Bilaga 4 till rapport

Bilddiagnostik vid misstanke om total hjärninfarkt
– en systematisk litteraturöversikt, rapport 282 (2018)

Bilaga 4 Tabeller, beskrivning av studier

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Table 1 Sensitivity of four-vessel angiography with clinical diagnosis of brain death as reference test

First author **Country** **Year** **Reference**	**Population**	**Index test, Cerebral Angiography, four vessels (CA)**	**Reference test, clinical diagnosis of brain death (BD)**	**Flow and timing**
Bergquist et al Sweden 1972 [21]	***Study design*** Cross-sectional ***Patient spectrum*** n=28, subarachnoid hemorrhage (n=8) intracerebral hemorrhage (n=3), cerebral contusion (n=8) cerebral tumor (n=4), arteriovenous aneurysm (n=1), hypoxia (n=3), hepatic coma (n=1). ***Exclusion criteria*** Not reported	***Scoring system*** Filling level of the ICA, proximal and middle cerebral arteries and vertebral artery. Filling of extracranial branches of external carotid arteries. ***Description*** CA alone in 25 patients. Bilateral angiography in 3 patients, in one of these combined with CA. 45 ml contrast. Serial imaging 24 s. Duration of investigation 30 minutes. Lateral projections, supplemented with frontal projections over the neck. Subtraction technique. ***Number and number and competence level of radiologists*** Not reported	***Description*** The cause of cerebral injury was known, a clinical combination of arrest of ordinary respiration, deep unconsciousness with no automatic motor response, no reactions of the pupils to light. Isoelectric EEG recorded in all pts. ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and angiography*** Not reported

Bradac et al France 1974 [22]	***Study design*** Cross-sectional ***Patient spectrum*** n=16. Brain tumor (n=4), status after cardiac arrest (n=3), traumatic intracerebral hematoma or contusion (n=4) intracerebral hemorrhage (n=5). ***Exclusion criteria*** Not reported	***Scoring system*** Filling level of the ICA, proximal and middle cerebral arteries, vertebral arteries and external carotid arteries. ***Description*** CA in 10 pts, 27 ml/s. Image series of minimum 15 s, repeated after 30 min. Subtraction technique. ***Number and competence level of radiologists*** Not reported	***Description*** Deep coma, no response to stimuli, areflexia, fixed and dilated pupils not reacting to light, no spontaneous respiration, reduced blood pressure, hypothermia, isoelectric EEG. ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and angiography*** Not reported
Busse et al Germany 1974 [23]	***Study design*** Cross-sectional ***Patient spectrum*** n =32 (including two children, 4 and 8 months). Diagnoses not reported. ***Exclusion criteria*** Not reported	***Scoring system*** Level of filling of the ICA, proximal and middle cerebral arteries, vertebral arteries and external carotid arteries. ***Description*** CA in 22 pts. Contrast injection 18–22 ml/s. Imaging series of 13–16 s, repeated after 30 min. ***Number and competence level of radiologists*** Not recorded	***Description*** Clinically brain-dead patients. Specific criteria not reported. Isoelectric EEG. ***Competence and number of clinicians behind the BD diagnosis*** Not recorded	***Time at ICU before diagnosis of BD*** Not recorded ***Time between diagnosis of BD and angiography*** Not recorded

Combes et al France 2007 [24]	***Study design*** Cross-sectional, prospective, ***Patient spectrum*** n=43, severe head trauma (n=21), stroke (n=10) cerebral aneurysm rupture (n=10) meningitis (n=1), cerebral anoxia by cardiac arrest (n=1). ***Exclusion criteria*** No exclusion criteria	***Scoring system*** Cerebral blood flow arrest at the level of foramen magnum for the posterior circulation and the carotid siphon for the anterior circulation. ***Description*** After injection of contrast 15ml/s imaging every 5 s during 60 s. Lateral projection. ***Number and competence level of radiologists*** 2 radiologists trained in conventional angiography	***Description*** Complete and persistent absence of consciousness and spontaneous movements, no brain stem reflexes, no spontaneous breathing on apnea challenge despite hypercarbia. ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and angiography*** Delay between clinical BD and CTA 9.29 h (SD 7.57). CA performed immediately after CTA.
Greitz et al Sweden 1973 [10]	***Study design*** Cross-sectional ***Patient spectrum*** n=42. Patient data not reported. ***Exclusion criteria*** Not reported	***Scoring system*** Filling level of the ICA, proximal and middle cerebral arteries Filling of intracerebral veins. ***Description*** CA only: n=1 CA + unilateral carotid: n=18 CA + bilateral carotid + right vertebral: n=1	***Description*** Clinical signs of total brain infarction or “brain death”: all neurological signs of cerebral activity, reflexes involving cranial nerves included were abolished. EEG was recorded in 37 pts, isoelectric in all. ***Competence and number of clinicians behind the BD diagnosis***	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and angiogram*** Not reported ***Comment***

