

ORIGINAL ARTICLE

Technical Aids in the Diagnosis of Brain Death

A Comparison of SEP, AEP, EEG, TCD and CT Angiography

Stefan Welschehold, Stephan Boor, Katharina Reuland, Frank Thömke, Thomas Kerz, André Reuland, Christian Beyer, Martin Gartenschläger, Wolfgang Wagner, Alf Giese, Wibke Müller-Forell

SUMMARY

Background: The use of technical aids to confirm brain death is a controversial matter. Angiography with the intra-arterial administration of contrast medium is the international gold standard, but it is not allowed in Germany except in cases where it provides a potential mode of treatment. The currently approved tests in Germany are recordings of somatosensory evoked potentials (SSEP), brain perfusion scintigraphy, transcranial Doppler ultrasonography (TCD), and electroencephalography (EEG). CT angiography (CTA), a promising new alternative, is being increasingly used as well.

Methods: In a prospective, single-center study that was carried out from 2008 to 2011, 71 consecutive patients in whom brain death was diagnosed on clinical grounds underwent recording of auditory evoked potentials (AEP) and SSEP as well as EEG, TCD and CTA.

Results: The validity of CTA for the confirmation of brain death was 94%; the validity of the other tests was: 94% for EEG, 92% for TCD, 82% for SSEP, and 2% for AEP. In 61 of the 71 patients (86%), the EEG, TCD and CTA findings all accorded with the clinical diagnosis. The diagnosis of brain death was established beyond doubt in all patients.

Conclusion: In this study, the technical aids yielded discordant results in 14% of cases, necessitating interpretation by an expert examiner. The perfusion tests, in particular, can give false-positive results in patients with large cranial defects, skull fractures, or cerebrospinal fluid drainage. In such cases, electrophysiologic tests or a repeated clinical examination should be performed instead. CTA is a promising, highly reliable new method for demonstrating absent intracranial blood flow. In our view, it should be incorporated into the German guidelines for the diagnosis of brain death.

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The requirements and the procedure for the establishment of brain death are laid down by a German Medical Association guideline published in 1998 (1). Cessation of brain function is determined by two independent examiners who must agree on the presence of deep coma, the absence of brainstem reflexes (pupils moderately wide to wide open; no reaction to light; no corneal, cough, and oculocephalic reflexes; no reaction to trigeminal pain stimuli), and the absence of spontaneous respiration. In addition to clinical examination of brain death, the guideline demands demonstration of the irreversibility of the clinical deficits, either by technical means or a second clinical examination (12, 24, or 72 h later). For certain categories of patients technical examinations are obligatory. In infratentorial primary lesions, for example, brain death cannot be established by observation of the clinical deficits alone; additional determination of lack of cerebral blood flow or absence of cerebral electrical activity (zero-line EEG) is required (1).

The recent literature worldwide shows no consensus on the role of technical aids in the diagnosis of brain death. While some authors question the value of these examinations (2), others believe that greater importance should be attached to technical procedures (3). In Germany, the invasive and potentially complication-ridden nature of intra-arterial angiography of the brain supplying arteries to demonstrate cerebral circulatory arrest means that it may be performed only where there is potential therapeutic benefit (1, e1–e5). This “gold standard” procedure is thus not available in our country. The absence of cerebral circulation can therefore be demonstrated only by means of transcranial Doppler sonography of the cerebral vessels (TCD) or by cerebral perfusion scintigraphy. Other technical aids licensed in Germany include electrophysiological examinations to demonstrate absence of cerebral electrical activity: electroencephalography (EEG) can be used without restriction, but limits are placed on the application of somatosensory evoked potentials (SEP) and acoustic evoked potentials (AEP). None of these procedures are available in all hospitals.

According to the German Organ Transplantation Foundation, 26% of the diagnoses of brain death in

BOX

CT angiography (CTA): Protocol for examination and analysis● **Criteria**

Complete, documented determination of clinical deficits; mean arterial pressure over 60 mm Hg.

● **Plain scan**

Gantry tilted parallel to orbitomeatal plane. Spiral scan from base of skull to vertex: 120 kV, 170 mA. Reconstructed axial images with slice thickness 5 mm.

