampas et al. (8) proposed that CT angiography does not appear to be efficient for patients with craniectomy. Rieke et al. (21) found CT angiography to be false negative in 50% of patients with craniectomy according to both 7- and 4-point scales. Sawicki et al. (24) determined this value as 65% and found craniectomy to be an independent predictive factor of false negative CT angiography. In our study, the rate of false negativity among patients with open skull defects was 75% and 100% using the 4-point scale and other scales, respectively. However, only four patients had skull defects in our study which limits us to make a speculative comment on that issue. Considering the high rate of false negativity in patients with open skull defects, new studies focusing on this special group of patients must be designed to decide on the best confirmatory protocol.

If CT angiography were to be preferred as a confirmatory test, there should be no contradiction between the readers. Interobserver agreement should be sufficiently high to make a correct diagnosis. But to the best of our knowledge, only Sawicki et al. (24) compared interobserver agreement of three scales of CT angiography for the diagnosis of brain death. Agreement was high (89%–95%) for all scales in their study. In the present study, there was perfect agreement for diagnosis of brain death between readers when 10- and 7- point scales were used. This could be explained by use of subtraction images for each phase which are more reliable in case of subarachnoid hemorrhage or pseudo-subarachnoid hemorrhage. However, agreement was somewhat lower when using the 4-point scale (88%). This difference

might be explained by the small number of patients, open skull defects due to skull fracture or craniectomy, and interpretation difficulties due to cranial shift. Additionally, absence of a cutoff point for the contrast enhancement of an artery or a vein might have caused disagreement on some images. Interobserver agreement for opacification of scale vessels was high (91%–93.7%) for all three scales. However, calculated kappa coefficient was low for the 4-point scale. This is explained by Feinstein-Cicchetti paradox in which interobserver agreement coefficients are affected by prevalence of measures (25, 26). Lower values of coefficients are due to accumulation of low frequency discordance such as low frequency of negative CT angiography when the 4-point scale used. In such situations, percent agreement may be used as an indicator of interobserver concordance instead of the kappa value.

There are some limitations in the present study. First, results were not compared with another noninvasive or invasive confirmatory test. Second, a cutoff point for vessel opacification was not used. Those limitations probably influenced the degree of agreement on the diagnosis of brain death. But, we believe that interobserver discordance was minimized through the use subtraction images, which helped us overcome those limitations. Third, our study population was relatively small, as a result of which, sensitivity of the scoring systems, particularly of the 7- and 10-point scales, were lower than the previous reports. Fourth, there was no control group in the study, such as comatose patients who did not have brain death by clinical tests. In our institution, CT angiography is performed only after a diagnosis of brain death is made by clinical tests to avoid unnecessary intravenous contrast application. Hence, there were no true negatives or false positives, and specificity could not be estimated, similar to previous reports in the literature.

In conclusion, although CT angiography is a valuable, fast, and easily accessible confirmatory test for brain death diagnosis, application in clinical practice is not easy, since different studies with different scanning parameters and evaluation criteria in

the literature may be confounding. In comparison of diagnostic scoring systems, the 4-point scale appears significantly more sensitive than the 10- and 7-point scales. Interobserver agreement is high for all three scales when the subtraction images are used. Further studies should be performed with larger study populations to clear up confusing points about the evaluation criteria and establish the most sensitive and specific scoring system as an international consensus.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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