		Two serial 30 s imaging sequences, 30 min interval. Lateral and anteroposterior projections. Subtraction technique. ***Number and competence level of radiologists*** Not reported	Not reported	Filling of the external carotid and vertebral arteries not reported.
Sawicki et al Poland 2014 [25]	***Study design*** Cross-sectional, prospective, multicenter ***Patient spectrum*** n=82 at ICU. Traumatic brain injury (n=16) intracerebral hemorrhage (n=32), subarachnoidal hemorrhage (n=21) ischemic stroke (n=7) anoxia (n=6). ***Exclusion criteria*** Unresuscitated shock, hypothermia	***Scoring system*** No filling of intracranial vessels with normal flow in the external carotid arteries. Stasis filling- delayed, weak and persistent opacification of the proximal cerebral arterial segments without opacification of the cortical branches of venous outflow. ***Description*** AC via a femoral artery approach: n=67. Carotid and vertebral arteries catheterized selectively: n=15. Initially a non-enhanced CT scan as a reference. Second scanning after a 40 s delay after contrast	***Description*** Deep unresponsive coma of an established etiology capable of causing neurological death. Fixed dilated pupils. Absence of brainstem reflexes; no spontaneous eye movements, no muscle movements to a noxious stimulus, no corneal, gag/pharyngeal, cough/tracheal, oculo-cephalic vestibule-ocular fascial reactions. Clinical tests performed twice. ***Competence and number of clinicians behind the BD diagnosis*** 3 specialists (anesthesia and intensive care, neurology, neurosurgery)	***Time at ICU before diagnosis of BD*** 6–48 h ***Time between diagnosis of BD and angiogram*** Not reported

		injection 4 ml/s. 2 images/s during 50 s. Digital subtraction technique. ***Number and competence level of radiologists*** Local radiologists Competence not reported. Blinded to each other's assessments and clinical tests for BD.		

AAN = American Academy of Neurology; CTA = Computed tomography angiography; EEG = Elektroencefalografi; ICA = Interim Comprehensive Assessments; ICU = Intensivvårdsavdelning; SD = Standardavvikelse; pts = points

Table 2 Sensitivity of CTA with clinical diagnosis of brain death as reference test

First author **Country** **Reference**	**Population**	**Index test, Computed Tomography Angiography (CTA)**	**Reference test, clinical diagnosis of brain death (BD)**	**Flow and timing**
Combes et al France 2007 [24]	***Study design*** Cross-sectional, prospective ***Patient spectrum*** n=43 pts, severe head trauma (n=21), stroke (n=10) cerebral aneurysm rupture (n=10) meningitis (n=1), cerebral anoxia by cardiac arrest (n=1). ***Exclusion criteria*** No exclusion criteria	***Scoring system*** 10-points: ACA-A2, MCA-M4, PCA-P2, basilar artery, ICV, GCV. ***Description*** Three phases: 1.Initial scan without contrast 2. Second scan 25 s after start of contrast injection, Assessment of opacification in the superficial temporal arteries. 3. Third scan 60 s after start of phase 2. Contrast, 100 ml Iopromide, 4 ml/s in peripheral vein. Phase 3 used for assessment of BD. ***Number and number and competence level of radiologists*** 2 trained radiologists, blinded for angiography results	***Description*** Complete and persistent absence of consciousness and spontaneous movements, no brain stem reflexes, no spontaneous breathing on apnea challenge despite hypercarbia. ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** 9.29 (SD 7.57) h