● **CTA**

Bolus administration of 65 mL Imeron 400 (Bracco Imaging, Konstanz, Germany) followed by 30 mL isotonic saline solution via a high-pressure injector into an indwelling venous cannula or a central venous catheter. Infusion rate 3.5 mL/s. Automatic start of spiral scan from C6 to vertex via bolus tracking 5 s after attainment of radiodensity of at least 150 Hounsfield units in the common carotid artery; 120 kV, 200 mA. Reconstructed axial images with slice thickness 2 mm.

● **Evaluation**

Absence of contrast in the basilar artery, both M4 segments of the middle cerebral arteries, the A3 segments of the anterior cerebral arteries, and the P2 segments of the posterior cerebral arteries, with presence of contrast in both common carotid arteries, the external carotid arteries, and their branches, in particular the superficial temporal arteries (demonstration of correct contrast medium administration), is evaluated as proof of cerebral circulatory arrest.

Germany in 2010 took place in hospitals without a department of neurology or neurosurgery. The proportion of examinations at these hospitals carried out by an external consultant was 53% (e6). These figures reinforce the assumption that in a considerable number of cases determination of brain death involves a great deal of organization, potentially leading to delay.

The established procedures for demonstrating intracranial circulatory arrest have recently been joined by CT angiography (CTA), which has become increasingly common in the determination of brain death and has already been licensed for use in many countries (among them Austria, France, Switzerland, and Canada) (e7, e8). The almost universal availability, simplicity, and high resolution of CTA make it an attractive alternative for brain death diagnosis.

Our intention in carrying out the study described here was to describe the various procedures used to determine brain death, provide information that will be useful in deciding which of the available techniques to use, and compare the results of CTA with those of other forms of examination. To the best of our knowledge, no comparable study including CTA has been published to date.

Methods

Between February 2008 and December 2011, 71 patients with a mean age of 55 ± 18 years (range 18 to 88 years) were diagnosed as brain-dead at our hospital. In each case the clinical signs of brain death were ascertained by two physicians. EEG, TCD, SEP and AEP were carried out in all patients, accompanied by CTA with the relatives' consent. The study was approved by the local ethics committee. The standard procedures

established in Germany for demonstration of irreversibility were performed and analyzed in accordance with the German Medical Association's guidelines.

A 32-row CT scanner (Aquilion, Toshiba, Japan) was used for CTA. The examination protocol is described in the *Box*. Cerebral circulatory arrest was considered confirmed when CTA (arterial phase) showed no contrast medium uptake in the terminal vessels of the cerebral cortex (segments MCA-M4, ACA-A3, PCA-P2) and basilar artery.

Results

The underlying diseases in the 71 patients are listed in *Table 1*. In all cases brain death was confirmed by two independent examiners and one or more technical procedures.

In 58 of the 59 patients with supratentorial lesions, brain death was diagnosed after SEP demonstrated irreversible loss of cerebral functions. In the remaining patient SEP showed a positive response over the brainstem or upper cervical spine, correlating with positive residual flow on TCD and CTA. Repeat investigation on the following day showed results consistent with brain death.

The AEP technique showed wave I, or waves I and II, in only one of the 59 patients at the time when the clinical criteria of brain death were fulfilled; in the other 58 patients there was bilateral absence of potentials. In 18 patients irreversibility of the symptoms was confirmed by consecutive loss of AEPs over the course of treatment, i.e., on examination before the time of clinical brain death. The validity of AEP is thus 32% in patients with prior investigation but only 2% in those not examined until after the onset of clinical brain death.

TABLE 1

Underlying diseases of the brain-dead patients

Subarachnoid hemorrhage	21
Intracerebral hemorrhage	20
Craniocerebral trauma	19
Cerebellar hemorrhage/brain stem hemorrhage	7
Hypoxia	2
Malignant middle cerebral artery infarction	1
Basilar thrombosis	1

In four of the 71 patients, artifacts prevented interpretation of the EEG. The other 67 patients all exhibited no cerebral electrical activity (validity of EEG: 94%).

In 65 patients TCD showed a flow profile typical of brain death, with either early systolic peaks or oscillating flow. In two cases there was no sufficient bone window, so the intracranial flow could not be evaluated. In a further four cases there was residual flow, so according to the German Medical Association's guidelines cerebral circulatory arrest could not be confirmed (validity of TCD: 92%). In three of these cases there were large craniotomy defects; in the fourth, cranial fractures resulting from severe craniocerebral trauma.

