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Accuracy of Computed Tomographic Perfusion in Diagnosis of Brain Death: A Prospective Cohort Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: This study was designed to determine diagnostic accuracy of computed tomographic perfusion (CTP) compared to computed tomographic angiography (CTA) for the diagnosis of brain death (BD).

Material/Methods: Whole-brain CTP was performed in patients diagnosed with BD and in patients with devastating brain injury with preserved brainstem reflexes. CTA was derived from CTP datasets. Cerebral blood flow (CBF) and volume (CBV) were calculated in all brain regions. CTP findings were interpreted as confirming diagnosis of BD (positive) when CBF and CBV in all ROIs were below 10 mL/100 g/min and 1.0 mL/100 g, respectively. CTA findings were interpreted using a 4-point system.

Results: Fifty brain-dead patients and 5 controls were included. In brain-dead patients, CTP results revealed CBF 0.00–9.98 mL/100 g/min and CBV 0.00–0.99 mL/100 g, and were thus interpreted as positive in all patients. CTA results suggested 7 negative cases, providing 86% sensitivity.
In the non-brain-dead group, CTP results revealed CBF 2.37–37.59 mL/100 g/min and CBV 0.73–2.34 mL/100 g. The difference between values of CBF and CBV in the brain-dead and non-brain-dead groups was statistically significant (p=0.002 for CBF and p=0.001 for CBV). CTP findings in all non-brain-dead patients were interpreted as negative. This resulted in a specificity of 100% (95% CI, 0.31–1.00) for CTP in the diagnosis of BD. In all non-brain-dead patients, CTA revealed preserved intracranial filling and was interpreted as negative. This resulted in a specificity of 100% (95% CI, 0.31–1.00) for CTA in diagnosis of BD.

Conclusions: Whole-brain CTP seems to be a highly sensitive and specific method in diagnosis of BD.

MeSH Keywords: Brain Death • Four-Dimensional Computed Tomography • Multidetector Computed Tomography • Perfusion Imaging

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Background

The essential clinical diagnostic components of brain death (BD) must include evidence of an established etiology capable of causing BD, exclusion of confounders that can mimic BD, 2 independent confirmations by physical examination for the absence of all brainstem reflexes, and an apnea test. Numerous confounders can render clinical diagnosis of BD virtually impossible (e.g., the use of barbiturates or other sedatives, severe craniofacial trauma preventing appropriate clinical neurological examination, and high cervical spine injuries preventing the performance of the apnea test). Many of those confounders are increasingly in use in clinical practice (e.g., therapeutic hypothermia and decompressive craniectomy), although ancillary tests are required in situations where the clinical evaluation is impossible. Widely accepted ancillary tests include cerebral catheter angiography, perfusion scintigraphy, and transcranial Doppler ultrasonography. Recently, computed tomographic angiography (CTA) was introduced to the diagnosis of cerebral circulatory arrest. However, its use for confirmation of BD raises particular diagnostic challenges such as the potential persistence of blood flow in patients with clinically confirmed diagnosis of BD [1]. This diagnostic confusion is caused by the preserved filling of the cortical branches of the middle cerebral artery (MCA), the internal cerebral veins (ICV), or both, and this preservation is observed in 15% of brain-dead patients, according to recent meta-analyses [2,3].

However, the phenomenon of persistent intracranial opacification, also known as stasis filling, does not necessarily preclude the diagnosis of BD, as was shown by Sawicki et al. [4]. This hypothesis was supported by Shankar et al., who found computed tomographic perfusion (CTP) parameters consistent with nonviable brainstem in patients with preserved filling of supratentorial vessels when using CTA [5]. However, that study was limited to qualitative assessment of brainstem perfusion not providing values of perfusion parameters for the entire brain. In our study, calculations of perfusion parameters for the whole brain, with simultaneous assessment of vascular filling with CTP-derived CTA, were performed.

CTP is routinely used for evaluation of cerebral ischemia and vascularization of brain tumors. The technique enables calculation of cerebral blood flow (CBF) and volume (CBV) based on the first passage of a contrast bolus through the brain tissue. Confirmation of BD with CTP, as proposed in our study, is a new application of the method.

Because cerebral circulatory arrest commences at the capillary level, we hypothesized that the addition of whole-brain CTP to the commonly used CTA approach would reduce the frequency of negative findings obtained using CTA alone, increasing the sensitivity of the test for the confirmation of BD. Therefore, the present study was designed to determine the diagnostic accuracy of CTP compared to CTA for the diagnosis of BD.

Material and Methods

Study design

This prospective clinical study was approved by the responsible Ethics Committee.