Dupas et al. France 1998 [11]	***Study design*** Cross-sectional, prospective ***Patient spectrum*** n=14 at ICU. Head injury + subarachnoid hemorrhage (n=11), carotid dissection (n=1), intracranial hemorrhage (n=1), posterior fossa ischemic infarction (n=1) ***Exclusion criteria*** Not reported	***Scoring system*** 7-points scoring system: Non-opacification of (left and right) PCA, MCA, ICV and the GCV. Opacified superficial temporal arteries as a control. ***Description*** Two phase spiral CT. Three scanning sessions. Initially unenhanced images. Second scanning 20 s after injection of contrast in a peripheral vein, 3 ml/s scanning during 14 s. Third scanning 54 s (mean) later, used for evaluation. Subtraction technique. ***Number and competence level of radiologists*** 2 radiologists, blinded for results of confirmation test (CA or EEG) but not for clinical suspicion of BD	***Description*** Clinical assessment of BD not described For confirmation of BD: EEG (n=7), CA (n=5) or both (n=2) ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** CTA “as soon as possible” after EEG as confirmatory test

Frampas et al France 2009 [12]	***Study design*** Cross-sectional, prospective, multicenter ***Patient spectrum*** n=105 at ICU wards. Head trauma (n=36), cerebral hemorrhage (n=45), cerebral stroke (n=4), anoxia (n=11) cerebral hypertension (n=9). CTA data missing for n=7 pts ***Exclusion criteria*** Not reported	***Scoring system*** 7-points: According to [11]. 4-points: Non–opacification of MCA-M4 (left and right) and ICV (left and right). ***Description*** Protocol according to [11]. ***Number and competence level of radiologists*** Local radiologists and 3 expert radiologists	***Description*** "All clinical criteria for BD were present including a positive apnea test" ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** 87 h (mean) after apnea test ***Time between diagnosis of BD and CTA*** Not reported for first CTA, logistic problems (time to second CTA when the first was not conclusive was 99±68 h)
Leclerc et al France 2006 [28]	***Study design*** Cross-sectional, consecutive ***Patient spectrum*** n=15 at ICU. Head trauma (n=6), intracranial hemorrhage (n=5), ballistic brain injury (n=1) cardiac arrest (n=1), suicide by hanging (n=1), cerebral infarct (n=1). ***Exclusion criteria*** Not reported	***Scoring system*** 7-points according to [11]. ***Description*** Spiral CT. Protocol according to [11]. ***Number and competence level of radiologists*** 2 radiologists	***Description*** Total unresponsiveness to external stimuli including pain stimuli, absence of all cranial nerve reflexes (pupillary, oculocephalic, vestibuloocular, facial sensory and motor responses, pharyngeal and tracheal). Apnea test. ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** 10.2 h, (range 2–24) Repeated after 12 h if persisted circulation at first CTA ***Comment*** Visualisation of all vessels not possible in all pts due to their

				injuries. Most reliable result is absence of opacification in MCA and ICV.
Garrett et al USA 2017 [36]	***Study design*** Cross-sectional, prospective, consecutive ***Patient spectrum*** n=22. Diagnoses: hemorrhagic cerebrovascular accident (n=9), ischemic, cerebrovascular accident (n=1), gunshot (n=1), traumatic injury (n=4), subarachnoid hemorrhage (n=7). 16 pts met the clinical criteria for BD ***Exclusion criteria*** Not reported	***Scoring system*** Twelve vessels were assessed but 4-points [12] was used for confirmation of BD *D**escription*** Unenhanced CT of the head followed by CTA after 50 ml Omnipaque in antecubital vein, 4 ml/s and another CTA after 60 s delay. Axial, sagittal and coronal maximum intensity projection images obtained in the all sessions. Subtraction technique. ***Number and competence level of radiologists*** One independent neuroradiologist, not blinded.	***Description*** Evaluated according to AAN guidelines [56]. ***Competence and number of clinicians behind the BD diagnosis*** Not reported	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and angiogram*** Not reported

Kerhuel et al France 2014 [38]	***Study design*** Cross sectional, retrospective ***Patient spectrum*** Identified via the Organ and tissue harvesting department database. All adult pts (n=104) with clinical BD diagnosis on the ICU. Brain trauma (n=36), anoxic encephalopathy (n=22), aneurysmal subarachnoid hemorrhage (n=20), hemorrhagic stroke (n=13), ischemic stroke (n=11), brain infection (n=2). ***Exclusion criteria*** EEG based diagnosis only BD diagnosis prior to admission to ICU Substantial missing patient data	***Scoring system*** 7-scoring system [11] and 4-points scoring system [12]. ***Description*** Initially unenhanced images. Second, scanning sixty seconds after injection of contrast in a peripheral vein, 4 ml/s. Second scanning used for evaluation. Subtraction technique. ***Number and competence level of radiologists*** "Local attending radiologist"	***Description*** Glasgow coma scale of 3, cessation of all brainstem reflexes including spontaneous ventilation assessed by an apnea test (according to AAN guidelines) ***Competence and number of clinicians behind the BD diagnosis*** Intensive care physician	***Time at ICU before diagnosis of BD*** 9 h (range, 6–13) ***Time between diagnosis of BD and CTA*** 21 h (range, 12–35) ***Comments*** CTA sensitivity was significantly associated with time lapse from clinical diagnosis to CTA. Inconclusive CTA were found earlier (2 h) vs at 4 h (2–9), p=0.008.