CTA showed cerebral circulatory arrest in 67 of the 71 patients (validity of CTA: 94%).

In 49 of them, contrast filling in CTA ceased below or at the level of the base of the skull. In 18 cases residual filling of one or more proximal vessel segments was detected (M1, A1, V4) (Figure 1).

In the remaining four cases there was filling of one (n = 2) or more (n = 2) brain supplying vessels up to the periphery of the brain. In accordance with the CTA

protocol, this was classified as not consistent with cerebral circulatory arrest. Both of the patients in whom contrast medium flow was demonstrated up to the periphery in more than one vessel had extensive craniectomy defects and a residual flow profile on TCD, which was also inconsistent with cerebral circulatory arrest (Figure 2). EEG and SEP, however, showed no cerebral electrical activity. In one of these patients, CTA and TCD on the following day both showed absence of perfusion.

In 61 of the 71 patients (86%), EEG, TCD, and CTA agreed in showing findings consistent with the diagnosis of brain death.

Discussion

The ideal procedure for confirmation of brain death would be universally available, simple to perform (preferably at the bedside), and independent of the examiner and of any effects of medication, as well as possessing high sensitivity and specificity (4). It will already be clear that none of the existing procedures meets all of these criteria.

The evoked potential procedures in general can be used only in cases of secondary or supratentorial primary brain lesions, because an isolated infratentorial lesion can produce findings consistent with the typical signs of brain death. This limits the applicability of the AEP and SEP examinations. The AEP method should not be used for the first time when clinical deficits have already been demonstrated, because usually all components have failed and thus correct stimulation cannot be proved, as has been confirmed by other researchers (5).

For SEP, in contrast, correct stimulation can be proved by demonstration of a potential over the brachial plexus while the typical series of potentials breaks off above the lower cervical spine. In none of our patients did technical considerations prevent the procedure being carried out, and in no case were the results qualitatively unusable. The SEP procedure can thus be described as relatively robust.

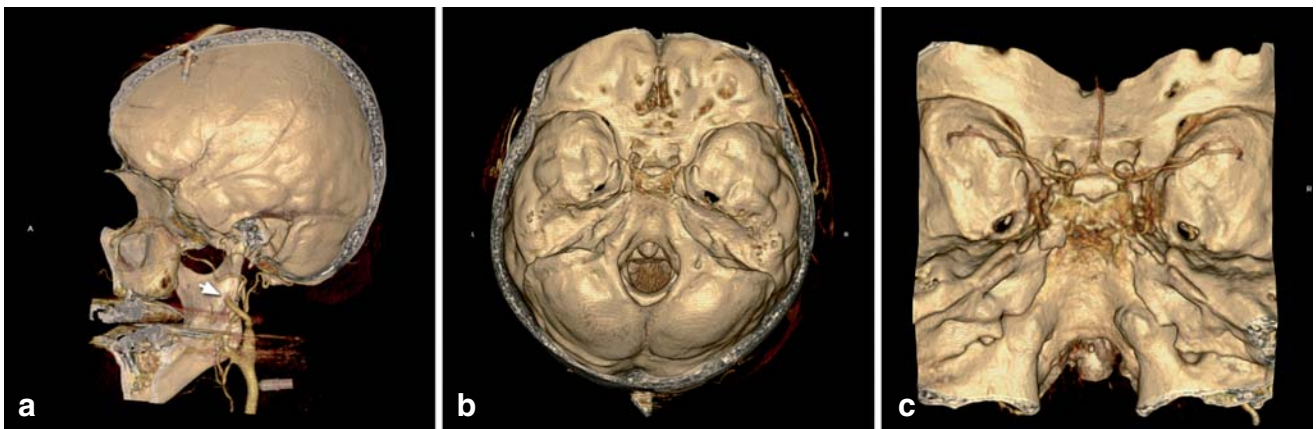


Figure 1: Typical CTA findings in a brain-dead patient. CM filling stops below the base of the skull in the internal carotid artery (arrow, Figure 1a), and no filling of intracranial vessels can be seen (Figure 1b). CM filling of proximal vessel segments without signs of filling of basilar artery and terminal cortical vessels (Figure 1c). CTA, CT angiography; CM, contrast medium