The study participants were recruited from consecutive patients admitted to the intensive care unit of our university hospital (tertiary center) showing clinical signs of BD: deep, unresponsive coma of established etiology capable of causing neurological death; requiring artificial ventilation; and absence of brainstem reflexes, including pupil, oculocephalic, oculovestibular, corneal, pharyngeal and tracheal reflexes. These patients comprised the study (brain-dead) group. The control (non-brain-dead) group consisted of patients with devastating brain injury, in coma, and on artificial ventilation, but with preserved brainstem reflexes. We excluded patients with refractory mean arterial blood pressure ≤60 mmHg.

All participants underwent brain volume scanning using CTP and CTA.

Shortly after radiological examinations, all patients from the brain-dead group underwent the procedure of BD declaration. This declaration was made after determination of coma, brainstem areflexia, and absence of respiratory drive using a 10-min apnea criterion. In concordance with national legal regulations, these tests were performed twice by 3 specialists. The study flowchart is presented in Figure 1. Transplantable organs were procured from most of the brain-dead patients. In some cases, organ donation was abandoned for medical reasons or because of a lack of consent from family members. In such situations, all forms of life support, including ventilation, were withdrawn, and patients underwent cardiopulmonary collapse within a short time.

CT data acquisition

Data were acquired using a 128-slice Siemens Definition AS+ CT scanner (Siemens Healthcare, Erlangen, Germany) after administration of iodinated contrast material (50 mL; Iomeron 400, Bracco Imaging, Konstanz, Germany) at a rate of 6 mL/s via a power injector through an 18-gauge intravenous line, followed by saline (30 mL) administered at the same rate. The scanning parameters were 80 kVp and 200 mAs. Scans were performed every 1.5 s for 60 s and were started with a delay of 4 s after contrast material injection, providing a total of 40

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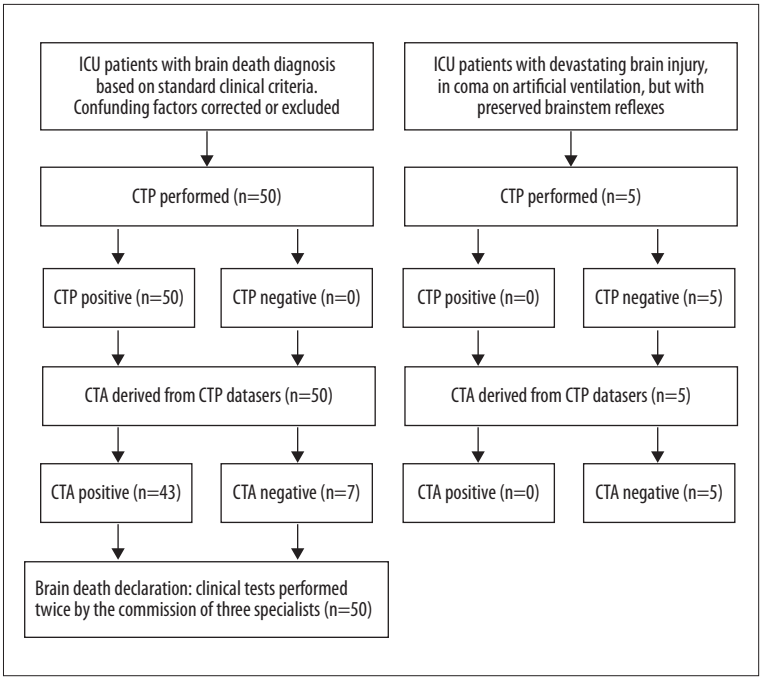

Figure 1. Study flow diagram. CTP – computed tomographic perfusion; CTA – computed tomographic angiography; MAP – mean arterial blood pressure. CTA- or CTP-positive means that the result confirms the diagnosis of BD and a negative result is inconsistent with the diagnosis of BD.

volume datasets. The total coverage in the z-axis was 96 mm, with a slice width of 10 mm obtained in 5-mm increments using a shuttle mode (adaptive 4-D spiral).

Postprocessing

CTP

Perfusion parameters were calculated using the commercial perfusion software package syngo.via(R) CT Neuro Perfusion Version 2012B (Siemens Healthcare, Forchheim, Germany) based on a deconvolution algorithm with least mean-square fitting. Processing was performed semiautomatically with the default settings used in routine clinical practice. The use of automatic motion correction was necessary to eliminate possible artifacts caused by ventilation and to-and-fro (shuttle) movement of the table during acquisition. Additional noise was removed using an automatic 4-D noise reduction tool to improve the quality of the image. An arterial input function (AIF) and a reference vessel were chosen from time-averaged maximum intensity projection (MIP) images. The AIF was manually set to the cavernous segment of the internal carotid artery (ICA). To eliminate partial volume averaging, the original AIF was corrected to the maximal enhancement measured in the reference vessel. This was the only possible choice, as none of the remaining arteries showed satisfactory enhancement in brain-dead patients. In all cases, this same vessel (i.e., the same cavernous segment of the ICA that was used for AIF) was used as a surrogate of venous output function. In the brain-dead group, the intracranial veins (including the routinely used superior sagittal sinus, torcular herophili, or transverse sinus) could not be used for the venous output function because they showed vestigial enhancement or entirely lacked enhancement. Major vessels were removed by relative "thresholding" applied to the maximal enhancement. Relative thresholds were set at 8% of the maximal enhancement. A normalization step, routinely used in clinical practice, was not performed in the present study because neither of the cerebral hemispheres could be used as a reference point for normal perfusion in brain-dead patients.