Marchand et al France 2016 [39]	***Study design*** Cross-sectional, consecutive ***Patient spectrum*** n=76. Intracranial aneurysm (n=25), traumatic brain injury (n=24), stroke (n=10), cerebral hemorrhage (n=9), cerebral anoxia (n=7), infection (n=1). ***Exclusion criteria*** Not reported	***Scoring system*** 4-points (revised) Non-opacification in ICVs and SPVs. ***Description*** Three scanning sessions. Initially unenhanced images. Second scanning 20 s after injection of contrast in a peripheral vein. Third scanning 60 s later was used for evaluation. Subtraction technique. ***Number and competence level of radiologists*** 2 trained radiologists (10 y experience) ("CTA interpretation requires the expertise of a senior radiologist")	***Description*** Clinical assessment: irreversible cessation of all functions of the entire brain, total and irreversible coma with a known cause, absence of brain stem reflexes and apnea. (apnea test not possible in 26 pts) ***Competence and number of clinicians behind the BD diagnosis*** Trained intensivists	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** 6 h (necessary to repeat after 6 h in 7 pts)
Quesnel et al France 2007 [29]	***Study design*** Cross-sectional, prospective ***Patient spectrum*** n=21 ICU pts from two hospitals. Intracranial hemorrhage (n=6), ischemic stroke (n=5), cerebral anoxia (n=5),	***Scoring system*** 7-points [11] ***Description*** Unenhanced CT of the head. Another CTA 20 s later and after contrast in antecubital vein, 3 ml/s. A third CTA after 60 s. Axial, sagittal and coronal	***Description*** Deep persistent unreactive coma, Glasgow coma scale 3, absence of brain stem reflexes, apnea test and lack of spontaneous ventilation. Clinical BD confirmed by EEG x 2, 4 h in between, first EEG used in this study followed by CTA	***Time at ICU before diagnosis of BD*** 29±30 h ***Time between diagnosis of BD and CTA*** 3 h (median)

	head injury (n= 4), brain tumor (n=1). ***Exclusion criteria*** Not reported	maximum intensity projection images also obtained in the CTA sets. ***Number and competence level of radiologists*** Independent trained radiologist (aware of suspicion of BD diagnosis but blinded for EEG results)	***Competence and number of clinicians behind the BD diagnosis*** Not reported	
Rieke et al Switzerland 2011 [30]	***Study design*** Cross-sectional, retrospective ***Patient spectrum*** n=29 adults at ICU. Anoxia (n=4), cerebrovascular disease (n=8), hemorrhage (n=7), suicide (n=1), trauma (n=8), other (n=8). ***Exclusion criteria*** Not reported	***Scoring system*** 7-points [11] and 4-points [12]. ***Description*** Unenhanced CT of the head. Another CTA and after 70 ml contrast into a peripheral vein, 4 ml/s. A third CTA followed for the late venous–phase. The CTA started automatically with the appearance of contrast in the aortic arch. The late phase series started 60 seconds after CTA start. ***Number and competence level of radiologists*** 2 experienced neuroradiologists	***Description*** According to Swiss guidelines ***Competence and number of clinicians behind the BD diagnosis*** Staff neurologist	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** Not reported (repeated every 6 h if necessary)