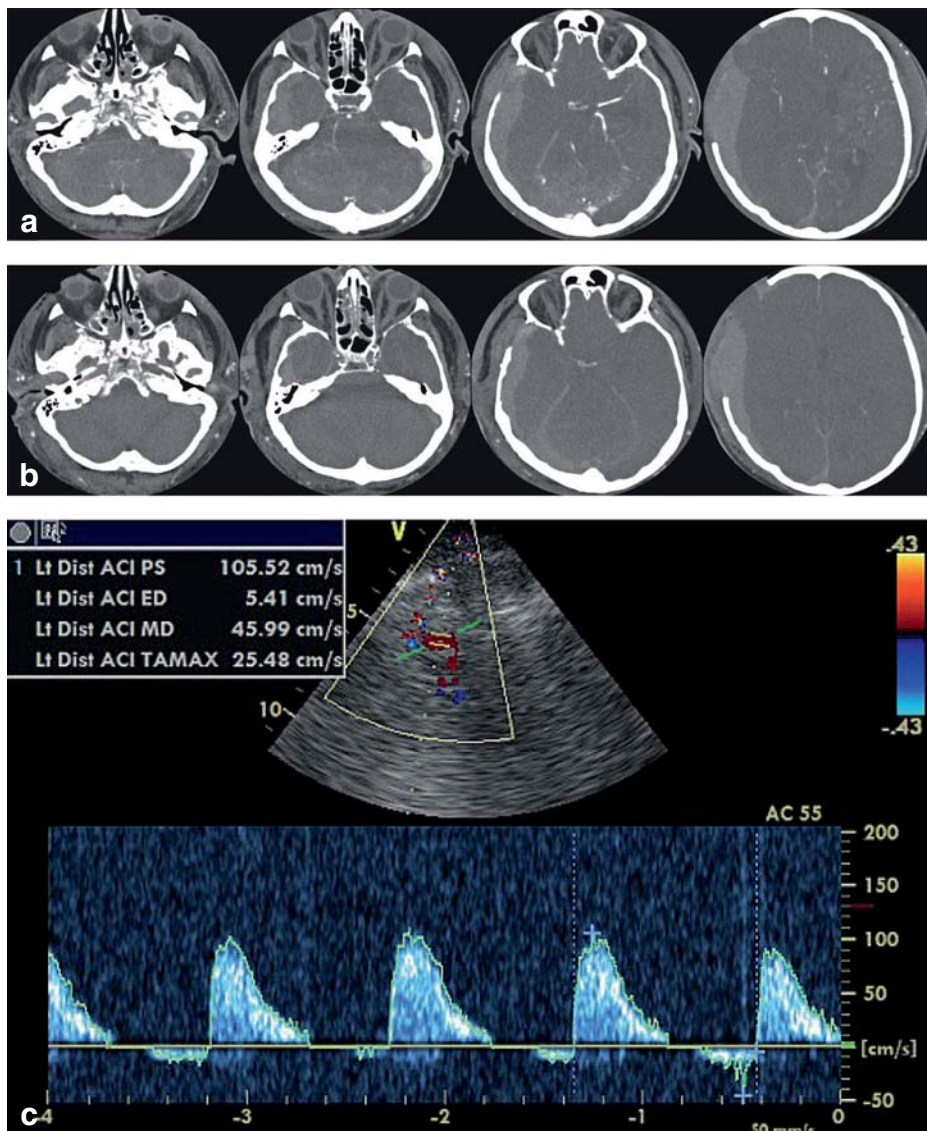


Figure 2:
A 71-year-old male patient after a serious road traffic accident: multiple injuries and acute subdural hematoma.

Deeply unconscious with anisocoria at the scene of the accident. After admission, diagnosis was followed by craniotomy and relief of an acute subdural hematoma. The polytrauma and hyperfibrinolysis led to secondary bleeding and loss of brainstem reflexes. After onset of clinical brain death, CTA (Figure 2a) and TCD (Figure 2c) both showed residual flow. Simultaneously, SEP showed a possibly positive response over the upper cervical spine and the brainstem. Thus irreversibility could not be demonstrated at that time. EEG, however, showed no cerebral electrical activity, a finding consistent with brain death. Repeat CTA a day later (Figure 2b) showed findings consistent with brain death in all phases of the examination.