To determine perfusion values from different brain regions, 1-cm^2 circular regions of interest (ROIs) circumscribing the brainstem, including the midbrain (n=2), pons (2), and medulla oblongata (2), as well as the cerebellum (8), cortical regions of the frontal (12), parietal (12), temporal (12), and occipital lobes (8), and the basal ganglia (8), were drawn bilaterally and placed on each 10-mm axial slice. This resulted in a total of 66 ROIs for each patient. Postprocessing, including selection of ROIs, was performed by a board-certified radiologist with over 10 years' experience in neuroradiology who was blinded to the results of clinical tests.

CTA

The CTA images were automatically reconstructed from the CT perfusion source images using syngo.via(R) CT Dynamic Angio Version 2012B (Siemens Healthcare, Forchheim, Germany) as timing-invariant (TI)-CTA. The TI-CTA provides angiography by overlapping all timeframes and displaying maximal enhancement over time. Due to the choice of temporal maximum, this technique is timing-invariant, which means that the maximal

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enhancement of a vessel is displayed independent of its contrast arrival time. Therefore, TI-CTA is not sensitive to delayed contrast material arrival in cerebral vessels, and thus should display any vessel present. This technique was previously described and shown to be reliable by Smit et al. [6].

Image analysis

CTP

CTP findings were interpreted as consistent with BD diagnosis (i.e., positive) when CBF and CBV values in all 66 ROIs were below the well-established thresholds for neuronal necrosis (i.e., 10 mL/100 g/min and 1.0 mL/100 g, respectively). CTP results were interpreted as negative (i.e., not confirming the BD diagnosis) when CBF and/or CBV in any ROI were above 10 mL/100 g/min and 1.0 mL/100 g, respectively.

CTA

The CTA data were derived from CTP datasets as TI-CTA. The images were analyzed first for the appearance and disappearance of contrast media in the superficial temporal artery branches to confirm that the contrast was injected properly and to eliminate the potential influence of hemodynamic perturbations. The presence of contrast in the different segments of the intracranial arteries was analyzed using CTA on a 4-point scale based on the lack of opacification of the cortical segments of the MCA and the 2 ICVs. A score of 1 was given for each of the non-opacified vessel segments.

The CTA findings were interpreted as consistent with a BD diagnosis (i.e., positive) if the exam revealed bilateral nonfilling of cortical segments of the MCA and bilateral nonfilling of the ICV (score 4). Negative results not confirming BD received scores of 0–3. This 4-point grading system was proposed by Leclerc et al. in 2006 [7].

A neuroradiologist with 10 years' experience in interpreting cerebral CTA and blinded to the results of clinical tests evaluated all CTA images.

Data collection

The following demographic and clinical data were collected: age, sex, and cause of brain injury categorized as vascular (ischemic stroke, non-traumatic intracranial hemorrhage), or traumatic or anoxic-ischemic injury. For each CTP ROI, the following parameters were recorded: CBF, CBV, and contrast-to-noise ratio (CNR). The CNR was calculated using the formula:

$$CNR=(\text{peak HU mean}-\text{baseline HU mean})/\text{baseline HU SD}$$

where HU represents Hounsfield units and SD represents standard deviation.

Each CTA opacification of the cortical branches of the MCA and ICV was noted bilaterally.

Statistical analysis

The χ^2 test was used to compare the sensitivities of CTP and CTA in the diagnosis of BD. Differences between perfusion parameters of brain-dead and non-brain-dead groups was calculated using the Friedman ANOVA test. A value of $p<0.05$ was considered statistically significant. Statistica 12 software (StatSoft Inc., Tulsa, OK, USA) was used for statistical analyses. A biomedical statistician reviewed the manuscript for clarity of statistical analyses and data presentation.

Results

Fifty patients (27 females, 23 males) with a mean age of 55±18 years (range, 17–78 years) were enrolled in the brain-dead group. No patients were excluded due to refractory mean arterial blood pressure ≤60 mmHg. Of the 50 patients enrolled, the cause of brain injury was vascular in 36 (72%), traumatic in 5 (10%), and anoxic-ischemic in 9 (18%) patients.

The non-brain-dead group consisted of 5 patients (3 females, 2 males) with a mean age of 49±18 years (range, 37–71 years). The cause of brain injury was vascular in 4 (80%) patients, and anoxic-ischemic in 1 (20%) patient.