Sahin et al Turkey 2015 [40]	***Study design*** Cross-sectional, retrospective ***Patient spectrum*** n=25 (including two children 8 and 14 y old). Intracranial traumatic hemorrhage (n=11) intracranial non- traumatic hemorrhage (n=8), ischemic events (n=6). ***Exclusion criteria*** Reversible pathologies, e.g. metabolic and endocrine disorders, hypothermia, intoxication, sedation	***Scoring system*** 10-points: MCA, ACA, PCA, basilar artery, ICV, GCV 7-points [11] and 4-points [12]. ***Description*** Initially unenhanced images. Second scanning 20 s after injection of 80–85 ml contrast in a peripheral vein, 3 ml/s. Third scanning 60 s after contrast was used for evaluation. Subtraction technique. ***Number and competence level of radiologists*** 2 radiologists with 3 and 5 y experience respectively	***Description*** Unresponsive coma, absence of brain stem reflexes and positive apnea test. ***Competence and number of clinicians behind the BD diagnosis*** Council of physicians specialized in neurology, neurosurgery anesthesia and cardiology	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** 6 to 24 h
Sawicki et al Poland 2014 [25]	***Study design*** Cross-sectional study, prospective, multicenter ***Patient spectrum*** n=82 at ICU at three hospitals. Traumatic brain injury (n=16) intracerebral hemorrhage (n=32), subarachnoidal hemorrhage (n=21),	***Scoring system*** Opacification of superficial temporal arteries. Non-opacification in: ACA-A3, MCA-M4 left and right, PCA-P2 left and right, BA, ICV left and right, GCV Diagnosis of BD was established according to	***Description*** Deep unresponsive coma of an established etiology capable of causing neurological death. Fixed dilated pupils. Absence of brainstem reflexes; no spontaneous eye movements, no muscle movements to a noxious stimulus, no corneal, gag/pharyngeal,	***Time at ICU before diagnosis of BD*** 6-48 h ***Time between diagnosis of BD and angiogram*** Not reported

	ischemic stroke (n=7), anoxia (n=6). ***Exclusion criteria*** Unresuscitated shock, hypothermia	the 10, 7 [11] and 4 points [12] systems. ***Description*** Initial non- enhanced CT scan. Scan after 40 s delay after injection of contrast 80 ml, 4 ml/s during 20 s ***Number and competence level of radiologists*** Two local radiologists blinded to each other's´ assessments, results of clinical tests and angiography. Competence not reported	cough/tracheal, oculo-cephalic vestibule-ocularfascial reactions. Clinical tests performed twice. ***Competence and number of clinicians behind the BD diagnosis*** 3 specialists (anesthesia and intensive care, neurology, neurosurgery)	
Shankar et al Canada 2012 [43]	***Study design*** Cross-sectional, consecutive, retrospective ***Patient spectrum*** n=11 at ICU. Intracerebral hemorrhage (n=3), subdural hemorrhage (n=1), subarachnoid hemorrhage (n=5), collapse after occipital nerve block (n=1), cardiac arrest (n=1). ***Exclusion criteria***	***Scoring system*** 7- points [11] and 4-points [12]. ***Description*** Scan volume using an adaptive spiral scanning technique "shuttle mode". 40 ml contrast injected at a rate 5 ml/s, saline flush, 5 s start delay. Two sets of axial images for CTA and perfusion analyses respectively. Automatic identification of arterial and venous	***Description*** According to Canadian guidelines. ***Competence and number of clinicians behind the BD diagnosis*** Two qualified physicians	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** 1–72 h

	Unresuscitated shock, hypothermia	vessels, vessel segmentation threshold was reviewed by a single radiologist ***Number and competence level of radiologists*** Not reported		
Welschehold et al Germany 2013 [44]	***Study design*** Cross-sectional, prospective, two ICU ***Patient spectrum*** n=63. Intracerebral hemorrhage (n=19), subarachnoid hemorrhage (n=18), traumatic brain injury (n=16), cerebellar or brain stem hemorrhage (n=6), hypoxia (n=2), stroke (n=2). ***Exclusion criteria*** Not reported	***Scoring system*** 10-points: MCA-M1, ACA-A3, PCA-P2, BA, ICV, GCV vein 7-points [11] 4-points [12]. ***Description*** First unenhanced scan Second scanning after injection of contrast in a peripheral vein, 3.5 ml/s. Scanning 5 s after opacification in common cerebral artery. The third scanning, 55 s after the second, was used for evaluation. ***Number and competence level of radiologists*** Neuroradiologist and neurointensivist/neurosurgeon together	***Description*** Clinical BD according to German guidelines. ***Competence and number of clinicians behind the BD diagnosis*** Two physicians with expertise in neurological/neurosurgical intensive care medicine	***Time at ICU before diagnosis of BD*** Not reported ***Time between diagnosis of BD and CTA*** Maximum 6 h

AAN = American Academy of Neurology; ACA = a. cerebri anterior; CT = Datortomografi; EEG = Elektroencefalografi; GCV = v. Galeni; ICU = Intensivvårdsavdelning; ICV = v. cerebri interna; MCA = a. cerebri media; PCA = a. cerebri posterior; SD = Standardavvikelse; SPV = v. petrosus superior