CTA, CT angiography;
 TCD, transcranial Doppler sonography;
 SEP, somatosensory evoked potentials;
 EEG, electroencephalography

Beyond doubt, the technical procedure with which there has been the longest and most extensive experience is EEG. The irreversibility of the signs of clinical brain death can be demonstrated by the absence of cerebral electrical activity (1, e9). One essential limitation of the EEG procedure is in patients with persisting drug effects and strong artifacts (6, 7).

Apart from the above-mentioned classic electrophysiological techniques, perfusion methods can also be used for diagnosis of brain death. They demonstrate the absence of brain perfusion in the presence of normal perfusion of the rest of the organism. TCD has a validity of 92%, similar to EEG, and this has been confirmed by other research teams (8–11). Yet others, however, have reported much lower validity for TCD, down to 57% (e10, e11). Besides the limited assessability of intracranial flow when no adequate bone window is available, another disadvantage of TCD is residual flow in patients with

large craniotomy defects, skull fractures, and CSF drainage (10, e12, e13). It is known that residual cerebral blood flow can persist on TCD in such cases despite brain death. Furthermore, the sole absence of intracranial flow signal cannot be interpreted as proof of cerebral circulatory arrest, as it may result from lack of a sound window or from cessation of cerebral perfusion. Moreover, there may be no signal because not all segments of the major cerebral arteries have been reliably identified. For these reasons TCD examinations should be carried out before perfusion ceases, to document the findings and permit unambiguous interpretation (12, e14). The intra- and interobserver variability inherent in the method introduces a further element of uncertainty. In Germany, therefore, the examiner who demonstrates the absence of intracranial flow during the course of brain death diagnosis must have found the same result on a previous occasion (1).

TABLE 2

Validity of the various techniques

Technique	Validity
CTA	94%
EEG	94%
TCD	92%
SEP	82%
AEP	2%/32%

CTA, CT angiography; EEG, electroencephalography; TCD, transcranial Doppler sonography; SEP, somatosensory evoked potentials; AEP, acoustic evoked potentials

For the sake of completeness it should be mentioned that cerebral circulatory arrest cannot be concluded unless TCD is backed up by Doppler sonography of the extracranial carotid artery.

The validities of the techniques used in our study are shown in *Table 2*.

The majority of the examinations discussed here (EEG, evoked potentials, TCD) can be carried out on the ward. What they all have in common is that specialized apparatus is required and the results can be interpreted only by suitably qualified physicians. Since

many cases of brain death occur in hospitals where these criteria are not met, considerable effort may be involved with respect to transporting equipment and staff.

The use of CTA for demonstrating cerebral circulatory arrest was first described by Dupas et al. in 1998 (13). Several subsequent studies supported their conclusions (14–19). Thereupon, some countries licensed CTA as a technical aid in the diagnosis of brain death (e8, e15). The central criticisms of CTA are that there is still no consensus on the parameters for scanning and analysis, and that the studies to date have examined various vascular territories, sometimes excluding the posterior circulation, or solely the arterial or the venous phase of CTA was investigated. This may be the reason why some studies have shown low sensitivity or validity (20–22). An overview of the most important publications on this subject is given in *Table 3*. In our own study, the validity of the arterial phase of CTA for demonstration of cerebral circulatory arrest was 94%. Vascular analysis in the venous phase seems to yield more false-positive results and should thus be forgone (23, e16). However, it must be ensured that not only anterior circulation but also the vessels of the posterior cranial fossa are analyzed. Evaluation of only the distal branches of the middle cerebral artery and the deep cerebral veins is unacceptable in the context of brain death diagnosis. Finally, demonstration that contrast medium filling stops below the base of the skull or

TABLE 3

Overview of the principal published studies on the use of CTA to demonstrate cerebral circulatory arrest