In the brain-dead group, the CTP findings revealed CBF from 0.00 to 9.98 mL/100 g/min (mean, 1.98±1.68 mL/100 g/min) and CBV from 0.00 to 0.99 mL/100 g (mean, 0.14±0.12 mL/100 g). In all 50 patients, values in all ROIs (including brainstem) were below the thresholds of 10 mL/100 g/min for CBF and 1.0 mL/100 g for CBV. Therefore, we interpreted the CTP findings in all brain-dead patients as positive (i.e., the results confirmed the diagnosis of BD). This resulted in a sensitivity of 100% (95% CI, 0.91–1.00) for CTP in the diagnosis of BD. The values of the perfusion parameters for individual patients are presented in Figure 2.

The use of TI-CTA in brain-dead patients showed 7 negative results because preserved cortical or deep venous filling was noted, which is inconsistent with the diagnosis of BD (Table 1). CTA and CTP results in one of these patients are presented in Figure 3. This resulted in a sensitivity of 86% (95% CI, 0.73–0.94) for CTA in the diagnosis of BD.

We found a statistically significant difference between the sensitivities of CTP and CTA in the diagnosis of BD ($p=0.006$; χ^2 test).

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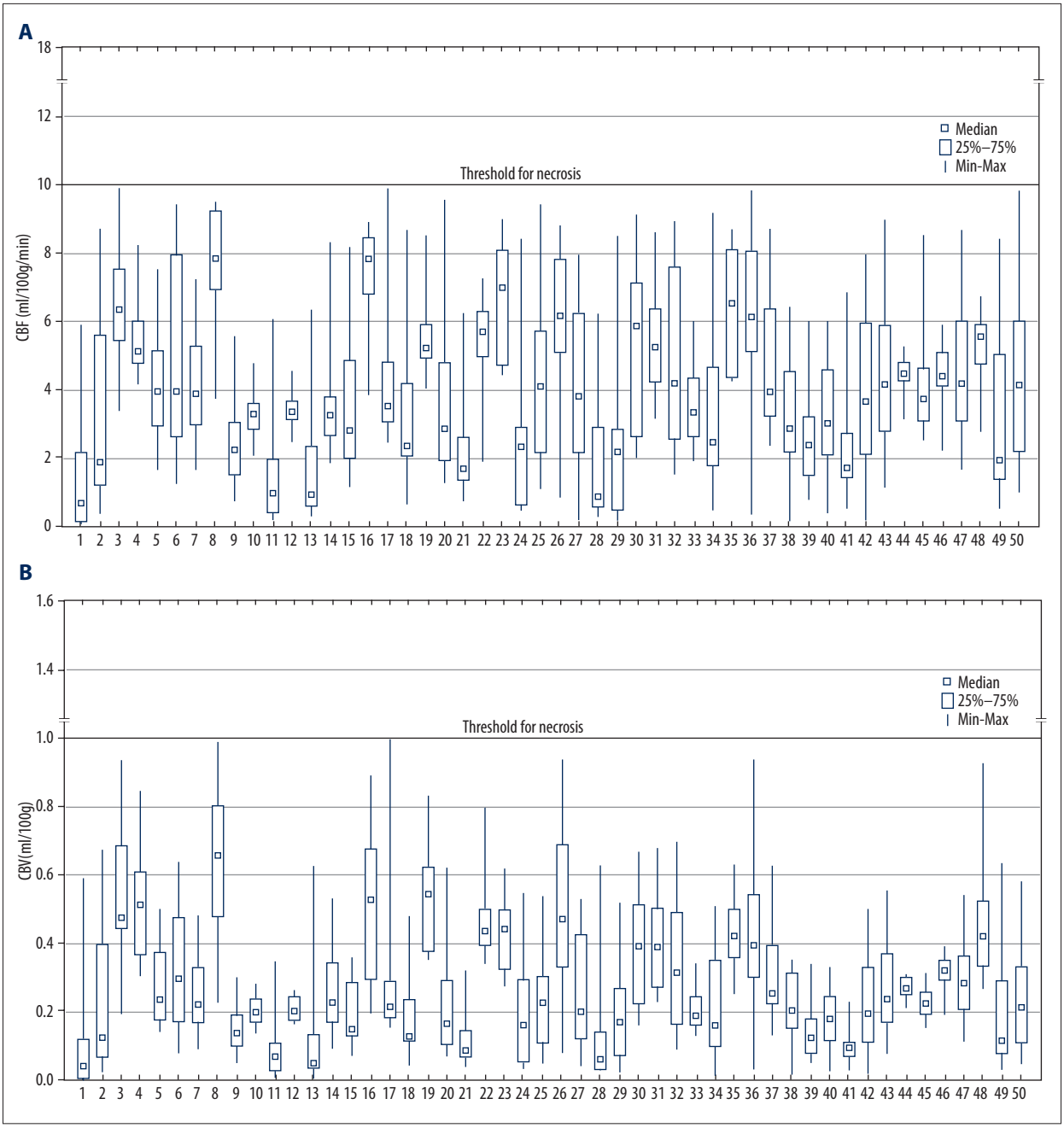

Figure 2. The distribution of CBF (**A**) and CBV (**B**) in 50 patients diagnosed with BD. Box plots present values obtained from 66 ROIs for each patient covering all brain regions. Data are presented as medians, 25–75% interquartile ranges, minimums, and maximums. In all cases, the perfusion values are below the thresholds for nonviable tissue.

In the non-brain-dead group, the CTP findings revealed CBF from 2.37 to 37.59 mL/100 g/min (mean, 14.56±7.34 mL/100 g/min) and CBV from 0.73 to 2.34 mL/100 g (mean, 1.75±0.69 mL/100 g). We found a statistically significant difference between the values of CBF and CBV in the brain-dead and non-brain-dead group (p=0.002 for CBF and p=0.001 for CBV; Friedman ANOVA test) (Figure 4).

In all non-brain-dead patients, values of CBF and CBV in all ROIs positioned in the brainstem were above 10 mL/100 g/min for CBF and 1.0 mL/100 g for CBV. However, we found some regions in the supratentorial compartment showing values below10 mL/100 g/min for CBF and 1.0 mL/100 g for CBV, corresponding with localization of brain injury. Figure 5 presents CTP and CTA results in one of these patients. Therefore, we interpreted the CTP findings in all non-brain-dead patients as

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Table 1. Patient's characteristics and imaging findings in cases of false negative CTA results.

#	Sex	Age	Cause of brain injury	CTA opacification				BD diagnosis
				MCA-M4 right	MCA-M4 left	ICV right	ICV left	
5	M	56	Vasc	0	1	1	1	Negative
8	M	71	Vasc	0	0	0	1	Negative
17	M	73	Tbi	1	0	1	1	Negative
23	F	34	Vasc	0	0	1	1	Negative
29	M	50	Vasc	0	1	1	1	Negative
41	M	44	Vasc	0	0	1	1	Negative
47	M	51	Vasc	1	0	1	1	Negative

Vasc – ischemic stroke and non-traumatic intracranial hemorrhage; Tbi – traumatic brain injury.