Authors	Year of publication	Number of patients	Cerebral perfusion defined as absent when no contrast medium detected in following vessels:	Evaluation in:		Comparison with other procedures	Validity of CTA
				arterial phase	venous phase		
Dupas, et al. (13)	1998	14	ACA-A3, MCA-M4, PCA-P1, BA	X		EEG and/or angiography	100%
First descriptive study introducing arterial and venous CTA compared with a healthy control group, featuring detailed analysis of individual segments of vessels							
Leclerc, et al. (31)	2006	15	MCA-M3, ICV		X	None	93%
Combes, et al. (15)	2007	43	ACA-A2, MCA-M4, PCA-P2, BA, ICV, GCV		X	Angiography	70%
Quesnel, et al. (22)	2007	21	ACA-A3, MCA-M4, ICV, GCV		X	EEG	52%
Frapas, et al. (18)	2009	105	ACA-A3, MCA-M4, ICV, GCV (MCA-M4, ICV)		X	None	63% (86%)
Escudero, et al. (32)	2009	27	Circulatory arrest at level of skull base and foramen magnum	X		TCD, EEG	89%
Berenguer, et al. (23)	2010	25	Circulatory arrest at level of skull base and foramen magnum	X		Scintigraphy	86%
Bohatyrewicz, et al. (14)	2010	24	ACA-A3, MCA-M4, BA, ICV	X		Angiography	100%

ACA, segments of the anterior cerebral artery; MCA, segments of the middle cerebral artery; PCA, segments of the posterior cerebral artery; BA, basilar artery; GCV, great cerebral vein; ICV, internal cerebral vein; CTA, CT angiography; TCD, transcranial Doppler sonography; EEG, electroencephalography

reaches only the proximal vessel segments, with no depiction of the terminal vessels of the cortex and the posterior territory, is functionally equivalent to cerebral circulatory arrest (14, 24).

CTA possesses several advantages over other procedures. First of all, not all hospitals are equipped to perform and analyze tests of neurological function. However, CTA is almost universally available. Further advantages of CTA include its clear depiction of contrast medium uptake in the vascular system and its examiner-independent reproducibility. In addition, no cases of renal damage from administration of the contrast medium have been reported with adherence to the usual standards. On the basis of our findings and those published by other research groups, and because its validity is comparable to that of TCD and EEG, we recommend that CTA be considered for approval as an additional technical aid for confirmation of cerebral circulatory arrest in Germany.

Different techniques may yield discrepant results in patients with the clinical symptoms of brain death. Only in 86% of those in our study was there agreement among EEG, TCD, and CTA. The evoked potential procedures were not included in this analysis because they are not applicable to infratentorial lesions. In a number of patients with absent cerebral electrical activity on EEG and absent SEP components in the cerebrum and brainstem, perfusion techniques showed highly restricted but not completely abolished blood flow, particularly in patients with craniotomy defects. Other authors have also reported a certain proportion of discordant findings (25, 26). This phenomenon is well known, repeatedly leads to insecurity in the treatment team, and has often been cited in the lay press to cast doubt on the reliability of brain death diagnosis. A few authors have therefore taken the view that additional technical aids just serve to increase confusion and are thus superfluous (2). However, this occasional lack of agreement ultimately rests on the different methods behind the various procedures. In general, any examination that shows residual activity or residual perfusion in a person who is clinically brain-dead should be re-

peated to show that this finding disappears with time. Nevertheless, under certain conditions (residual) intracranial perfusion may well persist despite irreversible loss of function of the tissues supplied. Particularly in the case of skull defects, the absence of the bone may mean that the intracranial pressure increase stays below the systemic perfusion pressure, so that residual intracranial blood flow can be demonstrated (e17, 26–30). In such cases one must consider whether eventual cerebral circulatory arrest can be expected and evaluation should be repeated, or whether irreversibility should be demonstrated by other means.

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Conflict of interest statement

Thömke, Boor, Wagner, Reuland K, Reuland A, Welschehold, Müller-Forell, Giese: These authors declare that no conflict of interest exists.

Dr. Gartenschläger has received reimbursement of congress attendance fees from Schering and Guerbet and reimbursement of travel costs from Picker and Toshiba. He has received lecture fees from Glaxo SmithKline and funds paid into a third-party account by Philips Medical Systems.

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Dr. Beyer acts as a consultant for Maquet.

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KEY MESSAGES

- Technical procedures have an established place in the diagnosis of brain death, but in a certain proportion of cases—14% in our study—they yield discordant results.
- Most frequently this involves false-positive results regarding perfusion in patients with cranial defects, skull fractures, or CSF drainage.
- CT angiography for demonstration of cerebral circulatory arrest is comparable with the long-established procedures for diagnosis of brain death.
- In contrast to the established procedures, CT angiography is available in almost all hospitals and is simple to perform.

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