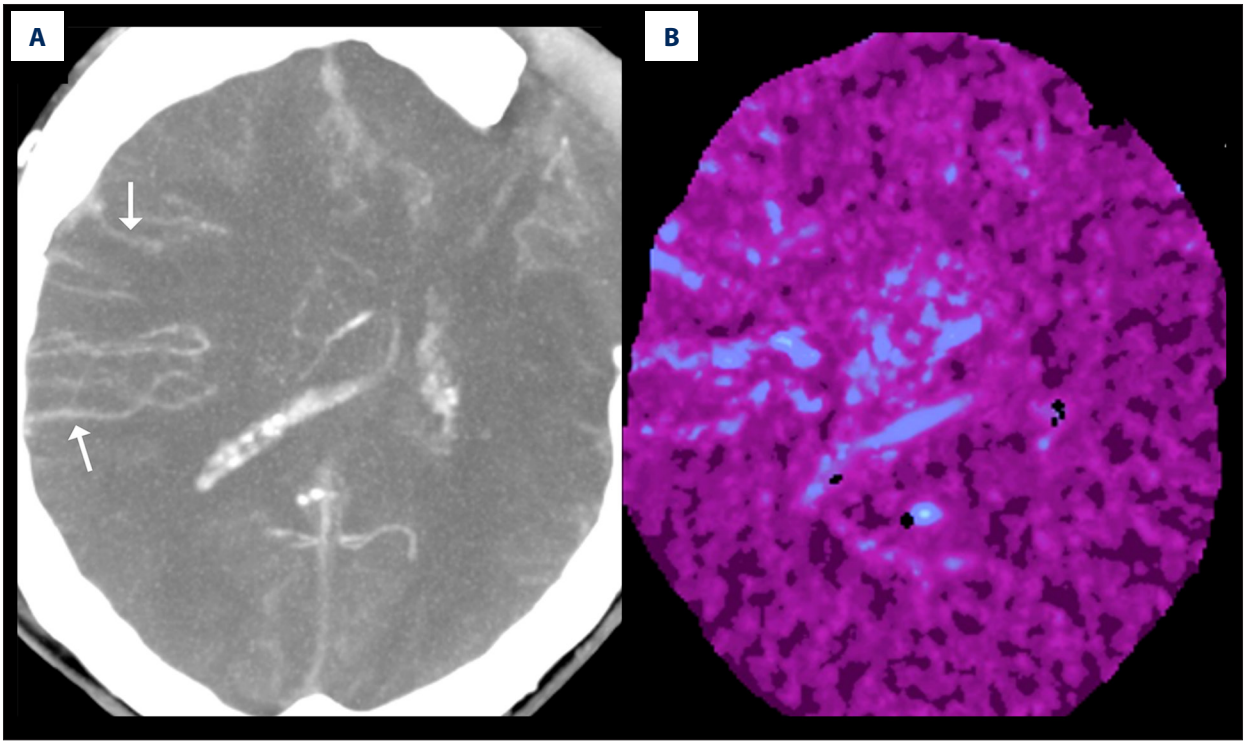

Figure 3. Results of CTA (**A**) and CTP (**B**) in the patient clinically diagnosed with brain death. CTA shows filling of cortical branches of the right MCA (arrows) and was classified as negative (i.e., inconsistent with the diagnosis of BD). CTP reveals perfusion values below the thresholds for nonviable tissue and was interpreted as positive (i.e., consistent with the diagnosis of BD).

negative (i.e., the results excluded the diagnosis of BD). This resulted in a specificity of 100% (95% CI, 0.31–1.00) for CTP in the diagnosis of BD.

In all non-brain-dead patients, TI-CTA revealed preserved cortical and deep venous filling and was interpreted as negative (i.e., inconsistent with the diagnosis of BD). This resulted in a specificity of 100% (95% CI, 0.31–1.00) for CTA in the diagnosis of BD.

The evaluation of image quality showed a mean CNR of 0.34±0.21 (range, 0.09–0.85) in the brain-dead group, while mean CNR in the non-brain-dead group was 9.26±2.51 (range, 7.43–11.19). We found a statistically significant difference in CNR values between the brain-dead and non-brain-dead groups (p<0.001; Friedman ANOVA test).

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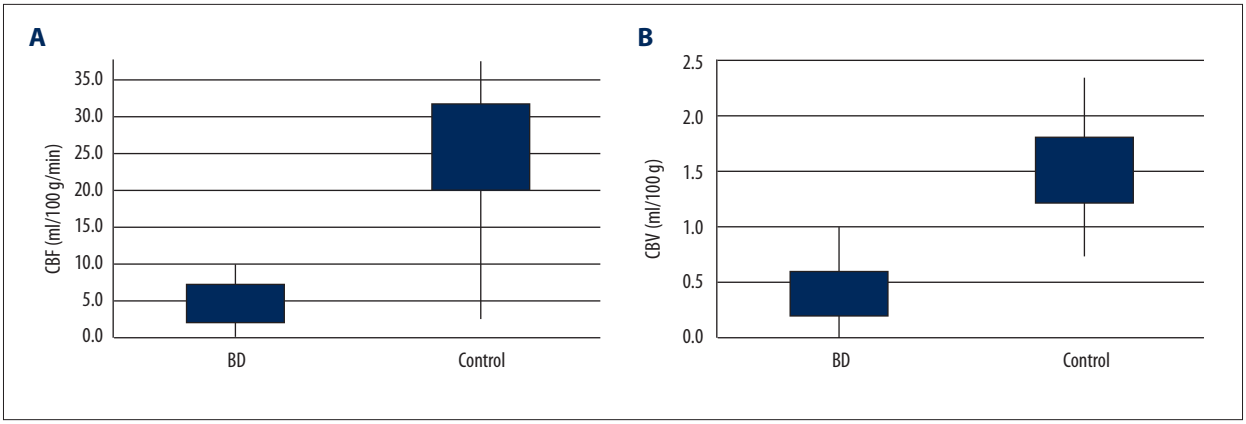

Figure 4. Distribution of CBF (**A**) and CBV (**B**) values in BD patients and controls. Box plots present values obtained from all ROIs covering all brain regions in all patients from the groups. Data are presented as 25–75% interquartile ranges, minimums, and maximums. BD – brain-dead group. We found a statistically significant difference between the values of CBF and CBV in the brain-dead and control group (p=0.002 for CBF and p=0.001 for CBV; Friedman ANOVA test).

Discussion

An ideal ancillary test should not have any false-positive results (i.e., declaration of death when in fact the patient is not dead). Our results show that both CTA and CTP fulfill this condition, as they achieved 100% specificity.

Our study revealed 100% sensitivity of CTP in the diagnosis of BD, revealing whole-brain nonviability in all brain-dead patients, including those in whom the results of CTA was false-negative (i.e., it showed preserved intracranial filling).

This is consistent with the results of previous research by Sawicki et al. and by Shankar et al., who found that preserved intracranial opacification can be observed in cases in which CTP shows nonviability of the brain [4,5]. This apparent discrepancy may be explained by greater susceptibility of capillaries to intracranial hypertension compared with large- and medium-size vessels. Therefore, the gradual increase in intracranial pressure causes cessation of capillary blood flow reflected by CTP, as contrast can still fill more proximal arteries for some time, which is detectable in CTA. This phenomenon is a serious limitation in the application of CTA for the diagnosis of BD. A recent meta-analysis showed a sensitivity of 85% for CTA in the diagnosis of BD [2]. We achieved a similarly low sensitivity of 86% using this approach, although, based on our findings, performing CTP as an adjunct to CTA in negative CTA cases could significantly increase the sensitivity of the test, but not affecting the its specificity.

The present study includes several improvements over previous research. To the best of our knowledge, this is the first study evaluating CTP and CTA results in comatose patients with preserved brain stem function as the control group. This enabled us to assess specificity of CTP and CTA in the diagnosis of BD.

We assessed the whole brain using CTP, whereas Sawicki et al. and Shankar et al. evaluated only a limited part of the brain [4,5]. In addition, the present study is the first to use TI-CTA to diagnose BD. This approach enables the detection of intracranial opacification regardless of delay in contrast arrival. In our study, the images obtained from the 4th to 60th s after contrast injection were compiled into a single image. Thus, the use of TI-CTA avoids the problem of having to select the correct delay for CTA scanning after contrast injection in the diagnosis of BD. This issue is still debated, and no consensus has been reached so far [8]. Different approaches are proposed; for example, according to current French guidelines, intracranial filling is assessed 60 s after contrast injection, whereas in German national regulations it is assessed in the arterial phase [9–11]. Moreover, TI-CTA can be derived from CTP datasets (as in the present study); thus, both tests can be performed following a single injection of contrast.

Although the use of CTP in brain-dead patients should register the absence of whole-brain CBF and CBV, the results of the present study do not confirm this assumption, since CBF and CBV values were found to be slightly higher than zero. Darby et al. [12] reported similar results (a mean CBF of 1.6±2.0 ml/100 g/min) in 8 brain-dead patients evaluated using Xe-CT. Additionally, using Xe-CT, Ashwal et al. [13] also found a mean CBF of 1.3±1.6 ml/100 g/min in 10 clinically brain-dead children.

These previous results suggest the existence of preserved residual CBF, which may preclude or complicate the diagnosis of BD. However, the ability of CTP to differentiate between extremely reduced blood flow and the absence of blood flow was studied by Uwano et al. [14] using digital phantoms simulating CBF of 0–2.4 ml/100 g/min and CBV of 0–0.16 ml/100 g. Using different software packages, they discovered that CBF and CBV values for true zero-flow phantoms were actually slightly higher

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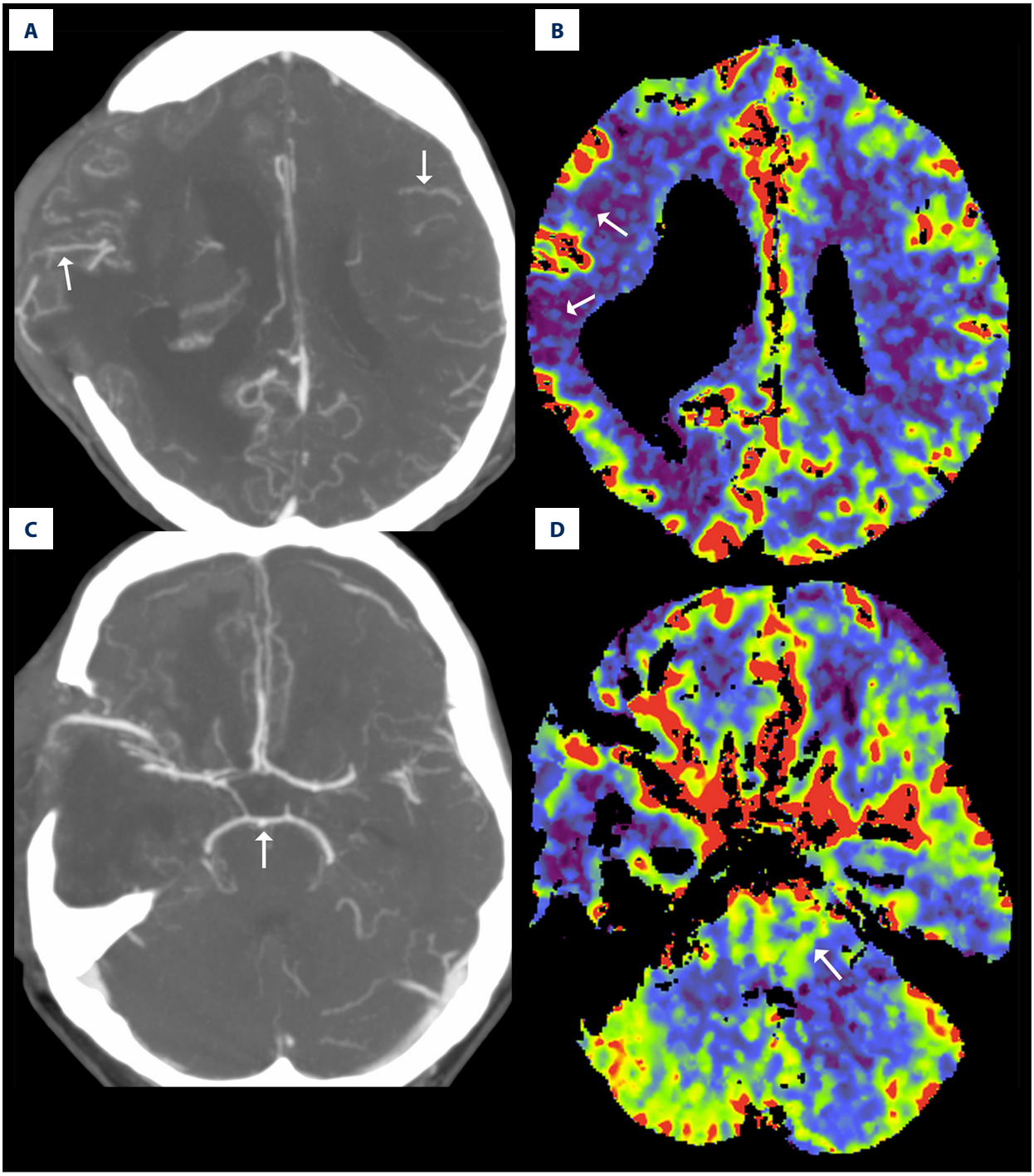

Figure 5. Results of CTA (**A, C**) and CTP (**B, D**) in the patient with devastating brain injury following cardiac arrest, in coma on artificial ventilation, but with preserved brainstem reflexes. CTA shows preserved bilateral filling of cortical branches of the MCAs (arrows in **A**) and the basilar artery (arrow in **C**); this result was interpreted as negative (i.e., inconsistent with the diagnosis of BD). CTP reveals decreased CBF in the right fronto-parietal region (arrows in **B**) with preserved cerebral perfusion in all other regions, including the brainstem (arrow in **D**). This result was interpreted as negative (i.e., not consistent with the diagnosis of BD).

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than zero. These results suggest that the precision of analysis of tissue-attenuation curves with very small amplitude can be affected by noise. In the present study, this small amplitude is reflected by low CNR (0.34±0.21), which was close to 10 in the non-brain-dead group. With such a low CNR, small fluctuations in the tissue-attenuation curve caused by image noise could be mistaken for a slight degree of blood flow.

It should be noted that CBF and CBV values in our study were slightly higher than the values noted for zero-flow phantoms by Uwano et al. [14]. There are 2 other factors which could contribute to the data discrepancy. Firstly, Uwano et al. used mathematical models to generate AIF and the reference vessel curves. These models are known to be different from the tissue-attenuation curves registered *in vivo* in brain-dead patients. The selection of both AIF and the maximal enhancement reference vessel is known to affect calculation of CBF and CBV. Kealey et al. [15] reported that low maximum enhancement of the reference vessel resulted in overestimation of CBF and CBV. It should be noted that the mean maximal enhancement in the present study was markedly lower when compared to those routinely observed in brain-dead groups in CTP studies. The lower maximal enhancement of the reference vessel in brain-dead patients is likely caused by poor infiltration of contrast medium into the ICAs associated with intracranial hypertension, resulting in an overestimation of CBF and CBV in our study. Secondly, although Uwano et al. also found substantial differences in values between algorithms, reflecting the different susceptibility to image noise, they did not use the same software used in our study. It remains possible, therefore, that the software used in the present study is associated with a higher susceptibility to noise than those utilized in previous studies involving phantom tests.

Taken together, these data suggest that the positive CBF and CBV values observed in the present study should be interpreted as the effect of image noise, not an indicator of residual cerebral flow in brain-dead patients. The problem of the inability of CTP software to show zero CBF and CBV values in dead brain tissue might be addressed with further improvements in denoising techniques and/or the use of a deconvolution algorithm.

Limitations of the study

Limitations of the present study include its relatively small samples, particularly in the non-brain-dead group. Furthermore, it cannot be excluded that application of different perfusion algorithms and choice of different vessels for AIF or VOF may affect the results of CTP. Therefore, the evaluation of differentially calculated perfusion algorithms and use of alternative AIFs or reference vessels, such as the superficial temporal artery and vein, are warranted.

Conclusions

We found that whole-brain CTP is a highly sensitive and specific method for diagnosis of BD. CTP used together with the commonly applied CTA may increase the sensitivity of the test.

Conflict of interest

None.

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